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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/720,205	05/25/2007	John M. Kovarik	34053-US-PCT	5868

1095 7590 12/21/2011

NOVARTIS
CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 101/2
EAST HANOVER, NJ 07936-1080

EXAMINER	
BLAKELY III, NELSON CLARENCE	
ART UNIT	PAPER NUMBER
1629	

MAIL DATE	DELIVERY MODE
12/21/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Examiner-Initiated Interview Summary	Application No.	Applicant(s)	
	11/720,205	KOVARIK ET AL.	
	Examiner	Art Unit	
	NELSON BLAKELY III	1629	

All participants (applicant, applicant's representative, PTO personnel):

(1) *Nelson C Blakely III (Examiner)*. (3)_____.

(2) *Karen DeBenedictis (Attorney)*. (4)_____.

Date of Interview: *13 December 2011*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☐ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☐103 ☐Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: _____.

Identification of prior art discussed: _____.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

In a voicemail message on 12/13/2011, Attorney of Record DeBenedictis confirmed that no response was filed with the Office.

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/Nelson C Blakely III/ Examiner, Art Unit 1629	/Jeffrey S. Lundgren/ Supervisory Patent Examiner, Art Unit 1629

Notice of Abandonment	Application No.	Applicant(s)
	11/720,205	KOVARIK ET AL.
	Examiner	Art Unit
	NELSON BLAKELY III	1629

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

This application is abandoned in view of:

1. ☒ Applicant's failure to timely file a proper reply to the Office letter mailed on *25 May 2011*.
   (a) ☐ A reply was received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the period for reply (including a total extension of time of _____ month(s)) which expired on _____.
   (b) ☐ A proposed reply was received on _____, but it does not constitute a proper reply under 37 CFR 1.113 (a) to the final rejection.
   (A proper reply under 37 CFR 1.113 to a final rejection consists only of: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114).
   (c) ☐ A reply was received on _____ but it does not constitute a proper reply, or a bona fide attempt at a proper reply, to the non-final rejection. See 37 CFR 1.85(a) and 1.111. (See explanation in box 7 below).
   (d) ☒ No reply has been received.

2. ☐ Applicant's failure to timely pay the required issue fee and publication fee, if applicable, within the statutory period of three months from the mailing date of the Notice of Allowance (PTOL-85).
   (a) ☐ The issue fee and publication fee, if applicable, was received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the statutory period for payment of the issue fee (and publication fee) set in the Notice of Allowance (PTOL-85).
   (b) ☐ The submitted fee of $_____ is insufficient. A balance of $_____ is due.
   The issue fee required by 37 CFR 1.18 is $_____. The publication fee, if required by 37 CFR 1.18(d), is $_____.
   (c) ☐ The issue fee and publication fee, if applicable, has not been received.

3. ☐ Applicant's failure to timely file corrected drawings as required by, and within the three-month period set in, the Notice of Allowability (PTO-37).
   (a) ☐ Proposed corrected drawings were received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the period for reply.
   (b) ☐ No corrected drawings have been received.

4. ☐ The letter of express abandonment which is signed by the attorney or agent of record, the assignee of the entire interest, or all of the applicants.

5. ☐ The letter of express abandonment which is signed by an attorney or agent (acting in a representative capacity under 37 CFR 1.34(a)) upon the filing of a continuing application.

6. ☐ The decision by the Board of Patent Appeals and Interference rendered on _____ and because the period for seeking court review of the decision has expired and there are no allowed claims.

7. ☐ The reason(s) below:

See attached Interview Summary.

/Jeffrey S. Lundgren/ Supervisory Patent Examiner, Art Unit 1629	

Petitions to revive under 37 CFR 1.137(a) or (b), or requests to withdraw the holding of abandonment under 37 CFR 1.181, should be promptly filed to minimize any negative effects on patent term.

CASE PAT034053-US-PCT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE PCT NATIONAL STAGE APPLICATION OF
Kovarik, John M. et al.
INTERNATIONAL APPLICATION NO: PCT/US2005/43044
FILED: November 28, 2005
U.S. APPLICATION NO: 11/720205
35 USC §371 DATE: May 25, 2007
FOR: Dosage Regimen of an S1P Receptor Agonist

Art Unit: 1614
Examiner: Blakely III, Nelson

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

PETITION FOR EXTENSION OF TIME

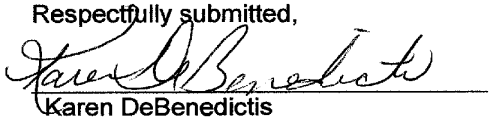
Sir:

The Office Action of May 25, 2011 has a shortened statutory time set to expire on August 25, 2011. A three-month extension is hereby requested pursuant to 37 CFR §1.136(a).

The response to said Office Action is a request for filing a continued application of the above-identified application.

Please charge Deposit Account No. 19-0134 in the name of Novartis in the amount of $1270 for payment of the extension fee. The Commissioner is hereby authorized to charge any additional fees under 37 CFR §1.17 which may be required, or credit any overpayment, to Account No. 19-0134 in the name of Novartis.

Respectfully submitted,



Karen DeBenedictis
Attorney for Applicant
Reg. No. 32,977

Novartis Pharmaceuticals Corporation
One Health Plaza, Bldg. 101
East Hanover, NJ 07936
+1 862 7783785

Date: 11/22/11

Electronic Patent Application Fee Transmittal	
Application Number:	11720205
Filing Date:	25-May-2007
Title of Invention:	DOSAGE REGIMEN OF AN S1P RECEPTOR AGONIST
First Named Inventor/Applicant Name:	John M. Kovarik
Filer:	Karen DeBenedictis/Denise Cooper
Attorney Docket Number:	34053-US-PCT
Filed as Large Entity	

U.S. National Stage under 35 USC 371 Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 3 months with $0 paid	1253	1	1270	1270

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
		Total in USD ($)		**1270**

Electronic Acknowledgement Receipt	
EFS ID:	11468721
Application Number:	11720205
International Application Number:	
Confirmation Number:	5868
Title of Invention:	DOSAGE REGIMEN OF AN S1P RECEPTOR AGONIST
First Named Inventor/Applicant Name:	John M. Kovarik
Customer Number:	1095
Filer:	Karen DeBenedictis/Denise Cooper
Filer Authorized By:	Karen DeBenedictis
Attorney Docket Number:	34053-US-PCT
Receipt Date:	22-NOV-2011
Filing Date:	25-MAY-2007
Time Stamp:	17:31:39
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$1270
RAM confirmation Number	4664
Deposit Account	190134
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Extension of Time	34053_Ext.pdf	46255 c67b4ee934e5b58a2f5bb35da182fa550d29156a	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30356 dd1ffe169f0b908e08292596a2f790a2f65cecac	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	76611		

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New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/08a (07-09)
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Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	11/720205
Filing Date	November 28, 2005
First Named Inventor	Kovarik, John M. et al.
Art unit	1614
Examiner Name	Blakely III, Nelson
Attorney Docket Number	PAT034053-US-PCT

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		US-			
		US-			
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FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
		EP 1431275 A1	06-23-2004	Kyorin Pharmaceutical Co., Ltd.		☐
		EP 1431284 A1	06-23-2011	Kyorin Pharmaceutical Co., Ltd.		☐
		WO 2004/103306	12-02-2004	IRM LLC		☐
		EP 0627406 A1	12-07-1994	Yoshitomi Pharmaceutical Industries, Ltd.		☐
						☐
						☐

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw a line through citation if not in conformance and not considered. Include copy of this form with the next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kind Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

PTO/SB/08b (07-09)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet	2	of	2

Complete if Known	
Application Number	11/720205
Filing Date	November 28, 2005
First Named Inventor	Kovarik, John M. et al.
Art unit	1614
Examiner Name	Blakely III, Nelson
Attorney Docket Number	PAT034053-US-PCT

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
		A.N. Okoto " Lechenie autoimunnogo tireoditida" (Treatment of autoimmune thryroiditis). Vitebsk, 1998. Found 06 May 2011 http://rustamsamedov.narod.ru/physlib/thyreoiditauto.html.	☐
		G.L. Vyshkovski. Index of Pharmaceuticals. Annual Index, 5, 2003, OOO "RLS-2003". P.1016.	☐
		I.B. Mikhailov. "Osnovi ratsionalnoi farmakoterapii" (Theory of rational pharmacotherapy. Tutorial on clinical pharmacotherapy for students of pediatric and medical departments of institutions of higher education. St. Petersburg "Foliant". P.32 1999	☐
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Examiner Signature		**Date Considered**	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw a line through citation if not in conformance and not considered. Include copy of this form with the next communication to applicant.
[1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached.
This collection of information is required by 37 CFR 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 431 275 A1

(12) EUROPEAN PATENT APPLICATION

published in accordance with Art. 158(3) EPC

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(51) Int Cl.[7]: **C07C 217/34**, C07C 217/56, C07C 217/64, C07C 255/54, C07C 317/22, C07C 323/20, C07D 213/30, A61K 31/137, A61K 31/138, A61K 31/277, A61K 31/4409, A61P 11/02, A61P 11/06, A61P 17/00, A61P 17/16, A61P 27/14, A61P 29/00, A61P 37/06, A61P 37/08

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25.07.2002 JP 2002216191

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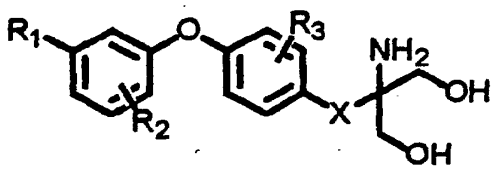
(54) DIARYL ETHER DERIVATIVE, ADDITION SALT THEREOF, AND IMMUNOSUPPRESSANT

(57) The present invention provides diaryl ether derivatives that exhibit significant immunosuppressive effects with less side effects.

The diaryl derivatives of the present invention are represented by the following general formula (1):



(1)

one example is 2-amino-2-[4-(3-benzyloxyphenoxy)-2-chlorophenyl)propyl-1,3-propanediol.

EP 1 431 275 A1

Printed by Jouve, 75001 PARIS (FR)

Description

TECHNICAL FIELD

[0001] The present invention relates to diaryl ether derivatives, salts and hydrates thereof that are useful as an immunosuppressive agent.

TECHNICAL BACKGROUND

[0002] Immunosuppressive agents are widely used as a treatment for autoimmune diseases such as rheumatoid arthritis, nephritis, osteoarthritis and systemic lupus erythematosus, chronic inflammatory diseases such as inflammatory bowel disease, and allergic diseases such as asthma and dermatitis. Progress in medicine has led to an increase in the number of tissue and organ transplantations performed each year. In such a situation of modern medicine, having as much control as possible over the rejection following transplantation is a key to successful transplantation. Immunosuppressive agents also play a significant role to this end.

[0003] Among immunosuppressors commonly used in organ transplantation are antimetabolites, such as azathioprine and mycophenolate mofetil, calcineurin inhibitors, such as cyclosporin A and tacrolimus, and corticosteroid, such as prednisolone. Some of these drugs are not effective enough while others require continuous monitoring of the blood drug level to avoid renal failure and other serious side effects. Thus, none of conventional immunosuppressive agents are satisfactory in view of efficacy and potential side effects.

[0004] Multiple drug combined-therapy, in which different immunosuppressive drugs with different mechanisms of action are used, is becoming increasingly common with the aims of alleviating the side effects of the drugs and achieving sufficient immunosuppressive effects. Also, development of new types of immunosuppressive agents that have completely different mechanisms of action is sought.

[0005] In an effort to respond to such demands, the present inventors conducted a search for new types of immunosuppressive agents with main emphasis on 2-amino-1,3-propanediol derivatives.

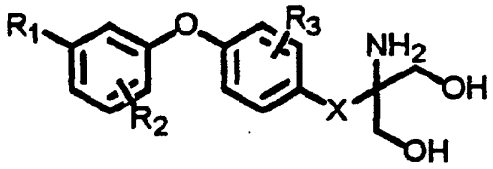
[0006] While the use of 2-amino-1,3-propanediol derivatives as immunosuppressive agents has been disclosed in PCT publication WO94/08943 (YOSHITOMI PHARMACEUTICAL INDUSTRIES, Ltd., TAITO Co., Ltd.) and in Japanese Patent Publication No. Hei 9-2579602 (YOSHITOMI PHARMACEUTICAL INDUSTRIES, Ltd., TAITO Co., Ltd.), it has not been previously known that 2-amino-1,3-propanediol derivatives having a diaryl ether group, which are subjects of the present invention, can serve as an effective immunosuppressor.

DISCLOSURE OF THE INVENTION

[0007] Accordingly, it is an objective of the present invention to provide a diaryl ether derivative that exhibits significant immunosuppressive effects with little side effects.

[0008] In the course of studies on immunosuppressive agents that have different mechanisms of action from antimetabolites and calcineurin inhibitors, the present inventors discovered that novel diaryl ether derivatives that have a different structure from conventional immunosuppressors exhibit strong immunosuppressive effects. Specifically, the compounds are such that one of the aryl groups includes, at its para-position, a carbon chain with an aminopropanediol group and the other aryl group includes a substituent at its meta-position. This discovery led the present inventors to devise the present invention.

[0009] The present invention thus is an immunosuppressive agent containing as an active ingredient at least one of a diaryl ether derivative, a pharmaceutically acceptable salt and hydrate thereof, the diaryl ether derivative represented by the following general formula (1):

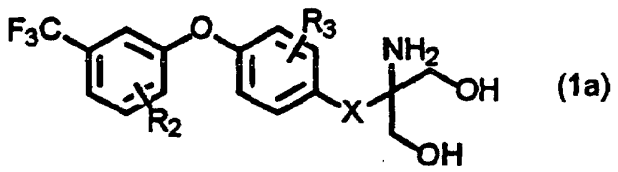


(1)

wherein R_1 is halogen, trihalomethyl, hydroxy, lower alkyl having 1 to 7 carbon atoms, substituted or unsubstituted phenyl, aralkyl, lower alkoxy having 1 to 4 carbon atoms, trifluoromethyloxy, phenoxy, cyclohexylmethyloxy, substituted or unsubstituted aralkyloxy, pyridylmethyloxy, cinnamyloxy, naphthylmethyloxy, phenoxymethyl, hydroxymethyl, hy-

droxyethyl, lower alkylthio having 1 to 4 carbon atoms, lower alkylsulfinyl having 1 to 4 carbon atoms, lower alkylsulfonyl having 1 to 4 carbon atoms, benzylthio, acetyl, nitro, or cyano; R_2 is hydrogen, halogen, trihalomethyl, lower alkoxy having 1 to 4 carbon atoms, lower alkyl having 1 to 7 carbon atoms, phenethyl, or benzyloxy; R_3 is hydrogen, halogen, trifluoromethyl, lower alkoxy having 1 to 4 carbon atoms, hydroxy, benzyloxy, lower alkyl having 1 to 7 carbon atoms, phenyl, lower alkoxymethyl having 1 to 4 carbon atoms, or lower alkylthio having 1 to 4 carbon atoms; and X is-$(CH_2)_n$- (n is an integer from 1 to 4), -OCH_2CH_2-, or -$CH{=}CHCH_2$-.

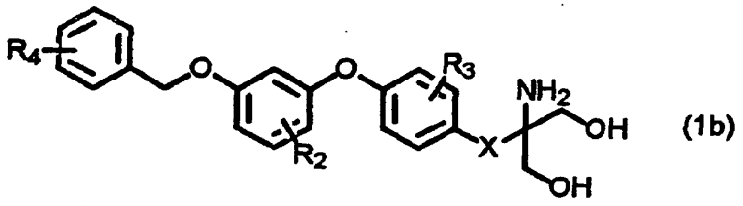
[0010] More specifically, the present invention is an immunosuppressive agent containing as an active ingredient at least one of a diaryl ether derivative, a pharmaceutically acceptable salt and hydrate thereof, the diaryl ether derivative represented by the following general formula (1a):



(1a)

wherein R_2, R_3, and X are the same as defined above.

[0011] Furthermore, the present invention is an immunosuppressive agent containing as an active ingredient at least one of a diaryl ether derivative, a pharmaceutically acceptable salt and hydrate thereof, the diaryl ether derivative represented by the following general formula (1b):



(1b)

wherein R_2, R_3, and X are the same as defined above; and R_4 is hydrogen, halogen, trifluoromethyl, lower alkoxy having 1 to 4 carbon atoms, or lower alkyl having 1 to 7 carbon atoms.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012]

Fig. 1 is a graph showing activities of a test compound in a mouse skin graft model.
Fig. 2 is a graph showing activities of a test compound in a mouse skin graft model.
Fig. 3 is a graph showing activities of a test compound in a mouse skin graft model.
Fig. 4 is a graph showing activities of a test compound in a mouse skin graft model.
Fig. 5 is a graph showing activities of a test compound in a mouse skin graft model.
Fig. 6 is a graph showing activities of a test compound in a mouse skin graft model.
Fig. 7 is a graph showing activities of a test compound in a mouse skin graft model.
Fig. 8 is a graph showing activities of a test compound in a mouse skin graft model.

BEST MODE FOR CARRYING OUT THE INVENTION

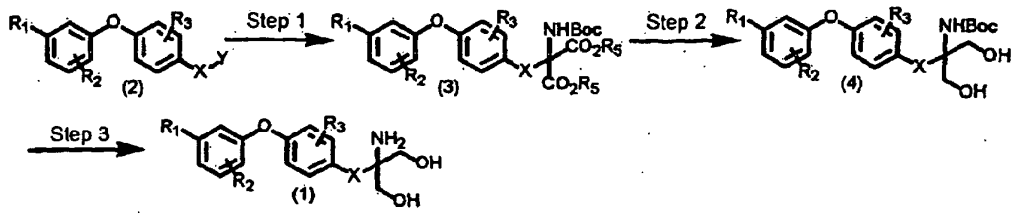
[0013] The compounds of the general formulae (1), (1a) and (1b) are novel compounds. Examples of the pharmaceutically acceptable salt of the compound of the general formula (1) include acid salts, such as hydrochloride, hydrobromide, acetate, trifluoroacetate, methanesulfonate, citrate, and tartrate.

[0014] In the general formula (1), the term 'halogen atom' includes fluorine, chlorine, bromine, and iodine atom. The term 'trihalomethyl group' includes trifluoromethyl and trichloromethyl. The phrase 'lower alkyl group having 1 to 7 carbon atoms' includes straight-chained or branched hydrocarbons having 1 to 7 carbon atoms, such as methyl, ethyl,

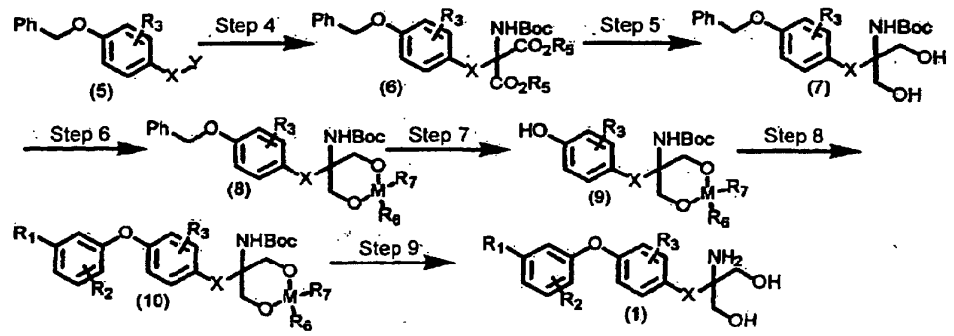
propyl, isopropyl, butyl, t-butyl, pentyl, hexyl, and heptyl. The phrase 'substituted or unsubstituted phenoxy group' includes those that have, at any position of its benzene ring, a halogen atom, such as fluorine, chlorine, bromine and iodine, trifluoromethyl, lower alkyl having 1 to 4 carbon atoms, or lower alkoxy having 1 to 4 carbon atoms. The term 'aralkyl group' as in 'aralkyl group' or 'aralkyloxy group' includes benzyl, diphenylmethyl, phenethyl, and phenylpropyl. The term 'lower alkyl group' as used in 'lower alkoxyl group having 1 to 4 carbon atoms,' 'lower alkylthio group having 1 to 4 carbon atoms,' 'lower alkylsulfinyl group having 1 to 4 carbon atoms,' or 'lower alkylsulfonyl group having 1 to 4 carbon atoms,' includes straight-chained or branched hydrocarbons having 1 to 4 carbon atoms, such as methyl, ethyl, propyl, isopropyl, and butyl. The phrase 'substituted or unsubstituted aralkyl group' includes those that have, at any position of its benzene ring, a halogen atom, such as fluorine, chlorine, bromine and iodine, trifluoromethyl, lower alkyl having 1 to 4 carbon atoms, or lower alkoxy having 1 to 4 carbon atoms.

[0015] According to the present invention, the compounds of the general formula (1) can be produced in the following pathways:

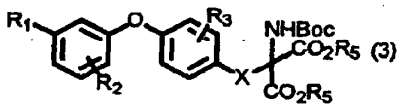
Synthetic pathway 1



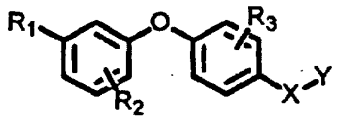
Synthetic pathway 2



[0016] The compound appearing in the synthetic pathway 1 and represented by the following general formula (3):

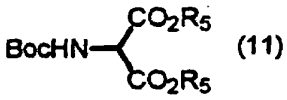


(wherein R_5 is lower alkyl having 1 to 4 carbon atoms; Boc is t-butoxycarbonyl; and R_1, R_2, R_3, and X are the same as described above) can be prepared by reacting a compound of the following general formula (2):



(2)

(wherein Y is chlorine, bromine, or iodine; and R_1, R_2, R_3, and X are as described above) with a compound of the following general formula (11):

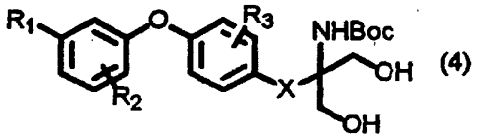


(11)

(wherein R_5 and Boc are as described above) in the presence of a base (Step 1).

[0017] This reaction can be carried out using a reaction solvent such as 1,4-dioxane, dimethylsulfoxide (DMSO), N, N-dimethylformamide (DMF), tetrahydrofuran (THF), or ethanol at a reaction temperature of 0°C to reflux temperature, preferably at a temperature of 80°C to 100°C, in the presence of an inorganic base such as sodium hydride, potassium hydride, sodium alkoxide, and potassium alkoxide.

[0018] The compound appearing in the synthetic pathway 1 and represented by the following general formula (4):

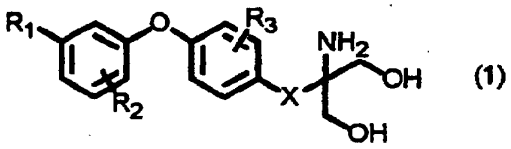


(4)

(wherein R_1, R_2, R_3, R_4, X, and Boc are as described above) can be prepared by the reduction of the compound of the general formula (3) (Step 2).

[0019] This reaction can be carried out at a reaction temperature of 0°C to reflux temperature, preferably at room temperature, using an alkylborane derivative, such as borane (BH_3) and 9-borabicyclo[3.3.1]nonane (9-BBN), or a metal hydride complex, such as diisobutylaluminum hydride ((iBu)2AlH), sodium borohydride ($NaBH_4$) and lithium aluminum hydride ($LiAlH_4$), preferably lithium borohydride ($LiBH_4$), and using a reaction solvent such as THF, ethanol and methanol.

[0020] The compound appearing in the synthetic pathway 1 and represented by the general formula (1):

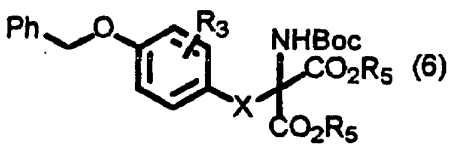


(1)

(wherein R_1, R_2, R_3, and X are as described above) can be prepared by the acidolysis of the compound of the general formula (4) (Step 3).

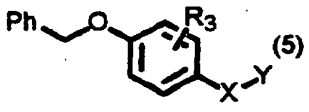
[0021] This reaction can be carried out at a reaction temperature in the range of 0°C to room temperature in an inorganic or organic acid, such as acetic acid, hydrochloric acid, hydrobromic acid, methanesulfonic acid and trifluoroacetic acid, or in a mixed solvent with an organic solvent such as methanol, ethanol, THF, 1,4-dioxane, and ethyl acetate.

[0022] The compound appearing in the synthetic pathway 2 and represented by the following general formula (6):



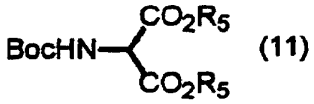
(6)

(wherein R_3, R_5, X, and Boc are as described above) can be prepared by reacting the compound represented by the following general formula (5):



(5)

(wherein R_3, X, and Y are as described above) with the compound of the general formula (11):

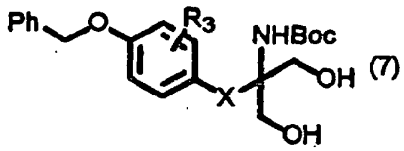


(11)

(wherein R_5, and Boc are as described above) in the presence of a base (Step 4).

[0023] This reaction can be carried out using a reaction solvent such as 1,4-dioxane, DMSO, DMF, THF, or ethanol at a reaction temperature in the range of 0°C to reflux temperature, preferably 80°C to 100°C, in the presence of an inorganic base such as sodium hydride, potassium hydride, sodium alkoxide, and potassium alkoxide.

[0024] The compound appearing in the synthetic pathway 2 and represented by the following general formula (7):

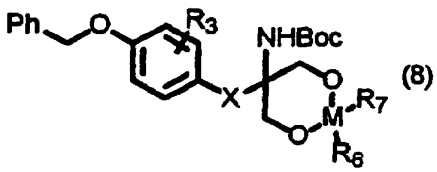


(7)

(where R_3 and X are as described above) can be prepared by the reduction of the compound of the general formula (6) (Step 5).

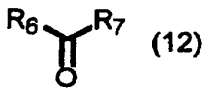
[0025] This reaction can be carried out at a reaction temperature of 0°C to reflux temperature, preferably at room temperature, using an alkylborane derivative, such as BH_3 and 9-BBN, or a metal hydride complex, such as $(iBu)_2AlH$, $NaBH_4$ and $LiAlH_4$, preferably $LiBH_4$, and using a reaction solvent such as THF, ethanol, and methanol.

[0026] The compound appearing in the synthetic pathway 2 and represented by the following general formula (8):



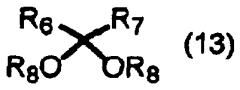
(8)

(wherein M is carbon or silicon; R6 and R7 are each independently hydrogen or lower alkyl having 1 to 4 carbon atoms; and R_3, X and Boc are as described above) can be prepared by reacting the compound of the general formula (7) with a compound of the general formula (12):



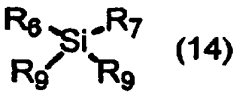
(12)

(where R_6 and R_7 are as described above) or a compound of the general formula (13):



(13)

(wherein R_8 is lower alkyl having 1 to 4 carbon atoms; and R_6 and R_7 are as described above) or a compound of the general formula (14):



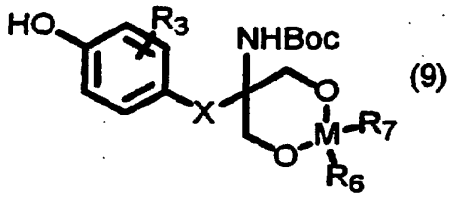
(14)

(wherein R_9 is chlorine or trifluoromethansulfonyloxy; and R_6 and R_7 are as described above) (Step 6).

[0027] The reaction between the compound of the general formula (7) and the compound of the general formula (12) or the compound of the general formula (13) can be carried out at a reaction temperature of room temperature to 100°C either in the presence of a Lewis acid such as zinc chloride or in the presence of an acid catalyst such as camphorsulfonic acid, paratoluenesulfonic acid, and pyridinium paratoluenesulfonic acid, and either in the absence of solvent or in the presence of a reaction solvent such as DMF, THF, and methylene chloride.

[0028] The reaction between the compound of the general formula (7) and the compound of the general formula (14) can be carried out at a reaction temperature of 0°C to 100°C in the presence of a base such as triethylamine, pyridine, 2,6-lutidine, and imidazole, using a reaction solvent such as DMF, THF, methylene chloride, chloroform, and acetonitrile.

[0029] The compound appearing in the synthetic pathway 2 and represented by the general formula (9):

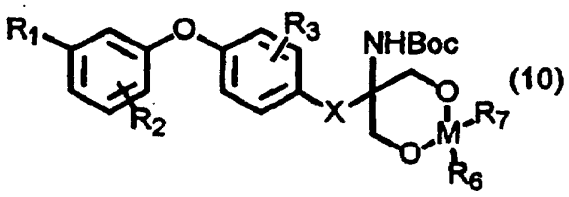


(9)

(wherein R_3, R_6, R_7, X, Boc, and M are as described above) can be prepared by the hydrogenolysis of the compound of the general formula (8) (Step 7).

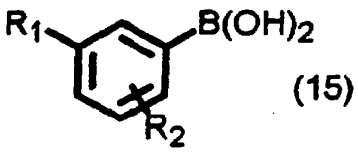
[0030] This reaction can be carried out at a temperature in the range of room temperature to 100°C in the presence of a reduction catalyst, such as palladium carbon, platinum carbon, platinum oxide, rhodium carbon, and ruthenium carbon, in a solvent, such as ethanol, methanol, THF, DMF, and ethyl acetate, under a hydrogen pressure that is atmospheric pressure or higher.

[0031] The compound appearing in the synthetic pathway 2 and represented by the general formula (10):



(10)

[wherein R_1, R_2, R_3, R_6, R_7, X, Boc, and M are as described above] can be prepared by reacting the compound of the general formula (9) with a compound of the general formula (15) :

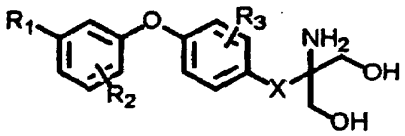


(15)

(wherein R_1 and R_2 are as described above) in the presence of copper acetate (Step 8).

[0032] This reaction can be carried out at room temperature in the presence or absence of a molecular sieve, using copper acetate as a reaction promoter and methylene chloride or chloroform as a solvent, in the presence of a base, such as triethylamine.

[0033] The compound appearing in the synthetic pathway 2 and represented by the general formula (1):



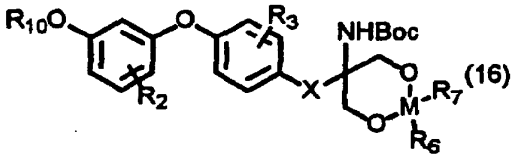
(1)

(wherein R1, R2, R3, and X are as described above) can be prepared by the acidolysis, or desilylation followed by acidolysis, of the compound of the general formula (10) (Step 9) .

[0034] This reaction can be carried out at a reaction temperature of 0°C to room temperature in an inorganic or organic acid, such as acetic acid, hydrochloric acid, hydrobromic acid, methanesulfonic acid, trifluoroacetic acid, or in a mixed solution with an organic solvent, such as methanol, ethanol, THF, 1,4-dioxane, and ethyl acetate.

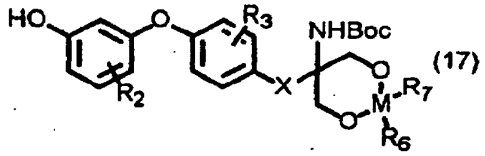
[0035] When M in the general formula (10) is a silicon atom, the compound of the general formula (1) can be synthesized by reacting potassium fluoride, cesium fluoride, or tetrabutylammonium fluoride at a temperature of 0°C to room temperature in a solvent such as THF, DMF, and 1,4-dioxane and then subjecting the resulting compound to the above-described acidolysis.

[0036] Of the compounds of the general formula (10), those represented by the general formula (16) in which R_1 is a substituted or unsubstituted aralkyloxy group:



(16)

(wherein R_{10} is substituted or unsubstituted aralkyl; and R_2, R_3, R_6, R_7, X, Boc, and M are as described above) can also be prepared by reacting a compound of the general formula (17):



(17)

(wherein R_2, R_3, R_6, R_7, X, Boc, and M are as described above) with a compound of the general formula (18):

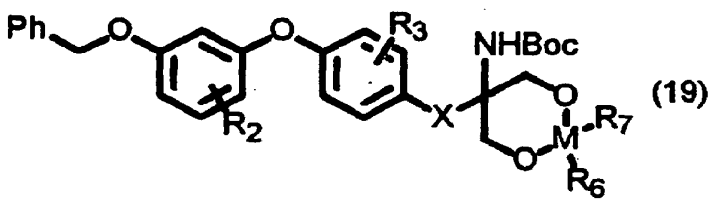
$$R_{10}Y' \qquad (18)$$

(wherein Y' is halogen or hydroxy; and R_{10} is as described above).

[0037] When Y' is a halogen atom, the reaction can be carried out at a reaction temperature in the range of room temperature to 80°C, using an organic base, such as triethylamine, and pyridine, or an inorganic base, such as sodium hydride, sodium carbonate, and potassium carbonate, and using a reaction solvent, such as THF, DMF, and 1,4-dioxane:

[0038] When Y' is a hydroxy, the reaction can be carried out at room temperature in the presence of diethyl azodicarboxylate or triphenylphosphine, using THF as a solvent.

[0039] The compound of the general formula (17) can be prepared by the hydrogenolysis of a compound of the general formula (19):

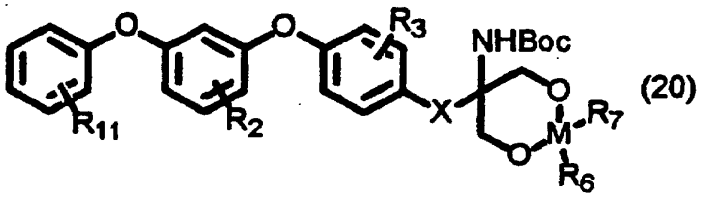


(19)

(wherein R_2, R_3, R_6, R_7, X, Boc, and M are as described above).

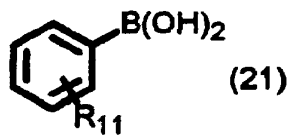
[0040] This reaction can be carried out at a temperature in the range of room temperature to 100°C in the presence of a reduction catalyst, such as palladium carbon, platinum carbon, platinum oxide, rhodium carbon, and ruthenium carbon, in a solvent, such as ethanol, methanol, THF, DMF, and ethyl acetate, under a hydrogen pressure that is atmospheric pressure or higher.

[0041] Of the compounds represented by the general formula (10), those represented by the general formula (20) in which R_1 is a substituted or unsubstituted phenoxy group:



(20)

(wherein R_{11} is hydrogen, halogen, trifluoromethyl, lower alkyl having 1 to 4 carbon atoms, or lower alkoxy having 1 to 4 carbon atoms; and R_2, R_3, R_6, R_7, X, Boc, and M are as described above) can be prepared by reacting the compound of the general formula (17) with a compound of the general formula (21):



(21)

(wherein R_{11} is as described above) in the presence of copper acetate.

[0042] This reaction can be carried out preferably at room temperature in the presence or absence of a molecular sieve, using copper acetate as a reaction promoter and methylene chloride or chloroform as a solvent, in the presence of a base, such as triethylamine.

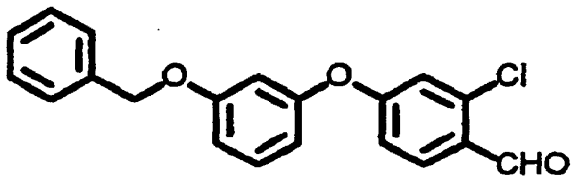
Examples

[0043] The present invention will now be described with reference to examples, which are not intended to limit the scope of the invention in any way.

<Reference Example 1>

4-(3-benzyloxyphenoxy)-2-chlorobenzaldehyde

[0044]

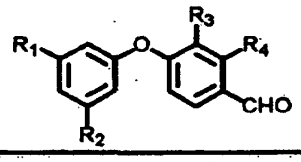


[0045] Potassium carbonate (5.53g) was added to a DMF solution (70ml) of 2-chloro-4-fluorobenzaldehyde (3.35g) and 3-benzyloxyphenol (4.23g) and the solution was stirred for 3 hours while heated to 150°C. The reaction mixture was decanted into water and was extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 6:1). In this manner, the desired product (6.73g) was obtained as a colorless powder.

<Reference Examples 2 through 37>

[0046] Using various phenol derivatives and aldehydes, compounds shown in Table 1 were synthesized in the same manner as in Reference Example 1 above.

Table 1

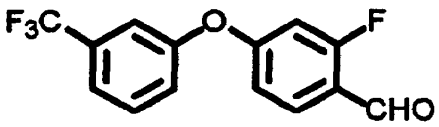


Reference Example	R1	R2	R3	R4	Reference Example	R1	R2	R3	R4
2	CF_3	H	H	H	20	$PhCH_2O$	$PhCH_2O$	H	Cl
3	CF_3	H	MeO	H	21	$PhCH_2O$	Cl	H	Cl
4	CF_3	H	H	MeO	22	$PhCH_2O$	H	H	Br
5	CF_3	H	Cl	H	23	$PhCH_2O$	H	H	CF_3
6	CF_3	H	H	Cl	24	$PhCH_2O$	H	H	Ph
7	CF_3	H	H	$PhCH_2O$	25	MeO	CF3	H	H
8	CF_3	H	CF_3	H	26	MeO	CF3	H	Cl
9	CF_3	H	H	CF_3	27	t-Bu	H	H	H
10	CF_3	CF_3	H	Cl	28	MeS	H	H	H
11	CF3	$Ph(CH_2)_2$	H	H	29	$n\text{-}C_5H_{11}$	H	H	H
12	$Ph(CH_2)_2$	$Ph(CH_2)_2$	H	H	30	$n\text{-}C_7H_{15}$	H	H	H
13	$Ph(CH_2)_2$	H	H	Cl	31	i-Pr	i-PrO	H	H
14	$Ph(CH_2)_2$	H	H	CF_3	32	i-Pr	i-PrO	H	Cl
15	$Ph(CH_2)_2$	$Ph(CH_2)_2$	H	Cl	33	i-Pr	i-Pr	H	Cl
16	$Ph(CH_2)_2$	$Ph(CH_2)_2$	H	CF_3	34	Cl	Cl	H	Cl
17	$PhCH_2O$	H	H	H	35	$PhCH_2S$	H	H	H
18	$PhCH_2O$	$PhCH_2O$	H	H	36	$PhCH_2S$	H	H	Cl
19	$PhCH_2O$	H	H	i-Pr	37	Me	H	H	H

<Reference Example 38>

2-fluoro-4-[(3-trifluoromethyl)phenoxy]benzaldehyde

[0047]

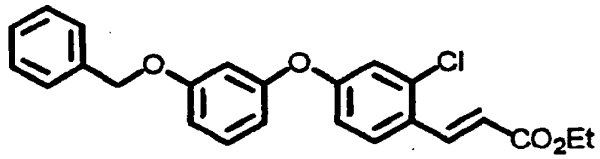


[0048] 3-(trifluoromethyl)phenylboric acid (1.03g) and 2-fluoro-4-hydroxybenzaldehyde (760mg) were dissolved in methylene chloride. While the solution was stirred, copper acetate (985mg), molecular sieve 4A (800mg), and triethylamine (3.76mL) were added. After 6 and 24 hours, the same amount of copper acetate was added and the mixture was stirred for additional 48 hours. The insoluble material was then filtered out and the filtrate was decanted into water and was extracted with ethyl acetate. The organic phase was washed with water and then with a saturated aqueous solution of sodium chloride and was dried with anhydrous magnesium sulfate. Subsequently, the solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 7:1, and then 2:1). In this manner, the desired product (265mg) was obtained as a yellow oil.

<Reference Example 39>

Ethyl 4'-(3-benzyloxyphenoxy)-2'-chlorocinnamate

[0049]

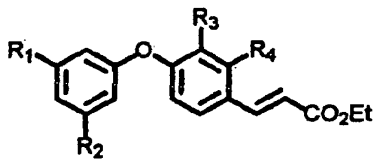


[0050] Under argon, 60% sodium hydride (960mg) was added to a THF solution (150ml) of ethyl (diethylphosphono) acetate (4.8mL) at 0°C and the mixture was stirred for 30 minutes. A THF solution (20mL) of the compound of Reference Example 1 (6.73g) was then added dropwise. With the temperature maintained, the mixture was further stirred for 1 hour, followed by addition of water and then extraction with ethyl acetate. The organic phase was washed with water and then with a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 6:1). In this manner, the desired product (7.36g) was obtained as a colorless oil.

<Reference Examples 40 through 76>

[0051] Using the compounds of Reference Examples 2 through 38, the compounds shown in Table 2 below were synthesized in the same manner as in Reference Example 39 above.

Table 2

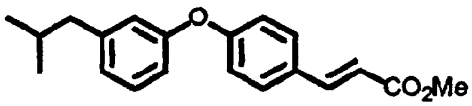


Reference Example	R1	R2	R3	R4	Reference Example	R1	R2	R3	R4
40	CF_3	H	H	H	59	$PhCH_2O$	Cl	H	Cl
41	CF_3	H	MeO	H	60	$PhCH_2O$	H	H	Br
42	CF_3	H	H	MeO	61	$PhCH_2O$	H	H	CF_3
43	CF_3	H	Cl	H	62	$PhCH_2O$	H	H	Ph
44	CF_3	H	H	Cl	63	MeO	CF3	H	H
45	CF_3	H	H	$PhCH_2O$	64	MeO	CF3	H	Cl
46	CF_3	H	CF_3	H	65	t-Bu	H	H	H
47	CF_3	H	H	CF_3	66	MeS	H	H	H
48	CF_3	CF_3	H	Cl	67	$n\text{-}C_5H_{11}$	H	H	H
49	CF3	$Ph(CH_2)_2$	H	H	68	$n\text{-}C_7H_{15}$	H	H	H
50	$Ph(CH_2)_2$	$Ph(CH_2)_2$	H	H	69	i-Pr	i-PrO	H	H
51	$Ph(CH_2)_2$	H	H	Cl	70	i-Pr	i-PrO	H	Cl
52	$Ph(CH_2)_2$	H	H	CF_3	71	i-Pr	i-Pr	H	Cl
53	$Ph(CH_2)_2$	$Ph(CH_2)_2$	H	Cl	72	Cl	Cl	H	Cl
54	$Ph(CH_2)_2$	$Ph(CH_2)_2$	H	CF_3	73	$PhCH_2S$	H	H	H
55	$PhCH_2O$	H	H	H	74	$PhCH_2S$	H	H	Cl
56	$PhCH_2O$	$PhCH_2O$	H	H	75	CF_3	H	H	F
57	$PhCH_2O$	$PhCH_2O$	H	Cl	76	Me	H	H	H
58	$PhCH_2O$	H	H	i-Pr					

<Reference Example 77>

Methyl 4'-(3-isobutylphenoxy)cinnamate

[0052]

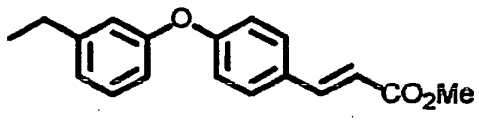


[0053] Potassium carbonate (622mg) was added to a DMF solution (10ml) of 3-isobutylphenol (451mg) and methyl 4'-fluorocinnamate (541mg), and the solution was stirred for 8 hours while heated to 140°C. The reaction mixture was decanted into water and was extracted with ethyl acetate. The organic phase was washed with water and then with a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 30:1). In this manner, the desired product (278mg) was obtained as a yellow oil.

<Reference Example 78>

Methyl 4'-(3-ethylphenoxy)cinnamate

[0054]

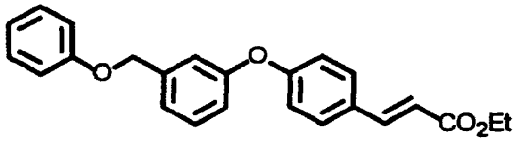


[0055] Using 3-ethylphenol and methyl 4'-fluorocinnamate, reactions were carried out in the same manner as in Reference Example 77 above. The desired product was obtained as a yellow oil.

<Reference Example 79>

Ethyl 4'-[(3-phenoxymethyl)phenoxy]cinnamate

[0056]

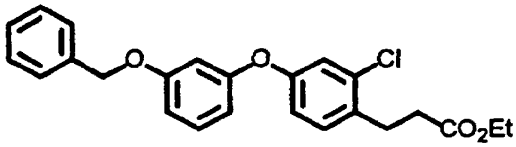


[0057] The compound of Reference Example 76 (2.82g) was dissolved in carbon tetrachloride (50mL). Following addition of N-bromosuccinimide (2.31g), the solution was stirred under exposure to light while heated. After 24 hours, the solvent was removed by distillation under reduced pressure, and the residue was extracted with ethyl acetate. The organic phase was washed with water and then with a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 6:1). In this manner, ethyl 4'-[(3-bromomethyl) phenoxy]cinnamate (1.30g) was obtained as a yellow oil. To a DMF solution (25mL) of the resulting bromide (1.24g), phenol (380mg) and potassium carbonate (500mg) were added, and the mixture was stirred for 3 hours at 60°C. Subsequently, the reaction mixture was decanted into water and was extracted with ethyl acetate. The organic phase was washed with water and then with a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 4:1). In this manner, the desired product (1.30g) was obtained as a colorless oil.

<Reference Example 80>

Ethyl 4'-[(3-benzyloxy)phenoxy]-2'-chlorodihydrocinnamate

[0058]

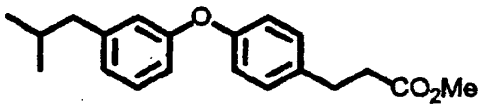


[0059] The compound of Reference Example 39 (7.36g) was dissolved in ethanol (100mL). While the solution was stirred at 0°C, bismuth chloride (2.84g) was added. Sodium borohydride (2.72g) was then added in three portions and the mixture was subsequently stirred for 3 hours at room temperature. Ice water was then added to the reaction mixture and the crystallized inorganic deposits were filtered out through celite. The resulting filtrate was extracted with ethyl acetate. The organic phase was washed with water and then with a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure. In this manner, the desired product (7.40g) was obtained as a colorless oil (Method A).

<Reference Example 81>

Methyl 4'-(3-isobutylphenoxy)dihydrocinnamate

[0060]

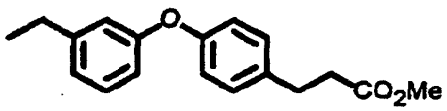


[0061] The compound of Reference Example 77 (278mg) was dissolved in ethanol (5mL), and 10% Pd/C (70.0mg) was added to the solution. The resulting mixture was then stirred for 2 hours at room temperature under hydrogen. The catalyst was filtered out and the filtrate was concentrated under reduced pressure to obtain the desired product as a colorless oil (Method B).

<Reference Example 82>

Methyl 4'-(3-ethylphenoxy)dihydrocinnamate

[0062]

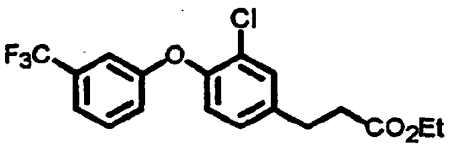


[0063] Using the compound of Reference Example 78, reactions were carried out in the same manner as in Reference Example 81 above. In this manner, the desired product was obtained as a colorless oil.

<Reference Example 83>.

Ethyl 3'-chloro-4'-[(3-trifluoromethyl)phenoxy]dihydrocinnamate

[0064]



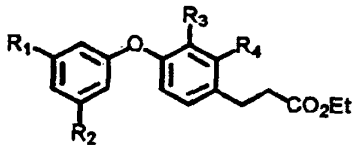
[0065] The compound of Reference Example 43 (2.29g) was dissolved in ethyl acetate (30mL), and 5% Pd/C-ethylenediamine complex (230mg) was added to the solution. The resulting mixture was then stirred for 3.5 hours at room

temperature under hydrogen. The catalyst was then filtered out and the filtrate was concentrated under reduced pressure to obtain the desired product (2.30g) as a pale yellow oil (Method C).

<Reference Examples 84 through 118>

[0066] Using the compounds of Reference Examples 40 through 42, 44 through 65, 67 through 75, and 79, reactions were carried out in the same manner as in Reference Examples 80 through 83 above to synthesize compounds as shown in Table 3 below.

Table 3

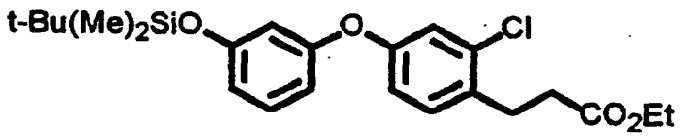


Reference Example	R1	R2	R3	R4	Process	Reference Example	R1	R2	R3	R4	Process
84	CF_3	H	H	H	B	101	$PhCH_2O$	$PhCH_2O$	H	Cl	A
85	CF_3	H	MeO	H	B	102	$PhCH_2O$	Cl	H	Cl	A
86	CF_3	H	H	MeO	B	103	$PhCH_2O$	H	H	Br	A
87	CF_3	H	H	Cl	C	104	$PhCH_2O$	H	H	CF_3	A
88	CF_3	H	H	$PhCH_2O$	C	105	$PhCH_2O$	H	H	Ph	A
89	CF_3	H	CF_3	H	B	106	MeO	CF3	H	H	A
90	CF_3	H	H	CF_3	B	107	MeO	CF3	H	Cl	A
91	CF_3	CF_3	H	Cl	A	108	t-Bu	H	H	H	B
92	CF3	$Ph(CH_2)_2$	H	H	B	109	$n\text{-}C_5H_{11}$	H	H	H	B
93	$Ph(CH_2)_2$	$Ph(CH_2)_2$	H	H	B	110	$n\text{-}C_7H_{15}$	H	H	H	B
94	$Ph(CH_2)_2$	H	H	Cl	A	111	i-Pr	i-PrO	H	H	B
95	$Ph(CH_2)_2$	H	H	CF_3	B	112	i-Pr	i-PrO	H	Cl	C
96	$Ph(CH_2)_2$	$Ph(CH_2)_2$	H	Cl	A	113	i-Pr	i-Pr	H	Cl	C
97	$Ph(CH_2)_2$	$Ph(CH_2)_2$	H	CF_3	B	114	Cl	Cl	H	Cl	A
98	$PhCH_2O$	H	H	H	A	115	$PhCH_2S$	H	H	H	A
99	$PhCH_2O$	$PhCH_2O$	H	H	A	116	$PhCH_2S$	H	H	Cl	A
100	$PhCH_2O$	H	H	i-Pr	A	117	$PhOCH_2$	H	H	H	A
						118	CF_3	H	H	F	B

<Reference Example 119>

Ethyl 4'-[(3-*t*-butyldimethylsiloxy)phenoxy]-2'-chlorodihydrocinnamate

[0067]



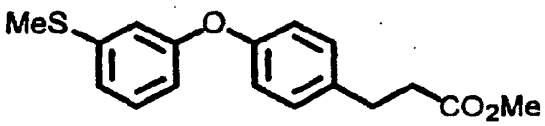
[0068] Using the compound of Reference Example 39, reactions were carried out in the same manner as in Reference Example 83 (Method C). The resulting phenol (7.10g) was dissolved in DMF (80mL), and imidazole (1.80g) and t-butyldimethylchlorosilane (3.98g) were added to the solution. The mixture was then stirred overnight at room temperature. Subsequently, the mixture was decanted into water and was extracted with ethyl acetate. The organic phase

was washed with water and then with a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 4:1). In this manner, the desired product (8.86g) was obtained as a colorless oil.

<Reference Example 120>

Methyl 4'-[(3-methylthio)phenoxy]dihydrocinnamate

[0069]

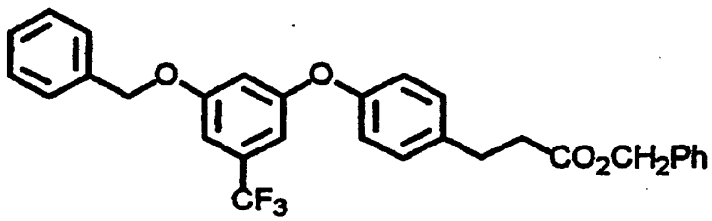


[0070] Under argon, the compound of Reference Example 66 (4.07g) was dissolved in methanol (50mL). While the solution was stirred at 10°C, magnesium (1.00g) was added to the solution. With the temperature maintained, the mixture was further stirred for 3 hours, followed by addition of diluted hydrochloric acid and then extraction with ethyl acetate. The organic phase was washed with water and then with a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure to obtain the desired product (3.70g) as a colorless oil.

<Reference Example 121>

Benzyl 4'-[3-benzyloxy-5-(trifluoromethyl)phenoxy] dihydrocinnamate

[0071]

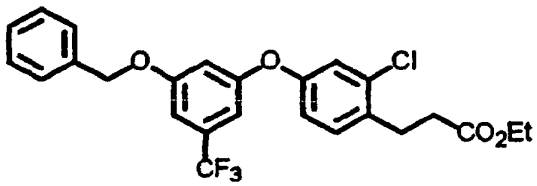


[0072] The compound of Reference Example 106 (840mg) was dissolved in methylene chloride (20mL). While the solution was stirred at 0°C, a 1mol/L boron tribromide-methylene chloride solution (3.42mL) was added dropwise. Subsequently, the mixture was stirred overnight at room temperature. Ice water was then added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure. In this manner, 4'-(3-trifluoromethyl-5-hydroxyphenoxy)dihydrocinnamate (750mg) was obtained as a light brown powder. The powder so produced was dissolved in DMF (50mL), followed by the addition of potassium carbonate (1.04g) and benzyl bromide (0.602mL). The mixture was then stirred at room temperature for 8 hours, decanted into ice water, and extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was then dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure to obtain the desired product as a brown oil.

<Reference Example 122>

Ethyl 4'-[3-benzyloxy-5-(trifluoromethyl)phenoxy]-2'-chlorodihydrocinnamate

[0073]

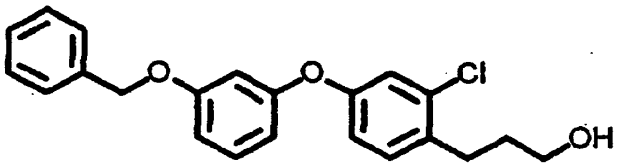


[0074] Using the compound of Reference Example 107, 2'-chloro-4'-(3-trifluoromethyl-5-hydroxyphenoxy)dihydrocinnamic acid was obtained in the same manner as in Reference Example 121 above. The cinnamic acid (1.47g) so obtained was dissolved in ethanol (10mL). While the solution was stirred at 0°C, thionyl chloride (3mL) was added dropwise. With the temperature maintained, the solution was stirred for additional 2 hours. The solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 10:1 and then 6:1). As a result, ethyl 2'-chloro-4'-(3-trifluoromethyl-5-hydroxyphenoxy)dihydrocinnamate (1.38g) was obtained as a colorless oil. Using potassium carbonate and benzyl bromide, the resultant ester was subjected to benzyl-etherification as with Reference Example 121 above. In this manner, the desired product was obtained as a colorless oil.

<Reference Example 123>

4'-[(3-benzyloxy)phenoxy]-2'-chlorodihydrocinnamyl alcohol

[0075]

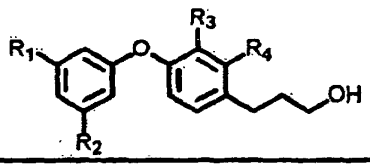


[0076] The compound of Reference Example 80 (7.40g) was dissolved in THF (100mL). While the solution was stirred at 0°C, lithium aluminum hydride (500mg) was added. After 10 minutes, a 20% aqueous solution of NaOH was added and the crystallized insoluble inorganic deposits were filtered out through celite. The filtrate was then extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure to obtain the desired product (6.37g) as a colorless oil.

<Reference Examples 124 through 163>

[0077] Using the compounds of Reference Examples 81 through 105 and 108 through 122, the compounds shown in Table 4 below were synthesized in the same manner as in Reference Example 123 above.

Table 4

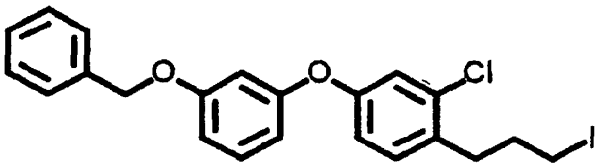


Reference Example	R1	R2	R3	R4	Reference Example	R1	R2	R3	R4
124	CF_3	H	H	H	144	$PhCH_2O$	$PhCH_2O$	H	Cl
125	CF_3	H	MeO	H	145	$PhCH_2O$	Cl	H	Cl
126	CF_3	H	H	MeO	146	$PhCH_2O$	H	H	Br
127	CF_3	H	Cl	H	147	$PhCH_2O$	H	H	CF_3
128	CF_3	H	H	Cl	148	$PhCH_2O$	H	H	Ph
129	CF_3	H	H	$PhCH_2O$	149	$PhCH_2O$	CF_3	H	H
130	CF_3	H	CF_3	H	150	$PhCH_2O$	CF_3	H	Cl
131	CF_3	H	H	CF_3	151	t-Bu	H	H	H
132	CF_3	CF_3	H	Cl	152	MeS	H	H	H
133	CF3	$Ph(CH_2)_2$	H	H	153	n-C_5H_{11}	H	H	H
134	CF3	H	H	F	154	n-C_7H_{15}	H	H	H
135	$Ph(CH_2)_2$	$Ph(CH_2)_2$	H	H	155	i-Pr	i-PrO	H	H
136	$Ph(CH_2)_2$	H	H	Cl	156	i-Pr	i-PrO	H	Cl
137	$Ph(CH_2)_2$	H	H	CF_3	157	i-Pr	i-Pr	H	Cl
138	$Ph(CH_2)_2$	$Ph(CH_2)_2$	H	Cl	158	Cl	Cl	H	Cl
139	$Ph(CH_2)_2$	$Ph(CH_2)_2$	H	CF_3	159	$PhCH_2S$	H	H	H
140	$PhCH_2O$	H	H	H	160	$PhCH_2S$	H	H	Cl
141	$PhCH_2O$	$PhCH_2O$	H	H	161	Et	H	H	H
142	$tBuMe_2SiO$	H	H	Cl	162	i-Bu	H	H	H
143	$PhCH_2O$	H	H	i-Pr	163	$PhOCH_2$	H	H	H

<Reference Example 164>

4'-[(3-benzyloxy)phenoxy]-2'-chlorodihydrocinnamyl iodide

[0078]

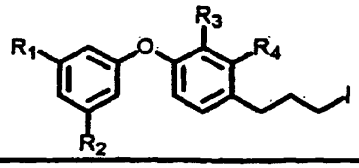


[0079] The compound of Reference Example 123 (6.37g) was dissolved in THF (150mL). While the solution was stirred at 0°C, imidazole (2.45g), triphenylphosphine (9.44g), and iodine (9.14g) were added. With the temperature maintained, the solution was further stirred for 1 hour. Subsequently, water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 20:1). In this manner, the desired product (7.90g) was obtained as a colorless oil.

<Reference Examples 165 through 204>

[0080] Using the compounds of Reference Examples 124 through 163, the compounds shown in Table 5 below were synthesized in the same manner as in Reference Example 164 above.

Table 5

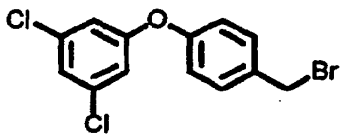


Reference Example	R1	R2	R3	R4	Reference Example	R1	R2	R3	R4
165	CF_3	H	H	H	185	$PhCH_2O$	$PhCH_2O$	H	Cl
166	CF_3	H	MeO	H	186	$PhCH_2O$	Cl	H	Cl
167	CF_3	H	H	MeO	187	$PhCH_2O$	H	H	Br
168	CF_3	H	Cl	H	188	$PhCH_2O$	H	H	CF_3
169	CF_3	H	H	Cl	189	$PhCH_2O$	H	H	Ph
170	CF_3	H	H	$PhCH_2O$	190	$PhCH_2O$	CF_3	H	H
171	CF_3	H	CF_3	H	191	$PhCH_2O$	CF_3	H	Cl
172	CF_3	H	H	CF_3	192	t-Bu	H	H	H
173	CF_3	CF_3	H	Cl	193	MeS	H	H	H
174	CF3	$Ph(CH_2)_2$	H	H	194	$n\text{-}C_5H_{11}$	H	H	H
175	CF3	H	H	F	195	$n\text{-}C_7H_{15}$	H	H	H
176	$Ph(CH_2)_2$	$Ph(CH_2)_2$	H	H	196	i-Pr	i-PrO	H	H
177	$Ph(CH_2)_2$	H	H	Cl	197	i-Pr	i-PrO	H	Cl
178	$Ph(CH_2)_2$	H	H	CF_3	198	i-Pr	i-Pr	H	Cl
179	$Ph(CH_2)_2$	$Ph(CH_2)_2$	H	Cl	199	Cl	Cl	H	Cl
180	$Ph(CH_2)_2$	$Ph(CH_2)_2$	H	CF_3	200	$PhCH_2S$	H	H	H
181	$PhCH_2O$	H	H	H	201	$PhCH_2S$	H	H	Cl
182	$PhCH_2O$	$PhCH_2O$	H	H	202	Et	H	H	H
183	t-$BuMe_2SiO$	H	H	Cl	203	i-Bu	H	H	H
184	$PhCH_2O$	H	H	i-Pr	204	$PhOCH_2$	H	H	H

<Reference Example 205>

4-(3,5-dichlorophenoxy)benzyl bromide

[0081]



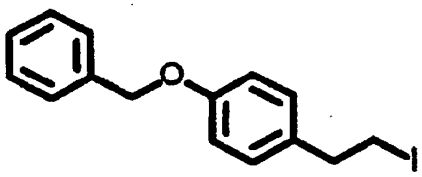
[0082] Using 3,5-dichlorophenol and 4-fluorobenzaldehyde, reactions were carried out in the same manner as in Reference Example 1 to obtain 4-(3,5-dichlorophenoxy)benzaldehyde. The subsequent reactions were carried out in

the same manner as in Reference Example 123, except that sodium borohydride was used in place of lithium aluminum hydride. This gave 4-(3,5-dichlorophenoxy)benzyl alcohol. The alcohol (2.03g) and carbon tetrabromide (2.75g) in methylene chloride (30mL) were stirred at 0°C, and triphenyl phosphine (2.17g) was added to the solution. The resulting mixture was stirred for 1 hour at 0°C and then for 30 minutes at room temperature. Subsequently, the solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 20:1). In this manner, the desired product (3.12g) was obtained as a colorless oil.

<Reference Example 206>

4'-benzyloxyphenethyl iodide

[0083]

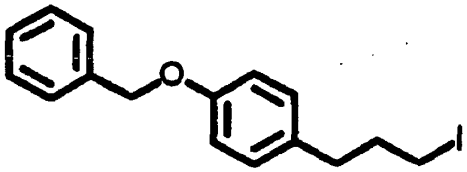


[0084] Using ethyl 4'-(benzyloxy)phenyl acetate as a starting material, reactions were carried out in the same manner as in Reference Example 123 to obtain 4'-benzyloxyphenethyl alcohol. Using the alcohol, reactions were then carried out in the same manner as in Reference Example 164 to obtain the desired product as a pale yellow oil.

<Reference Example 207>

4'-benzyloxy=dihydrocinnamyl iodide

[0085]

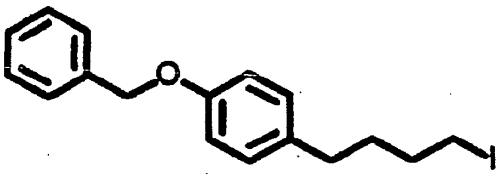


[0086] Using 4'-benzyloxydihydrocinnamyl alcohol, reactions were carried out in the same manner as in Reference Example 164 to obtain the desired product as a yellow powder.

<Reference Example 208>

1-benzyloxy-4-iodobutylbenzene

[0087]

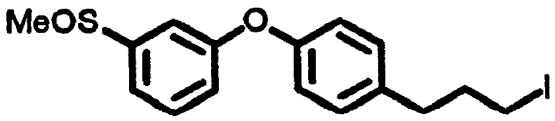


[0088] Using methyl 4-(4-benzyloxyphenyl)butyrate as a starting material, reactions were carried out in the same manner as in Reference Example 206 to obtain the desired product as a colorless oil.

<Reference Example 209>

1-iodopropyl-4-[(3-methanesulfinyl)phenoxy]benzene

[0089]

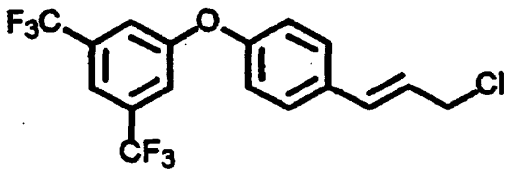


[0090] The compound of Reference Example 193 (1.80g) was dissolved in methylene chloride (30mL). While the solution was stirred at 0°C, m-chloroperbenzoic acid (770mg) was added in small portions. With the temperature maintained, the mixture was stirred for 24 hours at room temperature and water was added to the mixture. The resulting mixture was then extracted with ethyl acetate. The organic phase was sequentially washed with a saturated aqueous solution of sodium carbonate and a saturated aqueous solution of sodium chloride and was then dried with anhydrous sodium sulfate. Subsequently, the solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 2:1 and then 1:2). In this manner, the desired product (1.29g) was obtained as a yellow oil.

<Reference Example 210>

4'-[(3,5-bistrifluoromethyl)phenoxy]cinnamyl chloride

[0091]

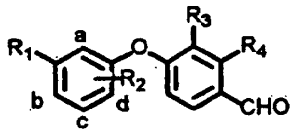


[0092] Ethyl 4'-[(3,5-bistrifluoromethyl)phenoxy]cinnamate(500mg) was dissolved in THF (20mL). While the solution was stirred at 0°C, a 1mol/L diisobutylaluminum hydride-toluene solution (3.0mL) was added. With the temperature maintained, the solution was stirred for 1.5 hours, and a 2mol/L aqueous solution of sodium hydroxide was added to the solution. The resulting mixture was then extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was then dried with anhydrous sodium sulfate. Subsequently, the solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 3:1). This gave an alcohol (377mg) as a colorless oil. The alcohol so obtained (296mg) was dissolved in DMF (5mL), and lithium chloride (35.0mg), collidine (0.120mL), and methanesulfonyl chloride (0.070mL) were added to the solution at 0°C. With the temperature maintained, the mixture was stirred for 1 hour. Subsequently, the reaction mixture was decanted into water and was extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 20:1). In this manner, the desired product (241mg) was obtained as a colorless powder.

<Reference Examples 211 through 219>

[0093] The compounds were synthesized in the same manner as in Reference Example 1.

Table 6

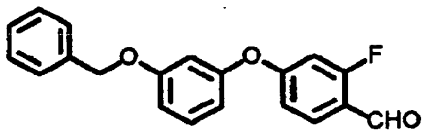


Reference Example	R1	R2	R3	R4	Reference Example	R1	R2	R3	R4
211	$Ph(CH_2)_2$	c-CF_3	H	Cl	216	CF_3	a-Cl	H	H
212	$PhCH_2O$	c-H	H	Me	217	CF_3	b-Cl	H	H
213	$PhCH_2O$	c-H	H	Et	218	CF_3	d-Cl	H	H
214	$PhCH_2O$	c-H	H	SMe	219	CF_3	c-NO_2	H	H
215	PhO	c-H	H	Cl					

<Reference Example 220>

2-fluoro-4-[(3-benzyloxy)phenoxy]benzaldehyde

[0094]

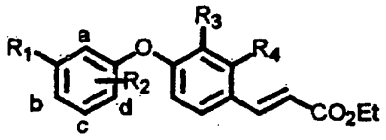


[0095] Using 3-benzyloxyphenyboric acid and 2-fluoro-4-hydroxybenzaldehyde, the desired product was obtained as a colorless oil in the same manner as in Reference Example 38.

<Reference Examples 221 through 230>

[0096] Using the compounds of Reference Examples 211 though 220, the compounds were synthesized in the same manner as in Reference Example 39.

Table 7

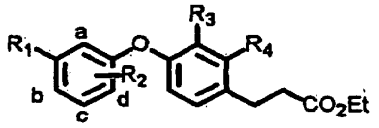


Reference Example	R1	R2	R3	R4	Reference Example	R1	R2	R3	R4
221	$Ph(CH_2)_2$	c-CF_3	H	Cl	226	CF_3	a-Cl	H	H
222	$PhCH_2O$	c-H	H	Me	227	CF_3	b-Cl	H	H
223	$PhCH_2O$	c-H	H	Et	228	CF_3	d-Cl	H	H
224	$PhCH_2O$	c-H	H	SMe	229	CF_3	c-NO_2	H	H
225	PhO	c-H	H	Cl	230	$PhCH_2O$	c-H	H	F

<Reference Examples 231 through 239>

[0097] Using the compounds of Reference Examples 221 though 228 and 230, the compounds were synthesized in the same manner as in Reference Examples 80 through 83.

Table 8

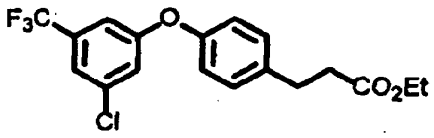


Reference Example	R1	R2	R3	R4	Reference Example	R1	R2	R3	R4
231	$Ph(CH_2)_2$	c-CF_3	H	Cl	236	CF_3	a-Cl	H	H
232	$PhCH_2O$	c-H	H	Me	237	CF_3	b-Cl	H	H
233	$PhCH_2O$	c-H	H	Et	238	CF_3	d-Cl	H	H
234	$PhCH_2O$	c-H	H	SMe	239	$PhCH_2O$	c-H	H	F
235	PhO	c-H	H	Cl					

<Reference Examples 240>

Ethyl 4'-[3-chloro-5-(trifluoromethyl)phenoxy]dihydrocinnamate

[0098]



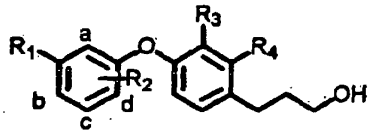
[0099] Using the compound of Reference Example 2.29, reactions were carried out in the same manner as in Reference Example 81 to obtain ethyl 4'-[3-amino-5-(trifluoromethyl)phenoxy]dihydrocinnamate. A MeCN solution (15mL) of this compound (1.27g) was added to a MeCN solution (40mL) of copper chloride (725mg) and tBuONO (0.51mL).

The mixture was then stirred for 3 hours at room temperature, and water was added to the mixture. The resulting mixture was extracted with ethyl acetate. The organic phase was then washed with water and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 20:1). In this manner, the desired product (1.10g) was obtained as a pale yellow oil .

<Reference Examples 241 through 250>

[0100] Using the compounds of Reference Examples 231 through 240, the compounds were synthesized in the same manner as in Reference Example 123.

Table 9

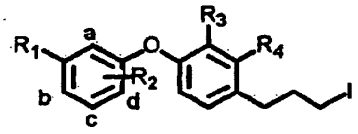


Reference Example	R1	R2	R3	R4	Reference Example	R1	R2	R3	R4
241	$Ph(CH_2)_2$	c-CF_3	H	Cl	246	CF_3	a-Cl	H	H
242	$PhCH_2O$	c-H	H	Me	247	CF_3	b-Cl	H	H
243	$PhCH_2O$	c-H	H	Et	248	CF_3	d-Cl	H	H
244	$PhCH_2O$	c-H	H	SMe	249	CF_3	c-Cl	H	H
245	PhO	c-H	H	Cl	250	$PhCH_2O$	c-H	H	F

<Reference Examples 251 through 260>

[0101] Using the compounds of Reference Examples 241 through 250, the compounds were synthesized in the same manner as in Reference Example 164.

Table 10

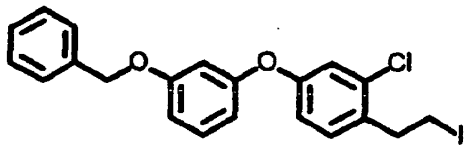


Reference Example	R1	R2	R3	R4	Reference Example	R1	R2	R3	R4
251	$Ph(CH_2)_2$	c-CF_3	H	Cl	256	CF_3	a-Cl	H	H
252	$PhCH_2O$	c-H	H	Me	257	CF_3	b-Cl	H	H
253	$PhCH_2O$	c-H	H	Et	258	CF_3	d-Cl	H	H
254	$PhCH_2O$	c-H	H	SMe	259	CF_3	c-Cl	H	H
255	PhO	c-H	H	Cl	260	$PhCH_2O$	c-H	H	F

<Reference Example 261>

4'-[(3-benzyloxy)phenoxy]-2'-chlorophenethyl iodide

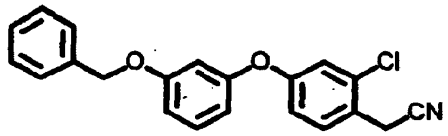
[0102]



<Reference Example 261-1>

4'-[(3-benzyloxy)phenoxy]-2'-chlorobenzyl cyanide

[0103]

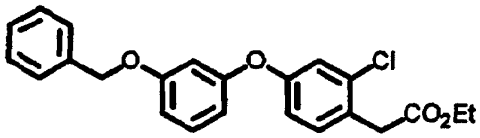


[0104] Using the compound of Reference Example 1, reactions were carried out in the same manner as in Reference Example 205 to obtain 4-[(3-benzyloxy)phenoxy]-2-chlorobenzyl bromide as a colorless oil. A DMSO solution (10mL) of the bromide (1.38g) was added dropwise to a solution (2mL water and 5mL DMSO) of KCN (245mg) at 90°C, and the mixture was stirred for 10 minutes and then for another 30 minutes at room temperature. Subsequently, ice water was added to the mixture and the mixture was extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was then concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 5:1). In this manner, the desired product (1.02g) was obtained as a colorless oil.

<Reference Example 261-2>

Ethyl 4'-[(3-benzyloxy)phenoxy]-2'-chlorophenylacetate

[0105]



[0106] A solution (30mL) of the compound of Reference Example 261-1 (1.02g) and potassium hydroxide (819mg) in a mixed solvent of water (2mL) and ethanol (30mL) was refluxed for 12 hours. The solution was made acidic by the addition of hydrochloric acid and was extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was concentrated under reduced pressure and the resulting concentrate was dissolved in ethanol (10mL) and thionyl chloride (1.0mL) was added to the solution. The mixture was subsequently stirred for 1 hour at room temperature. The solvent was removed by distillation and the residue was purified by silica gel column chromatography (hexane: ethyl

acetate = 10:1). In this manner, the desired product (1.01g) was obtained as a colorless oil.

<Reference Example 261-3>

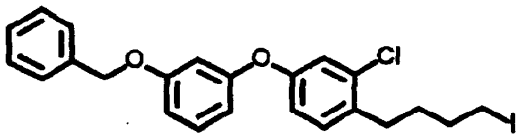
4'-[(3-benzyloxy)phenoxy]-2'-chlorophenethyl iodide

[0107] Using the compound of Reference Example 251-2, reactions were carried out in the same manner as in Reference Example 123 to obtain an alcohol. Then, using this alcohol, subsequent reactions are carried out in the same manner as in Reference Example 164 to obtain the desired product as a yellow oil.

<Reference Example 262>

4-[(3-benzyloxy)phenoxy]-2-chloro-1-iodobutylbenzene

[0108]

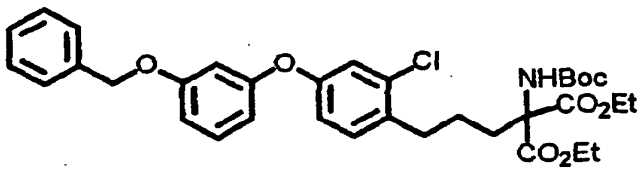


[0109] Using the compound of Reference Example 164, reactions were carried out in the same manner as in Reference Example 261 to obtain the desired product as a pale yellow oil.

<Example 1>

Ethyl 5-[4-(3-benzyloxyphenoxy)-2-chlorophenyl]-2-*t*-butoxycarbonylamino-2-ethoxycarbonylpentanoate

[0110]

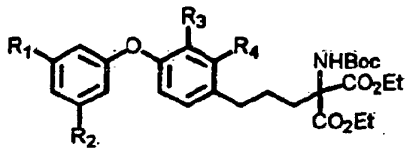


[0111] Under argon, sodium -t-butoxide (1.40g) was added, at room temperature, to a solution of diethyl 2-*t*-butoxycarbonylaminomalonate (3.60mL) in a mixed solvent of THF (130mL) and DMF (20mL). The resulting mixture was stirred for 30 minutes at 80°C. The temperature was decreased down to room temperature and a THF solution (20mL) of the compound of Reference Example 164 (6.22g) was added dropwise. Subsequently, the mixture was refluxed for 5 hours and was decanted into ice water. The resulting mixture was extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was then removed by distillation under reduced pressure, and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 4:1). In this manner, the desired product (6.84g) was obtained as a colorless oil.
FABMS : 626 ([M+H]+)
^{1}H-NMR (400MHz, $CDCl_3$) δ 1.22-1.30(6H, m), 1.42(9H, s), 1.57(2H, br s), 2.37(2H, br), 2.70(2H, t, J=7.8Hz), 4.19-4.29 (4H, m), 5.03(2H, s), 5.95(1H, bs), 6.57-6.62(2H, m), 6.74(1H, dd, J=8.3, 2.4Hz), 6.83(1H, dd, J=8.3, 2.4Hz), 6.98(1H, d,. J=2.4Hz), 7.13(1H, d, J=8.3Hz), 7.23(1H, t, J=8.3Hz), 7.33-7.43(5H, m)

<Examples 2 through 42>

[0112] Using the compounds of Reference Examples 165 through 204 and 209, reactions were carried out in the same manner as in Example 1 above to obtain the compounds shown in Table 11 below.

Table 11



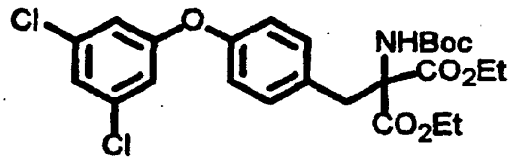
Example	R1	R2	R3	R4	Characteristics	Yield(%)
2	CF_3	H	H	H	Colorless oil	100
3	CF_3	H	MeO	H	Colorless oil	100
4	CF_3	H	H	MeO	Colorless oil	100
5	CF_3	H	Cl	H	Colorless oil	100
6	CF_3	H	H	Cl	Colorless oil	100
7	CF_3	H	H	$PhCH_2O$	Colorless oil	100
8	CF_3	H	CF_3	H	Colorless oil	100
9	CF_3	H	H	CF_3	Colorless oil	92
10	CF_3	CF_3	H	Cl	Colorless oil	89
11	CF_3	$Ph(CH_2)_2$	H	H	Colorless oil	97
12	CF_3	H	H	F	Colorless oil	100
13	$Ph(CH_2)_2$	$Ph(CH_2)_2$	H	H	Colorless oil	95
14	$Ph(CH_2)_2$	H	H	Cl	Colorless oil	83
15	$Ph(CH_2)_2$	H	H	CF_3	Colorless oil	90
16	$Ph(CH_2)_2$	$Ph(CH_2)_2$	H	Cl	Colorless oil	98
17	$Ph(CH_2)_2$	$Ph(CH_2)_2$	H	CF_3	Colorless oil	100
18	$PhCH_2O$	H	H	H	Colorless oil	95
19	$PhCH_2O$	$PhCH_2O$	H	H	Colorless oil	-
20	$PhCH_2O$	$PhCH_2O$	H	Cl	Colorless oil	-
21	$PhCH_2O$	Cl	H	Cl	Colorless oil	100
22	$PhCH_2O$	H	H	Br	Colorless oil	100
23	$PhCH_2O$	H	H	CF_3	Colorless oil	100
24	$PhCH_2O$	H	H	Ph	Colorless oil	-
25	$PhCH_2O$	CF_3	H	H	Colorless oil	99
26	$PhCH_2O$	CF_3	H	Cl	Colorless oil	91
27	t-Bu	H	H	H	Colorless oil	64
28	MeS	H	H	H	Colorless oil	83
29	$n\text{-}C_5H_{11}$	H	H	H	Colorless oil	86
30	$n\text{-}C_7H_{15}$	H	H	H	Colorless oil	88
31	i-Pr	i-PrO	H	H	Colorless oil	95
32	i-Pr	i-PrO	H	Cl	Colorless oil	100
33	i-Pr	i-Pr	H	Cl	Colorless oil	66
34	Cl	Cl	H	Cl	Colorless oil	74
35	$PhCH_2S$	H	H	H	Colorless oil	-
36	$PhCH_2S$	H	H	Cl	Colorless oil	-
37	Et	H	H	H	Colorless oil	100
38	i-Bu	H	H	H	Colorless oil	76
39	MeSO	H	H	H	Colorless oil	100
40	$t\text{-}BuMe_2SiO$	H	H	Cl	Colorless oil	82
41	$PhOCH_2$	H	H	H	Colorless oil	100
42	$PhCH_2O$	H	H	i-Pr	Colorless oil	-

The mark "-" means yield is shown in Table 12 as a total yield.

<Example 43>

Ethyl 2-*t*-butoxycarbonylamino-2-ethoxycarbonyl-3-[4-(3,5-dichlorophenoxy)phenyl]propionate

[0113]

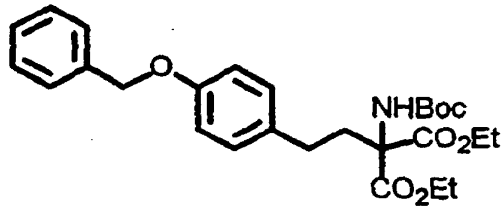


[0114] Using the compound of Reference Example 205, reactions were carried out in the same manner as in Example 1 to obtain the desired product as a colorless oil.
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.28(6H, t, J=7.3Hz), 1.47(9H, br s), 3.62(2H, br s), 4.19-4.31(4H, m), 5.79(1H, br s), 6.85 (2H, d, J=2.0Hz), 6.92(2H, d, J=8.8Hz), 7.04-7.08(3H, m)

<Example 44>

Ethyl 4-[(4-benzyloxy)phenyl]-2-*t*-butoxycarbonylamino-2-ethoxycarbonylbutyrate

[0115]

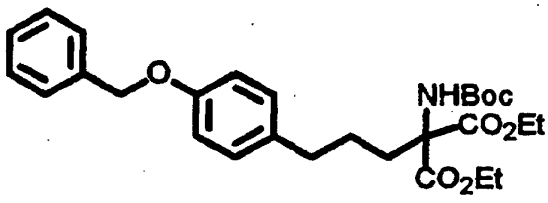


[0116] Using the compound of Reference Example 206, reactions were carried out in the same manner as in Example 1 to obtain the desired product as a colorless oil.
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.23(6H, t, J=7.3Hz), 1.44(9H, s), 2.44-2.48(2H,m), 2.60(2H, br s), 4.13-4.31(4H, m), 5.04 (2H, s), 5.99(1H, br s), 6.88(2H, d, J=8.8Hz), 7.07(2H, d, J=8.3Hz), 7.29-7.44(5H, m)

<Example 45>

Ethyl 5-[(4-benzyloxy)phenyl]-2-*t*-butoxycarbonylamino-2-ethoxycarbonylpentanoate

[0117]



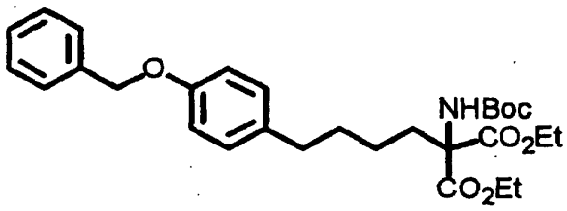
[0118] Using the compound of Reference Example 207, reactions were carried out in the same manner as in Example

1 to obtain the desired product as a light yellow oil.
^{1}H-NMR (400MHz, $CDCl_3$) δ 1.22(6H, t, J=7.1Hz), 1.42(9H, s), 1.44-1.47(2H,m), 2.31(2H, br s), 2.57(2H, t, J=7.6Hz), 4.11-4.27(4H, m), 5.03(2H, s), 5.92(1H, br s), 6.88(2H, d, J=8.8Hz), 7.06(2H, d, J=8.8Hz), 7.29-7.43(5H, m)

<Example 46>

Ethyl 6-[(4-benzyloxy)phenyl]-2-*t*-butoxycarbonylamino-2-ethoxycarbonylhexanoate

[0119]

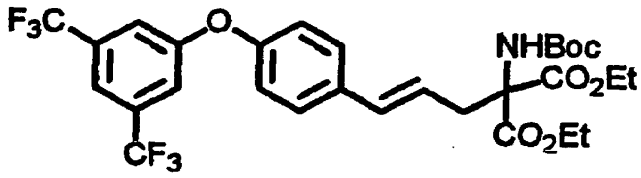


[0120] Using the compound of Reference Example 208, reactions were carried out in the same manner as in Example 1 to obtain the desired product as a colorless oil.
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.16-1.24(2H, m), 1.23(6H, t, J=7.1Hz), 1.42(9H, s), 1.56-1.63(2H, m), 2.30(2H, br), 2.54 (2H, t, J=7.8Hz), 4:16-4.29(4H, m), 5.03(2H, s), 5.92(1H, br s), 6.88(2H, d, J=8.3Hz), 7.06(2H, d, J=8.3Hz), 7.32-7.44 (5H, m)

<Example 47>

Ethyl 5-[4-(3,5-bistrifluoromethylphenoxy)phenyl]-2-*t*-butoxycarbonylamino-2-ethoxycarbonyl-4-pentenoate

[0121]

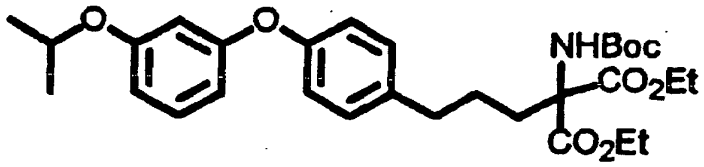


[0122] Using the compound of Reference Example 210, reactions were carried out in the same manner as in Example 1 to obtain the desired product as a colorless oil.
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.27(6H, t, J=7.0Hz), 1.44(9H, s), 3.20(2H, d, J=7.0Hz), 4.20-4.32(4H, m), 5.97(1H, br s), 6.02(1H, dt, J=15.9, 7.0Hz), 6.45(1H, d, J=15.9Hz), 6.98(2H, d, J=8.5Hz), 7.36(2H, d, J=8.5Hz), 7.38(2H, s), 7.57(1H, s)

<Example 48>

Ethyl 2-*t*-butoxycarbonylamino-2-ethoxycarbonyl-5-[4-(3-isopropoxyphenoxy)phenyl]pentanoate

[0123]

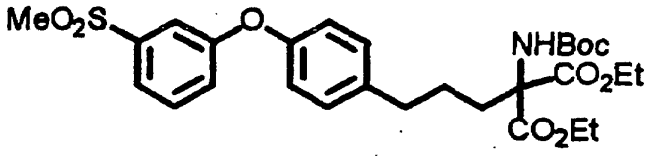


[0124] The compound of Example 18 was reduced by catalytic reduction as in Reference Example 81. The resultant phenol (850mg) was dissolved in DMF (20mL), and 2-iodopropane (0.2mL) and potassium carbonate (500mg) were added to the solution. The mixture was then stirred for 4 hours at 60°C. Subsequently, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 4:1). In this manner, the desired product (760mg) was obtained as a colorless oil.
^{1}H-NMR (400MHz, $CDCl_3$) δ 1.23(6H, t, J=7.3Hz), 1.31(6H, d, J=5.9Hz), 1.42(9H, s), 1.45-1.52(2H, m), 2.34(2H, br), 2.61(2H, t, J=7.8Hz), 4.17-4.27(4H, m), 4.50(1H, heptet, J=5.9Hz), 5.94(1H, br s), 6.50-6.53(2H, m), 6.59-6.62(1H, m), 6.92(2H, d, J=8.8Hz), 7.10(2H, d, J=8.8Hz), 7.18(1H, t, J=8.8Hz)

<Example 49>

Ethyl 2-*t*-butoxycarbonylamino-2-ethoxycarbonyl-5-[4-(3-methanesulfonylphenoxy)phenyl]pentanoate

[0125]

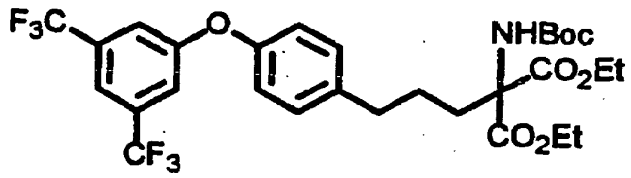


[0126] The compound of Example 28 (1.00g) was dissolved in methylene chloride (30mL) and m-chloroperbenzoic acid (610mg) was added to the solution. The mixture was then stirred for 6 hours at room temperature. Subsequently, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 1:1). In this manner, the desired product (610mg) was obtained as a colorless oil.
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.24(6H, t, J=7.3Hz), 1.42(9H, s), 1.47-1.56(2H, m), 2.34(2H, br), 2.64(2H, t, J=7.8Hz), 3.04(3H, s), 4.18-4.26(4H, m), 5.95(1H, br), 6.95(2H, d, J=8.8Hz), 7.17(2H, t, J=8.8Hz), 7.20-7.30(3H,m), 7.47-7.52 (2H, m), 7.62(1H, d, J=8.8Hz)

<Example 50>

Ethyl 5-[4-(3,5-bistrifluoromethylphenoxy)phenyl]-2-*t*-butoxycarbonylamino-2-ethoxycarbonylpentanoate

[0127]

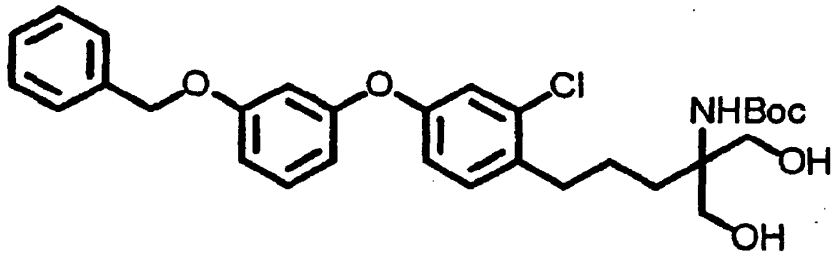


[0128] The compound of Example 44 was reduced by catalytic reduction as in Reference Example 81. The resultant phenol was reacted with 3,5-bis(trifluoromethyl)phenylboric acid in the same manner as in Reference Example 38 to obtain the desired product as a pale yellow oil.
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.24(6H, t, J=7.3Hz), 1.43(9H, s), 1.47-1.58(4H, m), 2.36(2H, br s), 2.66(2H, t, J=7.3Hz), 4.18-4.26(4H, m), 5.96(1H, br s), 6.96(2H, d, J=8.3Hz), 7.20(2H, d, J=8.3Hz), 7.36(2H, s), 7.55(1H, s)

<Example 51>

2-[4-(3-benzyloxyphenoxy)-2-chlorophenyl]propyl-2-*t*-butoxycarbonylamino-1,3-propanediol

[0129]

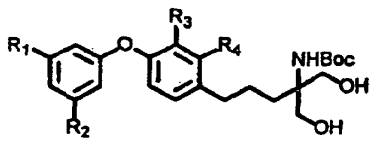


[0130] The compound of Example 1 (6.84g) was dissolved in THF (150mL). While the solution was stirred at 0°C, lithium borohydride (960mg) was added to the solution. Ethanol (10mL) was then added to the mixture and the mixture was stirred for 8 hours as the temperature was gradually increased to room temperature. Subsequently, ice water was added to the mixture and the organic solvent was removed by distillation under reduced pressure. A 10% aqueous solution of citric acid was added to the residue to adjust the pH to 3, and the mixture was extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was then removed by distillation under reduced pressure. The residue was purified by silica gel column chromatography (hexane: ethyl acetate = 1:1) to obtain the desired product (3.50g) as a colorless viscous oil.
FABMS : 542 ([M+H] +)
^{1}H-NMR (400MHz, $CDCl_3$) δ 1.43(9H, s), 1.66(4H, br s), 2.69(2H, t, J=6.8Hz), 3.40(2H, br), 3.60(2H, dd, J=11.3, 5.9Hz), 3.84(2H, dd, J=11.3, 3.8Hz), 4.92(1H, br s), 5.03(2H,. s), 6.59-6.62(2H, m), 6.75(1H, dd, J=8.3, 2.5Hz), 6.84(1H, dd, J=8.3, 2.5Hz), 7.00(1H, d, J=2.5Hz), 7.14(1H, d, J=8.3Hz), 7.24(1H, t, J=8.3Hz), 7.31-7.43(5H, m)

<Examples 52 through 95>

[0131] Using the compounds of Examples 2 through 42 and 48 through 50, reactions were carried out in the same manner as in Example 51 above to synthesize the compounds shown in Table 12 below.

Table 12



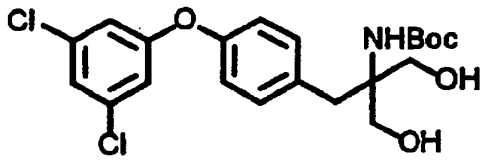
Example	R1	R2	R3	R4	Characteristics	Yield (%)
52	CF_3	H	H	H	Colorless oil	71
53	CF_3	H	MeO	H	Colorless oil	76
54	CF_3	H	H	MeO	Colorless oil	45
55	CF_3	H	Cl	H	Colorless oil	58
56	CF_3	H	H	Cl	Colorless oil	68
57	CF_3	H	H	$PhCH_2O$	Colorless oil	64
58	CF_3	H	CF_3	H	Colorless oil	68
59	CF_3	H	H	CF_3	Colorless oil	41
60	CF_3	CF_3	H	Cl	Colorless oil	77
61	CF_3	$Ph(CH_2)_2$	H	H	Colorless oil	80
62	CF_3	H	H	F	Colorless oil	63
63	$Ph(CH_2)_2$	$Ph(CH_2)_2$	H	H	Colorless oil	71
64	$Ph(CH_2)_2$	H	H	Cl	Colorless oil	84
65	$Ph(CH_2)_2$	H	H	CF_3	Colorless oil	72
66	$Ph(CH_2)_2$	$Ph(CH_2)_2$	H	Cl	Colorless oil	61
67	$Ph(CH_2)_2$	$Ph(CH_2)_2$	H	CF_3	Colorless oil	54
68	$PhCH_2O$	H	H	H	Colorless oil	76
69	$PhCH_2O$	$PhCH_2O$	H	H	Colorless oil	(45)
70	$PhCH_2O$	$PhCH_2O$	H	Cl	Colorless oil	(17)
71	$PhCH_2O$	Cl	H	Cl	Colorless oil	61
72	$PhCH_2O$	H	H	Br	Colorless oil	61
73	$PhCH_2O$	H	H	CF_3	Colorless oil	83
74	$PhCH_2O$	H	H	Ph	Colorless oil	(50)
75	$PhCH_2O$	CF_3	H	H	Colorless oil	83
76	$PhCH_2O$	CF_3	H	Cl	Colorless oil	67
77	t-Bu	H	H	H	Colorless oil	78
78	MeS	H	H	H	Colorless powder	56
79	$n\text{-}C_5H_{11}$	H	H	H	Colorless oil	98
80	$n\text{-}C_7H_{15}$	H	H	H	Colorless oil	90
81	i-Pr	i-PrO	H	H	Colorless oil	72
82	i-Pr	i-PrO	H	Cl	Colorless oil	82
83	i-Pr	i-Pr	H	Cl	Colorless oil	33
84	Cl	Cl	H	Cl	Colorless oil	79
85	$PhCH_2S$	H	H	H	Colorless oil	(20)
86	$PhCH_2S$	H	H	Cl	Colorless oil	(11)
87	Et	H	H	H	Colorless oil	76
88	i-Bu	H	H	H	Colorless oil	92
89	MeSO	H	H	H	Colorless oil	67
90	$MeSO_2$	H	H	H	Colorless amorphous	78
91	i-PrO	H	H	H	Colorless oil	89
92	$tBuMe_2SiO$	H	H	Cl	Colorless oil	68
93	CF_3	CF_3	H	H	Colorless oil	72
94	$PhOCH_2$	H	H	H	Colorless oil	64
95	$PhCH_2O$	H	H	i-Pr	Colorless oil	(62)

In the parentheses, shown is the total yield of the two steps.

<Example 96>

2-t-butoxycarbonylamino-2-[4-(3,5-dichlorophenoxy)benzyl]-1,3-propanediol

[0132]

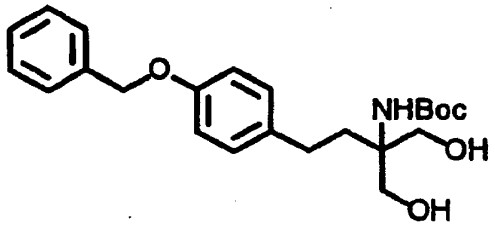


[0133] Using the compound of Example 43, reactions were carried out in the same manner as in Example 51 to obtain the desired product as a colorless amorphous.
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.46(9H, s), 2.94(2H, s), 3.60(2H, d, J=11.7Hz), 3.75(2H, d, J=11.7Hz), 4.93(1H, br s), 6.87(2H, d, J=2.0Hz), 6.98(2H, d, J=8.8Hz), 7.08(1H, t, J=2.0Hz), 7.26(2H, d, J=8.8Hz)

<Example 97>

2-(4-benzyloxyphenyl)ethyl-2-*t*-butoxycarbonylamino-1,3-propanediol

[0134]

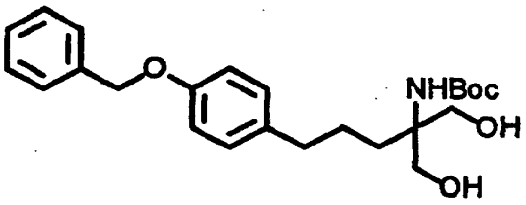


[0135] Using the compound of Example 44, reactions were carried out in the same manner as in Example 51 to obtain the desired product as a colorless powder.
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.45(9H, s), 1.83-1.88(2H, m), 2.54-2.59(2H, m), 3.39 (2H, br s) , 3. 64 (2H, d, J=11. 2Hz) , 3. 88 (2H, d, J=11.2Hz), 5.01(1H,br s), 5.03(2H, s), 6.90(2H, d, J=8.3Hz), 7.10(2H, d, J=8.3Hz), 7.30-7.44(5H, m)

<Example 98>

2-[(4-benzyloxy)phenyl]propyl-2-*t*-butoxycarbonylamino-1,3-propanediol

[0136]



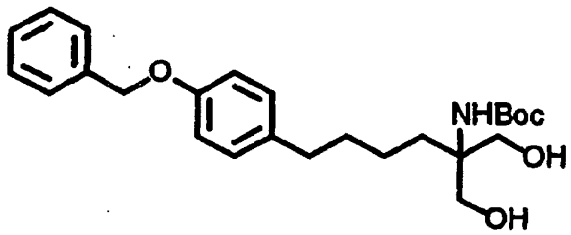
[0137] Using the compound of Example 45, reactions were carried out in the same manner as in Example 51 to

obtain the desired product as a pale yellow oil.
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.43(9H, s), 1.50-1.70(4H, m), 2.52-2.57(2H, m), 3.57(2H, d, J=11.2Hz), 3.82(2H, d, J=11.2Hz), 4.86(1H, br s), 5.04(2H,s), 6.90(2H, d, J=8.8Hz), 7.08(2H, d, J=8.8Hz), 7.31-7.44(5H, m)

<Example 99>

2-[(4-benzyloxy)phenyl]butyl-2-*t*-butoxycarbonylamino-1,3-propanediol

[0138]

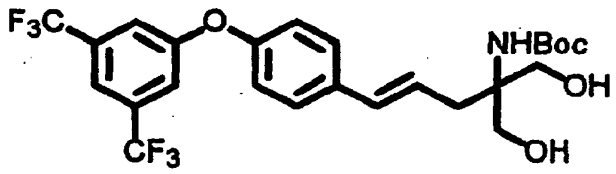


[0139] Using the compound of Example 46, reactions were carried out in the same manner as in Example 51 to obtain the desired product as a colorless oil.
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.27-1.35(2H, m), 1.43(9H, s), 1.54-1.63(4H, m), 2.56(2H, t, J=7.6Hz), 3.41(2H, br s), 3.58 (2H, d, J=11.7Hz), 3.82(2H, d, J=11.7Hz), 4.88(1H, br s), 5.04(2H, s), 6.89(2H, d, J=8.8Hz), 7.07(2H, d, J=8.8Hz), 7.33-7.43(5H, m)

<Example 100>

2-[4'-(3,5-bistrifluoromethylphenoxy)cinnamyl]-2-*t*-butoxycarbonylamino-1,3-propanediol

[0140]

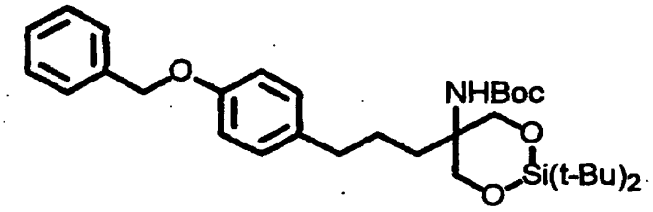


[0141] Using the compound of Example 47, reactions were carried out in the same manner as in Example 51 to obtain the desired product as a colorless amorphous.
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.44(9H, s), 2.55(2H, d, J=7.8Hz), 3.65(2H, d, J=11.2Hz), 3.78(2H, br), 3.85(2H, d, J=11.2Hz), 5.12(1H, s), 6.20(1H, dt, J=16.1, 7.8Hz), 6.51(1H, d, J=16.1 Hz), 7.01(2H, d, J=8.3Hz), 7.38(2H,s), 7.39 (2H, d, J=8.3Hz), 7.57(1H, s)

<Example 101>

5-[(4-benzyloxy)phenyl]propyl-5-*t*-butoxycarbonylamino-2,2-di-*t*-butyl-1,3,2-dioxasilane

[0142]

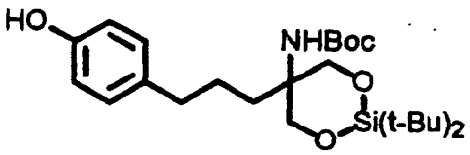


[0143] At 0°C, a methylene chloride solution (5mL) of di-*t*-butylsilyl bistrifluoromethanesulfonate (1.67g) was added to a DMF solution (30mL) of the compound of Example 98 (1.50g) and 2,6-lutidine (0.841mL). With the temperature maintained, the mixture was stirred for 1 hour. Subsequently, the mixture was decanted into ice water and was extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was then removed by distillation under reduced pressure. The residue was purified by silica gel column chromatography (hexane: ethyl acetate = 20:1) to obtain the desired product (1.67g) as a colorless powder.
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.04(9H, s), 1.06(9H, s), 1.42(9H, s), 1.46-1.56(4H, br s), 2.51(2H, t, J=6.8Hz), 3.88(2H, d, J=11.2Hz), 4.22(2H, d, J=11.2Hz), 4.90(1H, br s), 5.04(2H, s), 6.89(2H, d, J=8.3Hz), 7.06(2H, d, J=8.3Hz), 7.32-7.44 (5H, m)

<Example 102>

5-*t*-butoxycarbonylamino-2,2-di-*t*-butyl-5-(4-hydroxyphenyl)propyl-1,3,2-dioxasilane

[0144]

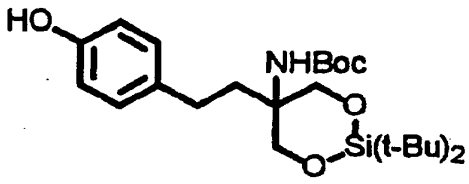


[0145] Using the compound of Example 101, catalytic reduction was carried out in the same manner as in Reference Example 81 to obtain the desired product as a pale brown amorphous.
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.04(9H, s), 1.06(9H, s), 1.43(9H, s), 1.47-1.61(4H, m), 2.49(2H, t, J=6.8Hz), 3.88(2H, d, J=11.3Hz), 4.22(2H, d, J=11.3Hz), 4.88(1H, br s), 4.91(1H, br s), 6.74(2H, d, J=8.3Hz), 6.99(2H, d, J=8.3Hz)

<Example 103>

5-*t*-butoxycarbonylamino-2,2-di-*t*-butyl-5-(4-hydroxyphenyl)ethyl-1,3,2-dioxasilane

[0146]

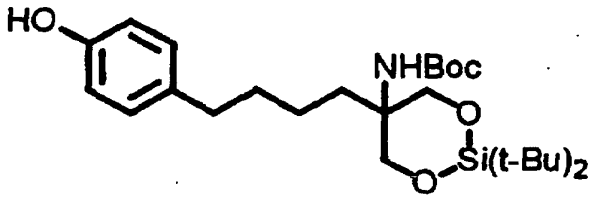


[0147] Using the compound of Example 97, reactions were carried out in the same manner as in Examples 101 and 102 to obtain the desired product as a colorless powder.
^{1}H-NMR (400MHz, $CDCl_3$) δ 1.06(9H, s), 1.07(9H, s), 1.46(9H, s), 1.79(2H,; m), 2.44-2.50(2H, m), 3.93(2H, d, J=11.2Hz), 4.26(2H, d, J=11.2Hz), 4.92(1H, br s), 5.01(1H, br s), 6.73(2H, d, J=8.3Hz), 7.01(2H, d, J=8.3Hz)

<Example 104>

5-*t*-butoxycarbonylamino-2,2-di-*t*-butyl-5-(4-hydroxyphenyl)butyl-1,3,2-dioxasilane

[0148]

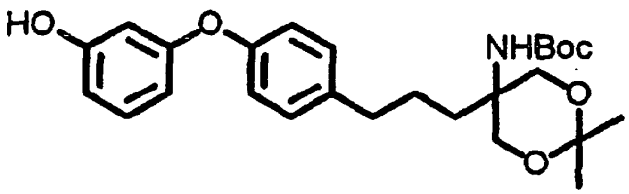


[0149] Using the compound of Example 99, reactions were carried out in the same manner as in Examples 101 and 102 to obtain the desired product as a colorless amorphous.
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.05 (9H, s), 1.07(9H, s), 1.20-1.30(2H, m), 1.42(9H, s), 1.50-1.60(4H, m), 2.51(2H, t, J=7.6Hz), 3.89(2H, d, J=11.2Hz), 4.22(2H, d, J=11.2Hz), 4.78(1H, br s), 4.91(1H, br s), 6.73(2H, d, J=8.3Hz), 7.00 (2H, d, J=8.3Hz)

<Example 105>

5-*t*-butoxycarbonylamino-5-[4-(3-hydroxyphenoxy)phenyl]propyl-2,2-dimethyl-1,3-dioxane

[0150]



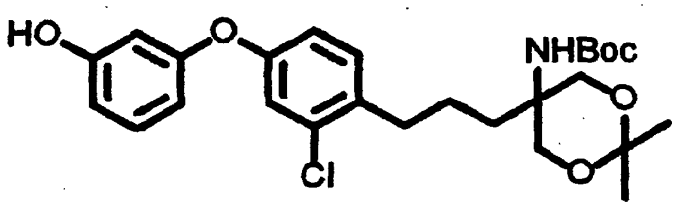
[0151] 2,2-dimethoxypropane (7.4mL) and paratoluenesulfonic acid (100mg) were added to a DMF solution (30mL) of the compound of Example 68 (3.00g). The mixture was stirred for 6 hours while heated to 80°C. Subsequently, the mixture was decanted into water and was extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was then removed by distillation under reduced pressure. The residue was purified by silica gel column chromatography (hexane: ethyl acetate = 3:1) to obtain the acetonide (2.68g) as a colorless powder. The resultant acetonide was reduced by catalytic reduction as in Reference Example 81 to obtain the desired product (2.23g) as a colorless powder.

^{1}H-NMR(400MHz, $CDCl_3$) δ 1.40(3H, s), 1.42(12H, s), 1.54-1.69(4H, m), 2.61(2H, t, J=7.8Hz), 3.63(2H, d, J=11.2Hz), 3.87(2H, d, J=11.2Hz), 4.86(1H,br), 5.29(1H, br s), 6.32(1H, br s), 6.52(1H, dd, J=8.3, 2.4Hz), 6.57(1H, dd, J=8.3, 2.4Hz), 6.95(2H, d, J=8.3Hz), 7.13(2H, d, J=8.3Hz), 7.16(1H, t, J=8.3Hz)

<Example 106>

5-*t*-butoxycarbonylamino-5-[2-chloro-4-(3-hydroxyphenoxy)phenyl]propyl-2,2-dimethyl-1,3-dioxane

[0152]



[0153] Using the compound of Example 51, reactions were carried out in the same manner as in Example 105 to obtain the desired product as a colorless powder.

[0154] Alternatively, an acetonide (3.21g) obtained by using the compound of Example 92 was dissolved in THF (100mL). While the solution was stirred at 0°C, a 1mol/L tetrabutylammoniumfluoride-THF solution (10mL) was added dropwise. After 10 minutes, water was added to the mixture and the mixture was extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was then removed by distillation under reduced pressure to obtain the desired product (2.60g).

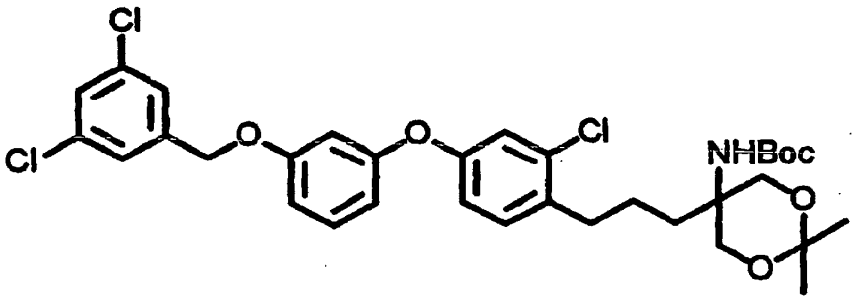
FABMS : 492 ([M+H]+)

^{1}H-NMR (400MHz, $CDCl_3$) δ 1.41(3H, s), 1.42(12H, s), 1.55-1.73(4H, m), 2.70(2H, t, J=7.3Hz), 3.66(2H, d, J=11.7Hz), 3.88(2H, d, J=11.7Hz), 4.89(1H,br), 5.97(1H, br), 6.40(1H, br s), 6.56(1H, dd, J=8.3, 2.4Hz), 6.62(1H, dd, J=8.3, 2.4Hz), 6.86(1H, dd, J=8.3, 2.4Hz), 7.01(1H, d, J=2.4Hz), 7.14(1H, d, J=8.3Hz), 7.18(1H, d, J=8.3Hz)

<Example 107>

5-*t*-butoxycarbonylamino-5-[2-chloro-4-(3-(3,5-dichlorobenzyloxy)phenoxy)phenyl]propyl-2,2-dimethyl-1,3-dioxane

[0155]



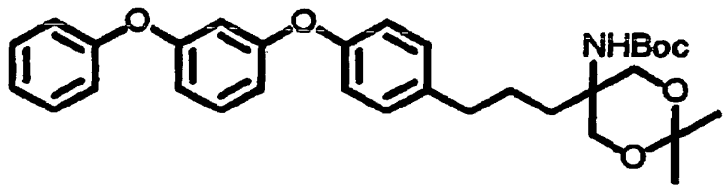
[0156] Diethyl azodicarboxylate (0.31mL) was added to a THF solution (5mL) containing the compound of Example 106 (650mg), 3,5-dichlorobenzyl alcohol (350mg), triphenylphosphine (530mg). The mixture was stirred for 18 hours. Subsequently, water was added to the mixture and the mixture was extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was then removed by distillation under reduced pressure. The residue was purified by silica gel column chromatography (hexane: ethyl acetate = 3:1) to obtain the desired product (440mg) as a colorless powder.

^{1}H-NMR(400MHz, $CDCl_3$) δ 1.41(3H, s), 1.42(3H, s), 1.43(9H, s), 1.54-1.60(2H, m), 1.75(2H, br), 2.69(2H, t, J=7.3Hz), 3.66(2H, d, J=11.7Hz), 3.88(2H, d, J=11.7Hz), 4.89(1H, br), 4.98(2H, s), 6.58-6.64(2H, m), 6.70(1H, dd, J=8.3, 2.4Hz), 6.84(1H, dd, J=8.3, 2.4Hz), 7.00(1H, d, J=2.4Hz), 7.15(1H, d, J=8.3Hz), 7.22-7.32(4H, m)

<Example 108>

5-*t*-butoxycarbonylamino-2,2-dimethyl-5-[4-(3-phenoxy) phenoxyphenyl] propyl-1,3-dioxane

[0157]



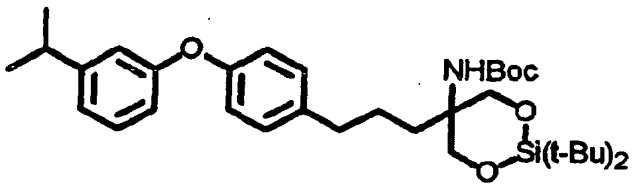
[0158] The compound of Example 105 was reacted with phenylboric acid in the same manner as in Reference Example 38 to obtain the desired product as a colorless powder.

^{1}H-NMR (400MHz, $CDCl_3$) δ 1.40(3H, s), 1.42(3H, s), 1.43(9H, s), 1.54-1.61(2H, m), 1.70(2H, br), 2.58(2H, t, J=7.3Hz), 3.64(2H, d, J=11.2Hz), 3.89(2H, d, J=11.2Hz), 4.87(1H,br), 6.66-6.71(3H, m), 6.94(2H, d, J=8.3Hz), 7.02(2H, d, J=8.3 Hz), 7.11-7.13(3H, m), 7.21(1H, t, J=8.3Hz), 7.34(2H, t, J=8.3Hz)

<Example 109>

5-*t*-butoxycarbonylamino-2,2-di-*t*-butyl-5-[4-(3-isopropylphenoxy)phenyl]propyl-1,3,2-dioxasilane

[0159]

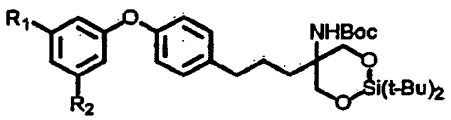


[0160] The compound of Example 102 (200mg), 3-isopropylphenylboric acid (141mg), anhydrous copper acetate (II) (97.4mg), and molecular sieve powder-4A (400mg) were suspended in dichloromethane (5mL). Triethylamine (120μL) was then added to the suspension and the suspension was stirred for 8 hours at room temperature. Subsequently, additional 3-isopropylphenylboric acid (141mg) and triethylamine (120μL) were added and the resulting mixture was further stirred overnight at room temperature. The reaction mixture was diluted with a mixture of hexane and ethyl acetate (hexane: ethyl acetate = 2:1) and was filtered through celite to remove insoluble materials. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 30:1) to obtain the desired product (188mg) as a colorless oil.
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.05(9H, s), 1.07(9H, s), 1.23(6H, d, J=6.8Hz), 1.43(9H, s), 1.55(4H, br s), 2.55(2H, t, J=7.1Hz), 2.84-2.91(1H, m), 3.89(2H, d, J=11.7Hz), 4.23(2H, d, J=11.7Hz), 4.91(1H, br s), 6.75-6.79(1H, m), 6.89-6.91 (1H, m), 6.91(2H, d, J=8.8Hz), 6.95(1H, d, J=7.8Hz), 7.09(2H, d, J=8.8Hz), 7.22(1H, t, J=7.8Hz)

<Examples 110 through 125>

[0161] The compound of Example 102 was reacted with different phenylboric acids in the same manner as in Example 109 described above to synthesize the compounds shown in Table 13 below.

Table 13



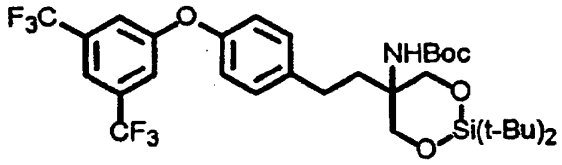
Example	R1	R2	Yield (%)	Characteristics	Example	R1	R2	Yield(%)	Characteristics
110	F	H	60	Colorless oil	118	CH_2OH	H	41	Colorless powder
111	Cl	H	61	Colorless oil	119	Ac	H	80	Pale yellow oil
112	Br	H	59	Colorless oil	120	NO_2	H	-	Pale yellow powder
113	Me	H	84	Colorless oil	121	CN	H	44	Colorless oil
114	Ph	H	74	Colorless amorphous	122	F	F	79	Colorless oil
115	MeO	H	69	Colorless oil	123	Cl	Cl	60	Pale yellow oil
116	EtO	H	76	Colorless oil	124	CF_3	CF_3	83	Colorless oil
117	CF_3O	H	68	Colorless oil	125	CHO	H	74	Colorless oil

The mark "-" means yield is shown in Table 15 as a total yield.

<Example 126>

5-*t*-butoxycarbonylamino-2,2-di-*t*-butyl-5-[4-(3,5-bistrifluoromethylphenoxy)phenyl]ethyl-1,3,2-dioxasilane

[0162]

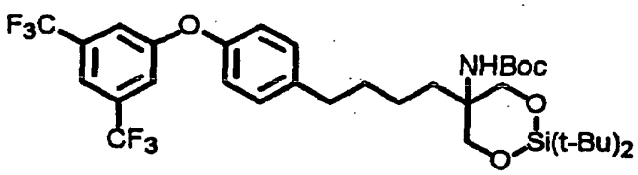


[0163] The compound of Example 103 was reacted with 3,5-bis(trifluoromethyl)phenylboric acid in the same manner as in Example 109 to obtain the desired product as a colorless powder.
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.07(9H, s), 1.09(9H, s), 1.47(9H, s), 1.87(2H, m), 2.55-2.60(2H, m), 3.97(2H, d, J=11.2Hz), 4.28(2H, d, J=11.2Hz), 5.05(1H, br s), 6.96(2H, d, J=8.3Hz), 7.21(2H, d, J=8.3Hz), 7.34(2H, s), 7.54(1H, s)

<Example 127>

5-*t*-butoxycarbonylamino-2,2-di-*t*-butyl-5-[4-(3,5-bistrifluoromethylphenoxy)phenyl]butyl-1,3,2-dioxasilane

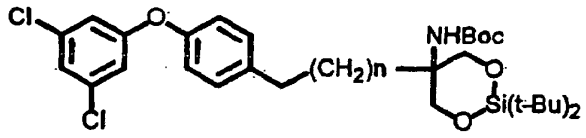
[0164]



[0165] The compound of Example 104 was reacted with 3,5-bis(trifluoromethyl)phenylboric acid in the same manner as in Example 109 to obtain the desired product as a colorless oil.
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.05(9H, s), 1.08(9H, s), 1.25-1.31(2H, m), 1.42(9H, s), 1.55-1.63(4H, m), 2.61(2H, t, J=7.8Hz), 3.91(2H, d, J=11.2Hz), 4.23(2H, d, J=11.2Hz), 4.92(1H; br s), 6.95(2H, d, J=8.3Hz), 7.19(2H, d,J=8.3Hz), 7.36(2H, s), 7.54(1H, s)

<Examples 128 and 129>

[0166] The compounds of Examples 103 and 104 were reacted with 3,5-dichlorophenylboric acid in the same manner as in Example 109 to obtain the following products:

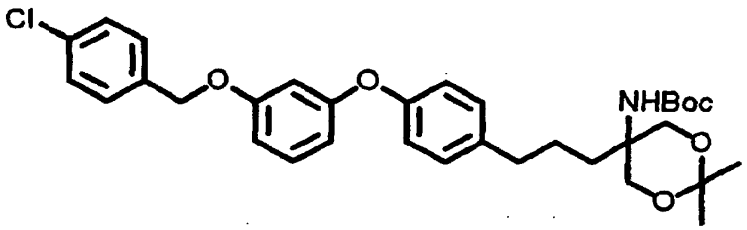


Example	n	Yield (%)	Characteristics	Example	n	Yield (%)	Characteristics
128	**1**	**49**	Colorless oil	**129**	**3**	**67**	Colorless oil

<Example 130>

5-t-butoxycarbonylamino-5-[4-(3-(4-chlorobenzyloxy)phenoxy)phenyl]propyl-2,2-dimethyl-1,3-dioxane

[0167]

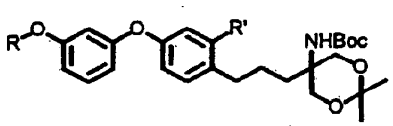


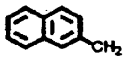
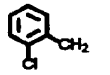
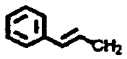
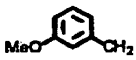
[0168] Potassium carbonate (150mg) and p-chlorobenzyl bromide (103mg) were added to a DMF solution (5mL) of the compound of Example 105 (150mg) and the mixture was stirred for 1 hour at 70°C. Subsequently, the mixture was decanted into water and was extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was then removed by distillation under reduced pressure. The residue was purified by silica gel column chromatography (hexane: ethyl acetate = 3:1) to obtain the desired product (170mg) as a colorless powder.
^{1}H-NMR (400MHz, $CDCl_3$) δ 1.40(3H, s), 1.42(3H, s), 1.44(9H, s), 1.56-1.61(2H, m), 1.71(2H, br), 2.59(2H, t, J=7.3Hz), 3.64(2H, d, J=11.7Hz), 3.89(2H, d, J=11.7Hz), 4.87(1H,br), 4.98(2H, s), 6.58-6.60(2H, m), 6.66-6.68(1H, m), 6.92(2H, d, J=8.3Hz), 7.12(2H, d, J=8.3Hz), 7.20 (1H, t, J=8.3Hz), 7.34(4H, s).

<Examples 131 through 143>

[0169] The compounds of Example 105 and 106 were reacted with different alkylhalides in the same manner as in Example 130 described above to synthesize the compounds shown in Table 14 below:

Table 14

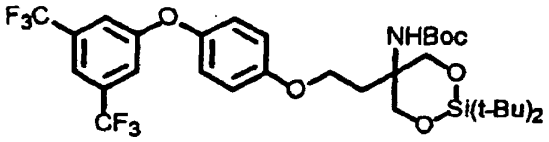


Example	R	R'	Characteristics	Yield(%)	Example	R	R'	Characteristics	Yield(%)
131		H	Colorless powder	100	137		H	Colorless amorphous	86
132		H	Colorless powder	100	138		H	Pale yellow powder	100
133		Cl	Colorless powder	75	139		H	Colorless powder	100
134		Cl	Colorless powder	94	140		H	Colorless amorphous	76
135		Cl	Colorless powder	100	141	Ph_2CH	H	Colorless powder	58
136		H	Colorless powder	85	142		H	Colorless oil	100
					143		Cl	Colorless powder	84

<Example 144>

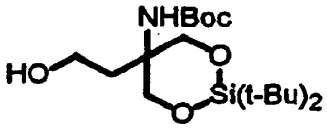
5-*t*-butoxycarbonylamino-2,2-di-*t*-butyl-5-[4-(3,5-bistrifluoromethylphenoxy) phenyloxy]ethyl-1,3,2-dioxasilane

[0170]



a) 5-*t*-butoxycarbonylamino-2,2-di-*t*-butyl-5-hydroxyethyl-1,3,2-dioxasilane

[0171]



[0172] Using benzylbromoethylether and diethyl 2-t-butoxycarbonylaminomalonate, reactions were carried out in the same manner as in Example 1. Subsequently, the reaction processes of Examples 51 and 103 were sequentially followed to give the desired product as a colorless powder.

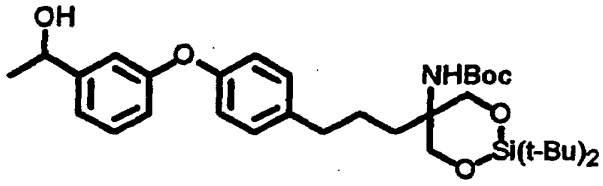
b) 5-*t*-butoxycarbonylamino-2,2-di-*t*-butyl-5-[4-(3,5-bistrifluoromethylphenoxy)phenyloxy]ethyl-1,3,2-dioxasilane

[0173] Using the hydroxy derivative obtained above, reactions were carried out in the same manner as in Reference Example 164 to obtain an iodide, which in turn was reacted with 4-[(3,5-bistrifluoromethyl)phenoxy]phenol to give the desired product as a colorless amorphous.
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.08(9H, s), 1.11(9H, s), 1.44(9H, s), 2.04(2H, br s), 4.04-4.07(4H, br), 4.42(2H, d, J=11.2Hz), 5.10(1H, br s), 6.92(.2H, d, J=8.5Hz), 7.00(2H, d, J=8.5Hz), 7.32(2H, s), 7.52(1H, s)

<Example 145>

5-*t*-butoxycarbonylamino-2,2-di-*t*-butyl-5-[4-(3-(1-hydroxyethyl)phenoxy)phenyl]propyl-1,3,2-dioxasilane

[0174]



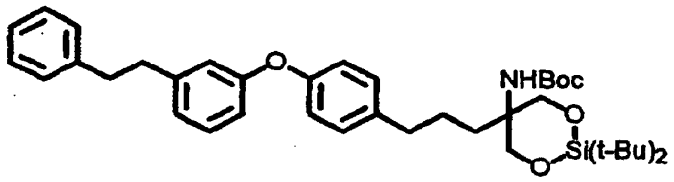
[0175] The compound of Example 125 (126mg) was dissolved in THF (3.0mL) and the solution was cooled to -78°C under argon. A 1mol/L methyllithium-ether solution (0.252mL) was added to the solution and the temperature of the mixture was slowly raised to 0°C. A 5% aqueous solution of citric acid was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was then removed by distillation under reduced pressure. The residue was purified by silica gel column chromatography (hexane: ethyl ac-

etate = 5:1) to obtain the desired product (90.7mg) as a colorless oil.
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.05 (9H, s), 1.07(9H, s), 1.42(9H, s), 1.48(3H, d, J=6.3Hz), 1.55(4H, br s), 1.78(1H, m), 2.56(2H, t, J=6.8Hz), 3.90(2H, d, J=11.7Hz), 4.23(2H, d, J=11.7Hz), 4.87 (1H, q, J=6.5Hz), 4.91(1H, br s), 6.86-6.89 (1H, m), 6.92(2H, d, J=8. 8Hz) , 7.03 (1H, t, J=2. 0Hz) , 7.07-7.12(3H, m), 7.29(1H, t, J=8.3Hz)

<Example 146>

5-*t*-butoxycarbonylamino-2,2-di-*t*-butyl-5-[4-(3-phenetyl)phenoxy]phenyl]propyl-1,3,2-dioxasilane

[0176]

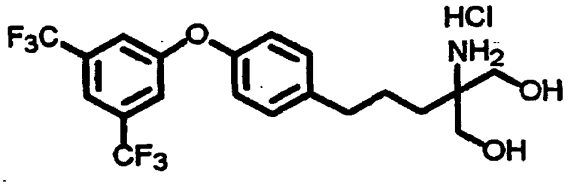


[0177] Benzylphosphonylchloride (152mg) was dissolved in THF (2mL) and sodium-t-butoxide (37.6mg) was added to the solution at 0°C. The mixture was stirred for 30 minutes at room temperature and was again cooled to 0°C, at which time a THF solution (2mL) of the compound of Example 125 (202mg) was added. The reaction mixture was stirred for 1 hour at this temperature and for additional 1 hour at room temperature, followed by addition of a 5% aqueous solution of citric acid. The mixture was then extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was then removed by distillation under reduced pressure. The residue was purified by silica gel column chromatography (hexane: ethyl acetate = 30:1) to give a styryl derivative as a colorless oil. The styryl derivative so obtained was reduced by catalytic reduction as in Reference Example 81 to obtain the desired product (168mg) as a colorless oil.
^{1}H-NMR (400MHz, $CDCl_3$) δ 1.05(9H, s), 1.07(9H, s), 1.43(9H, s), 1.57(4H, br s), 2.56(2H, t, J=7.1Hz), 2.90(4H, m), 3.90(2H, d, J=11.2Hz), 4.23(2H, d, J=11.2Hz), 4.92(1H, br s), 6.79-6.83(2H, m), 6.88(2H, d, J=8.3Hz), 6.89-6.92(1H, m), 7.09(2H, d, J=8.3Hz), 7.14-7.24(4H, m), 7.25-7.29(2H, m)

<Example 147>

2-amino-2-[4-(3,5-bistrifluoromethylphenoxy)phenyl]propyl-1,3-propanediol hydrochloride

[0178]



[0179] Ethyl acetate (20mL) containing 3mol/L hydrochloric acid was added to a methanol solution (10mL) of the compound of Example 93 (1.28g) and the mixture was stirred overnight at room temperature. The solvent was removed by distillation under reduced pressure. A mixture of ethyl acetate and hexane (ethyl acetate: hexane = 1:1) was added to the residue and the crystals were collected by filtration. After drying, the desired product (1.07g) was obtained as a colorless powder.

[0180] Alternatively, the compound of Example 124 was used in the reaction process of Example 150 to give the same product.
FABMS:438 ([M+H]+)
^{1}H-NMR (400MHz, DMSO-d_6) δ 1.55-1.58(4H, br), 2.58(2H, t, J=6.8Hz), 3.40-3.47(4H, m), 5.31(1H, br), 7.13(2H, d,

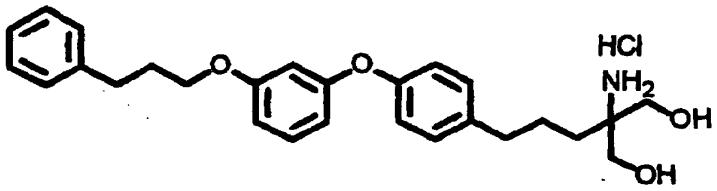
J=8.3Hz), 7.31(2H, d, J=8.3Hz), 7.56(2H, s), 7.76(1H, br), 7.83(1H, s). Melting point = 194-196°C

Elemental analysis (%): $C_{20}H_{21}F_6NO_3 \cdot HCl$			
	C	H	N
Calcd.	50.70	4.68	2.96
Found	50.70	4.66	2.91

<Example 148>

2-amino-2-[4-(3-phenylpropyloxyphenoxy)phenyl]propyl-1,3-propanediol hydrochloride

[0181]

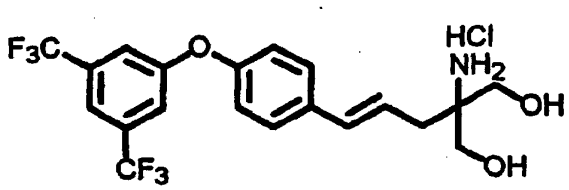


[0182] The compound of Example 138 was reduced by catalytic reduction as in Reference Example 81. Subsequently, the reaction processes of Example 147 were followed to give the desired product as a colorless powder.
Melting point: 95-98°C
FABMS:436 ([M+H]+)
^{1}H-NMR (400MHz, DMSO-d_6) δ 1.56 (4H, br), 1.97(2H, quintet, 7.3Hz), 2.49-2.53(2H, m), 3.39-3.46(4H, m), 3.92(2H, t, J=7.3Hz), 5.30(1H, br), 6.47-6.49(2H, m), 6.66-6.69(1H, m), 6.95(2H, d, J=8.8Hz), 7.12-7.29(8H, m), 7.68-7.72(2H, m)

<Example 149>

2-amino-2-[4'-(3,5-bistrifluoromethylphenoxy)cinnamyl]-1,3-propanediol hydrochloride

[0183]

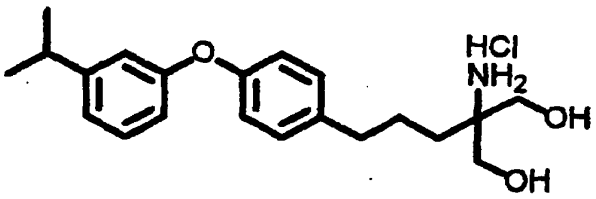


[0184] Using the compound of Example 100, reactions were carried out in the same manner as in Example 147 to obtain the desired product as a colorless powder.
Melting point = 203-206°C
FABMS: 436 ([M+H]+)
^{1}H-NMR (400MHz, DMSO-d_6) δ 3.32(2H, d, J=7.5Hz), 3.48(4H, br), 6.23(1H, dt, J=15.5, 7.5Hz), 6.53(1H, d, 15.5Hz), 7.17(2H, d, J=8.8Hz), 7.52(2H, d, J=8.8Hz), 7.60(2H, s), 7.85(1H, s)

<Example 150>

2-amino-2-[4-(3-isopropylphenoxy)phenyl]propyl-1,3-propanediol hydrochloride

[0185]

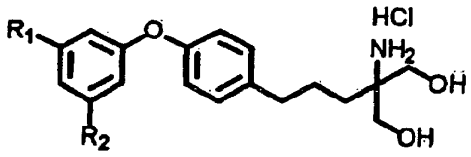


[0186] The compound of Example 109 (188mg) was dissolved in THF (3.0mL) and a 1mol/L tetrabutylammonium-fluoride-THF solution (1.61mL) was added to the solution. The mixture was stirred for 2 hours at room temperature. Subsequently, water was added to the mixture and the mixture was extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was then removed by distillation under reduced pressure. The residue was purified by silica gel column chromatography (hexane: ethyl acetate = 3:2) to obtain the diol as a colorless oil. The diol so obtained was treated in the same manner as in Example 147 to give the desired product (107mg) as a colorless amorphous.
FABMS: 344 ([M+H]+)
^{1}H-NMR (400MHz, DMSO-d_6) δ 1.17(6H, d, J=6.8Hz), 1.55(4H, br s),-2.53(2H, br), 2.81-2.89(1H, m), 3.39-3.49(4H, m), 5.30(2H, t, J=5.1Hz), 6.71(1H, dd, J=8.3, 2.4Hz), 6.87(1H, t, J=2.0Hz), 6.91(2H, d, J=8.8Hz), 6.99(1H, d, J=8.3Hz), 7.19(2H, d, J=8.8Hz), 7.26(1H, t, J=8.3Hz), 7.71(3H, br s)

<Examples 151 through 166>

[0187] The compounds of Examples 110 through 123 and the compounds of Examples 145 and 146 were treated in the same manner as in Example 150 above to synthesize the compounds shown in Table 15 below:

Table 15



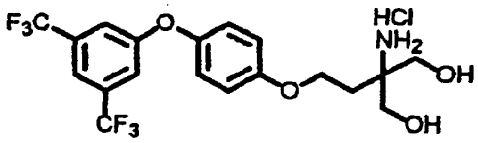
Example	R1	R2	Yield (%)	Characteristics	FABMS [M+H]+	Melting Point (°C)
151	F	H	88	Colorless powder	320	131-133
152	Cl	H	88	Colorless powder	336	125-127
153	Br	H	88	Colorless powder	380	154-156
154	Me	H	92	Pale brown amorphous	316	
155	Ph	H	87	Colorless powder	378	164-166
156	MeO	H	83	Pale brown amorphous	332	
157	EtO	H	88	Colorless powder	346	115-117
158	CF_3O	H	86	Pale brown amorphous	386	
159	CH_2OH	H	84	Colorless powder	332	180-182
160	Ac	H	85	Yellow amorphous	344	
161	NO_2	H	(9)	Pale yellow amorphous	347	
162	CN	H	92	Pale yellow oil*	327	
163	F	F	79	Pale yellow amorphous	338	
164	Cl	Cl	82	Pale yellow powder**	370	75-77
165	$Ph(CH_2)_2$	H	85	Colorless powder	406	165-167
166	MeCH(OH)	H	85	Yellow amorphous	346	

In the parentheses(), shown is the total yield from the previous table.
The mark "*" means it was isolated as a CF_3CO_2H salt.
The mark "**"means it was isolated as free form.

<Example 167>

2-amino-2-[4-(3,5-bistrifluoromethylphenoxy)phenoxy]ethyl-1,3-propanediol hydrochloride

[0188]

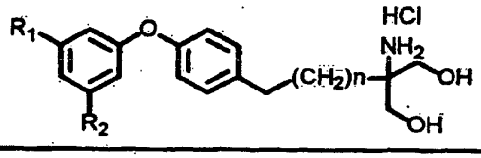


[0189] Using the compound of Example 144, reactions were carried out in the same manner as in Example 150 to obtain the desired product as a colorless powder.
Melting point = 151-155°C
FABMS : 440 ([M+H] +)
^{1}H-NMR (400MHz, DMSO-d_6) δ 2.04 (2H, t, J=6.5Hz), 3.54(4H, s), 4.11 (2H, d,J=6.5Hz), 7.04(2H, d, J=9.2Hz), 7.19 (2H, d, J=9.2Hz), 7.50(2H, s), 7.80(1H, s)

<Examples 168 through 171>

[0190] The compounds of Examples 96 and 126 through 129 were treated in the same manner as in Example 150 above to synthesize the compounds shown in Table 16 below:

Table 16

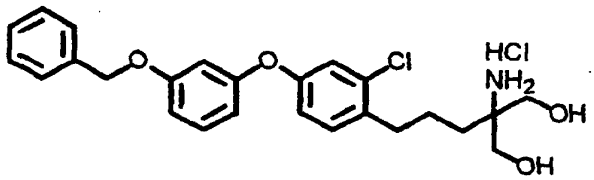


Example	R1	R2	n	Yield (%)	Characteristics	FABMS $[M+H]^+$	Melting point (°C)
168	Cl	Cl	0	80	Colorless powder	342	110-111
169	Cl	Cl	1	99	Pale yellow amorphous	356	
170	Cl	Cl	3	89	Colorless amorphous	384	
171	CF_3	CF_3	1	81	Colorless powder	424	116-118
172	CF_3	CF_3	3	96	Colorless amorphous	452	

<Example 173>

2-amino-2-[4-(3-benzyloxyphenoxy)-2-chlorophenyl]propyl-1,3-propanediol hydrochloride

[0191]



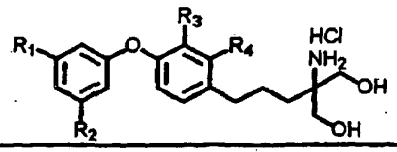
[0192] The compound of Example 51 was treated in the same manner as in Example 147 to obtain the desired product as a colorless powder.
FABMS: 442 ([M+H]+)
^{1}H-NMR (400MHz, DMSO-d_6) δ 1.58 (4H, br s), 2. 63 (2H, br s), 3.39-3.45(4H, m), 5.08(2H, s), 5.31(2H, br), 6.56(1H, dd, J=8.3, 2.4Hz), 6.66(1H, t, J=2.4Hz), 6.83(1H, dd, J=8.3, 2.4Hz), 6.94(1H, dd, J=8.3, 2.4Hz), 7.05(1H, d, J=2.4Hz), 7.28-7.43(7H, m), 7.71(3H, br)
Melting point = 105-106°C (EtOH-iPr20)

Elemental analysis(%): $C_{25}H_{28}ClNO_4$•HCl			
	C	H	N
Calcd.	62.76	6.11	2.93
Found	62.76	6.05	2.92

<Examples 174 through 233>

[0193] The compounds of Examples 52 through 91, 94, 95, 107, 108, and 130 through 143 were treated in the same manner as in Example 147 to synthesize the compounds shown in Tables 17 and 18 below:

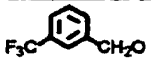
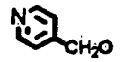
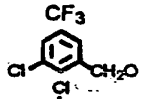
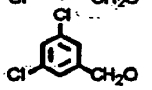
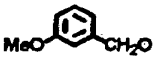
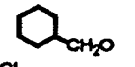
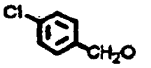
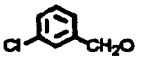
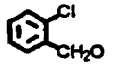
Table 17



Example	R1	R2	R3	R4	Yield (%)	Characteristics	FABMS $[M+H]^+$	Melting point (°C)
174	CF_3	H	H	H	89	Colorless powder	370	146-148
175	CF_3	H	MeO	H	100	Colorless oil	400	
176	CF_3	H	H	MeO	92	Colorless amorphous	400	
177	CF_3	H	Cl	H	100	Colorless powder	404	120-122
178	CF_3	H	H	Cl	100	Colorless amorphous	404	
179	CF_3	H	H	$PhCH_2O$	85	Colorless powder	476	120-123
180	CF_3	H	CF_3	H	99	Colorless powder	438	124-128
181	CF_3	H	H	CF_3	90	Colorless amorphous	438	
182	CF_3	CF_3	H	Cl	79	Colorless powder	472	123-125
183	CF_3	$Ph(CH_2)_2$	H	H	87	Colorless powder	474	110-112
184	CF_3	H	H	F	85	Colorless oil	388	
185	$Ph(CH_2)_2$	$Ph(CH_2)_2$	H	H	96	Colorless amorphous	510	
186	$Ph(CH_2)_2$	H	H	Cl	91	Colorless amorphous	440	
187	$Ph(CH_2)_2$	H	H	CF_3	94	Colorless amorphous	474	
188	$Ph(CH_2)_2$	$Ph(CH_2)_2$	H	Cl	93	Colorless amorphous	544	
189	$Ph(CH_2)_2$	$Ph(CH_2)_2$	H	CF_3	93	Colorless amorphous	578	
190	$PhCH_2O$	H	H	H	91	Colorless amorphous	408	
191	$PhCH_2O$	$PhCH_2O$	H	H	100	Colorless powder	514	92-95
192	$PhCH_2O$	$PhCH_2O$	H	Cl	100	Colorless amorphous	548	
193	$PhCH_2O$	Cl	H	Cl	91	Colorless powder	476	89-91
194	$PhCH_2O$	H	H	Br	98	Colorless amorphous	488	
195	$PhCH_2O$	H	H	CF_3	100	Colorless powder	476	72-76
196	$PhCH_2O$	H	H	Ph	98	Colorless amorphous	484	
197	$PhCH_2O$	CF_3	H	H	91	Colorless amorphous	476	
198	$PhCH_2O$	CF_3	H	Cl	94	Colorless powder	510	114-116
199	t-Bu	H	H	H	100	Colorless amorphous	358	
200	MeS	H	H	H	89	Colorless amorphous	348	
201	$n\text{-}C_5H_{11}$	H	H	H	99	Colorless amorphous	372	
202	$n\text{-}C_7H_{15}$	H	H	H	74	Yellow amorphous	400	
203	i-Pr	iPrO	H	H	93	Colorless amorphous	402	
204	i-Pr	iPrO	H	Cl	97	Colorless amorphous	436	
205	i-Pr	i-Pr	H	Cl	95	Colorless amorphous	420	
206	Cl	Cl	H	Cl	92	Colorless amorphous	404	
207	$PhCH_2S$	H	H	H	100	Colorless amorphous	424	
208	$PhCH_2S$	H	H	Cl	100	Colorless amorphous	458	
209	Et	H	H	H	87	Pale yellow amorphous	330	
210	i-Bu	H	H	H	92	Colorless amorphous	358	
211*	OH	H	H	H	98	Colorless powder	318	174-176
212	i-PrO	H	H	H	94	Colorless amorphous	360	
213	PhO	H	H	H	100	Colorless amorphous	394	

The mark "*" means the step was carried out after catalytic reduction of the compound of Example 68.

Table 18

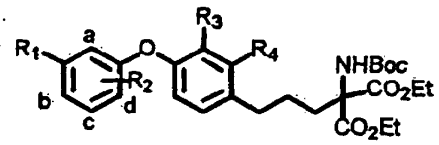
Example	R1	R2	R3	R4	Yield (%)	Characteristics	FABMS $[M+H]^+$	Melting point °C
214		H	H	H	100	Colorless powder	476	89-92
215		H	H	H	85	Colorless amorphous	409	
216		H	H	H	93	Colorless powder	458	170-173
217	Ph_2CHO	H	H	H	91	Colorless powder	484	153-156
218	$Ph(CH_2)_2O$	H	H	H	90	Colorless amorphous	422	
219		H	H	H	100	Colorless amorphous	434	
220	$PhOCH_2$	H	H	H	97	Colorless powder	408	119-122
221	MeSO	H	H	H	100	Colorless amorphous	364	
222	$MeSO_2$	H	H	H	100	Colorless powder	380	147-150
223 **	CF_3	H	H	OH	97	Colorless amorphous	386	
224		H	H	Cl	100	Colorless powder	476	94-98
225		H	H	Cl	83	Colorless powder	510	92-95
226		H	H	Cl	94	Colorless amorphous	472	
227		H	H	Cl	100	Colorless powder	456	84-86
228		H	H	Cl	76	Colorless powder	510	88-91
229	$PhCH_2O$	H	H	i-Pr	97	Colorless amorphous	450	
230		H	H	H	90	Colorless powder	414	125-127
231		H	H	H	100	Colorless powder	442	195-197
232		H	H	H	100	Colorless powder	442	130-132
233		H	H	H	100	Colorless powder	442	94-96

The mark "**" means the step was carried out after catalytic reduction of the compound of Example 57.

<Examples 234 through 243>

[0194] Using the compounds of Reference Examples 241 through 250, reactions were carried out in the same manner as in Example 1 to synthesize the compounds below:

Table 19



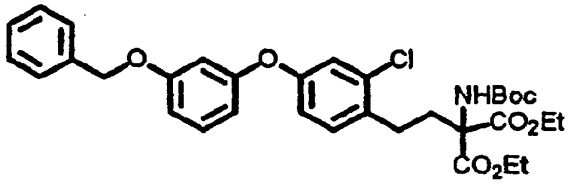
Example	R1	R2	R3	R4	Characteristics	Yield (%)
234	$Ph(CH_2)_2$	c-CF_3	H	Cl	Colorless oil	93
235	$PhCH_2O$	c-H	H	Me	Colorless oil	100
236	$PhCH_2O$	c-H	H	Et	Colorless oil	72
237	$PhCH_2O$	c-H	H	SMe	Colorless oil	-
238	PhO	c-H	H	Cl	Colorless oil	92
239	CF_3	a-Cl	H	H	Colorless oil	100
240	CF_3	b-Cl	H	H	Colorless oil	94
241	CF_3	d-Cl	H	H	Pale yellow oil	72
242	CF_3	c-Cl	H	H	Pale yellow oil	41
243	$PhCH_2O$	c-H	H	F	Colorless oil	-

The mark "-" means yield is shown in Table 20 as a total yield.

<Example 244>

Ethyl 4-[4-(3-benzyloxyphenoxy)-2-chloro]phenyl-2-*t*-butoxycarbonylamino-2-ethoxycarbonylbutyrate

[0195]

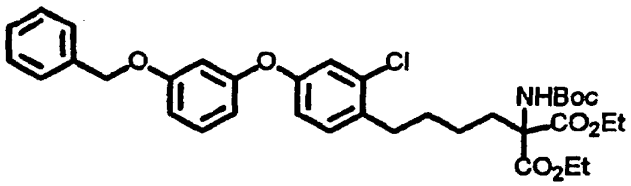


[0196] Using the compound of Example 261, reactions were carried out in the same manner as in Example 1 to obtain the desired product as a colorless oil.
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.23-1.32(6H, m), 1.45(9H, s), 2.59(4H, br), 4.22-4.34(4H, m), 5.03(2H, s), 6.58-6.62(2H, m), 6.75(1H, dd, J=8.3Hz, 2.4Hz), 6.83(1H, dd, J=8.3Hz, 2.4Hz), 6.98(1H, d, J=2.4Hz), 7.12(1H, d, J=8.3 Hz), 7.23 (1H, t, J=8.3Hz), 7.30-7.42(5H, m)

<Example 245>

Ethyl 6-[4-(3-benzyloxyphenoxy)-2-chloro]phenyl-2-*t*-butoxycarbonylamino-2-ethoxycarbonylhexanoate

[0197]

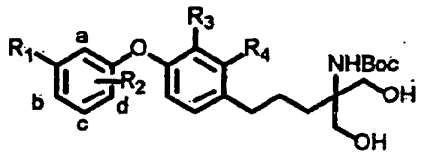


[0198] Using the compound of Example 262, reactions were carried out in the same manner as in Example 1 to obtain the desired product as a colorless oil.
^{1}H-NMR (400MHz, $CDCl_3$) δ 1.24(6H, t, J=7.3Hz), 1.43(9H, s), 1.58-1.67(4H, m), 2.33(2H, br), 2.67(2H, t, J=7.8Hz), 4.18-4.32(4H, m), 5.03(2H, s), 5.95 (1H, br s), 6.57-6.60(1H, m), 6.62(1H, t, J=2.4Hz), 6.74(1H, dd, J=8.3Hz, 2.4Hz), 6.83(1H, dd, J=8.3Hz, 2.4Hz), 6.99(1H, d, J=2.4Hz), 7.12(1H, d, J=8.3 Hz), 7.23(1H, t, J=8.3Hz), 7.30-7.42(5H, m)

<Examples 246 through 255>

[0199] Using the compounds of Examples 234 through 243, reactions were carried out in the same manner as in Example 51 to synthesize the compounds below:

Table 20

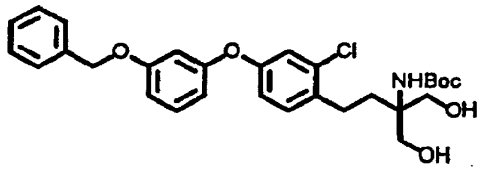


Reference example	R1	R2	R3	R4	Characteristics	Yield (%)
246	$Ph(CH_2)_2$	c-CF_3	H	Cl	Colorless oil	46
247	$PhCH_2O$	c-H	H	Me	Colorless oil	75
248	$PhCH_2O$	c-H	H	Et	Colorless oil	61
249	$PhCH_2O$	c-H	H	SMe	Colorless oil	38
250	PhO	c-H	H	Cl	Colorless oil	76
251	CF_3	a-Cl	H	H	Colorless oil	57
252	CF_3	b-Cl	H	H	Colorless oil	62
253	CF_3	d-Cl	H	H	Colorless oil	37
254	CF_3	c-Cl	H	H	Colorless oil	51
255	$PhCH_2O$	c-H	H	F	Colorless oil	34

<Example 256>

2-[4-(3-benzyloxyphenoxy)-2-chlorophenyl]ethyl-2-*t*-butoxycarbonylamino-1,3-propanediol

[0200]

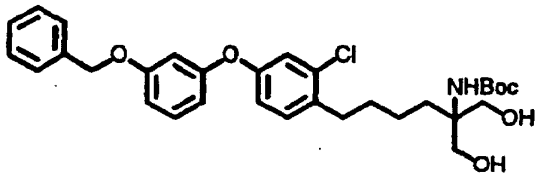


[0201] The compound of Example 244 was treated in the same manner as in Example 51 to obtain the desired product as a colorless powder.
^{1}H-NMR (400MHz, $CDCl_3$) δ 1.46(9H, s), 1.83-1.87(2H, m), 2.69-2.73(2H, m), 3.35(2H, br), 3.67(2H, dd, J=11.7Hz, 5.9Hz), 3.92(2H, dd, J=11.7Hz, 4.9Hz), 5.03(2H, s), 5.10(1H, s), 6.57-6.62(2H, m), 6.75(1H, dd, J=8.3Hz, 2.4Hz), 6.85 (1H, dd, J=8.3Hz, 2.4Hz), 7.00(1H, d, J=2.4Hz), 7.17(1H, d,J=8.3 Hz), 7.24(1H, t, J=8.3Hz), 7.32-7.42(5H, m)

<Example 257>

2-[4-(3-benzyloxyphenoxy)-2-chlorophenyl)butyl-2-*t*-butoxycarbonylamino-1,3-propanediol

[0202]

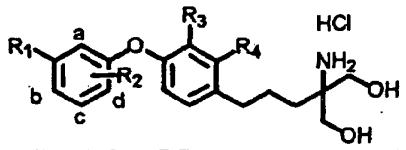


[0203] The compound of Example 245 was treated in the same manner as in Example 51 to obtain the desired product as a colorless oil.
^{1}H-NMR (400MHz, $CDCl_3$) δ 1.44(9H, s), 1.61(6H, br), 2.70(2H, t, J=7.3Hz), 3.46(2H, br), 3.57-3.60(2H, m), 3.84(2H, d, J=9.8Hz), 4.92(1H, s), 5.03(2H, s), 6.59-6.63(2H, m), 6.73-6.76(1H, m), 6.84(1H, dd, J=8.3Hz, 2.4Hz), 7.00(1H, d, J=2.4Hz), 7.13(1H, d, J=8.3Hz), 7.24(1H, t, J=8.3 Hz), 7.23-7.43(5H, m)

<Examples 258 through 267>

[0204] Using the compounds of Examples 246 through 255, reactions were carried out in the same manner as in Example 147 to synthesize the compounds below:

Table 21

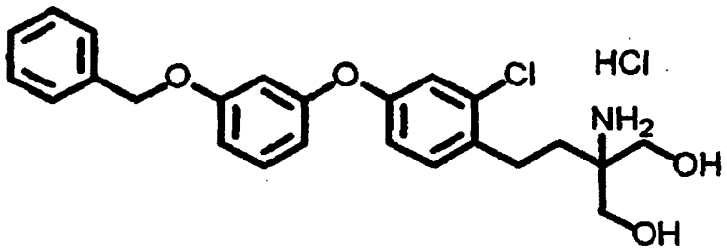


Example	R1	R2	R3	R4	Yield (%)	Characteristics	FABMS $[M+H]^+$	Melting Point (°C)
258	$Ph(CH_2)_2$	c-CF_3	H	Cl	98	Pale yellow amorphous	508	
259	$PhCH_2O$	c-H	H	Me	92	Yellow amorphous	422	
260	$PhCH_2O$	c-H	H	Et	100	Pale yellow amorphous	436	
261	$PhCH_2O$	c-H	H	SMe	100	Colorless amorphous	454	
262	PhO	c-H	H	Cl	92	Colorless amorphous	428	
263	CF_3	a-Cl	H	H	93	Pale yellow amorphous	404	
264	CF_3	b-Cl	H	H	99	Colorless powder	404	133-136
265	CF_3	d-Cl	H	H	78	Pale yellow amorphous	404	
266	CF_3	c-Cl	H	H	76	Colorless powder	404	180-182
267	$PhCH_2O$	c-H	H	F	100	Colorless powder	426	71-73

<Example 268>

2-amino-2-[4-(3-benzyloxyphenoxy)-2-chlorophenyl]ethyl-1,3-propanediol hydrochloride

[0205]

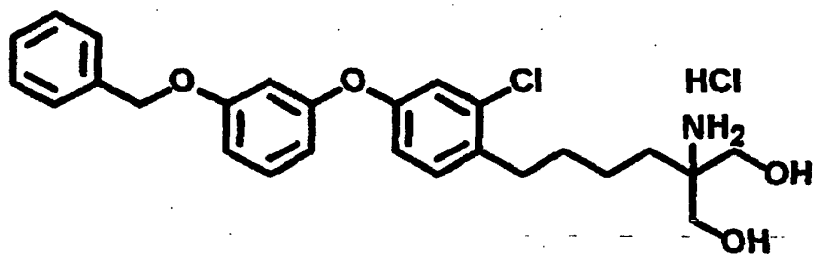


[0206] The compound of Example 256 was treated in the same manner as in Example 147 to obtain the desired product as a colorless powder.
FABMS : 428 ([M+H] +)
^{1}H-NMR(400MHz, DMSO-d_6) δ 1.75-1.79(2H, m), 2.68-2.72(2H, m), 3.51-3.55(4H, m), 5.08(2H, s), 5.40(2H, t, J=4.9Hz), 6.57(1H, dd, J=8.3Hz, 2.4Hz), 6.67(1H, t, J=2.4Hz), 6.83(1H, dd, J=8.3Hz, 2.4Hz), 6.95(1H, dd, J=8.3Hz, 2.4Hz), 7.05(1H, d, J=2.4Hz), 7.27-7.43(7H, m), 7.88(3H, br)
Melting point = 150-152°C

<Example 269>

2-amino-2-[4-(3-benzyloxyphenoxy)-2-chlorophenyl]butyl-1,3-propanediol hydrochloride

[0207]



[0208] The compound of Example 257 was treated in the same manner as in Example 147 to obtain the desired product as a pale yellow amorphous.
FABMS : 456 ([M+H]+)
^{1}H-NMR(400MHz, DMSO-d_6) δ 1.30-1.40(2H, m), 1.46-1.60(4H, m), 2.64(2H, t, J=7.8Hz), 3.39-3.48(4H, m), 5.08(2H, s), 5.32(2H, t, J=5.4Hz), 6.57(1H, dd, J=8.3Hz, 2.4Hz), 6.67(1H, t, J=2.4Hz), 6.82(1H, dd, J=8.3Hz, 2.4Hz), 6.91(1H, dd, J=8.3Hz, 2.4Hz), 7.03(1H, d, J=2.4Hz), 7.27-7.43(7H, m), 7.76(3H, br) Melting point = 95-97°C

[0209] The following experiments were conducted to prove the effectiveness of the compounds of the present invention.

<Experiment 1>

Ability of test compounds to suppress host vs graft rejection in mice

[0210] This experiment was performed according to the method described in *Transplantation,* 55, No.3 (1993): 578-591. Spleens were collected from 9 to 11 week old male BALB/c mice (CLEA JAPAN Inc., CHARLES RIVER JAPAN Inc., or JAPAN SLC Inc.). The spleens were placed in a phosphate-buffered saline (PBS(-), NISSUI PHARMACEUTICAL Co., Ltd.) or in an RPMI-1640 medium (GIBCO INDUSTRIES Inc., or IWAKI GLASS Co., Ltd.) and were either passed through a stainless steel mesh, or gently pressed between two slide glasses and then passed through a cell strainer (70μm, Falcon), to form a cell suspension. The suspension was then centrifuged and the supernatant was discarded. An ammonium chloride-Tris isotonic buffer was added to the suspension to lyse erythrocytes. The cells were then centrifuged and washed three times in PBS (-) or RPMI-1640 medium and were resuspended in an RPMI-1640 medium. To this suspension, mitomycin C (KYOWA HAKKO KOGYO Co., Ltd.) was added to a final concentration of 25μg/mL and the suspension was incubated for 30 minutes at 37°C in a 5% CO_2 atmosphere.. The cells were again centrifuged and washed in PBS (-) or RPMI-1640 medium and were resuspended in an RPMI-1640 medium so that the medium would contain 2.5 X 10^8 cells/mL. This suspension served as a "stimulation cell suspension." Using a 27G needle along with a microsyringe (Hamilton), 20μL (5 X 10^6 cells/mouse) of the stimulation cell suspension was subcutaneously injected into the right hind footpad of 7 to 9 week old male C3H/HeN mice (CLEA JAPAN Inc., CHARLES RIVER JAPAN Inc., or JAPAN SLC Inc.). A group of mice was injected with RPMI-1640 medium alone to serve as normal control. 4 days after the injection, right popliteal lymph nodes were collected and were weighed on a Mettler AT201 electronic scale (METTLER TOLEDO Co., Ltd.). Each animal was intraperitoneally administered a test compound once a day for four consecutive days starting on the day of the injection of the stimulation cells (*i.e.*, total of 4 times). Controls were administered a vehicle that has the same composition as that used in the preparation of the test compounds. The results are shown in Table 22 below:

Table 22

Example No.	Dose (mg/)kg)	Inhibition (%)	Example No.	Dose (mg/kg)	Inhibition (%)	Example No.	Dose (mg/ kg)	Inhibition (%).
147	10	82	186	1	87	212	10	78

Table 22 (continued)

Example No.	Dose (mg/)kg)	Inhibition (%)	Example No.	Dose (mg/kg)	Inhibition (%)	Example No.	Dose (mg/ kg)	Inhibition (%).
148	3	78	187	3	78	213	3	68
150	10	78	188	3	68	214	3	79
157	10	50	189	3	54	215	3	76
164	10	82	190	10	83	217	3	66
166	10	91	191	3	95	218	3	92
169	10	86	192	0.3	93	219	3	53
170	10	71	194	0.3	85	220	3	77
171	10	79	195	3	69	223	10	63
172	10	78	197	3	93	224	0.3	76
173	3	100	198	3	92	225	0.03	70
174	10	62	200	10	50	226	3	89
175	10	64	202	10	92	227	3	93
176	10	63	203	10	77	228	0.3	74
177	10	71	204	10	79	230	3	67
178	10	82	205	10	84	231	3	83
181	10	98	206	10	76	232	3	92
182	3	78	207	3	69	233	3	85
183	3	102	208	3	90			
184	3	64	209	10	71			
185	3	63	210	10	76			

<Experiment 2>

Ability of test compounds to suppress delayed-type hypersensitivity in mice.

[0211] This experiment was performed according to the method described in *Methods in Enzymology*, 300 (1999): 345-363. 1-fluoro-2,4-dinitrobenzene (DNFB, NACALAI TESQUE Inc.) was dissolved in a mixture of acetone and olive oil (acetone: olive oil = 4:1) to a concentration of 1% (v/v). 10μL of this 1% DNFB solution was applied to the footpad of each hind leg of male BALB/c mice (JAPAN SLC Inc. or CHARLES RIVER JAPAN Inc.) for sensitization. The sensitization was done for 2 consecutive days (day 0 and day 1). On day 5, the ears of the mice were challenged with the antigen to induce delayed-type hypersensitive responses: First, the thickness of each ear was measured by the dial thickness gauge G (0.01-10mm, OZAKI MFG Co., Ltd.). Next, a test compound was administered. 30 minutes after the administration, 10μL of a 0.2% (v/v) DNFB solution was applied to the inner and outer surfaces of the right ear of each animal for antigen challenge. The left ear of each animal was challenged with the solvent alone. 24 hours after the challenge, the increase in the ear thickness was measured for each ear and the difference between the right and the left ears was determined for each individual. The test compound was dissolved, or suspended, in an ultra pure water and was orally administered at a dose of 0,1mL/10g of body weight. A control group was administered ultra pure water alone. The results are shown in Table 23 below:

Table 23

Example No. 173	Dose (mg/kg)	Inhibition (%)
	3	64
178	10	72
181	10	69
182	30	101
190	3	67
195	30	64
198	3	57

<Experiment 3>

Activities of test compounds on skin transplantation model in mice

[0212] Effects of the test compounds were examined on skin transplantation model in mice. The experimental procedure was referred to the method described in *Journal of Experimental Biology,* 28, No.3 (1951); 385-405.

[0213] First, dorsal skin from male DBA/2 mice were stripped of the fatty layer and the panniculus carnosus, and cut into circular grafts with a diameter of 8mm. Next, graft bed, a circular area, approximately 8mm in diameter, was prepared in the back of anesthetized.male BALB/c mice with a scalpel while the skin was pinched by forceps. Each graft obtained from the DBA/2 mice was placed on the graft bed formed in the backs of the BALB/c mice and was secured with a strip of adhesive bandage while held down from the top. 6 days after transplantation, the bandage was removed and the graft was subsequently observed everyday. The activity of each compound was evaluated based on the length of the survival period, which is defined as the number of days for rejection. Each test compound was dissolved in ultra pure water and was orally administered once a day, starting from the day of transplantation. In a similar manner, the control group was administered ultra pure water alone.

[0214] The results are shown in Figs. 1 through 8.

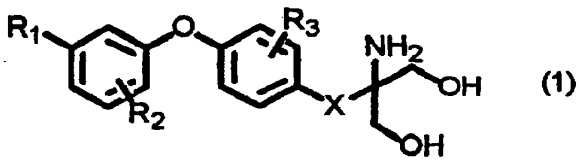
[0215] As can be seen from the results, the compounds of the present invention represented by the general formula (1) have proven effective in animal model.

INDUSTRIAL APPLICABILITY

[0216] As set forth, the present invention has been devised in recognition of the fact that novel diaryl derivatives, in particular those in which one of the aryl groups includes, at its para-position, a carbon chain with an aminopropanediol group and the other aryl group includes a substituent at its meta-position, exhibit strong immunosuppressive effects. Acting as effective immunosuppressors, the compounds of the present invention have a strong potential as a prophylactic or therapeutic agent against rejection in organ or bone marrow transplantation, autoimmune diseases, rheumatoid arthritis, psoriasis, atopic dermatitis, bronchial asthma, pollinosis and various other diseases.

Claims

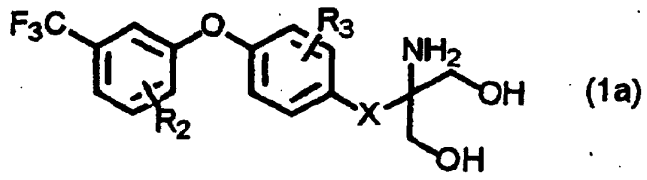
1. A diaryl ether derivative, a pharmaceutically acceptable salt or hydrate thereof, the diaryl ether derivative represented by the following general formula (1):



(1)

wherein R_1 is halogen, trihalomethyl, hydroxy, lower alkyl having 1 to 7 carbon atoms, phenyl, aralkyl, lower alkoxy having 1 to 4 carbon atoms, trifluoromethyloxy, substituted or unsubstituted phenoxy, cyclohexylmethyloxy, substituted or unsubstituted aralkyloxy, pyridylmethyloxy, cinnamyloxy, naphthylmethyloxy, phenoxymethyl, hydroxymethyl, hydroxyethyl, lower alkylthio having 1 to 4 carbon atoms, lower alkylsulfinyl having 1 to 4 carbon atoms, lower alkylsulfonyl having 1 to 4 carbon atoms, benzylthio, acetyl, nitro, or cyano; R_2 is hydrogen, halogen, trihalomethyl, lower alkoxy having 1 to 4 carbon atoms, lower alkyl having 1 to 7 carbon atoms, phenethyl, or benzyloxy; R_3 is hydrogen, halogen, trifluoromethyl, lower alkoxy having 1 to 4 carbon atoms, hydroxy, benzyloxy, lower alkyl having 1 to 7 carbon atoms, phenyl, lower alkoxymethyl having 1 to 4 carbon atoms, or lower alkylthio having 1 to 4 carbon atoms; and X is $-(CH_2)_n-$(n is an integer from 1 to 4), $-OCH_2CH_2-$, or $-CH=CHCH_2-$.

2. The diaryl ether derivative, pharmaceutically acceptable. salt and hydrate thereof according to claim 1, wherein the compound of the general formula (1) is a compound represented by the following general formula (1a):



(1a)

wherein R_2, R_3, and X are the same as defined above.

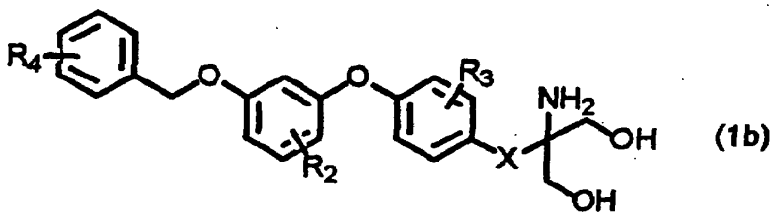
3. The diaryl ether derivative, pharmaceutically acceptable salt and hydrate thereof according to claim 2, wherein R_3 is fluorine.

4. The diaryl ether derivative, pharmaceutically acceptable salt and hydrate thereof according to claim 2, wherein R_3 is chlorine.

5. The diaryl ether derivative, pharmaceutically acceptable salt and hydrate thereof according to claim 2, wherein R_3 is trifluoromethyl.

6. The diaryl ether derivative, pharmaceutically acceptable salt and hydrate thereof according to claim 2, wherein X is $-(CH_2)_m-$ (wherein m is an integer from 2 to 4).

7. The diaryl ether derivative, pharmaceutically acceptable salt and hydrate thereof according to claim 1, wherein the compound of the general formula (1) is a compound represented by the following general formula (1b):



(1b)

wherein R_2, R_3, and X are the same as defined above; and R_4 is hydrogen, halogen, trifluoromethyl, lower alkoxy having 1 to 4 carbon atoms, or lower alkyl having 1 to 7 carbon atoms.

8. The diaryl ether derivative, pharmaceutically acceptable salt and hydrate thereof according to claim 7, wherein R_3 is fluorine.

9. The diaryl ether derivative, pharmaceutically acceptable salt and hydrate thereof according to claim 2, wherein R_3 is chlorine.

10. The diaryl ether derivative, pharmaceutically acceptable salt and hydrate thereof according to claim 7, wherein R_3 is trifluoromethyl.

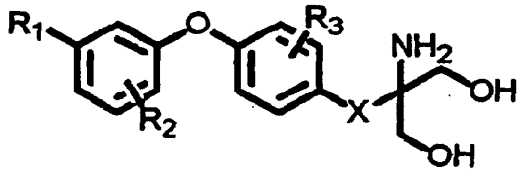
11. The diaryl ether derivative, pharmaceutically acceptable salt and hydrate thereof according to claim 7, wherein X is $-(CH_2)_m-$ (wherein m is an integer from 2 to 4).

12. The diaryl ether derivative, pharmaceutically acceptable salt and hydrate thereof according to claim 1, wherein the compound of the general formula (1) is

1) 2-amino-2-[4-(3-benzyloxyphenoxy)-2-chlorophenyl]propyl-1,3-propanediol;
2) 2-amino-2-[4-(3-benzyloxyphenoxy)phenyl]propyl-1,3-propanediol;
3) 2-amino-2-[4-(3-benzyloxyphenoxy)-2-chlorophenyl]ethyl-1,3-propanediol;
4) 2-amino-2-[4-(3-benzyloxyphenoxy)-2-chlorophenyl]butyl-1,3-propanediol;

5) 2-amino-2-[4-(3-(3',5'-dichlorobenzyloxy)phenoxy)-2-chlorophenyl]propyl-1,3-propanediol;
6) 2-amino-2-[4-(3-(3'-chlorobenzyloxy)phenoxy)-2-chlorophenyl]propyl-2,3-propanediol;
7) 2-amino-2-[4-(3-(3'-trifluoromethylbenzyloxy) phenoxy)-2-chlorophenyl]propyl-1,3-propanediol;
8) 2-amino-2-[4-(3-benzyloxyphenoxy)-2-trifluoromethylphenyl]propyl-1,3-propanediol;.
9) 2-amino-2-[4-(3,5-bistrifluoromethylphenoxy)phenyl]propyl-1,3-propanediol;
10) 2-amino-2-[4-(3,5-bistrifluoromethyl-2-chlorophenoxy)phenyl]propyl-1,3-propanediol;
11) 2-amino-2-[4-(3,5-bistrifluoromethylphenoxy)phenyl]ethyl-1,3-propanediol;
12) 2-amino-2-[2-chloro-4-(3-trifluoromethylphenoxy)phenyl]propyl-1,3-propanediol;
13) 2-amino-2-[2-trifluoromethyl-4-(3-trifluoromethylphenoxy)phenyl]propyl-1,3-propanediol;
14) 2-amino-2-[4-(3,5-dichlorophenoxy)phenyl]propyl-1,3-propanediol;
15) 2-amino-2-[4-(3-benzyloxy-5-trifluoromethylphenoxy)phenyl]propyl-1,3-propanediol; or
16) 2-amino-2-[2-fluoro-4-(3-trifluoromethylphenoxy)phenyl]propyl-1,3-propanediol.

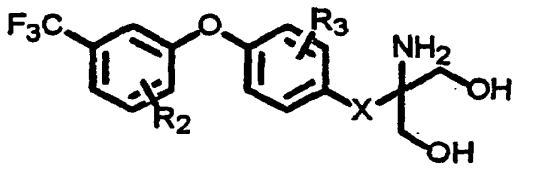
13. An immunosuppressive agent containing as an active ingredient at least one of a diaryl ether derivative, a pharmaceutically acceptable salt and hydrate thereof, the diaryl ether derivative represented by the following general formula (1):



(1)

wherein R_1 is halogen, trihalomethyl, hydroxy, lower alkyl having 1 to 7 carbon atoms, substituted or unsubstituted phenyl, aralkyl, lower alkoxy having 1 to 4 carbon atoms, trifluoromethyloxy, phenoxy, cyclohexylmethyloxy, substituted or unsubstituted aralkyloxy, pyridylmethyloxy, cinnamyloxy, naphthylmethyloxy, phenoxymethyl, hydroxymethyl, hydroxyethyl, lower alkylthio having 1 to 4 carbon atoms, lower alkylsulfinyl having 1 to 4 carbon atoms, lower alkylsulfonyl having 1 to 4 carbon atoms, benzylthio, acetyl, nitro, or cyano; R_2 is hydrogen, halogen, trihalomethyl, lower alkoxy having 1 to 4 carbon atoms, lower alkyl having 1 to 7 carbon atoms, phenethyl, or benzyloxy; R_3 is hydrogen, halogen, trifluoromethyl, lower alkoxy having 1 to 4 carbon atoms, hydroxy, benzyloxy, lower alkyl having 1 to 7 carbon atoms, phenyl, lower alkoxymethyl having 1 to 4 carbon atoms, or lower alkylthio having 1 to 4 carbon atoms; and X is-$(CH_2)_n$- (n is an integer from 1 to 4), -OCH_2CH_2-, or -$CH{=}CHCH_2$-.

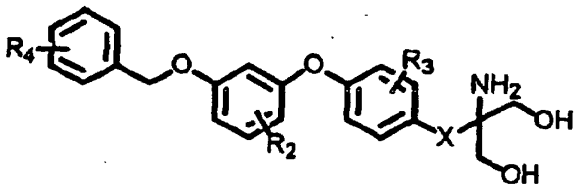
14. An immunosuppressive agent containing as an active ingredient at least one of the diaryl ether derivative, pharmaceutically acceptable salt and hydrate thereof according to claim 13, wherein the compound of the general formula (1) is a compound represented by the following general formula (1a):



(1a)

wherein R_2, R_3, and X are the same as defined above.

15. An immunosuppressive agent containing as an active ingredient at least one of the diaryl ether derivative, pharmaceutically acceptable salt and hydrate thereof according to claim 13, wherein the compound of the general formula (1) is a compound represented by the following general formula (1b) :



(1b)

wherein R_2, R_3, and X are the same as defined above; and R_4 is hydrogen, halogen, trifluoromethyl, lower alkoxy having 1 to 4 carbon atoms, or lower alkyl having 1 to 7 carbon atoms.

16. The immunosuppressive agent according to any one of claims 13 to 15, serving as a prophylactic or therapeutic agent against rejection in organ or bone marrow transplantation.

17. The immunosuppressive agent according to any one of claims 13 to 15, serving as a prophylactic or therapeutic agent against autoimmune diseases.

18. The immunosuppressive agent according to any one of claims 13 to 15, serving as a prophylactic or therapeutic agent against rheumatoid arthritis.

19. The immunosuppressive agent according to any one of claims 13 to 15, serving as a prophylactic or therapeutic agent against psoriasis or atopic dermatitis.

20. The immunosuppressive agent according to any one of claims 13 to 15, serving as a prophylactic or therapeutic agent against bronchial asthma or pollinosis.

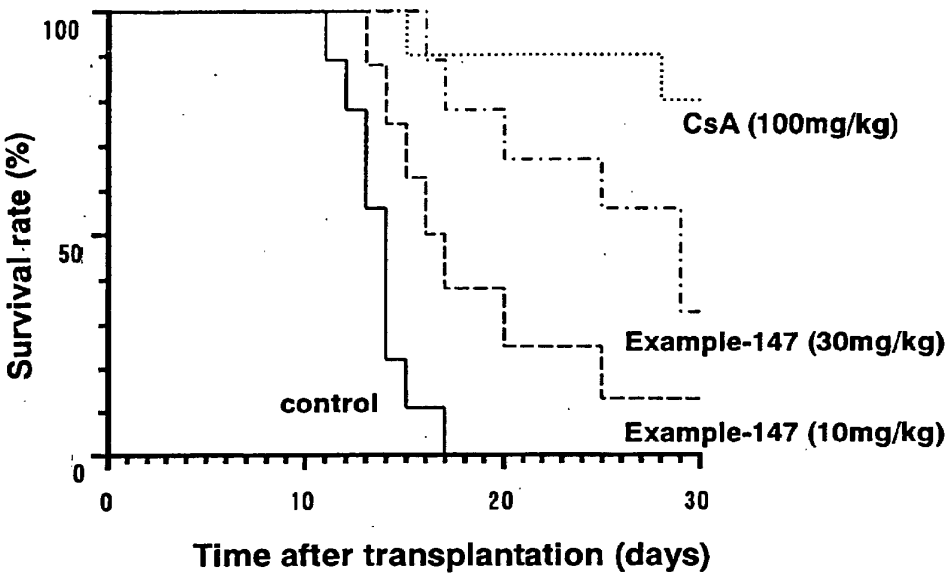


FIG.1

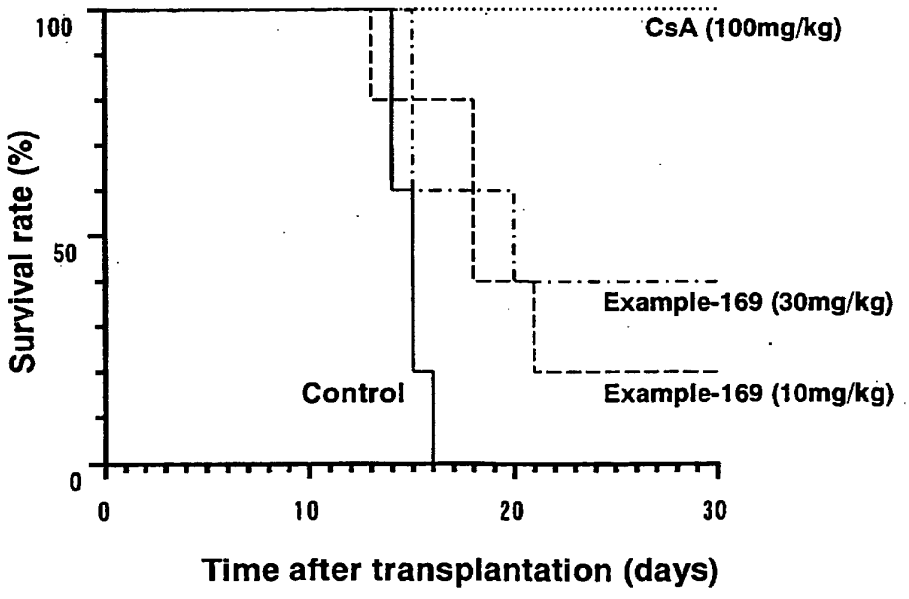


FIG.2

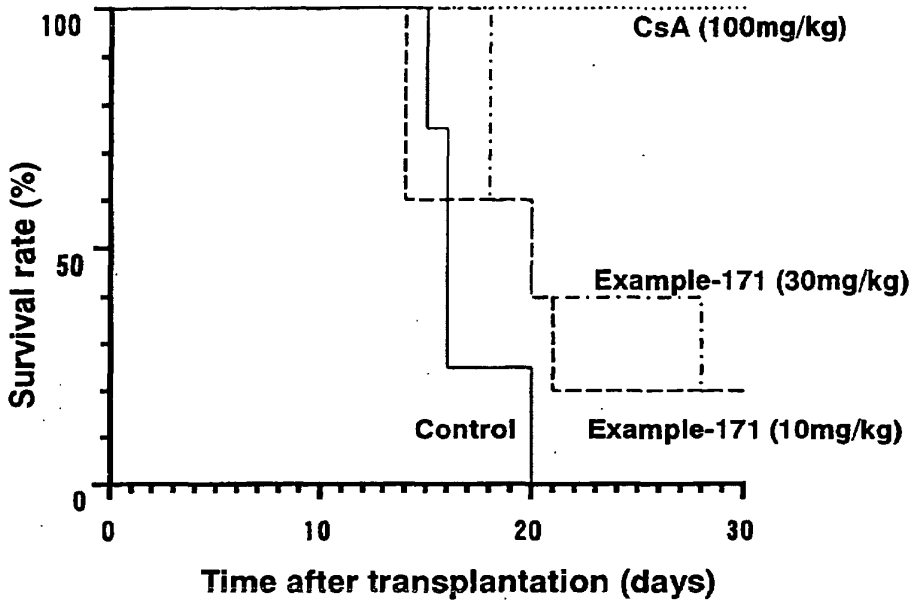


FIG.3

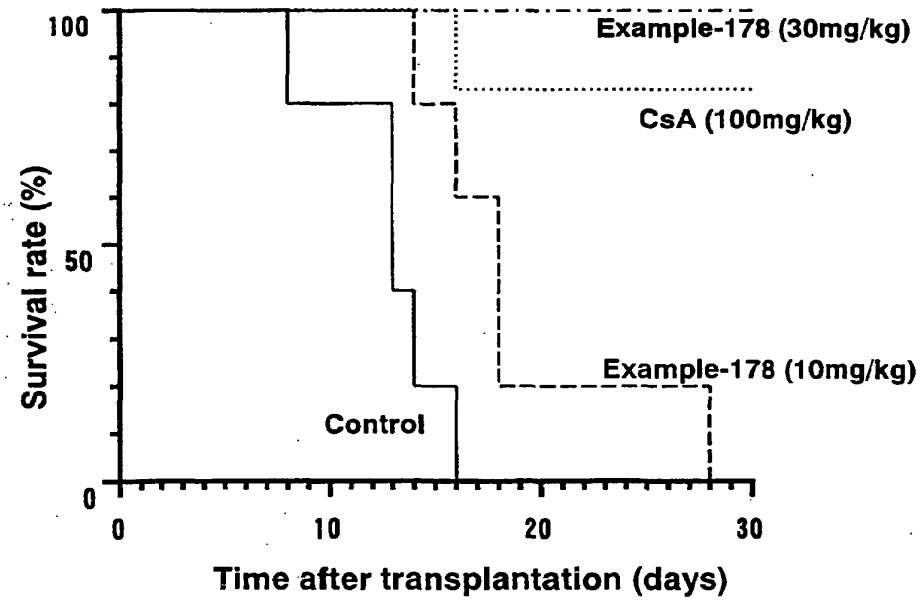


FIG.4

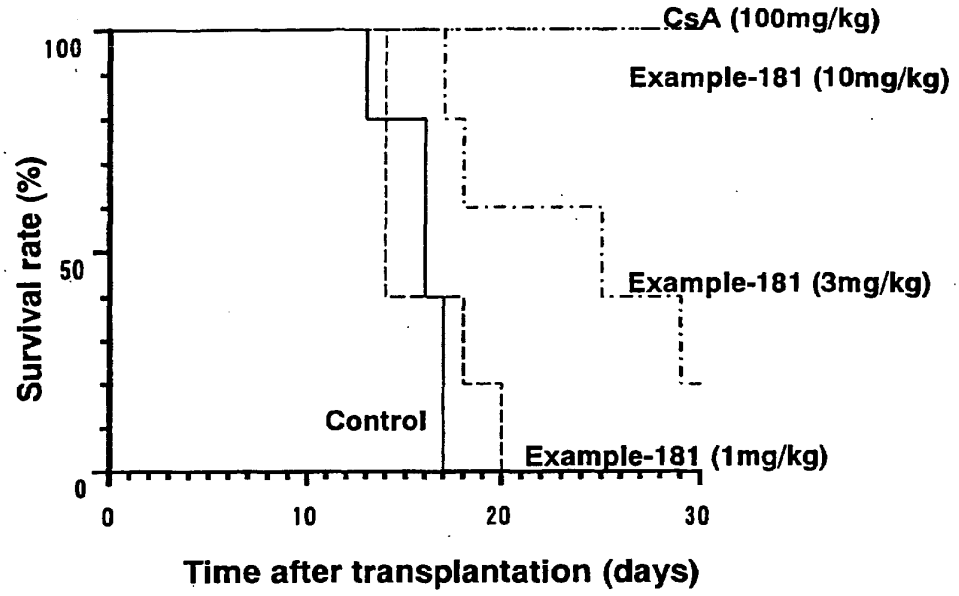


FIG.5

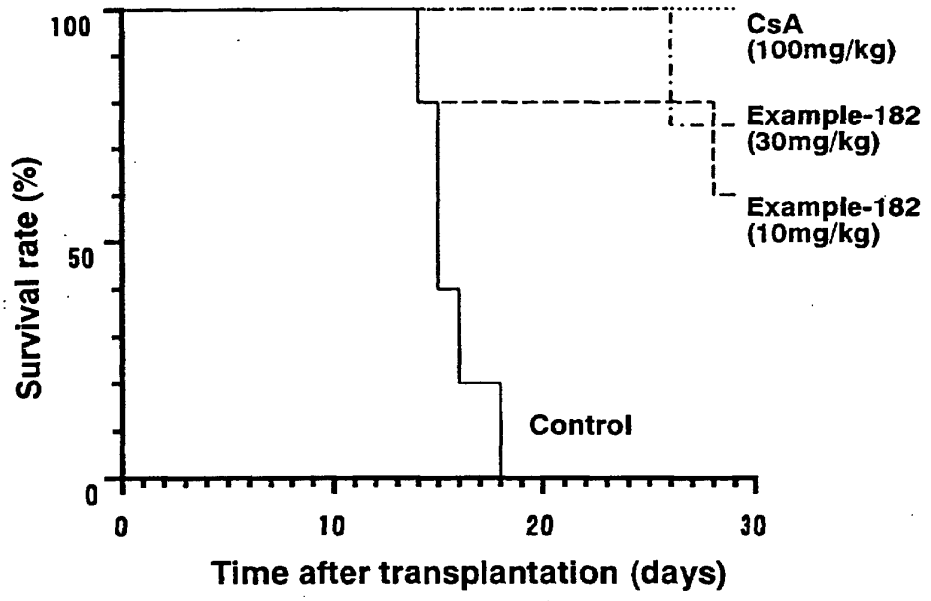


FIG.6

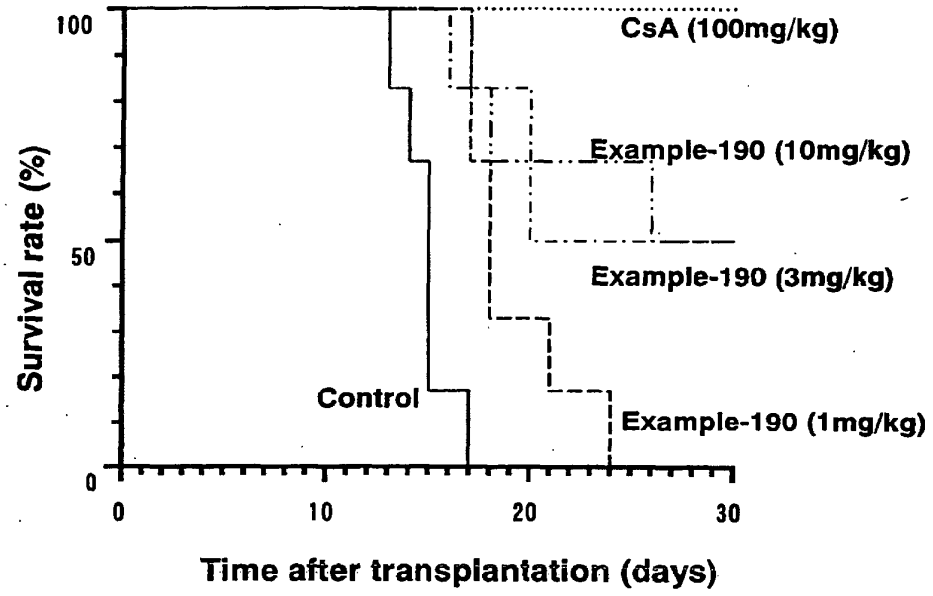


FIG.7

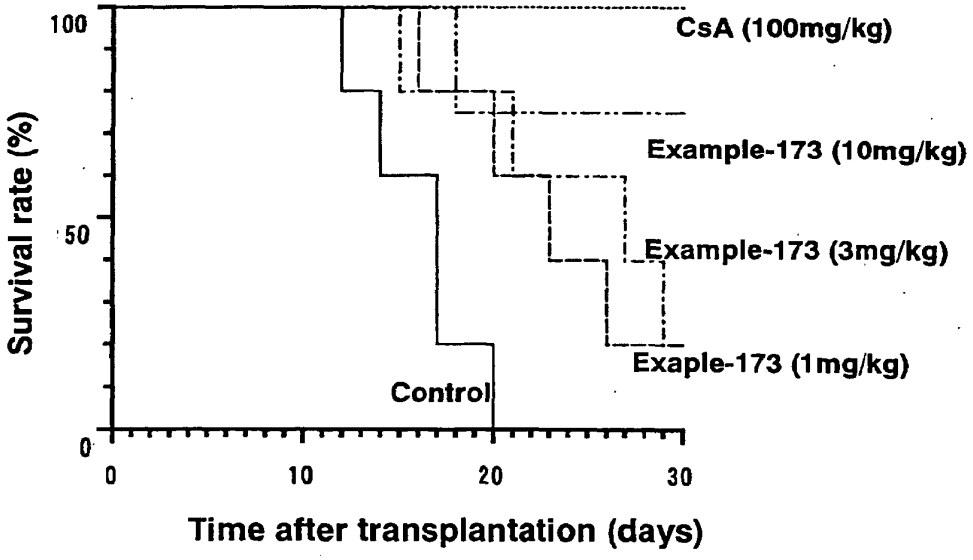


FIG.8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP02/09864

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[7] C07C217/34, 217/56, 217/64, 255/54, 317/22, 323/20,
C07D213/30, A61K31/137, 31/138, 31/277, 31/4409,
A61P11/02, 11/06, 17/00, 17/16, 27/14, 29/00, 37/06, 37/08
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[7] C07C217/34, 217/56, 217/64, 255/54, 317/22, 323/20,
C07D213/30, A61K31/137, 31/138, 31/277, 31/4409,
A61P11/02, 11/06, 17/00, 17/16, 27/14, 29/00, 37/06, 37/08

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAPLUS(STN), REGISTRY(STN), CAOLD(STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5604229 A (Yoshitomi Pharmaceutical Industries, Ltd.), 18 February, 1997 (18.02.97), Column 1, line 65 to column 3, line 50; column 67 & WO 94/08943 A1 & EP 627406 A1 & US 5719176 A & US 5952316 A & KR 155015 B1	1-20
A	EP 1002792 A1 (Yoshitomi Pharmaceutical Industries, Ltd.), 24 May, 2000 (24.05.00), Claims & WO 98/45249 A1 & AU 9865230 A & BR 9808481 A & NZ 500713 A & CN 1259117 A & US 6214873 B1 & MX 9909124 A1 & KR 2001006004 A	1-20

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
06 December, 2002 (06.12.02)	24 December, 2002 (24.12.02)
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer
Facsimile No.	Telephone No.

Form PCT/ISA/210 (second sheet) (July 1998)

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(86) International application number:
PCT/JP2002/009865

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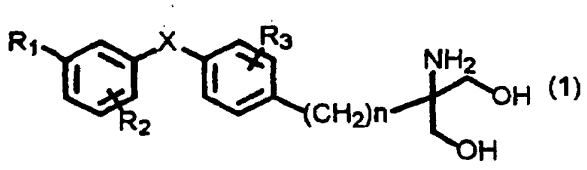
(54) DIARYL SULFIDE DERIVATIVE, ADDITION SALT THEREOF, AND IMMUNOSUPPRESSANT

(57) The present invention provides diaryl sulfide derivatives that exhibit significant immunosuppressive effects with less side effects.

The diaryl derivatives of the present invention are represented by the following general formula (1):



One example is 2-amino-2-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]propyl-1,3-propanediol.

EP 1 431 284 A1

Printed by Jouve, 75001 PARIS (FR)

Description

TECHNICAL FIELD

[0001] The present invention relates to diaryl sulfide derivatives, salts and hydrates thereof that are useful as an immunosuppressive agent.

TECHNICAL BACKGROUND

[0002] Immunosuppressive agents are widely used as a treatment for autoimmune diseases such as rheumatoid arthritis, nephritis, osteoarthritis and systemic lupus erythematosus, chronic inflammatory diseases such as inflammatory bowel disease, and allergic diseases such as asthma and dermatitis. Progress in medicine has led to an increase in the number of tissue and organ transplantations performed each year. In such a situation of modern medicine, having as much control as possible over the rejection following transplantation is a key to successful transplantation. Immunosuppressive agents also play a significant role to this end.

[0003] Among immunosuppressors commonly used in organ transplantation are antimetabolites, such as azathioprine and mycophenolate mofetil, calcineurin inhibitors, such as cyclosporin A and tacrolimus, and corticosteroid, such as prednisolone. Despite their popularity, some of these drugs are not effective enough while others require continuous monitoring of the blood drug level to avoid renal failure and other serious side effects. Thus, none of conventional immunosuppressive agents are satisfactory in view of efficacy and potential side effects.

[0004] Multiple drug combined-therapy, in which different immunosuppressive drugs with different mechanisms of action are used, is becoming increasingly common with the aims of alleviating the side effects of the drugs and achieving sufficient immunosuppressive effects. Also, development of new types of immunosuppressive agents that have completely different mechanisms of action is sought.

[0005] In an effort to respond to such demands, the present inventors conducted a search for new types of immunosuppressive agents with main emphasis on 2-amino-1,3-propanediol derivatives.

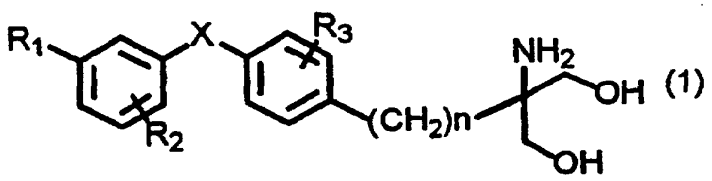
[0006] While the use of 2-amino-1,3-propanediol derivatives as immunosuppressive agents has been disclosed in PCT publication WO94/08943 (YOSHITOMI PHARMACEUTICAL INDUSTRIES, Ltd., TAITO Co., Ltd.) and in Japanese Patent Publication No. Hei 9-2579602 (YOSHITOMI PHARMACEUTICAL INDUSTRIES, Ltd., TAITO Co., Ltd.), it has not been previously known that 2-amino-1,3-propanediol derivatives having a diaryl sulfide group, which are subjects of the present invention, can serve as an effective immunosuppressor.

DISCLOSURE OF THE INVENTION

[0007] Accordingly, it is an objective of the present invention to provide a diaryl sulfide derivative that exhibits significant immunosuppressive effects with little side effects.

[0008] In the course of studies on immunosuppressive agents that have different mechanisms of action from antimetabolites and calcineurin inhibitors, the present inventors discovered that novel diaryl sulfide derivatives that have a different structure from conventional immunosuppressors exhibit strong immunosuppressive effects. Specifically, the compounds are such that one of the aryl groups includes, at its para-position, a carbon chain with an aminopropanediol group and the other aryl group includes a substituent at its meta-position. This discovery led the present inventors to devise the present invention.

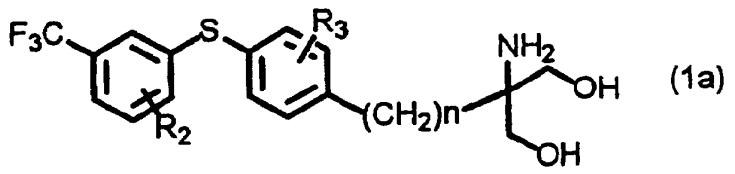
[0009] The present invention thus is an immunosuppressive agent containing as an active ingredient at least one of a diaryl sulfide derivative, a pharmaceutically acceptable salt and hydrate thereof, the diaryl sulfide derivative represented by the following general formula (1):



wherein R_1 is halogen, trihalomethyl, hydroxy, lower alkyl having 1 to 7 carbon atoms, substituted or unsubstituted

phenyl, aralkyl, lower alkoxy having 1 to 4 carbon atoms, trifluoromethyloxy, phenoxy, cyclohexylmethyloxy, substituted or unsubstituted aralkyloxy, pyridylmethyloxy, cinnamyloxy, naphthylmethyloxy, phenoxymethyl, hydroxymethyl, hydroxyethyl, lower alkylthio having 1 to 4 carbon atoms, lower alkylsulfinyl having 1 to 4 carbon atoms, lower alkylsulfonyl having 1 to 4 carbon atoms, benzylthio, acetyl, nitro, or cyano; R_2 is hydrogen, halogen, trihalomethyl, lower alkoxy having 1 to 4 carbon atoms, lower alkyl having 1 to 7 carbon atoms, phenethyl, or benzyloxy; R_3 is hydrogen, halogen, trifluoromethyl, lower alkoxyl having 1 to 4 carbon atoms, hydroxy, benzyloxy, lower alkyl having 1 to 7 carbon atoms, phenyl, or lower alkoxymethyl having 1 to 4 carbon atoms; X is S, SO, or SO_2; and n is an integer from 1 to 4.

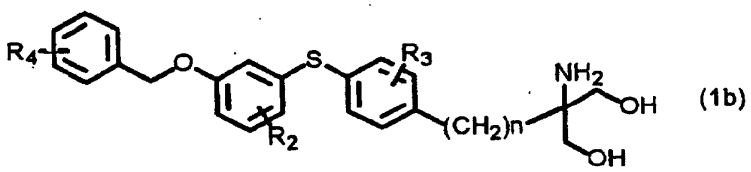
[0010] More specifically, the present invention is an immunosuppressive agent containing as an active ingredient at least one of a diaryl sulfide derivative, a pharmaceutically acceptable salt and hydrate thereof, the diaryl sulfide derivative represented by the following general formula (1a):



(1a)

wherein R_2, R_3, and n are the same as defined above.

[0011] Furthermore, the present invention is an immunosuppressive agent containing as an active ingredient at least one of a diaryl sulfide derivative, a pharmaceutically acceptable salt and hydrate thereof, the diaryl sulfide derivative represented by the following general formula (1b):



(1b)

wherein R_2, R_3, and n are the same as defined above; and R_4 is hydrogen, halogen, lower alkyl having 1 to 7 carbon atoms, lower alkoxy having 1 to 4 carbon atoms, or trifluoromethyl.

[0012] The compounds of the general formulae (1), (1a), and (1b) are each a novel compound.

[0013] Examples of the pharmaceutically acceptable salt of the compound of the general formula (1) include acid salts, such as hydrochloride, hydrobromide, acetate, trifluoroacetate, methanesulfonate, citrate, and tartrate.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014]

Fig. 1 is a graph showing activities of a test compound in a mouse skin graft model.
Fig. 2 is a graph showing activities of a test compound in a mouse skin graft model.
Fig. 3 is a graph showing activities of a test compound in a mouse skin graft model.

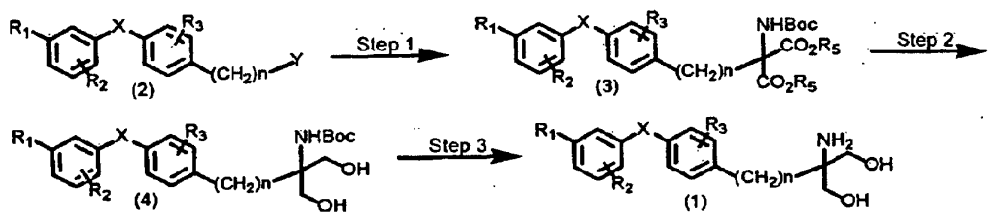
BEST MODE FOR CARRYING OUT THE INVENTION

[0015] With regard to the general formula (1), the term 'halogen atom' encompasses fluorine, chlorine, bromine, and iodine atom. The term 'trihalomethyl group' encompasses trifluoromethyl and trichloromethyl. The phrase 'lower alkyl group having 1 to 7 carbon atoms' encompasses straight-chained or branched hydrocarbons having 1 to 7 carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl, hexyl, and heptyl. The phrase 'substituted or unsubstituted phenoxy group' encompasses those that have, at any position of its benzene ring, a halogen atom, such as fluorine, chlorine, bromine and iodine, trifluoromethyl, lower alkyl having 1 to 4 carbon atoms, or lower alkoxy having

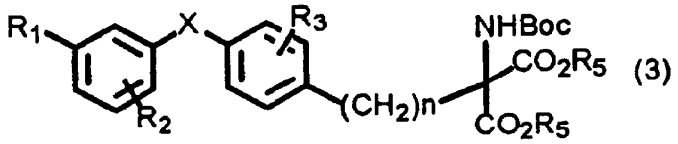
1 to 4 carbon atoms. The term 'aralkyl group' as in 'aralkyl group' or 'aralkyloxy group' encompasses benzyl, diphenylmethyl, phenethyl, and phenylpropyl. The term 'lower alkyl group' as used in 'lower alokoxy group having 1 to 4 carbon atoms,' 'lower alkylthio group having 1 to 4 carbon atoms,' 'lower alkylsulfinyl group having 1 to 4 carbon atoms,' or 'lower alkylsulfonyl group having 1 to 4 carbon atoms,' encompasses straight-chained or branched hydrocarbons having 1 to 4 carbon atoms, such as methyl, ethyl, propyl, isopropyl, and butyl. The phrase 'substituted or unsubstituted aralkyl group' encompasses those that have, at any position of its benzene ring, a halogen atom, such as fluorine, chlorine, bromine and iodine, trifluoromethyl, lower alkyl having 1 to 4 carbon atoms, or lower alkoxy having 1 to 4 carbon atoms.

[0016] According to the present invention, the compounds of the general formula (1) can be produced in the following pathways:

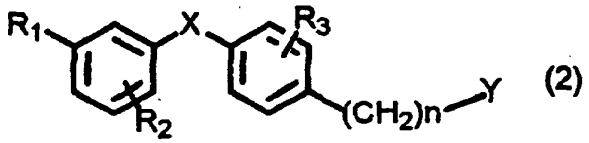
Synthetic Pathway 1



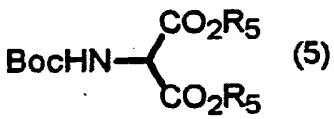
[0017] The compound involved in the synthetic pathway 1 that is represented by the following general formula (3):



(wherein R_5 is lower alkyl having 1 to 4 carbon atoms; Boc is *t*-butoxycarbonyl; and R_1, R_2, R_3, X and n are the same as described above) can be prepared by reacting a compound of the following general formula (2):



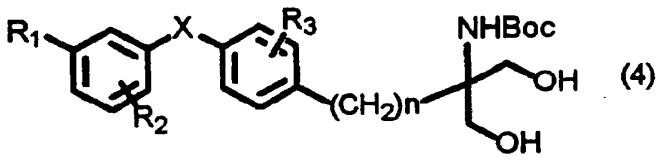
(wherein Y is chlorine, bromine, or iodine; and R_1, R_2, R_3, X and n are as described above) with a compound of the following general formula (5):



(wherein R_5 and Boc are as described above) in the presence of a base (Step 1).

[0018] This reaction can be carried out using a reaction solvent such as methanol, ethanol, 1,4-dioxane, dimethylsulfoxide (DMSO), N,N-dimethylformamide (DMF), or tetrahydrofuran (THF) at a reaction temperature of 0°C to reflux temperature, preferably at a temperature of 80°C to 100°C, in the presence of an inorganic base such as sodium hydride, potassium hydride, sodium alkoxide, and potassium alkoxide.

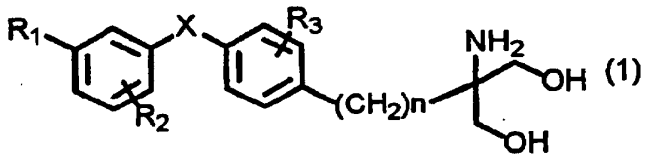
[0019] The compound involved in the synthetic pathway 1 that is represented by the following general formula (4):



(wherein R_1, R_2, R_3, X, Boc, and n are as described above) can be prepared by the reduction of the compound of the general formula (3) (Step 2).

[0020] This reaction can be carried out at a reaction temperature of 0°C to reflux temperature, preferably at room temperature, using an alkylborane derivative, such as borane (BH_3) and 9-borabicyclo[3.3.1]nonane (9-BBN), or a metal hydride complex, such as diisobutylaluminum hydride ((iBu)2AlH), sodium borohydride ($NaBH_4$) and lithium aluminum hydride ($LiAlH_4$), preferably lithium borohydride ($LiBH_4$), and using a reaction solvent such as THF, ethanol and methanol.

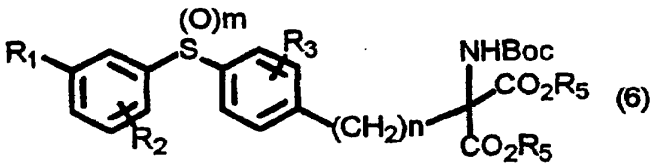
[0021] The compound involved in the synthetic pathway 1 that is represented by the general formula (1):



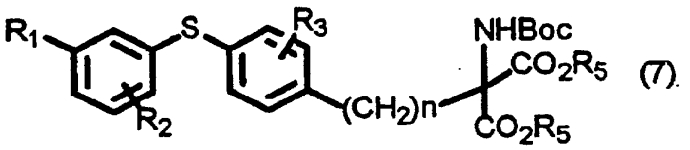
(wherein R_1, R_2, R_3, X and n are as described above) can be prepared by the acidolysis of the compound of the general formula (4) (Step 3).

[0022] This reaction can be carried out at a reaction temperature in the range of 0°C to room temperature in an inorganic or organic acid, such as acetic acid, hydrochloric acid, hydrobromic acid, methanesulfonic acid and trifluoroacetic acid, or in a mixed solvent with an organic solvent such as methanol, ethanol, THF, 1,4-dioxane, and ethyl acetate.

[0023] Of the compounds of the general formula (3), those in which X is either SO or SO_2, namely, those represented by the following general formula (6):



(wherein m is an integer of 1 or 2; and R_1, R_2, R_3, R_5, Boc, and n are as described above) may also be prepared by the oxidizing a compound represented by the following general formula (7):

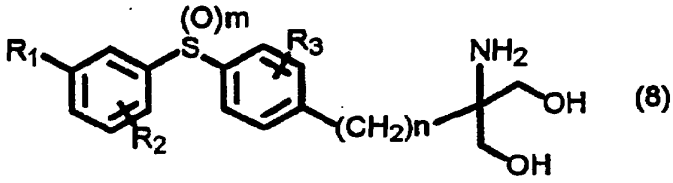


(7)

(wherein R_1, R_2, R_3, R_5, Boc, and n are as described above).

[0024] This reaction can be carried out using a reaction solvent, such as 1,4-dioxane, DMSO, DMF, THF, methylene chloride or chloroform, along with an oxidizing agent, such as potassium permanganate, m-chloroperbenzoic acid or aqueous hydrogen peroxide, at a reaction temperature of 0°C to reflux temperature, preferably at room temperature.

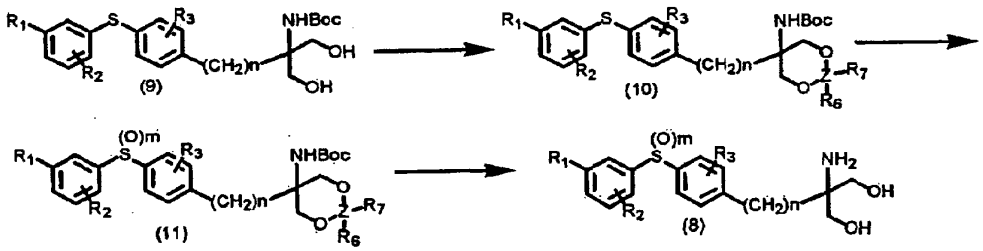
[0025] Of the compounds of the general formula (1), those in which X is either SO or SO_2, namely, those represented by the following general formula (8)):



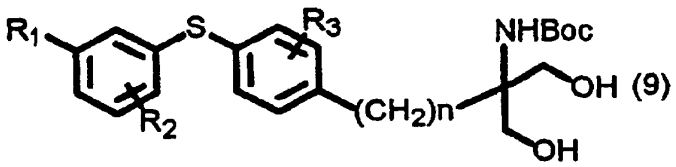
(8)

(wherein R_1, R_2, R_3, Boc, m, and n are as described above) may also be prepared by the following synthetic pathway:

Synthetic pathway 2

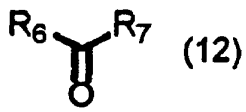


[0026] Specifically, a compound represented by the following general formula (9):



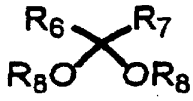
(9)

(wherein R_1, R_2, R_3, Boc, and n are as described above) can be reacted either with a compound represented by the following general formula (12):



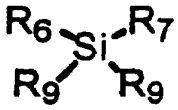
(12)

(wherein R_6 and R_7 each independently represent hydrogen or lower alkyl having 1 to 4 carbon atoms), or with a compound represented by the following general formula (13):



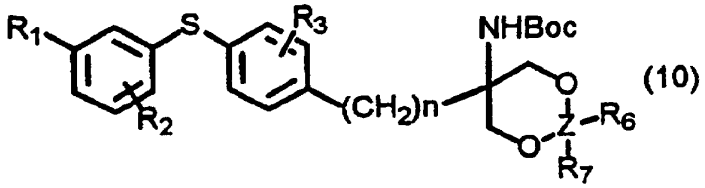
(13)

(wherein R_8 is lower alkyl having 1 to 4 carbon atoms; and R_6 and R_7 are as described above), or with a compound represented by the following general formula (14):



(14)

(wherein R_9 is chlorine or trifluoromethanesulfonyloxy; and R_6 and R_7 are as described above) to produce a compound represented by the following general formula (10):



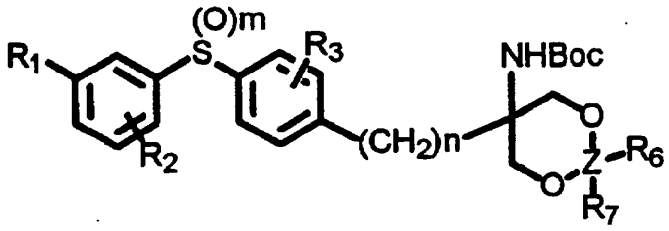
(10)

(whrein Z is carbon or silicon; and R_1, R_2, R_3, R_6, R_7, Boc, and n are as described above).

[0027] The reaction between the compound of the general formula (9) and the compound of the general formula (12) or the compound of the general formula (13) can be carried out at a reaction temperature in the range of room temperature to 100°C either in the presence of a Lewis acid such as zinc chloride or in the presence of an acid catalyst such as camphorsulfonic acid, paratoluenesulfonic acid, and pyridinium paratoluenesulfonic acid, and may be carried out either in the absence of solvent or in the presence of a reaction solvent such as DMF, THF, and methylene chloride.

[0028] The reaction between the compound of the general formula (9) and the compound of the general formula (14) can be carried out at a reaction temperature of 0°C to 100°C in the presence of a base, such as triethylamine, pyridine, 2,6-lutidine, and imidazole, and can be carried out using a reaction solvent such as DMF, THF, methylene chloride, chloroform, and acetonitrile.

[0029] The compound involved in the synthetic pathway 2 that is represented by the following general formula (11):



(11)

(wherein R_1, R_2, R_3, R_6, R_7, Z, Boc, m and n are as described above) can be prepared by the oxidizing the compound of the general formula (10).

[0030] This reaction can be carried out using a reaction solvent, such as 1,4-dioxane, DMSO, DMF, THF, methylene chloride or chloroform, along with an oxidizing agent, such as potassium permanganate, m-chloroperbenzoic acid or aqueous hydrogen peroxide, at a reaction temperature of 0°C to reflux temperature, preferably at room temperature.

[0031] The compound of the general formula (8) involved in the synthetic pathway 2 can be prepared by the acidolysis, or desilylation followed by acidolysis, of the compound of the general formula (11).

[0032] This reaction can be carried out at a reaction temperature of 0°C to room temperature in an inorganic or organic acid, such as acetic acid, hydrochloric acid, hydrobromic acid, methanesulfonic acid, trifluoroacetic acid, or in a mixed solution with an organic solvent, such as methanol, ethanol, THF, 1,4-dioxane, and ethyl acetate.

[0033] When Z in the general formula (11) is a silicon atom, the compound of the general formula (11) may also be synthesized by a reaction with potassium fluoride, cesium fluoride, or tetrabutylammonium fluoride, carried out at a temperature of 0°C to room temperature in a solvent such as THF, DMF, 1,4-dioxane, followed by the above-described acidolysis.

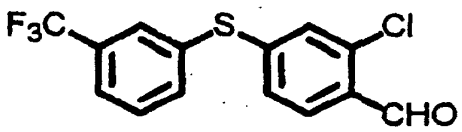
Examples

[0034] The present invention will now be described with reference to examples, which are provided by way of example only and are not intended to limit the scope of the invention in any way.

<Reference Example 1>

2-chloro-4-[(3-trifluoromethyl)phenylthio]benzaldehyde

[0035]

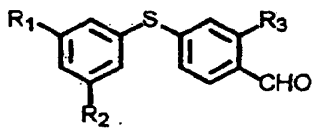


[0036] Potassium carbonate (2.76g) was added to a solution of 2-chloro-4-fluorobenzaldehyde (1.15g) and 3-(trifluoromethyl)thiophenol (1.33g) in DMF (20mL) and the mixture was stirred for 1 hour while heated to 120°C. The reaction mixture was poured into water and was extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 10:1). In this manner, the desired product (1.96g) was obtained as a pale yellow oil.

<Reference Examples 2 through 9>

[0037] Using various thiophenols and aldehydes, the compounds shown in Table 1 below were each synthesized in the same manner as described above.

Table 1

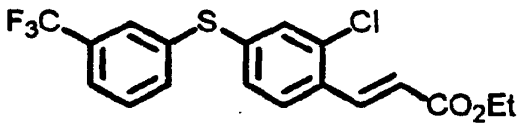


Reference Example	R1	R2	R3	Reference Example	R1	R2	R3
2	CF_3	H	H	6	MeO	H	H
3	CF_3	H	CF_3	7	MeO	H	Cl
4	CF_3	CF_3	H	8	MeO	H	CF_3
5	CF_3	CF_3	Cl	9	Cl	Cl	H

<Reference Example 10>

Ethyl 2'-chloro-4'-[(3-trifluoromethyl)phenylthio]cinnamate

[0038]

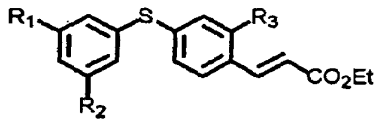


[0039] Under argon, 60% sodium hydride (272mg) was added to a solution of ethyl (diethylphosphono)acetate (1.35mL) in THF (30ml) at 0°C and the mixture was stirred for 30 minutes. A solution of the compound of Reference Example 1 (1.96g) in THF (15mL) was then added dropwise. With the temperature maintained, the mixture was further stirred for 2 hours, followed by addition of water and then extraction with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 10:1). In this manner, the desired product (1.72g) was obtained as a colorless oil.

<Reference Examples 11 through 18>

[0040] Using the compounds of Reference Examples 2 through 9, the compounds shown in Table 2 below were each synthesized in the same manner as described above.

Table 2

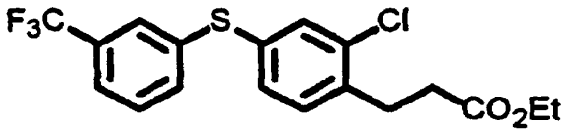


Reference Example	R1	R2	R3	Reference Example	R1	R2	R3
11	CF_3	H	H	15	MeO	H	H
12	CF_3	H	CF_3	16	MeO	H	Cl
13	CF_3	CF_3	H	17	MeO	H	CF_3
14	CF_3	CF_3	Cl	18	Cl	Cl	H

<Reference Example 19>

Ethyl 2'-chloro-4'-(3-trifluoromethylphenylthio)dihydrocinnamate

[0041]

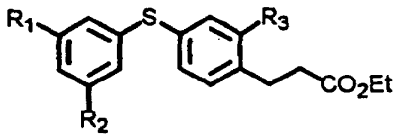


[0042] The compound of Reference Example 10 (1.72g) was dissolved in ethanol (70mL). Bismuth chloride (703mg) was then added to the solution while the solution was stirred at 0°C. To the resulting mixture, sodium borohydride (673mg) was added in small portions, and the mixture was stirred for 1 hour at the same temperature and subsequently for 3 hours at room temperature. Ice water was then added to the reaction mixture and the crystallized inorganic deposits were filtered out through celite. The filtrate was extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure. In this manner, the desired product (1.50g) was obtained as a colorless oil.

<Reference Examples 20 through 25>

[0043] Using the compounds of Reference Examples 11, 12, and 14 through 17, the compounds shown in Table 3 below were each synthesized in the same manner as described above.

Table 3

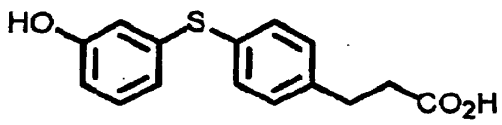


Reference Example	R1	R2	R3	Reference Example	R1	R2	R3
20	CF_3	H	H	23	MeO	H	H
21	CF_3	H	CF_3	24	MeO	H	Cl
22	CF_3	CF_3	Cl	25	MeO	H	CF_3

<Reference Example 26>

4'-(3-hydroxyphenylthio)dihydrocinnamic acid

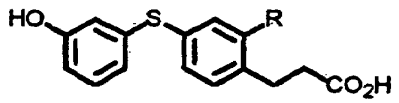
[0044]



[0045] Under argon, a 1mol/L solution of boron tribromide in methylene chloride (20mL) was added to a solution of the compound of Reference Example 23 (3.20g) in methylene chloride (50mL), and the mixture was stirred for 8 hours until room temperature. Water was then added to the mixture and the mixture was extracted with ethyl acetate. The organic phase was sequentially washed with water, a saturated aqueous solution of sodium bicarbonate, and a saturated aqueous solution of sodium chloride, and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 2:1). In this manner, the desired product (2.00g) was obtained as a colorless powder.

<Reference Examples 27 and 28>

[0046] Using the compounds of Reference Examples 24 and 25, the compounds shown below were each synthesized in the same manner as in Reference Example 26.

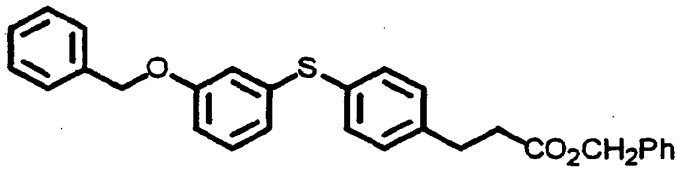


Reference Example	R	Reference Example	R
27	Cl	28	CF_3

<Reference Example 29>

Benzyl 4'-(3-benzyloxyphenylthio)dihydrocinnamate

[0047]

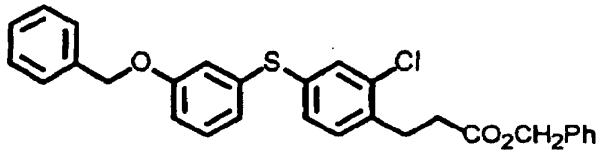


[0048] The compound of Reference Example 26 (2.00g) was dissolved in DMF (30mL), and benzyl bromide (2.4mL) and potassium carbonate (2.00g) were added to the solution. The mixture was stirred at 60°C for 2 hours. Water was then added to the mixture and the mixture was extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 5:1). In this manner, the desired product (2.29g) was obtained as a colorless oil.

<Reference Example 30>

Benzyl 4'-(3-benzyloxyphenylthio)-2'-chlorodihydrocinnamate

[0049]

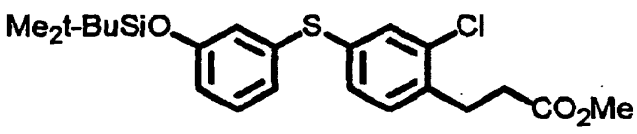


[0050] Using the compound of Reference Example 27, the reaction was carried out in the same manner as in Reference Example 29 to obtain the desired product as a yellow oil.

<Reference Example 31>

Methyl 4'-[(3-*t*-butyldimethylsiloxy)phenylthio]-2'-chlorodihydrocinnamate

[0051]



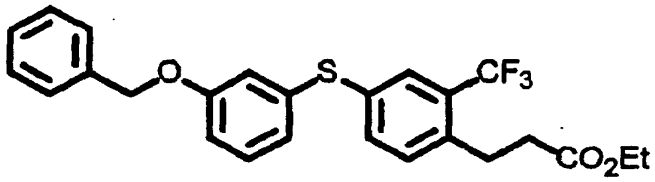
[0052] To a methanol solution (70mL) of the compound of Reference Example 27 (6.20g), thionyl chloride (2.2mL) was added dropwise and the mixture was refluxed for 1 hour. The solvent was removed by distillation under reduced pressure to obtain a methyl ester as a colorless oil (5.80g). The resulting ester (5.80g) was dissolved in DMF (80mL)

to form a solution. To this solution, imidazole (1.57g) and *t*-butyldimethylchlorosilane (3.47g) were added at 0°C and the mixture was stirred for 7 hours until room temperature was reached. Subsequently, water was added to the mixture and the mixture was extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 5:1). In this manner, the desired product (7.26g) was obtained as a colorless oil.

<Reference Example 32>

Ethyl 4'-(3-benzyloxyphenylthio)-2'-trifluoromethyldihydrocinnamate

[0053]

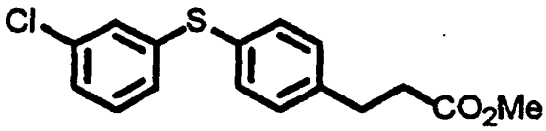


[0054] Using ethanol, the compound of Reference Example 28 was subjected to the same process as that of Reference Example 31 to synthesize an ethyl ester, which in turn was subjected to the same process as that of Reference Example 29 to obtain a pale yellow oil.

<Reference Example 33>

Ethyl 4'-(3-chlorophenylthio)dihydrocinnamate

[0055]

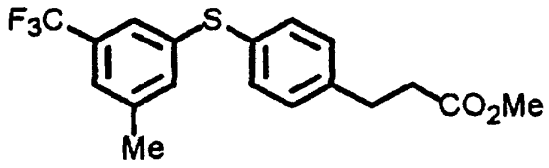


[0056] Under argon, the compound of Reference Example 18 (3.60g) was dissolved in methanol (50mL). Magnesium (500mg) was then added to the solution while the solution was stirred at 10°C. The solution was stirred for another 1 hour at this temperature, followed by addition of magnesium (250mg) and further stirring for 3 hours. Subsequently, diluted hydrochloric acid was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure to obtain the desired product (3.13g) as a pale yellow oil.

<Reference Example 34>

Methyl 4'-(3-trifluoromethyl-5-methylphenylthio)dihydrocinnamate

[0057]

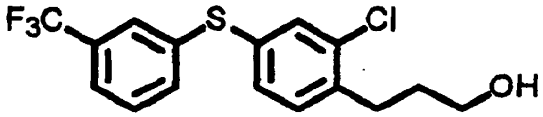


[0058] Using the compound of Reference Example 13, the reaction was carried out in the same manner as in Reference Example 33 to obtain the desired product as a colorless oil.

<Reference Example 35>

2'-chloro-4'-(3-trifluoromethylphenylthio)dihydrocinnamyl alcohol

[0059]

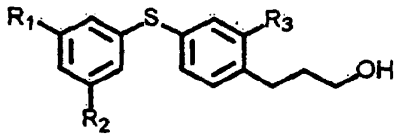


[0060] The compound of Reference Example 19 (1.50g) was dissolved in THF (30mL). Lithium aluminum hydride (200mg) was then added to the solution while the solution was stirred at 0°C. After 30 minutes, a 20% NaOH solution was added and the crystallized inorganic deposits were removed by filtration through celite. The filtrate was extracted with ethyl acetate and the organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure to obtain the desired product (1.38g) as a colorless oil.

<Reference Examples 36 through 45>

[0061] Using the compounds of Reference Examples 20 through 22, 24, and 29 through 34, the reactions were carried out in the same manner as in Reference Example 35 to synthesize the compounds shown in Table 4 below.

Table 4

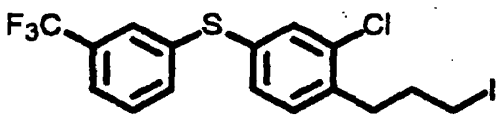


Reference Example	R1	R2	R3	Reference Example	R1	R2	R3
36	CF_3	H	H	41	$PhCH_2O$	H	H
37	CF_3	H	CF_3	42	$PhCH_2O$	H	Cl
38	CF_3	CF_3	Cl	43	$PhCH_2O$	H	CF_3
39	CF_3	Me	H	44	t-$BuMe_2SiO$	H	Cl
40	MeO	H	Cl	45	Cl	H	H

<Reference Example 46>

2'-chloro-4'-(3-trifluoromethylphenylthio)dihydrocinnamyl iodide

[0062]

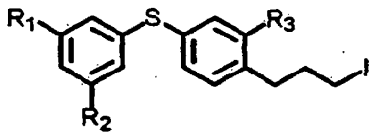


[0063] The compound of Reference Example 35 (1.38g) was dissolved in THF (20mL). Imidazole (545mg), triphenylphosphine (2.10g) and iodine (2.00g) were added to the solution while the solution was stirred at 0°C. The reaction mixture was further stirred for 2 hours at this temperature and another 1.5 hours at room temperature, followed by the addition of imidazole (160mg), triphenylphosphine (600mg) and iodine (500mg). The mixture was subsequently stirred overnight. Water and then sodium thiosulfate were added to the reaction mixture, followed by extraction with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 50:1). In this manner, the desired product (1.55g) was obtained as a colorless oil.

<Reference Examples 47 through 56>

[0064] Using the compounds of Reference Examples 36 through 45, the reactions were carried out in the same manner as in Reference Example 46 to synthesize the compounds shown in Table 5 below.

Table 5

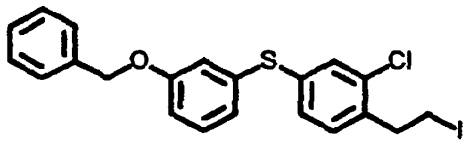


Reference Example	R1	R2	R3	Reference Example	R1	R2	R3
47	CF_3	H	H	52	$PhCH_2O$	H	H
48	CF_3	H	CF_3	53	$PhCH_2O$	H	Cl
49	CF_3	CF_3	Cl	54	$PhCH_2O$	H	CF_3
50	CF_3	Me	H	55	$t\text{-}BuMe_2SiO$	H	Cl
51	MeO	H	Cl	56	Cl	H	H

<Reference Example 57>

4'-(3-benzyloxyphenylthio)-2'-chlorophenethyl iodide

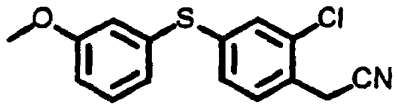
[0065]



<Reference Example 57-1>

2'-chloro-4'-(3-methoxyphenylthio)benzyl cyanide

[0066]

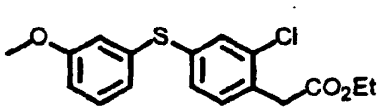


[0067] The compound of Reference Example 7 was treated in the same manner as in Reference Example 35 to obtain an alcohol. The alcohol (5.64g) was dissolved in methylene chloride (100mL) and phosphorus tribromide (2.25mL) was added dropwise. The mixture was stirred at room temperature for 1 hour, followed by addition of ice water and extraction with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation to obtain a pale yellow oil. The oil and potassium cyanide (1.56g) were dissolved in a mixed solvent of DMSO (25mL) and water (10mL) and the solution was stirred at 90°C for 5 hours. Water was then added to the mixture and the mixture was extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 10:1). In this manner, the desired cyanide form (3.81g) was obtained as a pale yellow oil.

<Reference Example 57-2>

Ethyl 2'-chloro-4'-(3-methoxyphenylthio)phenylacetate

[0068]

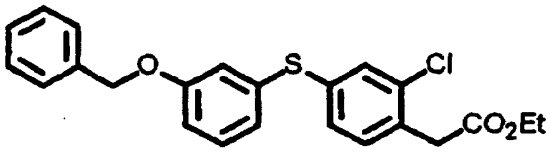


[0069] The above cyanide (3.81g) and potassium hydroxide (3.68g) were dissolved in a mixed solvent of ethanol (80mL) and water (10mL) and the solution was refluxed for 6 hours. The solution was then allowed to cool and the insoluble deposits were removed by filtration. The filtrate was neutralized with diluted hydrochloric acid and was extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation and ethanol (50mL) and thionyl chloride (2mL) were added to the resulting residue. The mixture was stirred at room temperature for 1 hour and the solvent was removed by distillation. The resulting residue was purified by silica gel column chromatography (hexane: ethyl acetate = 10:1). In this manner, the desired ethyl ester form (3.89g) was obtained as a colorless oil.

<Reference Example 57-3>

Ethyl 4'-(3-benzyloxyphenylthio)-2'-chlorophenyl acetate

[0070]



[0071] The desired ethyl ester was treated in the same manner as in Reference Example 26 and then in the same manner as in Reference Example 57-2 to form an ethyl ester, which in turn was subjected to the same process as that of Reference Example 29 to obtain a benzyl ether.

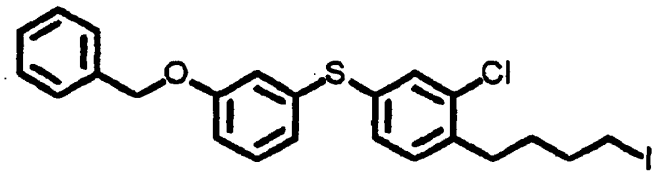
4'-(3-benzyloxyphenylthio)-2'-chlorophenethyl iodide

[0072] The compound of Reference Example 57-3 was used as the starting material and was subjected to the same process as that of Reference Example 35 to obtain 4'-(3-benzyloxyphenylthio)-2'-chlorophenethyl alcohol, which in turn was subjected to the same process as that of Reference Example 46 to obtain the desired product as a colorless oil.

<Reference Example 58>

1-(3-benzyloxyphenylthio)-3-chloro-4-iodobutyl benzene

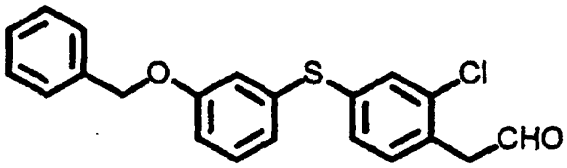
[0073]



<Reference Example 58-1>

4-(3-benzyloxyphenylthio)-2-chlorophenethylaldehyde

[0074]

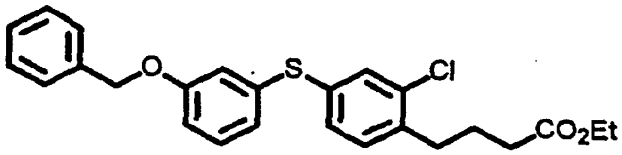


[0075] The compound of Reference Example 57-3 was subjected to alkaline hydrolysis and then to condensation with N,O-dimethylhydroxyamine to form an amid, which in turn was reduced in the same manner as in Reference Example 35 to obtain the aldehyde as a yellow oil.

<Reference Example 58-2>

Ethyl 4-[(3-benzyloxyphenylthio)-2-chlorophenyl]butyric acid

[0076]



[0077] The compound of Reference Example 58-1 was treated in the same manner as in Reference Example 10 and then in the same manner as in Reference Example 19 to obtain the desired ethyl butyrate derivative.

1-(3-benzyloxyphenylthio)-3-chloro-4-iodobutylbenzene

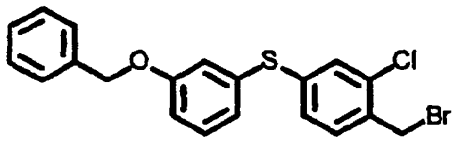
[0078] The compound of Reference Example 58-2 was used as the starting material and was subjected to the same

process as that of Reference Example 57 to obtain the desired product as a colorless oil.

<Reference Example 59>

4'-(3-benzyloxyphenylthio)-2'-chlorobenzyl bromide

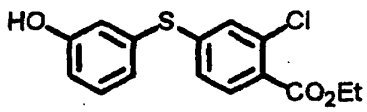
[0079]



<Reference Example 59-1>

Ethyl 2-chloro-4-(3-hydroxyphenylthio)benzoate

[0080]



[0081] 2-chloro-4-fluorobenzonitrile, in place of 2-chloro-4-fluorobenzaldehyde, was used in the same process as that of Reference Example 1 to obtain 2-chloro-4-(3-methoxyphenylthio)benzonitrile, which in turn was hydrolyzed in the same manner as in Reference Example 57-2. Then, in the same fashion as in Reference Example 26, methoxy group was removed from the reaction product and the product was subjected to esterification to obtain the desired product as a yellow oil.

<Reference Example 59-2>

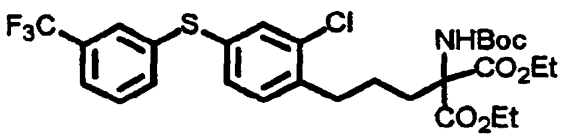
4'-(3-benzyloxyphenylthio)-2'-chlorobenzyl bromide

[0082] The compound of Reference Example 59-1 was subjected to the same process as that of Reference Example 29 to obtain a benzyl ether, which in turn was treated in the same manner as in Reference Example 35 to form an alcohol. Subsequently, using carbon tetrabromide in place of iodine, the reaction product was treated in the same manner as in Reference Example 46. In this manner, the desired product was obtained as a colorless oil.

<Example 1>

Ethyl 2-*t*-butoxycarbonylamino-5-[2-chloro-4-(3-trifluoromethylphenylthio)]phenyl-2-ethoxycarbonylpentanoate

[0083]



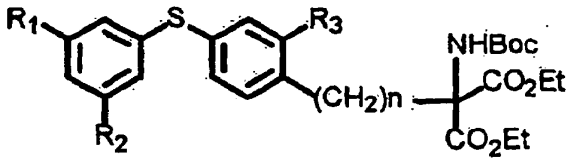
[0084] Under argon and at room temperature, sodium-*t*-butoxide (490mg) was added to diethyl 2-*t*-butoxycarbonylaminomalonate (1.3mL) dissolved in a mixed solvent of THF (35mL) and DMF (4mL). The mixture was then stirred at 80°C for 20 minutes and was allowed to cool to room temperature. A solution of the compound of Reference Example 46 (1.55g) in THF (5mL) was added to the mixture. Subsequently, the mixture was refluxed for 5 hours and was then poured into ice water. The resulting mixture was extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 5:1). In this manner, the desired product (1.87g) was obtained as a colorless oil.

^{1}H-NMR (400MHz, $CDCl_3$) δ 1.22-1.36(6H, m), 1.42(9H, s), 1.45-1.53(2H, m), 2.37(2H, br), 2.74(2H, t, J=7.8Hz), 4.23 (4H, m), 5.94(1H, s), 7.16-7.21(2H, m), 7.36-7.56(5H, m)

<Examples 2 through 13>

[0085] Using the compounds of Reference Examples 47 through 58, the reactions were carried out in the same manner as in Example 1 to synthesize the compounds shown in Table 6 below:

Table 6



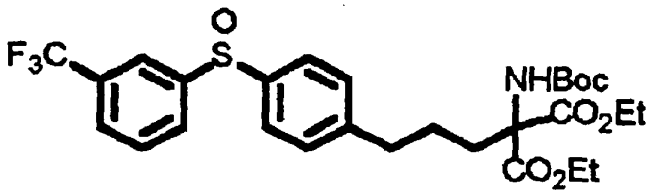
Example	R1	R2	R3	n	Yield (%)	Characteristics
2	CF_3	H	H	3	90	Colorless oil
3	CF_3	H	CF_3	3	53	Paleyellow oil
4	CF_3	CF_3	Cl	3	66	Colorless oil
5	CF_3	Me	H	3	100	Colorless oil
6	MeO	H	Cl	3	87	Colorless oil
7	$PhCH_2O$	H	H	3	-	Colorless oil
8	$PhCH_2O$	H	Cl	2	100	Paleyellow oil
9	$PhCH_2O$	H	Cl	3	100	Colorless oil
10	$PhCH_2O$	H	Cl	4	100	Colorless oil
11	$PhCH_2O$	H	CF_3	3	100	Colorless oil
12	t-$BuMe_2SiO$	H	Cl	3	-	Colorless oil
13	Cl	H	H	3	82	Colorless oil

The mark "-" means yield is shown in Table 7 as a total yield.

<Example 14>

Ethyl 2-*t*-butoxycarbonylamino-2-ethoxycarbonyl-5-[4-(3-trifluoromethylphenylsulfinyl)]phenylpentanoate

[0086]



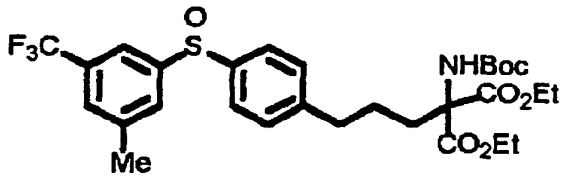
[0087] The compound of Example 2 (1.50g) was dissolved in methylene chloride (80mL) and, while the solution was stirred at 0°C, m-chloroperbenzoic acid (450mg) was added in small portions. The resulting mixture was stirred for 1 hour at the same temperature and then another 2 hours at room temperature, followed by the addition of water. The resulting mixture was extracted with ethyl acetate. The organic phase was sequentially washed with a saturated aqueous solution of sodium bicarbonate and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 1:1). In this manner, the desired product (1.10g) was obtained as a colorless oil.

^{1}H-NMR(400MHz, $CDCl_3$) δ 1.18-1.21(6H, m), 1.40(9H, s), 1.44-1.52(2H, m), 2.30(2H, br), 2.66(2H, t, J=7.3Hz), 4.14-4.22(4H, m), 5.91(1H, br), 7.27(2H, d, J=8.3Hz), 7.56(2H, d, J=8.3Hz), 7.59(1H, t, J=8.3Hz), 7.69(1H, d, J=8.3Hz), 7.78(1H, d, J=8.3Hz), 7.95(1H, s)

<Example 15>

Ethyl 2-*t*-butoxycarbonylamino-5-[4-(3-trifluoromethyl-5-methylphenylsulfinyl)]phenyl-2-ethoxycarbonylpentanoate

[0088]



[0089] Using the compound of Example 5, the reaction was carried out in the same manner as in Example 14 to obtain the desired product as a colorless oil.

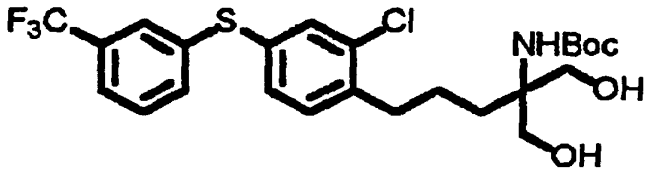
FABMS : 600 ([M+H]+)

^{1}H-NMR(400MHz, $CDCl_3$) δ 1.18-1.22(6H, m), 1.41(9H, s), 1.46-1.50(2H, m), 2.31(2H, br), 2.45(3H, s), 2.66(2H, t, J=7.3Hz), 4.14-4.22(4H, m), 5.92(1H, br s), 7.27(2H, d, J=7.8Hz), 7.48(1H, s), 7.55(2H, d, J=7.8Hz), 7.62(1H, s), 7.70 (1H, s)

<Example 16>

2-*t*-butoxycarbonylamino-2-[2-chloro-4-(3-trifluoromethylphenylthio)phenyl]propyl-1,3-propanediol

[0090]

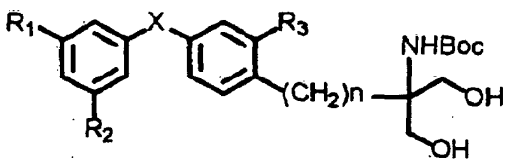


[0091] The compound of Example 1 (1.87g) was dissolved in THF (30mL) and lithium borohydride (675mg) was added to the solution while the solution was stirred at 0°C. Subsequently, ethanol (5mL) was added to the solution and the mixture was stirred overnight while allowed to gradually warm to room temperature. Ice water was then added to the reaction mixture and the organic solvent was removed by distillation under reduced pressure. 10% aqueous citric acid was added to the residue to adjust the pH to 3 and the mixture was extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 1:1) to obtain the desired product (1.10g) as a colorless oil.
FABMS : 520 ([M+H]+)
^{1}H-NMR(400MHz, $CDCl_3$) δ 1. 43 (9H, s), 1.62-1.65(4H, m), 2.72(2H,br), 3.31(2.H, br), 3.57-3.62(2H, m), 3.81-3.85 (2H, m), 4.93(1H, s), 7.20-7.27(3H, m), 7.38-7.55(4H, m)

<Examples 17 through 30>

[0092] Using the compounds of Examples 2 through 15, the reactions were carried out in the same manner as in Example 16 to synthesize the compounds shown in Table 7 below.

Table 7



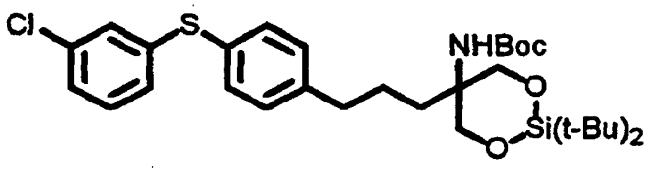
Example	R1	R2	R3	X	n	Yield(%)	Characteristics
17	CF_3	H	H	S	3	89	Colorless powder
18	CF_3	H	H	SO	3	71	Colorless amorphous
19	CF_3	H	CF_3	S	3	51	Colorless oil
20	CF_3	CF_3	Cl	S	3	66	Colorless amorphous
21	CF_3	Me	H	S	3	81	Colorless powder
22	CF_3	Me	H	SO	3	65	Colorless powder
23	MeO	H	Cl	S	3	56	Colorless oil
24	$PhCH_2O$	H	H	S	3	(45)	Colorless oil
25	$PhCH_2O$	H	Cl	S	2	41	Colorless oil
26	$PhCH_2O$	H	Cl	S	3	65	Colorless oil
27	$PhCH_2O$	H	Cl	S	4	76	Colorless oil
28	$PhCH_2O$	H	CF_3	S	3	66	Colorless oil
29	t-$BuMe_2SiO$	H	Cl	S	3	(33)	Colorless oil
30	Cl	H	H	S	3	41	Colorless oil

In the parentheses, shown is the total yield of the two steps.

<Example 31>

5-*t*-butoxycarbonylamino-2,2-di-*t*-butyl-5-[(3-chlorophenylthio)phenyl]propyl-1,3,2-dioxasilane

[0093]

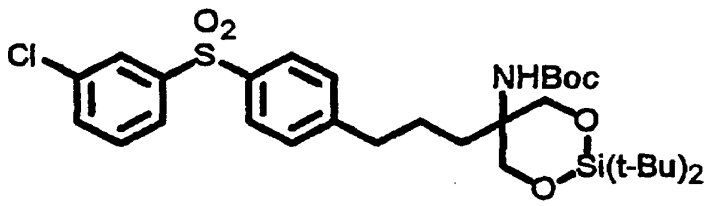


[0094] At 0°C, di-*t*-butylsilyl bis(trifluoromethanesulfonate) (0.55mL) was added to a DMF solution (15mL) containing the compound of Example 30 (490mg) and 2,6-lutidine (0.35mL). The mixture was stirred for 5 hours until room temperature and was poured into ice water. The mixture was then extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 8:1) to obtain the desired product (630mg) as a colorless powder. ^{1}H-NMR(400MHz, $CDCl_3$) δ 1.05(9H, s), 1.06(9H, s), 1.43(9H, s),1.57-1.62(4H, m), 2.58(2H, br), 3.89(2H, d, J=10.7Hz), 4.22(2H, d, J=10.7Hz), 4.92(1H, br s), 7.09-7.20(6H, m), 7.34(2H, d, J=8.3Hz)

<Example 32>

5-*t*-butoxycarbonylamino-2,2-di-*t*-butyl-5-[(3-chlorophenylsulfonyl)phenyl]propyl-1,3,2-dioxasilane

[0095]



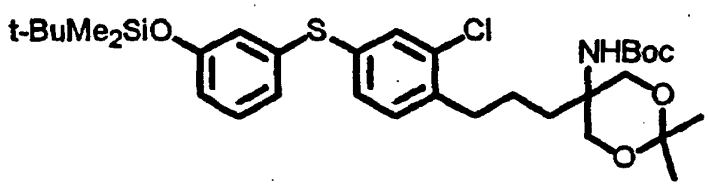
[0096] The compound of Example 31 was oxidized in the same manner as in Example 14 to obtain the desired product as a colorless powder.

^{1}H-NMR(400MHz, $CDCl_3$) δ 1.04(9H, s), 1.05(9H, s), 1.41(9H, s), 1.55-1.57(4H, m), 2.63(2H, br), 3.86(2H, d, J=11.2Hz), 4.19(2H, d, J=11.2Hz), 4.92(1H, br), 7.29(2H, d, J=8.3Hz), 7.44(1H, t, J=8.3Hz), 7.50-7.53(1H, m), 7.80-7.85(1H, m), 7.84(2H, d, J=8.3Hz), 7.91-7.92(1H, m)

<Example 33>

5-*t*-butoxycarbonylamino-5-[4-(3-*t*-butoxydimethylsiloxyphenylthio)-2-chlorophenyl]propyl-2,2-dimethyl-1,3-dioxane

[0097]

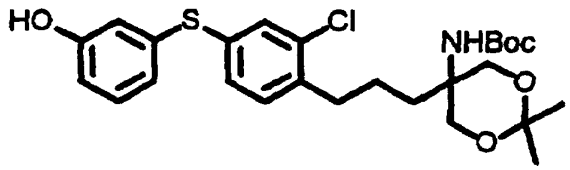


[0098] To a solution of the compound of Example 29 (1.88g) in DMF (30mL), 2,2-dimethoxypropane (2.5mL) along with p-toluenesulfonic acid (100mg) was added and the mixture was stirred for 5 hours while heated at 80°C. The reaction mixture was poured into water and was extracted with ethyl acetate. The organic phase was then sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 3:1) to obtain the desired product (1.11g) as a colorless powder.

<Example 34>

5-*t*-butoxycarbonylamino-5-[2-chloro-4-(3-hydroxyphenylthio)phenyl]propyl-2,2-dimethyl-1,3-dioxane

[0099]

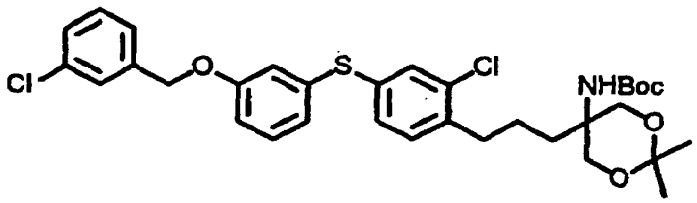


[0100] To a solution of the compound of Example 33 (1.10g) in THF (20mL), a 1mol/L solution of tetrabutylammonium fluoride in THF (5mL) was added. After 10 minutes, the reaction mixture was poured into water and was extracted with ethyl acetate.
The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure to obtain the desired product (900mg) as a colorless powder.
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.39(9H, s), 1.40(3H, s), 1.41(3H, s), 1.60(4H, br s), 2.78(2H, br s), 3.64(2H, d, J=11.7Hz), 3.83(2H, d, J=11.7Hz), 4.89(1H,br), 7.27(1H, br), 6.53(1H, br), 6.65(1H, d, J=6.9Hz), 6.85(1H, d,J=8.3Hz), 7.11-7.16 (2H, m), 7.26-7.28(1H, m), 7.45(1H, br s)

<Example 35>

5-*t*-butoxycarbonylamino-5-[2-chloro-4-(3-(3-chlorobenzyloxy)phenylthio)phenyl]propyl-2,2-dimethyl-1,3-dioxane

[0101]

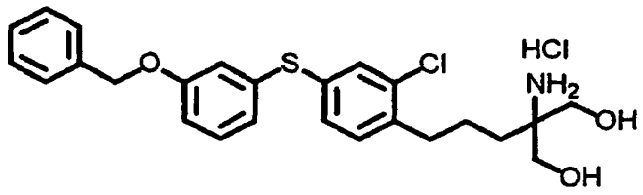


[0102] To a solution of the compound of Example 34 (500mg) in DMF (10mL), potassium carbonate (500mg) and m-chlorobenzyl bromide (0.16mL) were added and the mixture was stirred at 70°C for 1 hour. The reaction mixture was then poured into water and was extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 3:1) to obtain the desired product (520mg) as a colorless powder.
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.41(3H, s), 1.42(12H, s), 1.53-1.56(2H, m), 1.76(2H, br), 2.69(2H, t, J=7.8Hz), 3.65(2H, d, J=11.7Hz), 3.88(2H, d, J=11.7Hz), 4.88(1H, br), 4.99(2H, s), 6.86(1H, dd, J=8.3, 2.0Hz), 6.92-6.95(2H, m), 7.11-7.16 (2H, m), 7.21-7.32(5H, m), 7.40(1H, s)

<Example 36>

2-amino-2-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]propyl-1,3-propanediol hydrochloride

[0103]



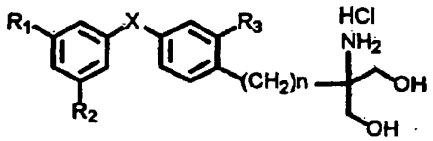
[0104] Ethyl acetate (100mL) containing 3mol/L hydrochloric acid was added to a methanol solution (150mL) of the compound of Example 26 (6.91g) and the mixture was stirred at room temperature for 1 hour. The solvent was removed by distillation under reduced pressure. A mixture of methylene chloride and hexane (methylene chloride:hexane = 1:5) was added to the residue and the resultant crystals were collected by filtration. After drying, the desired product (5.75g) was obtained as a colorless powder.
FABMS: 458([M+H]+)
^{1}H-NMR(400MHz, DMSO-d_6) δ 1.57(4H, br s), 2.64(2H, br s), 3.36-3.46(4H, m), 5.09(2H, s), 5.31(2H, t, J=4.9Hz), 6.89(1H, d, J=8.3Hz), 6.95(1H, t, J=2.0Hz), 6.99(1H, dd, J=8.3Hz, 2.0Hz), 7.23(1H, dd, J=7.8Hz, 2.0Hz), 7.29(8H, m), 7.70(3H, br s) Melting point = 132-133°C (EtOH-iPr_2O)

Elemental analysis (%): $C_{25}H_{28}ClNO_3S$·HCl			
	C	H	N
Calcd.	60.72	5.91	2.83
Found	60.71	5.85	2.91

<Examples 37 through 45>

[0105] Using the compounds of Examples 16 through 24, the reactions were carried out in the same manner as in Example 36 to synthesize the compounds shown in Table 8 below.

Table 8

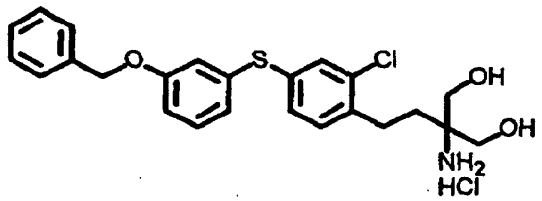


Example	R1	R2	R3	X	n	Yield(%)	Characteristics	FABMS $[M+H]^+$	Melting point °C
37	CF_3	H	H	S	3	94	Colorless powder	386	140-143
38	CF_3	H	H	SO	3	97	Colorless amorphous	402	
39	CF_3	H	Cl	S	3	93	Colorless powder	420	194-197
40	CF_3	H	CF_3	S	3	83	Colorless powder	453	107-112
41	CF_3	CF_3	Cl	S	3	93	Colorless powder	488	159-162
42	CF_3	Me	H	S	3	86	Colorless powder	400	117-119
43	CF_3	Me	H	SO	3	88	Colorless amorphous	416	
44	MeO	H	Cl	S	3	90	Yellow powder	382	98-100
45	$PhCH_2O$	H	H	S	3	100	Colorless powder	424	97-100

<Example 46>

2-amino-2-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]ethyl-1,3-propanediol hydrochloride

[0106]



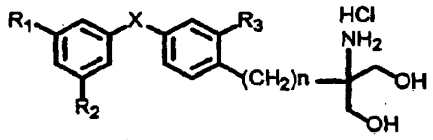
[0107] Using the compound of Example 25, the reaction was carried out in the same manner as in Example 36 to obtain the desired product.
^{1}H-NMR(400MHz, DMSO-d_6) δ 1.75-1.79(2H, m), 2.69-2.73(2H, m), 3.54(2H, s), 5.10(2H, s), 5.40(2H, t, J=4.0Hz), 6.91(1H, dd, J=8.3Hz, 1.8Hz), 6.96(1H, t, J=1.8Hz), 7.00(1H, dd, J=8.3Hz, 1.8Hz), 7.26(1H, dd, J=8.8Hz, 1.8Hz), 7.30-7.42(8H, m), 7.82(3H, br)
FABMS: 444([M+H]+) Melting point = 143-145°C (EtOH-iPr_2O)

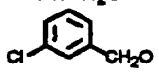
Elemental analysis (%): $C_{24}H_{26}ClNO_3S$·HCl			
	C	H	N
Calcd.	60.00	5.66	2.92
Found	59.88	5.61	2.97

<Examples 47 through 51>

[0108] Using the compounds of Examples 27, 28, 30, 32, and 35, the reactions were carried out in the same manner as in Example 36 to synthesize the compounds shown in Table 9 below.

Table 9



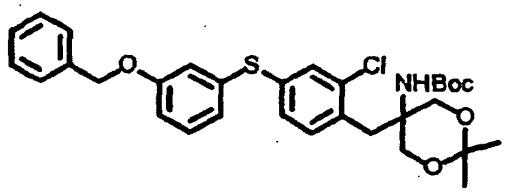
Example	R1	R2	R3	X	n	Yield(%)	Characteristics	FABMS $[M+H]^+$	Melting point °C
47	$PhCH_2O$	H	Cl	S	4	88	Colorless powder	472	91-93
48	$PhCH_2O$	H	CF_3	S	3	85	Colorless powder	492	86-98
49		H	Cl	S	3	100	Colorless powder	492	95-98
50	Cl	H	H	S	3	77	Colorless powder	352	122-125
51*	Cl	H	H	SO_2	3	97	Colorless powder	384	171-174

*Carried out after Bu_4NF treatment.

<Example 52>

5-*t*-butoxycarbonylamino-5-[2-chloro-4-(3-benzyloxyphenylthio)phenyl]methyl-2,2-dimethyl-1,3-dioxane

[0109]

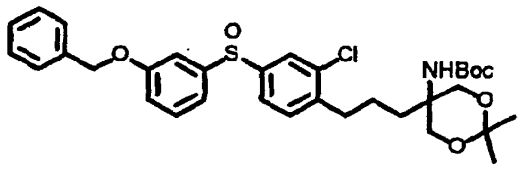


[0110] Using the compound of Reference Example 59, the reaction was carried out in the same manner as in Example 1 to synthesize an ester, which in turn was subjected to the same process as that of Reference Example 16 to be converted to a diol. Subsequently, the diol was treated in the same manner as in Example 35 to obtain the desired product as a yellow oil. ^{1}H-NMR(400MHz, $CDCl_3$) δ 1.43(6H, s), 1.46(9H, s), 3.23(2H, s), 3.83(2H, d, J=11.7Hz), 3.89 (2H, d, J=11.7Hz), 4.84(1H, br s), 5.03(2H, s), 6.91(1H, ddd, J=8.3Hz, 2.4Hz, 1.0Hz), 6.95-6.99(2H, m), 7.12(1H, dd, J=8.3Hz, 2.0Hz), 7.22-7.41(8H, m)

<Example 53>

5-*t*-butoxycarbonylamino-5-[2-chloro-4-(3-benzyloxyphenylsulfinyl)phenyl]propyl-2,2-dimethyl-1,3-dioxane

[0111]

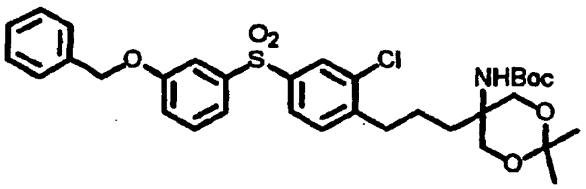


[0112] The compound of Example 26 was subjected to the reaction in the same manner as in Example 35 and was subsequently oxidized in the same fashion as in Example 14 to obtain the desired product as a colorless powder.
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.40(3H, s), 1.41(12H, s), 1.51-1.56(2H, m), 1.73-1.75(2H, m), 2.72(2H, t, J=7.8Hz), 3.64 (2H, d, J=11.7Hz), 3.85(2H, d, J=11.7Hz), 4.87(1H, br s), 5.09(2H, s), 7.05(1H, dd, J=8.3Hz, 2.9Hz), 7.19(1H, d, J=8.3Hz), 7.22-7.42(9H, m), 7.59(1H, d,J=2.9Hz)

<Example 54>

5-*t*-butoxycarbonylamino-5-[2-chloro-4-(3-benzyloxyphenylsulfonyl)phenyl]propyl-2,2-dimethyl-1,3-dioxane

[0113]

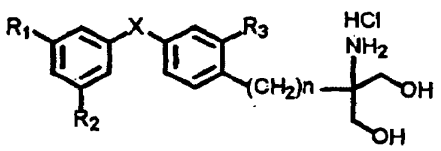


[0114] The compound of Example 53 was oxidized in the same manner as in Example 14 to obtain the desired product as a colorless powder.
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.40(3H, s), 1.41(12H, s), 1.53-1.60(2H, m), 1.73-1.75(2H, m), 2.74(2H, t, J=7.3Hz), 3.64 (2H, d, J=11.7Hz), 3.84(2H, d, J=11.7Hz), 4.87(1H, br s), 5.10(2H, s), 7.15(1H, dd, J=7.8Hz, 1.5Hz), 7.31-7.53(9H, m), 7.69(1H, dd, J =7.8Hz, 2Hz), 7.86(1H, d, J=1.5Hz)

<Examples 55 through 57>

[0115] Using the compounds of Examples 52 through 54, the reactions were carried out in the same manner as in Example 36 to synthesize the compounds shown in Table 10 below.

Table 10



Example	R1	R2	R3	X	n	Yield(%)	Characteristics	FABMS $[M+H]^+$	Melting point °C
55	$PhCH_2O$	H	Cl	S	1	86	Colorless powder	430	163-165
56	$PhCH_2O$	H	Cl	SO	3	85	Pale brown amorphous	474	
57	$PhCH_2O$	H	Cl	SO_2	3	96	Brown powder	490	60-62

[0116] The following experiments were conducted to prove the effectiveness of the compounds of the present invention.

<Experiment 1>

Ability of test compounds to suppress graft host vs rejection in mice

[0117] This experiment was performed according to the method described in *Transplantation,* 55, No.3 (1993): 578-591. Spleens were collected from 9 to 11 week old male BALB/c mice (CLEA JAPAN Inc., CHARLES RIVER JAPAN Inc., or JAPAN SLC Inc.). The spleens were placed in a phosphate-buffered saline (PBS(-), NISSUI PHARMACEUTICAL Co., Ltd.) or in an RPMI-1640 medium (GIBCO INDUSTRIES Inc., or IWAKI GLASS Co., Ltd.) and were either passed through a stainless steel mesh, or gently pressed between two slide glasses and then passed through a cell strainer (70μm, Falcon), to form a cell suspension. The suspension was then centrifuged and the supernatant was discarded. An ammonium chloride-Tris isotonic buffer was added to the suspension to lyse erythrocytes. The cells were then centrifuged and washed three times in PBS (-) or RPMI-1640 medium and were resuspended in an RPMI-1640 medium. To this suspension, mitomycin C (KYOWA HAKKO KOGYO Co., Ltd.) was added to a final concentration of 25μg/mL and the suspension was incubated for 30 minutes at 37°C in a 5% CO_2 atmosphere. The cells were again centrifuged and washed in PBS (-) or RPMI-1640 medium and were resuspended in an RPMI-1640 medium so that the medium would contain 2.5 X 10^8 cells/mL. This suspension served as a "stimulation cell suspension." Using a 27G needle along with a microsyringe (Hamilton), 20μL (5 X 10^6 cells/mouse) of the stimulation cell suspension was subcutaneously injected into the right hind footpad of 7 to 9 week old male C3H/HeN mice (CLEA JAPAN Inc., CHARLES RIVER JAPAN Inc., or JAPAN SLC Inc.). A group of mice was injected with RPMI-1640 medium alone to serve as normal control. 4 days after the injection, right popliteal lymph nodes were collected and were weighed on a Mettler AT201 electronic scale (METTLER TOLEDO Co., Ltd.). Each animal was intraperitoneally administered a test compound once a day for four consecutive days starting on the day of the injection of the stimulation cells (i.e., total of 4 times). Controls were administered a vehicle that has the same composition as that used in the preparation of the test compounds. The results are shown in Table 11 below:

Table 11

Example No.	Dose (mg/kg)	Inhibition (%)	Example No.	Dose (mg/kg)	Inhibition (%)
36	0.03	85	45	0.3	101
37	10	92	46	0.3	80
38	10	56	47	0.3	87
39	0.3	83	48	0.3	48
41	3	89	49	0.3	63
42	10	76	51	10	50
43	10	64			

<Experiment 2>

Ability of test compounds to suppress delayed-type hypersensitivity in mice.

[0118] This experiment was performed according to the method described in *Methods in Enzymology*, 300 (1999): 345-363. 1-fluoro-2,4-dinitrobenzene (DNFB, NACALAI TESQUE Inc.) was dissolved in a mixture of acetone and olive oil (acetone: olive oil = 4:1) to a concentration of 1% (v/v). 10μL of the 1% DNFB solution was applied to the footpad of each hind leg of male BALB/c mice (JAPAN SLC Inc. or CHARLES RIVER JAPAN Inc.) for sensitization. The sensitization was done for 2 consecutive days (day 0 and day 1). On day 5, the mice were challenged with the antigen to induce delayed-type hypersensitive responses: First, the initial thickness of each ear was measured by the dial thickness gauge G (0.01-10mm, OZAKI MFG Co., Ltd.) and a test compound was administered. 30 minutes after the administration, 10μL of a 0.2% (v/v) DNFB solution was applied to the inner and outer surfaces of the right ear of each animal for antigen challenge. The left ear of each animal was challenged with the solvent alone. 24 hours after the challenge, the increase in the ear thickness was measured for each ear and the difference in thickness between the right and the left ears was determined for each individual. The test compound was dissolved, or suspended, in an ultra pure water and was orally administered at a dose of 0.1mL/10g of body weight. A control group was administered ultra pure water alone. The results are shown in Table 12 below:

Table 12

Example No.	Dose **(mg/kg)**	Inhibition **(%)**
36	**1**	**86**
37	**30**	**87**
39	**3**	**55**
49	**30**	**81**

<Experiment 3>

Activities of test compounds on skin transplantation model in mice

[0119] Effects of the test compounds were examined on skin transplantation model in mice. The experimental procedure was referred to the method described in *Journal of Experimental Biology*, 28, No.3 (1951); 385-405.

[0120] First, dorsal skin from male DBA/2 mice were stripped of the fatty layer and the panniculus carnosus and, cut into circular grafts with a diameter of 8mm. Next, graft bed, a circular area, approximately 8mm in diameter, was prepared in the back of anesthetized male BALB/c mice with a scalpel while the skin was pinched by forceps. Each graft obtained from the DBA/2 mice was placed on the graft bed formed in the backs of the BALB/c mice and was secured with a strip of adhesive bandage while held down from the top. 6 days after transplantation, the bandage was removed and the graft was subsequently observed everyday. The activity of each compound was evaluated based on the length of the graft survival period, which is defined as the number of days for rejection. Each test compound was dissolved in ultra pure water and was orally administered once a day, starting from the day of transplantation. In a similar fashion, the control group was administered ultra pure water alone.

[0121] The results are shown in Figs. 1 through 3.

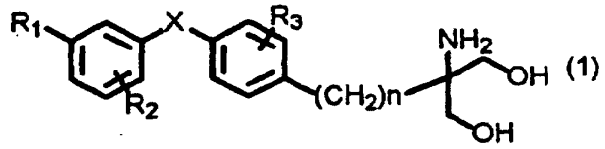
[0122] As can be seen from the results, the compounds of the present invention represented by the general formula (1) have proven effective in animal model.

INDUSTRIAL APPLICABILITY

[0123] As set forth, the present invention has been devised in recognition of the fact that the novel diaryl sulfide derivatives, in particular those in which one of the aryl groups includes, at its para-position, a carbon chain with an aminopropanediol group and the other of the aryl groups includes a substituent at its meta-position, exhibit strong immunosuppressive effects. Effective immunosuppressors, the compounds of the present invention have a strong potential as a prophylactic or therapeutic agent against rejection in organ or bone marrow transplantation, autoimmune diseases, rheumatoid arthritis, psoriasis, atopic dermatitis, bronchial asthma, pollinosis and various other diseases.

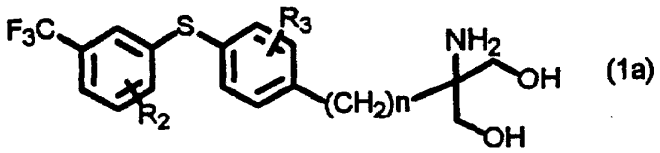
Claims

1. A diaryl sulfide derivative, a pharmaceutically acceptable salt or hydrate thereof, the diaryl sulfide derivative represented by the following general formula (1):



wherein R_1 is halogen, trihalomethyl, hydroxy, lower alkyl having 1 to 7 carbon atoms, phenyl, aralkyl, lower alkoxy having 1 to 4 carbon atoms, trifluoromethyloxy, substituted or unsubstituted phenoxy, cyclohexylmethyloxy, substituted or unsubstituted aralkyloxy, pyridylmethyloxy, cinnamyloxy, naphthylmethyloxy, phenoxymethyl, hydroxymethyl, hydroxyethyl, lower alkylthio having 1 to 4 carbon atoms, lower alkylsulfinyl having 1 to 4 carbon atoms, lower alkylsulfonyl having 1 to 4 carbon atoms, benzylthio, acetyl, nitro, or cyano; R_2 is hydrogen, halogen, trihalomethyl, lower alkoxy having 1 to 4 carbon atoms, lower alkyl having 1 to 7 carbon atoms, phenethyl, or benzyloxy; R_3 is hydrogen, halogen, trifluoromethyl, lower alkoxy having 1 to 4 carbon atoms, hydroxy, benzyloxy, lower alkyl having 1 to 7 carbon atoms, phenyl, or lower alkoxymethyl having 1 to 4 carbon atoms; X is S, SO, or SO_2; and n is an integer from 1 to 4).

2. The diaryl sulfide derivative, pharmaceutically acceptable salt and hydrate thereof according to claim 1, wherein the compound of the general formula (1) is a compound represented by the following general formula (1a):

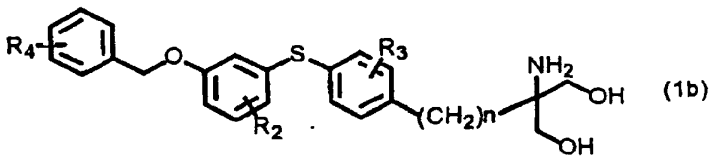


wherein R_2, R_3, and n are the same as defined above.

3. The diaryl sulfide derivative, pharmaceutically acceptable salt and hydrate thereof according to claim 2, wherein R_3 is chlorine.

4. The diaryl sulfide derivative, pharmaceutically acceptable salt and hydrate thereof according to claim 2, wherein R_3 is trifluoromethyl.

5. The diaryl sulfide derivative, pharmaceutically acceptable salt and hydrate thereof according to claim 1, wherein the compound of the general formula (1) is a compound represented by the following general formula (1b):



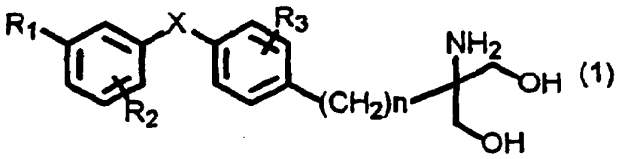
wherein R_2, R_3, and n are the same as defined above; and R_4 is hydrogen, halogen, lower alkyl having 1 to 7 carbon atoms, lower alkoxy having 1 to 4 carbon atoms, or trifluoromethyl.

6. The diaryl sulfide derivative, pharmaceutically acceptable salt and hydrate thereof according to claim 5, wherein R_3 is chlorine.

7. The diaryl sulfide derivative, pharmaceutically acceptable salt and hydrate thereof according to claim 5, wherein R_3 is trifluoromethyl.

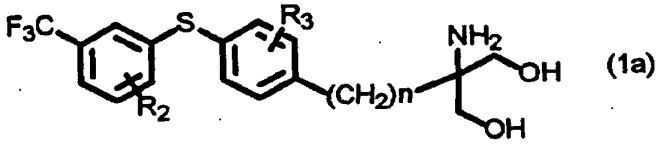
8. The diaryl ether derivative, pharmaceutically acceptable salt and hydrate thereof according to claim 1, wherein the compound of the general formula (1) is 1) 2-amino-2-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]propyl-1,3-propanediol;2)2-amino-2-[4-(3-benzyloxyphenylthio)phenyl]propyl-1,3-propanediol;3)2-amino-2-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]ethyl-1,3-propanediol; 4) 2-amino-2-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]butyl-1,3-propanediol; 5) 2-amino-2-[4-(3-(3'-chlorobenzyloxy)phenylthio)-2-chlorophenyl]propyl-1,3-propanediol; 6) 2-amino-2-[4-(3-benzyloxyphenylthio)-2-trifluoromethylphenyl]propyl-1,3-propanediol; 7) 2-amino-2-[4-(3,5-bis-trifluoromethyl-2-chlorophenylthio)phenyl]propyl-1,3-propanediol; 8) 2-amino-2-[4-(3-trifluoromethylphenylthio)phenyl]propyl-1,3-propanediol; 9) 2-amino-2-[2-chloro-4-(3-trifluoromethylphenylthio)phenyl]propyl-1,3-propanediol; or 10) 2-amino-2-[2-trifluoromethyl-4-(3-trifluoromethylphenylthio)phenyl]propyl-1,3-propanediol.

9. An immunosuppressive agent containing as an active ingredient at least one of a diaryl sulfide derivative, a pharmaceutically acceptable salt and a hydrate thereof, the diaryl sulfide derivative represented by the following general formula (1):



wherein R_1 is halogen, trihalomethyl, hydroxy, lower alkyl having 1 to 7 carbon atoms, substituted or unsubstituted phenyl, aralkyl, lower alkoxy having 1 to 4 carbon atoms, trifluoromethyloxy, phenoxy, cyclohexylmethyloxy, substituted or unsubstituted aralkyloxy, pyridylmethyloxy, cinnamyloxy, naphthylmethyloxy, phenoxymethyl, hydroxymethyl, hydroxyethyl, lower alkylthio having 1 to 4 carbon atoms, lower alkylsulfinyl having 1 to 4 carbon atoms, lower alkylsulfonyl having 1 to 4 carbon atoms, benzylthio, acetyl, nitro, or cyano; R_2 is hydrogen, halogen, trihalomethyl, lower alkoxy having 1 to 4 carbon atoms, lower alkyl having 1 to 7 carbon atoms, phenethyl, or benzyloxy; R_3 is hydrogen, halogen, trifluoromethyl, lower alkoxy having 1 to 4 carbon atoms, hydroxy, benzyloxy, lower alkyl having 1 to 7 carbon atoms, phenyl, or lower alkoxymethyl having 1 to 4 carbon atoms; and X is S, SO, or SO_2; and n is an integer from 1 to 4.

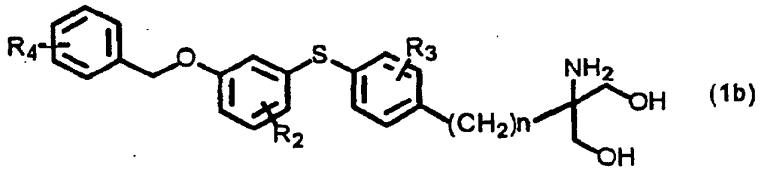
10. The immunosuppressive agent according to claim 9, containing as an active ingredient at least one of a diaryl sulfide derivative, a pharmaceutically acceptable salt and a hydrate thereof, wherein the compound of the general formula (1) is a compound represented by the following general formula (1a):



wherein R_2, R_3, and n are the same as defined above.

11. The immunosuppressive agent according to claim 9, containing as an active ingredient at least one of a diaryl sulfide derivative, a pharmaceutically acceptable salt and a hydrate thereof, wherein the compound of the general

formula (1) is a compound represented by the following general formula (1b):



(1b)

wherein R_2, R_3, and n are the same as defined above; and R_4 is hydrogen, halogen, lower alkyl having 1 to 7 carbon atoms, lower alkoxy having 1 to 4 carbon atoms, or trifluoromethyl.

12. The immunosuppressive agent according to any one of claims 9 to 11, serving as a prophylactic or therapeutic agent against autoimmune diseases.

13. The immunosuppressive agent according to any one of claims 9 to 11, serving as a prophylactic or therapeutic agent against rheumatoid arthritis.

14. The immunosuppressive agent according to any one of claims 9 to 11, serving as a prophylactic or therapeutic agent against psoriasis or atopic dermatitis.

15. The immunosuppressive agent according to any one of claims 9 to 11, serving as a prophylactic or therapeutic agent against bronchial asthma or pollinosis.

16. The immunosuppressive agent according to any one of claims 9 to 11, serving as a prophylactic or therapeutic agent against rejection in organ or bone marrow transplantation.

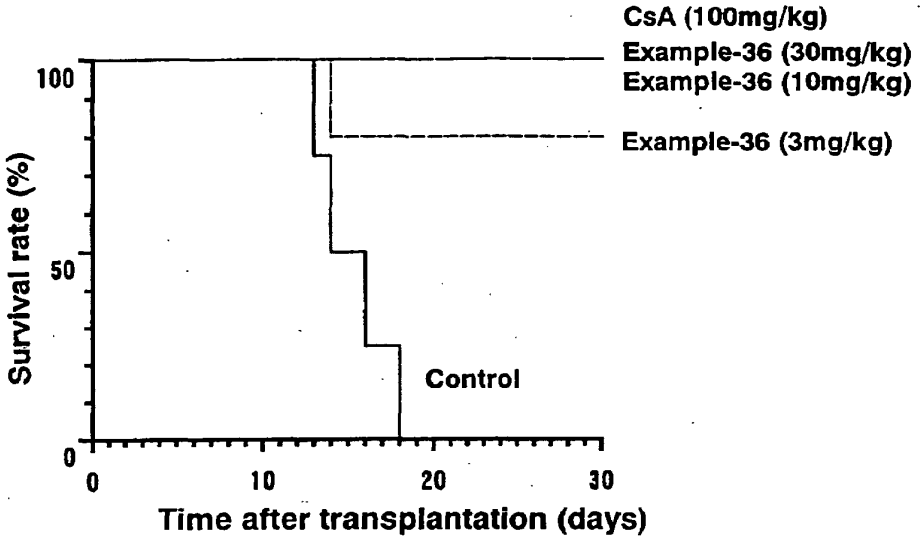


FIG.1

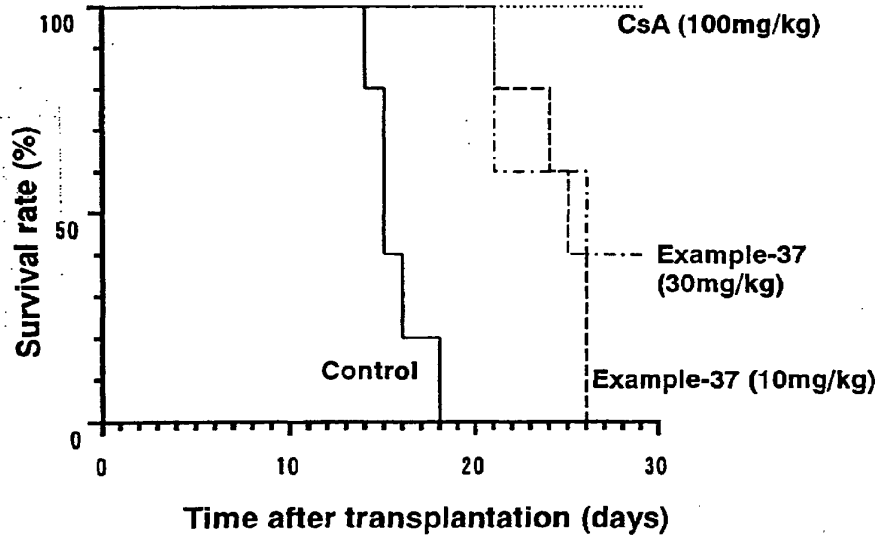


FIG.2

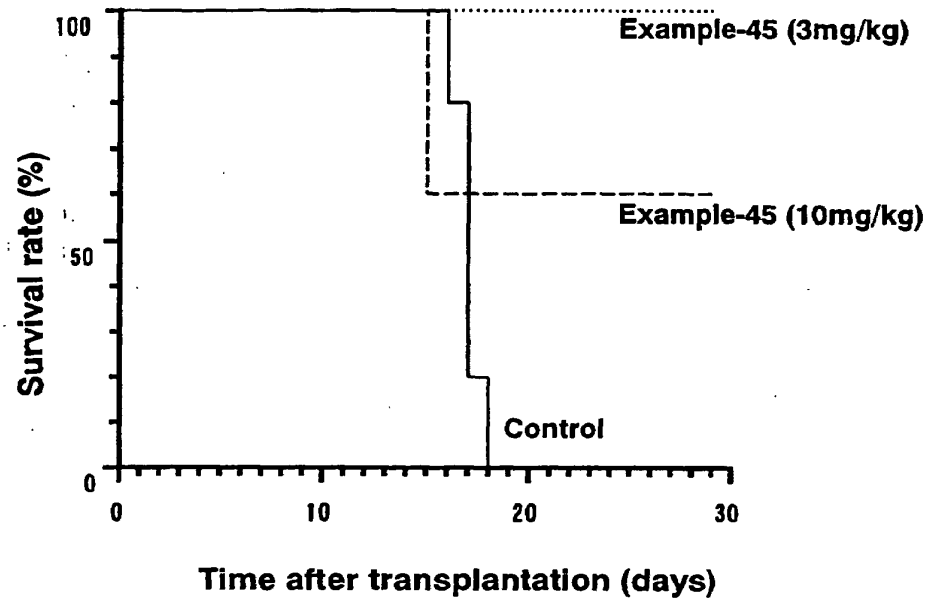


FIG.3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP02/09865

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[7] C07C317/32, 323/32, A61K31/145, A61P11/06, 17/00, 17/06, 29/00, 37/06, 37/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[7] C07C317/32, 323/32, A61K31/145, A61P11/06, 17/00, 17/06, 29/00, 37/06, 37/08

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAPLUS(STN), REGISTRY(STN), CAOLD(STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5604229 A (Yoshitomi Pharmaceutical Industries, Ltd.), 18 February, 1997 (18.02.97), Column 1, line 65 to column 3, line 50; column 67 & WO 94/08943 A1 & EP 627406 A1 & US 5719176 A & US 5952316 A & KR 155015 B1	1-16
A	EP 1002792 A1 (Yoshitomi Pharmaceutical Industries, Ltd.), 24 May, 2000 (24.05.00), Claims & WO 98/45249 A1 & AU 9865230 A & BR 9808481 A & NZ 500713 A & CN 1259117 A & US 6214873 B1 & MX 9909124 A1 & KR 2001006004 A	1-16

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
06 December, 2002 (06.12.02)	24 December, 2002 (24.12.02)
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer
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(51) Int. Cl.[5]: **C07C 215/10**, C07C 233/18, C07C 215/24, C07C 215/28, C07C 323/25, C07C 225/06, C07C 229/22, C07C 219/04, C07C 217/28, A61K 31/13, A61K 31/195

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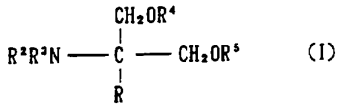
(54) **2-AMINO-1,3-PROPANEDIOL COMPOUND AND IMMUNOSUPPRESSANT.**

(57) A 2-amino-1,3-propanediol compound represented by general formula (I) or a pharmaceutically acceptable salt thereof, and an immunosuppressant containing the same as the active ingredient. In said formula R represents optionally substituted linear or branched carbon chain, optionally substituted aryl or optionally substituted cycloalkyl; and R^2, R^3, R^4 and R^5, which may be the same or different from one another, represent each hydrogen, alkyl, aralkyl, acyl or alkoxycarbonyl. The compound is immunodepressant and useful as an inhibitor against rejection in organ or bone marrow transplantation, as a preventive or remedy for autoimmune

EP 0 627 406 A1

diseases and so forth, or a reagent in the medical and pharmaceutical fields.



(I)

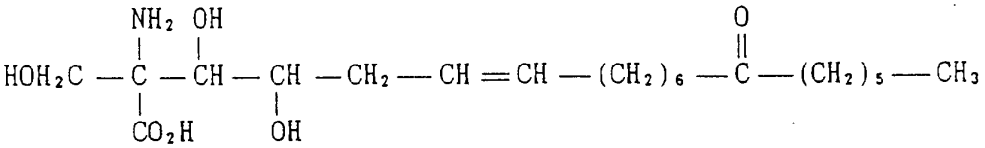
Technical Field

The present invention relates to 2-amino-1,3-propanediol compounds useful as pharmaceuticals, particularly as an immunosuppressant.

Background Art

In recent years, cyclosporin is in use for suppressing rejection developed in transplanting organs. Inclusive of the compounds currently under development, the so-called immunosuppressants are expected to be useful as therapeutic agents for articular rheumatism and so on. Said cyclosporin, however, also poses problems of side effects such as renal disorders.

Meanwhile, Japanese Patent Unexamined Publication No. 104087/1989 discloses that an immunosuppressive substance is obtained from a liquid culture of *Isaria sinclairii* and said substance has been confirmed to be (2S,3R,4R)-(E)-2-amino-3,4-dihydroxy-2-hydroxymethyl-14-oxoicosa-6-enoic acid of the formula



disclosed in US Patent No. 3928572. In addition, Japanese Patent Unexamined Publication No. 128347/1991 states that a series of said compound has an immunosuppressive action.

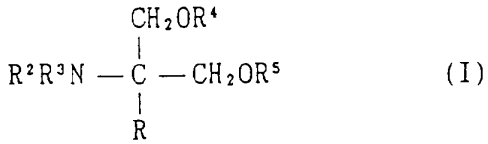
Referring to Merck Index, 11th edition, it is described that 2-amino-2-methyl-1,3-propanediol (Index No. 460), 2-amino-2-ethyl-1,3-propanediol (Index No. 451) and 2-amino-2-hydroxymethyl-1,3-propanediol (also called tromethamine, Index No. 9684) can be used as surfactants, intermediates for pharmaceuticals, emulsifiers or gas adsorbents and that tromethamine is medically usable as an alkalization agent. In Japanese Patent Unexamined Publication No. 416/1987, a hair dye containing 2-amino-2-(C1-C5 alkyl)-1,3-propanediol is disclosed. US Patent No. 4910218 and J. Med. Chem., vol. 33, 2385-2393 (1990) teach 2-amino-2-(methyl or ethyl)-1,3-propanediol as an intermediate for an antitumor agent. Also, Japanese Patent Unexamined Publication No. 192962/1984 teaches that the aforementioned 2-amino-2-(C1-C5 alkyl)-1,3-propanediol or 2-amino-1,3-propanediol can be used as a stabilizer for an antigen or antibody-sensitized latex reagent. Moreover, US Patent No. 3062839 teaches 2-methyl- or ethyl-amino-2-(furylmethyl, phenylmethyl or phenylmethyl substituted by lower alkyl, lower alkoxy, chloro, hydroxy or unsubstituted amine)-1,3-propanediol having a tranquilizer action and J. Org. Chem., vol. 25, 2057-2059 (1960) teaches 2-methylamino-2-(phenylmethyl or phenylmethyl substituted by 2-methyl, 3-methyl, 4-methyl, 4-methoxy or 4-hydroxy)-1,3-propanediol. It is not known, however, that these compounds have immunosuppressive actions such as suppression of rejection developed in organ transplantation, prevention and treatment of autoimmune diseases and the like.

An object of the present invention is to provide novel 2-amino-1,3-propanediol compounds having superior immunosuppressive action with less side effects.

Disclosure of the Invention

The present invention relates to

(1) a 2-amino-1,3-propanediol compound of the formula



(I)

wherein

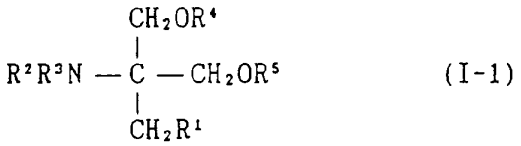
R is an optionally substituted straight- or branched carbon chain which may have, in the chain, a bond, a hetero atom or a group selected from the group consisting of a double bond, a triple bond, oxygen, sulfur, sulfinyl, sulfonyl, -N-(R^6)- where R^6 is hydrogen, alkyl, aralkyl, acyl or alkoxycarbonyl, carbonyl, optionally substituted arylene, optionally substituted cycloalkylene, optionally substituted heteroarylene and an alicycle thereof, and which may be substituted, at the chain end thereof, by a double bond, a triple bond, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted heteroaryl or an alicycle thereof; an optionally substituted aryl, an optionally substituted cycloalkyl, an optionally substituted heteroaryl or an alicycle thereof; and

R^2, R^3, R^4 and R^5 are the same or different and each is a hydrogen, an alkyl, an aralkyl, an acyl or an alkoxycarbonyl, or R^4 and R^5 may be bonded to form an alkylene chain which may be substituted by alkyl, aryl or aralkyl;

wherein the optionally substituted straight- or branched carbon chain may have a substituent selected from the group consisting of alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, alkylenedioxy, acyl, alkylamino, alkylthio, acylamino, alkoxycarbonyl, alkoxycarbonylamino, acyloxy, alkylcarbamoyl, haloalkyl, haloalkoxy, nitro, halogen, amino, hydroxyimino, hydroxy, carboxy, optionally substituted aryl, optionally substituted aryloxy, optionally substituted cycloalkyl, optionally substituted heteroaryl and an alicycle thereof; the aforementioned optionally substituted arylene, optionally substituted cycloalkylene, optionally substituted heteroarylene and an alicycle thereof may have a substituent selected from the group consisting of alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, alkylenedioxy, acyl, alkylamino, alkylthio, acylamino, alkoxycarbonyl, alkoxycarbonylamino, acyloxy, alkylcarbamoyl, haloalkyl, haloalkoxy, nitro, halogen, amino, hydroxy and carboxy; and the optionally substituted aryl, optionally substituted aryloxy, optionally substituted cycloalkyl, optionally substituted heteroaryl and an alicycle thereof may have a substituent selected from the group consisting of alkyl, alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, alkylenedioxy, acyl, alkylamino, alkylthio, acylamino, alkoxycarbonyl, alkoxycarbonylamino, acyloxy, alkylcarbamoyl, haloalkyl, haloalkoxy, nitro, halogen, amino, hydroxy and carboxy;

provided that when R is C1-C5 alkyl, the alkyl should be substituted and when R is furylmethyl, phenylmethyl or phenylmethyl substituted by lower alkyl, lower alkoxy, chloro, hydroxy or amino, one of R^2 and R^3 is not methyl or ethyl, and a pharmaceutically acceptable salt thereof;

(2) a 2-amino-1,3-propanediol compound according to the above-mentioned (1), having the formula



(I-1)

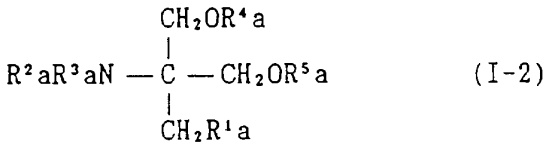
wherein

R^1 is an optionally substituted straight- or branched carbon chain which may have, in the chain, a bond, a hetero atom or a group selected from the group consisting of a double bond, a triple bond, oxygen, sulfur, sulfinyl, sulfonyl, -N-(R^6)- where R^6 is hydrogen, alkyl, aralkyl, acyl or alkoxycarbonyl, carbonyl, optionally substituted arylene, optionally substituted cycloalkylene, optionally substituted heteroarylene and an alicycle thereof; and which may be substituted, at the chain end (ω-position) thereof, by a double bond, a triple bond, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted heteroaryl or an alicycle thereof; an optionally substituted aryl, an optionally substituted cycloalkyl, an optionally substituted heteroaryl or an alicycle thereof; and

R^2, R^3, R^4 and R^5 are the same or different and each is a hydrogen, an alkyl, an aralkyl, an acyl or an alkoxycarbonyl, or R^4 and R^5 may be bonded to form an alkylene chain which may be substituted by alkyl, aryl or aralkyl;

wherein the optionally substituted straight- or branched carbon chain may have a substituent selected

from the group consisting of alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, alkylenedioxy, acyl, alkylamino, alkylthio, acylamino, alkoxycarbonyl, alkoxycarbonylamino, acyloxy, alkylcarbamoyl, haloalkyl, haloalkoxy, nitro, halogen, amino, hydroxyimino, hydroxy, carboxy, optionally substituted aryl, optionally substituted aryloxy, optionally substituted cycloalkyl, optionally substituted heteroaryl and an alicycle thereof; and the aforementioned optionally substituted arylene, optionally substituted cycloalkylene, optionally substituted heteroarylene, an alicycle thereof, optionally substituted aryl, optionally substituted aryloxy, optionally substituted cycloalkyl, optionally substituted heteroaryl and an alicycle thereof may have a substituent selected from the group consisting of alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, alkylenedioxy, acyl, alkylamino, alkylthio, acylamino, alkoxycarbonyl, alkoxycarbonylamino, acyloxy, alkylcarbamoyl, haloalkyl, haloalkoxy, nitro, halogen, amino, hydroxy and carboxy;
provided that when R^1 is C1-C4 alkyl, the alkyl should be substituted and when R^1 is furyl, phenyl or phenyl substituted by lower alkyl, lower alkoxy, chloro, hydroxy or amino, one of R^2 and R^3 is not methyl or ethyl, and a pharmaceutically acceptable salt thereof;
(3) a 2-amino-1,3-propanediol compound according to the above-mentioned (1) or (2), having the formula



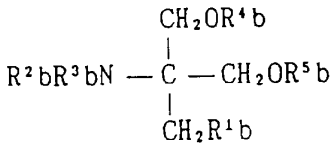
(I-2)

wherein

R^1a is an optionally substituted straight- or branched carbon chain which may have, in the chain, a bond, a hetero atom or a group selected from the group consisting of a double bond, a triple bond, oxygen, sulfur, sulfinyl, sulfonyl, $-N(R^6)-$ where R^6 is hydrogen, alkyl, aralkyl, acyl or alkoxycarbonyl, carbonyl, optionally substituted phenylene and optionally substituted cycloalkylene; an optionally substituted phenyl or an optionally substituted cycloalkyl; and

R^2a, R^3a, R^4a and R^5a are the same or different and each is a hydrogen, an alkyl, an acyl or an alkoxycarbonyl;

wherein the optionally substituted phenyl and optionally substituted cycloalkyl may have a substituent selected from the group consisting of optionally substituted straight- or branched carbon chain which may have, in the chain, a bond, a hetero atom or a group selected from the group consisting of a double bond, a triple bond, oxygen, sulfur, sulfinyl, sulfonyl, $-N(R^6)-$ where R^6 is hydrogen, alkyl, aralkyl, acyl or alkoxycarbonyl, carbonyl, optionally substituted phenylene and optionally substituted cycloalkylene; alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, alkylenedioxy, acyl, alkylamino, alkylthio, acylamino, alkoxycarbonyl, alkoxycarbonylamino, acyloxy, alkylcarbamoyl, haloalkyl, nitro, halogen, amino, hydroxy, carboxy, optionally substituted phenyl, optionally substituted phenoxy and optionally substituted cycloalkyl; the optionally substituted carbon chain may have a substituent selected from the group consisting of alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, alkylenedioxy, acyl, alkylamino, alkylthio, acylamino, alkoxycarbonyl, alkoxycarbonylamino, acyloxy, alkylcarbamoyl, haloalkyl, nitro, halogen, amino, hydroxy, carboxy, optionally substituted phenyl, optionally substituted phenoxy and optionally substituted cycloalkyl; and the aforementioned optionally substituted phenylene, optionally substituted cycloalkylene, optionally substituted phenyl, optionally substituted phenoxy and optionally substituted cycloalkyl may have a substituent selected from the group consisting of alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, alkylenedioxy, acyl, alkylamino, alkylthio, acylamino, alkoxycarbonyl, alkoxycarbonylamino, acyloxy, alkylcarbamoyl, haloalkyl, nitro, halogen, amino, hydroxy and carboxy; provided that when R^1a is C1-C4 alkyl, the alkyl should be substituted and when R^1a is furyl, phenyl or phenyl substituted by lower alkyl, lower alkoxy, chloro, hydroxy or amino, one of R^2a and R^3a is not methyl or ethyl, and a pharmaceutically acceptable salt thereof;
(4) a 2-amino-1,3-propanediol compound according to the above-mentioned (3), having the formula



(I-3)

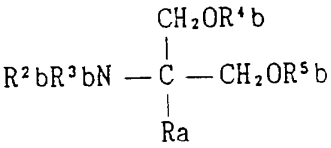
wherein

R^1b is an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted phenyl or an optionally substituted cycloalkyl, and

R^2b, R^3b, R^4b and R^5b are the same or different and each is a hydrogen, an alkyl or an acyl;

wherein the optionally substituted alkyl, optionally substituted alkenyl and optionally substituted alkynyl may have a substituent selected from the group consisting of alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, acyl, alkylamino, alkylthio, acylamino, alkoxycarbonyl, alkoxycarbonylamino, acyloxy, alkylcarbamoyl, nitro, halogen, amino, hydroxy, carboxy, optionally substituted phenyl and optionally substituted cycloalkyl; and the aforementioned optionally substituted phenyl and optionally substituted cycloalkyl may have 1 to 3 substituents selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, acyl, alkylamino, alkylthio, acylamino, alkoxycarbonyl, alkoxycarbonylamino, acyloxy, alkylcarbamoyl, haloalkyl, nitro, halogen, amino, hydroxy and carboxy; provided that when R^1b is C1-C4 alkyl, the alkyl should be substituted and when R^1b is furyl, phenyl or phenyl substituted by lower alkyl, lower alkoxy, chloro, hydroxy or amino, one of R^2b and R^3b is not methyl or ethyl, and a pharmaceutically acceptable salt thereof;

(5) a 2-amino-1,3-propanediol compound according to the above-mentioned (1), (2), (3) or (4), having the formula



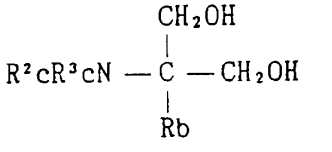
(I-4)

wherein

Ra is a straight- or branched chain alkyl having 12 to 22 carbon atoms, which may have, in the chain, a bond or a hetero atom selected from the group consisting of a double bond, a triple bond, oxygen, sulfur, sulfinyl, sulfonyl, $-N(R^6)-$ where R^6 is hydrogen, alkyl, aralkyl, acyl or alkoxycarbonyl, and carbonyl, and which may have, as a substituent, alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, acyl, alkylamino, alkylthio, acylamino, alkoxycarbonyl, alkoxycarbonylamino, acyloxy, alkylcarbamoyl, nitro, halogen, amino, hydroxyimino, hydroxy or carboxy, and

R^2b, R^3b, R^4b and R^5b are the same or different and each is a hydrogen, an alkyl or an acyl, and a pharmaceutically acceptable salt thereof;

(6) a 2-amino-1,3-propanediol compound according to the above-mentioned (5), having the formula



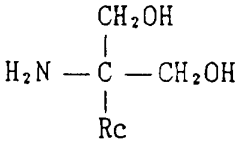
(I-5)

wherein

Rb is a straight- or branched chain alkyl having 13 to 20 carbon atoms, which may have, in the chain, an oxygen atom and which may have, as a substituent, nitro, halogen, amino, hydroxy or carboxy, and

R^2c and R^3c are the same or different and each is a hydrogen or an alkyl, and a pharmaceutically acceptable salt thereof;

(7) a 2-amino-1,3-propanediol compound according to the above-mentioned (5) or (6), having the formula



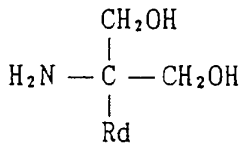
(I-6)

wherein

Rc is a straight- or branched chain alkyl having 13 to 20 carbon atoms or a straight- or branched chain alkyl having 13 to 20 carbon atoms which is substituted by halogen, and a pharmaceutically acceptable salt thereof;

(8) a 2-amino-1,3-propanediol compound according to the above-mentioned (5), (6) or (7), which is selected from 2-amino-2-tridecyl-1,3-propanediol, 2-amino-2-tetradecyl-1,3-propanediol, 2-amino-2-pentadecyl-1,3-propanediol, 2-amino-2-hexadecyl-1,3-propanediol, 2-amino-2-heptadecyl-1,3-propanediol, 2-amino-2-octadecyl-1,3-propanediol, 2-amino-2-nonadecyl-1,3-propanediol, 2-amino-2-icosyl-1,3-propanediol, 2-amino-2-(12-fluorododecyl)-1,3-propanediol and 2-amino-2-(14-fluorotetradecyl)-1,3-propanediol, and a pharmaceutically acceptable salt thereof;

(9) a 2-amino-1,3-propanediol compound according to the above-mentioned (1), (2), (3) or (4), having the formula



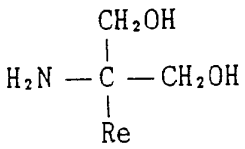
(I-7)

wherein

Rd is a phenylalkyl, a substituted phenylalkyl, a cycloalkylalkyl, a substituted cycloalkylalkyl, a heteroarylalkyl, a substituted heteroarylalkyl, a heterocyclic alkyl or a substituted heterocyclic alkyl,

wherein the alkyl moiety may have, in the carbon chain, a bond or a hetero atom selected from the group consisting of a double bond, a triple bond, oxygen, sulfur, sulfinyl, sulfonyl, $-N(R^6)-$ where R^6 is hydrogen, alkyl, aralkyl, acyl or alkoxycarbonyl, and carbonyl, and may have, as a substituent, alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, acyl, alkylamino, alkylthio, acylamino, alkoxycarbonyl, alkoxycarbonylamino, acyloxy, alkylcarbamoyl, nitro, halogen, amino, hydroxy or carboxy; and the substituted phenylalkyl, substituted cycloalkylalkyl, substituted heteroarylalkyl and substituted heterocyclic alkyl may have a substituent selected from the group consisting of alkyl, alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, haloaralkyloxy, aralkyloxyalkyl, phenoxyalkyl, phenoxyalkoxy, alkylenedioxy, acyl, alkylamino, alkylthio, acylamino, alkoxycarbonyl, alkoxycarbonylamino, acyloxy, alkylcarbamoyl, haloalkyl, haloalkoxy, nitro, halogen, amino, hydroxy and carboxy, and a pharmaceutically acceptable salt thereof;

(10) a 2-amino-1,3-propanediol compound according to the above-mentioned (9), having the formula



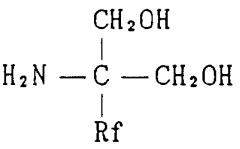
(I-8)

wherein

Re is a phenylalkyl wherein the alkyl moiety is a straight- or branched chain having 6 to 20 carbon atoms; a phenylalkyl which may be substituted by a straight- or branched chain C6-C20 alkyl optionally substituted by halogen, a straight- or branched chain C6-C20 alkoxy optionally substituted by halogen, a straight- or branched chain C6-C20 alkenyloxy, phenylalkoxy, halophenylalkoxy, phenylalkoxyalkyl, phenoxyalkoxy or phenoxyalkyl; a cycloalkylalkyl wherein the alkyl moiety is a straight- or branched chain having 6 to 20 carbon atoms; a cycloalkylalkyl substituted by a straight- or branched chain alkyl having 6 to 20 carbon atoms; a heteroarylalkyl wherein the alkyl moiety is a straight- or branched chain having 6 to 20 carbon atoms; a heteroarylalkyl substituted by a straight- or branched chain alkyl having 6 to 20 carbon atoms; a heterocyclic alkyl wherein the alkyl moiety is a straight- or branched chain having 6 to 20 carbon atoms, or a heterocyclic alkyl substituted by a straight- or branched chain alkyl having 6 to 20 carbon atoms;

wherein the alkyl moiety may have, in the carbon chain, a bond or a hetero atom selected from the group consisting of a double bond, a triple bond, oxygen, sulfur, sulfinyl, sulfonyl, -N(R^6)- where R^6 is hydrogen, alkyl, aralkyl, acyl or alkoxycarbonyl, and carbonyl, and may have, as a substituent, alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, acyl, alkylamino, alkylthio, acylamino, alkoxycarbonyl, alkoxycarbonylamino, acyloxy, alkylcarbamoyl, nitro, halogen, amino, hydroxy or carboxy, and a pharmaceutically acceptable salt thereof;

(11) a 2-amino-1,3-propanediol compound according to the above-mentioned (9) or (10), having the formula



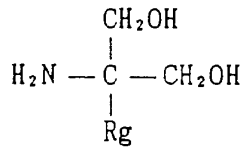
(I-9)

wherein

Rf is a phenylalkyl wherein the alkyl moiety is a straight-or branched chain having 6 to 20 carbon atoms which may have, in the carbon chain, one or two oxygen atoms; a phenylalkyl which may be substituted by a straight- or branched chain C6-C20 alkyl optionally substituted by halogen, a straight- or branched chain C6-C20 alkoxy optionally substituted by halogen, a straight- or branched chain C6-C20 alkenyloxy, phenylalkoxy, halophenylalkoxy, phenylalkoxyalkyl, phenoxyalkoxy or phenoxyalkyl; a cycloalkylalkyl wherein the alkyl moiety is a straight- or branched chain having 6 to 20 carbon atoms which may have, in the carbon chain, one or two oxygen atoms; a cycloalkylalkyl substituted by a straight- or branched chain alkyl having 6 to 20 carbon atoms; a heteroarylalkyl wherein the alkyl moiety is a straight- or branched chain having 6 to 20 carbon atoms which may have, in the carbon chain, one or two oxygen atoms; a heteroarylalkyl substituted by a straight- or branched chain alkyl having 6 to 20 carbon atoms; a heterocyclic alkyl wherein the alkyl moiety is a straight- or branched chain having 6 to 20 carbon atoms which may have, in the carbon chain, one or two oxygen atoms, or a heterocyclic alkyl substituted by a straight-or branched chain alkyl having 6 to 20 carbon atoms;

wherein the alkyl moiety may have, in the carbon chain, a substituent selected from the group consisting of alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, acyl, alkylamino, alkylthio, acylamino, alkoxycarbonyl, alkoxycarbonylamino, acyloxy, alkylcarbamoyl, nitro, halogen, amino, hydroxy and carboxy, and a pharmaceutically acceptable salt thereof;

(12) a 2-amino-1,3-propanediol compound according to the above-mentioned (9), (10) or (11), having the formula

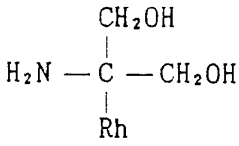


(I-10)

wherein

Rg is a phenylalkyl wherein the alkyl moiety is a straight-or branched chain having 6 to 20 carbon atoms which may have, in the carbon chain, one or two oxygen atoms, a phenylalkyl which may be substituted by a straight- or branched chain C6-C14 alkyl optionally substituted by halogen, a straight- or branched chain C6-C14 alkoxy optionally substituted by halogen, a straight- or branched chain C6-C14 alkenyloxy, phenylalkoxy, halophenylalkoxy, phenylalkoxyalkyl, phenoxyalkoxy or phenoxyalkyl; a cycloalkylalkyl wherein the alkyl moiety has 6 to 20 carbon atoms; a cycloalkylalkyl substituted by a straight- or branched chain alkyl having 6 to 14 carbon atoms; a heteroarylalkyl wherein the alkyl moiety has 6 to 20 carbon atoms; a heteroarylalkyl substituted by a straight- or branched chain alkyl having 6 to 14 carbon atoms; a heterocyclic alkyl wherein the alkyl moiety has 6 to 20 carbon atoms, or a heterocyclic alkyl substituted by a straight- or branched chain alkyl having 6 to 14 carbon atoms, and a pharmaceutically acceptable salt thereof;

(13) a 2-amino-1,3-propanediol compound according to the above-mentioned (12), having the formula



(I-11)

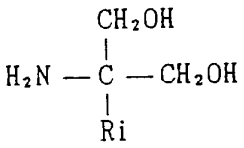
wherein

Rh is a phenylalkyl wherein the alkyl moiety has 6 to 20 carbon atoms, a phenylalkoxyalkyl wherein the alkyl moiety and alkoxy moiety have 6 to 20 carbon atoms in total, a phenoxyalkyl wherein the alkyl moiety has 6 to 20 carbon atoms or a phenoxyalkoxyalkyl wherein the alkyl moiety and alkoxy moiety have 6 to 20 carbon atoms in total, and a pharmaceutically acceptable salt thereof;

(14) a 2-amino-1,3-propanediol compound according to the above-mentioned (13), which is selected from the group consisting of 2-amino-2-(8-phenyloctyl)-1,3-propanediol, 2-amino-2-(9-phenyl-nonyl)-1,3-propanediol, 2-amino-2-(10-phenyldecyl)-1,3-propanediol, 2-amino-2-(11-phenylundecyl)-1,3-propanediol, 2-amino-2-(12-phenyldodecyl)-1,3-propanediol, 2-amino-2-(13-phenyltridecyl)-1,3-propanediol, 2-amino-2-(14-phenyltetradecyl)-1,3-propanediol, 2-amino-2-(15-phenylpentadecyl)-1,3-propanediol, 2-amino-2-(16-phenylhexadecyl-1,3-propanediol, 2-amino-2-[6-(8-phenyloctyloxy)hexyl]-1,3-propanediol, 2-amino-2-(8-phenylmethyloxyoctyl)-1,3-propanediol, 2-amino-2-(9-phenoxynonyl)-1,3-propanediol, 2-amino-2-(12-phenoxydodecyl)-1,3-propanediol and 2-amino-2-[6-(2-phenoxyethyloxy)hexyl]-1,3-propanediol, and a pharmaceutically acceptable salt thereof;

(15) a 2-amino-1,3-propanediol compound according to the above-mentioned (13) which is selected from the group consisting of 2-amino-2-(10-phenyldecyl)-1,3-propanediol, 2-amino-2-(13-phenyltridecyl)-1,3-propanediol, 2-amino-2[6-(8-phenyloctyloxy)hexyl]-1,3-propanediol, 2-amino-2-(8-phenylmethyloxyoctyl)-1,3-propanediol, 2-amino-2-(9-phenoxynonyl)-1,3-propanediol, 2-amino-2-(12-phenoxydodecyl)-1,3-propanediol and 2-amino-2-[6-(2-phenoxyethyloxy)hexyl]-1,3-propanediol, and a pharmaceutically acceptable salt thereof;

(16) a 2-amino-1,3-propanediol compound according to the above-mentioned (12), having the formula



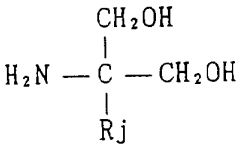
(I-12)

wherein

Ri is a phenylalkyl substituted by a straight- or branched chain C6-C14 alkyl optionally substituted by halogen, a straight- or branched chain C6-C14 alkoxy optionally substituted by halogen or a straight- or branched chain C6-C14 alkenyloxy;

wherein the alkyl moiety of phenylalkyl may be substituted by hydroxy, and a pharmaceutically acceptable salt thereof;

(17) a 2-amino-1,3-propanediol compound according to the above-mentioned (16), having the formula



(I-13)

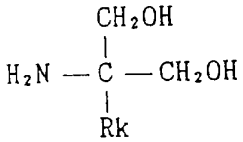
wherein

Rj is a phenylalkyl substituted by a straight- or branched chain C6-C14 alkyl optionally substituted by halogen, a straight- or branched chain C6-C14 alkoxy optionally substituted by halogen or a straight- or branched chain C6-C14 alkenyloxy, wherein the alkyl moiety is a C2-C6 alkyl optionally substituted by hydroxy, and a pharmaceutically acceptable salt thereof;

(18) a 2-amino-1,3-propanediol compound according to the above-mentioned (16) or (17), which is selected from the group consisting of 2-amino-2-[2-(4-heptylphenyl)ethyl]-1,3-propanediol, 2-amino-2-[2-(4-octylphenyl)ethyl]-1,3-propanediol, 2-amino-2-[2-(4-nonylphenyl)ethyl]-1,3-propanediol 2-amino-2-[2-(4-decylphenyl)ethyl]-1,3-propanediol, 2-amino-2-[2-(4-undecylphenyl)ethyl]-1,3-propanediol, 2-amino-2-[2-(4-dodecylphenyl)ethyl]-1,3-propanediol, 2-amino-2-[2-(4-tridecylphenyl)-ethyl]-1,3-propanediol, 2-amino-2-[2-(4-tetradecylphenyl)ethyl]-1,3-propanediol, 2-amino-2-[2-(4-hexyloxyphenyl)ethyl]-1,3-propanediol, 2-amino-2-[2-(4-heptyloxyphenyl)ethyl]-1,3-propanediol, 2-amino-2-[2-(4-octyloxyphenyl)ethyl]-1,3-propanediol, 2-amino-2-[2-(4-nonyloxyphenyl)ethyl]-1,3-propanediol, 2-amino-2-[2-(4-decyloxyphenyl)ethyl]-1,3-propanediol, 2-amino-2-[2-(4-undecyloxyphenyl)ethyl]-1,3-propanediol, 2-amino-2-[2-(4-dodecyloxyphenyl)ethyl]-1,3-propanediol, 2-amino-2-[2-(4-tridecyloxyphenyl)ethyl]-1,3-propanediol, 2-amino-2-[2-(4-(8-fluorooctyl)phenyl)ethyl]-1,3-propanediol, 2-amino-2-[2-(4-(12-fluorododecyl)phenyl)ethyl]-1,3-propanediol, 2-amino-2-[2-(4-(7-fluoroheptyloxy)phenyl)ethyl]-1,3-propanediol,2-amino-2-[2-(4-(11-fluoroundecyloxy)phenyl)ethyl]-1,3-propanediol and 2-amino-2-[2-(4-(7-octenyloxy)phenyl)ethyl]-1,3-propanediol, and a pharmaceutically acceptable salt thereof;

(19) a 2-amino-1,3-propanediol compound according to the above-mentioned (16) or (17), which is selected from the group consisting of 2-amino-2-[2-(4-heptylphenyl)ethyl]-1,3-propanediol, 2-amino-2-[2-(4-octylphenyl)ethyl]-1,3-propanediol, 2-amino-2-[2-(4-nonylphenyl)ethyl]-1,3-propanediol, 2-amino-2-[2-(4-decylphenyl)ethyl]-1,3-propanediol, 2-amino-2-[2-(4-undecylphenyl)ethyl]-1,3-propanediol, 2-amino-2-[2-(4-dodecylphenyl)ethyl]-1,3-propanediol, 2-amino-2-[2-(4-heptyloxyphenyl)ethyl]-1,3-propanediol, 2-amino-2-[2-(4-octyloxyphenyl)ethyl]-1,3-propanediol, 2-amino-2-[2-(4-nonyloxyphenyl)ethyl]-1,3-propanediol, 2-amino-2-[2-(4-undecyloxyphenyl)ethyl]-1,3-propanediol, and 2-amino-2-[2-(4-(7-octenyloxy)-phenyl)ethyl]-1,3-propanediol, and a pharmaceutically acceptable salt thereof;

(20) a 2-amino-1,3-propanediol compound according to the above-mentioned (12), having the formula

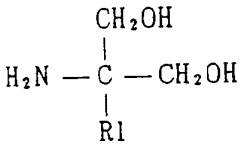


(I-14)

wherein

Rk is a phenylalkyl substituted by phenylalkoxy, halophenylalkoxy, phenylalkoxyalkyl, phenoxyalkoxy or phenoxyalkyl, and a pharmaceutically acceptable salt thereof;

(21) a 2-amino-1,3-propanediol compound according to the above-mentioned (20), having the formula



(I-15)

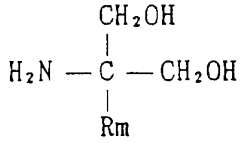
wherein

Rl is a phenylalkyl substituted by phenylalkoxy wherein the alkoxy moiety has 2 to 8 carbon atoms, halophenylalkoxy wherein the alkoxy moiety has 2 to 8 carbon atoms, phenylalkoxyalkyl wherein the alkoxy moiety and alkyl moiety have 2 to 8 carbon atoms in total, phenoxyalkoxy wherein the alkoxy moiety has 2 to 8 carbon atoms or phenoxyalkyl wherein the alkyl moiety has 2 to 8 carbon atoms, where the alkyl moiety has 2 to 6 carbon atoms, and a pharmaceutically acceptable salt thereof;

(22) a 2-amino-1,3-propanediol compound according to the above-mentioned (20) or (21), which is selected from the group consisting of 2-amino-2-[2-(4-phenylmethyloxyphenyl)ethyl]-1,3-propanediol, 2-amino-2-[2-(4-(2-phenylethyloxy)phenyl)ethyl]-1,3-propanediol, 2-amino-2-[2-(4-(3-phenylpropyloxy)-phenyl)-ethyl]-1,3-propanediol, 2-amino-2-[2-(4-(4-phenylbutyloxy)-phenyl)ethyl]-1,3-propanediol,2-amino-2-[2-(4-(5-phenylpentyloxy)phenyl)ethyl]-1,3-propanediol,2-amino-2-[2-(4-(6-phenylhexyloxy)phenyl)ethyl]-1,3-propanediol, 2-amino-2-[2-(4-(7-phenylheptyloxy)phenyl)ethyl]-1,3-propanediol,2-amino-2-[2-(4-(8-phenyloctyloxy)phenyl)ethyl]-1,3-propanediol, 2-amino-2-[4-(6-(4-fluorophenyl)hexyloxy)phenyl)ethyl]-1,3-propanediol, 2-amino-2-[2-(4-(5-phenylpentyloxymethyl)phenyl)ethyl]-1,3-propanediol, 2-amino-2-[2-(4-(4-phenoxybutyloxy)phenyl)ethyl]-1,3-propanediol,2-amino-2-[2-(4-(5-phenoxypentyloxy)phenyl)-ethyl]-1,3-propanediol, 2-amino-2-[2-(4-(6-phenoxyhexyloxy)-phenyl)ethyl]-1,3-propanediol, 2-amino-2-[2-(4-(7-phenoxyheptyloxy)phenyl)ethyl]-1,3-propanediol, 2-amino-2-[2-(4-(4-phenoxybutyl)phenyl)ethyl]-1,3-propanediol, 2-amino-2-[2-(4-(5-phenoxypentyl)phenyl)ethyl]-1,3-propanediol, 2-amino-2-[2-(4-(6-phenoxyhexyl)phenyl)ethyl]-1,3-propanediol and 2-amino-2-[2-(4-(7-phenoxyheptyl)phenyl)ethyl]-1,3-propanediol, and a pharmaceutically acceptable salt thereof;

(23) a 2-amino-1,3-propanediol compound according to the above-mentioned (20) or (21) which is selected from the group consisting of 2-amino-2-[2-(4-(6-phenylhexyloxy)phenyl)ethyl]-1,3-propanediol and 2-amino-2-[2-(4-(5-phenylpentyloxymethyl)-phenyl)ethyl]-1,3-propanediol, and a pharmaceutically acceptable salt thereof;

(24) a 2-amino-1,3-propanediol compound according to the above-mentioned (12), having the formula



(I-16)

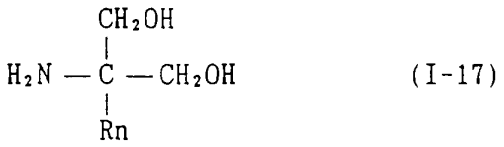
wherein

Rm is an alkyl-substituted cycloalkylalkyl wherein the alkyl moiety has 6 to 20 carbon atoms in

total, and a pharmaceutically acceptable salt thereof;

(25) a 2-amino-1,3-propanediol compound according to the above-mentioned (24), which is selected from the group consisting of 2-amino-2-[3-(4-heptylcyclohexyl)propyl]-1,3-propanediol, 2-amino-2-[4-(4-butylcyclohexyl)butyl]-1,3-propanediol, 2-amino-2-[2-(4-octylcyclohexyl)ethyl)-1,3-propanediol, 2-amino-2-[2-(4-nonylcyclohexyl)ethyl]-1,3-propanediol and 2-amino-2-[2-(4-dodecylcyclohexyl)ethyl]-1,3-propanediol, and a pharmaceutically acceptable salt thereof;

(26) a 2-amino-1,3-propanediol compound according to the above-mentioned (12), having the formula



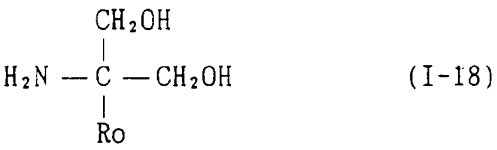
(I-17)

wherein

Rn is a 1-alkyl-substituted piperidin-4-ylalkyl wherein the alkyl moiety has 6 to 20 carbon atoms in total, and a pharmaceutically acceptable salt thereof;

(27) a 2-amino-1,3-propanediol compound according to the above-mentioned (26), which is selected from the group consisting of 2-amino-2-[2-(1-octylpiperidin-4-yl)ethyl]-1,3-propanediol and 2-amino-2-[2-(1-dodecylpiperidin-4-yl)ethyl]-1,3-propanediol, and a pharmaceutically acceptable salt thereof;

(28) a 2-amino-1,3-propanediol compound according to the above-mentioned (12), having the formula



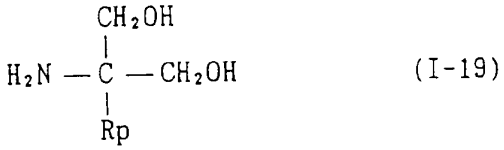
(I-18)

wherein

Ro is a thienylalkyl wherein the alkyl moiety has 6 to 20 carbon atoms, an alkyl-substituted thienylalkyl wherein the alkyl moiety has 6 to 20 carbon atoms in total, pyridylalkyl wherein the alkyl moiety has 6 to 20 carbon atoms or an alkyl-substituted pyridylalkyl wherein the alkyl moiety has 6 to 20 carbon atoms in total, and a pharmaceutically acceptable salt thereof;

(29) a 2-amino-1,3-propanediol compound according to the above-mentioned (28), which is selected from the group consisting of 2-amino-2-[2-(5-octyl-2-thienyl)ethyl]-1,3-propanediol, 2-amino-2-[2-(5-nonyl-2-thienyl)ethyl]-1,3-propanediol, 2-amino-2-[2-(5-decyl-2-thienyl)ethyl]-1,3-propanediol, 2-amino-2-[2-(5-dodecyl-2-thienyl)ethyl]-1,3-propanediol, 2-amino-2-[13-(2-thienyl)-tridecyl]-1,3-propanediol, 2-amino-2-[2-(5-octyl-2-pyridyl)-ethyl]-1,3-propanediol, 2-amino-2-[2-(5-decyl-2-pyridyl)ethyl]-1,3-propanediol, 2-amino-2-[13-(2-pyridyl)tridecyl]-1,3-propanediol, 2-amino-2-[2-(2-octyl-5-pyridyl)ethyl]-1,3-propanediol, 2-amino-2-[2-(2-decyl-5-pyridyl)ethyl]-1,3-propanediol and 2-amino-2-[13-(3-pyridyl)tridecyl]-1,3-propanediol, and a pharmaceutically acceptable salt thereof;

(30) a 2-amino-1,3-propanediol compound according to the above-mentioned (1) or (2), having the formula

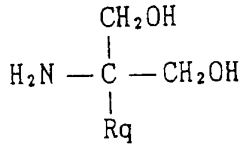


(I-19)

wherein

Rp is a phenyl substituted by C6-C18 alkyl, a cycloalkyl, a heteroaryl or a heterocycle, and a pharmaceutically acceptable salt thereof;

(31) a 2-amino-1,3-propanediol compound according to the above-mentioned (30), having the formula



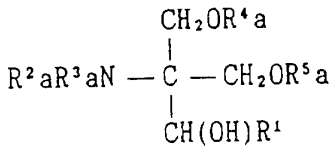
(I-20)

wherein

Rq is a phenyl substituted by C6-C18 alkyl, and a pharmaceutically acceptable salt thereof;

(32) a 2-amino-1,3-propanediol compound according to the above-mentioned (30) or (31), which is selected from the group consisting of 2-amino-2-(4-decylphenyl)-1,3-propanediol, 2-amino-2-(4-dodecylphenyl)-1,3-propanediol, 2-amino-2-(4-tetradecylphenyl)-1,3-propanediol and 2-amino-2-(4-hexadecylphenyl)-1,3-propanediol, and a pharmaceutically acceptable salt thereof;

(33) a 2-amino-1,3-propanediol compound according to the above-mentioned (1) or (2), having the formula



(I-21)

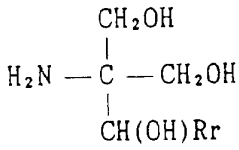
wherein

R^1 is an optionally substituted straight- or branched carbon chain which may have, in the chain, a bond, a hetero atom or a group selected from the group consisting of a double bond, a triple bond, oxygen, sulfur, sulfinyl, sulfonyl, -N(R^6)- where R^6 is hydrogen, alkyl, aralkyl, acyl or alkoxycarbonyl, and carbonyl, optionally substituted arylene, optionally substituted cycloalkylene, optionally substituted heteroarylene and an alicycle thereof, and which may be substituted, at the chain end (ω-position) thereof, by a double bond, a triple bond, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted heteroaryl or an alicycle thereof, an optionally substituted aryl, an optionally substituted cycloalkyl, an optionally substituted heteroaryl or an alicycle thereof, and

R^2a, R^3a, R^4a and R^5a are the same or different and each is a hydrogen, an alkyl, an acyl or an alkoxycarbonyl;

wherein the optionally substituted straight- or branched carbon chain may have a substituent selected from the group consisting of alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, alkylenedioxy, acyl, alkylamino, alkylthio, acylamino, alkoxycarbonyl, alkoxycarbonylamino, acyloxy, alkylcarbamoyl, haloalkyl, haloalkoxy, nitro, halogen, amino, hydroxyimino, hydroxy, carboxy, optionally substituted aryl, optionally substituted aryloxy, optionally substituted cycloalkyl, optionally substituted heteroaryl and an alicycle thereof; and the aforementioned optionally substituted arylene, optionally substituted cycloalkylene, optionally substituted heteroarylene, an alicycle thereof, optionally substituted aryl, optionally substituted aryloxy, optionally substituted cycloalkyl, optionally substituted heteroaryl and an alicycle thereof may have a substituent selected from the group consisting of alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, alkylenedioxy, acyl, alkylamino, alkylthio, acylamino, alkoxycarbonyl, alkoxycarbonylamino, acyloxy, alkylcarbamoyl, haloalkyl, haloalkoxy, nitro, halogen, amino, hydroxy and carboxy, and a pharmaceutically acceptable salt thereof;

(34) a 2-amino-1,3-propanediol compound according to the above-mentioned (33), having the formula



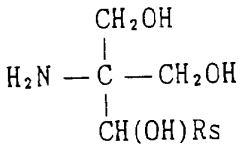
(I-22)

wherein

Rr is an alkyl optionally substituted by hydroxy and/or hydroxyimino which may have, in the chain, a double bond or carbonyl, and a pharmaceutically acceptable salt thereof;

(35) a 2-amino-1,3-propanediol compound according to the above-mentioned (33) or (34), which is selected from the group consisting of 2-amino-2-(1,2,12-trihydroxy-4-octadecenyl)-1,3-propanediol, 2-amino-2-(1,2-dihydroxy-4-octadecenyl)-1,3-propanediol, 2-amino-2-(1,2-dihydroxyoctadecyl)-1,3-propanediol, 2-amino-2-(1,12-dihydroxy-4-octadecenyl)-1,3-propanediol, 2-amino-2-(1,2,4-trihydroxybutyl)-1,3-propanediol, 2-amino-2-(1,2,12-trihydroxyoctadecyl)-1,3-propanediol and 2-amino-2-(1,12-dihydroxyoctadecyl)-1,3-propanediol and a pharmaceutically acceptable salt thereof;

(36) a 2-amino-1,3-propanediol compound according to the above-mentioned (33), having the formula



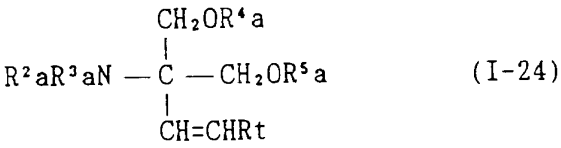
(I-23)

wherein

Rs is a phenylalkyl substituted by a straight- or branched chain C6-C14 alkyl optionally substituted by halogen, a straight- or branched chain C6-C14 alkoxy optionally substituted by halogen or a straight- or branched chain C6-C14 alkenyloxy, and a pharmaceutically acceptable salt thereof;

(37) a 2-amino-1,3-propanediol compound according to the above-mentioned (36), which is selected from the group consisting of 2-amino-2-[1-hydroxy-2-(4-octylphenyl)ethyl]-1,3-propanediol, 2-amino-2-[2-(4-dodecylphenyl)-1-hydroxyethyl]-1,3-propanediol, 2-amino-2-[2-(4-heptyloxyphenyl)-1-hydroxyethyl]-1,3-propanediol, 2-amino-2-[1-hydroxy-2-(4-undecyloxyphenyl)ethyl]-1,3-propanediol, 2-amino-2-[2-(4-(8-fluorooctyl)phenyl)-1-hydroxyethyl]-1,3-propanediol, 2-amino-2-[2-(4-(12-fluorododecyl)phenyl)-1-hydroxyethyl]-1,3-propanediol, 2-amino-2-[2-(4-(7-fluoroheptyloxy)phenyl)-1-hydroxyethyl]-1,3-propanediol and 2-amino-2-[1-hydroxy-2-(4-(11-fluoroundecyloxy)phenyl)ethyl]-1,3-propanediol, and a pharmaceutically acceptable salt thereof;

(38) a 2-amino-1,3-propanediol compound according to the above-mentioned (1) or (2), having the formula



(I-24)

wherein

Rt is an optionally substituted straight- or branched carbon chain which may have, in the chain, a bond, a hetero atom or a group selected from the group consisting of a double bond, a triple bond, oxygen, sulfur, sulfinyl, sulfonyl, -N(R^6)- where R^6 is hydrogen, alkyl, aralkyl, acyl or alkoxycarbonyl, carbonyl, optionally substituted arylene, optionally substituted cycloalkylene, optionally substituted heteroarylene and an alicycle thereof,

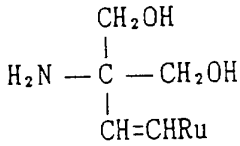
an optionally substituted aryl, an optionally substituted cycloalkyl, an optionally substituted heteroaryl or an alicycle thereof, and

R^2a, R^3a, R^4a and R^5a

are the same or different and each is a hydrogen, an alkyl, an acyl or an alkoxycarbonyl;

wherein the optionally substituted straight- or branched carbon chain may have a substituent selected from the group consisting of alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, alkylenedioxy, acyl, alkylamino, alkylthio, acylamino, alkoxycarbonyl, alkoxycarbonylamino, acyloxy, alkylcarbamoyl, haloalkyl, haloalkoxy, nitro, halogen, amino, hydroxy, carboxy, optionally substituted aryl, optionally substituted aryloxy, optionally substituted cycloalkyl, optionally substituted heteroaryl and an alicycle thereof; and the aforementioned optionally substituted arylene, optionally substituted cycloalkylene, optionally substituted heteroarylene, an alicycle thereof, optionally substituted aryl, optionally substituted aryloxy, optionally substituted cycloalkyl, optionally substituted heteroaryl and an alicycle thereof may have a substituent selected from the group consisting of alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, alkylenedioxy, acyl, alkylamino, alkylthio, acylamino, alkoxycarbonyl, alkoxycarbonylamino, acyloxy, alkylcarbamoyl, haloalkyl, haloalkoxy, nitro, halogen, amino, hydroxy and carboxy, and a pharmaceutically acceptable salt thereof;

(39) a 2-amino-1,3-propanediol compound according to the above-mentioned (38), having the formula



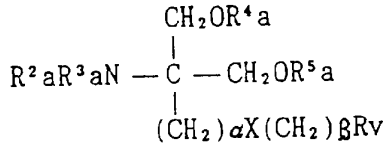
(I-25)

wherein

Ru is a phenyl substituted by alkyl having 4 to 16 carbon atoms, and a pharmaceutically acceptable salt thereof;

(40) a 2-amino-1,3-propanediol compound according to the above-mentioned (38) or (39), which is selected from the group consisting of 2-amino-2-[2-(4-octylphenyl)ethenyl]-1,3-propanediol, 2-amino-2-[2-(4-decylphenyl)ethenyl]-1,3-propanediol, 2-amino-2-[2-(4-dodecylphenyl)ethenyl]-1,3-propanediol and 2-amino-2-[2-(4-tetradecylphenyl)ethenyl]-1,3-propanediol, and a pharmaceutically acceptable salt thereof;

(41) a 2-amino-1,3-propanediol compound according to the above-mentioned (1) or (2), having the formula



(I-26)

wherein

Rv is an optionally substituted aryl, an optionally substituted cycloalkyl, an optionally substituted heteroaryl or an alicycle thereof;

R^2a, R^3a, R^4a and R^5a

are the same or different and each is a hydrogen, an alkyl, an acyl or an alkoxycarbonyl;

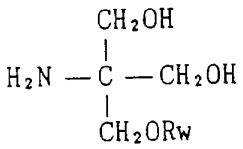
X is an oxygen, a sulfur, a sulfinyl, a sulfonyl, -N(R^6)-where R^6 is hydrogen, alkyl, aralkyl, acyl or alkoxycarbonyl; and

α and β

are 0 or an integer of 1-20 provided that $\alpha + \beta = 5$-20, wherein the optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted heteroaryl and an alicycle thereof may have a substituent selected from the group consisting of alkyl, alkoxy, alkenyloxy, alkynyloxy, aral-

kyloxy, alkylenedioxy, acyl, alkylamino, alkylthio, acylamino, alkoxycarbonyl, alkoxycarbonylamino, acyloxy, alkylcarbamoyl, haloalkyl, haloalkoxy, nitro, halogen, amino, hydroxy and carboxy, and a pharmaceutically acceptable salt thereof;

(42) a 2-amino-1,3-propanediol compound according to the above-mentioned (41), having the formula



(I-27)

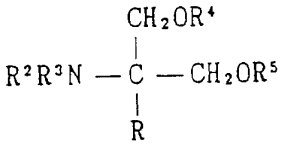
wherein

Rw is a phenyl substituted by C4-C16 alkyl, and a pharmaceutically acceptable salt thereof;

(43) a 2-amino-1,3-propanediol compound according to the above-mentioned (41) or (42), which is selected from the group consisting of 2-amino-2-(4-octylphenoxymethyl)-1,3-propanediol, 2-amino-2-(4-decylphenoxymethyl)-1,3-propanediol, 2-amino-2-(4-dodecylphenoxymethyl)-1,3-propanediol and 2-amino-2-(4-tetradecylphenoxymethyl)-1,3-propanediol, and a pharmaceutically acceptable salt thereof;

(44) a pharmaceutical composition comprising either one of the above-mentioned compounds (1) through (4);

(45) an immunosuppressant comprising a 2-amino-1,3-propanediol compound of the formula



(I-28)

wherein

R is an optionally substituted straight- or branched carbon chain which may have, in the chain, a bond, a hetero atom or a group selected from the group consisting of a double bond, a triple bond, oxygen, sulfur, sulfinyl, sulfonyl, -N-(R^6)- where R^6 is hydrogen, alkyl, aralkyl, acyl or alkoxycarbonyl, carbonyl, optionally substituted arylene, optionally substituted cycloalkylene, optionally substituted heteroarylene and an alicycle thereof, and which may be substituted, at the chain end thereof, by a double bond, a triple bond, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted heteroaryl or an alicycle thereof, an optionally substituted aryl, an optionally substituted cycloalkyl, an optionally substituted heteroaryl or an alicycle thereof, and

R^2, R^3, R^4 and R^5 are the same or different and each is a hydrogen, an alkyl, an aralkyl, an acyl or an alkoxycarbonyl, or R^4 and R^5 may be bonded by an alkylene chain which may be substituted by alkyl, aryl or aralkyl;

wherein the optionally substituted straight- or branched carbon chain may have a substituent selected from the group consisting of alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, alkylenedioxy, acyl, alkylamino, alkylthio, acylamino, alkoxycarbonyl, alkoxycarbonylamino, acyloxy, alkylcarbamoyl, haloalkyl, haloalkoxy, nitro, halogen, amino, hydroxyimino, hydroxy, carboxy, optionally substituted aryl, optionally substituted aryloxy, optionally substituted cycloalkyl, optionally substituted heteroaryl and an alicycle thereof; the aforementioned optionally substituted arylene, optionally substituted cycloalkylene, optionally substituted heteroarylene and an alicycle thereof may have a substituent selected from the group consisting of alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, alkylenedioxy, acyl, alkylamino, alkylthio, acylamino, alkoxycarbonyl, alkoxycarbonylamino, acyloxy, alkylcarbamoyl, haloalkyl, haloalkoxy, nitro, halogen, amino, hydroxy and carboxy; and the optionally substituted aryl, optionally substituted aryloxy, optionally substituted cycloalkyl, optionally substituted heteroaryl and an alicycle thereof may have a

substituent selected from the group consisting of alkyl, alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, alkylenedioxy, acyl, alkylamino, alkylthio, acylamino, alkoxycarbonyl, alkoxycarbonylamino, acyloxy, alkylcarbamoyl, haloalkyl, haloalkoxy, nitro, halogen, amino, hydroxy and carboxy, and a pharmaceutically acceptable salt thereof;

(46) an immunosuppressant comprising a 2-amino-1,3-propanediol compound or a pharmaceutically acceptable salt thereof according to either one of the aforementioned (1) through (43);

(47) a pharmaceutical agent according to the aforementioned (45) or (46), wherein the immunosuppressant is an agent for suppressing rejection;

(48) a pharmaceutical agent according to the aforementioned (45) or (46), wherein the immunosuppressant is an agent for the prevention and treatment of autoimmune diseases; and

(49) a pharmaceutical agent according to the aforementioned (48), wherein the agent for the prevention and treatment of autoimmune diseases is an agent for the prevention and treatment of rheumatism.

The groups represented by respective symbols in the present specification are explained in the following.

The carbon chain at R, R^1, R^1a or Rt is a straight- or branched carbon chain having 1 to 30 carbon atoms and is exemplified by methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, isopentyl, tert-pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, nonadecyl, icosyl, henicosyl, docosyl, tricosyl, tetracosyl, pentacosyl, hexacosyl, heptacosyl, octacosyl, nonacosyl and triacontyl.

The arylene at R, R^1 or Rt is exemplified by phenylene and naphthylene, with preference given to phenylene.

The cycloalkylene at R, R^1, R^1a or Rt is that having 3 to 10 carbon atoms and is exemplified by cyclopropylene, cyclobutylene, cyclopentylene, cyclohexylene, cycloheptylene, cyclooctylene, cyclononylene and cyclodecylene, with preference given to cyclohexylene.

The heteroarylene at R, R^1 or Rt is a 5- or 6-membered heteroarylene optionally having, in the ring, 1 or 2 hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom and is exemplified by thiophen-(2,4-, 2,5- or 3,4-)ylene, furan-(2,4-, 2,5- or 3,4-)ylene, pyrrol-(1,3-, 2,4-, 2,5- or 3,4-)ylene, imidazol-(1,4-, 2,4- or 2,5-)ylene, thiazol-(2,4- or 2,5-)ylene, isothiazol-(3,4- or 3,5-)ylene, oxazol-(2,4- or 2,5-)ylene, isoxazol-(3,4- or 3,5-)ylene, pyridin-(2,4-, 2,5-, 2,6- or 3,5-)ylene, pyrimidin-(2,4- or 2,5-)ylene, pyrazin-2,5-ylene, pyridazin-(3,5- or 3,6-)ylene and pyran-(2,4-, 2,5- or 2,6-)ylene, with preference given to thiophen-2,5-ylene and pyridin-2,5-ylene.

The alicycle of the aforementioned heteroarylene at R, R^1 or Rt is the aforementioned heteroarylene when saturated and is exemplified by pyrrolidine-(1,3-, 2,4-, 2,5- or 3,4-)ylene, piperidine-(1,4-, 2,4-, 2,5-, 2,6- or 3,5-)ylene, piperazine-1,4-ylene,morpholine-2,4 or 3,4-ylene and thiomorpholine-2,4 or 3,4-ylene.

The aryl at R, R^1, Rt or Rv is exemplified by phenyl and naphthyl, with preference given to phenyl.

The cycloalkyl at R, R^1, R^1a, R^1b, Rp, Rt or Rv is cycloalkyl having 3 to 10 carbon atoms and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl and cyclodecyl, with preference given to cyclohexyl.

The heteroaryl at R, R^1, Rp, Rt or Rv is a 5- or 6-membered heteroaryl optionally having, in the ring, 1 to 4 hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom and includes, for example, monocyclic heteroaryl such as thienyl(2-thienyl, 3-thienyl), furyl(2-furyl, 3-furyl), pyrrolyl (1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl), imidazolyl(2-imidazolyl, 4-imidazolyl), pyrazolyl(3-pyrazolyl, 4-pyrazolyl), triazolyl, tetrazolyl, thiazolyl(2-thiazolyl, 4-thiazolyl), isothiazolyl(3-isothiazolyl, 4-isothiazolyl), oxazolyl(2-oxazolyl, 4-oxazolyl), isooxazolyl(3-isooxazolyl, 4-isooxazolyl), pyridyl(2-pyridyl, 3-pyridyl, 4-pyridyl), pyrazinyl, pyrimidinyl(2-pyrimidinyl, 4-pyrimidinyl), pyridazinyl(3-pyridazinyl, 4-pyridazinyl) or pyranyl(2-pyranyl, 3-pyranyl, 4-pyranyl), and bicyclic heteroaryl such as indolyl(2-indolyl, 3-indolyl), quinolyl(2-quinolyl, 3-quinolyl), isoquinolyl(1-isoquinolyl, 3-isoquinolyl), benzofuranyl(2-benzofuranyl, 3-benzofuranyl), benzothienyl(2-benzothienyl, 3-benzothienyl), 1H-benzimidazol-2-yl or chromenyl(2-chromenyl, 3-chromenyl, 4-chromenyl).

The alicycle of the aforementioned heteroaryl at R, R^1, Rt or Rv is the above-mentioned monocyclic heteroaryl when saturated and includes, for example, pyrrolidinyl(1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl), piperidyl(2-piperidyl, 3-piperidyl, 4-piperidyl), piperidino, piperazinyl, morpholinyl and thiomorpholinyl.

The heterocycle at Rp means an alicycle of heteroaryl.

The alkyl at R^1b or Rr is a straight- or branched chain alkyl having 1 to 30 carbon atoms and is exemplified by methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, isopentyl, tert-pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, nonadecyl, icosyl, henicosyl, docosyl, tricosyl, tetracosyl, pentacosyl, hexacosyl, heptacosyl,

octacosyl, nonacosyl and triacontyl.

The straight- or branched chain alkyl having 12 to 22 carbon atoms at Ra and the straight- or branched chain alkyl having 13 to 20 carbon atoms at Rb or Rc are the above-mentioned alkyl having the specified numbers of carbon atoms.

The alkenyl at R^1b is a straight- or branched chain alkenyl having 2 to 30 carbon atoms and includes, for example, ethenyl, propenyl, isopropenyl, butenyl, isobutenyl, pentenyl, isopentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl, undecenyl, dodecenyl, tridecenyl, tetradecenyl, pentadecenyl, hexadecenyl, heptadecenyl, octadecenyl, nonadecenyl, icosenyl, henicosenyl, docosenyl, tricosenyl, tetracosenyl, pentacosenyl, hexacosenyl, heptacosenyl, octacosenyl, nonacosenyl and triacontenyl.

The alkynyl at R^1b is a straight- or branched chain alkynyl having 2 to 30 carbon atoms and includes, for example, ethynyl, propynyl, isopropynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, decynyl, undecynyl, dodecynyl, tridecynyl, tetradecynyl, pentadecynyl, hexadecynyl, heptadecynyl, octadecynyl, nonadecynyl, icosynyl, henicosynyl, docosynyl, tricosynyl, tetracosynyl, pentacosynyl, hexacosynyl, heptacosynyl, octacosynyl, nonacosynyl and triacontynyl.

The phenylalkyl at Rd, Re, Rf, Rg, Ri, Rk or Rs is that where the alkyl moiety is a straight- or branched chain alkyl having 1 to 30 carbon atoms and includes, for example, benzyl, 1-phenylethyl, 2-phenylethyl, 1-phenylpropyl, 2-phenylpropyl, 3-phenylpropyl, 4-phenylbutyl, 5-phenylpentyl, 6-phenylhexyl, 7-phenylheptyl, 8-phenyloctyl, 9-phenylnonyl, 10-phenyldecyl, 11-phenylundecyl, 12-phenyldodecyl, 13-phenyltridecyl, 14-phenyltetradecyl, 15-phenylpentadecyl, 16-phenylhexadecyl, 17-phenylheptadecyl, 18-phenyloctadecyl, 19-phenylnonadecyl, 20-phenylicosyl, 21-phenylhenicosyl, 22-phenyldocosyl, 23-phenyltricosyl, 24-phenyltetracosyl, 25-phenylpentacosyl, 26-phenylhexacosyl, 27-phenylheptacosyl, 28-phenyloctacosyl, 29-phenylnonacosyl and 30-phenyltriacontyl.

The phenylalkyl at Re, Rf, Rg or Rh where the alkyl moiety has 6 to 20 carbon atoms and that at Rj or Rl where the alkyl moiety has 2 to 6 carbon atoms are the above-mentioned phenylalkyl having the specified numbers of carbon atoms.

The phenylalkoxyalkyl at Rh where the alkyl moiety and alkoxy moiety have 6 to 20 carbon atoms in total is exemplified by 5-phenylmethyloxypentyl, 6-phenylmethyloxyhexyl, 7-phenylmethyloxyheptyl, 8-phenylmethyloxyoctyl, 9-phenylmethyloxynonyl, 10-phenylmethyloxydecyl, 12-phenylmethyloxydodecyl, 14-phenylmethyloxytetradecyl, 16-phenylmethyloxyhexadecyl, 18-phenylmethyloxyoctadecyl, 2-(8-phenyloctyloxy)ethyl, 3-(8-phenyloctyloxy)propyl, 4-(8-phenyloctyloxy)butyl, 5-(8-phenyloctyloxy)pentyl, 6-(8-phenyloctyloxy)hexyl and 7-(8-phenyloctyloxy)heptyl.

The phenoxyalkyl at Rh where the alkyl moiety has 6 to 20 carbon atoms is exemplified by 6-phenoxyhexyl, 7-phenoxyheptyl, 8-phenoxyoctyl, 9-phenoxynonyl, 10-phenoxydecyl, 11-phenoxyundecyl, 12-phenoxydodecyl, 13-phenoxytridecyl, 14-phenoxytetradecyl, 15-phenoxypentadecyl, 16-phenoxyhexadecyl, 17-phenoxyheptadecyl, 18-phenoxyoctadecyl, 19-phenoxynonadecyl and 20-phenoxyicosyl.

The phenoxyalkoxyalkyl at Rh where the alkyl moiety and alkoxy moiety have 6 to 20 carbon atoms in total is exemplified by 5-(2-phenoxyethyloxy)pentyl, 6-(2-phenoxyethyloxy)hexyl, 7-(2-phenoxyethyloxy)-heptyl, 8-(2-phenoxyethyloxy)octyl, 5-(3-phenoxypropyloxy)pentyl, 6-(3-phenoxypropyloxy)hexyl, 7-(3-phenoxypropyloxy)heptyl, 8-(3-phenoxypropyloxy)octyl, 5-(4-phenoxybutyloxy)pentyl, 6-(4-phenoxybutyloxy)hexyl, 7-(4-phenoxybutyloxy)heptyl, 8-(4-phenoxybutyloxy)octyl, 5-(6-phenoxyhexyloxy)pentyl, 6-(6-phenoxyhexyloxy)hexyl, 7-(6-phenoxyhexyloxy)heptyl and 8-(6-phenoxyhexyloxy)octyl.

The cycloalkylalkyl at Rd, Re, Rf or Rg is that where the alkyl moiety is a straight- or branched chain alkyl having 1 to 30 carbon atoms and the cycloalkyl moiety is a cycloalkyl having 3 to 10 carbon atoms, and is exemplified by cyclohexylmethyl, 1-cyclohexylethyl, 2-cyclohexylethyl, 1-cyclohexylpropyl, 2-cyclohexylpropyl, 3-cyclohexylpropyl, 4-cyclohexylbutyl, 5-cyclohexylpentyl, 6-cyclohexylhexyl, 7-cyclohexylheptyl, 8-cyclohexyloctyl, 9-cyclohexylnonyl, 10-cyclohexyldecyl, 11-cyclohexylundecyl, 12-cyclohexyldodecyl, 13-cyclohexyltridecyl, 14-cyclohexyltetradecyl, 15-cyclohexylpentadecyl, 16-cyclohexylhexadecyl, 17-cyclohexylheptadecyl, 18-cyclohexyloctadecyl, 19-cyclohexylnonadecyl, 20-cyclohexylicosyl, 21-cyclohexylhenicosyl, 22-cyclohexyldocosyl, 23-cyclohexyltricosyl, 24-cyclohexyltetracosyl, 25-cyclohexylpentacosyl, 26-cyclohexylhexacosyl, 27-cyclohexylheptacosyl, 28-cyclohexyloctacosyl, 29-cyclohexylnonacosyl and 30-cyclohexyltriacontyl.

The cycloalkylalkyl at Re, Rf or Rg where the alkyl moiety has 6 to 20 carbon atoms is the above-mentioned cycloalkylalkyl having the specified numbers of carbon atoms.

The alkyl-substituted cycloalkylalkyl at Rm where the alkyl moiety has 6 to 20 carbon atoms is exemplified by 3-(4-heptylcyclohexyl)propyl,4-(4-butylcyclohexyl)butyl, 2-(4-octylcyclohexyl)ethyl, 2-(4-nonylcyclohexyl)ethyl and 2-(4-dodecylcyclohexyl)ethyl.

The heteroarylalkyl at Rd, Re, Rf or Rg is that where the alkyl moiety is a straight- or branched chain alkyl having 1 to 30 carbon atoms and is exemplified by thienylalkyl and pyridylalkyl such as (thienyl or

pyridyl)methyl, 1-(thienyl or pyridyl)ethyl, 2-(thienyl or pyridyl)ethyl, 1-(thienyl or pyridyl)propyl, 2-(thienyl or pyridyl)propyl, 3-(thienyl or pyridyl)propyl, 4-(thienyl or pyridyl)butyl, 5-(thienyl or pyridyl)pentyl, 6-(thienyl or pyridyl)hexyl, 7-(thienyl or pyridyl)heptyl, 8-(thienyl or pyridyl)octyl, 9-(thienyl or pyridyl)nonyl, 10-(thienyl or pyridyl)decyl, 11-(thienyl or pyridyl)undecyl, 12-(thienyl or pyridyl)dodecyl, 13-(thienyl or pyridyl)tridecyl, 14-(thienyl or pyridyl)tetradecyl, 15-(thienyl or pyridyl)pentadecyl, 16-(thienyl or pyridyl)hexadecyl, 17-(thienyl or pyridyl)heptadecyl, 18-(thienyl or pyridyl)-octadecyl, 19-(thienyl or pyridyl)nonadecyl, 20-(thienyl or pyridyl)icosyl, 21-(thienyl or pyridyl)henicosyl, 22-(thienyl or pyridyl)docosyl, 23-(thienyl or pyridyl)-tricosyl, 24-(thienyl or pyridyl)tetracosyl, 25-(thienyl or pyridyl)pentacosyl, 26-(thienyl or pyridyl)hexacosyl, 27-(thienyl or pyridyl)-heptacosyl, 28-(thienyl or pyridyl)octacosyl, 29-(thienyl or pyridyl)nonacosyl and 30-(thienyl or pyridyl)triacontyl.

The heteroarylalkyl at Re, Rf or Rg where the alkyl moiety has 6 to 20 carbon atoms is the above-mentioned heteroarylalkyl having the specified numbers of carbon atoms.

The alkyl-substituted thienylalkyl at Ro where the alkyl moiety has 6 to 20 carbon atoms in total is exemplified by 2-(5-octyl-2-thienyl)ethyl, 2-(5-nonyl-2-thienyl)ethyl, 2-(5-decyl-2-thienyl)ethyl and 2-(5-dodecyl-2-thienyl)ethyl.

The thienylalkyl at Ro where the alkyl moiety has 6 to 20 carbon atoms is thienylalkyl from among the above-mentioned heteroarylalkyls. Preferred is 13-(2-thienyl)tridecyl.

The alkyl-substituted pyridylalkyl at Ro where the alkyl moiety has 6 to 20 carbon atoms in total is exemplified by 2-(5-octyl-2-pyridyl)ethyl, 2-(5-decyl-2-pyridyl)ethyl, 2-(2-octyl-5-pyridyl)ethyl and 2-(2-decyl-5-pyridyl)ethyl.

The pyridylalkyl at Ro where the alkyl moiety has 6 to 20 carbon atoms is pyridylalkyl from among the above-mentioned heteroarylalkyls. Preferred are 13-(2-pyridyl)tridecyl and 13-(3-pyridyl)tridecyl.

The heterocyclic alkyl at Rd, Re, Rf or Rg where the alkyl moiety is a straight- or branched chain alkyl having 1 to 30 carbon atoms and heterocyclic means an alicycle of heteroaryl, is exemplified by 4-piperidylmethyl, 1-(4-piperidyl)ethyl, 2-(4-piperidyl)ethyl, 1-(4-piperidyl)propyl, 2-(4-piperidyl)propyl, 3-(4-piperidyl)propyl, 4-(4-piperidyl)butyl, 5-(4-piperidyl)-pentyl, 6-(4-piperidyl)hexyl, 7-(4-piperidyl)heptyl, 8-(4-piperidyl)octyl, 9-(4-piperidyl)nonyl, 10-(4-piperidyl)decyl, 11-(4-piperidyl)undecyl, 12-(4-piperidyl)dodecyl, 13-(4-piperidyl)tridecyl, 14-(4-piperidyl)tetradecyl, 15-(4-piperidyl)-pentadecyl, 16-(4-piperidyl)hexadecyl, 17-(4-piperidyl)-heptadecyl, 18-(4-piperidyl)octadecyl, 19-(4-piperidyl)-nonadecyl, 20-(4-piperidyl)icosyl, 21-(4-piperidyl)-henicosyl, 22-(4-piperidyl)docosyl, 23-(4-piperidyl)tricosyl, 24-(4-piperidyl)tetracosyl, 25-(4-piperidyl)pentacosyl, 26-(4-piperidyl)hexacosyl, 27-(4-piperidyl)heptacosyl, 28-(4-piperidyl)octacosyl, 29-(4-piperidyl)nonacosyl and 30-(4-piperidyl)triacontyl.

The heterocyclic alkyl at Re, Rf or Rg where the alkyl moiety has 6 to 20 carbon atoms is the above-mentioned heterocyclic alkyl having the specified numbers of carbon atoms.

The 1-alkyl-substituted piperidin-4-ylalkyl at Rn where the alkyl moiety has 6 to 20 carbon atoms in total is, for example, 2-(1-octylpiperidin-4-yl)ethyl and 2-(1-dodecylpiperidin-4-yl)-ethyl.

The alkyl as a substitutent at R, R^1b, Rd, Rm, Rn, Ro or Rv is a straight- or branched chain alkyl having 1 to 20 carbon atoms and is exemplified by methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, nonadecyl and icosyl.

The straight- or branched chain alkyl having 6 to 20 carbon atoms as a substituent at Re or Rf, the straight- or branched chain alkyl having 6 to 14 carbon atoms as a substituent at Rg, Ri, Rj or Rs, the alkyl having 6 to 18 carbon atoms as a substituent at Rp or Rq and the alkyl having 4 to 16 carbon atoms as a substituent at Ru or Rw are the above-mentioned alkyls having the specified numbers of carbon atoms.

The alkoxy as a substituent at R, R^1, R^1a, R^1b, Ra, Rd, Re, Rf, Rt or Rv is a straight- or branched chain alkoxy having 1 to 20 carbon atoms and is exemplified by methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy, isopentyloxy, tert-pentyloxy, hexyloxy, heptyloxy, octyloxy, nonyloxy, decyloxy, undecyloxy, dodecyloxy, tridecyloxy, tetradecyloxy, pentadecyloxy, hexadecyloxy, heptadecyloxy, octadecyloxy, nonadecyloxy and icosyloxy.

The straight- or branched chain alkoxy having 6 to 20 carbon atoms as a substituent at Re or Rf and the straight- or branched chain alkoxy having 6 to 14 carbon atoms as a substituent at Rg, Ri, Rj or Rs are the above-mentioned alkoxys having the specified numbers of carbon atoms.

The alkenyloxy as a substituent at R, R^1, R^1a, R^1b, Ra, Rd, Re, Rf, Rt or Rv is that where the alkenyl moiety is a straight- or branched chain alkenyl having 2 to 20 carbon atoms and is exemplified by vinyloxy, propenyloxy, isopropenyloxy, butenyloxy, isobutenyloxy, pentenyloxy, isopentenyloxy, hexenyloxy, heptenyloxy, octenyloxy, nonenyloxy, decenyloxy, undecenyloxy, dodecenyloxy, tridecenyloxy, tetradecenyloxy, pentadecenyloxy, hexadecenyloxy, heptadecenyloxy, octadecenyloxy, nonadecenyloxy and icosenyloxy.

The straight- or branched chain alkenyloxy having 6 to 20 carbon atoms as a substituent at Re or Rf and the straight- or branched chain alkenyloxy having 6 to 14 carbon atoms as a substituent at Rg, Ri, Rj or Rs are the above-mentioned alkenyloxys having the specified numbers of carbon atoms.

The alkynyloxy as a substituent at R, R^1, R^1a, R^1b, Ra, Rd, Re, Rf, Rt or Rv is that where the alkynyl moiety is a straight- or branched chain alkynyl having 2 to 20 carbon atoms and is exemplified by ethynyloxy, propynyloxy, butynyloxy, pentynyloxy, hexynyloxy, heptynyloxy, octynyloxy, nonynyloxy, decynyloxy, undecynyloxy, dodecynyloxy, tridecynyloxy, tetradecynyloxy, pentadecynyloxy, hexadecynyloxy, heptadecynyloxy, octadecynyloxy, nonadecynyloxy and icosynyloxy.

The aralkyloxy as a substituent at R, R^1, R^1a, R^1b, Ra, Rd, Re, Rf, Rt or Rv is that wherein the aralkyl is that where the alkyl moiety is a straight- or branched chain alkyl having 1 to 20 carbon atoms and the aralkyloxy is exemplified by phenylalkoxy such as benzyloxy, 2-phenethyloxy, 1-phenylethyloxy, 1-phenylpropyloxy, 2-phenylpropyloxy, 3-phenylpropyloxy, 4-phenylbutyloxy, 5-phenylpentyloxy, 6-phenylhexyloxy, 7-phenylheptyloxy, 8-phenyloctyloxy, 9-phenylnonyloxy, 10-phenyldecyloxy, 11-phenylundecyloxy, 12-phenyldodecyloxy 13-phenyltridecyloxy or 14-phenyltetradecyloxy, and naphthylalkoxy such as naphthylmethyl or 2-naphthylethyl, with preference given to phenylalkoxy.

The phenylalkoxy as a substituent at Re, Rf, Rg or Rk is phenylalkoxy of the aforementioned aralkyloxy.

The phenylalkoxy as a substituent at RI where the alkoxy moiety has 2 to 8 carbon atoms is phenylalkoxy of the aforementioned aralkyloxy, having the specified numbers of carbon atoms.

The alkylenedioxy as a substituent at R, R^1, R^1a, Rd, Rt or Rv is alkylenedioxy where the alkylene moiety is a straight- or branched chain alkylene having 1 to 20 carbon atoms and is exemplified by methylenedioxy, ethylenedioxy, propylenedioxy, trimethylenedioxy, butylenedioxy, 1,2-dimethylethylenedioxy, pentamethylenedioxy, hexamethylenedioxy, heptamethylenedioxy, octamethylenedioxy, nonamethylenedioxy, decamethylenedioxy, undecamethylenedioxy, dodecamethylenedioxy, tridecamethylenedioxy, tetradecamethylenedioxy, pentadecamethylenedioxy, hexadecamethylenedioxy, heptadecamethylenedioxy, octadecamethylenedioxy, nonadecamethylenedioxy and icosamethylenedioxy, with preference given to methylenedioxy and ethylenedioxy.

The acyl as a substituent at R, R^1, R^1a, R^1b, Ra, Rd, Re, Rf, Rt or Rv is optionally substituted alkanoyl or aroyl, in which alkanoyl is a straight- or branched chain alkanoyl having 1 to 20 carbon atoms, and is exemplified by formyl, acetyl, propionyl, butyryl, isobutyryl, pentanoyl, hexanoyl, heptanoyl, octanoyl, nonanoyl, decanoyl, undecanoyl, dodecanoyl, tridecanoyl, tetradecanoyl, pentadecanoyl, hexadecanoyl, heptadecanoyl, octadecanoyl, nonadecanoyl and icosanoyl, where alkanoyl may be substituted by phenyl. Examples of the alkanoyl optionally substituted by phenyl include phenylacetyl and phenylpropionyl. Examples of aroyl include benzoyl.

The alkylamino as a substituent at R, R^1, R^1a, R^1b, Ra, Rd, Re, Rf, Rt or Rv is that where the alkyl moiety is a straight- or branched chain alkyl having 1 to 20 carbon atoms, and is exemplified by methylamino, ethylamino, propylamino, isopropylamino, butylamino, isobutylamino, sec-butylamino, tert-butylamino, pentylamino, isopentylamino, tert-pentylamino, hexylamino, heptylamino, octylamino, nonylamino, decylamino, undecylamino, dodecylamino, tridecylamino, tetradecylamino, pentadecylamino, hexadecylamino, heptadecylamino, octadecylamino, nonadecylamino and icosylamino.

The alkylthio as a substituent at R, R^1, R^1a, R^1b, Ra, Rd, Re, Rf, Rt or Rv is that where the alkyl moiety is a straight- or branched chain alkyl having 1 to 20 carbon atoms, and is exemplified by methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec-butylthio, tert-butylthio, pentylthio, isopentylthio, tert-pentylthio, hexylthio, heptylthio, octylthio, nonylthio, decylthio, undecylthio, dodecylthio, tridecylthio, tetradecylthio, pentadecylthio, hexadecylthio, heptadecylthio, octadecylthio, nonadecylthio and icosylthio.

The acylamino as a substituent at R, R^1, R^1a, R^1b, Ra, Rd, Re, Rf, Rt or Rv is that where the acyl moiety is a straight- or branched chain alkanoyl having 1 to 20 carbon atoms, and is exemplified by formylamino, acetylamino, propionylamino, butyrylamino, isobutyrylamino, pentanoylamino, pivaloylamino, hexanoylamino, heptanoylamino, octanoylamino, nonanoylamino, decanoylamino, undecanoylamino, dodecanoylamino, tridecanoylamino, tetradecanoylamino, pentadecanoylamino, hexadecanoylamino, heptadecanoylamino, octadecanoylamino, nonadecanoylamino and icosanoylamino.

The alkoxycarbonyl as a substituent at R, R^1, R^1a, R^1b, Ra, Rd, Re, Rf, Rt or Rv is that where the alkoxy moiety is an optionally substituted straight- or branched chain alkoxy having 1 to 20 carbon atoms, and is exemplified by methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl, isopentyloxycarbonyl, tert-pentyloxycarbonyl, hexyloxycarbonyl, heptyloxycarbonyl, octyloxycarbonyl, nonyloxycarbonyl, decyloxycarbonyl, undecyloxycarbonyl, dodecyloxycarbonyl, tridecyloxycarbonyl, tetradecyloxycarbonyl, pentadecyloxycarbonyl, hexadecyloxycarbonyl, heptadecyloxycarbonyl, octadecyloxycarbonyl, nonadecyloxycarbonyl and icosylox-

ycarbonyl, which may be substituted by phenyl. Examples thereof include benzyloxycarbonyl.

The alkoxycarbonylamino as a substituent at R, R^1, R^1a, R^1b, Ra, Rd, Re, Rf, Rt or Rv is that where the alkoxy moiety is an optionally substituted straight- or branched chain alkoxy having 1 to 20 carbon atoms, and is exemplified by methoxycarbonylamino, ethoxycarbonylamino, propoxycarbonylamino, isoproporycarbonylamino, butoxycarbonylamino, isobutoxycarbonylamino, tert-butoxycarbonylamino, pentyloxycarbonylamino, isopentyloxycarbonylamino, tert-pentyloxycarbonylamino, hexyloxycarbonylamino, heptyloxycarbonylamino, octyloxycarbonylamino, nonyloxycarbonylamino, decyloxycarbonylamino, undecyloxycarbonylamino, dodecyloxycarbonylamino, tridecyloxycarbonylamino, tetradecyloxycarbonylamino, pentadecyloxycarbonylamino, hexadecyloxycarbonylamino, heptadecyloxycarbonylamino, octadecyloxycarbonylamino, nonadecyloxycarbonylamino and icosyloxycarbonylamino, which may be substituted by phenyl. Examples thereof include benzyloxycarbonylamino.

The acyloxy as a substituent at R, R^1, R^1a, R^1b, Ra, Rd, Re, Rf, Rt or Rv is that where the acyl moiety is a straight- or branched chain alkanoyl having 2 to 20 carbon atoms, and is exemplified by acetoxy, propionyloxy, butyryloxy, isobutyryloxy, pivaloyloxy, pentanoyloxy, hexanoyloxy, heptanoyloxy, octanoyloxy, nonanoyloxy, decanoyloxy, undecanoyloxy, dodecanoyloxy, tridecanoyloxy, tetradecanoyloxy, pentadecanoyloxy, hexadecanoyloxy, heptadecanoyloxy, octadecanoyloxy, nonadecanoyloxy and icosanoyloxy.

The alkylcarbamoyl as a substituent at R, R^1, R^1a, R^1b, Ra, Rd, Re, Rf, Rt or Rv is that where the alkyl moiety is a straight- or branched chain alkyl having 1 to 20 carbon atoms, and is exemplified by methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, butylcarbamoyl, pentylcarbamoyl, hexylcarbamoyl, heptylcarbamoyl, octylcarbamoyl, nonylcarbamoyl, decylcarbamoyl, undecylcarbamoyl, dodecylcarbamoyl, tridecylcarbamoyl, tetradecylcarbamoyl, pentadecylcarbamoyl, hexadecylcarbamoyl, heptadecylcarbamoyl, octadecylcarbamoyl, nonadecylcarbamoyl and icosylcarbamoyl.

The haloalkyl as a substituent at R, R^1, R^1a, R^1b, Rd, Rt or Rv is that where the alkyl moiety is a straight- or branched chain alkyl having 1 to 20 carbon atoms, and is exemplified by fluoromethyl, trifluoromethyl, chloromethyl, 2,2,2-trifluoroethyl, perfluoroethyl, 3-chloropropyl, 3-fluoropropyl, 4-chlorobutyl, 4-fluorobutyl, 5-chloropentyl, 6-chlorohexyl, 6-fluorohexyl, 7-chloroheptyl, 7-fluoroheptyl, 8-fluorooctyl, 9-fluorononyl, 10-fluorodecyl, 11-fluoroundecyl, 12-fluorododecyl, 13-fluorotridecyl, 14-fluorotetradecyl, 15-fluoropentadecyl, 16-fluorohexadecyl, 17-fluoroheptadecyl, 18-fluorooctadecyl, 19-fluorononadecyl and 20-fluoroicosyl.

The haloalkoxy as a substituent at R, R^1, Rd, Rt or Rv has 1 to 20 carbon atoms, and is exemplified by chloromethoxy, bromomethoxy, fluoromethoxy, dichloromethoxy, dibromomethoxy, difluoromethoxy, 2-chloroethoxy, 2-fluoroethoxy, 2,2,2-trifluoroethoxy, 3-chloropropoxy, 3-fluoropropoxy, 2,2,3,3-tetrafluoropropoxy, 4-chlorobutoxy, 4-fluorobutoxy, 5-chloropentyloxy, 5-fluoropentyloxy, 6-chlorohexyloxy, 6-fluorohexyloxy, 7-chloroheptyloxy, 7-fluoroheptyloxy, 8-fluorooctyloxy, 9-fluorononyloxy, 10-fluorodecyloxy, 11-fluoroundecyloxy, 12-fluorododecyloxy, 13-fluorotridecyloxy, 14-fluorotetradecyloxy, 15-fluoropentadecyloxy, 16-fluorohexadecyloxy, 17-fluoroheptadecyloxy, 18-fluorooctadecyloxy, 19-fluorononadecyloxy and 20-fluoroicosyloxy.

The halogen as a substituent at R, R^1, R^1a, R^1b, Ra, Rb, Rc, Rd, Re, Rf, Rg, Ri, Rj, Rs, Rt or Rv is exemplified by fluorine, chlorine, bromine and iodine.

The aryl as a substituent at R, R^1 or Rt is exemplified by phenyl and naphthyl, with preference given to phenyl.

The aryloxy as a substituent at R, R^1 or Rt is exemplified by phenoxy and naphthyloxy, with preference given to phenoxy.

The cycloalkyl as a substituent at R, R^1, R^1a, R^1b or Rt is that having 3 to 10 carbon atoms and is exemplified by cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl and cyclodecyl, with preference given to cyclohexyl.

The heteroaryl as a substituent at R, R^1 or Rt is a 5- or 6-membered heteroaryl optionally having, in the ring, 1 to 4 hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom and includes, for example, monocyclic heteroaryl such as thienyl(2-thienyl, 3-thienyl), furyl(2-furyl, 3-furyl), pyrrolyl(1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl), imidazolyl(2-imidazolyl, 4-imidazolyl etc.), pyrazolyl(3-pyrazolyl, 4-pyrazolyl etc.), triazolyl, tetrazolyl, thiazolyl(2-thiazolyl, 4-thiazolyl), isothiazolyl(3-isothiazolyl, 4-isothiazolyl), oxazolyl(2-oxazolyl, 4-oxazolyl), isoxazolyl(3-isooxazolyl, 4-isooxazolyl), pyridyl(2-pyridyl, 3-pyridyl, 4-pyridyl), pyrazinyl, pyrimidinyl(2-pyrimidinyl, 4-pyrimidinyl), pyridazinyl(3-pyridazinyl, 4-pyridazinyl) and pyranyl(2-pyranyl, 3-pyranyl, 4-pyranyl), and bicyclic heteroaryl such as indolyl(2-indolyl, 3-indoly]), quinolyl(2-quinolyl, 3-quinolyl), isoquinolyl(1-isoquinolyl, 3-isoquinolyl), benzofuranyl(2-benzofuranyl, 3-benzofuranyl), benzothienyl(2-benzothienyl, 3-benzothienyl), 1H-benzimidazol-2-yl or chromenyl(2-chromenyl, 3-chromenyl, 4-chromenyl).

The alicycle of the aforementioned heteroaryl as a substituent at R, R^1 or Rt is the above-mentioned monocyclic heteroaryl when saturated such as pyrrolidinyl(1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl), piperidyl(2-piperidy], 3-piperidyl, 4-piperidyl), piperidino, piperazinyl, morpholinyl or thiomorpholinyl.

The carbon chain as a substituent at R^1a is a straight- or branched carbon chain having 1 to 30 carbon atoms such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, isopentyl, tert-pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, nonadecyl, icosyl, henicosyl, docosyl, tricosyl, tetracosyl, pentacosyl, hexacosyl, heptacosyl, octacosyl, nonacosyl or triacontyl.

The alkenyl as a substituent at R^1b is a straight- or branched chain alkenyl having 2 to 20 carbon atoms such as ethenyl, propenyl, isopropenyl, butenyl, isobutenyl, pentenyl, isopentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl, undecenyl, dodecenyl, tridecenyl, tetradecenyl, pentadecenyl, hexadecenyl, heptadecenyl, octadeceny], nonadecenyl or icosenyl.

The alkynyl as a substituent at R^1b is a straight- or branched chain alkynyl having 2 to 20 carbon atoms such as ethynyl, propynyl, isopropynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, decynyl, undecynyl, dodecynyl, tridecynyl, tetradecynyl, pentadecynyl, hexadecynyl, heptadecynyl, octadecynyl, nonadecynyl or icosynyl.

The haloaralkyloxy as a substituent at Rd is that including aralkyl where the alkyl moiety is a straight- or branched chain alkyl having 1 to 20 carbon atoms, and is exemplified by halophenylalkoxy such as 4-fluorobenzyloxy, 2-(4-fluorophenyl)-ethyloxy, 1-(4-fluorophenyl)ethyloxy, 1-(4-fluorophenyl)-propyloxy, 2-(4-fluorophenyl)propyloxy, 3-(4-fluorophenyl)-propyloxy, 4-(4-fluorophenyl)butyloxy, 5-(4-fluorophenyl)-pentyloxy, 6-(4-fluorophenyl)hexyloxy, 7-(4-fluorophenyl)-heptyloxy, 8-(4-fluorophenyl)octyloxy, 9-(4-fluorophenyl)-nonyloxy, 10-(4-fluorophenyl)decyloxy, 11-(4-fluorophenyl)-undecyloxy, 12-(4-fluorophenyl)-dodecyloxy, 13-(4-fluorophenyl)-tridecyloxy or 14-(4-fluorophenyl)tetradecyloxy, and halonaphthylalkoxy such as (7-fluoro-2-naphthyl)methyloxy or 2-(7-fluoro-2-naphthyl)ethyloxy, with preference given to halophenylalkoxy.

The halophenylalkoxy as a substituent at Re, Rf, Rg or Rk is that of the aforementioned haloaralkyloxy.

The halophenylalkoxy as a substituent at Rl, where the alkoxy moiety has 2 to 8 carbon atoms, is halophenylalkoxy of the aforementioned haloaralkyloxy, having the specified numbers of carbon atoms.

The aralkyloxyalkyl as a substituent at Rd is that where the alkyl moiety and the alkyl moiety of the aralkyl are straight- or branched chain alkyls having 1 to 20 carbon atoms and have 2 to 20 carbon atoms in total, and is exemplified by phenylalkoxyalkyl such as phenylmethyloxymethyl, 2-phenylethyloxymethyl, 3-phenylpropyloxymethyl, 4-phenylbutyloxymethyl, 5-phenylpentyloxymethyl, 6-phenylhexyloxymethyl, 7-phenylheptyloxymethyl, 8-phenyloctyloxymethyl, 9-phenylnonyloxymethyl, 10-phenyldecyloxymethyl, 12-phenyldodecyloxymethyl, 14-phenyltetradecyloxymethyl, 16-phenylhexadecyloxymethyl or 18-phenyloctadecyloxymethyl, and naphthylalkoxyalkyl such as 4-(2-naphthyl)butyloxymethyl, 5-(2-naphthyl)-pentyloxymethyl or 6-(2-naphthyl)hexyloxymethyl, with preference given to phenylalkoxyalkyl.

The phenylalkoxyalkyl as a substituent at Re, Rf, Rg or Rk is that of the aforementioned aralkyloxyalkyl.

The phenylalkoxyalkyl as a substituent at Rl, where the alkoxy moiety and the alkyl moiety have 2 to 8 carbon atoms in total, is phenylalkoxyalkyl of the aforementioned aralkyloxyalkyl, having the specified numbers of carbon atoms, in which the carbon number of the alkoxy moiety and the alkyl moiety is respectively 1 to 7, with total being 2 to 8.

The phenoxylalkyl as a substituent at Rd, Re, Rf, Rg or Rk is that where the alkyl moiety is a straight- or branched chain alkyl having 1 to 20 carbon atoms and is exemplified by phenoxymethyl, 1-phenoxyethyl, 2-phenoxyethyl, 1-phenoxypropyl, 2-phenoxypropyl, 3-phenoxypropyl, 4-phenoxybutyl, 5-phenoxypentyl, 6-phenoxyhexyl, 7-phenoxyheptyl, 8-phenoxyoctyl, 9-phenoxynonyl, 10-phenoxydecyl, 11-phenoxyundecyl, 12-phenoxydodecyl, 13-phenoxytridecyl, 14-phenoxytetradecyl, 15-phenoxypentadecyl, 16-phenoxyhexadecyl, 17-phenoxyheptadecyl, 18-phenoxyoctadecyl, 19-phenoxynonadecyl and 20-phenoxyicosyl.

The phenoxyalkyl as a substituent at Rl, where the alkyl moiety has 2 to 8 carbon atoms, is the aforementioned phenoxyalkyl having the specified numbers of carbon atoms.

The phenoxyalkoxy as a substituent at Rd, Re, Rf, Rg or Rk is that where the alkoxy moiety is a straight- or branched chain alkoxy having 1 to 20 carbon atoms and is exemplified by phenoxymethoxy, 1-phenoxyethyloxy, 2-phenoxyethyloxy, 1-phenoxypropyloxy, 2-phenoxypropyloxy, 3-phenoxypropyloxy, 4-phenoxybutyloxy, 5-phenoxypentyloxy, 6-phenoxyhexyloxy, 7-phenoxyheptyloxy, 8-phenoxyoctyloxy, 9-phenoxynonyloxy, 10-phenoxydecyloxy, 11-phenoxyundecyloxy, 12-phenoxydodecyloxy, 13-phenoxytridecyloxy, 14-phenoxytetradecyloxy, 15-phenoxypentadecyloxy, 16-phenoxyhexadecyloxy, 17-phenoxyheptadecyloxy, 18-phenoxyoctadecyloxy, 19-phenoxynonadecyloxy and 20-phenoxyicosyloxy.

The phenoxyalkoxy as a substituent at Rl, where the alkoxy moiety has 2 to 8 carbon atoms, is the aforementioned phenoxyalkoxy having the specified numbers of carbon atoms.

The alkyl at R^2, R^2a, R^2b, R^2c, R^3, R^3a, R^3b, R^3c, R^4, R^4a, R^4b, R^5, R^5a, R^5b or R^6 is that having 1 to 20 carbon atoms and is exemplified by methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, isopentyl, tert-pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, nonadecyl and icosyl.

The aralkyl at R^2, R^3, R^4, R^5 or R^6 is that where the alkyl moiety is a straight- or branched chain alkyl having 1 to 20 carbon atoms and is exemplified by benzyl, 1-phenylethyl, 2-phenylethyl, 1-phenylpropyl, 2-phenylpropyl, 3-phenylpropyl, 4-phenylbutyl, 5-phenylpentyl, 6-phenylhexyl, 7-phenylheptyl, 8-phenyloctyl, 9-phenylnonyl, 10-phenyldecyl, 11-phenylundecyl, 12-phenyldodecyl, 13-phenyltridecyl, 14-phenyltetradecyl, 15-phenylpentadecyl, 16-phenylhexadecyl, 17-phenylheptadecyl, 18-phenyloctadecyl, 19-phenylnonadecyl and 20-phenylicosyl.

The acyl at R^2, R^2a, R^2b, R^3, R^3a, R^3b, R^4, R^4a, R^4b, R^5, R^5a, R^5b or R^6 is optionally substituted alkanoyl or aroyl where the alkanoyl is a straight- or branched chain alkanoyl having 1 to 20 carbon atoms, and alkoanoyl is exemplified by formyl, acetyl, propionyl, butyryl, isobutyryl, pentanoyl, hexanoyl, heptanoyl, octanoyl, nonanoyl, decanoyl, undecanoyl, dodecanoyl, tridecanoyl, tetradecanoyl, pentadecanoyl, hexadecanoyl, heptadecanoyl, octadecanoyl, nonadecanoyl and icosanoyl, which may be substituted by phenyl. Examples thereof include phenylacetyl and phenylpropionyl. Examples of aroyl include benzoyl.

The alkoxycarbonyl at R^2, R^2a, R^3, R^3a, R^4, R^4a, R^5, R^5a or R^6 is that where the alkoxy moiety is an optionally substituted straight- or branched chain alkoxy having 1 to 20 carbon atoms and is exemplified by methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl, isopentyloxycarbonyl, tert-pentyloxycarbonyl, hexyloxycarbonyl, heptyloxycarbonyl, octyloxycarbonyl, nonyloxycarbonyl, decyloxycarbonyl, undecyloxycarbonyl, dodecyloxycarbonyl, tridecyloxycarbonyl, tetradecyloxycarbonyl, pentadecyloxycarbonyl, hexadecyloxycarbonyl, heptadecyloxycarbonyl, octadecyloxycarbonyl, nonadecyloxycarbonyl and icosyloxycarbonyl, which may be substituted by phenyl. Examples thereof include benzyloxycarbonyl.

The alkylene chain formed by R^4 and R^5 is a straight- or branched chain alkylene having 1 to 5 carbon atoms and is exemplified by methylene, ethylene, trimethylene, propylene, butylene, 1,2-dimethylethylene and pentamethylene.

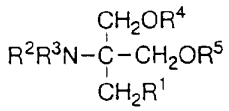
The alkyl as a substituent at R^4 or R^5 is a straight- or branched chain alkyl having 1 to 5 carbon atoms and is exemplified by methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl and pentyl.

The aryl as a substituent at R^4 or R^5 is, for example, phenyl or naphthyl.

The aralkyl as a substituent at R^4 or R^5 is that where the alkyl moiety is a straight- or branched chain alkyl having 1 to 5 carbon atoms and is exemplified by benzyl, 2-phenethyl, 1-phenylethyl, 1-phenylpropyl, 2-phenylpropyl, 3-phenylpropyl, 4-phenylbutyl and 5-phenylpentyl.

The alkylene chain formed by R^4 and R^5, which is substituted by alkyl, aryl or aralkyl, is preferably ethylidene, isopropylidene, benzylidene or 2-phenylethylidene.

The preferable compounds of the present invention are shown in the following tables.



R^1	R^2	R^3	R^4	R^5
$CH(CH_3)_2$	H	H	H	H
$CH(CH_3)C_2H_5$	H	H	H	H
$CH(CH_3)C_3H_7$	H	H	H	H
$C(CH_3)_3$	H	H	H	H
$C(CH_3)_2C_2H_5$	H	H	H	H
$C(CH_3)_2C_3H_7$	H	H	H	H
C_5H_{11}	H	H	H	H
C_5H_{11}	$COCH_3$	H	$COCH_3$	$COCH_3$
C_6H_{13}	H	H	H	H
C_7H_{15}	H	H	H	H
C_7H_{15}	$COCH_3$	H	$COCH_3$	$COCH_3$
C_8H_{17}	H	H	H	H
C_9H_{19}	H	H	H	H
C_9H_{19}	$COCH_3$	H	$COCH_3$	$COCH_3$
$C_{10}H_{21}$	H	H	H	H
$C_{11}H_{23}$	H	H	H	H
$C_{11}H_{23}$	$COCH_3$	H	$COCH_3$	$COCH_3$
$[CH_2CH(CH_3)(CH_2)_2]_2CH_2CH(CH_3)_2$	H	H	H	H
$[CH_2CH(CH_3)(CH_2)_2]_2CH_2CH(CH_3)_2$	$COCH_3$	H	$COCH_3$	$COCH_3$
$C_{12}H_{25}$	H	H	H	H
$C_{12}H_{25}$	$COCH_3$	H	$COCH_3$	$COCH_3$
$C_{13}H_{27}$	H	H	H	H
$C_{13}H_{27}$	CH_3	CH_3	H	H
$(CH_2)_3CH(CH_3)C_{10}H_{21}$	H	H	H	H
$C_{14}H_{29}$	H	H	H	H
$C_{14}H_{29}$	$COCH_3$	H	$COCH_3$	$COCH_3$
$C_{15}H_{31}$	H	H	H	H
$C_{16}H_{33}$	H	H	H	H
$C_{17}H_{35}$	H	H	H	H
$C_{17}H_{35}$	C_2H_5	H	H	H

R^1	R^2	R^3	R^4	R^5
$C_{17}H_{35}$	H	H	$COCH_3$	$COCH_3$
$C_{17}H_{35}$	COC_4H_9	H	$COCH_3$	$COCH_3$
$C_{17}H_{35}$	COC_4H_9	H	H	H
$C_{17}H_{35}$	C_5H_{11}	H	H	H
$C_{17}H_{35}$	COC_9H_{19}	H	$COCH_3$	$COCH_3$
$C_{17}H_{35}$	COC_9H_{19}	H	H	H
$C_{17}H_{35}$	$C_{10}H_{21}$	H	H	H
$C_{17}H_{35}$	CH_3	CH_3	$COCH_3$	$COCH_3$
$C_{17}H_{35}$	CH_3	CH_3	H	H
$C_{18}H_{37}$	H	H	H	H
$C_{19}H_{39}$	H	H	H	H
$C_{20}H_{41}$	H	H	H	H
$C_{21}H_{43}$	H	H	H	H
$C_{22}H_{45}$	H	H	H	H
$C_{23}H_{47}$	H	H	H	H
$C_{24}H_{49}$	H	H	H	H
$C_{25}H_{51}$	H	H	H	H
$C_{26}H_{53}$	H	H	H	H
$C_{27}H_{55}$	H	H	H	H
$C_{28}H_{57}$	H	H	H	H
$C_{29}H_{59}$	H	H	H	H
$CH=CH_2$	H	H	H	H
$CH=CHCH_3$	H	H	H	H
$CH=CHC_2H_5$	H	H	H	H
$CH=CHC_3H_7$	H	H	H	H
$CH=CHC_4H_9$	H	H	H	H
$CH=CHC_5H_{11}$	H	H	H	H
$CH=CHC_6H_{13}$	H	H	H	H
$CH=CHC_7H_{15}$	H	H	H	H
$CH=CHC_9H_{19}$	H	H	H	H
$CH=CHC_{11}H_{23}$	H	H	H	H
$CH=CHC_{13}H_{27}$	H	H	H	H
$CH=CHC_{15}H_{31}$	H	H	H	H
$CH=CHC_{17}H_{35}$	H	H	H	H

R^1	R^2	R^3	R^4	R^5
$CH=CHC_{27}H_{55}$	H	H	H	H
$CH_2CH=CH_2$	H	H	H	H
$CH_2CH=CHCH_3$	H	H	H	H
$CH_2CH=CHC_2H_5$	H	H	H	H
$CH_2CH=CHC_3H_7$	H	H	H	H
$CH_2CH=CHC_4H_9$	H	H	H	H
$CH_2CH=CHC_5H_{11}$	H	H	H	H
$CH_2CH=CHC_6H_{13}$	H	H	H	H
$CH_2CH=CHC_8H_{17}$	H	H	H	H
$CH_2CH=CHC_{10}H_{21}$	H	H	H	H
$CH_2CH=CHC_{12}H_{25}$	H	H	H	H
$CH_2CH=CHC_{14}H_{29}$	H	H	H	H
$CH_2CH=CHC_{16}H_{33}$	H	H	H	H
$CH_2CH=CHC_{26}H_{53}$	H	H	H	H
$(CH_2)_2CH=CH_2$	H	H	H	H
$(CH_2)_2CH=CHCH_3$	H	H	H	H
$(CH_2)_2CH=CHC_2H_5$	H	H	H	H
$(CH_2)_2CH=CHC_3H_7$	H	H	H	H
$(CH_2)_2C(CH_3)=CHC_4H_9$	H	H	H	H
$(CH_2)_2CH=CHC_4H_9$	H	H	H	H
$(CH_2)_2CH=CHC_5H_{11}$	H	H	H	H
$(CH_2)_2CH=CHC_7H_{15}$	H	H	H	H
$(CH_2)_2CH=CHC_9H_{19}$	H	H	H	H
trans: $(CH_2)_2CH=CHC_9H_{19}$	H	H	H	H
cis: $(CH_2)_2CH=CHC_9H_{19}$	H	H	H	H
$(CH_2)_2CH=CHC_{11}H_{23}$	H	H	H	H
$(CH_2)_2CH=CHC_{13}H_{27}$	H	H	H	H
$(CH_2)_2CH=CHC_{15}H_{31}$	H	H	H	H
$(CH_2)_2CH=CHC_{25}H_{51}$	H	H	H	H
$(CH_2)_3CH=CH_2$	H	H	H	H
$(CH_2)_3CH=CHCH_3$	H	H	H	H
$(CH_2)_3CH=CHC_2H_5$	H	H	H	H
$(CH_2)_3C(CH_3)=CHC_3H_7$	H	H	H	H
$(CH_2)_3CH=CHC_3H_7$	H	H	H	H

R^1	R^2	R^3	R^4	R^5
$(CH_2)_3CH=CHC_4H_9$	H	H	H	H
$(CH_2)_3CH=CHC_6H_{13}$	H	H	H	H
$(CH_2)_3CH=CHC_8H_{17}$	H	H	H	H
$(CH_2)_3CH=CHC_{10}H_{21}$	H	H	H	H
$(CH_2)_3CH=CHC_{12}H_{25}$	H	H	H	H
$(CH_2)_3CH=CHC_{14}H_{29}$	H	H	H	H
$(CH_2)_3CH=CHC_{24}H_{49}$	H	H	H	H
$(CH_2)_4CH=CH_2$	H	H	H	H
$(CH_2)_4CH=CHCH_3$	H	H	H	H
$(CH_2)_4CH=CHC_2H_5$	H	H	H	H
$(CH_2)_4CH=CHC_3H_7$	H	H	H	H
$(CH_2)_4CH=CHC_5H_{11}$	H	H	H	H
$(CH_2)_4CH=CHC_7H_{15}$	H	H	H	H
$(CH_2)_4CH=CHC_9H_{19}$	H	H	H	H
$(CH_2)_4CH=CHC_{11}H_{23}$	H	H	H	H
$(CH_2)_4CH=CHC_{13}H_{27}$	H	H	H	H
$(CH_2)_4CH=CHC_{23}H_{47}$	H	H	H	H
$(CH_2)_5CH=CH_2$	H	H	H	H
$(CH_2)_5CH=CHCH_3$	H	H	H	H
$(CH_2)_5CH=CHC_2H_5$	H	H	H	H
$(CH_2)_5CH=CHC_4H_9$	H	H	H	H
$(CH_2)_5CH=CHC_6H_{13}$	H	H	H	H
$(CH_2)_5CH=CHC_8H_{17}$	H	H	H	H
$(CH_2)_5CH=CHC_{10}H_{21}$	H	H	H	H
$(CH_2)_5CH=CHC_{12}H_{25}$	H	H	H	H
$(CH_2)_5CH=CHC_{22}H_{45}$	H	H	H	H
$(CH_2)_6CH=CH_2$	H	H	H	H
$(CH_2)_6CH=CHCH_3$	H	H	H	H
$(CH_2)_6CH=CHC_3H_7$	H	H	H	H
$(CH_2)_6CH=CHC_5H_{11}$	H	H	H	H
$(CH_2)_6CH=CHC_7H_{15}$	H	H	H	H
$(CH_2)_2CH(C_2H_5)(CH_2)_3CH=CHC_9H_{19}$	H	H	H	H
$(CH_2)_6CH=CHC_9H_{19}$	H	H	H	H
$(CH_2)_6CH=CHC_{11}H_{23}$	H	H	H	H

R^1	R^2	R^3	R^4	R^5
$(CH_2)_6CH=CHC_{21}H_{43}$	H	H	H	H
$(CH_2)_7CH=CH_2$	H	H	H	H
$(CH_2)_7CH=CHC_2H_5$	H	H	H	H
$(CH_2)_7CH=CHC_4H_9$	H	H	H	H
$(CH_2)_7CH=CHC_6H_{13}$	H	H	H	H
$(CH_2)_7CH=CHC_8H_{17}$	H	H	H	H
$(CH_2)_7CH=CHC_{10}H_{21}$	H	H	H	H
$(CH_2)_7CH=CHC_{20}H_{41}$	H	H	H	H
$(CH_2)_8CH=CHCH_3$	H	H	H	H
$(CH_2)_8CH=CHC_3H_7$	H	H	H	H
$(CH_2)_8CH=CHC_5H_{11}$	H	H	H	H
$(CH_2)_8CH=CHC_7H_{15}$	H	H	H	H
$(CH_2)_8CH=CHC_9H_{19}$	H	H	H	H
$(CH_2)_8CH=CHC_{19}H_{39}$	H	H	H	H
$(CH_2)_{10}CH=CHCH_3$	H	H	H	H
$(CH_2)_{10}CH=CHC_3H_7$	H	H	H	H
$(CH_2)_3CH(C_3H_7)(CH_2)_6CH=CHC_5H_{11}$	H	H	H	H
$(CH_2)_{10}CH=CHC_5H_{11}$	H	H	H	H
$(CH_2)_{10}CH=CHC_7H_{15}$	H	H	H	H
$(CH_2)_{10}CH=CHC_{17}H_{35}$	H	H	H	H
$(CH_2)_{12}CH=CHCH_3$	H	H	H	H
$(CH_2)_{12}CH=CHC_3H_7$	H	H	H	H
$(CH_2)_{12}CH=CHC_5H_{11}$	H	H	H	H
$(CH_2)_{12}CH=CHC_{15}H_{31}$	H	H	H	H
$(CH_2)_{14}CH=CHCH_3$	H	H	H	H
$(CH_2)_{14}C(CH_3)=CHC_3H_7$	H	H	H	H
$(CH_2)_{14}CH=CHC_3H_7$	H	H	H	H
$(CH_2)_{14}CH=CHC_{13}H_{27}$	H	H	H	H
$(CH_2)_{16}CH=CHCH_3$	H	H	H	H
$(CH_2)_{16}CH=CHC_{11}H_{23}$	H	H	H	H
$(CH_2)_{19}CH=CHC_8H_{17}$	H	H	H	H
$(CH_2)_{20}CH=CHC_7H_{15}$	H	H	H	H
$(CH_2)_{22}CH=CHC_5H_{11}$	H	H	H	H
$(CH_2)_{24}CH=CHC_3H_7$	H	H	H	H

R^1	R^2	R^3	R^4	R^5
$(CH_2)_{26}CH=CHCH_3$	H	H	H	H
$[CH=C(CH_3)CH_2CH_2]_3$-H	H	H	H	H
$[CH=C(CH_3)CH_2CH_2]_3$-H	$COCH_3$	H	$COCH_3$	$COCH_3$
$C\equiv CH$	H	H	H	H
$C\equiv CCH_3$	H	H	H	H
$C\equiv CC_2H_5$	H	H	H	H
$C\equiv CC_3H_7$	H	H	H	H
$C\equiv CC_4H_9$	H	H	H	H
$C\equiv CC_5H_{11}$	H	H	H	H
$C\equiv CC_6H_{13}$	H	H	H	H
$C\equiv CC_7H_{15}$	H	H	H	H
$C\equiv CC_9H_{19}$	H	H	H	H
$C\equiv CC_{11}H_{23}$	H	H	H	H
$C\equiv CC_{12}H_{25}$	H	H	H	H
$C\equiv CC_{12}H_{25}$	$COCH_3$	H	$COCH_3$	$COCH_3$
$C\equiv CC_{13}H_{27}$	H	H	H	H
$C\equiv CC_{15}H_{31}$	H	H	H	H
$C\equiv CC_{17}H_{35}$	H	H	H	H
$C\equiv CC_{27}H_{55}$	H	H	H	H
$CH_2C\equiv CH$	H	H	H	H
$CH_2C\equiv CCH_3$	H	H	H	H
$CH_2C\equiv CC_2H_5$	H	H	H	H
$CH_2C\equiv CC_3H_7$	H	H	H	H
$CH_2C\equiv CC_4H_9$	H	H	H	H
$CH_2C\equiv CC_5H_{11}$	H	H	H	H
$CH_2C\equiv CC_6H_{13}$	H	H	H	H
$CH_2C\equiv CC_8H_{17}$	H	H	H	H
$CH_2C\equiv CC_{10}H_{21}$	H	H	H	H
$CH_2C\equiv CC_{12}H_{25}$	H	H	H	H
$CH_2C\equiv CC_{14}H_{29}$	H	H	H	H
$CH_2C\equiv CC_{16}H_{33}$	H	H	H	H
$CH_2C\equiv CC_{25}H_{53}$	H	H	H	H
$(CH_2)_2C\equiv CH$	H	H	H	H
$(CH_2)_2C\equiv CCH_3$	H	H	H	H

R^1	R^2	R^3	R^4	R^5
$(CH_2)_2C\equiv CC_2H_5$	H	H	H	H
$(CH_2)_2C\equiv CC_3H_7$	H	H	H	H
$(CH_2)_2C\equiv CC_4H_9$	H	H	H	H
$(CH_2)_2C\equiv CC_5H_{11}$	H	H	H	H
$(CH_2)_2C\equiv CC_7H_{15}$	H	H	H	H
$(CH_2)_2C\equiv CC_9H_{19}$	H	H	H	H
$(CH_2)_2C\equiv CC_{11}H_{23}$	H	H	H	H
$(CH_2)_2C\equiv CC_{13}H_{27}$	H	H	H	H
$(CH_2)_2C\equiv CC_{15}H_{31}$	H	H	H	H
$(CH_2)_2C\equiv CC_{25}H_{51}$	H	H	H	H
$(CH_2)_3C\equiv CH$	H	H	H	H
$(CH_2)_3C\equiv CCH_3$	H	H	H	H
$(CH_2)_3C\equiv CC_2H_5$	H	H	H	H
$(CH_2)_3C\equiv CC_3H_7$	H	H	H	H
$(CH_2)_3C\equiv CC_4H_9$	H	H	H	H
$(CH_2)_3C\equiv CC_6H_{13}$	H	H	H	H
$(CH_2)_3C\equiv CC_8H_{17}$	H	H	H	H
$(CH_2)_2CH(CH_3)C\equiv CC_{10}H_{21}$	H	H	H	H
$(CH_2)_3C\equiv CC_{10}H_{21}$	H	H	H	H
$(CH_2)_3C\equiv CC_{12}H_{25}$	H	H	H	H
$(CH_2)_3C\equiv CC_{14}H_{29}$	H	H	H	H
$(CH_2)_3C\equiv CC_{24}H_{49}$	H	H	H	H
$(CH_2)_4C\equiv CH$	H	H	H	H
$(CH_2)_4C\equiv CCH_3$	H	H	H	H
$(CH_2)_4C\equiv CC_2H_5$	H	H	H	H
$(CH_2)_4C\equiv CC_3H_7$	H	H	H	H
$(CH_2)_4C\equiv CC_5H_{11}$	H	H	H	H
$(CH_2)_4C\equiv CC_7H_{15}$	H	H	H	H
$(CH_2)_4C\equiv CC_9H_{19}$	H	H	H	H
$(CH_2)_4C\equiv CC_{11}H_{23}$	H	H	H	H
$(CH_2)_4C\equiv CC_{13}H_{27}$	H	H	H	H
$(CH_2)_4C\equiv CC_{23}H_{47}$	H	H	H	H
$(CH_2)_5C\equiv CH$	H	H	H	H
$(CH_2)_5C\equiv CCH_3$	H	H	H	H

R^1	R^2	R^3	R^4	R^5
$(CH_2)_3C\equiv CC_2H_5$	H	H	H	H
$(CH_2)_3C\equiv CC_4H_9$	H	H	H	H
$(CH_2)_5C\equiv CC_6H_{13}$	H	H	H	H
$(CH_2)_5C\equiv CC_8H_{17}$	H	H	H	H
$(CH_2)_5C\equiv CC_{10}H_{21}$	H	H	H	H
$(CH_2)_5C\equiv CC_{12}H_{25}$	H	H	H	H
$(CH_2)_5C\equiv CC_{22}H_{45}$	H	H	H	H
$(CH_2)_6C\equiv CH$	H	H	H	H
$(CH_2)_6C\equiv CCH_3$	H	H	H	H
$(CH_2)_6C\equiv CC_3H_7$	H	H	H	H
$(CH_2)_6C\equiv CC_5H_{11}$	H	H	H	H
$(CH_2)_6C\equiv CC_7H_{15}$	H	H	H	H
$(CH_2)_6C\equiv CC_9H_{19}$	H	H	H	H
$(CH_2)_6C\equiv CC_{11}H_{23}$	H	H	H	H
$(CH_2)_6C\equiv CC_{21}H_{43}$	H	H	H	H
$(CH_2)_7C\equiv CH$	H	H	H	H
$(CH_2)_7C\equiv CC_2H_5$	H	H	H	H
$(CH_2)_7C\equiv CC_4H_9$	H	H	H	H
$(CH_2)_7C\equiv CC_5H_{13}$	H	H	H	H
$(CH_2)_2CH(CH_3)(CH_2)_4C\equiv CC_8H_{17}$	H	H	H	H
$(CH_2)_7C\equiv CC_8H_{17}$	H	H	H	H
$(CH_2)_7C\equiv CC_{10}H_{21}$	H	H	H	H
$(CH_2)_7C\equiv CC_{20}H_{41}$	H	H	H	H
$(CH_2)_8C\equiv CCH_3$	H	H	H	H
$(CH_2)_8C\equiv CC_3H_7$	H	H	H	H
$(CH_2)_8C\equiv CC_5H_{11}$	H	H	H	H
$(CH_2)_8C\equiv CC_7H_{15}$	H	H	H	H
$(CH_2)_8C\equiv CC_9H_{19}$	H	H	H	H
$(CH_2)_8C\equiv CC_{19}H_{39}$	H	H	H	H
$(CH_2)_{10}C\equiv CCH_3$	H	H	H	H
$(CH_2)_{10}C\equiv CC_3H_7$	H	H	H	H
$(CH_2)_{10}C\equiv CC_5H_{11}$	H	H	H	H
$(CH_2)_3CH(CH_3)(CH_2)_6C\equiv CC_7H_{15}$	H	H	H	H
$(CH_2)_{10}C\equiv CC_7H_{15}$	H	H	H	H

R^1	R^2	R^3	R^4	R^5
$(CH_2)_{10}C\equiv CC_{17}H_{35}$	H	H	H	H
$(CH_2)_{12}C\equiv CCH_3$	H	H	H	H
$(CH_2)_{12}C\equiv CC_3H_7$	H	H	H	H
$(CH_2)_{12}C\equiv CC_5H_{11}$	H	H	H	H
$(CH_2)_{12}C\equiv CC_{15}H_{31}$	H	H	H	H
$(CH_2)_{14}C\equiv CCH_3$	H	H	H	H
$(CH_2)_{14}C\equiv CC_3H_7$	H	H	H	H
$(CH_2)_{14}C\equiv CC_{13}H_{27}$	H	H	H	H
$(CH_2)_{16}C\equiv CCH_3$	H	H	H	H
$(CH_2)_{16}C\equiv CC_{11}H_{23}$	H	H	H	H
$(CH_2)_{18}C\equiv CC_9H_{19}$	H	H	H	H
$(CH_2)_{20}C\equiv CC_7H_{15}$	H	H	H	H
$(CH_2)_{22}C\equiv CC_5H_{11}$	H	H	H	H
$(CH_2)_{24}C\equiv CC_3H_7$	H	H	H	H
$(CH_2)_{26}C\equiv CCH_3$	H	H	H	H
CH_2OH	H	H	H	H
$(CH_2)_2OH$	H	H	H	H
$CH_2(OH)CH_3$	H	H	H	H
$(CH_2)_3OH$	H	H	H	H
$(CH_2)_4OH$	H	H	H	H
$(CH_2)_5OH$	H	H	H	H
$(CH_2)_6OH$	H	H	H	H
$(CH_2)_7OH$	H	H	H	H
$(CH_2)_8OH$	H	H	H	H
$(CH_2)_9OH$	H	H	H	H
$(CH_2)_{10}OH$	H	H	H	H
$(CH_2)_{11}OH$	H	H	H	H
$(CH_2)_6CH(C_6H_{13})OH$	H	H	H	H
$(CH_2)_6CH(C_6H_{13})OH$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_{17}OH$	H	H	H	H
$(CH_2)_{19}OH$	H	H	H	H
$(CH_2)_{29}OH$	H	H	H	H
COOH	H	H	H	H
CH_2COOH	H	H	H	H

R^1	R^2	R^3	R^4	R^5
$(CH_2)_2COOH$	H	H	H	H
$(CH_2)_3COOH$	H	H	H	H
$(CH_2)_4COOH$	H	H	H	H
$(CH_2)_5COOH$	H	H	H	H
$(CH_2)_6COOH$	H	H	H	H
$(CH_2)_7COOH$	H	H	H	H
$(CH_2)_8COOH$	H	H	H	H
$(CH_2)_9COOH$	H	H	H	H
$(CH_2)_{10}COOH$	H	H	H	H
$(CH_2)_{11}COOH$	H	H	H	H
$(CH_2)_{17}COOH$	H	H	H	H
$(CH_2)_{19}COOH$	H	H	H	H
$(CH_2)_{25}COOH$	H	H	H	H
CH_2COOCH_3	H	H	H	H
$CH_2COOC_2H_5$	H	H	H	H
$CH_2COOC_{10}H_{21}$	H	H	H	H
$CH_2COOC_{14}H_{29}$	H	H	H	H
$(CH_2)_2COOCH_3$	H	H	H	H
$(CH_2)_2COOC_2H_5$	H	H	H	H
$(CH_2)_2COOC_{10}H_{21}$	H	H	H	H
$(CH_2)_2COOC_{13}H_{27}$	H	H	H	H
$(CH_2)_3COOCH_3$	H	H	H	H
$(CH_2)_3COOC_2H_5$	H	H	H	H
$(CH_2)_3COOC_{10}H_{21}$	H	H	H	H
$(CH_2)_3COOC_{12}H_{25}$	H	H	H	H
$(CH_2)_4COOCH_3$	H	H	H	H
$(CH_2)_4COOC_2H_5$	H	H	H	H
$(CH_2)_4COOC_{10}H_{21}$	H	H	H	H
$(CH_2)_4COOC_{11}H_{23}$	H	H	H	H
$(CH_2)_5COOCH_3$	H	H	H	H
$(CH_2)_5COOC_2H_5$	H	H	H	H
$(CH_2)_5COOC_{10}H_{21}$	H	H	H	H
$(CH_2)_6COOCH_3$	H	H	H	H
$(CH_2)_6COOC_2H_5$	H	H	H	H

R^1	R^2	R^3	R^4	R^5
$(CH_2)_8COOC_9H_{19}$	H	H	H	H
$(CH_2)_7COOCH_3$	H	H	H	H
$(CH_2)_7COOC_2H_5$	H	H	H	H
$(CH_2)_7COOC_8H_{17}$	H	H	H	H
$(CH_2)_8COOCH_3$	H	H	H	H
$(CH_2)_3CH(C_4H_9)COOC_2H_5$	H	H	H	H
$(CH_2)_8COOC_7H_{15}$	H	H	H	H
$(CH_2)_9COOCH_3$	H	H	H	H
$(CH_2)_9COOC_2H_5$	H	H	H	H
$(CH_2)_9COOC_6H_{13}$	H	H	H	H
$(CH_2)_{10}COOCH_3$	H	H	H	H
$(CH_2)_{10}COOCH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_{10}COOC_2H_5$	H	H	H	H
$(CH_2)_{10}COOC_5H_{11}$	H	H	H	H
$(CH_2)_{11}COOCH_3$	H	H	H	H
$(CH_2)_{11}COOC_2H_5$	H	H	H	H
$(CH_2)_{11}COOC_4H_9$	H	H	H	H
$(CH_2)_{17}COOCH_3$	H	H	H	H
$(CH_2)_{17}COOC_2H_5$	H	H	H	H
$(CH_2)_{17}COOC_{10}H_{21}$	H	H	H	H
$(CH_2)_{19}COOCH_3$	H	H	H	H
$(CH_2)_{19}COOC_2H_5$	H	H	H	H
$(CH_2)_{19}COOC_{10}H_{21}$	H	H	H	H
$(CH_2)_{29}COOCH_3$	H	H	H	H
$(CH_2)_{29}COOC_2H_5$	H	H	H	H
$(CH_2)_{29}COOC_{10}H_{21}$	H	H	H	H
CH_2OCOCH_3	H	H	H	H
$CH_2OCOC_2H_5$	H	H	H	H
$CH_2OCOC_3H_7$	H	H	H	H
$CH_2OCOC_{14}H_{29}$	H	H	H	H
$(CH_2)_2OCOCH_3$	H	H	H	H
$(CH_2)_2OCOC_2H_5$	H	H	H	H
$(CH_2)_2OCOC_3H_7$	H	H	H	H
$(CH_2)_2OCOC_{13}H_{27}$	H	H	H	H

R^1	R^2	R^3	R^4	R^5
$(CH_2)_3OCOCH_3$	H	H	H	H
$(CH_2)_3OCOC_2H_5$	H	H	H	H
$(CH_2)_3OCOC_3H_7$	H	H	H	H
$(CH_2)_3OCOC_{12}H_{25}$	H	H	H	H
$(CH_2)_4OCOCH_3$	H	H	H	H
$(CH_2)_4OCOC_2H_5$	H	H	H	H
$(CH_2)_4OCOC_3H_7$	H	H	H	H
$(CH_2)_4OCOC_{11}H_{23}$	H	H	H	H
$(CH_2)_5OCOCH_3$	H	H	H	H
$(CH_2)_5OCOC_2H_5$	H	H	H	H
$(CH_2)_5OCOC_3H_7$	H	H	H	H
$(CH_2)_5OCOC_{10}H_{21}$	H	H	H	H
$(CH_2)_6OCOCH_3$	H	H	H	H
$(CH_2)_6OCOC_2H_5$	H	H	H	H
$(CH_2)_6OCOC_3H_7$	H	H	H	H
$(CH_2)_6OCOC_9H_{19}$	H	H	H	H
$(CH_2)_7OCOCH_3$	H	H	H	H
$(CH_2)_7OCOC_2H_5$	H	H	H	H
$(CH_2)_7OCOC_3H_7$	H	H	H	H
$(CH_2)_7OCOC_8H_{17}$	H	H	H	H
$(CH_2)_8OCOCH_3$	H	H	H	H
$(CH_2)_8OCOC_2H_5$	H	H	H	H
$(CH_2)_8OCOC_3H_7$	H	H	H	H
$(CH_2)_8OCOC_7H_{15}$	H	H	H	H
$(CH_2)_9OCOCH_3$	H	H	H	H
$(CH_2)_9OCOC_2H_5$	H	H	H	H
$(CH_2)_2CH(C_6H_{13})OCOC_3H_7$	H	H	H	H
$(CH_2)_9OCOC_6H_{13}$	H	H	H	H
$(CH_2)_{10}OCOCH_3$	H	H	H	H
$(CH_2)_{10}OCOC_2H_5$	H	H	H	H
$(CH_2)_{10}OCOC_3H_7$	H	H	H	H
$(CH_2)_{10}OCOC_5H_{11}$	H	H	H	H
$(CH_2)_{11}OCOCH_3$	H	H	H	H
$(CH_2)_{11}OCOC_2H_5$	H	H	H	H

R^1	R^2	R^3	R^4	R^5
$(CH_2)_{11}OCOC_3H_7$	H	H	H	H
$(CH_2)_{11}OCOC_4H_9$	H	H	H	H
$(CH_2)_{17}OCOCH_3$	H	H	H	H
$(CH_2)_{17}OCOC_2H_5$	H	H	H	H
$(CH_2)_{17}OCOC_3H_7$	H	H	H	H
$(CH_2)_{17}OCOC_9H_{19}$	H	H	H	H
$(CH_2)_{19}OCOCH_3$	H	H	H	H
$(CH_2)_{19}OCOC_2H_5$	H	H	H	H
$(CH_2)_{19}OCOC_3H_7$	H	H	H	H
$(CH_2)_{19}OCOC_9H_{19}$	H	H	H	H
$(CH_2)_{29}OCOCH_3$	H	H	H	H
$(CH_2)_{29}OCOC_2H_5$	H	H	H	H
$(CH_2)_{29}OCOC_3H_7$	H	H	H	H
$(CH_2)_{29}OCOC_9H_{19}$	H	H	H	H
$CH(CH_3)OCOCH_3$	H	H	H	H
$CH(CH_3)OCOC_2H_5$	H	H	H	H
$CH(CH_3)OCOC_3H_7$	H	H	H	H
$CH(CH_3)OCOC_{14}H_{29}$	H	H	H	H
$CH_2COC_7H_{15}$	H	H	H	H
$CH_2COC_9H_{19}$	H	H	H	H
$CH_2COC_{11}H_{23}$	H	H	H	H
$(CH_2)_6COC_6H_{13}$	H	H	H	H
$(CH_2)_6COC_6H_{13}$	$COCH_3$	H	$COCH_3$	$COCH_3$
$CH_2COC_{15}H_{31}$	H	H	H	H
$CH_2COC_{17}H_{35}$	H	H	H	H
$(CH_2)_2SC_{12}H_{25}$	H	H	H	H
$(CH_2)_2SC_{12}H_{25}$	$COCH_3$	H	$COCH_3$	$COCH_3$
$CH_2CH(C_7H_{15})SCH_3$	H	H	H	H
$CH_2CH(C_7H_{15})SC_2H_5$	H	H	H	H
$CH_2CH(C_7H_{15})SC_7H_{15}$	H	H	H	H
$(CH_2)_9SCH_3$	H	H	H	H
$(CH_2)_9SC_2H_5$	H	H	H	H
$(CH_2)_9SC_7H_{15}$	H	H	H	H
$CH_2CH(C_9H_{19})SCH_3$	H	H	H	H

R^1	R^2	R^3	R^4	R^5
$CH_2CH(C_9H_{19})SC_2H_5$	H	H	H	H
$CH_2CH(C_9H_{19})SC_7H_{15}$	H	H	H	H
$(CH_2)_{11}SCH_3$	H	H	H	H
$(CH_2)_{11}SC_2H_5$	H	H	H	H
$(CH_2)_{11}SC_7H_{15}$	H	H	H	H
$CH_2CH(C_{11}H_{23})SCH_3$	H	H	H	H
$CH_2CH(C_{11}H_{23})SC_2H_5$	H	H	H	H
$CH_2CH(C_{11}H_{23})SC_3H_7$	H	H	H	H
$(CH_2)_{13}SCH_3$	H	H	H	H
$(CH_2)_{13}SC_2H_5$	H	H	H	H
$(CH_2)_{13}SC_7H_{15}$	H	H	H	H
$CH_2CH(C_{15}H_{31})SCH_3$	H	H	H	H
$CH_2CH(C_{15}H_{31})SC_2H_5$	H	H	H	H
$CH_2CH(C_{15}H_{31})SC_{10}H_{21}$	H	H	H	H
$CH_2CH(C_{17}H_{35})SCH_3$	H	H	H	H
$CH_2CH(C_{17}H_{35})SC_2H_5$	H	H	H	H
$CH_2CH(C_{17}H_{35})SC_{10}H_{21}$	H	H	H	H
CH_2NH_2	H	H	H	H
$(CH_2)_2NH_2$	H	H	H	H
$(CH_2)_3NH_2$	H	H	H	H
$(CH_2)_4NH_2$	H	H	H	H
$(CH_2)_5NH_2$	H	H	H	H
$(CH_2)_6NH_2$	H	H	H	H
$(CH_2)_3CH(C_3H_7)NH_2$	H	H	H	H
$(CH_2)_8NH_2$	H	H	H	H
$(CH_2)_9NH_2$	H	H	H	H
$(CH_2)_{10}NH_2$	H	H	H	H
$(CH_2)_{11}NH_2$	H	H	H	H
$(CH_2)_{17}NH_2$	H	H	H	H
$(CH_2)_{19}NH_2$	H	H	H	H
$(CH_2)_{29}NH_2$	H	H	H	H
$CH_2NHCOOCH_3$	H	H	H	H
$CH_2NHCOOC_2H_5$	H	H	H	H
$CH_2NHCOOC_{10}H_{21}$	H	H	H	H

R^1	R^2	R^3	R^4	R^5
$CH_2NHCOOC_{14}H_{29}$	H	H	H	H
$(CH_2)_2NHCOOCH_3$	H	H	H	H
$(CH_2)_2NHCOOC_2H_5$	H	H	H	H
$(CH_2)_2NHCOOC_{10}H_{21}$	H	H	H	H
$(CH_2)_2NHCOOC_{13}H_{27}$	H	H	H	H
$(CH_2)_3NHCOOCH_3$	H	H	H	H
$(CH_2)_3NHCOOC_2H_5$	H	H	H	H
$(CH_2)_3NHCOOC_{10}H_{21}$	H	H	H	H
$(CH_2)_3NHCOOC_{12}H_{25}$	H	H	H	H
$(CH_2)_4NHCOOCH_3$	H	H	H	H
$(CH_2)_4NHCOOC_2H_5$	H	H	H	H
$(CH_2)_4NHCOOC_{10}H_{21}$	H	H	H	H
$(CH_2)_4NHCOOC_{11}H_{23}$	H	H	H	H
$(CH_2)_5NHCOOCH_3$	H	H	H	H
$(CH_2)_5NHCOOC_2H_5$	H	H	H	H
$(CH_2)_5NHCOOC_{10}H_{21}$	H	H	H	H
$(CH_2)_6NHCOOCH_3$	H	H	H	H
$(CH_2)_6NHCOOC_2H_5$	H	H	H	H
$(CH_2)_6NHCOOC_9H_{19}$	H	H	H	H
$(CH_2)_7NHCOOCH_3$	H	H	H	H
$(CH_2)_7NHCOOC_2H_5$	H	H	H	H
$(CH_2)_7NHCOOC_8H_{17}$	H	H	H	H
$(CH_2)_8NHCOOCH_3$	H	H	H	H
$(CH_2)_8NHCOOC_2H_5$	H	H	H	H
$(CH_2)_8NHCOOC_7H_{15}$	H	H	H	H
$(CH_2)_9NHCOOCH_3$	H	H	H	H
$(CH_2)_9NHCOOC_2H_5$	H	H	H	H
$(CH_2)_9NHCOOC_6H_{13}$	H	H	H	H
$(CH_2)_{10}NHCOOCH_3$	H	H	H	H
$(CH_2)_{10}NHCOOC_2H_5$	H	H	H	H
$(CH_2)_{10}NHCOOC_5H_{11}$	H	H	H	H
$(CH_2)_{11}NHCOOCH_3$	H	H	H	H
$(CH_2)_{11}NHCOOC_2H_5$	H	H	H	H
$(CH_2)_{11}NHCOOC_4H_9$	H	H	H	H

R^1	R^2	R^3	R^4	R^5
$(CH_2)_{17}NHCOOCH_3$	H	H	H	H
$(CH_2)_{17}NHCOOC_2H_5$	H	H	H	H
$(CH_2)_{17}NHCOOC_{10}H_{21}$	H	H	H	H
$(CH_2)_9CH(C_{10}H_{21})NHCOOCH_3$	H	H	H	H
$(CH_2)_{19}NHCOOC_2H_5$	H	H	H	H
$(CH_2)_{19}NHCOOC_{10}H_{21}$	H	H	H	H
$(CH_2)_{29}NHCOOCH_3$	H	H	H	H
$(CH_2)_{29}NHCOOC_2H_5$	H	H	H	H
$(CH_2)_{29}NHCOOC_{10}H_{21}$	H	H	H	H
$CH_2NHCOCH_3$	H	H	H	H
$CH_2NHCOC_2H_5$	H	H	H	H
$CH_2NHCOC_3H_7$	H	H	H	H
$CH_2NHCOC_{11}H_{23}$	H	H	H	H
$CH_2NHCOC_{14}H_{29}$	H	H	H	H
$(CH_2)_2NHCOCH_3$	H	H	H	H
$(CH_2)_2NHCOC_2H_5$	H	H	H	H
$(CH_2)_2NHCOC_3H_7$	H	H	H	H
$(CH_2)_2NHCOC_{13}H_{27}$	H	H	H	H
$(CH_2)_3NHCOCH_3$	H	H	H	H
$(CH_2)_3NHCOC_2H_5$	H	H	H	H
$(CH_2)_3NHCOC_3H_7$	H	H	H	H
$(CH_2)_3NHCOC_{12}H_{25}$	H	H	H	H
$(CH_2)_4NHCOCH_3$	H	H	H	H
$(CH_2)_4NHCOC_2H_5$	H	H	H	H
$(CH_2)_4NHCOC_3H_7$	H	H	H	H
$(CH_2)_4NHCOC_{11}H_{23}$	H	H	H	H
$(CH_2)_5NHCOCH_3$	H	H	H	H
$(CH_2)_5NHCOC_2H_5$	H	H	H	H
$(CH_2)_5NHCOC_3H_7$	H	H	H	H
$(CH_2)_5NHCOC_{10}H_{21}$	H	H	H	H
$(CH_2)_6NHCOCH_3$	H	H	H	H
$(CH_2)_6NHCOC_2H_5$	H	H	H	H
$(CH_2)_6NHCOC_3H_7$	H	H	H	H
$(CH_2)_6NHCOC_9H_{19}$	H	H	H	H

R^1	R^2	R^3	R^4	R^5
$(CH_2)_7NHCOCH_3$	H	H	H	H
$(CH_2)_7NHCOC_2H_5$	H	H	H	H
$(CH_2)_7NHCOC_3H_7$	H	H	H	H
$(CH_2)_7NHCOC_8H_{17}$	H	H	H	H
$(CH_2)_8NHCOCH_3$	H	H	H	H
$(CH_2)_8NHCOC_2H_5$	H	H	H	H
$(CH_2)_8NHCOC_3H_7$	H	H	H	H
$(CH_2)_8NHCOC_7H_{15}$	H	H	H	H
$(CH_2)_9NHCOCH_3$	H	H	H	H
$(CH_2)_9NHCOC_2H_5$	H	H	H	H
$(CH_2)_4CH(C_4H_9)NHCOC_3H_7$	H	H	H	H
$(CH_2)_9NHCOC_6H_{13}$	H	H	H	H
$(CH_2)_{10}NHCOCH_3$	H	H	H	H
$(CH_2)_{10}NHCOC_2H_5$	H	H	H	H
$(CH_2)_{10}NHCOC_3H_7$	H	H	H	H
$(CH_2)_{10}NHCOC_5H_{11}$	H	H	H	H
$(CH_2)_{11}NHCOCH_3$	H	H	H	H
$(CH_2)_{11}NHCOC_2H_5$	H	H	H	H
$(CH_2)_{11}NHCOC_3H_7$	H	H	H	H
$(CH_2)_{11}NHCOC_4H_9$	H	H	H	H
$(CH_2)_{17}NHCOCH_3$	H	H	H	H
$(CH_2)_{17}NHCOC_2H_5$	H	H	H	H
$(CH_2)_{17}NHCOC_3H_7$	H	H	H	H
$(CH_2)_{17}NHCOC_9H_{19}$	H	H	H	H
$(CH_2)_{19}NHCOCH_3$	H	H	H	H
$(CH_2)_{19}NHCOC_2H_5$	H	H	H	H
$(CH_2)_{19}NHCOC_3H_7$	H	H	H	H
$(CH_2)_{19}NHCOC_9H_{19}$	H	H	H	H
$(CH_2)_{29}NHCOCH_3$	H	H	H	H
$(CH_2)_{29}NHCOC_2H_5$	H	H	H	H
$(CH_2)_{29}NHCOC_3H_7$	H	H	H	H
$(CH_2)_{29}NHCOC_9H_{19}$	H	H	H	H
$CH(CH_3)NHCOCH_3$	H	H	H	H
$CH(CH_3)NHCOC_2H_5$	H	H	H	H

R^1	R^2	R^3	R^4	R^5
$CH(CH_3)NHCOC_3H_7$	H	H	H	H
$CH(CH_3)NHCOC_{14}H_{29}$	H	H	H	H
CH_2NHCH_3	H	H	H	H
$CH_2NHC_2H_5$	H	H	H	H
$CH_2NHC_3H_7$	H	H	H	H
$CH_2NHC_{12}H_{25}$	H	H	H	H
$CH_2NHC_{15}H_{31}$	H	H	H	H
$(CH_2)_2NHCH_3$	H	H	H	H
$(CH_2)_2NHC_2H_5$	H	H	H	H
$(CH_2)_2NHC_3H_7$	H	H	H	H
$(CH_2)_2NHC_{14}H_{29}$	H	H	H	H
$(CH_2)_3NHCH_3$	H	H	H	H
$(CH_2)_3NHC_2H_5$	H	H	H	H
$(CH_2)_3NHC_3H_7$	H	H	H	H
$(CH_2)_3NHC_{13}H_{27}$	H	H	H	H
$(CH_2)_4NHCH_3$	H	H	H	H
$(CH_2)_4NHC_2H_5$	H	H	H	H
$(CH_2)_4NHC_3H_7$	H	H	H	H
$(CH_2)_4NHC_{12}H_{25}$	H	H	H	H
$(CH_2)_5NHCH_3$	H	H	H	H
$(CH_2)_5NHC_2H_5$	H	H	H	H
$(CH_2)_5NHC_3H_7$	H	H	H	H
$(CH_2)_5NHC_{11}H_{23}$	H	H	H	H
$(CH_2)_6NHCH_3$	H	H	H	H
$(CH_2)_6NHC_2H_5$	H	H	H	H
$(CH_2)_6NHC_3H_7$	H	H	H	H
$(CH_2)_6NHC_{10}H_{21}$	H	H	H	H
$(CH_2)_7NHCH_3$	H	H	H	H
$(CH_2)_7NHC_2H_5$	H	H	H	H
$(CH_2)_7NHC_3H_7$	H	H	H	H
$(CH_2)_7NHC_9H_{19}$	H	H	H	H
$(CH_2)_8NHCH_3$	H	H	H	H
$(CH_2)_8NHC_2H_5$	H	H	H	H
$(CH_2)_8NHC_3H_7$	H	H	H	H

R^1	R^2	R^3	R^4	R^5
$(CH_2)_8NHC_8H_{17}$	H	H	H	H
$(CH_2)_9NHCH_3$	H	H	H	H
$(CH_2)_9NHC_2H_5$	H	H	H	H
$(CH_2)_9NHC_3H_7$	H	H	H	H
$(CH_2)_9NHC_7H_{15}$	H	H	H	H
$(CH_2)_{10}NHCH_3$	H	H	H	H
$(CH_2)_{10}NHC_2H_5$	H	H	H	H
$(CH_2)_{10}NHC_3H_7$	H	H	H	H
$(CH_2)_{10}NHC_6H_{13}$	H	H	H	H
$(CH_2)_{11}NHCH_3$	H	H	H	H
$(CH_2)_{11}NHC_2H_5$	H	H	H	H
$(CH_2)_{11}NHC_3H_7$	H	H	H	H
$(CH_2)_4CH(C_6H_{13})NHC_5H_{11}$	H	H	H	H
$(CH_2)_{17}NHCH_3$	H	H	H	H
$(CH_2)_{17}NHC_2H_5$	H	H	H	H
$(CH_2)_{17}NHC_3H_7$	H	H	H	H
$(CH_2)_{17}NHC_{10}H_{21}$	H	H	H	H
$(CH_2)_{19}NHCH_3$	H	H	H	H
$(CH_2)_{19}NHC_2H_5$	H	H	H	H
$(CH_2)_{19}NHC_3H_7$	H	H	H	H
$(CH_2)_{19}NHC_{10}H_{21}$	H	H	H	H
$(CH_2)_{29}NHCH_3$	H	H	H	H
$(CH_2)_{29}NHC_2H_5$	H	H	H	H
$(CH_2)_{29}NHC_3H_7$	H	H	H	H
$(CH_2)_{29}NHC_{10}H_{21}$	H	H	H	H
$CONHCH_3$	H	H	H	H
$CONHC_2H_5$	H	H	H	H
$CONHC_{10}H_{21}$	H	H	H	H
$COOC_{15}H_{31}$	H	H	H	H
$CH_2CONHCH_3$	H	H	H	H
$CH_2CONHC_2H_5$	H	H	H	H
$CH_2CONHC_{10}H_{21}$	H	H	H	H
$CH_2CONHC_{14}H_{29}$	H	H	H	H
$(CH_2)_3CONHCH_3$	H	H	H	H

R^1	R^2	R^3	R^4	R^5
$(CH_2)_3CONHC_2H_5$	H	H	H	H
$(CH_2)_3CONHC_{10}H_{21}$	H	H	H	H
$(CH_2)_3CONHC_{12}H_{25}$	H	H	H	H
$(CH_2)_4CONHCH_3$	H	H	H	H
$(CH_2)_4CONHC_2H_5$	H	H	H	H
$(CH_2)_4CONHC_{10}H_{21}$	H	H	H	H
$(CH_2)_4CONHC_{11}H_{23}$	H	H	H	H
$(CH_2)_5CONHCH_3$	H	H	H	H
$(CH_2)_5CONHC_2H_5$	H	H	H	H
$(CH_2)_5CONHC_{10}H_{21}$	H	H	H	H
$(CH_2)_6CONHCH_3$	H	H	H	H
$(CH_2)_6CONHC_2H_5$	H	H	H	H
$(CH_2)_6CONHC_{10}H_{21}$	H	H	H	H
$(CH_2)_7CONHCH_3$	H	H	H	H
$(CH_2)_7CONHC_2H_5$	H	H	H	H
$(CH_2)_7CONHC_8H_{17}$	H	H	H	H
$(CH_2)_8CONHCH_3$	H	H	H	H
$(CH_2)_8CONHC_2H_5$	H	H	H	H
$(CH_2)_8CONHC_7H_{15}$	H	H	H	H
$(CH_2)_9CONHCH_3$	H	H	H	H
$(CH_2)_9CONHC_2H_5$	H	H	H	H
$(CH_2)_9CONHC_8H_{13}$	H	H	H	H
$(CH_2)_{10}CONHCH_3$	H	H	H	H
$(CH_2)_{10}CONHC_2H_5$	H	H	H	H
$(CH_2)_{10}CONHC_5H_{11}$	H	H	H	H
$(CH_2)_{11}CONHCH_3$	H	H	H	H
$(CH_2)_{11}CONHC_2H_5$	H	H	H	H
$(CH_2)_{11}CONHC_4H_9$	H	H	H	H
$(CH_2)_{17}CONHCH_3$	H	H	H	H
$(CH_2)_8CH(C_8H_{17})CONHC_2H_5$	H	H	H	H
$(CH_2)_{17}CONHC_{10}H_{21}$	H	H	H	H
$(CH_2)_{19}CONHCH_3$	H	H	H	H
$(CH_2)_{19}CONHC_2H_5$	H	H	H	H
$(CH_2)_{19}CONHC_{10}H_{21}$	H	H	H	H

R^1	R^2	R^3	R^4	R^5
$(CH_2)_{29}CONHCH_3$	H	H	H	H
$(CH_2)_{29}CONHC_2H_5$	H	H	H	H
$(CH_2)_{29}CONHC_{10}H_{21}$	H	H	H	H
CH_2NO_2	H	H	H	H
$(CH_2)_2NO_2$	H	H	H	H
$(CH_2)_3NO_2$	H	H	H	H
$(CH_2)_4NO_2$	H	H	H	H
$(CH_2)_5NO_2$	H	H	H	H
$(CH_2)_6NO_2$	H	H	H	H
$(CH_2)_7NO_2$	H	H	H	H
$(CH_2)_8NO_2$	H	H	H	H
$(CH_2)_9NO_2$	H	H	H	H
$(CH_2)_{10}NO_2$	H	H	H	H
$(CH_2)_4CH(C_6H_{13})NO_2$	H	H	H	H
$(CH_2)_{17}NO_2$	H	H	H	H
$(CH_2)_{19}NO_2$	H	H	H	H
$(CH_2)_{29}NO_2$	H	H	H	H
CH_2Cl	H	H	H	H
$(CH_2)_2Cl$	H	H	H	H
$(CH_2)_3Cl$	H	H	H	H
$(CH_2)_4Cl$	H	H	H	H
$(CH_2)_5Cl$	H	H	H	H
$(CH_2)_6Cl$	H	H	H	H
$(CH_2)_7Cl$	H	H	H	H
$(CH_2)_8Cl$	H	H	H	H
$(CH_2)_9Cl$	H	H	H	H
$(CH_2)_{10}Cl$	H	H	H	H
$(CH_2)_{11}Cl$	H	H	H	H
$(CH_2)_{17}Cl$	H	H	H	H
$(CH_2)_{19}Cl$	H	H	H	H
$(CH_2)_{29}Cl$	H	H	H	H
CH_2Br	H	H	H	H
$(CH_2)_2Br$	H	H	H	H
$(CH_2)_3Br$	H	H	H	H

R^1	R^2	R^3	R^4	R^5
$(CH_2)_4Br$	H	H	H	H
$(CH_2)_5Br$	H	H	H	H
$(CH_2)_6Br$	H	H	H	H
$(CH_2)_7Br$	H	H	H	H
$(CH_2)_8Br$	H	H	H	H
$(CH_2)_2CHBrC_6H_{13}$	H	H	H	H
$(CH_2)_{10}Br$	H	H	H	H
$(CH_2)_{11}Br$	H	H	H	H
$(CH_2)_{17}Br$	H	H	H	H
$(CH_2)_{19}Br$	H	H	H	H
$(CH_2)_{28}Br$	H	H	H	H
CH_2F	H	H	H	H
$(CH_2)_2F$	H	H	H	H
$(CH_2)_3F$	H	H	H	H
$(CH_2)_4F$	H	H	H	H
$(CH_2)_5F$	H	H	H	H
$(CH_2)_6F$	H	H	H	H
$(CH_2)_7F$	H	H	H	H
$(CH_2)_8F$	H	H	H	H
$(CH_2)_9F$	H	H	H	H
$(CH_2)_{10}F$	H	H	H	H
$(CH_2)_{11}F$	H	H	H	H
$(CH_2)_{11}F$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_{12}F$	H	H	H	H
$(CH_2)_{12}F$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_3CHFC_7H_{15}$	H	H	H	H
$(CH_2)_{13}F$	H	H	H	H
$(CH_2)_{13}F$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_{12}CHF_2$	H	H	H	H
$(CH_2)_{12}CHF_2$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_{12}CF_3$	H	H	H	H
$(CH_2)_{12}CF_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_{14}F$	H	H	H	H
$(CH_2)_{14}F$	$COCH_3$	H	$COCH_3$	$COCH_3$

R^1	R^2	R^3	R^4	R^5
$(CH_2)_{17}F$	H	H	H	H
$(CH_2)_{19}F$	H	H	H	H
$(CH_2)_{29}F$	H	H	H	H
CH_2OCH_3	H	H	H	H
$CH_2OC_2H_5$	H	H	H	H
$CH_2OC_{15}H_{31}$	H	H	H	H
$(CH_2)_2OCH_3$	H	H	H	H
$(CH_2)_2OC_2H_5$	H	H	H	H
$(CH_2)_2OC_{15}H_{31}$	H	H	H	H
$(CH_2)_3OCH_3$	H	H	H	H
$(CH_2)_3OC_2H_5$	H	H	H	H
$(CH_2)_3OC_{13}H_{27}$	H	H	H	H
$(CH_2)_4OCH_3$	H	H	H	H
$(CH_2)_4OC_2H_5$	H	H	H	H
$(CH_2)_4OC_{12}H_{25}$	H	H	H	H
$(CH_2)_5OC_8H_{17}$	H	H	H	H
$(CH_2)_5OC_8H_{17}$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_5OC_{11}H_{23}$	H	H	H	H
$(CH_2)_6OC_7H_{15}$	H	H	H	H
$(CH_2)_6OC_7H_{15}$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_6OC_{10}H_{21}$	H	H	H	H
$(CH_2)_7OC_6H_{13}$	H	H	H	H
$(CH_2)_7OC_6H_{13}$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_7OC_9H_{19}$	H	H	H	H
$(CH_2)_8OC_5H_{11}$	H	H	H	H
$(CH_2)_8OC_5H_{11}$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_8OC_8H_{17}$	H	H	H	H
$(CH_2)_9OC_7H_{15}$	H	H	H	H
$(CH_2)_{10}OC_6H_{13}$	H	H	H	H
$(CH_2)_{11}OC_5H_{11}$	H	H	H	H
$(CH_2)_{12}OC_4H_9$	H	H	H	H
$(CH_2)_{13}OC_3H_7$	H	H	H	H
$(CH_2)_{14}OC_2H_5$	H	H	H	H
$(CH_2)_{15}OCH_3$	H	H	H	H

R^1	R^2	R^3	R^4	R^5
$CH_2OCH_2CH=CH_2$	H	H	H	H
$(CH_2)_2OCH_2CH=CH_2$	H	H	H	H
$(CH_2)_3OCH_2CH=CH_2$	H	H	H	H
$(CH_2)_9OCH_2CH=CH_2$	H	H	H	H
$(CH_2)_{13}OCH_2CH=CH_2$	H	H	H	H
$CH_2OCH_2CH=CHCH_3$	H	H	H	H
$(CH_2)_2OCH_2CH=CHCH_3$	H	H	H	H
$(CH_2)_3OCH_2CH=CHCH_3$	H	H	H	H
$(CH_2)_9OCH_2CH=CHCH_3$	H	H	H	H
$(CH_2)_{12}OCH_2CH=CHCH_3$	H	H	H	H
$CH_2OCH_2CH=CHC_7H_{15}$	H	H	H	H
$(CH_2)_2OCH_2CH=CHC_7H_{15}$	H	H	H	H
$(CH_2)_3OCH_2CH=CHC_7H_{15}$	H	H	H	H
$(CH_2)_6OCH_2CH=CHC_7H_{15}$	H	H	H	H
$(CH_2)_9OCH_2CH=CHC_7H_{15}$	H	H	H	H
$CH_2OCH_2C\equiv CH$	H	H	H	H
$(CH_2)_2OCH_2C\equiv CH$	H	H	H	H
$(CH_2)_3OCH_2C\equiv CH$	H	H	H	H
$(CH_2)_9OCH_2C\equiv CH$	H	H	H	H
$(CH_2)_{11}CH(CH_3)OCH_2C\equiv CH$	H	H	H	H
$CH_2OCH_2C\equiv CCH_3$	H	H	H	H
$(CH_2)_2OCH_2C\equiv CCH_3$	H	H	H	H
$(CH_2)_3OCH_2C\equiv CCH_3$	H	H	H	H
$(CH_2)_9OCH_2C\equiv CCH_3$	H	H	H	H
$(CH_2)_{12}OCH_2C\equiv CCH_3$	H	H	H	H
$CH_2OCH_2C\equiv CC_7H_{15}$	H	H	H	H
$(CH_2)_2OCH_2C\equiv CC_7H_{15}$	H	H	H	H
$(CH_2)_3OCH_2C\equiv CC_7H_{15}$	H	H	H	H
$(CH_2)_6OCH_2C\equiv CC_7H_{15}$	H	H	H	H
$(CH_2)_9OCH_2C\equiv CC_7H_{15}$	H	H	H	H
$CH_2OCH_2C_6H_5$	H	H	H	H
$CH_2O(CH_2)_2C_6H_5$	H	H	H	H
$CH_2O(CH_2)_3C_6H_5$	H	H	H	H
$(CH_2)_2OCH_2C_6H_5$	H	H	H	H

R^1	R^2	R^3	R^4	R^5
$(CH_2)_2O(CH_2)_2C_6H_5$	H	H	H	H
$(CH_2)_2O(CH_2)_3C_6H_5$	H	H	H	H
$(CH_2)_3OCH_2C_6H_5$	H	H	H	H
$(CH_2)_3O(CH_2)_2C_6H_5$	H	H	H	H
$(CH_2)_3O(CH_2)_3C_6H_5$	H	H	H	H
$(CH_2)_4OCH_2C_6H_5$	H	H	H	H
$(CH_2)_4O(CH_2)_2C_6H_5$	H	H	H	H
$(CH_2)_4O(CH_2)_3C_6H_5$	H	H	H	H
$(CH_2)_5O(CH_2)_2C_6H_5$	H	H	H	H
$(CH_2)_5O(CH_2)_3C_6H_5$	H	H	H	H
$(CH_2)_5O(CH_2)_3C_6H_5$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_6O(CH_2)_2C_6H_5$	H	H	H	H
$(CH_2)_7OCH_2C_6H_5$	H	H	H	H
$(CH_2)_7OCH_2C_6H_5$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_7O(CH_2)_2C_6H_5$	H	H	H	H
$(CH_2)_8O(CH_2)_2C_6H_5$	H	H	H	H
$(CH_2)_9O(CH_2)_2C_6H_5$	H	H	H	H
$(CH_2)_{10}O(CH_2)_2C_6H_5$	H	H	H	H
$(CH_2)_{11}O(CH_2)_2C_6H_5$	H	H	H	H
$(CH_2)_{12}O(CH_2)_2C_6H_5$	H	H	H	H
$(CH_2)_8CH(C_4H_9)O(CH_2)_2C_6H_5$	H	H	H	H
$(CH_2)_{14}O(CH_2)_2C_6H_5$	H	H	H	H
$(CH_2)_{15}O(CH_2)_2C_6H_5$	H	H	H	H
$C_{17}H_{35}$	CH_3	H	H	H
$C_{17}H_{35}$	CH_3	CH_3	H	H
$C_{17}H_{35}$	$C_{18}H_{37}$	H	H	H
$C_{17}H_{35}$	$C_{18}H_{37}$	$C_{18}H_{37}$	H	H
$C_{17}H_{35}$	$COCH_3$	H	H	H
$C_{17}H_{35}$	$COC_{17}H_{35}$	H	H	H
$CH_2C_6H_5$	H	H	H	H
$CH_2C_6H_5$	$COCH_3$	H	$COCH_3$	$COCH_3$
$CH(CH_3)C_6H_5$	H	H	H	H
$CH=CHC_6H_5$	H	H	H	H
$CH=CHC_6H_5$	$COCH_3$	H	$COCH_3$	$COCH_3$

R^1	R^2	R^3	R^4	R^5
$C\equiv CC_6H_5$	H	H	H	H
$C\equiv CC_6H_5$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_3C_6H_5$	H	H	H	H
$CH_2CH(CH_3)C_6H_5$	H	H	H	H
$CH_2CH(CH_3)C_6H_5$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_4C_6H_5$	H	H	H	H
$(CH_2)_5C_6H_5$	H	H	H	H
$(CH_2)_5C_6H_5$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_6C_6H_5$	H	H	H	H
$(CH_2)_7C_6H_5$	H	H	H	H
$(CH_2)_8C_6H_5$	H	H	H	H
$(CH_2)_9C_6H_5$	H	H	H	H
$(CH_2)_9C_6H_5$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_9C_6H_{11}$	H	H	H	H
$(CH_2)_{11}C_6H_5$	H	H	H	H
$(CH_2)_{12}C_6H_5$	H	H	H	H
$(CH_2)_{12}C_6H_5$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_{13}C_6H_5$	H	H	H	H
$(CH_2)_{15}C_6H_5$	H	H	H	H
$(CH_2)_{17}C_6H_5$	H	H	H	H
$(CH_2)_{19}C_6H_5$	H	H	H	H
$(CH_2)_{20}C_6H_5$	H	H	H	H
C_6H_4-3-CH_3	H	H	H	H
C_6H_4-4-CH_3	H	H	H	H
C_6H_4-3-C_2H_5	H	H	H	H
C_6H_4-4-C_2H_5	H	H	H	H
C_6H_4-3-C_3H_7	H	H	H	H
C_6H_4-2-C_3H_7	H	H	H	H
C_6H_4-4-C_3H_7	H	H	H	H
C_6H_4-3-C_4H_9	H	H	H	H
C_6H_4-4-C_4H_9	H	H	H	H
C_6H_4-3-C_8H_{13}	H	H	H	H
C_6H_4-4-C_9H_{19}	H	H	H	H
C_6H_4-4-C_9H_{19}	$COCH_3$	H	$COCH_3$	$COCH_3$

R^1	R^2	R^3	R^4	R^5
C_5H_{10}-3-C_6H_{13}	H	H	H	H
C_6H_4-4-C_6H_{13}	H	H	H	H
C_6H_4-3-$C_{10}H_{21}$	H	H	H	H
C_6H_4-4-$C_{10}H_{21}$	H	H	H	H
C_6H_4-3-$C_{12}H_{25}$	H	H	H	H
C_6H_4-4-$C_{12}H_{25}$	H	H	H	H
C_6H_4-3-$C_{20}H_{41}$	H	H	H	H
C_6H_4-4-$C_{20}H_{41}$	H	H	H	H
$CH_2C_6H_4$-3-CH_3	H	H	H	H
$CH_2C_6H_4$-4-CH_3	H	H	H	H
$CH_2C_6H_4$-3-C_2H_5	H	H	H	H
$CH_2C_6H_4$-4-C_2H_5	H	H	H	H
$CH_2C_6H_4$-3-C_3H_7	H	H	H	H
$CH_2C_6H_4$-4-C_3H_7	H	H	H	H
$CH_2C_6H_4$-3-C_4H_9	H	H	H	H
$CH_2C_6H_4$-4-C_4H_9	H	H	H	H
$CH_2C_6H_4$-3-C_6H_{13}	H	H	H	H
$CH_2C_6H_4$-2-C_4H_9	H	H	H	H
$CH_2C_6H_4$-2-C_6H_{13}	H	H	H	H
$CH_2C_6H_4$-4-C_6H_{13}	H	H	H	H
$CH_2C_6H_4$-4-$(CH_2)_3CH(CH_3)_2$	H	H	H	H
$CH_2C_6H_4$-4-$(CH_2)_3CH(CH_3)_2$	$COCH_3$	H	$COCH_3$	$COCH_3$
$CH_2C_6H_4$-4-C_7H_{15}	H	H	H	H
$CH_2C_6H_4$-4-C_7H_{15}	$COCH_3$	H	$COCH_3$	$COCH_3$
$CH_2C_6H_4$-4-C_8H_{17}	H	H	H	H
$CH_2C_6H_4$-4-C_8H_{17}	$COCH_3$	H	H	H
$CH_2C_6H_4$-4-C_8H_{17}	$COCH_3$	H	$COCH_3$	$COCH_3$
$CH_2C_6H_4$-4-C_8H_{17}	CH_3	CH_3	H	H
$CH_2C_6H_4$-2-C_8H_{17}	H	H	H	H
$CH_2C_6H_4$-2-C_8H_{17}	$COCH_3$	H	$COCH_3$	$COCH_3$
$CH_2C_6H_4$-3-C_8H_{17}	H	H	H	H
$CH_2C_6H_4$-3-C_8H_{17}	$COCH_3$	H	$COCH_3$	$COCH_3$
$CH_2C_6H_4$-3-$C_{10}H_{21}$	H	H	H	H
$CH_2C_6H_4$-4-$C_{10}H_{21}$	H	H	H	H

R^1	R^2	R^3	R^4	R^5
$CH_2C_6H_4$-3-$C_{12}H_{25}$	H	H	H	H
$CH_2C_6H_4$-4-$C_{12}H_{25}$	H	H	H	H
$CH_2C_6H_4$-4-$C_{12}H_{25}$	$COCH_3$	H	$COCH_3$	$COCH_3$
$CH_2C_6H_4$-3-$C_{20}H_{41}$	H	H	H	H
$CH_2C_6H_4$-4-$C_{20}H_{41}$	H	H	H	H
$(CH_2)_2C_6H_4$-3-CH_3	H	H	H	H
$(CH_2)_2C_6H_4$-4-CH_3	H	H	H	H
$(CH_2)_2C_6H_4$-3-C_2H_5	H	H	H	H
$(CH_2)_2C_7H_{12}$-3-C_2H_5	H	H	H	H
$(CH_2)_2C_6H_4$-4-C_2H_5	H	H	H	H
$(CH_2)_2C_6H_4$-3-C_3H_7	H	H	H	H
$(CH_2)_2C_6H_4$-4-C_3H_7	H	H	H	H
$(CH_2)_2C_6H_4$-3-C_4H_9	H	H	H	H
$(CH_2)_2C_6H_4$-4-C_4H_9	H	H	H	H
$(CH_2)_2C_6H_4$-3-C_6H_{13}	H	H	H	H
$(CH_2)_2C_6H_4$-4-C_6H_{13}	H	H	H	H
$(CH_2)_2C_6H_{10}$-4-C_7H_{15}	H	H	H	H
$(CH_2)_2C_6H_{10}$-4-C_7H_{15}	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2C_6H_4$-4-C_7H_{15}	H	H	H	H
$(CH_2)_2C_6H_4$-4-C_7H_{15}	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2C_6H_4$-3-$C_{10}H_{21}$	H	H	H	H
$(CH_2)_2C_6H_4$-4-$C_{10}H_{21}$	H	H	H	H
$(CH_2)_2C_6H_4$-4-$C_{11}H_{23}$	H	H	H	H
$(CH_2)_2C_6H_4$-4-$C_{11}H_{23}$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2C_6H_4$-3-$C_{12}H_{25}$	H	H	H	H
$(CH_2)_2C_6H_4$-4-$C_{12}H_{25}$	H	H	H	H
$(CH_2)_2C_6H_4$-3-$C_{20}H_{41}$	H	H	H	H
$(CH_2)_2C_6H_4$-4-$C_{20}H_{41}$	H	H	H	H
$(CH_2)_3C_6H_4$-3-CH_3	H	H	H	H
$(CH_2)_3C_6H_4$-4-CH_3	H	H	H	H
$(CH_2)_3C_6H_4$-3-C_2H_5	H	H	H	H
$(CH_2)_3C_6H_4$-4-C_2H_5	H	H	H	H
$(CH_2)_3C_6H_4$-3-C_3H_7	H	H	H	H
$(CH_2)_3C_6H_4$-4-C_3H_7	H	H	H	H

R^1	R^2	R^3	R^4	R^5
$(CH_2)_3C_6H_4$-3-C_4H_9	H	H	H	H
$(CH_2)_3C_6H_{10}$-4-C_4H_9	H	H	H	H
$(CH_2)_3C_6H_{10}$-4-C_4H_9	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_3C_6H_4$-4-C_4H_9	H	H	H	H
$(CH_2)_3C_6H_4$-4-C_4H_9	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_3C_6H_4$-3-C_6H_{13}	H	H	H	H
$(CH_2)_3C_6H_4$-4-C_6H_{13}	H	H	H	H
$(CH_2)_3C_6H_4$-4-C_6H_{13}	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_3C_6H_4$-4-C_8H_{17}	H	H	H	H
$(CH_2)_3C_6H_4$-4-C_8H_{17}	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_3C_6H_4$-3-$C_{10}H_{21}$	H	H	H	H
$(CH_2)_3C_6H_4$-4-$C_{10}H_{21}$	H	H	H	H
$(CH_2)_3C_6H_4$-2-$C_{10}H_{21}$	H	H	H	H
$(CH_2)_3C_6H_4$-3-$C_{12}H_{25}$	H	H	H	H
$(CH_2)_3C_6H_4$-4-$C_{12}H_{25}$	H	H	H	H
$(CH_2)_3C_6H_4$-3-$C_{20}H_{41}$	H	H	H	H
$(CH_2)_3C_6H_4$-4-$C_{20}H_{41}$	H	H	H	H
$(CH_2)_4C_6H_4$-3-CH_3	H	H	H	H
$(CH_2)_4C_6H_4$-4-CH_3	H	H	H	H
$(CH_2)_4C_6H_4$-3-C_2H_5	H	H	H	H
$(CH_2)_4C_6H_4$-4-C_2H_5	H	H	H	H
$(CH_2)_4C_6H_4$-3-C_3H_7	H	H	H	H
$CH_2CH=CHCH_2C_6H_4$-3-C_3H_7	H	H	H	H
$(CH_2)_4C_6H_4$-4-C_3H_7	H	H	H	H
$(CH_2)_4C_6H_4$-3-C_4H_9	H	H	H	H
$(CH_2)_4C_6H_4$-4-C_4H_9	H	H	H	H
$(CH_2)_4C_6H_4$-3-C_6H_{13}	H	H	H	H
$(CH_2)_4C_6H_4$-4-C_6H_{13}	H	H	H	H
$(CH_2)_4C_6H_4$-3-$C_{10}H_{21}$	H	H	H	H
$(CH_2)_4C_6H_4$-4-$C_{10}H_{21}$	H	H	H	H
$(CH_2)_4C_6H_4$-2-$C_{12}H_{25}$	H	H	H	H
$(CH_2)_4C_6H_4$-3-$C_{12}H_{25}$	H	H	H	H
$(CH_2)_4C_6H_4$-4-$C_{12}H_{25}$	H	H	H	H
$(CH_2)_4C_6H_{10}$-4-$C_{12}H_{25}$	H	H	H	H

R^1	R^2	R^3	R^4	R^5
$(CH_2)_4C_6H_4$-3-$C_{20}H_{41}$	H	H	H	H
$(CH_2)_4C_6H_4$-4-$C_{20}H_{41}$	H	H	H	H
$(CH_2)_5C_6H_4$-3-CH_3	H	H	H	H
$(CH_2)_5C_6H_4$-4-CH_3	H	H	H	H
$(CH_2)_5C_6H_4$-3-C_2H_5	H	H	H	H
$(CH_2)_5C_6H_4$-4-C_2H_5	H	H	H	H
$(CH_2)_5C_6H_4$-3-C_3H_7	H	H	H	H
$(CH_2)_5C_6H_4$-4-C_3H_7	H	H	H	H
$(CH_2)_5C_6H_4$-3-C_4H_9	H	H	H	H
$(CH_2)_5C_6H_4$-4-C_4H_9	H	H	H	H
$(CH_2)_5C_6H_4$-4-C_4H_9	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_5C_6H_4$-2-C_6H_{13}	H	H	H	H
$(CH_2)_5C_6H_4$-3-C_6H_{13}	H	H	H	H
$(CH_2)_5C_6H_4$-4-C_6H_{13}	H	H	H	H
$(CH_2)_5C_6H_4$-3-$C_{10}H_{21}$	H	H	H	H
$(CH_2)_5C_6H_4$-4-$C_{10}H_{21}$	H	H	H	H
$(CH_2)_5C_6H_{10}$-4-$C_{10}H_{21}$	H	H	H	H
$(CH_2)_5C_5H_4$-3-$C_{12}H_{25}$	H	H	H	H
$(CH_2)_5C_5H_4$-4-$C_{12}H_{25}$	H	H	H	H
$(CH_2)_5C_5H_4$-3-$C_{20}H_{41}$	H	H	H	H
$(CH_2)_5C_5H_4$-4-$C_{20}H_{41}$	H	H	H	H
$(CH_2)_7C_5H_4$-3-C_7H_{15}	H	H	H	H
$(CH_2)_7C_5H_4$-4-C_6H_{13}	H	H	H	H
$(CH_2)_7C_5H_4$-4-C_2H_5	H	H	H	H
$(CH_2)_7C_5H_4$-4-C_2H_5	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_7C_5H_4$-4-C_6H_{13}	H	H	H	H
$(CH_2)_7C_5H_4$-4-C_6H_{13}	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2CH=C(C_2H_7)C_6H_{10}$-4-$C_6H_{13}$	H	H	H	H
$(CH_2)_9C_6H_4$-3-C_5H_{11}	H	H	H	H
$(CH_2)_9C_6H_4$-4-C_4H_9	H	H	H	H
$(CH_2)_{11}C_6H_4$-3-C_3H_7	H	H	H	H
$(CH_2)_{11}C_6H_4$-4-C_2H_5	H	H	H	H
$(CH_2)_{13}C_6H_4$-3-CH_3	H	H	H	H
C_6H_4-3-$CH=CH_2$	H	H	H	H

R^1	R^2	R^3	R^4	R^5
C_6H_4-4-CH=CH_2	H	H	H	H
$CH_2C_6H_4$-3-CH=CH_2	H	H	H	H
$CH_2C_6H_4$-4-CH=CH_2	H	H	H	H
$CH_2C_6H_4$-3-CH=$CHCH_3$	H	H	H	H
$CH_2C_6H_4$-4-CH=$CHCH_3$	H	H	H	H
$CH_2C_6H_4$-2-CH=$CHCH_3$	H	H	H	H
$CH_2C_6H_4$-3-CH=CHC_8H_{17}	H	H	H	H
$CH_2C_6H_4$-4-CH=CHC_8H_{17}	H	H	H	H
$(CH_2)_2C_6H_4$-3-CH=CH_2	H	H	H	H
$(CH_2)_2C_6H_4$-4-CH=CH_2	H	H	H	H
$(CH_2)_2C_6H_4$-3-CH=$CHCH_3$	H	H	H	H
$(CH_2)_2C_6H_4$-4-CH=$CHCH_3$	H	H	H	H
$(CH_2)_2C_6H_{10}$-4-CH=$CHCH_3$	H	H	H	H
$(CH_2)_2C_6H_4$-3-CH=CHC_8H_{17}	H	H	H	H
$(CH_2)_2C_6H_4$-4-CH=CHC_8H_{17}	H	H	H	H
$(CH_2)_3C_6H_4$-3-CH=CH_2	H	H	H	H
$(CH_2)_3C_6H_4$-4-CH=CH_2	H	H	H	H
$(CH_2)_3C_6H_4$-3-CH=$CHCH_3$	H	H	H	H
$(CH_2)_3C_6H_4$-4-CH=$CHCH_3$	H	H	H	H
$(CH_2)_3C_6H_4$-3-CH=CHC_8H_{17}	H	H	H	H
$(CH_2)_3C_6H_4$-4-CH=CHC_8H_{17}	H	H	H	H
$CH_2CH(CH_3)C_6H_4$-4-CH=CHC_8H_{17}	H	H	H	H
$(CH_2)_4C_6H_4$-3-CH=CH_2	H	H	H	H
$(CH_2)_4C_6H_4$-4-CH=CH_2	H	H	H	H
$(CH_2)_4C_6H_4$-3-CH=$CHCH_3$	H	H	H	H
$(CH_2)_4C_6H_4$-4-CH=$CHCH_3$	H	H	H	H
$(CH_2)_4C_6H_4$-2-CH=CHC_8H_{17}	H	H	H	H
$(CH_2)_4C_6H_4$-3-CH=CHC_8H_{17}	H	H	H	H
$CH_2CH(C_2H_5)$-C_5H_8-3-CH=CHC_8H_{17}	H	H	H	H
$(CH_2)_4C_6H_4$-4-CH=CHC_8H_{17}	H	H	H	H
CH=$CH(CH_2)_2C_6H_4$-4-CH=CHC_8H_{17}	H	H	H	H
$(CH_2)_5C_6H_4$-3-CH=CH_2	H	H	H	H
$(CH_2)_5C_6H_4$-4-CH=CH_2	H	H	H	H
$(CH_2)_5C_6H_4$-3-CH=$CHCH_3$	H	H	H	H

R^1	R^2	R^3	R^4	R^5
$(CH_2)_5C_6H_4$-4-CH=CHCH$_3$	H	H	H	H
$(CH_2)_5C_6H_4$-3-CH=CHC$_8$H$_{17}$	H	H	H	H
$(CH_2)_5C_6H_4$-4-$(CH_2)_4$CH=CHC$_4$H$_9$	H	H	H	H
$(CH_2)_7C_6H_4$-3-CH=CH$_2$	H	H	H	H
$(CH_2)_7C_6H_4$-4-CH=CH$_2$	H	H	H	H
$(CH_2)_7$-C$_6$H$_{10}$-3-CH=CHCH$_3$	H	H	H	H
$(CH_2)_7C_6H_4$-3-CH$_2$CH=CH$_2$	H	H	H	H
$(CH_2)_7C_6H_4$-4-CH=CHCH$_3$	H	H	H	H
$(CH_2)_7C_6H_4$-3-$(CH_2)_4$CH=CHC$_4$H$_9$	H	H	H	H
$(CH_2)_7C_6H_4$-4-$(CH_2)_6$CH=CHC$_2$H$_5$	H	H	H	H
C_6H_4-3-C≡CH	H	H	H	H
C_6H_4-4-C≡CH	H	H	H	H
C$_6$H$_{10}$-4-C≡CH	H	H	H	H
$CH_2C_6H_4$-3-C≡CH	H	H	H	H
$CH_2C_6H_4$-4-C≡CH	H	H	H	H
$CH_2C_6H_4$-3-C≡CCH$_3$	H	H	H	H
$CH_2C_6H_4$-4-C≡CCH$_3$	H	H	H	H
$CH_2C_6H_4$-3-$(CH_2)_6$C≡CC$_2$H$_5$	H	H	H	H
$CH_2C_6H_4$-4-$(CH_2)_3$C≡CC$_5$H$_{11}$	H	H	H	H
$CH_2C_6H_4$-2-$(CH_2)_3$C≡CC$_5$H$_{11}$	H	H	H	H
CH_2C$_6$H$_{10}$-4-$(CH_2)_3$C≡CC$_5$H$_{11}$	H	H	H	H
$(CH_2)_2C_6H_4$-3-C≡CH	H	H	H	H
$(CH_2)_2C_6H_4$-4-C≡CH	H	H	H	H
$(CH_2)_2C_6H_4$-3-C≡CCH$_3$	H	H	H	H
$(CH_2)_2C_6H_4$-4-C≡CCH$_3$	H	H	H	H
$(CH_2)_2C_6H_4$-4-$(CH_2)_2$C≡CCH$_3$	H	H	H	H
$(CH_2)_2C_6H_4$-3-$(CH_2)_3$C≡CC$_5$H$_{11}$	H	H	H	H
$(CH_2)_2C_6H_4$-3-C≡CC$_8$H$_{17}$	H	H	H	H
$(CH_2)_3C_6H_4$-3-C≡CH	H	H	H	H
$(CH_2)_3C_6H_4$-4-C≡CH	H	H	H	H
$(CH_2)_3C_6H_4$-3-C≡CCH$_3$	H	H	H	H
CH(C$_2$H$_5$)C$_6$H$_4$-4-C≡CCH$_3$	H	H	H	H
$(CH_2)_3C_6H_4$-3-$(CH_2)_4$C≡CC$_4$H$_9$	H	H	H	H
$(CH_2)_3C_6H_4$-2-C≡CC$_8$H$_{17}$	H	H	H	H

R^1	R^2	R^3	R^4	R^5
$CH_2CH(CH_3)C_6H_{10}$-2-$(CH_2)_3C\equiv CC_5H_{11}$	H	H	H	H
$(CH_2)_3C_6H_4$-4-$C\equiv CC_8H_{17}$	H	H	H	H
$CH_2CH(CH_3)C_6H_{10}$-4-$(CH_2)_3C\equiv CC_5H_{11}$	H	H	H	H
$(CH_2)_4C_6H_4$-3-$C\equiv CH$	H	H	H	H
$(CH_2)_4C_6H_4$-4-$C\equiv CH$	H	H	H	H
$(CH_2)_4C_6H_4$-3-$C\equiv CCH_3$	H	H	H	H
$(CH_2)_4C_6H_4$-4-$CH_2C\equiv CH$	H	H	H	H
$(CH_2)_4C_6H_4$-3-$C\equiv CC_8H_{17}$	H	H	H	H
$(CH_2)_4C_6H_4$-4-$(CH_2)_8C\equiv CH$	H	H	H	H
$(CH_2)_4C_5H_8$-4-$(CH_2)_6C\equiv CH$	H	H	H	H
$CH_2CH=CHCH_2C_5H_8$-4-$(CH_2)_6C\equiv CH$	H	H	H	H
$(CH_2)_5C_6H_4$-3-$C\equiv CH$	H	H	H	H
$(CH_2)_5C_6H_4$-4-$C\equiv CH$	H	H	H	H
$(CH_2)_5C_6H_4$-2-$C\equiv CH$	H	H	H	H
$(CH_2)_5C_6H_4$-2-$C\equiv CH$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_5C_6H_4$-3-$CH_2C\equiv CH$	H	H	H	H
$(CH_2)_5C_6H_4$-4-$C\equiv CCH_3$	H	H	H	H
$(CH_2)_2CH(C_2H_5)C_6H_4$-3-$(CH_2)_2C\equiv CC_5H_{13}$	H	H	H	H
$(CH_2)_5C_6H_4$-4-$C\equiv CC_8H_{17}$	H	H	H	H
$(CH_2)_7C_6H_4$-3-$C\equiv CH$	H	H	H	H
$(CH_2)_7C_6H_4$-4-$C\equiv CH$	H	H	H	H
$(CH_2)_7C_6H_4$-3-$CH_2C\equiv CH$	H	H	H	H
$(CH_2)_7C_6H_4$-3-$C\equiv CCH_3$	H	H	H	H
$(CH_2)_3CH(C_3H_7)C_6H_4$-3-$(CH_2)_5C\equiv CC_3H_7$	H	H	H	H
$(CH_2)_7C_6H_4$-4-$C\equiv CC_8H_{17}$	H	H	H	H
$(CH_2)_7C_8H_{12}$-4-$(CH_2)_4C\equiv CC_4H_9$	H	H	H	H
$C\equiv C(CH_2)_3CH(CH_3)C_6H_4$-4-$C\equiv CC_8H_{17}$	H	H	H	H
C_6H_4-3-OCH_3	H	H	H	H
C_6H_4-4-OCH_3	H	H	H	H
C_6H_4-3-OC_2H_5	H	H	H	H
C_6H_4-4-OC_2H_5	H	H	H	H
C_6H_4-3-OC_3H_7	H	H	H	H
C_6H_4-4-OC_3H_7	H	H	H	H
C_6H_4-3-OC_4H_9	H	H	H	H

R^1	R^2	R^3	R^4	R^5
C_6H_4-2-OC_4H_9	H	H	H	H
C_6H_{10}-3-OC_4H_9	H	H	H	H
C_6H_4-4-OC_4H_9	H	H	H	H
C_6H_4-3-OC_6H_{13}	H	H	H	H
C_6H_4-4-OC_6H_{13}	H	H	H	H
C_6H_4-4-OC_8H_{17}	H	H	H	H
C_6H_4-4-OC_8H_{17}	$COCH_3$	H	$COCH_3$	$COCH_3$
C_6H_4-3-$OC_{10}H_{21}$	H	H	H	H
C_6H_4-4-$OC_{10}H_{21}$	H	H	H	H
C_6H_4-4-$OC_{10}H_{21}$	$COCH_3$	H	$COCH_3$	$COCH_3$
C_6H_4-3-$OC_{12}H_{25}$	H	H	H	H
C_6H_4-4-$OC_{12}H_{25}$	H	H	H	H
C_6H_4-3-$OC_{20}H_{41}$	H	H	H	H
C_6H_4-4-$OC_{20}H_{41}$	H	H	H	H
$CH_2C_6H_4$-3-OCH_3	H	H	H	H
$CH_2C_6H_4$-4-OCH_3	H	H	H	H
$CH_2C_6H_4$-3-OC_2H_5	H	H	H	H
$CH_2C_6H_4$-4-OC_2H_5	H	H	H	H
$CH_2C_6H_4$-3-OC_3H_7	H	H	H	H
$CH_2C_6H_4$-4-OC_3H_7	H	H	H	H
$CH_2C_6H_4$-2-OC_4H_9	H	H	H	H
$CH_2C_6H_4$-3-OC_4H_9	H	H	H	H
$CH_2C_6H_4$-4-OC_4H_9	H	H	H	H
$CH_2C_6H_4$-4-OC_5H_{11}	H	H	H	H
$CH_2C_6H_4$-4-OC_5H_{11}	$COCH_3$	H	$COCH_3$	$COCH_3$
$CH_2C_6H_4$-4-OC_6H_{13}	H	H	H	H
$CH_2C_6H_4$-4-OC_6H_{13}	$COCH_3$	H	$COCH_3$	$COCH_3$
$CH_2C_6H_4$-4-OC_7H_{15}	H	H	H	H
$CH_2C_6H_4$-4-OC_7H_{15}	$COCH_3$	H	$COCH_3$	$COCH_3$
$CH_2C_6H_4$-4-$O(CH_2)_6CH=CH_2$	H	H	H	H
$CH_2C_6H_4$-4-$O(CH_2)_6CH=CH_2$	$COCH_3$	H	$COCH_3$	$COCH_3$
$CH_2C_6H_4$-4-OC_8H_{17}	H	H	H	H
$CH_2C_6H_4$-4-OC_8H_{17}	$COCH_3$	H	$COCH_3$	$COCH_3$
$CH_2C_6H_4$-4-OC_9H_{19}	H	H	H	H

R^1	R^2	R^3	R^4	R^5
$CH_2C_6H_4$-4-OC_9H_{19}	$COCH_3$	H	$COCH_3$	$COCH_3$
$CH_2C_6H_4$-3-OC_6H_{13}	H	H	H	H
$CH_2C_6H_4$-4-OC_6H_{13}	H	H	H	H
$CH_2C_6H_4$-3-$OC_{10}H_{21}$	H	H	H	H
$CH_2C_6H_4$-4-$OC_{10}H_{21}$	H	H	H	H
$CH_2C_6H_4$-4-$OC_{11}H_{23}$	H	H	H	H
$CH_2C_6H_4$-4-$OC_{11}H_{23}$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2C_6H_4$-3-OCH_3	H	H	H	H
$(CH_2)_2C_6H_4$-4-OCH_3	H	H	H	H
$(CH_2)_2C_6H_4$-3-OC_2H_5	H	H	H	H
$(CH_2)_2C_6H_4$-4-OC_2H_5	H	H	H	H
$(CH_2)_2C_6H_4$-3-OC_3H_7	H	H	H	H
$(CH_2)_2C_6H_4$-4-OC_3H_7	H	H	H	H
$(CH_2)_2C_6H_4$-3-OC_4H_9	H	H	H	H
$(CH_2)_2C_5H_8$-3-OC_4H_9	H	H	H	H
$(CH_2)_2C_6H_4$-4-OC_4H_9	H	H	H	H
$(CH_2)_2C_6H_4$-3-OC_6H_{13}	H	H	H	H
$(CH_2)_2C_6H_4$-4-OC_6H_{13}	H	H	H	H
$(CH_2)_2C_6H_4$-4-OC_6H_{13}	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2C_6H_4$-4-OC_7H_{15}	H	H	H	H
$(CH_2)_2C_6H_4$-4-OC_7H_{15}	$COCH_3$	H	H	H
$(CH_2)_2C_6H_4$-3-OC_7H_{15}	H	H	H	H
$(CH_2)_2C_6H_4$-3-OC_7H_{15}	$COCH_3$	H	H	H
$(CH_2)_2C_6H_4$-4-OC_8H_{17}	H	H	H	H
$(CH_2)_2C_6H_4$-4-OC_8H_{17}	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2C_6H_4$-3-$OC_{10}H_{21}$	H	H	H	H
$(CH_2)_2C_6H_4$-4-$OC_{10}H_{21}$	H	H	H	H
$CH{=}CHC_6H_4$-4-$OC_{10}H_{21}$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2C_6H_4$-3-$OC_{11}H_{23}$	$COCH_3$	H	H	H
$(CH_2)_2C_6H_4$-3-$OC_{11}H_{23}$	H	H	H	H
$(CH_2)_2C_6H_4$-3-$OC_{11}H_{23}$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2C_6H_4$-2-$OC_{12}H_{25}$	H	H	H	H
$(CH_2)_2C_6H_4$-3-$OC_{12}H_{25}$	H	H	H	H
$(CH_2)_2C_6H_4$-4-$OC_{12}H_{25}$	H	H	H	H

R^1	R^2	R^3	R^4	R^5
$(CH_2)_2C_6H_4$-3-$OC_{20}H_{41}$	H	H	H	H
$(CH_2)_2C_6H_4$-4-$OC_{20}H_{41}$	H	H	H	H
$(CH_2)_3C_6H_4$-3-OCH_3	H	H	H	H
$(CH_2)_3C_6H_4$-4-OCH_3	H	H	H	H
$(CH_2)_3C_6H_4$-3-OC_2H_5	H	H	H	H
$(CH_2)_3C_6H_4$-4-OC_2H_5	H	H	H	H
$(CH_2)_3C_6H_4$-3-OC_3H_7	H	H	H	H
$(CH_2)_3C_6H_4$-4-OC_3H_7	H	H	H	H
$(CH_2)_3C_6H_4$-3-OC_4H_9	H	H	H	H
$(CH_2)_3C_6H_4$-4-OC_4H_9	H	H	H	H
$(CH_2)_3C_6H_4$-4-OC_5H_{11}	H	H	H	H
$(CH_2)_3C_6H_4$-4-OC_5H_{11}	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_3C_6H_4$-3-OC_6H_{13}	H	H	H	H
$(CH_2)_3C_6H_4$-4-OC_6H_{13}	H	H	H	H
$(CH_2)_3C_6H_4$-4-OC_6H_{13}	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_3C_6H_4$-3-$OC_{10}H_{21}$	H	H	H	H
$(CH_2)_3C_6H_4$-2-$OC_{10}H_{21}$	H	H	H	H
$(CH_2)_3C_6H_4$-4-$OC_{10}H_{21}$	H	H	H	H
$(CH_2)_3C_6H_4$-3-$OC_{11}H_{23}$	H	H	H	H
$(CH_2)_3C_6H_4$-3-$OC_{11}H_{23}$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_3C_6H_4$-3-$OC_{12}H_{25}$	H	H	H	H
$(CH_2)_3C_6H_4$-4-$OC_{12}H_{25}$	H	H	H	H
$(CH_2)_3C_6H_4$-3-$OC_{20}H_{41}$	H	H	H	H
$(CH_2)_3C_6H_4$-4-$OC_{20}H_{41}$	H	H	H	H
$(CH_2)_3C_8H_{14}$-5-$OC_{20}H_{41}$	H	H	H	H
$(CH_2)_4C_6H_4$-3-OCH_3	H	H	H	H
$(CH_2)_4C_6H_4$-4-OCH_3	H	H	H	H
$(CH_2)_4C_6H_4$-3-OC_2H_5	H	H	H	H
$(CH_2)_4C_6H_4$-4-OC_2H_5	H	H	H	H
$(CH_2)_4C_6H_4$-3-OC_3H_7	H	H	H	H
$(CH_2)_4C_6H_4$-4-OC_3H_7	H	H	H	H
$(CH_2)_4C_6H_4$-4-OC_4H_9	H	H	H	H
$(CH_2)_4C_6H_4$-4-OC_4H_9	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_4C_6H_4$-3-OC_4H_9	H	H	H	H

R^1	R^2	R^3	R^4	R^5
$(CH_2)_4C_6H_4$-4-OC_4H_9	H	H	H	H
$(CH_2)_4C_6H_4$-3-OC_6H_{13}	H	H	H	H
$(CH_2)_4C_6H_{10}$-3-OC_6H_{13}	H	H	H	H
$(CH_2)_4C_6H_4$-4-OC_6H_{13}	H	H	H	H
$(CH_2)_4C_6H_4$-3-$OC_{10}H_{21}$	H	H	H	H
$CH_2CH{=}CHCH_2C_6H_4$-4-$OC_{10}H_{21}$	H	H	H	H
$(CH_2)_4C_6H_4$-3-$OC_{12}H_{25}$	H	H	H	H
$(CH_2)_4C_6H_4$-4-$OC_{12}H_{25}$	H	H	H	H
$(CH_2)_4C_6H_4$-3-$OC_{20}H_{41}$	H	H	H	H
$(CH_2)_4C_6H_4$-4-$OC_{20}H_{41}$	H	H	H	H
$(CH_2)_5C_6H_4$-2-OCH_3	H	H	H	H
$(CH_2)_5C_6H_4$-3-OCH_3	H	H	H	H
$(CH_2)_5C_6H_4$-4-OCH_3	H	H	H	H
$(CH_2)_5C_6H_4$-3-OC_2H_5	H	H	H	H
$(CH_2)_5C_6H_4$-4-OC_2H_5	H	H	H	H
$(CH_2)_5C_6H_4$-3-OC_3H_7	H	H	H	H
$(CH_2)_5C_6H_4$-4-OC_3H_7	H	H	H	H
$(CH_2)_5C_6H_4$-3-OC_4H_9	H	H	H	H
$(CH_2)_5C_6H_4$-4-OC_4H_9	H	H	H	H
$(CH_2)_5C_6H_4$-3-OC_6H_{13}	H	H	H	H
$(CH_2)_5C_6H_4$-4-OC_6H_{13}	H	H	H	H
$C{\equiv}C(CH_2)_3C_6H_4$-3-$OC_{10}H_{21}$	H	H	H	H
$C{\equiv}C(CH_2)_3C_6H_{10}$-3-$OC_{10}H_{21}$	H	H	H	H
$(CH_2)_5C_6H_4$-4-$OC_{10}H_{21}$	H	H	H	H
$(CH_2)_5C_6H_4$-3-$OC_{12}H_{25}$	H	H	H	H
$(CH_2)_5C_6H_4$-4-$OC_{12}H_{25}$	H	H	H	H
$(CH_2)_5C_6H_4$-3-$OC_{20}H_{41}$	H	H	H	H
$(CH_2)_5C_6H_4$-4-$OC_{20}H_{41}$	H	H	H	H
$(CH_2)_7C_6H_4$-4-OCH_3	H	H	H	H
$(CH_2)_7C_6H_4$-4-OCH_3	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_7C_6H_4$-3-OC_7H_{15}	H	H	H	H
$(CH_2)_7C_6H_4$-4-OC_6H_{13}	H	H	H	H
$(CH_2)_9C_6H_4$-2-OC_5H_{11}	H	H	H	H
$(CH_2)_9C_6H_4$-3-OC_5H_{11}	H	H	H	H

R^1	R^2	R^3	R^4	R^5
$(CH_2)_9C_6H_4$-4-OC_4H_9	H	H	H	H
$(CH_2)_{11}C_6H_4$-3-OC_3H_7	H	H	H	H
$(CH_2)_{11}C_6H_4$-4-OC_2H_5	H	H	H	H
$(CH_2)_{13}C_6H_4$-3-OCH_3	H	H	H	H
C_6H_4-3-$OCH=CH_2$	H	H	H	H
C_6H_4-4-$OCH=CH_2$	H	H	H	H
$CH_2C_6H_4$-3-$OCH=CH_2$	H	H	H	H
$CH_2C_6H_4$-4-$OCH=CH_2$	H	H	H	H
$CH_2C_6H_4$-3-$OCH_2CH=CH_2$	H	H	H	H
$CH_2C_6H_4$-4-$OCH_2CH=CH_2$	H	H	H	H
$CH_2C_6H_4$-3-$O(CH_2)_4CH=CHC_4H_9$	H	H	H	H
$CH_2C_6H_4$-4-$O(CH_2)_7CH=CHCH_3$	H	H	H	H
$(CH_2)_2C_6H_4$-3-$OCH_2CH=CH_2$	H	H	H	H
$(CH_2)_2C_6H_4$-4-$OCH_2CH=CH_2$	H	H	H	H
$(CH_2)_2C_5H_{10}$-4-$OCH_2CH=CH_2$	H	H	H	H
$(CH_2)_2C_6H_4$-3-$O(CH_2)_4CH=CHC_4H_9$	H	H	H	H
$(CH_2)_2C_6H_4$-4-$O(CH_2)_4CH=CHC_4H_9$	H	H	H	H
$(CH_2)_3C_6H_4$-3-$OCH_2CH=CH_2$	H	H	H	H
$(CH_2)_3C_6H_4$-4-$OCH_2CH=CH_2$	H	H	H	H
$(CH_2)_3C_6H_4$-3-$O(CH_2)_4CH=CHC_4H_9$	H	H	H	H
$(CH_2)_3C_6H_4$-4-$O(CH_2)_6CH=CHC_2H_5$	H	H	H	H
$(CH_2)_9C_6H_4$-3-$OCH_2CH=CH_2$	H	H	H	H
$(CH_2)_9C_6H_4$-4-$OCH_2CH=CH_2$	H	H	H	H
$(CH_2)_9C_6H_4$-3-$O(CH_2)_4CH=CHC_4H_9$	H	H	H	H
$(CH_2)_9C_6H_4$-4-$O(CH_2)_4CH=CHC_4H_9$	H	H	H	H
C_6H_4-3-$OC\equiv CH$	H	H	H	H
C_6H_4-4-$OC\equiv CH$	H	H	H	H
$CH_2C_6H_4$-3-$OC\equiv CH$	H	H	H	H
$CH_2C_6H_4$-4-$OC\equiv CH$	H	H	H	H
$CH_2C_6H_4$-3-$OCH_2C\equiv CH$	H	H	H	H
$CH_2C_6H_4$-4-$OCH_2C\equiv CH$	H	H	H	H
$CH_2C_6H_4$-3-$O(CH_2)_4C\equiv CC_4H_9$	H	H	H	H
$CH_2C_6H_4$-4-$O(CH_2)_4C\equiv CC_4H_9$	H	H	H	H
$(CH_2)_2C_6H_4$-3-$OCH_2C\equiv CH$	H	H	H	H

R^1	R^2	R^3	R^4	R^5
$(CH_2)_2C_6H_4$-4-$OCH_2C\equiv CH$	H	H	H	H
$(CH_2)_2C_5H_8$-2-$OCH_2C\equiv CH$	H	H	H	H
$(CH_2)_2C_6H_4$-3-$O(CH_2)_6C\equiv CC_2H_5$	H	H	H	H
$(CH_2)_2C_6H_4$-4-$O(CH_2)_4C\equiv CC_4H_9$	H	H	H	H
$(CH_2)_3C_6H_4$-3-$OCH_2C\equiv CH$	H	H	H	H
$(CH_2)_3C_6H_4$-4-$OCH_2C\equiv CH$	H	H	H	H
$(CH_2)_3C_6H_4$-3-$O(CH_2)_2C\equiv CC_6H_{13}$	H	H	H	H
$(CH_2)_3C_6H_4$-4-$O(CH_2)_7C\equiv CCH_3$	H	H	H	H
$(CH_2)_4C_6H_4$-2-$OCH_2C\equiv CH$	H	H	H	H
$(CH_2)_4C_6H_4$-3-$OCH_2C\equiv CH$	H	H	H	H
$(CH_2)_4C_6H_4$-4-$OCH_2C\equiv CH$	H	H	H	H
$(CH_2)_4C_6H_4$-3-$O(CH_2)_2C\equiv CC_6H_{13}$	H	H	H	H
$CH_2CH=CHCH_2C_6H_4$-4-$O(CH_2)_4C\equiv CC_4H_9$	H	H	H	H
$(CH_2)_5C_6H_4$-3-$OCH_2C\equiv CH$	H	H	H	H
$(CH_2)_2CH(C_2H_5)C_6H_4$-4-$OCH_2C\equiv CH$	H	H	H	H
$(CH_2)_2CH(C_2H_5)C_6H_{10}$-4-$OCH_2C\equiv CH$	H	H	H	H
$(CH_2)_5C_6H_4$-3-$O(CH_2)_5C\equiv CC_3H_7$	H	H	H	H
$(CH_2)_5C_6H_4$-4-$O(CH_2)_4C\equiv CC_4H_9$	H	H	H	H
$(CH_2)_7C_6H_4$-3-$OCH_2C\equiv CH$	H	H	H	H
$(CH_2)_7C_6H_4$-4-$OCH_2C\equiv CH$	H	H	H	H
$(CH_2)_7C_6H_4$-3-$O(CH_2)_5C\equiv CC_3H_7$	H	H	H	H
$(CH_2)_2C\equiv C(CH_2)_3C_6H_4$-4-$O(CH_2)_7C\equiv CCH_3$	H	H	H	H
$(CH_2)_9C_6H_4$-3-$OCH_2C\equiv CH$	H	H	H	H
$(CH_2)_9C_6H_4$-4-$O(CH_2)_2C\equiv CCH_3$	H	H	H	H
$(CH_2)_5CH(C_3H_7)C_6H_4$-3-$O(CH_2)_3C\equiv CC_5H_{11}$	H	H	H	H
$(CH_2)_9C_6H_4$-4-$O(CH_2)_6C\equiv CC_2H_5$	H	H	H	H
$(CH_2)_{11}C_6H_4$-3-$OCH_2C\equiv CH$	H	H	H	H
$(CH_2)_3C\equiv C(CH_2)_6C_6H_4$-4-$O(CH_2)_2C\equiv CCH_3$	H	H	H	H
$(CH_2)_{11}C_6H_4$-2-$O(CH_2)_2C\equiv CC_6H_{13}$	H	H	H	H
$(CH_2)_{11}C_6H_4$-3-$O(CH_2)_2C\equiv CC_6H_{13}$	H	H	H	H
$(CH_2)_{11}C_6H_4$-4-$O(CH_2)_8C\equiv CH$	H	H	H	H
$(CH_2)_{13}C_6H_4$-3-$O(CH_2)_2C\equiv CC_2H_5$	H	H	H	H
$(CH_2)_{13}C_6H_4$-4-$O(CH_2)_2C\equiv CCH_3$	H	H	H	H
$(CH_2)_4CH=CH(CH_2)_3C_6H_4$-3-$O(CH_2)_2C\equiv CC_6H_{13}$	H	H	H	H

R^1	R^2	R^3	R^4	R^5
$(CH_2)_{13}C_6H_4$-4-$O(CH_2)_8C\equiv CH$	H	H	H	H
C_6H_4-4-$OCH_2C_6H_5$	H	H	H	H
C_6H_{10}-4-$OCH_2C_6H_5$	H	H	H	H
C_6H_4-4-$O(CH_2)_2C_6H_5$	H	H	H	H
C_6H_{10}-4-$O(CH_2)_2C_6H_5$	H	H	H	H
C_6H_4-2-$O(CH_2)_4C_6H_5$	H	H	H	H
C_6H_4-4-$O(CH_2)_4C_6H_5$	H	H	H	H
C_6H_{10}-4-$O(CH_2)_4C_6H_5$	H	H	H	H
C_6H_4-4-$O(CH_2)_8C_6H_5$	H	H	H	H
C_6H_{10}-4-$O(CH_2)_{10}C_6H_5$	H	H	H	H
C_6H_4-4-$O(CH_2)_{12}C_6H_5$	H	H	H	H
C_6H_{10}-4-$O(CH_2)_{14}C_6H_5$	H	H	H	H
$(CH_2)_2C_6H_4$-2-$O(CH_2)_4C_6H_5$	H	H	H	H
$(CH_2)_2C_6H_4$-3-$O(CH_2)_4C_6H_5$	H	H	H	H
$(CH_2)_2C_6H_4$-4-$O(CH_2)_4C_6H_5$	H	H	H	H
$(CH_2)_2C_6H_{10}$-4-$O(CH_2)_4C_6H_5$	H	H	H	H
$(CH_2)_4C_6H_4$-4-$O(CH_2)_4C_6H_5$	H	H	H	H
$(CH_2)_5CH(CH_3)C_6H_4$-4-$O(CH_2)_4C_6H_5$	H	H	H	H
$CH_2CH=CHCH_2CH(C_2H_5)C_6H_4$-4-$O(CH_2)_4C_6H_5$	H	H	H	H
$CH_2CH=CHCH_2CH(C_2H_5)C_6H_{10}$-4-$O(CH_2)_4C_6H_5$	H	H	H	H
$(CH_2)_3C\equiv C(CH_2)_2C_6H_{10}$-4-$O(CH_2)_4C_6H_5$	H	H	H	H
$(CH_2)_{11}C_6H_4$-4-$O(CH_2)_4C_6H_5$	H	H	H	H
$(CH_2)_2C_6H_4$-4-$O(CH_2)_5C_6H_5$	H	H	H	H
$(CH_2)_2C_6H_{10}$-4-$O(CH_2)_6C_6H_5$	H	H	H	H
$(CH_2)_4C_6H_4$-4-$O(CH_2)_6C_6H_5$	H	H	H	H
$(CH_2)_5CH(CH_3)C_6H_4$-4-$O(CH_2)_{10}C_6H_5$	H	H	H	H
$CH_2CH=CHCH_2CH(C_2H_5)C_6H_4$-4-$O(CH_2)_{12}C_6H_5$	H	H	H	H
$CH_2CH=CHCH_2CH(C_2H_5)C_6H_{10}$-4-$O(CH_2)_{13}C_6H_5$	H	H	H	H
$(CH_2)_3C\equiv C(CH_2)_2C_6H_{10}$-4-$(CH_2)_3C_6H_5$	H	H	H	H
$(CH_2)_{11}C_6H_4$-4-$(CH_2)_5C_6H_5$	H	H	H	H
C_6H_4-4-$COCH_3$	H	H	H	H
C_6H_{10}-4-$COCH_3$	H	H	H	H
C_6H_4-4-COC_2H_5	H	H	H	H
C_6H_4-4-COC_5H_{11}	H	H	H	H

R^1	R^2	R^3	R^4	R^5
C_6H_{10}-4-COC_7H_{15}	H	H	H	H
C_6H_4-4-$COC_{13}H_{27}$	H	H	H	H
$CH_2C_6H_4$-2-$COCH_3$	H	H	H	H
$CH_2C_6H_{10}$-2-$COCH_3$	H	H	H	H
$CH_2C_6H_4$-3-$COCH_3$	H	H	H	H
$CH_2C_6H_{10}$-3-$COCH_3$	H	H	H	H
$CH_2C_6H_4$-4-$COCH_3$	H	H	H	H
$CH_2C_6H_{10}$-4-$COCH_3$	H	H	H	H
$(CH_2)_2C_6H_4$-4-$COCH_3$	H	H	H	H
$(CH_2)_2C_6H_4$-4-COC_6H_{13}	H	H	H	H
$(CH_2)_2C_6H_4$-4-COC_9H_{19}	H	H	H	H
$(CH_2)_2C_6H_4$-4-$COC_{10}H_{21}$	H	H	H	H
$(CH_2)_3C_6H_4$-4-COC_3H_7	H	H	H	H
$(CH_2)_3C_6H_4$-4-COC_9H_{19}	H	H	H	H
$(CH_2)_3C_6H_{10}$-4-COC_3H_7	H	H	H	H
$(CH_2)_4C_6H_4$-4-$COCH_3$	H	H	H	H
$(CH_2)_3CH(CH_3)C_6H_4$-3-COC_5H_{11}	H	H	H	H
$CH{=}CHCH_2CH(CH_3)C_6H_4$-3-$COC_5H_{11}$	H	H	H	H
$(CH_2)_7C_6H_4$-4-$COCH_3$	H	H	H	H
$(CH_2)_7C_6H_{10}$-4-$COCH_3$	H	H	H	H
$CH_2C{\equiv}C(CH_2)_4C_6H_{10}$-4-$COCH_3$	H	H	H	H
$CH_2C_6H_4$-4-COC_7H_{15}	H	H	H	H
$(CH_2)_9C_6H_4$-2-COC_7H_{15}	H	H	H	H
$(CH_2)_9C_6H_4$-3-COC_7H_{15}	H	H	H	H
$(CH_2)_9C_6H_4$-4-COC_7H_{15}	H	H	H	H
$(CH_2)_9C_8H_{14}$-4-COC_7H_{15}	H	H	H	H
$(CH_2)_{11}C_6H_4$-4-COC_3H_7	H	H	H	H
$(CH_2)_6CH(C_4H_9)C_6H_4$-4-COC_2H_5	H	H	H	H
$(CH_2)_{13}C_6H_4$-4-$COCH_3$	H	H	H	H
$(CH_2)_{10}C{\equiv}CCH(CH_3)C_6H_4$-4-$COCH_3$	H	H	H	H
$(CH_2)_{10}C{\equiv}CCH(CH_3)C_6H_4$-4-$COC_7H_{15}$	H	H	H	H
$(CH_2)_{14}CH(CH_3)C_6H_4$-4-$COCH_3$	H	H	H	H
$(CH_2)_{17}C_6H_4$-4-COC_4H_9	H	H	H	H
$(CH_2)_9C_6H_4$-4-COC_9H_{19}	H	H	H	H

R^1	R^2	R^3	R^4	R^5
$(CH_2)_9C_6H_{10}$-4-COC_9H_{19}	H	H	H	H
$(CH_2)_8CH(CH_3)C_6H_{10}$-4-$COC_{13}H_{27}$	H	H	H	H
$(CH_2)_2C_6H_4$-4-$COC_{17}H_{35}$	H	H	H	H
$(CH_2)_3C_6H_4$-4-$COC_{18}H_{37}$	H	H	H	H
C_6H_4-4-$NHCOCH_3$	H	H	H	H
C_6H_{10}-4-$NHCOCH_3$	H	H	H	H
C_6H_4-4-$NHCOC_2H_5$	H	H	H	H
C_6H_4-4-$NHCOC_5H_{11}$	H	H	H	H
C_6H_{10}-4-$NHCOC_7H_{15}$	H	H	H	H
C_6H_4-4-$NHCOC_{13}H_{27}$	H	H	H	H
$CH_2C_6H_4$-4-$NHCOCH_3$	H	H	H	H
$CH_2C_6H_{10}$-4-$NHCOCH_3$	H	H	H	H
$CH_2C_6H_4$-2-$NHCOCH_3$	H	H	H	H
$CH_2C_6H_4$-3-$NHCOCH_3$	H	H	H	H
$(CH_2)_2C_6H_4$-4-$NHCOCH_3$	H	H	H	H
$(CH_2)_2C_6H_4$-4-$NHCOC_9H_{19}$	H	H	H	H
$(CH_2)_2C_6H_4$-4-$NHCOC_9H_{19}$	$COOC(CH_3)_3$	H	H	H
$(CH_2)_3C_6H_4$-4-$NHCOC_3H_7$	H	H	H	H
$(CH_2)_3C_6H_{10}$-4-$NHCOC_3H_7$	H	H	H	H
$(CH_2)_4C_6H_4$-4-$NHCOCH_3$	H	H	H	H
$(CH_2)_3CH(CH_3)C_6H_4$-3-$NHCOC_5H_{11}$	H	H	H	H
$CH{=}CHCH_2CH(CH_3)C_6H_4$-3-$NHCOC_5H_{11}$	H	H	H	H
$(CH_2)_7C_6H_4$-4-$NHCOCH_3$	H	H	H	H
$(CH_2)_7C_6H_{10}$-4-$NHCOCH_3$	H	H	H	H
$CH_2C{\equiv}C(CH_2)_4C_6H_{10}$-4-$NHCOCH_3$	H	H	H	H
$CH_2C_6H_4$-4-$NHCOC_7H_{15}$	H	H	H	H
$(CH_2)_9C_6H_4$-4-$NHCOC_7H_{15}$	H	H	H	H
$(CH_2)_9C_6H_{14}$-4-$NHCOC_7H_{15}$	H	H	H	H
$(CH_2)_{11}C_6H_4$-4-$NHCOC_2H_7$	H	H	H	H
$(CH_2)_6CH(C_4H_9)C_6H_4$-4-$NHCOC_2H_5$	H	H	H	H
$(CH_2)_{13}C_6H_4$-4-$NHCOCH_3$	H	H	H	H
$(CH_2)_{10}C{\equiv}CCH(CH_3)C_6H_4$-4-$NHCOCH_3$	H	H	H	H
$(CH_2)_{10}C{\equiv}CCH(CH_3)C_6H_4$-4-$NHCOC_7H_{15}$	H	H	H	H
$(CH_2)_{14}CH(CH_3)C_6H_4$-4-$NHCOCH_3$	H	H	H	H

R^1	R^2	R^3	R^4	R^5
$(CH_2)_{17}C_6H_4$-4-$NHCOC_4H_9$	H	H	H	H
$(CH_2)_9C_6H_4$-4-$NHCOC_9H_{19}$	H	H	H	H
$(CH_2)_9C_6H_{10}$-4-$NHCOC_9H_{19}$	H	H	H	H
$(CH_2)_8CH(CH_3)C_6H_{10}$-4-$NHCOC_{13}H_{27}$	H	H	H	H
$(CH_2)_2C_6H_4$-4-$NHCOC_{17}H_{35}$	H	H	H	H
$(CH_2)_3C_6H_4$-4-$NHCOC_{18}H_{37}$	H	H	H	H
C_6H_4-4-$OCOCH_3$	H	H	H	H
C_6H_{10}-4-$OCOCH_3$	H	H	H	H
C_6H_4-4-$OCOC_2H_5$	H	H	H	H
C_6H_4-2-$OCOC_5H_{11}$	H	H	H	H
C_6H_4-4-$OCOC_5H_{11}$	H	H	H	H
C_6H_{10}-4-$OCOC_7H_{15}$	H	H	H	H
C_6H_4-4-$OCOC_{13}H_{27}$	H	H	H	H
$CH_2C_6H_4$-4-$OCOCH_3$	H	H	H	H
$CH_2C_6H_{10}$-4-$OCOCH_3$	H	H	H	H
$CH_2C_6H_4$-3-$OCOCH_3$	H	H	H	H
$(CH_2)_2C_6H_4$-4-$OCOCH_3$	H	H	H	H
$(CH_2)_3C_6H_4$-4-$OCOC_3H_7$	H	H	H	H
$(CH_2)_3C_6H_{10}$-4-$OCOC_3H_7$	H	H	H	H
$(CH_2)_4C_6H_4$-4-$OCOCH_3$	H	H	H	H
$(CH_2)_3CH(CH_3)C_6H_4$-3-$OCOC_5H_{11}$	H	H	H	H
$CH{=}CHCH_2CH(CH_3)C_6H_4$-3-$OCOC_5H_{11}$	H	H	H	H
$(CH_2)_7C_6H_4$-4-$OCOCH_3$	H	H	H	H
$(CH_2)_7C_6H_{10}$-4-$OCOCH_3$	H	H	H	H
$CH_2C{\equiv}C(CH_2)_4C_6H_{10}$-4-$OCOCH_3$	H	H	H	H
$CH_2C_6H_4$-2-$OCOC_7H_{15}$	H	H	H	H
$CH_2C_6H_4$-3-$OCOC_7H_{15}$	H	H	H	H
$CH_2C_6H_4$-4-$OCOC_7H_{15}$	H	H	H	H
$(CH_2)_9C_6H_4$-4-$OCOC_7H_{15}$	H	H	H	H
$(CH_2)_9C_8H_{14}$-4-$OCOC_7H_{15}$	H	H	H	H
$(CH_2)_{11}C_6H_4$-4-$OCOC_3H_7$	H	H	H	H
$(CH_2)_6CH(C_4H_9)C_6H_4$-4-$OCOC_2H_5$	H	H	H	H
$(CH_2)_{13}C_6H_4$-2-$OCOCH_3$	H	H	H	H
$(CH_2)_{13}C_6H_4$-3-$OCOCH_3$	H	H	H	H

R^1	R^2	R^3	R^4	R^5
$(CH_2)_{13}C_6H_4$-4-$OCOCH_3$	H	H	H	H
$(CH_2)_{10}C\equiv CCH(CH_3)C_6H_4$-4-$OCOCH_3$	H	H	H	H
$(CH_2)_{10}C\equiv CCH(CH_3)C_6H_4$-4-$OCOC_7H_{15}$	H	H	H	H
$(CH_2)_{14}CH(CH_3)C_6H_4$-4-$OCOCH_3$	H	H	H	H
$(CH_2)_{17}C_6H_4$-4-$OCOC_4H_9$	H	H	H	H
$(CH_2)_9C_6H_4$-4-$OCOC_9H_{19}$	H	H	H	H
$(CH_2)_9C_6H_{10}$-4-$OCOC_9H_{19}$	H	H	H	H
$(CH_2)_8CH(CH_3)C_6H_{10}$-4-$OCOC_{13}H_{27}$	H	H	H	H
$(CH_2)_2C_6H_4$-4-$OCOC_{17}H_{35}$	H	H	H	H
$(CH_2)_3C_6H_4$-4-$OCOC_{18}H_{37}$	H	H	H	H
C_5H_4-4-$COOCH_3$	H	H	H	H
C_6H_{10}-4-$COOCH_3$	H	H	H	H
C_6H_4-4-$COOC_2H_5$	H	H	H	H
C_6H_4-4-$COOC_4H_9$	H	H	H	H
C_6H_{10}-2-$COOC_8H_{17}$	H	H	H	H
C_6H_{10}-3-$COOC_8H_{17}$	H	H	H	H
C_6H_{10}-4-$COOC_8H_{17}$	H	H	H	H
C_6H_4-4-$COOC_{14}H_{29}$	H	H	H	H
$CH_2C_6H_4$-4-$COOCH_3$	H	H	H	H
$CH_2C_6H_{10}$-4-$COOCH_3$	H	H	H	H
$CH_2C_6H_4$-3-$COOCH_3$	H	H	H	H
$(CH_2)_2C_6H_4$-4-$COOCH_3$	H	H	H	H
$(CH_2)_3C_6H_4$-4-$COOC_4H_9$	H	H	H	H
$(CH_2)_3C_6H_{10}$-4-$COOC_4H_9$	H	H	H	H
$(CH_2)_4C_6H_4$-4-$COOCH_3$	H	H	H	H
$(CH_2)_3CH(CH_3)C_6H_4$-3-$COOC_6H_{13}$	H	H	H	H
$CH{=}CHCH_2CH(CH_3)C_6H_4$-3-$COOC_6H_{13}$	H	H	H	H
$(CH_2)_7C_6H_4$-2-$COOCH_3$	H	H	H	H
$(CH_2)_7C_6H_4$-3-$COOCH_3$	H	H	H	H
$(CH_2)_7C_6H_4$-4-$COOCH_3$	H	H	H	H
$(CH_2)_7C_6H_{10}$-4-$COOCH_3$	H	H	H	H
$CH_2C\equiv C(CH_2)_4C_6H_{10}$-4-$COOCH_3$	H	H	H	H
$CH_2C_6H_4$-4-$COOC_8H_{17}$	H	H	H	H
$(CH_2)_9C_6H_4$-4-$COOC_8H_{17}$	H	H	H	H

R^1	R^2	R^3	R^4	R^5
$(CH_2)_9C_8H_{14}$-4-$COOC_8H_{17}$	H	H	H	H
$(CH_2)_{11}C_6H_4$-4-$COOC_4H_9$	H	H	H	H
$(CH_2)_6CH(C_4H_9)C_6H_4$-4-$COOC_3H_7$	H	H	H	H
$(CH_2)_{13}C_6H_4$-4-$COOCH_3$	H	H	H	H
$(CH_2)_{10}C{=}CCH(CH_3)C_6H_4$-4-$COOCH_3$	H	H	H	H
$(CH_2)_{10}C{\equiv}CCH(CH_3)C_6H_4$-4-$COOC_8H_{17}$	H	H	H	H
$(CH_2)_{14}CH(CH_3)C_6H_4$-4-$COOCH_3$	H	H	H	H
$(CH_2)_{17}C_6H_4$-4-$COOC_5H_{11}$	H	H	H	H
$(CH_2)_9C_6H_4$-4-$COOC_{10}H_{21}$	H	H	H	H
$(CH_2)_9C_6H_{10}$-4-$COOC_{10}H_{21}$	H	H	H	H
$(CH_2)_8CH(CH_3)C_6H_{10}$-4-$COOC_{14}H_{29}$	H	H	H	H
$(CH_2)_2C_6H_4$-4-$COOC_{18}H_{37}$	H	H	H	H
$(CH_2)_3C_6H_4$-2-$COOC_{19}H_{39}$	H	H	H	H
$(CH_2)_3C_6H_4$-3-$COOC_{19}H_{39}$	H	H	H	H
$(CH_2)_3C_6H_4$-4-$COOC_{19}H_{39}$	H	H	H	H
C_6H_4-4-$NHCOOCH_3$	H	H	H	H
C_6H_{10}-4-$NHCOOCH_3$	H	H	H	H
C_6H_4-2-$NHCOOC_2H_5$	H	H	H	H
C_6H_4-3-$NHCOOC_2H_5$	H	H	H	H
C_6H_4-4-$NHCOOC_2H_5$	H	H	H	H
C_6H_4-4-$NHCOOC_4H_9$	H	H	H	H
C_6H_{10}-4-$NHCOOC_8H_{17}$	H	H	H	H
C_6H_4-4-$NHCOOC_{14}H_{29}$	H	H	H	H
$CH_2C_6H_4$-4-$NHCOOCH_3$	H	H	H	H
$CH_2C_6H_{10}$-4-$NHCOOCH_3$	H	H	H	H
$CH_2C_6H_4$-3-$NHCOOCH_3$	H	H	H	H
$(CH_2)_2C_6H_4$-2-$NHCOOCH_3$	H	H	H	H
$(CH_2)_2C_6H_4$-4-$NHCOOCH_3$	H	H	H	H
$(CH_2)_3C_6H_4$-4-$NHCOOC_4H_9$	H	H	H	H
$(CH_2)_3C_6H_{10}$-4-$NHCOOC_4H_9$	H	H	H	H
$(CH_2)_4C_6H_4$-4-$NHCOOCH_3$	H	H	H	H
$(CH_2)_3CH(CH_3)C_6H_4$-3-$NHCOOC_6H_{13}$	H	H	H	H
$CH{=}CHCH_2CH(CH_3)C_6H_4$-3-$NHCOOC_6H_{13}$	H	H	H	H
$(CH_2)_7C_6H_4$-4-$NHCOOCH_3$	H	H	H	H

R^1	R^2	R^3	R^4	R^5
$(CH_2)_7C_6H_{10}$-4-$NHCOOCH_3$	H	H	H	H
$CH_2C\equiv C(CH_2)_4C_6H_{10}$-4-$NHCOOCH_3$	H	H	H	H
$CH_2C_6H_4$-4-$NHCOOC_8H_{17}$	H	H	H	H
$(CH_2)_9C_6H_4$-4-$NHCOOC_8H_{17}$	H	H	H	H
$(CH_2)_9C_8H_{17}$-4-$NHCOOC_8H_{17}$	H	H	H	H
$(CH_2)_{11}C_6H_4$-4-$NHCOOC_4H_9$	H	H	H	H
$(CH_2)_6CH(C_4H_9)C_6H_4$-4-$NHCOOC_3H_7$	H	H	H	H
$(CH_2)_{13}C_6H_4$-4-$NHCOOCH_3$	H	H	H	H
$(CH_2)_{10}C\equiv CCH(CH_3)C_6H_4$-4-$NHCOOCH_3$	H	H	H	H
$(CH_2)_{10}C\equiv CCH(CH_3)C_6H_4$-4-$NHCOOC_8H_{17}$	H	H	H	H
$(CH_2)_{14}CH(CH_3)C_6H_4$-4-$NHCOOCH_3$	H	H	H	H
$(CH_2)_{17}C_6H_4$-4-$NHCOOC_5H_{11}$	H	H	H	H
$(CH_2)_9C_6H_4$-4-$NHCOOC_{10}H_{21}$	H	H	H	H
$(CH_2)_9C_6H_{10}$-4-$NHCOOC_{10}H_{21}$	H	H	H	H
$(CH_2)_8CH(CH_3)C_6H_{10}$-4-$NHCOOC_{14}H_{29}$	H	H	H	H
$(CH_2)_2C_6H_4$-4-$NHCOOC_{18}H_{37}$	H	H	H	H
$(CH_2)_3C_6H_4$-4-$NHCOOC_{19}H_{39}$	H	H	H	H
C_6H_4-4-$NHCH_3$	H	H	H	H
C_6H_{10}-4-$NHCH_3$	H	H	H	H
C_6H_4-4-NHC_2H_5	H	H	H	H
C_6H_4-4-NHC_4H_9	H	H	H	H
C_6H_{10}-4-NHC_8H_{17}	H	H	H	H
C_6H_4-4-$NHC_{14}H_{29}$	H	H	H	H
$CH_2C_6H_4$-4-$NHCH_3$	H	H	H	H
$CH_2C_6H_{10}$-4-$NHCH_3$	H	H	H	H
$CH_2C_6H_4$-3-$NHCH_3$	H	H	H	H
$CH_2C_6H_4$-4-$N(CH_3)C_{10}H_{21}$	H	H	H	H
$CH_2C_6H_4$-4-$N(CH_3)C_{10}H_{21}$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2C_6H_4$-4-$NHCH_3$	H	H	H	H
$(CH_2)_2C_6H_4$-4-$NHC_{10}H_{21}$	H	H	H	H
$(CH_2)_3C_6H_4$-4-NHC_4H_9	H	H	H	H
$(CH_2)_3C_6H_{10}$-4-NHC_4H_9	H	H	H	H
$(CH_2)_4C_6H_4$-4-$NHCH_3$	H	H	H	H
$(CH_2)_3CH(CH_3)C_6H_4$-2-NHC_6H_{13}	H	H	H	H

R^1	R^2	R^3	R^4	R^5
$(CH_2)_3CH(CH_3)C_6H_4$-3-NHC_6H_{13}	H	H	H	H
$CH=CHCH_2CH(CH_3)C_6H_4$-3-NHC_6H_{13}	H	H	H	H
$(CH_2)_7C_6H_4$-4-$NHCH_3$	H	H	H	H
$(CH_2)_7C_6H_{10}$-4-$NHCH_3$	H	H	H	H
$CH_2C\equiv C(CH_2)_4C_6H_{10}$-4-$NHCH_3$	H	H	H	H
$CH_2C_6H_4$-4-NHC_8H_{17}	H	H	H	H
$(CH_2)_9C_6H_4$-4-NHC_8H_{17}	H	H	H	H
$(CH_2)_9C_8H_{14}$-4-NHC_8H_{17}	H	H	H	H
$(CH_2)_{11}C_6H_4$-4-NHC_4H_9	H	H	H	H
$(CH_2)_5CH(C_4H_9)C_6H_4$-4-NHC_3H_7	H	H	H	H
$(CH_2)_{13}C_6H_4$-4-$NHCH_3$	H	H	H	H
$(CH_2)_{10}C\equiv CCH(CH_3)C_6H_4$-4-$NHCH_3$	H	H	H	H
$(CH_2)_{10}C\equiv CCH(CH_3)C_6H_4$-4-$NHC_8H_{17}$	H	H	H	H
$(CH_2)_{14}CH(CH_3)C_6H_4$-4-$NHCH_3$	H	H	H	H
$(CH_2)_{17}C_6H_4$-4-NHC_5H_{11}	H	H	H	H
$(CH_2)_9C_6H_4$-4-$NHC_{10}H_{21}$	H	H	H	H
$(CH_2)_9C_6H_{10}$-4-$NHC_{10}H_{21}$	H	H	H	H
$(CH_2)_8CH(CH_3)C_6H_{10}$-4-$NHC_{14}H_{29}$	H	H	H	H
$(CH_2)_2C_6H_4$-4-$NHC_{18}H_{37}$	H	H	H	H
$(CH_2)_3C_6H_4$-4-$NHC_{19}H_{39}$	H	H	H	H
C_6H_4-4-SCH_3	H	H	H	H
C_6H_{10}-4-SCH_3	H	H	H	H
C_6H_4-4-SC_2H_5	H	H	H	H
C_6H_4-4-SC_4H_9	H	H	H	H
C_6H_{10}-4-SC_8H_{17}	H	H	H	H
C_6H_4-4-SC_8H_{17}	H	H	H	H
C_6H_4-4-SC_8H_{17}	$COCH_3$	H	H	H
C_6H_4-4-$SC_{14}H_{29}$	H	H	H	H
$CH_2C_6H_4$-2-SCH_3	H	H	H	H
$CH_2C_6H_4$-3-SCH_3	H	H	H	H
$CH_2C_6H_4$-4-SCH_3	H	H	H	H
$CH_2C_6H_{10}$-4-SCH_3	H	H	H	H
$CH_2C_6H_4$-4-SC_7H_{15}	H	H	H	H
$CH_2C_6H_4$-4-SC_7H_{15}	$COCH_3$	H	$COCH_3$	$COCH_3$

R^1	R^2	R^3	R^4	R^5
$(CH_2)_2C_6H_4$-4-SCH_3	H	H	H	H
$(CH_2)_3C_6H_4$-4-SC_4H_9	H	H	H	H
$(CH_2)_3C_6H_{10}$-4-SC_4H_9	H	H	H	H
$(CH_2)_4C_6H_4$-4-SCH_3	H	H	H	H
$(CH_2)_3CH(CH_3)C_6H_4$-3-SC_6H_{13}	H	H	H	H
$CH{=}CHCH_2CH(CH_3)C_6H_4$-3-$SC_6H_{13}$	H	H	H	H
$(CH_2)_7C_6H_4$-4-SCH_3	H	H	H	H
$(CH_2)_7C_6H_{10}$-4-SCH_3	H	H	H	H
$CH_2C{\equiv}C(CH_2)_4C_6H_{10}$-4-$SCH_3$	H	H	H	H
$CH_2C_6H_4$-4-SC_8H_{17}	H	H	H	H
$(CH_2)_9C_6H_4$-4-SC_8H_{17}	H	H	H	H
$(CH_2)_5C_8H_{14}$-4-SC_8H_{17}	H	H	H	H
$(CH_2)_{11}C_5H_4$-4-SC_4H_9	H	H	H	H
$(CH_2)_6CH(C_4H_9)C_6H_4$-4-SC_3H_7	H	H	H	H
$(CH_2)_{13}C_6H_4$-4-SCH_3	H	H	H	H
$(CH_2)_{10}C{\equiv}CCH(CH_3)C_6H_4$-4-$SCH_3$	H	H	H	H
$(CH_2)_{10}C{\equiv}CCH(CH_3)C_6H_4$-4-$SC_8H_{17}$	H	H	H	H
$(CH_2)_{14}CH(CH_3)C_6H_4$-4-$SCH_3$	H	H	H	H
$(CH_2)_{17}C_6H_4$-4-SC_5H_{11}	H	H	H	H
$(CH_2)_9C_6H_4$-4-$SC_{10}H_{21}$	H	H	H	H
$(CH_2)_9C_6H_{10}$-4-$SC_{10}H_{21}$	H	H	H	H
$(CH_2)_6CH(CH_3)C_5H_{10}$-4-$SC_{14}H_{29}$	H	H	H	H
$(CH_2)_2C_5H_4$-4-$SC_{18}H_{37}$	H	H	H	H
$(CH_2)_3C_5H_4$-4-$SC_{19}H_{39}$	H	H	H	H
C_6H_4-4-$CONHCH_3$	H	H	H	H
C_6H_{10}-4-$CONHCH_3$	H	H	H	H
C_6H_4-4-$CONHC_2H_5$	H	H	H	H
C_5H_4-4-$CONHC_4H_9$	H	H	H	H
C_6H_{10}-4-$CONHC_8H_{17}$	H	H	H	H
C_6H_4-4-$CONHC_{14}H_{29}$	H	H	H	H
$CH_2C_5H_4$-4-$CONHCH_3$	H	H	H	H
$CH_2C_5H_{10}$-4-$CONHCH_3$	H	H	H	H
$CH_2C_5H_4$-2-$CONHCH_3$	H	H	H	H
$CH_2C_5H_4$-3-$CONHCH_3$	H	H	H	H

R^1	R^2	R^3	R^4	R^5
$(CH_2)_2C_6H_4$-4-$CONHCH_3$	H	H	H	H
$(CH_2)_3C_6H_4$-4-$CONHC_4H_9$	H	H	H	H
$(CH_2)_3C_6H_{10}$-4-$CONHC_4H_9$	H	H	H	H
$(CH_2)_4C_6H_4$-4-$CONHCH_3$	H	H	H	H
$(CH_2)_3CH(CH_3)C_6H_4$-3-$CONHC_6H_{13}$	H	H	H	H
$CH=CHCH_2CH(CH_3)C_6H_4$-3-$CONHC_6H_{13}$	H	H	H	H
$(CH_2)_7C_6H_4$-4-$CONHCH_3$	H	H	H	H
$(CH_2)_7C_6H_{10}$-4-$CONHCH_3$	H	H	H	H
$CH_2C\equiv C(CH_2)_4C_6H_{10}$-4-$CONHCH_3$	H	H	H	H
$CH_2C_6H_4$-4-$CONHC_8H_{17}$	H	H	H	H
$(CH_2)_9C_6H_4$-4-$CONHC_8H_{17}$	H	H	H	H
$(CH_2)_9C_8H_{14}$-4-$CONHC_8H_{17}$	H	H	H	H
$(CH_2)_{11}C_6H_4$-4-$CONHC_4H_9$	H	H	H	H
$(CH_2)_6CH(C_4H_9)C_6H_4$-4-$CONHC_3H_7$	H	H	H	H
$(CH_2)_{13}C_6H_4$-4-$CONHCH_3$	H	H	H	H
$(CH_2)_{10}C\equiv CCH(CH_3)C_6H_4$-4-$CONHCH_3$	H	H	H	H
$(CH_2)_{10}C\equiv CCH(CH_3)C_6H_4$-4-$CONHC_8H_{17}$	H	H	H	H
$(CH_2)_{14}CH(CH_3)C_6H_4$-4-$CONHCH_3$	H	H	H	H
$(CH_2)_{17}C_6H_4$-4-$CONHC_5H_{11}$	H	H	H	H
$(CH_2)_9C_6H_4$-4-$CONHC_{10}H_{21}$	H	H	H	H
$(CH_2)_9C_6H_{10}$-4-$CONHC_{10}H_{21}$	H	H	H	H
$(CH_2)_8CH(CH_3)C_6H_{10}$-4-$CONHC_{14}H_{29}$	H	H	H	H
$(CH_2)_2C_6H_4$-4-$CONHC_{18}H_{37}$	H	H	H	H
$(CH_2)_3C_6H_4$-4-$CONHC_{19}H_{39}$	H	H	H	H
C_6H_4-4-CH_2Br	H	H	H	H
C_6H_{10}-4-CH_2Br	H	H	H	H
C_6H_4-2-CH_2Br	H	H	H	H
C_6H_{10}-3-CH_2Br	H	H	H	H
C_6H_4-4-$(CH_2)_2F$	H	H	H	H
C_6H_4-3-$(CH_2)_4Cl$	H	H	H	H
C_6H_{10}-4-$(CH_2)_2CHFC_3H_7$	H	H	H	H
C_6H_4-4-$(CH_2)_7CHBrC_6H_{13}$	H	H	H	H
$CH_2C_6H_4$-4-CH_2Br	H	H	H	H
$CH_2C_6H_{10}$-2-CF_3	H	H	H	H

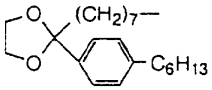
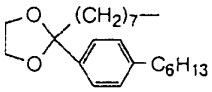
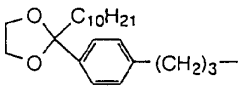
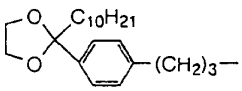
R^1	R^2	R^3	R^4	R^5
$CH_2C_6H_{10}$-3-CF_3	H	H	H	H
$CH_2C_6H_{10}$-4-CF_3	H	H	H	H
$CH_2C_6H_4$-4-CH_2Cl	H	H	H	H
$CH_2C_6H_4$-3-CH_2Br	H	H	H	H
$CH_2C_6H_4$-4-$(CH_2)_8F$	H	H	H	H
$CH_2C_6H_4$-4-$(CH_2)_8F$	$COCH_3$	H	$COCH_3$	$COCH_3$
$CH_2C_6H_4$-4-$CF_2C_7H_{15}$	H	H	H	H
$CH_2C_6H_4$-4-$CF_2C_7H_{15}$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2C_6H_4$-4-CH_2Br	H	H	H	H
$(CH_2)_3C_6H_4$-4-$(CH_2)_4Br$	H	H	H	H
$(CH_2)_3C_6H_{10}$-4-$(CH_2)_4Br$	H	H	H	H
$(CH_2)_4C_6H_4$-4-CH_2Cl	H	H	H	H
$(CH_2)_5C_6H_4$-3-CH_2Br	H	H	H	H
$CH{=}CHCH_2CH(CH_3)C_6H_4$-3-$(CH_2)_2CHClC_3H_7$	H	H	H	H
$(CH_2)_7C_6H_4$-4-CH_2F	H	H	H	H
$(CH_2)_7C_6H_{10}$-4-CH_2Br	H	H	H	H
$CH_2C{\equiv}C(CH_2)_4C_6H_{10}$-4-$CH_2Br$	H	H	H	H
$CH_2C_6H_4$-4-$(CH_2)_3CHFC_4H_9$	H	H	H	H
$(CH_2)_9C_6H_4$-4-$(CH_2)_5CHClC_2H_5$	H	H	H	H
$(CH_2)_9C_8H_{14}$-4-$(CH_2)_5CHClC_2H_5$	H	H	H	H
$(CH_2)_{11}C_6H_4$-3-$(CH_2)_4Cl$	H	H	H	H
$(CH_2)_6CH(C_4H_9)C_6H_4$-2-$CH_2CHBrCH_3$	H	H	H	H
$(CH_2)_{13}C_6H_4$-4-CH_2Br	H	H	H	H
$(CH_2)_{10}C{\equiv}CCH(CH_3)C_6H_4$-4-$CH_2Br$	H	H	H	H
$(CH_2)_{10}C{\equiv}CCH(CH_3)C_6H_4$-3-$(CH_2)_3CHFC_4H_9$	H	H	H	H
$(CH_2)_{14}CH(CH_3)C_6H_4$-4-$CH_2Br$	H	H	H	H
$(CH_2)_{17}C_6H_4$-4-$(CH_2)_2CHClC_2H_5$	H	H	H	H
$(CH_2)_9C_6H_4$-3-$(CH_2)_{10}Cl$	H	H	H	H
$(CH_2)_3C_6H_{10}$-4-$(CH_2)_7CHClC_2H_5$	H	H	H	H
$(CH_2)_8CH(CH_3)C_6H_{10}$-3-$(CH_2)_3CHFC_{10}H_{21}$	H	H	H	H
$(CH_2)_2C_6H_4$-3-$(CH_2)_9CBr_2C_8H_{17}$	H	H	H	H
$(CH_2)_3C_6H_4$-4-$(CH_2)_{18}CF_3$	H	H	H	H
C_6H_4-4-NH_2	H	H	H	H
C_6H_{10}-4-NH_2	H	H	H	H

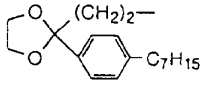
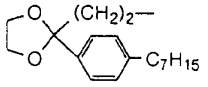
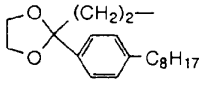
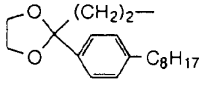
R^1	R^2	R^3	R^4	R^5
$CH_2C_6H_4$-4-NH_2	H	H	H	H
$CH_2C_6H_{10}$-4-NH_2	H	H	H	H
$CH_2C_6H_4$-3-NH_2	H	H	H	H
$(CH_2)_2C_6H_4$-4-NH_2	H	H	H	H
$(CH_2)_3C_6H_4$-4-NH_2	H	H	H	H
$(CH_2)_3C_6H_{10}$-2-NH_2	H	H	H	H
$(CH_2)_3C_6H_{10}$-4-NH_2	H	H	H	H
$(CH_2)_4C_6H_4$-4-NH_2	H	H	H	H
$(CH_2)_5C_6H_4$-3-NH_2	H	H	H	H
$CH{=}CHCH_2CH(CH_3)C_6H_4$-3-$NH_2$	H	H	H	H
$(CH_2)_7C_6H_4$-4-NH_2	H	H	H	H
$(CH_2)_7C_6H_{10}$-2-NH_2	H	H	H	H
$(CH_2)_7C_6H_{10}$-4-NH_2	H	H	H	H
$CH_2C{\equiv}C(CH_2)_4C_6H_{10}$-4-$NH_2$	H	H	H	H
$(CH_2)_9C_6H_4$-4-NH_2	H	H	H	H
$(CH_2)_9C_8H_{14}$-4-NH_2	H	H	H	H
$(CH_2)_{11}C_6H_4$-4-NH_2	H	H	H	H
$(CH_2)_6CH(C_4H_9)C_6H_4$-4-NH_2	H	H	H	H
$(CH_2)_{13}C_6H_4$-4-NH_2	H	H	H	H
$(CH_2)_{10}C{\equiv}CCH(CH_3)C_6H_4$-4-$NH_2$	H	H	H	H
$(CH_2)_3CH[(CH_2)_6C{\equiv}CC_2H_5]C_6H_4$-4-$NH_2$	H	H	H	H
$(CH_2)_{14}CH(CH_3)C_6H_4$-3-$NH_2$	H	H	H	H
$(CH_2)_{17}C_6H_4$-4-NH_2	H	H	H	H
$CH_2CH(C_7H_{15})C_6H_{10}$-4-$NH_2$	H	H	H	H
$(CH_2)_8CH(CH_3)C_6H_{10}$-4-$NH_2$	H	H	H	H
C_5H_4-4-NO_2	H	H	H	H
C_5H_{10}-4-NO_2	H	H	H	H
$CH_2C_6H_4$-4-NO_2	H	H	H	H
$CH_2C_6H_{10}$-4-NO_2	H	H	H	H
$CH_2C_5H_4$-3-NO_2	H	H	H	H
$(CH_2)_2C_6H_4$-4-NO_2	H	H	H	H
$(CH_2)_2C_6H_4$-4-NO_2	$COCH_3$	H	H	H
$(CH_2)_3C_6H_4$-4-NO_2	H	H	H	H
$(CH_2)_3C_6H_{10}$-4-NO_2	H	H	H	H

R^1	R^2	R^3	R^4	R^5
$(CH_2)_4C_6H_4$-4-NO_2	H	H	H	H
$(CH_2)_3CH(CH_3)C_6H_4$-3-NO_2	H	H	H	H
$CH=CHCH_2CH(CH_3)C_6H_4$-3-NO_2	H	H	H	H
$(CH_2)_7C_6H_4$-4-NO_2	H	H	H	H
$(CH_2)_7C_6H_{10}$-4-NO_2	H	H	H	H
$CH_2C\equiv C(CH_2)_4C_6H_{10}$-4-$NO_2$	H	H	H	H
$(CH_2)_9C_6H_4$-4-NO_2	H	H	H	H
$(CH_2)_9C_8H_{14}$-4-NO_2	H	H	H	H
$(CH_2)_{11}C_6H_4$-4-NO_2	H	H	H	H
$(CH_2)_5CH(C_4H_9)C_6H_4$-4-NO_2	H	H	H	H
$(CH_2)_{13}C_6H_4$-4-NO_2	H	H	H	H
$(CH_2)_{10}C\equiv CCH(CH_3)C_6H_4$-4-$NO_2$	H	H	H	H
$(CH_2)_3CH[(CH_2)_5C\equiv CC_2H_5]C_6H_4$-4-$NO_2$	H	H	H	H
$(CH_2)_{14}C\equiv CC_6H_4$-3-$NO_2$	H	H	H	H
$(CH_2)_{17}C_6H_4$-4-NO_2	H	H	H	H
$CH_2CH(C_7H_{15})C_6H_{10}$-4-$NO_2$	H	H	H	H
$(CH_2)_8CH(CH_3)C_5H_{10}$-4-$NO_2$	H	H	H	H
C_6H_4-4-OH	H	H	H	H
C_5H_{10}-4-OH	H	H	H	H
$CH_2C_5H_4$-4-OH	H	H	H	H
$CH_2C_5H_4$-4-OH	$COCH_3$	H	$COCH_3$	$COCH_3$
$CH_2C_5H_{10}$-4-OH	H	H	H	H
$CH_2C_5H_4$-3-OH	H	H	H	H
$(CH_2)_2C_6H_4$-4-OH	H	H	H	H
$(CH_2)_3C_6H_4$-4-OH	H	H	H	H
$(CH_2)_3C_6H_{10}$-4-OH	H	H	H	H
$(CH_2)_4C_6H_4$-4-OH	H	H	H	H
$(CH_2)_3CH(CH_3)C_6H_4$-3-OH	H	H	H	H
$CH=CHCH_2CH(CH_3)C_6H_4$-3-OH	H	H	H	H
$(CH_2)_7C_6H_4$-4-OH	H	H	H	H
$(CH_2)_7C_6H_{10}$-4-OH	H	H	H	H
$CH_2C\equiv C(CH_2)_4C_5H_{10}$-4-OH	H	H	H	H
$(CH_2)_3C_6H_4$-2-OH	H	H	H	H
$(CH_2)_9C_6H_4$-4-OH	H	H	H	H

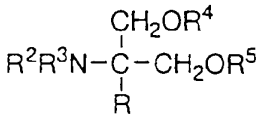
R^1	R^2	R^3	R^4	R^5
$(CH_2)_9C_8H_{14}$-4-OH	H	H	H	H
$(CH_2)_{11}C_6H_4$-4-OH	H	H	H	H
$(CH_2)_6CH(C_4H_9)C_6H_4$-4-OH	H	H	H	H
$(CH_2)_{13}C_6H_4$-4-OH	H	H	H	H
$(CH_2)_{10}C\equiv CCH(CH_3)C_6H_4$-4-OH	H	H	H	H
$(CH_2)_3CH[(CH_2)_6C\equiv CC_2H_5]C_6H_4$-4-OH	H	H	H	H
$(CH_2)_{14}CH(CH_3)C_6H_4$-3-OH	H	H	H	H
$(CH_2)_{17}C_6H_4$-4-OH	H	H	H	H
$CH_2CH(C_7H_{15})C_6H_{10}$-4-OH	H	H	H	H
$(CH_2)_8CH(CH_3)C_6H_{10}$-4-OH	H	H	H	H
C_6H_4-4-COOH	H	H	H	H
C_8H_{10}-4-COOH	H	H	H	H
$CH_2C_6H_4$-4-COOH	H	H	H	H
$CH_2C_6H_{10}$-4-COOH	H	H	H	H
$CH_2C_6H_4$-3-COOH	H	H	H	H
$(CH_2)_2C_6H_4$-4-COOH	H	H	H	H
$(CH_2)_3C_6H_4$-4-COOH	H	H	H	H
$(CH_2)_3C_6H_{10}$-4-COOH	H	H	H	H
$(CH_2)_4C_6H_4$-4-COOH	H	H	H	H
$(CH_2)_3CH(CH_3)C_6H_4$-3-COOH	H	H	H	H
$CH=CHCH_2CH(CH_3)C_6H_4$-2-COOH	H	H	H	H
$CH=CHCH_2CH(CH_3)C_6H_4$-3-COOH	H	H	H	H
$(CH_2)_7C_6H_4$-4-COOH	H	H	H	H
$(CH_2)_7C_6H_{10}$-2-COOH	H	H	H	H
$(CH_2)_7C_6H_{10}$-3-COOH	H	H	H	H
$(CH_2)_7C_6H_{10}$-4-COOH	H	H	H	H
$CH_2C\equiv C(CH_2)_4C_6H_{10}$-4-COOH	H	H	H	H
$(CH_2)_9C_6H_4$-4-COOH	H	H	H	H
$(CH_2)_9C_8H_{14}$-4-COOH	H	H	H	H
$(CH_2)_{11}C_6H_4$-4-COOH	H	H	H	H
$(CH_2)_6CH(C_4H_9)C_6H_4$-4-COOH	H	H	H	H
$(CH_2)_{13}C_6H_4$-4-COOH	H	H	H	H
$(CH_2)_{10}C\equiv CCH(CH_3)C_6H_4$-4-COOH	H	H	H	H
$(CH_2)_3CH[(CH_2)_6C\equiv CC_2H_5]C_6H_4$-4-COOH	H	H	H	H

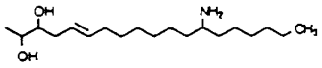
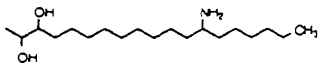
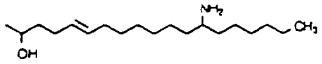
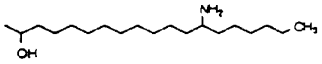
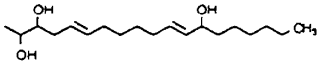
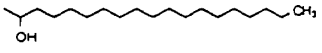
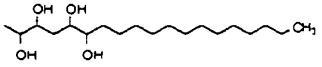
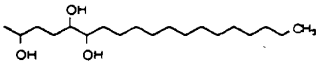
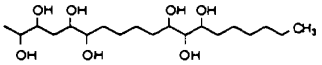
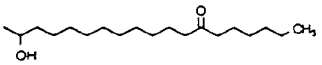
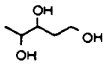
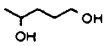
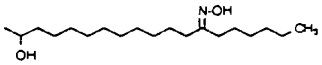
R^1	R^2	R^3	R^4	R^5
$(CH_2)_{14}CH(CH_3)C_6H_4$-3-COOH	H	H	H	H
$(CH_2)_{17}C_6H_4$-4-COOH	H	H	H	H
$CH_2CH(C_7H_{15})C_6H_{10}$-4-COOH	H	H	H	H
$(CH_2)_8CH(CH_3)C_6H_{10}$-4-COOH	H	H	H	H
C_6H_4-4-Br	H	H	H	H
C_6H_{10}-4-Cl	H	H	H	H
$CH_2C_6H_4$-4-Br	H	H	H	H
$CH_2C_6H_{10}$-4-Cl	H	H	H	H
$CH_2C_6H_4$-4-Cl	H	H	H	H
$CH_2C_6H_4$-4-F	H	H	H	H
$CH_2C_6H_4$-4-F	$COCH_3$	H	$COCH_3$	$COCH_3$
$CH_2C_6H_4$-3-F	H	H	H	H
$(CH_2)_2C_6H_4$-4-Br	H	H	H	H
$(CH_2)_3C_6H_4$-4-F	H	H	H	H
$(CH_2)_3C_6H_4$-4-Cl	H	H	H	H
$(CH_2)_3C_6H_4$-4-Cl	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_3C_6H_4$-4-Br	H	H	H	H
$(CH_2)_3C_6H_4$-4-Br	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_3C_6H_4$-4-I	H	H	H	H
$(CH_2)_3C_6H_{10}$-2-Br	H	H	H	H
$(CH_2)_3C_6H_{10}$-4-Br	H	H	H	H
$(CH_2)_4C_6H_4$-4-F	H	H	H	H
$(CH_2)_3CH(CH_3)C_6H_4$-2-Br	H	H	H	H
$(CH_2)_3CH(CH_3)C_6H_4$-3-Br	H	H	H	H
$CH{=}CHCH_2CH(CH_3)C_6H_4$-3-Br	H	H	H	H
$(CH_2)_7C_6H_4$-4-F	H	H	H	H
$(CH_2)_7C_6H_{10}$-4-Br	H	H	H	H
$CH_2C{\equiv}C(CH_2)_4C_6H_{10}$-4-Br	H	H	H	H
$(CH_2)_9C_6H_4$-4-F	H	H	H	H
$(CH_2)_9C_8H_{14}$-4-F	H	H	H	H
$(CH_2)_{11}C_6H_4$-4-Br	H	H	H	H
$(CH_2)_6CH(C_4H_9)C_6H_4$-4-F	H	H	H	H
$(CH_2)_{13}C_6H_4$-2-Br	H	H	H	H
$(CH_2)_{13}C_6H_4$-4-Br	H	H	H	H

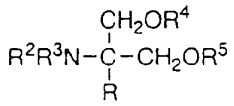
R^1	R^2	R^3	R^4	R^5
$(CH_2)_{10}C\equiv CCH(CH_3)C_6H_4$-4-Cl	H	H	H	H
$(CH_2)_3CH[(CH_2)_6C\equiv CC_2H_5]C_6H_4$-4-Br	H	H	H	H
$(CH_2)_{14}CH(CH_3)C_6H_4$-3-Cl	H	H	H	H
$(CH_2)_{17}C_6H_4$-4-Br	H	H	H	H
$CH_2CH(C_7H_{15})C_6H_{10}$-4-F	H	H	H	H
$(CH_2)_8CH(CH_3)C_6H_{10}$-4-Cl	H	H	H	H
$CH_2C_6H_3$(-4-NH_2)-3-Cl	H	H	H	H
$CH_2C_6H_9$(-4-NH_2)-2-CH_3	H	H	H	H
$CH_2C_6H_3$(-2-$NHCOCH_3$)-4-OCH_3	H	H	H	H
$(CH_2)_3C_6H_9$(-4-$COOC_2H_5$)-3-$C_{10}H_{21}$	H	H	H	H
$(CH_2)_4C_6H_2$(-4-Br)(-3-C_2H_5)-2-COOH	H	H	H	H
$(CH_2)_3CH(CH_3)C_6H_2$(-3-C_4H_9)(-2-F)-4-NO_2	H	H	H	H
$CH_2C_6H_3$(-3-F)-4-C_8H_{17}	H	H	H	H
$CH_2C_6H_3$(-3-F)-4-C_8H_{17}	$COCH_3$	H	$COCH_3$	$COCH_3$
$CH_2C_6H_3$(-2-C_2H_5)-4-C_8H_{17}	H	H	H	H
$CH_2C_6H_3$(-2-C_2H_5)-4-C_8H_{17}	$COCH_3$	H	$COCH_3$	$COCH_3$
$CH_2C_6H_3$(-3-CH_3)-4-C_8H_{17}	H	H	H	H
$CH_2C_6H_3$(-3-CH_3)-4-C_8H_{17}	$COCH_3$	H	$COCH_3$	$COCH_3$
$CH_2C_6H_3$(-4-OC_7H_{15})-3-OCH_3	H	H	H	H
$CH_2C_6H_3$(-4-OC_7H_{15})-3-OCH_3	$COCH_3$	H	$COCH_3$	$COCH_3$
$CH_2C_6H_3$(-4-OC_7H_{15})-3-CH_3	H	H	H	H
$CH_2C_6H_3$(-4-OC_7H_{15})-3-CH_3	$COCH_3$	H	$COCH_3$	$COCH_3$
	H	H	H	H
	$COCH_3$	H	$COCH_3$	$COCH_3$
	H	H	H	H
	$COCH_3$	H	$COCH_3$	$COCH_3$

R^1	R^2	R^3	R^4	R^5
	H	H	H	H
	$COCH_3$	H	$COCH_3$	$COCH_3$
	H	H	H	H
	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_5COC_6H_4$-4-C_6H_{13}	H	H	H	H
COC_6H_4-4-C_7H_{15}	H	H	H	H
COC_6H_4-4-C_7H_{15}	$COCH_3$	H	$COCH_3$	$COCH_3$
COC_6H_4-4-C_8H_{17}	H	H	H	H
COC_6H_4-4-C_8H_{17}	$COCH_3$	H	$COCH_3$	$COCH_3$
$CH(OH)C_6H_4$-4-C_7H_{15}	H	H	H	H
$CH(OH)C_6H_4$-4-C_7H_{15}	$COCH_3$	H	$COCH_3$	$COCH_3$
$CH(OH)C_6H_4$-4-C_8H_{17}	H	H	H	H
$CH(OH)C_6H_4$-4-C_8H_{17}	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_5OC_6H_4$-4-OC_6H_{13}	H	H	H	H
$(CH_2)_5OC_6H_4$-4-OC_6H_{13}	$COCH_3$	H	H	H
$CH_2C_6H_4$-4-$O(CH_2)_7F$	H	H	H	H
$CH_2C_6H_4$-4-$O(CH_2)_7F$	$COCH_3$	H	$COCH_3$	$COCH_3$
$CH_2C_6H_4$-4-$OCF_2C_6H_{13}$	H	H	H	H
$CH_2C_6H_4$-4-$OCF_2C_6H_{13}$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_8OC_6H_5$	H	H	H	H
$(CH_2)_8OC_6H_5$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_{11}OC_6H_5$	$COCH_3$	H	H	H
$(CH_2)_{11}OC_6H_5$	H	H	H	H
$(CH_2)_5O(CH_2)_2OC_6H_5$	H	H	H	H
$(CH_2)_5O(CH_2)_2OC_6H_5$	$COCH_3$	H	$COCH_3$	$COCH_3$
$CH_2C_6H_4OCH_2C_6H_5$	H	H	H	H
$CH_2C_6H_4OCH_2C_6H_5$	$COCH_3$	H	$COCH_3$	$COCH_3$
$CH_2C_6H_4O(CH_2)_6C_6H_5$	H	H	H	H

R^1	R^2	R^3	R^4	R^5
$CH_2C_6H_4O(CH_2)_6C_6H_5$	$COCH_3$	H	$COCH_3$	$COCH_3$
$CH_2C_6H_4CH_2O(CH_2)_5C_6H_5$	H	H	H	H
$CH_2C_6H_4CH_2O(CH_2)_5C_6H_5$	$COCH_3$	H	$COCH_3$	$COCH_3$



R	R^2	R^3	R^4	R^5
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H



R	R^2	R^3	R^4	R^5
C_6H_4-4-$(CH_2)_3CH_3$	H	H	H	H
C_6H_4-4-$(CH_2)_4CH_3$	H	H	H	H
C_6H_4-4-$(CH_2)_5CH_3$	H	H	H	H
C_6H_4-4-$(CH_2)_6CH_3$	H	H	H	H
C_6H_4-4-$(CH_2)_7CH_3$	H	H	H	H
C_6H_4-4-$(CH_2)_8CH_3$	H	H	H	H
C_6H_4-4-$(CH_2)_9CH_3$	H	H	H	H
C_6H_4-4-$(CH_2)_{10}CH_3$	H	H	H	H
C_6H_4-4-$(CH_2)_{11}CH_3$	H	H	H	H
C_6H_4-4-$(CH_2)_{12}CH_3$	H	H	H	H
C_6H_4-4-$(CH_2)_{13}CH_3$	H	H	H	H
C_6H_4-4-$(CH_2)_{14}CH_3$	H	H	H	H
C_6H_4-4-$(CH_2)_{15}CH_3$	H	H	H	H
C_6H_4-2-$(CH_2)_9CH_3$	H	H	H	H
C_6H_4-3-$(CH_2)_9CH_3$	H	H	H	H
C_6H_4-4-O-$(CH_2)_3CH_3$	H	H	H	H
C_6H_4-4-O-$(CH_2)_4CH_3$	H	H	H	H
C_6H_4-4-O-$(CH_2)_5CH_3$	H	H	H	H
C_6H_4-4-O-$(CH_2)_6CH_3$	H	H	H	H
C_6H_4-4-O-$(CH_2)_7CH_3$	H	H	H	H
C_6H_4-4-O-$(CH_2)_8CH_3$	H	H	H	H
C_6H_4-4-O-$(CH_2)_9CH_3$	H	H	H	H
C_6H_4-4-O-$(CH_2)_{10}CH_3$	H	H	H	H
C_6H_4-4-O-$(CH_2)_{11}CH_3$	H	H	H	H
C_6H_4-4-O-$(CH_2)_{12}CH_3$	H	H	H	H
C_6H_4-4-O-$(CH_2)_{13}CH_3$	H	H	H	H
C_6H_4-4-O-$(CH_2)_{14}CH_3$	H	H	H	H
C_6H_4-4-O-$(CH_2)_{14}CH_3$	H	H	H	H
C_6H_4-4-O-$(CH_2)_9F$	H	H	H	H
C_6H_4-4-O-$(CH_2)_{13}F$	H	H	H	H

R	R^2	R^3	R^4	R^5
$CH_2C_6H_4$-4-S-$(CH_2)_5CH_3$	H	H	H	H
$CH_2C_6H_4$-4-S-$(CH_2)_6CH_3$	H	H	H	H
$CH_2C_6H_4$-4-S-$(CH_2)_8CH_3$	H	H	H	H
$CH_2C_6H_4$-4-S-$(CH_2)_9CH_3$	H	H	H	H
$CH_2C_6H_4$-4-S-$(CH_2)_{10}CH_3$	H	H	H	H
$CH_2C_6H_4$-4-S-$(CH_2)_{11}CH_3$	H	H	H	H
$CH_2C_6H_4$-4-S-$(CH_2)_{12}CH_3$	H	H	H	H
$CH_2C_6H_4$-4-S-$(CH_2)_{13}CH_3$	H	H	H	H
$CH_2C_6H_4$-4-S(=O)$(CH_2)_5CH_3$	H	H	H	H
$CH_2C_6H_4$-4-S(=O)$(CH_2)_6CH_3$	H	H	H	H
$CH_2C_6H_4$-4-S(=O)$(CH_2)_7CH_3$	H	H	H	H
$CH_2C_6H_4$-4-S(=O)$(CH_2)_7CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$CH_2C_6H_4$-4-S(=O)$(CH_2)_8CH_3$	H	H	H	H
$CH_2C_6H_4$-4-S(=O)$(CH_2)_9CH_3$	H	H	H	H
$CH_2C_6H_4$-4-S(=O)$(CH_2)_{10}CH_3$	H	H	H	H
$CH_2C_6H_4$-4-S(=O)$(CH_2)_{11}CH_3$	H	H	H	H
$CH_2C_6H_4$-4-S(=O)$(CH_2)_{12}CH_3$	H	H	H	H
$CH_2C_6H_4$-4-S(=O)$(CH_2)_{13}CH_3$	H	H	H	H
$CH_2C_6H_4$-4-S(=O)$(CH_2)_5CH_3$	H	H	H	H
$CH_2C_6H_4$-4-S(=O)$_2(CH_2)_6CH_3$	H	H	H	H
$CH_2C_6H_4$-4-S(=O)$_2(CH_2)_7CH_3$	H	H	H	H
$CH_2C_6H_4$-4-S(=O)$_2(CH_2)_7CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$CH_2C_6H_4$-4-S(=O)$_2(CH_2)_8CH_3$	H	H	H	H
$CH_2C_6H_4$-4-S(=O)$_2(CH_2)_9CH_3$	H	H	H	H
$CH_2C_6H_4$-4-S(=O)$_2(CH_2)_{10}CH_3$	H	H	H	H
$CH_2C_6H_4$-4-S(=O)$_2(CH_2)_{11}CH_3$	H	H	H	H
$CH_2C_6H_4$-4-S(=O)$_2(CH_2)_{12}CH_3$	H	H	H	H
$CH_2C_6H_4$-4-S(=O)$_2(CH_2)_{13}CH_3$	H	H	H	H
$(CH_2)_2C_6H_4$-4-S(=O)$(CH_2)_6CH_3$	H	H	H	H
$(CH_2)_2C_6H_4$-4-S(=O)$(CH_2)_{10}CH_3$	H	H	H	H
$(CH_2)_2C_6H_4$-4-S(=O)$_2(CH_2)_6CH_3$	H	H	H	H
$(CH_2)_2C_6H_4$-4-S(=O)$_2(CH_2)_{10}CH_3$	H	H	H	H
$(CH_2)_2C_6H_4$-4-$(CH_2)_8CH_3$	H	H	H	H
$(CH_2)_2C_6H_4$-4-$(CH_2)_8CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$

R	R^2	R^3	R^4	R^5
$(CH_2)_2C_6H_4$-4-$(CH_2)_9CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2C_6H_4$-4-$(CH_2)_{10}CH_3$	H	H	H	H
$(CH_2)_2C_6H_4$-4-$(CH_2)_{10}CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2C_6H_4$-4-$(CH_2)_{11}CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2C_6H_4$-4-$(CH_2)_{12}CH_3$	H	H	H	H
$(CH_2)_2C_6H_4$-4-$(CH_2)_{12}CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2C_6H_4$-4-$(CH_2)_{13}CH_3$	H	H	H	H
$(CH_2)_2C_6H_4$-4-$(CH_2)_{14}CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2C_6H_4$-4-O-$(CH_2)_{12}CH_3$	H	H	H	H
$(CH_2)_2C_6H_4$-4-O-$(CH_2)_{12}CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2C_6H_4$-4-O-$(CH_2)_{13}CH_3$	H	H	H	H
$(CH_2)_2C_6H_4$-4-O-$(CH_2)_{13}CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2C_6H_4$-4-$(CH_2)_7F$	H	H	H	H
$(CH_2)_2C_6H_4$-4-$(CH_2)_7F$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2C_6H_4$-4-$(CH_2)_{12}F$	H	H	H	H
$(CH_2)_2C_6H_4$-4-$(CH_2)_{12}F$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2C_6H_4$-4-O-$(CH_2)_7F$	H	H	H	H
$(CH_2)_2C_6H_4$-4-O-$(CH_2)_7F$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2C_6H_4$-4-O-$(CH_2)_8F$	H	H	H	H
$(CH_2)_2C_6H_4$-4-O-$(CH_2)_8F$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2C_6H_4$-4-O-$(CH_2)_{11}F$	H	H	H	H
$(CH_2)_2C_6H_4$-4-O-$(CH_2)_{11}F$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2C_6H_{10}$-4-$(CH_2)_4CH_3$	H	H	H	H
$(CH_2)_2C_6H_{10}$-4-$(CH_2)_5CH_3$	H	H	H	H
$(CH_2)_2C_6H_{10}$-4-$(CH_2)_6CH_3$	H	H	H	H
$(CH_2)_2C_6H_{10}$-4-$(CH_2)_7CH_3$	H	H	H	H
$(CH_2)_2C_6H_{10}$-4-$(CH_2)_7CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2C_6H_{10}$-4-$(CH_2)_9CH_3$	H	H	H	H
$(CH_2)_2C_6H_{10}$-4-$(CH_2)_{10}CH_3$	H	H	H	H
$(CH_2)_2C_6H_{10}$-4-$(CH_2)_{11}CH_3$	H	H	H	H
$(CH_2)_2C_6H_{10}$-4-$(CH_2)_{11}CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2C_6H_{10}$-4-$(CH_2)_{12}CH_3$	H	H	H	H
$(CH_2)_2C_6H_{10}$-4-$(CH_2)_{13}CH_3$	H	H	H	H
$(CH_2)_{11}C_6H_5$	H	H	H	H

R	R^2	R^3	R^4	R^5
$(CH_2)_{15}C_6H_5$	H	H	H	H
$(CH_2)_{17}C_6H_5$	H	H	H	H
$(CH_2)_{19}C_6H_5$	H	H	H	H
$(CH_2)_8C_6H_4$-4-F	H	H	H	H
$(CH_2)_9C_6H_4$-4-F	H	H	H	H
$(CH_2)_{10}C_6H_4$-3-F	H	H	H	H
$(CH_2)_{10}C_6H_4$-3-F	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_{11}C_6H_4$-4-F	H	H	H	H
$(CH_2)_{12}C_6H_4$-4-F	H	H	H	H
$(CH_2)_{13}C_6H_4$-4-F	H	H	H	H
$(CH_2)_{10}C_6H_4$-4-F	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_{14}C_6H_4$-4-F	H	H	H	H
$(CH_2)_{15}C_6H_4$-4-F	H	H	H	H
$(CH_2)_{16}C_6H_4$-4-F	H	H	H	H
$(CH_2)_{17}C_6H_4$-4-F	H	H	H	H
$(CH_2)_{18}C_6H_4$-4-F	H	H	H	H
$(CH_2)_{19}C_6H_4$-4-F	H	H	H	H
$(CH_2)_{20}C_6H_4$-4-F	H	H	H	H
$(CH_2)_6O(CH_2)_2C_6H_5$	H	H	H	H
$(CH_2)_6O(CH_2)_2C_6H_5$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_9OCH_2C_6H_5$	H	H	H	H
$(CH_2)_8OCH_2C_6H_5$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2C_6H_4$-4-$OCH_2C_6H_5$	H	H	H	H
$(CH_2)_2C_6H_4$-4-$OCH_2C_6H_5$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2C_6H_4$-4-O-$(CH_2)_2C_6H_5$	H	H	H	H
$(CH_2)_2C_6H_4$-4-O-$(CH_2)_3C_6H_5$	H	H	H	H
$(CH_2)_2C_6H_4$-4-O-$(CH_2)_4C_6H_5$	H	H	H	H
$(CH_2)_2C_6H_4$-4-O-$(CH_2)_5C_6H_5$	H	H	H	H
$(CH_2)_2C_6H_4$-4-O-$(CH_2)_7C_6H_5$	H	H	H	H
$(CH_2)_2C_6H_4$-4-O-$(CH_2)_8C_6H_5$	H	H	H	H
$(CH_2)_2C_6H_4$-4-O-$(CH_2)_3OC_6H_5$	H	H	H	H
$(CH_2)_2C_6H_4$-4-O-$(CH_2)_4OC_6H_5$	H	H	H	H
$(CH_2)_2C_6H_4$-4-O-$(CH_2)_5OC_6H_5$	H	H	H	H
$(CH_2)_2C_6H_4$-4-O-$(CH_2)_6OC_6H_5$	H	H	H	H

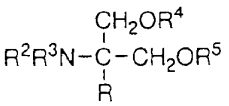
R	R^2	R^3	R^4	R^5
$(CH_2)_2C_6H_4$-4-O-$(CH_2)_7OC_6H_5$	H	H	H	H
$(CH_2)_2C_6H_4$-4-O-$(CH_2)_6OC_6H_5$	H	H	H	H
$(CH_2)_2C_6H_4$-4-$(CH_2)_3OC_6H_5$	H	H	H	H
$(CH_2)_2C_6H_4$-4-$(CH_2)_4OC_6H_5$	H	H	H	H
$(CH_2)_2C_6H_4$-4-$(CH_2)_5OC_6H_5$	H	H	H	H
$(CH_2)_2C_6H_4$-4-$(CH_2)_6OC_6H_5$	H	H	H	H
$(CH_2)_2C_6H_4$-4-$(CH_2)_7OC_6H_5$	H	H	H	H
$(CH_2)_2C_6H_4$-4-$(CH_2)_8OC_6H_5$	H	H	H	H
$(CH_2)_2C_6H_4$-4-O-$(CH_2)_2C_6H_4$-4-F	H	H	H	H
$(CH_2)_2C_6H_4$-4-O-$(CH_2)_3C_6H_4$-4-F	H	H	H	H
$(CH_2)_2C_6H_4$-4-O-$(CH_2)_4C_6H_4$-4-F	H	H	H	H
$(CH_2)_2C_6H_4$-4-O-$(CH_2)_5C_6H_4$-4-F	H	H	H	H
$(CH_2)_2C_6H_4$-4-O-$(CH_2)_5C_6H_4$-4-F	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2C_6H_4$-4-O-$(CH_2)_6C_6H_4$-4-F	H	H	H	H
$(CH_2)_2C_6H_4$-4-O-$(CH_2)_6C_6H_4$-4-F	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2C_6H_4$-4-O-$(CH_2)_7C_6H_4$-4-F	H	H	H	H
$(CH_2)_2C_6H_4$-4-O-$(CH_2)_8C_6H_4$-4-F	H	H	H	H
$(CH_2)_2C_6H_4$-4-$OCH_2C_6H_4$-4-F	H	H	H	H
$(CH_2)_2C_6H_4$-4-O-$(CH_2)_2C_6H_4$-4-F	H	H	H	H
$(CH_2)_2C_6H_4$-4-O-$(CH_2)_3C_6H_4$-4-F	H	H	H	H
$(CH_2)_2C_6H_4$-4-O-$(CH_2)_4C_6H_4$-4-F	H	H	H	H
$(CH_2)_2C_6H_4$-4-O-$(CH_2)_5C_6H_4$-4-F	H	H	H	H
$(CH_2)_2C_6H_4$-4-O-$(CH_2)_7C_6H_4$-4-F	H	H	H	H
$(CH_2)_2C_6H_4$-4-O-$(CH_2)_8C_6H_4$-4-F	H	H	H	H
$(CH_2)_2C_6H_4$-4-O-$(CH_2)_3OC_6H_4$-4-F	H	H	H	H
$(CH_2)_2C_6H_4$-4-O-$(CH_2)_4OC_6H_4$-4-F	H	H	H	H
$(CH_2)_2C_6H_4$-4-O-$(CH_2)_5OC_6H_4$-4-F	H	H	H	H
$(CH_2)_2C_6H_4$-4-O-$(CH_2)_6OC_6H_4$-4-F	H	H	H	H
$(CH_2)_2C_6H_4$-4-O-$(CH_2)_7OC_6H_4$-4-F	H	H	H	H
$(CH_2)_2C_6H_4$-4-O-$(CH_2)_8OC_6H_4$-4-F	H	H	H	H
$(CH_2)_2C_6H_4$-4-$(CH_2)_3OC_6H_4$-4-F	H	H	H	H
$(CH_2)_2C_6H_4$-4-$(CH_2)_4OC_6H_4$-4-F	H	H	H	H
$(CH_2)_2C_6H_4$-4-$(CH_2)_5OC_6H_4$-4-F	H	H	H	H
$(CH_2)_2C_6H_4$-4-$(CH_2)_6OC_6H_4$-4-F	H	H	H	H

R	R^2	R^3	R^4	R^5
$(CH_2)_2C_6H_4$-4-$(CH_2)_7OC_6H_4$-4-F	H	H	H	H
$(CH_2)_2C_6H_4$-4-$(CH_2)_8OC_6H_4$-4-F	H	H	H	H
$CH_2CH(OH)C_6H_4$-4-$(CH_2)_5CH_3$	H	H	H	H
$CH_2CH(OH)C_6H_4$-4-$(CH_2)_6CH_3$	H	H	H	H
$CH_2CHFC_6H_4$-4-$(CH_2)_7CH_3$	H	H	H	H
$CH_2CHFC_6H_4$-4-$(CH_2)_7CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$CH_2CHFC_6H_4$-4-$(CH_2)_8CH_3$	H	H	H	H
$CH_2CH(OH)C_6H_4$-4-$(CH_2)_9CH_3$	H	H	H	H
$CH_2CH(OH)C_6H_4$-4-$(CH_2)_{10}CH_3$	H	H	H	H
$CH_2CH(OH)C_6H_4$-4-$(CH_2)_{11}CH_3$	H	H	H	H
$CH_2CH(OH)C_6H_4$-4-$(CH_2)_{11}CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$CH_2CH(OH)C_6H_4$-4-$(CH_2)_{12}CH_3$	H	H	H	H
$CH_2CH(OH)C_6H_4$-4-$(CH_2)_{13}CH_3$	H	H	H	H
$CH(OH)CH(OH)C_6H_4$-4-$(CH_2)_5CH_3$	H	H	H	H
$CH(OH)CH(OH)C_6H_4$-4-$(CH_2)_6CH_3$	H	H	H	H
$CH(OH)CH(OH)C_6H_4$-4-$(CH_2)_7CH_3$	H	H	H	H
$CH(OH)CH(OH)C_6H_4$-4-$(CH_2)_7CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$CH(OH)CH(OH)C_6H_4$-4-$(CH_2)_8CH_3$	H	H	H	H
$CH(OH)CH(OH)C_6H_4$-4-$(CH_2)_9CH_3$	H	H	H	H
$CH(OH)CH(OH)C_6H_4$-4-$(CH_2)_{10}CH_3$	H	H	H	H
$CH(OH)CH(OH)C_6H_4$-4-$(CH_2)_{11}CH_3$	H	H	H	H
$CH(OH)CH(OH)C_6H_4$-4-$(CH_2)_{11}CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$CH(OH)CH(OH)C_6H_4$-4-$(CH_2)_{12}CH_3$	H	H	H	H
$CH(OH)CH_2C_6H_5$	H	H	H	H
$CH(OH)CH_2C_6H_4$-4-$(CH_2)_5CH_3$	H	H	H	H
$CH(OH)CH_2C_6H_4$-4-$(CH_2)_5CH_3$	H	H	H	H
$CH(OH)CH_2C_6H_4$-4-$(CH_2)_6CH_3$	$COCH_3$	H	H	H
$CH(OH)CH_2C_6H_4$-4-$(CH_2)_7CH_3$	H	H	H	H
$CH(OH)CH_2C_6H_4$-4-$(CH_2)_7CH_3$	$COCH_3$	H	H	H
$CH(OH)CH_2C_6H_4$-4-$(CH_2)_8CH_3$	H	H	H	H
$CH(OH)CH_2C_6H_4$-4-$(CH_2)_9CH_3$	H	H	H	H
$CH(OH)CH_2C_6H_4$-4-$(CH_2)_{10}CH_3$	H	H	H	H
$CH(OH)CH_2C_6H_4$-4-$(CH_2)_{11}CH_3$	H	H	H	H
$CH(OH)CH_2C_6H_4$-4-$(CH_2)_{11}CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$

R	R^2	R^3	R^4	R^5
$CH(OH)CH_2C_6H_4$-4-$(CH_2)_{12}CH_3$	H	H	H	H
$CH(OH)CH_2C_6H_4$-4-$(CH_2)_{13}CH_3$	H	H	H	H
$CH(OH)CH_2C_6H_4$-4-O-$(CH_2)_6C_6H_5$	H	H	H	H
$[CH(OH)]_2C_6H_4$-4-O-$(CH_2)_6C_6H_5$	H	H	H	H
$CH_2CH(OH)C_6H_4$-4-O-$(CH_2)_6C_6H_5$	H	H	H	H
$CH(OH)CH_2C_6H_4$-4-O-$(CH_2)_6C_6H_5$	$COCH_3$	H	$COCH_3$	$COCH_3$
$[CH(OH)]_2C_6H_4$-4-O-$(CH_2)_6C_6H_5$	$COCH_3$	H	$COCH_3$	$COCH_3$
$CH_2CH(OH)C_6H_4$-4-O-$(CH_2)_6C_6H_5$	$COCH_3$	H	$COCH_3$	$COCH_3$
$CH=CHC_6H_4$-4-$(CH_2)_5CH_3$	H	H	H	H
$CH=CHC_6H_4$-4-$(CH_2)_6CH_3$	H	H	H	H
$CH=CHC_6H_4$-4-$(CH_2)_7CH_3$	H	H	H	H
$CH=CHC_6H_4$-4-$(CH_2)_7CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$CH=CHC_6H_4$-4-$(CH_2)_8CH_3$	H	H	H	H
$CH=CHC_6H_4$-4-$(CH_2)_9CH_3$	H	H	H	H
$CH=CHC_6H_4$-4-$(CH_2)_{10}CH_3$	H	H	H	H
$CH=CHC_6H_4$-4-$(CH_2)_{11}CH_3$	H	H	H	H
$CH=CHC_6H_4$-4-$(CH_2)_{11}CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$CH=CHC_6H_4$-4-$(CH_2)_{12}CH_3$	H	H	H	H
$CH=CHC_6H_4$-4-$(CH_2)_{13}CH_3$	H	H	H	H
$CH_2CH=CHCH_2C_6H_4$-4-$(CH_2)_4CH_3$	H	H	H	H
$CH_2CH=CHCH_2C_6H_4$-4-$(CH_2)_5CH_3$	H	H	H	H
$CH_2CH=CHCH_2C_6H_4$-4-$(CH_2)_5CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$CH_2CH=CHCH_2C_6H_4$-4-$(CH_2)_6CH_3$	H	H	H	H
$CH_2CH=CHCH_2C_6H_4$-4-$(CH_2)_7CH_3$	H	H	H	H
$CH_2CH=CHCH_2C_6H_4$-4-$(CH_2)_8CH_3$	H	H	H	H
$CH_2CH=CHCH_2C_6H_4$-4-$(CH_2)_9CH_3$	H	H	H	H
$CH_2CH=CHCH_2C_6H_4$-4-$(CH_2)_9CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$CH_2CH=CHCH_2C_6H_4$-4-$(CH_2)_{10}CH_3$	H	H	H	H
$CH_2CH=CHCH_2C_6H_4$-4-$(CH_2)_{11}CH_3$	H	H	H	H
$CH_2OC_6H_4$-4-$(CH_2)_5CH_3$	H	H	H	H
$CH_2OC_6H_4$-4-$(CH_2)_6CH_3$	H	H	H	H
$CH_2OC_6H_4$-4-$(CH_2)_7CH_3$	H	H	H	H
$CH_2OC_6H_4$-4-$(CH_2)_7CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$CH_2OC_6H_4$-4-$(CH_2)_8CH_3$	H	H	H	H

R	R^2	R^3	R^4	R^5
$CH_2OC_6H_4$-4-$(CH_2)_9CH_3$	H	H	H	H
$CH_2OC_6H_4$-4-$(CH_2)_{10}CH_3$	H	H	H	H
$CH_2OC_6H_4$-4-$(CH_2)_{11}CH_3$	H	H	H	H
$CH_2OC_6H_4$-4-$(CH_2)_{11}CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$CH_2OC_6H_4$-4-$(CH_2)_{12}CH_3$	H	H	H	H
$CH_2OC_6H_4$-4-$(CH_2)_{13}CH_3$	H	H	H	H
$CH_2OCH_2C_6H_5$	H	H	H	H
$CH_2OCH_2C_6H_5$	$COCH_3$	H	$COCH_3$	$COCH_3$
$CH_2OCH_2C_6H_4$-4-$(CH_2)_6CH_3$	H	H	H	H
$CH_2O(CH_2)_2C_6H_4$-4-$(CH_2)_5CH_3$	H	H	H	H
$CH_2O(CH_2)_3C_6H_4$-4-$(CH_2)_4CH_3$	H	H	H	H
$CH_2O(CH_2)_4C_6H_4$-4-$(CH_2)_3CH_3$	H	H	H	H
$CH_2O(CH_2)_5C_6H_4$-4-$(CH_2)_2CH_3$	H	H	H	H
$CH_2O(CH_2)_6C_6H_4$-4-CH_2CH_3	H	H	H	H
$CH_2O(CH_2)_7C_6H_4$-4-CH_3	H	H	H	H
$CH_2O(CH_2)_8C_6H_5$	H	H	H	H
$CH_2O(CH_2)_{11}C_6H_5$	H	H	H	H
$CH_2OC_6H_4$-4-$O(CH_2)_4C_6H_5$	H	H	H	H
$CH_2OC_6H_4$-4-$O(CH_2)_5C_6H_5$	H	H	H	H
$CH_2OC_6H_4$-4-$O(CH_2)_6C_6H_5$	H	H	H	H
$CH_2OC_6H_4$-4-$O(CH_2)_6C_6H_5$	$COCH_3$	H	$COCH_3$	$COCH_3$
$CH_2OC_6H_4$-4-$O(CH_2)_6C_6H_4$-4-F	H	H	H	H
$CH_2OC_6H_4$-4-$O(CH_2)_7C_6H_5$	H	H	H	H
$CH_2OC_6H_4$-4-$O(CH_2)_8C_6H_5$	H	H	H	H
$CH_2OC_6H_4$-4-$O(CH_2)_9C_6H_5$	H	H	H	H
$(CH_2)_2C_6H_3$(3-OCH_3)-4-$OC_{11}H_{23}$	H	H	H	H
$(CH_2)_2C_6H_3$(3-OCH_3)-4-$OC_{11}H_{23}$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2C_6H_3$(2-F)-4-$(CH_2)_7CH_3$	H	H	H	H
$(CH_2)_2C_6H_3$(2-F)-4-$(CH_2)_7CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2C_6H_3$(2-F)-4-$(CH_2)_{11}CH_3$	H	H	H	H
$(CH_2)_2C_6H_3$(2-F)-4-$(CH_2)_{11}CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2C_6H_3$(3-F)-4-$O(CH_2)_6CH_3$	H	H	H	H
$(CH_2)_2C_6H_3$(3-F)-4-$O(CH_2)_6CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2C_6H_3$(3-F)-4-$O(CH_2)_{10}CH_3$	H	H	H	H

R	R^2	R^3	R^4	R^5
$(CH_2)_2C_6H_3$(3-F)-4-$O(CH_2)_{10}CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2C_6H_3$(2-F)-4-$O(CH_2)_6CH_3$	H	H	H	H
$(CH_2)_2C_6H_3$(2-F)-4-$O(CH_2)_6CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2C_6H_3$(2-F)-4-$O(CH_2)_{10}CH_3$	H	H	H	H
$(CH_2)_2C_6H_3$(2-F)-4-$O(CH_2)_{10}CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2C_6H_4$-4-$N(CH_3)C_7H_{15}$	H	H	H	H
$(CH_2)_2C_6H_4$-4-$N(CH_3)C_7H_{15}$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2C_6H_4$-4-$N(CH_3)C_{11}H_{23}$	H	H	H	H
$(CH_2)_2C_6H_4$-4-$N(CH_3)C_{11}H_{23}$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2C_6H_4$-4-$NHCOC_6H_{13}$	H	H	H	H
$(CH_2)_2C_6H_4$-4-$NHCOC_6H_{13}$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2C_6H_4$-4-$NHCOC_{10}H_{21}$	H	H	H	H
$(CH_2)_2C_6H_4$-4-$NHCOC_{10}H_{21}$	$COCH_3$	H	$COCH_3$	$COCH_3$



R	R^2	R^3	R^4	R^5
2-C_4H_2S-4-$(CH_2)_{10}CH_3$	H	H	H	H
CH_2-2-C_4H_2S-4-$(CH_2)_9CH_3$	H	H	H	H
CH_2-2-C_4H_2S-4-$(CH_2)_9CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2$-2-C_4H_2S-4-$(CH_2)_8CH_3$	H	H	H	H
$(CH_2)_2$-2-C_4H_2S-4-$(CH_2)_8CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_3$-2-C_4H_2S-4-$(CH_2)_7CH_3$	H	H	H	H
$(CH_2)_4$-2-C_4H_2S-4-$(CH_2)_6CH_3$	H	H	H	H
$(CH_2)_4$-2-C_4H_2S-4-$(CH_2)_6CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_5$-2-C_4H_2S-4-$(CH_2)_5CH_3$	H	H	H	H
$(CH_2)_5$-2-C_4H_2S-4-$(CH_2)_5CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_6$-2-C_4H_2S-4-$(CH_2)_4CH_3$	H	H	H	H
$(CH_2)_6$-2-C_4H_2S-4-$(CH_2)_4CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_7$-2-C_4H_2S-4-$(CH_2)_3CH_3$	H	H	H	H
$(CH_2)_7$-2-C_4H_2S-4-$(CH_2)_3CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_8$-2-C_4H_2S-4-$(CH_2)_2CH_3$	H	H	H	H
$(CH_2)_9$-2-C_4H_2S-4-CH_2CH_3	H	H	H	H
$(CH_2)_9$-2-C_4H_2S-4-CH_2CH_3	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_{10}$-2-C_4H_2S-4-CH_3	H	H	H	H
$(CH_2)_{10}$-2-C_4H_2S-4-CH_3	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_{11}$-2-C_4H_3S	H	H	H	H
$(CH_2)_{12}$-2-C_4H_3S	H	H	H	H
$(CH_2)_{13}$-2-C_4H_3S	H	H	H	H
$(CH_2)_{13}$-2-C_4H_3S	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_{14}$-2-C_4H_3S	H	H	H	H
$(CH_2)_{15}$-2-C_4H_3S	H	H	H	H
$(CH_2)_{15}$-2-C_4H_3S	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_{16}$-2-C_4H_3S	H	H	H	H
$(CH_2)_{17}$-2-C_4H_3S	H	H	H	H
$(CH_2)_{18}$-2-C_4H_3S	H	H	H	H
$(CH_2)_{18}$-2-C_4H_3S	$COCH_3$	H	$COCH_3$	$COCH_3$

R	R^2	R^3	R^4	R^5
$(CH_2)_2$-2-C_4H_2S-4-$(CH_2)_7CH_3$	H	H	H	H
$(CH_2)_2$-2-C_4H_2S-4-$(CH_2)_9CH_3$	H	H	H	H
$(CH_2)_2$-2-C_4H_2S-4-$(CH_2)_9CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2$-2-C_4H_2S-4-$(CH_2)_{10}CH_3$	H	H	H	H
$(CH_2)_2$-2-C_4H_2S-4-$(CH_2)_{10}CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2$-2-C_4H_2S-4-$(CH_2)_{11}CH_3$	H	H	H	H
$(CH_2)_2$-2-C_4H_2S-4-$(CH_2)_{11}CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2$-2-C_4H_2S-4-$(CH_2)_{12}CH_3$	H	H	H	H
$(CH_2)_2$-2-C_4H_2S-4-$(CH_2)_{12}CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2$-2-C_4H_2S-4-$CH_2C_6H_5$	H	H	H	H
$(CH_2)_2$-2-C_4H_2S-4-$(CH_2)_2C_6H_5$	H	H	H	H
$(CH_2)_2$-2-C_4H_2S-4-$(CH_2)_3C_6H_5$	H	H	H	H
$(CH_2)_2$-2-C_4H_2S-4-$(CH_2)_4C_6H_5$	H	H	H	H
$(CH_2)_2$-2-C_4H_2S-4-$(CH_2)_5C_6H_5$	H	H	H	H
$(CH_2)_2$-2-C_4H_2S-4-$(CH_2)_6C_6H_5$	H	H	H	H
$(CH_2)_2$-2-C_4H_2S-4-$(CH_2)_6C_6H_5$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2$-2-C_4H_2S-4-$(CH_2)_7C_6H_5$	H	H	H	H
$(CH_2)_2$-2-C_4H_2S-4-$(CH_2)_7C_6H_5$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2$-2-C_4H_2S-4-$(CH_2)_8C_6H_5$	H	H	H	H
$(CH_2)_2$-2-C_4H_2S-4-$(CH_2)_8C_6H_5$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2$-2-C_4H_2S-4-$(CH_2)_9C_6H_5$	H	H	H	H
$(CH_2)_2$-2-C_4H_2S-4-$(CH_2)_9C_6H_5$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2$-2-C_4H_2S-4-$(CH_2)_{10}C_6H_5$	H	H	H	H
$(CH_2)_2$-2-C_4H_2S-4-$(CH_2)_{10}C_6H_5$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2$-C_6H_4-4-CH_2-2-C_4H_3S	H	H	H	H
$(CH_2)_2$-C_6H_4-4-$(CH_2)_2$-2-C_4H_3S	H	H	H	H
$(CH_2)_2$-C_6H_4-4-$(CH_2)_3$-2-C_4H_3S	H	H	H	H
$(CH_2)_2$-C_6H_4-4-$(CH_2)_4$-2-C_4H_3S	H	H	H	H
$(CH_2)_2$-C_6H_4-4-$(CH_2)_5$-2-C_4H_3S	H	H	H	H
$(CH_2)_2$-C_6H_4-4-$(CH_2)_6$-2-C_4H_3S	H	H	H	H
$(CH_2)_2$-C_6H_4-4-$(CH_2)_6$-2-C_4H_3S	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2$-C_6H_4-4-$(CH_2)_7$-2-C_4H_3S	H	H	H	H
$(CH_2)_2$-C_6H_4-4-$(CH_2)_7$-2-C_4H_3S	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2$-C_6H_4-4-$(CH_2)_8$-2-C_4H_3S	H	H	H	H

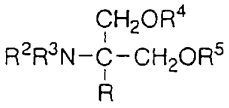
R	R^2	R^3	R^4	R^5
$(CH_2)_2$-C_6H_4-4-$(CH_2)_8$-2-C_4H_3S	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2$-C_6H_4-4-$(CH_2)_9$-2-C_4H_3S	H	H	H	H
$(CH_2)_2$-C_6H_4-4-$(CH_2)_9$-2-C_4H_3S	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2$-C_6H_4-4-$(CH_2)_{10}$-2-C_4H_3S	H	H	H	H
$(CH_2)_2$-C_6H_4-4-$(CH_2)_{10}$-2-C_4H_3S	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2$-C_6H_4-4-CH_2-3-C_4H_3S	H	H	H	H
$(CH_2)_2$-C_6H_4-4-$(CH_2)_2$-3-C_4H_3S	H	H	H	H
$(CH_2)_2$-C_6H_4-4-$(CH_2)_3$-3-C_4H_3S	H	H	H	H
$(CH_2)_2$-C_6H_4-4-$(CH_2)_4$-3-C_4H_3S	H	H	H	H
$(CH_2)_2$-C_6H_4-4-$(CH_2)_5$-3-C_4H_3S	H	H	H	H
$(CH_2)_2$-C_6H_4-4-$(CH_2)_6$-3-C_4H_3S	H	H	H	H
$(CH_2)_2$-C_6H_4-4-$(CH_2)_6$-3-C_4H_3S	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2$-C_6H_4-4-$(CH_2)_7$-3-C_4H_3S	H	H	H	H
$(CH_2)_2$-C_6H_4-4-$(CH_2)_7$-3-C_4H_3S	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2$-C_6H_4-4-$(CH_2)_8$-3-C_4H_3S	H	H	H	H
$(CH_2)_2$-C_6H_4-4-$(CH_2)_8$-3-C_4H_3S	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2$-C_6H_4-4-$(CH_2)_9$-3-C_4H_3S	H	H	H	H
$(CH_2)_2$-C_6H_4-4-$(CH_2)_9$-3-C_4H_3S	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2$-C_6H_4-4-$(CH_2)_{10}$-3-C_4H_3S	H	H	H	H
$(CH_2)_2$-C_6H_4-4-$(CH_2)_{10}$-3-C_4H_3S	$COCH_3$	H	$COCH_3$	$COCH_3$
2-C_4H_2S-5-$(CH_2)_9CH_3$	H	H	H	H
CH_2-2-C_4H_2S-5-$(CH_2)_8CH_3$	H	H	H	H
CH_2-2-C_4H_2S-5-$(CH_2)_8CH_3$	$COCH_3$	H	H	H
CH_2-2-C_4H_2S-5-$(CH_2)_8CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2$-2-C_4H_2S-5-$(CH_2)_7CH_3$	H	H	H	H
$(CH_2)_2$-2-C_4H_2S-5-$(CH_2)_7CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_3$-2-C_4H_2S-5-$(CH_2)_6CH_3$	H	H	H	H
$(CH_2)_3$-2-C_4H_2S-5-$(CH_2)_6CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_4$-2-C_4H_2S-5-$(CH_2)_4CH_3$	H	H	H	H
$(CH_2)_4$-2-C_4H_2S-5-$(CH_2)_4CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_5$-2-C_4H_2S-5-$(CH_2)_4CH_3$	H	H	H	H
$(CH_2)_5$-2-C_4H_2S-5-$(CH_2)_4CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_6$-2-C_4H_2S-5-$(CH_2)_3CH_3$	H	H	H	H
$(CH_2)_6$-2-C_4H_2S-5-$(CH_2)_3CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$

R	R^2	R^3	R^4	R^5
$(CH_2)_7$-2-C_4H_2S-5-$(CH_2)_2CH_3$	H	H	H	H
$(CH_2)_7$-2-C_4H_2S-5-CH_2CH_3	$COCH_3$	H	H	H
$(CH_2)_7$-2-C_4H_2S-5-CH_2CH_3	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_8$-2-C_4H_2S-5-CH_3	H	H	H	H
$(CH_2)_8$-2-C_4H_2S-5-CH_3	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_8$-3-C_4H_3S	H	H	H	H
$(CH_2)_9$-3-C_4H_3S	H	H	H	H
$(CH_2)_{10}$-3-C_4H_3S	H	H	H	H
$(CH_2)_{11}$-3-C_4H_3S	H	H	H	H
$(CH_2)_{12}$-3-C_4H_3S	H	H	H	H
$(CH_2)_{13}$-3-C_4H_3S	H	H	H	H
$(CH_2)_{14}$-3-C_4H_3S	H	H	H	H
$(CH_2)_{15}$-3-C_4H_3S	H	H	H	H
$(CH_2)_{16}$-3-C_4H_3S	H	H	H	H
$(CH_2)_{17}$-3-C_4H_3S	H	H	H	H
$(CH_2)_{18}$-3-C_4H_3S	H	H	H	H
$(CH_2)_2$-2-C_4H_2S-5-$(CH_2)_7CH_3$	H	H	H	H
$(CH_2)_2$-2-C_4H_2S-5-$(CH_2)_8CH_3$	H	H	H	H
$(CH_2)_2$-2-C_4H_2S-5-$(CH_2)_8CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2$-2-C_4H_2S-5-$(CH_2)_9CH_3$	H	H	H	H
$(CH_2)_2$-2-C_4H_2S-5-$(CH_2)_9CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2$-2-C_4H_2S-5-$(CH_2)_{10}CH_3$	H	H	H	H
$(CH_2)_2$-2-C_4H_2S-5-$(CH_2)_{10}CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2$-2-C_4H_2S-5-$(CH_2)_{12}CH_3$	H	H	H	H
$(CH_2)_2$-2-C_4H_2S-5-$(CH_2)_{12}CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2$-2-C_4H_2S-5-$CH_2C_6H_5$	H	H	H	H
$(CH_2)_2$-2-C_4H_2S-5-$(CH_2)_2C_6H_5$	H	H	H	H
$(CH_2)_2$-2-C_4H_2S-5-$(CH_2)_3C_6H_5$	H	H	H	H
$(CH_2)_2$-2-C_4H_2S-5-$(CH_2)_4C_6H_5$	H	H	H	H
$(CH_2)_2$-2-C_4H_2S-5-$(CH_2)_5C_6H_5$	H	H	H	H
$(CH_2)_2$-2-C_4H_2S-5-$(CH_2)_6C_6H_5$	H	H	H	H
$(CH_2)_2$-2-C_4H_2S-5-$(CH_2)_6C_6H_5$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2$-2-C_4H_2S-5-$(CH_2)_7C_6H_5$	H	H	H	H
$(CH_2)_2$-2-C_4H_2S-5-$(CH_2)_7C_6H_5$	$COCH_3$	H	$COCH_3$	$COCH_3$

R	R^2	R^3	R^4	R^5
$(CH_2)_2$-2-C_4H_2S-5-$(CH_2)_8C_6H_5$	H	H	H	H
$(CH_2)_2$-2-C_4H_2S-5-$(CH_2)_8C_6H_5$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2$-2-C_4H_2S-5-$(CH_2)_9C_6H_5$	H	H	H	H
$(CH_2)_2$-2-C_4H_2S-5-$(CH_2)_9C_6H_5$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2$-2-C_4H_2S-5-$(CH_2)_{10}C_6H_5$	H	H	H	H
$(CH_2)_2$-2-C_4H_2S-5-$(CH_2)_{10}C_6H_5$	$COCH_3$	H	$COCH_3$	$COCH_3$
3-C_4H_2S-4-$(CH_2)_{11}CH_3$	H	H	H	H
CH_2-3-C_4H_2S-4-$(CH_2)_{10}CH_3$	H	H	H	H
CH_2-3-C_4H_2S-4-$(CH_2)_{10}CH_3$	$COCH_3$	H	H	H
CH_2-3-C_4H_2S-4-$(CH_2)_{10}CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2$-3-C_4H_2S-4-$(CH_2)_9CH_3$	H	H	H	H
$(CH_2)_2$-3-C_4H_2S-4-$(CH_2)_9CH_3$	$COCH_3$	H	H	H
$(CH_2)_2$-3-C_4H_2S-4-$(CH_2)_9CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_3$-3-C_4H_2S-4-$(CH_2)_8CH_3$	H	H	H	H
$(CH_2)_3$-3-C_4H_2S-4-$(CH_2)_8CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_4$-3-C_4H_2S-4-$(CH_2)_7CH_3$	H	H	H	H
$(CH_2)_4$-3-C_4H_2S-4-$(CH_2)_7CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_5$-3-C_4H_2S-4-$(CH_2)_6CH_3$	H	H	H	H
$(CH_2)_5$-3-C_4H_2S-4-$(CH_2)_6CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_6$-3-C_4H_2S-4-$(CH_2)_5CH_3$	H	H	H	H
$(CH_2)_6$-3-C_4H_2S-4-$(CH_2)_5CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_7$-3-C_4H_2S-4-$(CH_2)_4CH_3$	H	H	H	H
$(CH_2)_7$-3-C_4H_2S-4-$(CH_2)_4CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_8$-3-C_4H_2S-4-$(CH_2)_3CH_3$	H	H	H	H
$(CH_2)_8$-3-C_4H_2S-4-$(CH_2)_3CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_9$-3-C_4H_2S-4-$(CH_2)_2CH_3$	H	H	H	H
$(CH_2)_{10}$-3-C_4H_2S-4-CH_2CH_3	$COCH_3$	H	H	H
$(CH_2)_{10}$-3-C_4H_2S-4-CH_2CH_3	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_{11}$-3-C_4H_2S-4-CH_3	H	H	H	H
$(CH_2)_{11}$-3-C_4H_2S-4-CH_3	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2$-3-C_4H_2S-4-$(CH_2)_8CH_3$	H	H	H	H
$(CH_2)_2$-3-C_4H_2S-4-$(CH_2)_9CH_3$	H	H	H	H
$(CH_2)_2$-3-C_4H_2S-4-$(CH_2)_9CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2$-3-C_4H_2S-4-$(CH_2)_{10}CH_3$	H	H	H	H

R	R^2	R^3	R^4	R^5
$(CH_2)_2$-3-C_4H_2S-4-$(CH_2)_{10}CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2$-3-C_4H_2S-4-$(CH_2)_{11}CH_3$	H	H	H	H
$(CH_2)_2$-3-C_4H_2S-4-$(CH_2)_{11}CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2$-3-C_4H_2S-4-$(CH_2)_{12}CH_3$	H	H	H	H
$(CH_2)_2$-3-C_4H_2S-4-$(CH_2)_{12}CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2$-3-C_4H_2S-4-$CH_2C_6H_5$	H	H	H	H
$(CH_2)_2$-3-C_4H_2S-4-$(CH_2)_2C_6H_5$	H	H	H	H
$(CH_2)_2$-3-C_4H_2S-4-$(CH_2)_3C_6H_5$	H	H	H	H
$(CH_2)_2$-3-C_4H_2S-4-$(CH_2)_4C_6H_5$	H	H	H	H
$(CH_2)_2$-3-C_4H_2S-4-$(CH_2)_5C_6H_5$	H	H	H	H
$(CH_2)_2$-3-C_4H_2S-4-$(CH_2)_6C_6H_5$	H	H	H	H
$(CH_2)_2$-3-C_4H_2S-4-$(CH_2)_6C_6H_5$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2$-3-C_4H_2S-4-$(CH_2)_7C_6H_5$	H	H	H	H
$(CH_2)_2$-3-C_4H_2S-4-$(CH_2)_7C_6H_5$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2$-3-C_4H_2S-4-$(CH_2)_8C_6H_5$	H	H	H	H
$(CH_2)_2$-3-C_4H_2S-4-$(CH_2)_8C_6H_5$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2$-3-C_4H_2S-4-$(CH_2)_9C_6H_5$	H	H	H	H
$(CH_2)_2$-3-C_4H_2S-4-$(CH_2)_9C_6H_5$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2$-3-C_4H_2S-4-$(CH_2)_{10}C_6H_5$	H	H	H	H
$(CH_2)_2$-3-C_4H_2S-4-$(CH_2)_{10}C_6H_5$	$COCH_3$	H	$COCH_3$	$COCH_3$
3-C_4H_2S-5-$(CH_2)_{10}CH_3$	H	H	H	H
CH_2-3-C_4H_2S-5-$(CH_2)_9CH_3$	H	H	H	H
CH_2-3-C_4H_2S-5-$(CH_2)_9CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2$-3-C_4H_2S-5-$(CH_2)_8CH_3$	H	H	H	H
$(CH_2)_2$-3-C_4H_2S-5-$(CH_2)_8CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_3$-3-C_4H_2S-5-$(CH_2)_7CH_3$	H	H	H	H
$(CH_2)_4$-3-C_4H_2S-5-$(CH_2)_6CH_3$	H	H	H	H
$(CH_2)_4$-3-C_4H_2S-5-$(CH_2)_6CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_5$-3-C_4H_2S-5-$(CH_2)_5CH_3$	H	H	H	H
$(CH_2)_5$-3-C_4H_2S-5-$(CH_2)_5CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_6$-3-C_4H_2S-5-$(CH_2)_4CH_3$	H	H	H	H
$(CH_2)_6$-3-C_4H_2S-5-$(CH_2)_4CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_7$-3-C_4H_2S-5-$(CH_2)_3CH_3$	H	H	H	H
$(CH_2)_7$-3-C_4H_2S-5-$(CH_2)_3CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$

R	R^2	R^3	R^4	R^5
$(CH_2)_8$-3-C_4H_2S-5-$(CH_2)_2CH_3$	H	H	H	H
$(CH_2)_9$-3-C_4H_2S-5-CH_2CH_3	H	H	H	H
$(CH_2)_9$-3-C_4H_2S-5-CH_2CH_3	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_{10}$-3-C_4H_2S-5-CH_3	H	H	H	H
$(CH_2)_{10}$-3-C_4H_2S-5-CH_3	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2$-3-C_4H_2S-5-$(CH_2)_7CH_3$	H	H	H	H
$(CH_2)_2$-3-C_4H_2S-5-$(CH_2)_9CH_3$	H	H	H	H
$(CH_2)_2$-3-C_4H_2S-5-$(CH_2)_9CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2$-3-C_4H_2S-5-$(CH_2)_{10}CH_3$	H	H	H	H
$(CH_2)_2$-3-C_4H_2S-5-$(CH_2)_{10}CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2$-3-C_4H_2S-5-$(CH_2)_{11}CH_3$	H	H	H	H
$(CH_2)_2$-3-C_4H_2S-5-$(CH_2)_{11}CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2$-3-C_4H_2S-5-$(CH_2)_{12}CH_3$	H	H	H	H
$(CH_2)_2$-3-C_4H_2S-5-$(CH_2)_{12}CH_3$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2$-3-C_4H_2S-5-$CH_2C_6H_5$	H	H	H	H
$(CH_2)_2$-3-C_4H_2S-5-$(CH_2)_2C_6H_5$	H	H	H	H
$(CH_2)_2$-3-C_4H_2S-5-$(CH_2)_3C_6H_5$	H	H	H	H
$(CH_2)_2$-3-C_4H_2S-5-$(CH_2)_4C_6H_5$	H	H	H	H
$(CH_2)_2$-3-C_4H_2S-5-$(CH_2)_5C_6H_5$	H	H	H	H
$(CH_2)_2$-3-C_4H_2S-5-$(CH_2)_6C_6H_5$	H	H	H	H
$(CH_2)_2$-3-C_4H_2S-5-$(CH_2)_6C_6H_5$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2$-3-C_4H_2S-5-$(CH_2)_7C_6H_5$	H	H	H	H
$(CH_2)_2$-3-C_4H_2S-5-$(CH_2)_7C_6H_5$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2$-3-C_4H_2S-5-$(CH_2)_8C_6H_5$	H	H	H	H
$(CH_2)_2$-3-C_4H_2S-5-$(CH_2)_8C_6H_5$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2$-3-C_4H_2S-5-$(CH_2)_9C_6H_5$	H	H	H	H
$(CH_2)_2$-3-C_4H_2S-5-$(CH_2)_9C_6H_5$	$COCH_3$	H	$COCH_3$	$COCH_3$
$(CH_2)_2$-3-C_4H_2S-5-$(CH_2)_{10}C_6H_5$	H	H	H	H
$(CH_2)_2$-3-C_4H_2S-5-$(CH_2)_{10}C_6H_5$	$COCH_3$	H	$COCH_3$	$COCH_3$



R	R^2	R^3	R^4	R^5
2-C_5H_3N-4-$(CH_2)_{10}CH_3$	H	H	H	H
CH_2-2-C_5H_3N-4-$(CH_2)_9CH_3$	H	H	H	H
$(CH_2)_3$-2-C_5H_3N-4-$(CH_2)_7CH_3$	H	H	H	H
$(CH_2)_4$-2-C_5H_3N-4-$(CH_2)_6CH_3$	H	H	H	H
$(CH_2)_5$-2-C_5H_3N-4-$(CH_2)_5CH_3$	H	H	H	H
$(CH_2)_6$-2-C_5H_3N-4-$(CH_2)_4CH_3$	H	H	H	H
$(CH_2)_7$-2-C_5H_3N-4-$(CH_2)_3CH_3$	H	H	H	H
$(CH_2)_8$-2-C_5H_3N-4-$(CH_2)_2CH_3$	H	H	H	H
$(CH_2)_9$-2-C_5H_3N-4-CH_2CH_3	H	H	H	H
$(CH_2)_{10}$-2-C_5H_3N-4-CH_3	H	H	H	H
CH_2-2-C_5H_4N	H	H	H	H
CH_2-2-C_5H_4N	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_{11}$-2-C_5H_4N	H	H	H	H
$(CH_2)_{11}$-2-C_5H_4N	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_9$-2-C_5H_4N	H	H	H	H
$(CH_2)_9$-2-C_5H_4N	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_{10}$-2-C_5H_4N	H	H	H	H
$(CH_2)_{10}$-2-C_5H_4N	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_{12}$-2-C_5H_4N	H	H	H	H
$(CH_2)_{12}$-2-C_5H_4N	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_{13}$-2-C_5H_4N	H	H	H	H
$(CH_2)_{13}$-2-C_5H_4N	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_{14}$-2-C_5H_4N	H	H	H	H
$(CH_2)_{14}$-2-C_5H_4N	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_{15}$-2-C_5H_4N	H	H	H	H
$(CH_2)_{15}$-2-C_5H_4N	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_{16}$-2-C_5H_4N	H	H	H	H
$(CH_2)_{16}$-2-C_5H_4N	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_{17}$-2-C_5H_4N	H	H	H	H
$(CH_2)_{17}$-2-C_5H_4N	CH_3CO	H	CH_3CO	CH_3CO

R	R^2	R^3	R^4	R^5
$(CH_2)_2$-2-C_5H_3N-4-$(CH_2)_8CH_3$	H	H	H	H
$(CH_2)_2$-2-C_5H_3N-4-$(CH_2)_8CH_3$	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-2-C_5H_3N-4-$(CH_2)_{12}CH_3$	H	H	H	H
$(CH_2)_2$-2-C_5H_3N-4-$(CH_2)_{12}CH_3$	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-2-C_5H_3N-4-CH_2-C_6H_5	H	H	H	H
$(CH_2)_2$-2-C_5H_3N-4-CH_2-C_6H_5	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-2-C_5H_3N-4-$(CH_2)_2$-C_6H_5	H	H	H	H
$(CH_2)_2$-2-C_5H_3N-4-$(CH_2)_2$-C_6H_5	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-2-C_5H_3N-4-$(CH_2)_3$-C_6H_5	H	H	H	H
$(CH_2)_2$-2-C_5H_3N-4-$(CH_2)_3$-C_6H_5	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-2-C_5H_3N-4-$(CH_2)_4$-C_6H_5	H	H	H	H
$(CH_2)_2$-2-C_5H_3N-4-$(CH_2)_4$-C_6H_5	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-2-C_5H_3N-4-$(CH_2)_5$-C_6H_5	H	H	H	H
$(CH_2)_2$-2-C_5H_3N-4-$(CH_2)_5$-C_6H_5	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-2-C_5H_3N-4-$(CH_2)_6$-C_6H_5	H	H	H	H
$(CH_2)_2$-2-C_5H_3N-4-$(CH_2)_6$-C_6H_5	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-2-C_5H_3N-4-$(CH_2)_7$-C_6H_5	H	H	H	H
$(CH_2)_2$-2-C_5H_3N-4-$(CH_2)_7$-C_6H_5	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-2-C_5H_3N-4-$(CH_2)_8$-C_6H_5	H	H	H	H
$(CH_2)_2$-2-C_5H_3N-4-$(CH_2)_8$-C_6H_5	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-2-C_5H_3N-4-$(CH_2)_9$-C_6H_5	H	H	H	H
$(CH_2)_2$-2-C_5H_3N-4-$(CH_2)_9$-C_6H_5	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-2-C_5H_3N-4-$(CH_2)_{10}$-C_6H_5	H	H	H	H
$(CH_2)_2$-2-C_5H_3N-4-$(CH_2)_{10}$-C_6H_5	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-C_6H_4-4-CH_2-2-C_5H_4N	H	H	H	H
$(CH_2)_2$-C_6H_4-4-CH_2-2-C_5H_4N	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-C_6H_4-4-$(CH_2)_2$-2-C_5H_4N	H	H	H	H
$(CH_2)_2$-C_6H_4-4-$(CH_2)_2$-2-C_5H_4N	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-C_6H_4-4-$(CH_2)_3$-2-C_5H_4N	H	H	H	H
$(CH_2)_2$-C_6H_4-4-$(CH_2)_3$-2-C_5H_4N	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-C_6H_4-4-$(CH_2)_4$-2-C_5H_4N	H	H	H	H
$(CH_2)_2$-C_6H_4-4-$(CH_2)_4$-2-C_5H_4N	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-C_6H_4-4-$(CH_2)_5$-2-C_5H_4N	H	H	H	H
$(CH_2)_2$-C_6H_4-4-$(CH_2)_5$-2-C_5H_4N	CH_3CO	H	CH_3CO	CH_3CO

R	R^2	R^3	R^4	R^5
$(CH_2)_2$-C_6H_4-4-$(CH_2)_6$-2-C_5H_4N	H	H	H	H
$(CH_2)_2$-C_6H_4-4-$(CH_2)_6$-2-C_5H_4N	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-C_6H_4-4-$(CH_2)_7$-2-C_5H_4N	H	H	H	H
$(CH_2)_2$-C_6H_4-4-$(CH_2)_7$-2-C_5H_4N	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-C_6H_4-4-$(CH_2)_8$-2-C_5H_4N	H	H	H	H
$(CH_2)_2$-C_6H_4-4-$(CH_2)_8$-2-C_5H_4N	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-C_6H_4-4-$(CH_2)_9$-2-C_5H_4N	H	H	H	H
$(CH_2)_2$-C_6H_4-4-$(CH_2)_9$-2-C_5H_4N	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-C_6H_4-4-$(CH_2)_{10}$-2-C_5H_4N	H	H	H	H
$(CH_2)_2$-C_6H_4-4-$(CH_2)_{10}$-2-C_5H_4N	CH_3CO	H	CH_3CO	CH_3CO
4-C_5H_3N-2-$(CH_2)_{10}CH_3$	H	H	H	H
CH_2-4-C_5H_3N-2-$(CH_2)_9CH_3$	H	H	H	H
$(CH_2)_3$-4-C_5H_3N-2-$(CH_2)_7CH_3$	H	H	H	H
$(CH_2)_4$-4-C_5H_3N-2-$(CH_2)_6CH_3$	H	H	H	H
$(CH_2)_5$-4-C_5H_3N-2-$(CH_2)_5CH_3$	H	H	H	H
$(CH_2)_6$-4-C_5H_3N-2-$(CH_2)_4CH_3$	H	H	H	H
$(CH_2)_7$-4-C_5H_3N-2-$(CH_2)_3CH_3$	H	H	H	H
$(CH_2)_8$-4-C_5H_3N-2-$(CH_2)_2CH_3$	H	H	H	H
$(CH_2)_9$-4-C_5H_3N-2-CH_2CH_3	H	H	H	H
$(CH_2)_{10}$-4-C_5H_3N-2-CH_3	H	H	H	H
CH_2-4-C_5H_4N	H	H	H	H
CH_2-4-C_5H_4N	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_{11}$-4-C_5H_4N	H	H	H	H
$(CH_2)_{11}$-4-C_5H_4N	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_9$-4-C_5H_4N	H	H	H	H
$(CH_2)_9$-4-C_5H_4N	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_{10}$-4-C_5H_4N	H	H	H	H
$(CH_2)_{10}$-4-C_5H_4N	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_{12}$-4-C_5H_4N	H	H	H	H
$(CH_2)_{12}$-4-C_5H_4N	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_{13}$-4-C_5H_4N	H	H	H	H
$(CH_2)_{13}$-4-C_5H_4N	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_{14}$-4-C_5H_4N	H	H	H	H
$(CH_2)_{14}$-4-C_5H_4N	CH_3CO	H	CH_3CO	CH_3CO

R	R^2	R^3	R^4	R^5
$(CH_2)_{15}$-4-C_5H_4N	H	H	H	H
$(CH_2)_{15}$-4-C_5H_4N	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_{16}$-4-C_5H_4N	H	H	H	H
$(CH_2)_{16}$-4-C_5H_4N	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_{17}$-4-C_5H_4N	H	H	H	H
$(CH_2)_{17}$-4-C_5H_4N	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-4-C_5H_3N-2-$(CH_2)_8CH_3$	H	H	H	H
$(CH_2)_2$-4-C_5H_3N-2-$(CH_2)_8CH_3$	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-4-C_5H_3N-2-$(CH_2)_{12}CH_3$	H	H	H	H
$(CH_2)_2$-4-C_5H_3N-2-$(CH_2)_{12}CH_3$	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-4-C_5H_3N-2-CH_2-C_6H_5	H	H	H	H
$(CH_2)_2$-4-C_5H_3N-2-CH_2-C_6H_5	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-4-C_5H_3N-2-$(CH_2)_2$-C_6H_5	H	H	H	H
$(CH_2)_2$-4-C_5H_3N-2-$(CH_2)_2$-C_6H_5	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-4-C_5H_3N-2-$(CH_2)_3$-C_6H_5	H	H	H	H
$(CH_2)_2$-4-C_5H_3N-2-$(CH_2)_3$-C_6H_5	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-4-C_5H_3N-2-$(CH_2)_4$-C_6H_5	H	H	H	H
$(CH_2)_2$-4-C_5H_3N-2-$(CH_2)_4$-C_6H_5	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-4-C_5H_3N-2-$(CH_2)_5$-C_6H_5	H	H	H	H
$(CH_2)_2$-4-C_5H_3N-2-$(CH_2)_5$-C_6H_5	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-4-C_5H_3N-2-$(CH_2)_6$-C_6H_5	H	H	H	H
$(CH_2)_2$-4-C_5H_3N-2-$(CH_2)_6$-C_6H_5	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-4-C_5H_3N-2-$(CH_2)_7$-C_6H_5	H	H	H	H
$(CH_2)_2$-4-C_5H_3N-2-$(CH_2)_7$-C_6H_5	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-4-C_5H_3N-2-$(CH_2)_8$-C_6H_5	H	H	H	H
$(CH_2)_2$-4-C_5H_3N-2-$(CH_2)_8$-C_6H_5	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-4-C_5H_3N-2-$(CH_2)_9$-C_6H_5	H	H	H	H
$(CH_2)_2$-4-C_5H_3N-2-$(CH_2)_9$-C_6H_5	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-2-C_5H_3N-2-$(CH_2)_{10}$-C_6H_5	H	H	H	H
$(CH_2)_2$-2-C_5H_3N-2-$(CH_2)_{10}$-C_6H_5	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-C_6H_4-4-CH_2-4-C_5H_4N	H	H	H	H
$(CH_2)_2$-C_6H_4-4-CH_2-4-C_5H_4N	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-C_6H_4-4-$(CH_2)_2$-4-C_5H_4N	H	H	H	H
$(CH_2)_2$-C_6H_4-4-$(CH_2)_2$-4-C_5H_4N	CH_3CO	H	CH_3CO	CH_3CO

R	R^2	R^3	R^4	R^5
$(CH_2)_2$-C_6H_4-4-$(CH_2)_3$-4-C_5H_4N	H	H	H	H
$(CH_2)_2$-C_6H_4-4-$(CH_2)_3$-4-C_5H_4N	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-C_6H_4-4-$(CH_2)_4$-4-C_5H_4N	H	H	H	H
$(CH_2)_2$-C_6H_4-4-$(CH_2)_4$-4-C_5H_4N	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-C_6H_4-4-$(CH_2)_5$-4-C_5H_4N	H	H	H	H
$(CH_2)_2$-C_6H_4-4-$(CH_2)_5$-4-C_5H_4N	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-C_6H_4-4-$(CH_2)_6$-4-C_5H_4N	H	H	H	H
$(CH_2)_2$-C_6H_4-4-$(CH_2)_6$-4-C_5H_4N	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-C_6H_4-4-$(CH_2)_7$-4-C_5H_4N	H	H	H	H
$(CH_2)_2$-C_6H_4-4-$(CH_2)_7$-4-C_5H_4N	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-C_6H_4-4-$(CH_2)_8$-4-C_5H_4N	H	H	H	H
$(CH_2)_2$-C_6H_4-4-$(CH_2)_8$-4-C_5H_4N	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-C_6H_4-4-$(CH_2)_9$-4-C_5H_4N	H	H	H	H
$(CH_2)_2$-C_6H_4-4-$(CH_2)_9$-4-C_5H_4N	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-C_6H_4-4-$(CH_2)_{10}$-4-C_5H_4N	H	H	H	H
$(CH_2)_2$-C_6H_4-4-$(CH_2)_{10}$-4-C_5H_4N	CH_3CO	H	CH_3CO	CH_3CO
2-C_5H_3N-5-$(CH_2)_9CH_3$	H	H	H	H
CH_2-2-C_5H_3N-5-$(CH_2)_3CH_3$	H	H	H	H
CH_2-2-C_5H_3N-5-$(CH_2)_8CH_3$	H	H	H	H
$(CH_2)_3$-2-C_5H_3N-5-$(CH_2)_6CH_3$	H	H	H	H
$(CH_2)_4$-2-C_5H_3N-5-$(CH_2)_5CH_3$	H	H	H	H
$(CH_2)_5$-2-C_5H_3N-5-$(CH_2)_4CH_3$	H	H	H	H
$(CH_2)_6$-2-C_5H_3N-5-$(CH_2)_3CH_3$	H	H	H	H
$(CH_2)_7$-2-C_5H_3N-5-$(CH_2)_2CH_3$	H	H	H	H
$(CH_2)_8$-2-C_5H_3N-5-CH_2CH_3	H	H	H	H
$(CH_2)_9$-2-C_5H_3N-5-CH_3	H	H	H	H
$(CH_2)_2$-2-C_5H_3N-5-$(CH_2)_7CH_3$	H	H	H	H
$(CH_2)_2$-2-C_5H_3N-5-$(CH_2)_7CH_3$	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-2-C_5H_3N-5-$(CH_2)_{11}CH_3$	H	H	H	H
$(CH_2)_2$-2-C_5H_3N-5-$(CH_2)_{11}CH_3$	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-2-C_5H_3N-5-CH_2-C_6H_5	H	H	H	H
$(CH_2)_2$-2-C_5H_3N-5-CH_2-C_6H_5	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-2-C_5H_3N-5-$(CH_2)_2$-C_6H_5	H	H	H	H
$(CH_2)_2$-2-C_5H_3N-5-$(CH_2)_2$-C_6H_5	CH_3CO	H	CH_3CO	CH_3CO

R	R^2	R^3	R^4	R^5
$(CH_2)_2$-2-C_5H_3N-5-$(CH_2)_3$-C_6H_5	H	H	H	H
$(CH_2)_2$-2-C_5H_3N-5-$(CH_2)_3$-C_6H_5	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-2-C_5H_3N-5-$(CH_2)_4$-C_6H_5	H	H	H	H
$(CH_2)_2$-2-C_5H_3N-5-$(CH_2)_4$-C_6H_5	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-2-C_5H_3N-5-$(CH_2)_5$-C_6H_5	H	H	H	H
$(CH_2)_2$-2-C_5H_3N-5-$(CH_2)_5$-C_6H_5	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-2-C_5H_3N-5-$(CH_2)_6$-C_6H_5	H	H	H	H
$(CH_2)_2$-2-C_5H_3N-5-$(CH_2)_6$-C_6H_5	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-2-C_5H_3N-5-$(CH_2)_7$-C_6H_5	H	H	H	H
$(CH_2)_2$-2-C_5H_3N-5-$(CH_2)_7$-C_6H_5	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-2-C_5H_3N-5-$(CH_2)_8$-C_6H_5	H	H	H	H
$(CH_2)_2$-2-C_5H_3N-5-$(CH_2)_8$-C_6H_5	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-2-C_5H_3N-5-$(CH_2)_9$-C_6H_5	H	H	H	H
$(CH_2)_2$-2-C_5H_3N-5-$(CH_2)_9$-C_6H_5	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-2-C_5H_3N-5-$(CH_2)_{10}$-C_6H_5	H	H	H	H
$(CH_2)_2$-2-C_5H_3N-5-$(CH_2)_{10}$-C_6H_5	CH_3CO	H	CH_3CO	CH_3CO
5-C_5H_3N-2-$(CH_2)_9CH_3$	H	H	H	H
CH_2-5-C_5H_3N-2-$(CH_2)_3CH_3$	H	H	H	H
CH_2-5-C_5H_3N-2-$(CH_2)_8CH_3$	H	H	H	H
$(CH_2)_3$-5-C_5H_3N-2-$(CH_2)_6CH_3$	H	H	H	H
$(CH_2)_4$-5-C_5H_3N-25-$(CH_2)_5CH_3$	H	H	H	H
$(CH_2)_5$-5-C_5H_3N-2-$(CH_2)_4CH_3$	H	H	H	H
$(CH_2)_6$-5-C_5H_3N-2-$(CH_2)_3CH_3$	H	H	H	H
$(CH_2)_7$-5-C_5H_3N-2-$(CH_2)_2CH_3$	H	H	H	H
$(CH_2)_8$-5-C_5H_3N-2-CH_2CH_3	H	H	H	H
$(CH_2)_9$-5-C_5H_3N-2-CH_3	H	H	H	H
$(CH_2)_2$-5-C_5H_3N-2-$(CH_2)_7CH_3$	H	H	H	H
$(CH_2)_2$-5-C_5H_3N-2-$(CH_2)_7CH_3$	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-5-C_5H_3N-2-$(CH_2)_{11}CH_3$	H	H	H	H
$(CH_2)_2$-5-C_5H_3N-2-$(CH_2)_{11}CH_3$	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-5-C_5H_3N-2-CH_2-C_6H_5	H	H	H	H
$(CH_2)_2$-5-C_5H_3N-2-CH_2-C_6H_5	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-5-C_5H_3N-2-$(CH_2)_2$-C_6H_5	H	H	H	H
$(CH_2)_2$-5-C_5H_3N-2-$(CH_2)_2$-C_6H_5	CH_3CO	H	CH_3CO	CH_3CO

R	R^2	R^3	R^4	R^5
$(CH_2)_2$-5-C_5H_3N-2-$(CH_2)_3$-C_6H_5	H	H	H	H
$(CH_2)_2$-5-C_5H_3N-2-$(CH_2)_3$-C_6H_5	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-5-C_5H_3N-2-$(CH_2)_4$-C_6H_5	H	H	H	H
$(CH_2)_2$-5-C_5H_3N-2-$(CH_2)_4$-C_6H_5	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-5-C_5H_3N-2-$(CH_2)_5$-C_6H_5	H	H	H	H
$(CH_2)_2$-5-C_5H_3N-2-$(CH_2)_5$-C_6H_5	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-5-C_5H_3N-2-$(CH_2)_6$-C_6H_5	H	H	H	H
$(CH_2)_2$-5-C_5H_3N-2-$(CH_2)_6$-C_6H_5	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-5-C_5H_3N-2-$(CH_2)_7$-C_6H_5	H	H	H	H
$(CH_2)_2$-5-C_5H_3N-2-$(CH_2)_7$-C_6H_5	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-5-C_5H_3N-2-$(CH_2)_8$-C_6H_5	H	H	H	H
$(CH_2)_2$-5-C_5H_3N-2-$(CH_2)_8$-C_6H_5	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-5-C_5H_3N-2-$(CH_2)_9$-C_6H_5	H	H	H	H
$(CH_2)_2$-5-C_5H_3N-2-$(CH_2)_9$-C_6H_5	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-5-C_5H_3N-2-$(CH_2)_{10}$-C_6H_5	H	H	H	H
$(CH_2)_2$-5-C_5H_3N-2-$(CH_2)_{10}$-C_6H_5	CH_3CO	H	CH_3CO	CH_3CO
2-C_5H_3N-6-$(CH_2)_{10}CH_3$	H	H	H	H
CH_2-2-C_5H_3N-6-$(CH_2)_9CH_3$	H	H	H	H
$(CH_2)_3$-2-C_5H_3N-6-$(CH_2)_7CH_3$	H	H	H	H
$(CH_2)_4$-2-C_5H_3N-6-$(CH_2)_6CH_3$	H	H	H	H
$(CH_2)_5$-2-C_5H_3N-6-$(CH_2)_5CH_3$	H	H	H	H
$(CH_2)_6$-2-C_5H_3N-6-$(CH_2)_4CH_3$	H	H	H	H
$(CH_2)_7$-2-C_5H_3N-6-$(CH_2)_3CH_3$	H	H	H	H
$(CH_2)_8$-2-C_5H_3N-6-$(CH_2)_2CH_3$	H	H	H	H
$(CH_2)_9$-2-C_5H_3N-6-CH_2CH_3	H	H	H	H
$(CH_2)_{10}$-2-C_5H_3N-6-CH_3	H	H	H	H
$(CH_2)_2$-2-C_5H_3N-6-$(CH_2)_8CH_3$	H	H	H	H
$(CH_2)_2$-2-C_5H_3N-6-$(CH_2)_8CH_3$	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-2-C_5H_3N-6-$(CH_2)_{12}CH_3$	H	H	H	H
$(CH_2)_2$-2-C_5H_3N-6-$(CH_2)_{12}CH_3$	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-2-C_5H_3N-6-CH_2-C_6H_5	H	H	H	H
$(CH_2)_2$-2-C_5H_3N-6-CH_2-C_6H_5	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-2-C_5H_3N-6-$(CH_2)_2$-C_6H_5	H	H	H	H
$(CH_2)_2$-2-C_5H_3N-6-$(CH_2)_2$-C_6H_5	CH_3CO	H	CH_3CO	CH_3CO

R	R^2	R^3	R^4	R^5
$(CH_2)_2$-2-C_5H_3N-6-$(CH_2)_3$-C_6H_5	H	H	H	H
$(CH_2)_2$-2-C_5H_3N-6-$(CH_2)_3$-C_6H_5	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-2-C_5H_3N-6-$(CH_2)_4$-C_6H_5	H	H	H	H
$(CH_2)_2$-2-C_5H_3N-6-$(CH_2)_4$-C_6H_5	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-2-C_5H_3N-6-$(CH_2)_5$-C_6H_5	H	H	H	H
$(CH_2)_2$-2-C_5H_3N-6-$(CH_2)_5$-C_6H_5	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-2-C_5H_3N-6-$(CH_2)_6$-C_6H_5	H	H	H	H
$(CH_2)_2$-2-C_5H_3N-6-$(CH_2)_6$-C_6H_5	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-2-C_5H_3N-6-$(CH_2)_7$-C_6H_5	H	H	H	H
$(CH_2)_2$-2-C_5H_3N-6-$(CH_2)_7$-C_6H_5	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-2-C_5H_3N-6-$(CH_2)_8$-C_6H_5	H	H	H	H
$(CH_2)_2$-2-C_5H_3N-6-$(CH_2)_8$-C_6H_5	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-2-C_5H_3N-6-$(CH_2)_9$-C_6H_5	H	H	H	H
$(CH_2)_2$-2-C_5H_3N-6-$(CH_2)_9$-C_6H_5	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-2-C_5H_3N-6-$(CH_2)_{10}$-C_6H_5	H	H	H	H
$(CH_2)_2$-2-C_5H_3N-6-$(CH_2)_{10}$-C_6H_5	CH_3CO	H	CH_3CO	CH_3CO
3-C_5H_3N-5-$(CH_2)_{10}CH_3$	H	H	H	H
CH_2-3-C_5H_3N-5-$(CH_2)_9CH_3$	H	H	H	H
$(CH_2)_3$-3-C_5H_3N-5-$(CH_2)_7CH_3$	H	H	H	H
$(CH_2)_4$-3-C_5H_3N-5-$(CH_2)_6CH_3$	H	H	H	H
$(CH_2)_5$-3-C_5H_3N-5-$(CH_2)_5CH_3$	H	H	H	H
$(CH_2)_6$-3-C_5H_3N-5-$(CH_2)_4CH_3$	H	H	H	H
$(CH_2)_7$-3-C_5H_3N-5-$(CH_2)_3CH_3$	H	H	H	H
$(CH_2)_8$-3-C_5H_3N-5-$(CH_2)_2CH_3$	H	H	H	H
$(CH_2)_9$-3-C_5H_3N-5-CH_2CH_3	H	H	H	H
$(CH_2)_{10}$-3-C_5H_3N-5-CH_3	H	H	H	H
$(CH_2)_{11}$-3-C_5H_4N	H	H	H	H
$(CH_2)_{11}$-3-C_5H_4N	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_9$-3-C_5H_4N	H	H	H	H
$(CH_2)_9$-3-C_5H_4N	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_{10}$-3-C_5H_4N	H	H	H	H
$(CH_2)_{10}$-3-C_5H_4N	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_{12}$-3-C_5H_4N	H	H	H	H
$(CH_2)_{12}$-3-C_5H_4N	CH_3CO	H	CH_3CO	CH_3CO

R	R^2	R^3	R^4	R^5
$(CH_2)_{13}$-3-C_5H_4N	H	H	H	H
$(CH_2)_{13}$-3-C_5H_4N	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_{14}$-3-C_5H_4N	H	H	H	H
$(CH_2)_{14}$-3-C_5H_4N	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_{15}$-3-C_5H_4N	H	H	H	H
$(CH_2)_{15}$-3-C_5H_4N	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_{16}$-3-C_5H_4N	H	H	H	H
$(CH_2)_{16}$-3-C_5H_4N	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_{17}$-3-C_5H_4N	H	H	H	H
$(CH_2)_{17}$-3-C_5H_4N	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-3-C_5H_3N-5-$(CH_2)_8CH_3$	H	H	H	H
$(CH_2)_2$-3-C_5H_3N-5-$(CH_2)_8CH_3$	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-3-C_5H_3N-5-$(CH_2)_{12}CH_3$	H	H	H	H
$(CH_2)_2$-3-C_5H_3N-5-$(CH_2)_{12}CH_3$	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-3-C_5H_3N-5-CH_2-C_6H_5	H	H	H	H
$(CH_2)_2$-3-C_5H_3N-5-$(CH_2)_7CH_3$	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-3-C_5H_3N-5-$(CH_2)_7CH_3$	H	H	H	H
$(CH_2)_2$-3-C_5H_3N-5-$(CH_2)_{11}CH_3$	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-3-C_5H_3N-5-$(CH_2)_{11}CH_3$	H	H	H	H
$(CH_2)_2$-3-C_5H_3N-5-CH_2-C_6H_5	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-3-C_5H_3N-5-$(CH_2)_2$-C_6H_5	H	H	H	H
$(CH_2)_2$-3-C_5H_3N-5-$(CH_2)_2$-C_6H_5	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-3-C_5H_3N-5-$(CH_2)_3$-C_6H_5	H	H	H	H
$(CH_2)_2$-3-C_5H_3N-5-$(CH_2)_3$-C_6H_5	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-3-C_5H_3N-5-$(CH_2)_4$-C_6H_5	H	H	H	H
$(CH_2)_2$-3-C_5H_3N-5-$(CH_2)_4$-C_6H_5	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-3-C_5H_3N-5-$(CH_2)_5$-C_6H_5	H	H	H	H
$(CH_2)_2$-3-C_5H_3N-5-$(CH_2)_5$-C_6H_5	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-3-C_5H_3N-5-$(CH_2)_6$-C_6H_5	H	H	H	H
$(CH_2)_2$-3-C_5H_3N-5-$(CH_2)_6$-C_6H_5	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-3-C_5H_3N-5-$(CH_2)_7$-C_6H_5	H	H	H	H
$(CH_2)_2$-3-C_5H_3N-5-$(CH_2)_7$-C_6H_5	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-3-C_5H_3N-5-$(CH_2)_8$-C_6H_5	H	H	H	H
$(CH_2)_2$-3-C_5H_3N-5-$(CH_2)_8$-C_6H_5	CH_3CO	H	CH_3CO	CH_3CO

R	R^2	R^3	R^4	R^5
$(CH_2)_2$-3-C_5H_3N-5-$(CH_2)_9$-C_6H_5	H	H	H	H
$(CH_2)_2$-3-C_5H_3N-5-$(CH_2)_9$-C_6H_5	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-3-C_5H_3N-5-$(CH_2)_{10}$-C_6H_5	H	H	H	H
$(CH_2)_2$-3-C_5H_3N-5-$(CH_2)_{10}$-C_6H_5	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-C_6H_4-4-CH_2-3-C_5H_4N	H	H	H	H
$(CH_2)_2$-C_6H_4-4-CH_2-3-C_5H_4N	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-C_6H_4-4-$(CH_2)_2$-3-C_5H_4N	H	H	H	H
$(CH_2)_2$-C_6H_4-4-$(CH_2)_2$-3-C_5H_4N	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-C_6H_4-4-$(CH_2)_3$-3-C_5H_4N	H	H	H	H
$(CH_2)_2$-C_6H_4-4-$(CH_2)_3$-3-C_5H_4N	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-C_6H_4-4-$(CH_2)_4$-3-C_5H_4N	H	H	H	H
$(CH_2)_2$-C_6H_4-4-$(CH_2)_4$-3-C_5H_4N	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-C_6H_4-4-$(CH_2)_5$-3-C_5H_4N	H	H	H	H
$(CH_2)_2$-C_6H_4-4-$(CH_2)_5$-3-C_5H_4N	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-C_6H_4-4-$(CH_2)_6$-3-C_5H_4N	H	H	H	H
$(CH_2)_2$-C_6H_4-4-$(CH_2)_6$-3-C_5H_4N	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-C_6H_4-4-$(CH_2)_7$-3-C_5H_4N	H	H	H	H
$(CH_2)_2$-C_6H_4-4-$(CH_2)_7$-3-C_5H_4N	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-C_6H_4-4-$(CH_2)_8$-3-C_5H_4N	H	H	H	H
$(CH_2)_2$-C_6H_4-4-$(CH_2)_8$-3-C_5H_4N	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-C_6H_4-4-$(CH_2)_9$-3-C_5H_4N	H	H	H	H
$(CH_2)_2$-C_6H_4-$(CH_2)_9$-3-C_5H_4N	CH_3CO	H	CH_3CO	CH_3CO
$(CH_2)_2$-C_6H_4-4-$(CH_2)_{10}$-3-C_5H_4N	H	H	H	H
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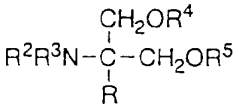
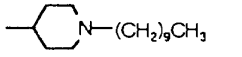
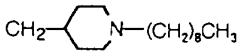
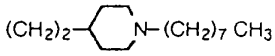
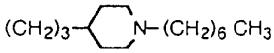
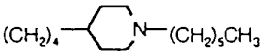
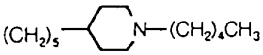
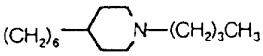
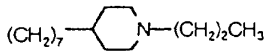
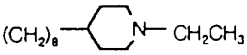
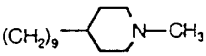
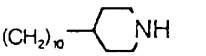
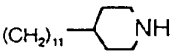
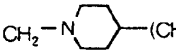
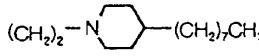
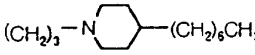
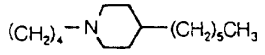
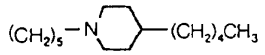
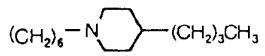
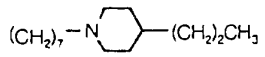
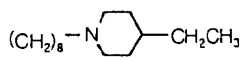
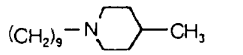
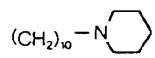
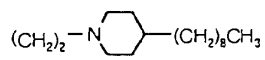
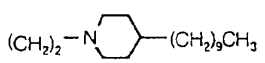
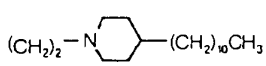
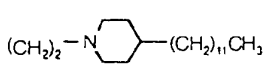
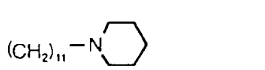
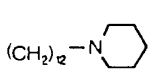
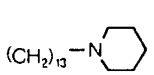
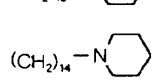
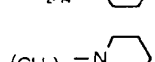
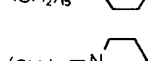
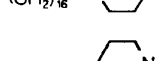
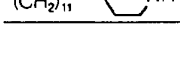
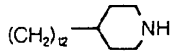
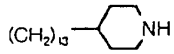
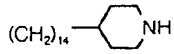
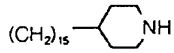
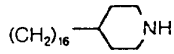
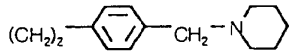
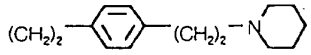
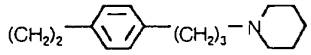
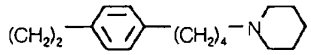
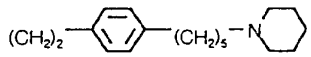
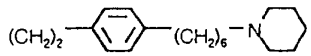
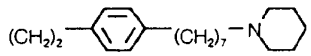
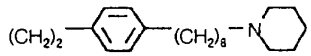
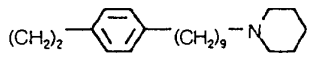
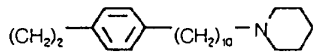
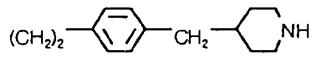
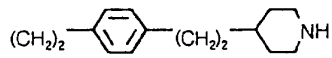
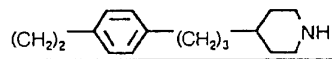


R	R^2	R^3	R^4	R^5
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	CH_3CO	H	CH_3CO	CH_3CO
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H

R	R^2	R^3	R^4	R^5
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	CH_3CO	H	CH_3CO	CH_3CO
	H	H	H	H
	H	H	H	H
	H	H	H	H
	CH_3CO	H	CH_3CO	CH_3CO
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H

R	R^2	R^3	R^4	R^5
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H

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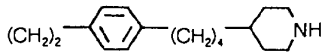
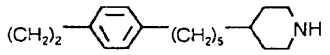
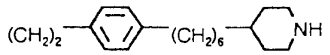
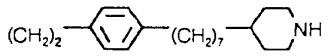
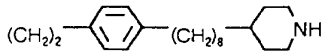
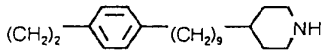
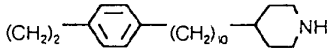
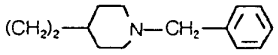
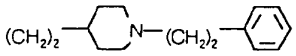
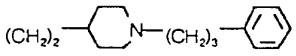
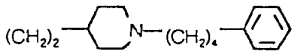
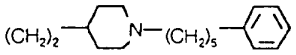
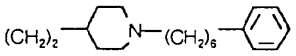
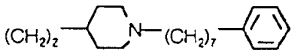
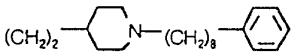
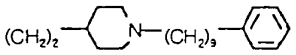
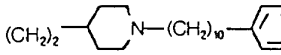
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H

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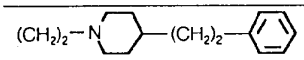
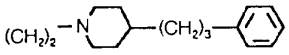
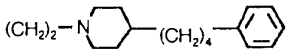
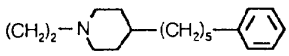
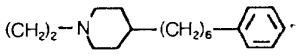
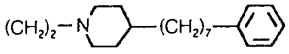
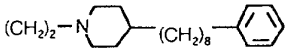
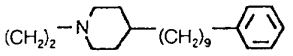
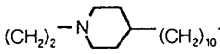
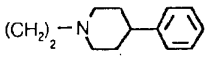
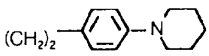
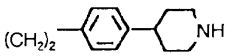
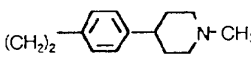
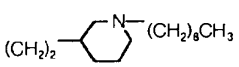
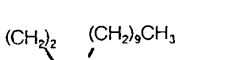
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
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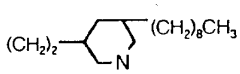
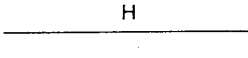
	H	H	H	H
	H	H	H	H

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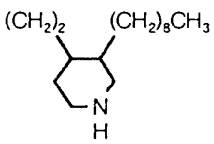
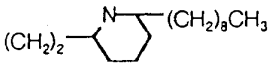
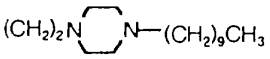
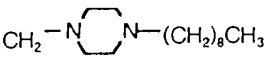
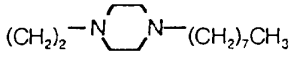
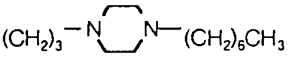
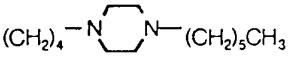
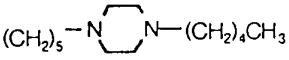
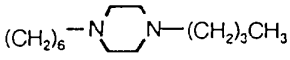
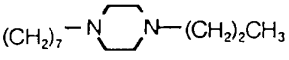
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H

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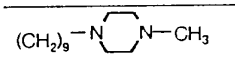
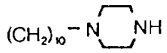
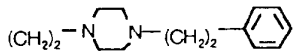
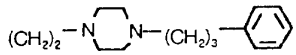
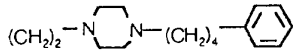
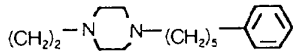
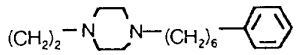
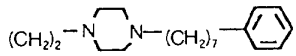
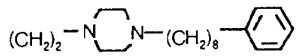
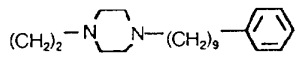
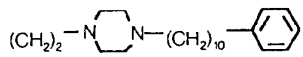
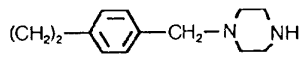
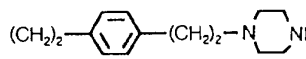
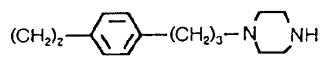
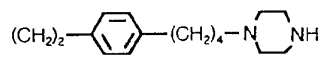
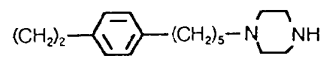
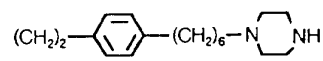
	H	H	H	H
	H	H	H	H
	CH_3CO	H	CH_3CO	CH_3CO
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
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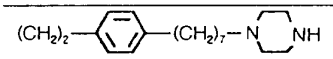
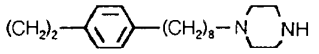
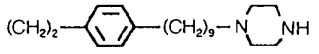
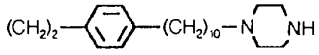
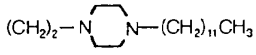
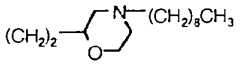
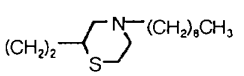
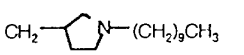
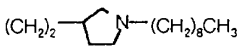
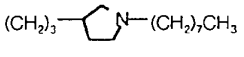
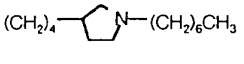
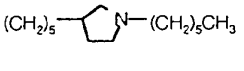
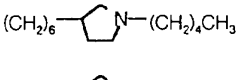
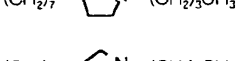
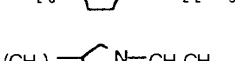
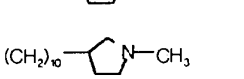
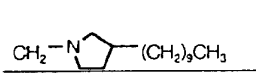
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
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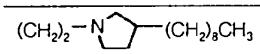
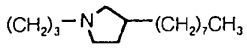
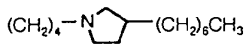
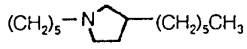
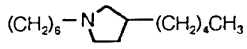
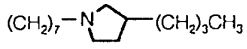
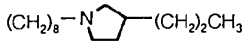
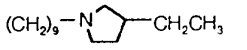
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
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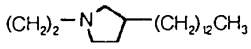
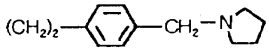
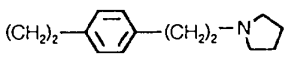
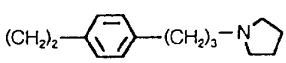
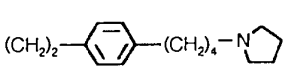
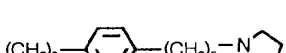
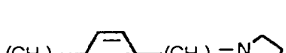
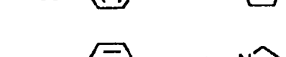
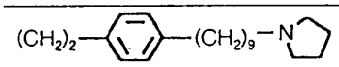
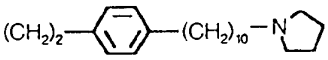
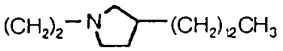
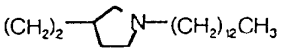
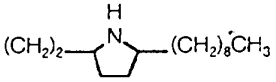
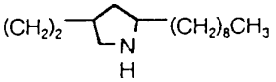
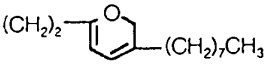
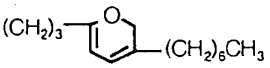
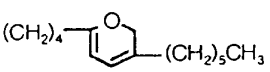
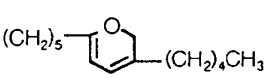
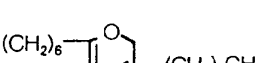
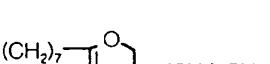
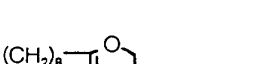
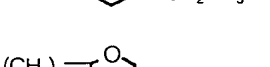
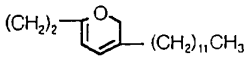
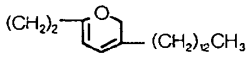
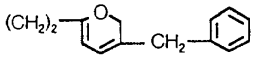
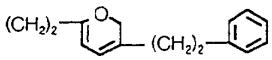
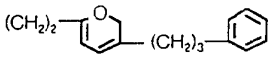
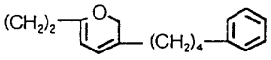
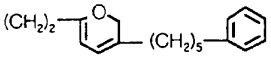
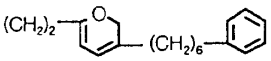
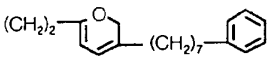
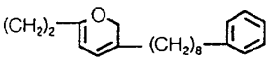
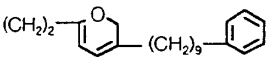
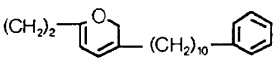
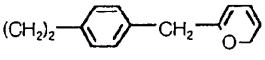
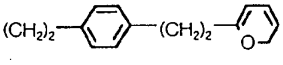
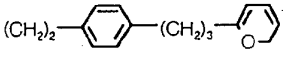
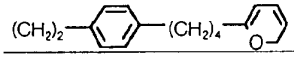
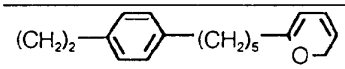
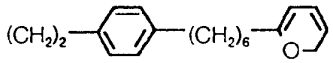
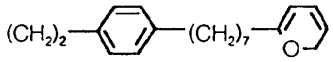
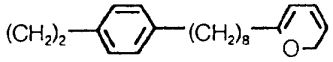
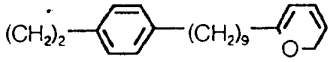
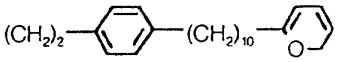
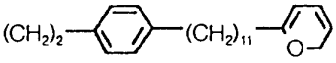
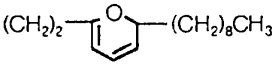
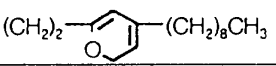
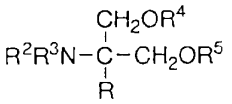
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	CH_3CO	H	CH_3CO	CH_3CO
	H	H	H	H
	H	H	H	H
	H	H	H	H

R	R^2	R^3	R^4	R^5
	H	H	H	H
	H	H	H	H
	CH_3CO	H	CH_3CO	CH_3CO
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	CH_3CO	H	CH_3CO	CH_3CO

R	R^2	R^3	R^4	R^5
	H	H	H	H
	H	H	H	H
	CH_3CO	H	CH_3CO	CH_3CO
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	CH_3CO	H	CH_3CO	CH_3CO
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H

R	R^2	R^3	R^4	R^5
	CH_3CO	H	CH_3CO	CH_3CO
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	CH_3CO	H	CH_3CO	CH_3CO
	H	H	H	H
	H	H	H	H
	H	H	H	H



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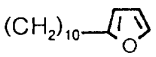
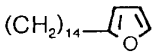
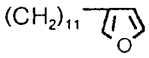
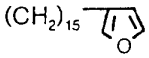
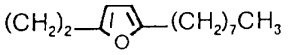
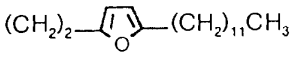
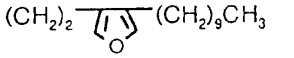
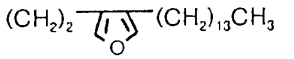
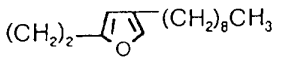
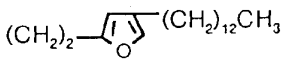
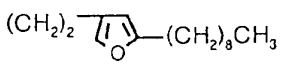
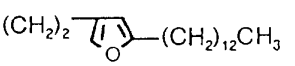
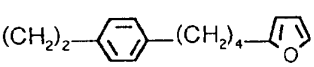
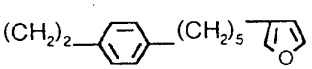
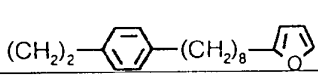
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H

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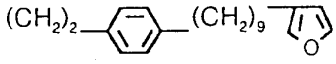
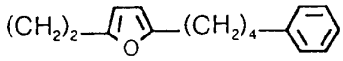
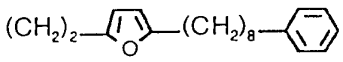
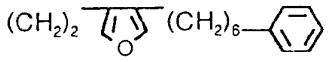
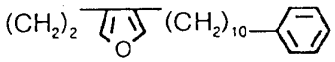
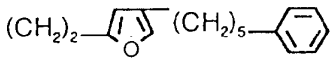
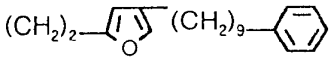
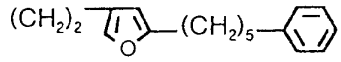
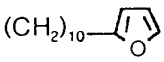
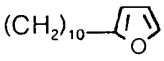
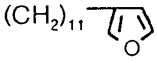
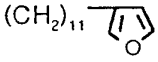
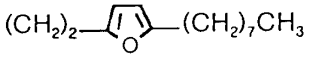
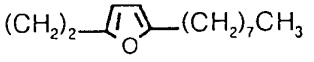
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	Ac	H	H	H
	Ac	H	Ac	Ac
	Ac	H	H	H
	Ac	H	Ac	Ac
	Ac	H	H	H
	Ac	H	Ac	Ac

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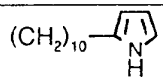
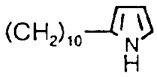
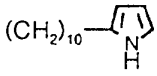
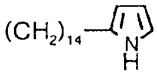
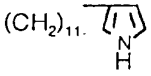
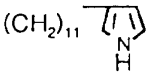
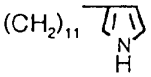
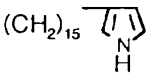
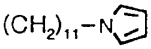
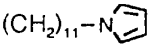
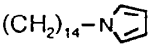
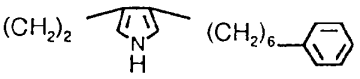
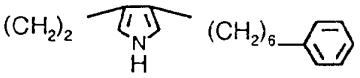
	H	H	H	H
	Ac	H	H	H
	Ac	H	Ac	Ac
	H	H	H	H
	H	H	H	H
	Ac	H	H	H
	Ac	H	Ac	Ac
	H	H	H	H
	H	H	H	H
	Ac	H	H	H
	H	H	H	H
	H	H	H	H
	Ac	H	H	H

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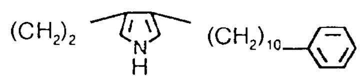
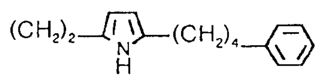
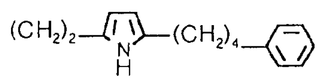
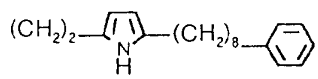
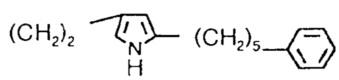
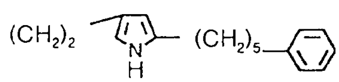
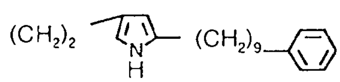
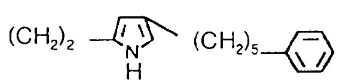
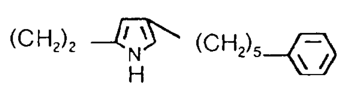
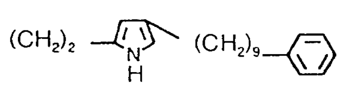
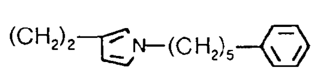
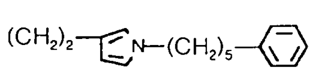
	H	H	H	H
	H	H	H	H
	Ac	H	H	H
	H	H	H	H
	H	H	H	H
	Ac	H	H	H
	H	H	H	H
	H	H	H	H
	Ac	H	H	H
	H	H	H	H
	H	H	H	H
	Ac	H	H	H

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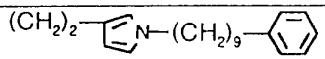
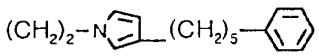
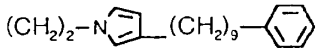
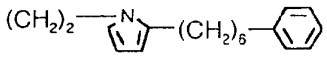
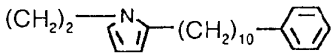
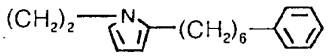
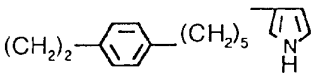
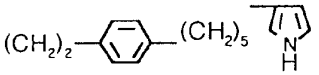
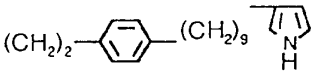
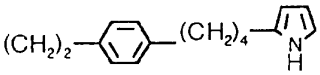
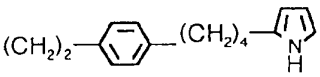
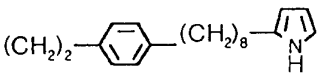
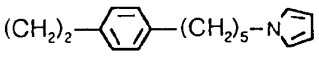
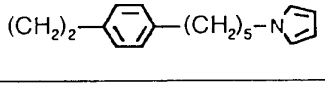
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	Ac	H	H	H
	H	H	H	H
	Ac	H	H	H
	H	H	H	H
	H	H	H	H
	Ac	H	H	H
	H	H	H	H
	H	H	H	H
	Ac	H	H	H

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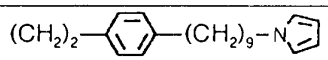
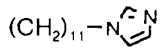
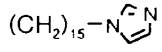
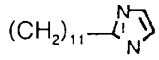
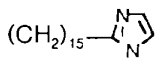
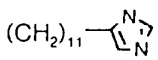
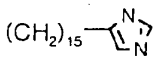
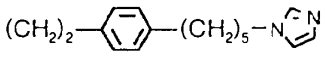
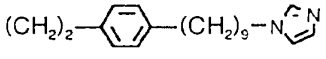
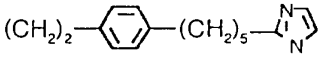
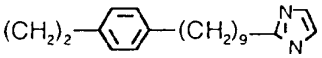
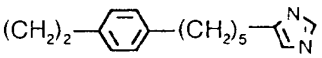
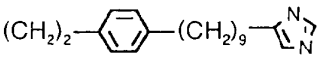
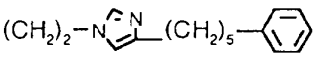
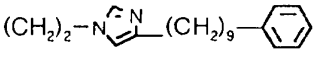
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H

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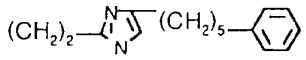
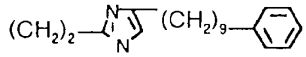
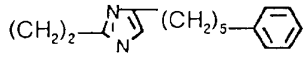
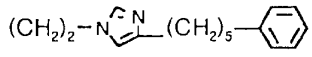
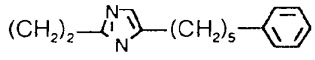
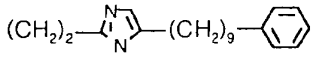
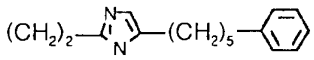
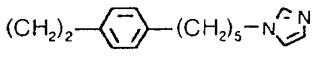
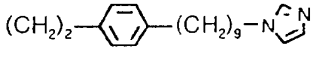
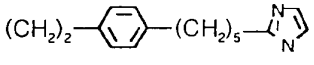
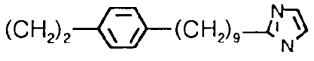
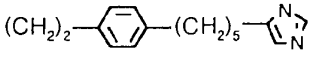
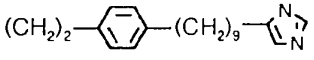
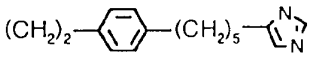
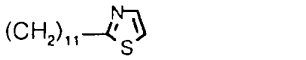
	H	H	H	H
	H	H	H	H
	Ac	H	H	H
	Ac	H	H	H
	H	H	H	H
	H	H	H	H
	Ac	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	Ac	H	H	H
	H	H	H	H

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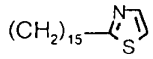
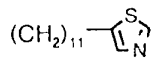
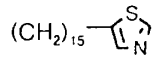
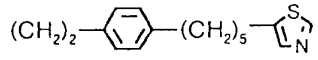
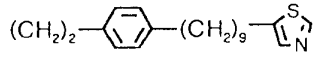
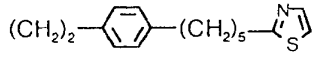
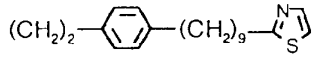
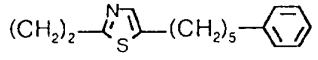
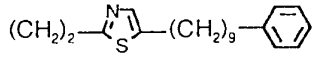
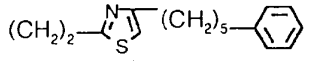
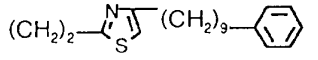
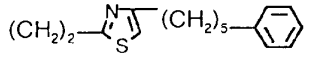
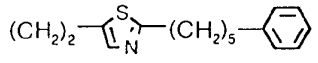
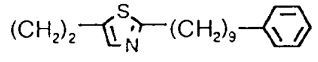
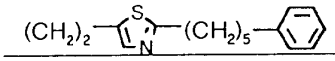
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	Ac	H	H	H
	H	H	H	H
	H	H	H	H
	Ac	H	H	H

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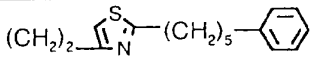
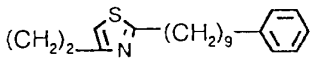
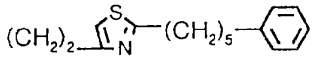
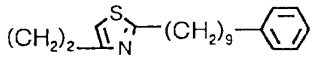
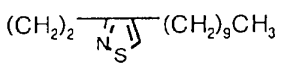
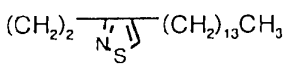
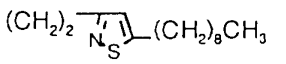
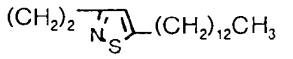
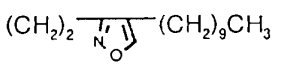
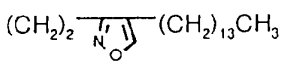
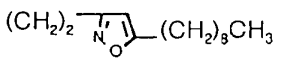
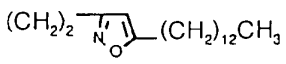
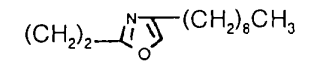
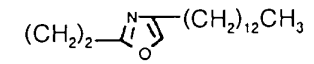
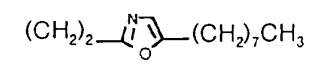
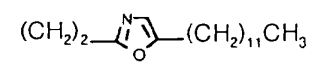
	H	H	H	H
	H	H	H	H
	Ac	H	H	H
	Ac	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H

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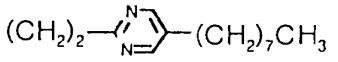
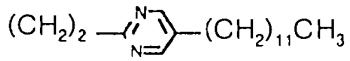
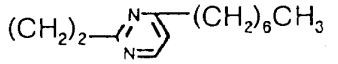
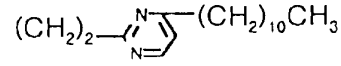
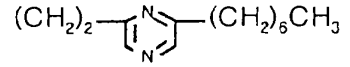
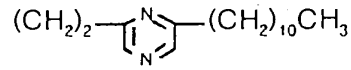
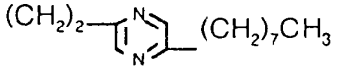
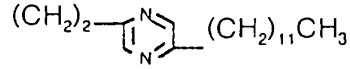
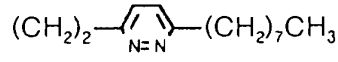
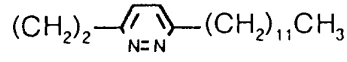
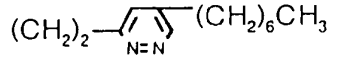
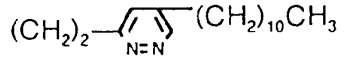
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H
	H	H	H	H

Examples of the pharmaceutically acceptable salts of the compounds of the formula (I) [hereinafter referred to as Compound (I)] include salts with inorganic acids, such as hydrochloride, hydrobromide and sulfate, salts with organic acids, such as acetate, fumarate, maleate, benzoate, citrate, malate, methanesulfonate and benzenesulfonate, and when carboxyl group is included, salts with metals such as sodium salt, potassium salt, calcium salt and aluminum salt, salts with amines, such as triethylamine and salts with dibasic amino acids, such as lysine. The compounds of the present invention encompass hydrates and solvates.

When the compounds of the present invention include geometric isomers, the present invention encompasses cis- compounds, trans- compounds and mixtures thereof. When the compounds of the present invention have one or more asymmetric centers in the molecule, various optical isomers are obtained. The present invention also encompasses optical isomers, racemates, diastereomers and mixtures

thereof.

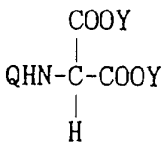
The compounds of the present invention can be produced by the following methods.

(method A)

A compound of the formula (II)

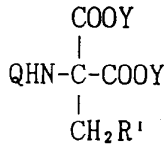
R^1CH_2 - G (II)

wherein R^1CH_2 is the same as the aforementioned R^1CH_2, R^1aCH_2, R^1bCH_2, Ra, Rb, Rc, Rd, Re, Rf, Rg, Rh, Ri, Rj, Rk, Rl, Rm, Rn or Ro which are encompassed in R, and G is a leaving group in wide use in the field of organic synthetic chemistry, such as halogen (fluorine, chlorine, bromine, iodine), methanesulfonyloxy, p-toluenesulfonyloxy or trifluoromethanesulfonyloxy [hereinafter referred to as Compound (II)], or when R^1 has a functional group (e.g. amino, hydroxyl group, mercapto, ketone, carboxyl), a compound with protection of the functional group as necessary [hereinafter referred to as. Compound B-(II)] is condensed, in the presence of a base, with a compound of the formula (III)



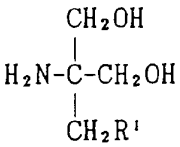
(III)

wherein Y is lower alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, tert-butyl) or aralkyl (e.g. benzyl, nitrobenzyl, methoxybenzyl, methylbenzyl), and Q is an amino-protecting group widely used in the field of organic synthetic chemistry, such as acetyl, benzoyl, tert-butoxycarbonyl or benzyloxycarbonyl, where the two Ys in the molecule in the formula may together form a ring such as dioxane and Q and Y in the molecule may together form a ring such as oxazolidine or oxazine [hereinafter referred to as Compound (III)] to give a compound of the formula (IV)



(IV)

wherein R^1, Q and Y are as defined above [hereinafter referred to as Compound (IV)], which is subjected to reduction of carboxyl with a suitable reducing agent and deprotection as necessary to give a compound of the formula (I-29)



(I-29)

wherein R^1 is as defined above [hereinafter referred to as Compound (I-29)] or an N- and/or O-protected compound thereof.

Examples of the base to be used in the condensation include sodium hydroxide, sodium methoxide, sodium ethoxide, sodium hydride, potassium hydride, lithium diisopropylamide, butyl lithium, lithium hexamethyldisilazane, triethylamine, diisopropylethylamine and 1,8-diazabicyclo[5.4.0]undeca-7-ene.

Examples of the organic solvent to be used in the condensation include methanol, ethanol, tert-butyl alcohol, tetrahydrofuran, diethyl ether, ethylene glycol dimethyl ether, dimethylformamide, dimethyl sulfoxide, benzene, toluene, xylene, dioxane, methylene chloride, chloroform, dichloroethane and acetonitrile.

The condensation generally proceeds at a temperature of from -20 °C to 150 °C and a temperature lower or higher than this temperature range may be selected on demand.

The condensation is generally carried out for 30 minutes to 2 days and the reaction period longer or shorter than the indicated period may be used as necessary.

After the condensation is carried out under the above-mentioned conditions or after removing the protecting group on demand, the Compound (IV) can be purified by a method known in the field of organic synthetic chemistry, such as solvent extraction, recrystallization, chromatography and a method using an ion exchange resin.

Examples of the reducing agent to be used in the reduction of carboxyl include metallic reducing reagent such as sodium borohydride, lithium borohydride or lithium aluminum hydride, and diborane.

Examples of the organic solvent to be used in the reduction of carboxyl include methanol, ethanol, tert-butyl alcohol, tetrahydrofuran, diethyl ether and ethylene glycol dimethyl ether.

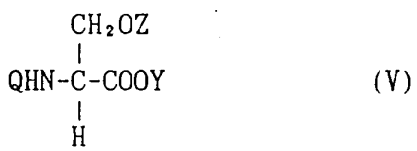
The temperature for the reduction of carboxyl is generally from -20 °C to 80 °C and a temperature lower or higher than this temperature range may be selected on demand.

The reduction of carboxyl is generally carried out for 30 minutes to 10 hours and the reaction period longer or shorter than the indicated period may be used as necessary.

After the reduction is carried out under the above-mentioned conditions or after removing the protecting group on demand, the objective compound can be purified by a method known in the field of organic synthetic chemistry, such as solvent extraction, recrystallization, chromatography and a method using an ion exchange resin.

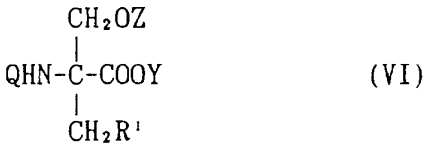
(Method B)

A Compound (II) or a Compound B-(II) is condensed, in the presence of a base, with a compound of the formula (V)



(V)

wherein Y and Q are as defined above, and Z is a hydroxy-protecting group widely used in the field of organic synthetic chemistry, such as acetyl, benzoyl, benzyl, trimethylsilyl, tert-butyldimethylsilyl, methoxymethyl, methoxyethoxymethyl or tetrahydropyranyl [hereinafter referred to as Compound (V)] to give a Compound of the formula (VI)



(VI)

wherein R^1, Q, Y and Z are as defined above [hereinafter referred to as Compound (VI)]. The obtained compound is then subjected to reduction of carboxyl with a suitable reducing agent and deprotection as necessary to give a compound (I-29) or an N- and/or O-protected compound thereof.

Examples of the base to be used in the condensation include sodium hydroxide, sodium methoxide, sodium ethoxide, sodium hydride, potassium hydride, lithium diisopropylamide, butyl lithium, lithium hexamethyldisilazane, triethylamine, diisopropylethylamine and 1,8-diazabicyclo[5.4.0]undeca-7-ene.

Examples of the organic solvent to be used in the condensation include methanol, ethanol, tert-butyl alcohol, tetrahydrofuran, diethyl ether, ethylene glycol dimethyl ether, dimethylformamide, dimethyl sulfoxide, benzene, toluene, xylene, dioxane, methylene chloride, chloroform, dichloroethane and acetonitrile.

The condensation generally proceeds at a temperature of from -20 °C to 150 °C and a temperature lower or higher than this temperature range may be selected on demand.

The condensation is generally carried out for 30 minutes to 2 days and the reaction period longer or shorter than the indicated period may be used as necessary.

After the condensation is carried out under the above-mentioned conditions or after removing the protecting group on demand, the Compound (VI) can be purified by a method known in the field of organic synthetic chemistry, such as solvent extraction, recrystallization, chromatography and a method using an ion exchange resin.

Examples of the reducing agent to be used for the reduction of carboxyl include metallic reducing reagent such as sodium borohydride, lithium borohydride or lithium aluminum hydride, and diborane.

Examples of the organic solvent to be used for the reduction of carboxyl include methanol, ethanol, tert-butyl alcohol, tetrahydrofuran, diethyl ether and ethylene glycol dimethyl ether.

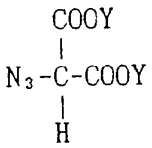
The temperature of the reduction of carboxyl is generally from -20 °C to 80 °C and a temperature lower or higher than this temperature range may be selected on demand.

The reduction of carboxyl is generally carried out for 30 minutes to 10 hours and the reaction period longer or shorter than the indicated period may be used as necessary.

After the reduction is carried out under the above-mentioned conditions or after removing the protecting group on demand, the objective compound can be purified by a method known in the field of organic synthetic chemistry, such as solvent extraction, recrystallization, chromatography and a method using an ion exchange resin.

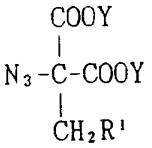
(Method C)

A Compound (II) or a Compound B-(II) is condensed, in the presence of a base, with a compound of the formula (VII)



(VII)

wherein Y is as defined above [hereinafter referred to as Compound (VII)] to give a compound of the formula (VIII)



(VIII)

wherein R^1 and Y are as defined above [hereinafter referred to as Compound (VIII)]. The obtained compound is then subjected to reduction of carboxyl and aside with a suitable reducing agent and deprotection as necessary to give a Compound (1-29) or an O-protected compound thereof.

Examples of the base to be used for the condensation include sodium hydroxide, sodium methoxide, sodium ethoxide, sodium hydride, potassium hydride, lithium diisopropylamide, butyl lithium, lithium hexamethyldisilazane, triethylamine, diisopropylethylamine and 1,8-diazabicyclo[5.4.0]undeca-7-ene.

Examples of the organic solvent to be used for the condensation include methanol, ethanol, tert-butyl alcohol, tetrahydrofuran, diethyl ether, ethylene glycol dimethyl ether, dimethylformamide, dimethyl sulfoxide, benzene, toluene, xylene, dioxane, methylene chloride, chloroform, dichloroethane and acetonitrile.

The condensation generally proceeds at a temperature of from -20 °C to 150 °C and a temperature lower or higher than this temperature range may be selected on demand.

The condensation is generally carried out for 30 minutes to 2 days and the reaction period longer or shorter than the indicated period may be used as necessary.

After the condensation is carried out under the above-mentioned conditions or after removing the protecting group on demand, the Compound (VIII) can be purified by a method known in the field of organic

synthetic chemistry, such as solvent extraction, recrystallization, chromatography and a method using an ion exchange resin.

Examples of the reducing agent to be used for the reduction of carboxyl include metallic reducing reagent such as sodium borohydride, lithium borohydride or lithium aluminum hydride, and diborane.

Examples of the organic solvent to be used for the reduction of carboxyl include methanol, ethanol, tert-butyl alcohol, tetrahydrofuran, diethyl ether and ethylene glycol dimethyl ether.

The temperature of the reduction of carboxyl is generally from -20 °C to 80 °C and a temperature lower or higher than this temperature range may be selected on demand.

The reduction is generally carried out for 30 minutes to 10 hours and the reaction period longer or shorter than the indicated period may be used as necessary.

Examples of the reducing agent to be used for the reduction of azide include metallic reducing reagent such as sodium borohydride, lithium borohydride or lithium aluminum hydride, and transition metal such as palladium-carbon, platinum oxide, Raney nickel, rhodium or ruthenium for catalytic reduction.

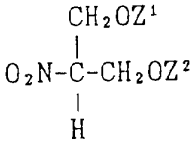
Examples of the organic solvent to be used for the reduction of azide include methanol, ethanol, tert-butyl alcohol, tetrahydrofuran, diethyl ether, dioxane, acetone, ethyl acetate, acetic acid, benzene, toluene, xylene, dimethylformamide and dimethyl sulfoxide.

The temperature of the reduction of azide is generally from -20 °C to 80 °C and a temperature lower or higher than this temperature range may be selected on demand.

After the reduction is carried out under the above-mentioned conditions or after removing the protecting group on demand, the objective compound can be purified by a method known in the field of organic synthetic chemistry, such as solvent extraction, recrystallization, chromatography and a method using an ion exchange resin.

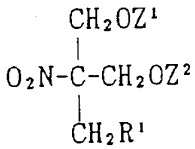
(Method D)

A Compound (II) or a Compound B-(II) is condensed, in the presence of a base, with a compound of the formula (IX)



(IX)

wherein Z^1 and Z^2 are the same or different and each is hydroxyl-protecting group widely used in the field of organic synthetic chemistry, such as acetyl, benzoyl, benzyl, trimethylsilyl, tert-butyldimethylsilyl, methoxymethyl, methoxyethoxymethyl or tetrahydropyranyl and Z^1 and Z^2 may together form a ring such as dioxane [hereinafter referred to as Compound (IX)] to give a compound of the formula (X)



(X)

wherein R^1, Z^1 and Z^2 are as defined above [hereinafter referred to as Compound (X)]. The obtained compound is then subjected to reduction of nitro with a suitable reducing agent and deprotection as necessary to give a Compound (I-29) or an O-protected compound thereof.

Examples of the base to be used for the condensation include sodium hydroxide, sodium methoxide, sodium ethoxide, sodium hydride, potassium hydride, lithium diisopropylamide, butyl lithium, lithium hexamethyldisilazane, triethylamine, diisopropylethylamine and 1,8-diazabicyclo[5.4.0]undeca-7-ene.

Examples of the organic solvent to be used for the condensation include methanol, ethanol, tert-butyl alcohol, tetrahydrofuran, diethyl ether, ethylene glycol dimethyl ether, dimethylformamide, dimethyl sulfoxide, benzene, toluene, xylene, dioxane, methylene chloride, chloroform, dichloroethane and acetonitrile.

The condensation generally proceeds at a temperature of from -20 °C to 150 °C and a temperature lower or higher than this temperature range may be selected on demand.

The condensation is generally carried out for 30 minutes to 2 days and the reaction period longer or shorter than the indicated period may be used as necessary.

After the condensation is carried out under the above-mentioned conditions or after removing the protecting group on demand, the Compound (X) can be purified by a method known in the field of organic synthetic chemistry, such as solvent extraction, recrystallization, chromatography and a method using an ion exchange resin.

Examples of the reducing agent to be used for the reduction of nitro include metallic reducing reagent such as sodium borohydride, lithium borohydride or lithium aluminum hydride, transition metal such as palladium-carbon, platinum oxide, Raney nickel, rhodium or ruthenium for catalytic reduction, and metal such as iron, zinc or tin.

Examples of the solvent to be used for the reduction of nitro include water, methanol, ethanol, tert-butyl alcohol, tetrahydrofuran, diethyl ether, dioxane, acetone, ethyl acetate, acetic acid, benzene, toluene, xylene, dimethylformamide and dimethyl sulfoxide.

The reduction of nitro generally proceeds at a temperature of from -20 °C to 80 °C and a temperature lower or higher than this temperature range may be selected on demand.

After the reduction is carried out under the above-mentioned conditions or after removing the protecting group on demand, the objective compound can be purified by a method known in the field of organic synthetic chemistry, such as solvent extraction, recrystallization, chromatography and a method using an ion exchange resin.

The above-mentioned methods A through D can be used for the synthesis of the compounds of the formulas (I-1) to (I-18).

(Method E)

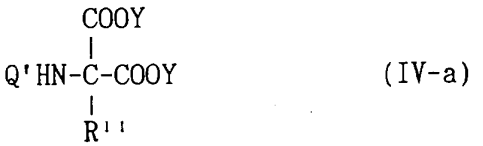
A compound of the formula (XI)

$(R^{II})_n$ - M (XI)

wherein R^{II} is the same as the aforementioned CH_2R^1, CH_2R^1a, CH_2R^1b, Ra, Rb, Rc, Rd, Re, Rf, Rg, Rh, Ri, Rj, Rk, Rl, Rm, Rn, Ro, Rp, Rq, CH=CHRt, CH=CHRu, $(CH_2)\alpha$-X-$(CH_2)\beta$Rv (when $\alpha \geq 1$) or CH_2ORw which are encompassed in R, M is a metal in wide use in the field of organic synthetic chemistry, such as lithium, magnesium chloride, magnesium bromide, magnesium iodide, copper, lithium copper or nickel, and n is an integer of 1 to 3 [hereinafter referred to as compound (XI)], or when R^{II} has a functional group (e.g. amino, hydroxyl group, mercapto, ketone, carboxyl), a compound with protection of the functional group as necessary [hereinafter referred to as Compound B-(XI)] is subjected to nucleophilic addition to a compound of the formula (XII)

(XII)

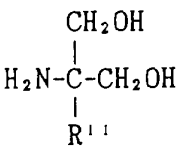
wherein Y is as defined above and Q' is an imino-protecting group in wide use in the field of organic synthetic chemistry, such as acetyl, benzoyl, tert-butoxycarbonyl or benzyloxycarbonyl [hereinafter referred to as Compound (XII)] to give a compound of the formula (IV-a)



(IV-a)

wherein R^{II}, Q' and Y are as defined above [hereinafter referred to as Compound (IV-a)]. The obtained compound is then subjected to reduction of carboxyl with a suitable reducing agent and deprotection as

necessary to give a compound of the formula (I-30)



(I-30)

wherein R^{II} is as defined above [hereinafter referred to as Compound (I-30)] or an N- and/or O-protected compound thereof.

Examples of the organic solvent to be used for the addition include tetrahydrofuran, diethyl ether, ethylene glycol dimethyl ether, dimethylformamide, dimethyl sulfoxide, benzene, toluene, xylene, dioxane, methylene chloride, chloroform, dichloroethane and acetonitrile.

The addition generally proceeds at a temperature of from -100 °C to 80 °C and a temperature lower or higher than this temperature range may be selected on demand.

The addition is generally carried out for 30 minutes to 2 days and the reaction period longer or shorter than the indicated period may be used as necessary.

After the addition is carried out under the above-mentioned conditions or after removing the protecting group on demand, the Compound (IV-a) can be purified by a method known in the field of organic synthetic chemistry, such as solvent extraction, recrystallization, chromatography and a method using an ion exchange resin.

Examples of the reducing agent to be used for the reduction of carboxyl include metallic reducing reagent such as sodium borohydride, lithium borohydride or lithium aluminum hydride, and diborane.

Examples of the organic solvent to be used for the reduction of carboxyl include methanol, ethanol, tert-butyl alcohol, tetrahydrofuran, diethyl ether and ethylene glycol dimethyl ether.

The reduction of carboxyl generally proceeds at a temperature of from -20 °C to 80 °C and a temperature lower or higher than this temperature range may be selected on demand.

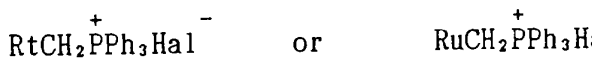
The reduction of carboxyl is generally carried out for 30 minutes to 10 hours and the reaction period longer or shorter than the indicated period may be used as necessary.

After the reduction is carried out under the above-mentioned conditions or after removing the protecting group on demand, the objective compound can be purified by a method known in the field of organic synthetic chemistry, such as solvent extraction, recrystallization, chromatography and a method using an ion exchange resin.

The instant method can be used for the synthesis of the compounds of the formulas (I-1) to (I-20), (I-24), (I-25), (I-26) when $\alpha \geqq 1$ and (I-27).

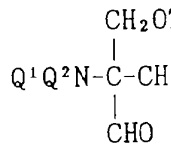
(Method F)

A compound of the formula (XIII)



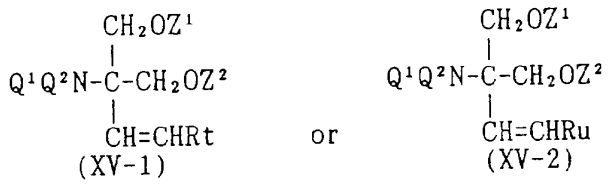
(XIII-1) or (XIII-2)

wherein Hal is halogen such as chlorine, bromine or iodine and. Rt and Ru are as defined above [hereinafter referred to as Compound (XIII-1) or Compound (XIII-2)], or when Rt and Ru have a functional group (e.g. amino, hydroxyl, mercapto, ketone, carboxyl), a compound with protection of the functional group as necessary [hereinafter referred to as Compound B-(XIII-1) or Compound B-(XIII-2)] is condensed, in the presence of a base, with a compound of the formula (XIV)



(XIV)

wherein Q^1 and Q^2 are amino-protecting groups widely used in the field of organic synthetic chemistry, such as acetyl, benzoyl, tert-butoxycarbonyl, benzyloxycarbonyl or benzyl and one of them may be hydrogen, and Z^1 and Z^2 are as defined above [hereinafter referred to as Compound (XIV)] to give a compound of the formula (XV)



(XV-1) or (XV-2)

wherein Rt, Ru, Q^1, Q^2, Z^1 and Z^2 are as defined above [hereinafter referred to as Compound (XV-1) or Compound (XV-2)]. The obtained compound is then subjected to deprotection as necessary to give a compound (I-24) or (I-25).

Examples of the base to be used in the condensation include sodium hydroxide, sodium methoxide, sodium ethoxide, potassium tert-butoxide, sodium hydride, potassium hydride, lithium diisopropylamide, butyl lithium, lithium hexamethyldisilazane, triethylamine, diisopropylethylamine, pyridine and 1,8-diazabicyclo[5.4.0]undeca-7-ene.

Examples of the solvent to be used for the condensation include water, methanol, ethanol, tert-butyl alcohol, tetrahydrofuran, diethyl ether, ethylene glycol dimethyl ether, dimethylformamide, dimethyl sulfoxide, benzene, toluene, xylene, dioxane, methylene chloride, chloroform, dichloroethane and acetonitrile.

The condensation generally proceeds at a temperature of from -20 °C to 150 °C and a temperature lower or higher than this temperature range may be selected on demand.

The condensation is generally carried out for 30 minutes to 2 days and the reaction period longer or shorter than the indicated period may be used as necessary.

After the condensation is carried out under the above-mentioned conditions or after removing the protecting group on demand, the Compound (XV-1) or (XV-2.) can be purified by a method known in the field of organic synthetic chemistry, such as solvent extraction, recrystallization, chromatography or a method using an ion exchange resin.

The instant method can be used for the synthesis of the compounds of the formulas (I-24) and (I-25). By reducing the double bond of the compounds of the formulas (I-24) and (I-25), or an N- and/or O-protected compound thereof, the compounds of the formulas (I-1) through (I-18) and (I-26) when $\alpha \geqq 2$ can be obtained.

Examples of the reducing agent to be used for the reduction of the double bond include metal reducing reagent such as sodium borohydride, lithium borohydride or lithium aluminum hydride, and transition metal such as palladium-carbon, platinum oxide, Raney nickel, rhodium or ruthenium for catalytic reduction.

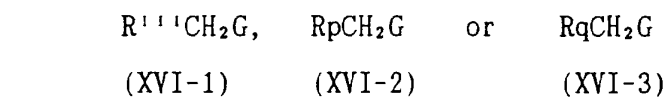
Examples of the organic solvent to be used for the reduction of the double bond include methanol, ethanol, tert-butyl alcohol, tetrahydrofuran, diethyl ether, dioxane, acetone, ethyl acetate, acetic acid, benzene, toluene, xylene, dimethylformamide and dimethyl sulfoxide.

The reduction of the double bond generally proceeds at a temperature of from -20 °C to 80 °C and a temperature lower or higher than this temperature range may be selected on demand.

After the reduction is carried out under the above-mentioned conditions or after removing the protecting group on demand, the objective compounds of the formulas (I-1) through (I-18) and (I-26) when $\alpha \geqq 2$ can be purified by a method known in the field of organic synthetic chemistry, such as solvent extraction, recrystallization, chromatography or a method using an ion exchange resin.

(Method G)

A compound of the formula (XVI)

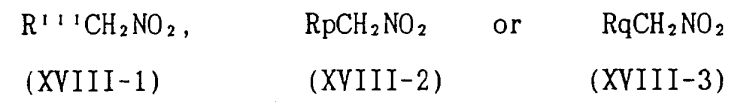


$R^{III}CH_2G$, (XVI-1) $RpCH_2G$ (XVI-2) or $RqCH_2G$ (XVI-3)

wherein R^{III} is the aforementioned CH_2R^1, CH_2R^1a, CH_2R^1b, Ra, Rb, Rc, Rd, Re, Rf, Rg, Rh, Ri, Rj, Rk, Rl, Rm, Rn or Ro which are encompassed in R, and Rp, Rq and G are as defined above [hereinafter referred to as Compound (XVI-1), Compound (XVI-2) or Compound (XVI-3)], or when R^{III}, Rp and Rq have a functional group (e.g. amino, hydroxyl, mercapto, ketone, carboxyl), a compound with protection thereof as necessary [hereinafter referred to as compound B-(XVI-1), Compound B-(XVI-2) or Compound B-(XVI-3)] is reacted with a compound of the formula (XVII)

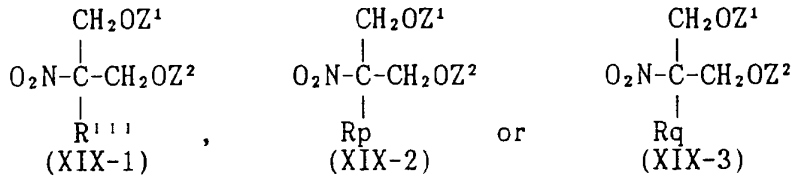
$M^{n+}(NO_2^-)_n$ (XVII)

wherein M is a metal such as sodium, potassium, magenesium, silver, calcium or lithium and n is an integer of 1 or 2 [hereinafter referred to as Compound (XVII)] to give a compound of the formula (XVIII)



$R^{III}CH_2NO_2$, (XVIII-1) $RpCH_2NO_2$ (XVIII-2) or $RqCH_2NO_2$ (XVIII-3)

wherein R^{III}, Rp and Rq are as defined above [hereinafter referred to as Compound (XVIII-1), Compound (XVIII-2) or Compound (XVIII-3)]. The obtained compound is condensed with formal in in the presence of a base, and then subjected to protection of hydroxyl as necessary to give a compound of the formula (XIX)



$O_2N-C(CH_2OZ^1)(CH_2OZ^2)(R^{III})$ (XIX-1), $O_2N-C(CH_2OZ^1)(CH_2OZ^2)(Rp)$ (XIX-2) or $O_2N-C(CH_2OZ^1)(CH_2OZ^2)(Rq)$ (XIX-3)

wherein R^{III}, Rp, Rq, Z^1 and Z^2 are as defined above [hereinafter referred to as Compound (XIX-1), Compound (XIX-2) or Compound (XIX-3)]. The obtained compound is then subjected to reduction of nitro with a suitable reducing agent and deprotection as necessary to give a desired compound inclusive of the compounds (I-19) and (I-20).

Examples of the solvent to be used for the condensation of nitrite (XVII) and the Compound (XVI-1), (XVI-2) or (XVI-3) include water, methanol, ethanol, tert-butyl alcohol, tetrahydrofuran, diethyl ether, ethylene glycol dimethyl ether, dimethylformamide, dimethyl sulfoxide, benzene, toluene, xylene, dioxane, methylene chloride, chloroform, dichloroethane and acetonitrile.

The condensation generally proceeds at a temperature of from -20 °C to 150 °C and a temperature lower or higher than this temperature range may be selected on demand.

The condensation is generally carried out for 30 minutes to 2 days and the reaction period longer or shorter than the indicated period may be used as necessary.

After the condensation is carried out under the above-mentioned conditions or after removing the protecting group on demand, the Compound (XVIII-1), (XVIII-2) or (XVIII-3) can be purified by a method known in the field of organic synthetic chemistry, such as solvent extraction, recrystallization, chromatography or a method using an ion exchange resin.

Examples of the solvent to be used for the condensation of the Compound (XVIII-1), (XVIII-2) or (XVIII-3) and, formalin include water, methanol, ethanol, tert-butyl alcohol, tetrahydrofuran, diethyl ether, ethylene glycol dimethyl ether, dimethylformamide, dimethyl sulfoxide, benzene, toluene, xylene, dioxane, methylene chloride, chloroform, dichloroethane and acetonitrile.

Examples of the base to be used for the condensation include sodium hydroxide, sodium methoxide, sodium ethoxide, sodium hydride, potassium hydride, triethylamine, diisopropylethylamine and 1,8-diazabicyclo[5.4.0]undeca-7-ene.

The condensation generally proceeds at a temperature of from -20 °C to 150 °C and a temperature lower or higher than this temperature range may be selected on demand.

The condensation is generally carried out for 30 minutes to 2 days and the reaction period longer or shorter than the indicated period may be used as necessary.

After the condensation is carried out under the above-mentioned conditions or after removing the protecting group on demand, the Compound (XIX-1), (XIX-2) or (XIX-3) can be purified by a method known in the field of organic synthetic chemistry, such as solvent extraction, recrystallization, chromatography or a method using an ion exchange resin.

Examples of the reducing agent to be used for the reduction of nitro include metallic reducing reagent such as sodium borohydride, lithium borohydride or lithium aluminum hydride, transition metal such as palladium-carbon, platinum oxide, Raney nickel, rhodium or ruthenium for catalytic reduction, and metal such as iron, zinc or tin.

Examples of the solvent to be used for the reduction of nitro include water, methanol, ethanol, tert-butyl alcohol, tetrahydrofuran, diethyl ether, dioxane, acetone, ethyl acetate, acetic acid, benzene, toluene, xylene, dimethylformamide and dimethyl sulfoxide.

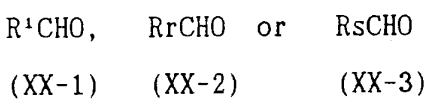
The reduction of nitro generally proceeds at a temperature of from -20 °C to 80 °C and a temperature lower or higher than this temperature range may be selected on demand.

After the reduction is carried out under the above-mentioned conditions or after removing the protecting group on demand, the objective compound can be purified by a method known in the field of organic synthetic chemistry, such as solvent extraction, recrystallization, chromatography or a method using an ion exchange resin.

The instant method is suitable for the synthesis of the compounds (I-19) and (I-20), as well as for the synthesis of the compounds of the formulas (I-1) through (I-18).

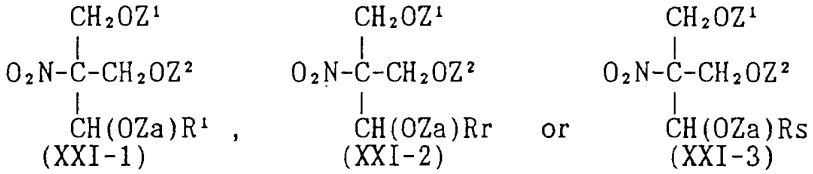
(Method H)

A compound of the formula (XX)



R^1CHO, (XX-1) RrCHO (XX-2) or RsCHO (XX-3)

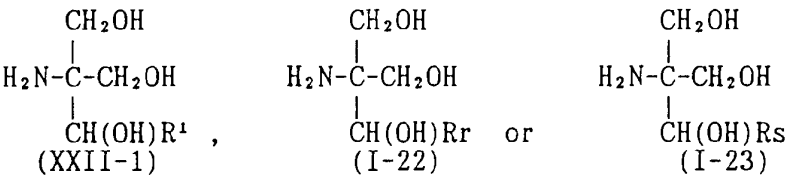
wherein R^1, Rr and Rs are as defined above [hereinafter referred to as Compound (XX-1), Compound (XX-2) or Compound (XX-3)] is condensed, in the presence of a base, with a Compound (IX) and subjected to protection of hydroxyl as necessary to give a compound of the formula (XXI)



(XXI-1), (XXI-2) or (XXI-3)

wherein R^1, Rr, Rs, Z^1 and Z^2 are as defined above and Za is hydrogen or a hydroxyl-protecting group in wide use in the field of organic synthetic chemistry, such as acetyl, benzoyl, benzyl, trimethylsilyl, tert-butyldimethylsilyl, methoxymethyl, methoxyethoxymethyl or tetrahydropyranyl [hereinafter referred to as Compound (XXI-1), Compound (XXI-2) or Compound (XXI-3)]. The obtained compound is then subjected to

reduction of nitro with a suitable reducing agent and deprotection as necessary to give a compound of the formula (XXII)



(XXII-1), (I-22), (I-23)

wherein R^1, Rr and Rs are as defined above [hereinafter referred to as Compound (XXII-1), Compound (I-22) or Compound (I-23)].

Examples of the base to be used for the condensation with aldehyde include sodium hydroxide, sodium methoxide, sodium ethoxide, sodium hydride, potassium hydride, lithium diisopropylamide, butyl lithium, lithium hexamethyldisilazane, triethylamine, diisopropylethylamine and 1,8-diazabicyclo-[5.4.0]undeca-7-ene.

Examples of the solvent to be used for the condensation include water, methanol, ethanol, tert-butyl alcohol, tetrahydrofuran, diethyl ether, ethylene glycol dimethyl ether, dimethylformamide, dimethyl sulfoxide, benzene, toluene, xylene, dioxane, methylene chloride, chloroform, dichloroethane and acetonitrile.

The condensation generally proceeds at a temperature of from -20 °C to 150 °C and a temperature lower or higher than this temperature range may be selected on demand.

The condensation is generally carried out for 30 minutes to 2 days and the reaction period longer or shorter than the indicated period may be used as necessary.

After the condensation is carried out under the above-mentioned conditions or after removing the protecting group on demand, the Compound (XXI-1), (XXI-2) or (XXI-3) can be purified by a method known in the field of organic synthetic chemistry, such as solvent extraction, recrystallization, chromatography or a method using an ion exchange resin.

Examples of the reducing agent to be used for the reduction of nitro include metal reducing reagent such as sodium borohydride, lithium borohydride or lithium aluminum hydride, transition metal such as palladium-carbon, platinum oxide, Raney nickel, rhodium or ruthenium for catalytic reduction, and metal such as iron, zinc or tin.

Examples of the solvent to be used for the reduction of nitro include water, methanol, ethanol, tert-butyl alcohol, tetrahydrofuran, diethyl ether, dioxane, acetone, ethyl acetate, acetic acid, benzene, toluene, xylene, dimethylformamide and dimethyl sulfoxide.

The reduction of nitro generally proceeds at a temperature of from -20 °C to 80 °C and a temperature lower or higher than this temperature range may be selected on demand.

After the reduction is carried out under the above-mentioned conditions or after removing the protecting group on demand, the Compound (XXII-1), (I-22) or (I-23) can be purified by a method known in the field of organic synthetic chemistry, such as solvent extraction, recrystallization, chromatography or a method using an ion exchange resin.

Accordingly, the instant method can be used for the synthesis of the compounds of the formulas (I-21) through (I-23).

(Method I)

Compound (XVIII-1) can be also produced by the following method.

A compound of the formula (XX')

$$R^ACHO \quad (XX')$$

wherein R^A is a straight- or branched carbon chain optionally having a substituent having a carbon number less 1 from that of the substituent at R^{III} [hereinafter referred to as Compound (XX')] is condensed with nitromethane in the presence of a base to give a compound of the formula (XXIII)

$$R^ACH=CHNO_2 \quad (XXIII)$$

wherein R^A is as defined above [hereinafter referred to as Compound (XXIII)]. The obtained compound is

then subjected to reduction of the double bond with a suitable reducing agent to give a compound (XVIII-1).

Examples of the solvent to be used for the condensation include water, methanol, ethanol, tert-butyl alcohol, tetrahydrofuran, diethyl ether, ethylene glycol dimethyl ether, dimethylformamide, dimethyl sulfoxide, benzene, toluene, xylene, dioxane, methylene chloride, chloroform, dichloroethane and acetonitrile.

Examples of the base to be used for the condensation include sodium hydroxide, sodium methoxide, sodium ethoxide, sodium hydride, potassium hydride, triethylamine, diisopropylethylamine and 1,8-diazabicyclo[5.4.0]undeca-7-ene.

The condensation generally proceeds at a temperature of from -20 °C to 150 °C and a temperature lower or higher than this temperature range may be selected on demand.

The condensation is generally carried out for 30 minutes to 2 days and the reaction period longer or shorter than the indicated period may be used as necessary.

After the condensation is carried out under the above-mentioned conditions or after removing the protecting group on demand, the Compound (XXIII) can be purified by a method known in the field of organic synthetic chemistry, such as solvent extraction, recrystallization, chromatography or a method using an ion exchange resin.

Examples of the reducing agent to be used for the reduction of the double bond include metallic reducing reagent such as lithium borohydride or lithium aluminum hydride, and transition metal such as palladium-carbon, platinum oxide, Raney nickel, rhodium or ruthenium for catalytic reduction.

Examples of the organic solvent to be used for the reduction of the double bond include methanol, ethanol, tert-butyl alcohol, tetrahydrofuran, diethyl ether, dioxane, acetone, ethyl acetate, acetic acid, benzene, toluene, xylene, dimethylformamide and dimethyl sulfoxide.

The reduction of the double bond generally proceeds at a temperature of from -20 °C to 80 °C and a temperature lower or higher than this temperature range may be selected on demand.

After the reduction is carried out under the above-mentioned conditions or after removing the protecting group on demand, the Compound (XVIII-1) can be purified by a method known in the field of organic synthetic chemistry, such as solvent extraction, recrystallization, chromatography or a method using an ion exchange resin.

(Method J)

Compound (XXI-1), Compound (XXI-2) and Compound (XXI-3) can be also produced by the following method.

A Compound (XX-1), (XX-2) or (XX-3) is condensed with nitromethane in the presence of a base and subjected to protection of hydroxyl as necessary to give a compound of the formula (XXIV)

$$R^1CH(OZa)CH_2NO_2, \quad RrCH(OZa)CH_2NO_2 \quad or \quad RsCH(OZa)CH_2NO_2$$

(XXIV-1) (XXIV-2) (XXIV-3)

wherein R^1, Rr, Rs and Za are as defined above [hereinafter referred to as Compound (XXIV-1), Compound (XXIV-2) or Compound (XXIV-3)]. The obtained compound is condensed with formalin in the presence of a base and then subjected to protection of hydroxyl as necessary to give a Compound (XXI-1), (XXI-2) or (XXI-3).

Examples of the solvent to be used for the condensation include water, methanol, ethanol, tert-butyl alcohol, tetrahydrofuran, diethyl ether, ethylene glycol dimethyl ether, dimethylformamide, dimethyl sulfoxide, benzene, toluene, xylene, dioxane, methylene chloride, chloroform, dichloroethane and acetonitrile.

Examples of the base to be used for the condensation include sodium hydroxide, sodium methoxide, sodium ethoxide, sodium hydride, potassium hydride, triethylamine, diisopropylethylamine and 1,8-diazabicyclo[5.4.0]undeca-7-ene.

The condensation generally proceeds at a temperature of from -20 °C to 150 °C and a temperature lower or higher than this temperature range may be selected on demand.

The condensation is generally carried out for 30 minutes to 2 days and the reaction period longer or shorter than the indicated period may be used as necessary.

After the condensation is carried out under the above-mentioned conditions or after removing the protecting group on demand, the Compound (XXIV-1), (XXIV-2) or (XXIV-3) can be purified by a method known in the field of organic synthetic chemistry, such as solvent extraction, recrystallization, chromatog-

raphy or a method using an ion exchange resin.

Examples of the solvent to be used for the condensation with formal in include water, methanol, ethanol, tert-butyl alcohol, tetrahydrofuran, diethyl ether, ethylene glycol dimethyl ether, dimethylformamide, dimethyl sulfoxide, benzene, toluene, xylene, dioxane, methylene chloride, chloroform, dichloroethane and acetonitrile.

Examples of the base to be used for the condensation include sodium hydroxide, sodium methoxide, sodium ethoxide, sodium hydride, potassium hydride, triethylamine, diisopropylethylamine and 1,8-diazabicyclo[5.4.0]undeca-7-ene.

The condensation generally proceeds at a temperature of from -20 °C to 150 °C and a temperature lower or higher than this temperature range may be selected on demand.

The condensation is generally carried out for 30 minutes to 2 days and the reaction period longer or shorter than the indicated period may be used as necessary.

After the condensation is carried out under the above-mentioned conditions or after removing the protecting group on demand, the Compound (XXI-1), (XXI-2) or (XXI-3) can be purified by a method known in the field of organic synthetic chemistry, such as solvent extraction, recrystallization, chromatography or a method using an ion exchange resin.

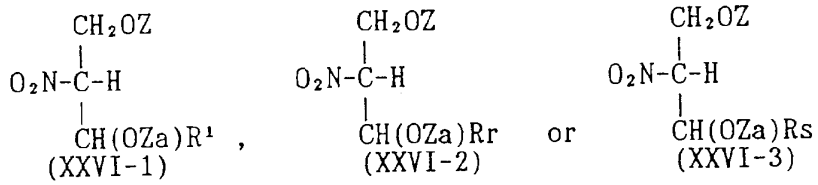
(Method K)

Compound (XXI-1), Compound (XXI-2) and Compound (XXI-3) can be also produced by the following method.

A compound (XXV)

$$ZOCH_2CH_2NO_2 \quad (XXV)$$

wherein Z is as defined above [hereinafter referred to as Compound (XXV)] is condensed with a Compound (XX-1), (XX-2) or (XX-3) in the presence of a base and subjected to protection of hydroxyl as necessary, to give a compound of the formula (XXVI)



(XXVI-1) , (XXVI-2) or (XXVI-3)

wherein R^1, Rr, Rs, Z and Za are as defined above [hereinafter referred to as Compound (XXVI-1), Compound (XXVI-2) or Compound (XXVI-3)]. The obtained compound is condensed with formalin in the presence of a base and then subjected to protection of hydroxyl as necessary to give a Compound (XXI-1), (XXI-2) or (XXI-3).

Examples of the solvent to be used for the condensation include water, methanol, ethanol, tert-butyl alcohol, tetrahydrofuran, diethyl ether, ethylene glycol dimethyl ether, dimethylformamide, dimethyl sulfoxide, benzene, toluene, xylene, dioxane, methylene chloride, chloroform, dichloroethane and acetonitrile.

Examples of the base to be used for the condensation include sodium hydroxide, sodium methoxide, sodium ethoxide, sodium hydride, potassium hydride, triethylamine, diisopropylethylamine and 1,8-diazabicyclo[5.4.0]undeca-7-ene.

The condensation generally proceeds at a temperature of from -20 °C to 150 °C and a temperature lower or higher than this temperature range may be selected on demand.

The condensation is generally carried out for 30 minutes to 2 days and the reaction period longer or shorter than the indicated period may be used as necessary.

After the condensation is carried out under the above-mentioned conditions or after removing the protecting group on demand, the Compound (XXVI-1), (XXVI-2) or (XXVI-3) can be purified by a method known in the field of organic synthetic chemistry, such as solvent extraction, recrystallization, chromatography or a method using an ion exchange resin.

Examples of the solvent to be used for the condensation with formal in include water, methanol, ethanol, tert-butyl alcohol, tetrahydrofuran, diethyl ether, ethylene glycol dimethyl ether, dimethylformamide,

dimethyl sulfoxide, benzene, toluene, xylene, dioxane, methylene chloride, chloroform, dichloroethane and acetonitrile.

Examples of the base to be used for the condensation include sodium hydroxide, sodium methoxide, sodium ethoxide, sodium hydride, potassium hydride, triethylamine, diisopropylethylamine and 1,8-diazabicyclo[5.4.0]undeca-7-ene.

The condensation generally proceeds at a temperature of from -20 °C to 150 °C and a temperature lower or higher than this temperature range may be selected on demand.

The condensation is generally carried out for 30 minutes to 2 days and the reaction period longer or shorter than the indicated period may be used as necessary.

After the condensation is carried out under the above-mentioned conditions or after removing the protecting group on demand, the Compound (XXI-1), (XXI-2) or (XXI-3) can be purified by a method known in the field of organic synthetic chemistry, such as solvent extraction, recrystallization, chromatography or a method using an ion exchange resin.

(Method L)

A compound of the formula (XXVII)

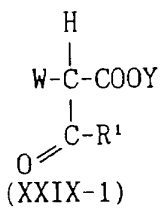
WCH_2COOY (XXVII)

wherein W is azide, nitro or amino protected by a suitable protecting group and Y is as defined above [hereinafter referred to as Compound (XXVII)] is condensed, in the presence of a base, with a compound of the formula (XXVIII)

R^1COHal, $RrCOHal$ or $RsCOHal$

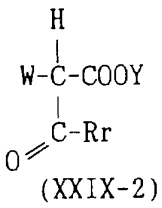
(XXVIII-1) (XXVIII-2) (XXVIII-3)

wherein R^1, Rr, Rs and Hal are as defined above [hereinafter referred to as Compound (XXVIII-1), Compound (XXVIII-2) or Compound (XXVIII-3)] to give a compound of the formula (XXIX)



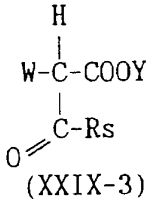
(XXIX-1)

,



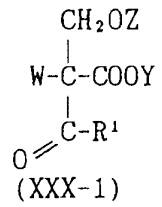
(XXIX-2)

or



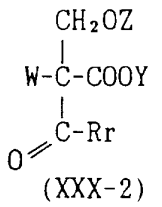
(XXIX-3)

wherein R^1, Rr, Rs, W and Y are as defined above [hereinafter referred to as Compound (XXIX-1), Compound (XXIX-2) or Compound (XXIX-3)]. The obtained compound is condensed with formalin in the presence of a base and subjected to protection of hydroxyl as necessary to give a compound of the formula (XXX)



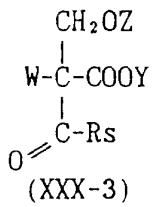
(XXX-1)

,



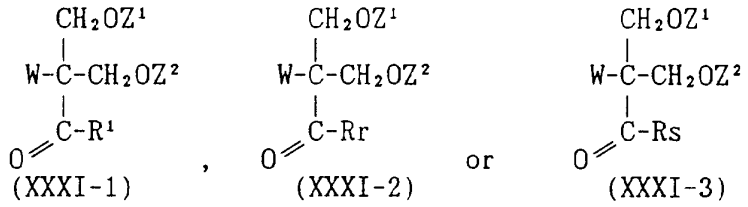
(XXX-2)

or



(XXX-3)

wherein R^1, Rr, Rs, W, Y and Z are as defined above [hereinafter referred to as Compound (XXX-1), Compound (XXX-2) or Compound (XXX-3)]. The obtained compound is subjected to reduction of carboxyl with a suitable reducing agent and protection of hydroxyl as necessary to give a compound of the formula (XXXI)



(XXXI-1) , (XXXI-2) or (XXXI-3)

wherein R^1, Rr, Rs, W, Z^1 and Z^2 are as defined above [hereinafter referred to as Compound (XXXI-1), Compound (XXXI-2) or Compound (XXXI-3)] and the obtained compound is subjected to reduction of carbonyl with a suitable reducing agent, and reduction and deprotection as necessary, to give a Compound (XXII-1), (I-22) or (I-23).

Examples of the solvent to be used for the condensation include water, methanol, ethanol, tert-butyl alcohol, tetrahydrofuran, diethyl ether, ethylene glycol dimethyl ether, dimethylformamide, dimethyl sulfoxide, benzene, toluene, xylene, dioxane, methylene chloride, chloroform, dichloroethane and acetonitrile.

Examples of the base to be used for the condensation include sodium hydroxide, sodium methoxide, sodium ethoxide, sodium hydride, potassium hydride, triethylamine, diisopropylethylamine and 1,8-diazabicyclo[5.4.0]undeca-7-ene.

The condensation generally proceeds at a temperature of from -20 °C to 150 °C and a temperature lower or higher than this temperature range may be selected on demand.

The condensation is generally carried out for 30 minutes to 2 days and the reaction period longer or shorter than the indicated period may be used as necessary.

After the condensation is carried out under the above-mentioned conditions or after removing the protecting group on demand, the Compound (XXIX-1), (XXIX-2) or (XXIX-3) can be purified by a method known in the field of organic synthetic chemistry, such as solvent extraction, recrystallization, chromatography or a method using an ion exchange resin.

Examples of the solvent to be used for the condensation with formal in include water, methanol, ethanol, tert-butyl alcohol, tetrahydrofuran, diethyl ether, ethylene glycol dimethyl ether, dimethylformamide, dimethyl sulfoxide, benzene, toluene, xylene, dioxane, methylene chloride, chloroform, dichloroethane and acetonitrile.

Examples of the base to be used for the condensation include sodium hydroxide, sodium methoxide, sodium ethoxide, sodium hydride, potassium hydride, triethylamine, diisopropylethylamine and 1,8-diazabicyclo[5.4.0]undeca-7-ene.

The condensation generally proceeds at a temperature of from -20 °C to 150 °C and a temperature lower or higher than this temperature range may be selected on demand.

The condensation is generally carried out for 30 minutes to 2 days and the reaction period longer or shorter than the indicated period may be used as necessary.

After the condensation is carried out under the above-mentioned conditions or after removing the protecting group on demand, the Compound (XXX-1), (XXX-2) or (XXX-3) can be purified by a method known in the field of organic synthetic chemistry, such as solvent extraction, recrystallization, chromatography or a method using an ion exchange resin.

Examples of the reducing agent to be used for the reduction of carboxyl include metallic reducing reagent such as sodium borohydride, lithium borohydride or lithium aluminum hydride, and diborane.

Examples of the organic solvent to be used for the reduction of carboxyl include methanol, ethanol, tert-butyl alcohol, tetrahydrofuran, diethyl ether and ethylene glycol dimethyl ether.

The reduction of carboxyl generally proceeds at a temperature of from -20 °C to 80 °C and a temperature lower or higher than this temperature range may be selected on demand.

The reduction of carboxyl is generally carried out for 30 minutes to 10 hours and the reaction period longer or shorter than the indicated period may be used as necessary.

After the reduction is carried out under the above-mentioned conditions or after removing the protecting group on demand, the Compound (XXXI-1), (XXXI-2) or (XXXI-3) can be purified by a method known in the

field of organic synthetic chemistry, such as solvent extraction, recrystallization, chromatography or a method using an ion exchange resin.

Examples of the reducing agent to be used for the reduction of carbonyl include metallic reducing reagent such as sodium borohydride, lithium borohydride or lithium aluminum hydride, and diborane.

Examples of the organic solvent to be used for the reduction of carbonyl include methanol, ethanol, tert-butyl alcohol, tetrahydrofuran, diethyl ether and ethylene glycol dimethyl ether.

The reduction of carbonyl generally proceeds at a temperature of from -20 °C to 80 °C and a temperature lower or higher than this temperature range may be selected on demand.

The reduction of carbonyl is generally carried out for 30 minutes to 10 hours and the reaction period longer or shorter than the indicated period may be used as necessary.

When (i) W = azide, examples of the reducing agent to be used for the reduction of azide include metallic reducing agent such as sodium borohydride, lithium borohydride or lithium aluminum hydride, and transition metal such as palladium-carbon, platinum oxide, Raney nickel, rhodium or ruthenium for catalytic reduction.

Examples of the organic solvent to be used for the reduction of azide include methanol, ethanol, tert-butyl alcohol, tetrahydrofuran, diethyl ether, dioxane, acetone, ethyl acetate, acetic acid, benzene, toluene, xylene, dimethylformamide and dimethyl sulfoxide.

The reduction of azide generally proceeds at a temperature of from -20 °C to 80 °C and a temperature lower or higher than this temperature range may be selected on demand.

When (ii) W = nitro, examples of the reducing agent to be used for the reduction of nitro include metallic reducing reagent such as sodium borohydride, lithium borohydride or lithium aluminum hydride, transition metal such as palladium-carbon, platinum oxide, Raney nickel, rhodium or ruthenium for catalytic reduction, and metal such as iron, zinc or tin.

Examples of the solvent to be used for the reduction of nitro include water, methanol, ethanol, tert-butyl alcohol, tetrahydrofuran, diethyl ether, dioxane, acetone, ethyl acetate, acetic acid, benzene, toluene, xylene, dimethylformamide and dimethyl sulfoxide.

The reduction of nitro generally proceeds at a temperature of from -20 °C to 80 °C and a temperature lower or higher than this temperature range may be selected on demand.

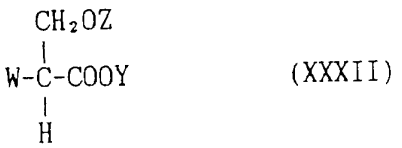
After the reduction is carried out under the above-mentioned conditions or after removing the protecting group on demand, the Compound (XXII-1), (I-22) or (I-23) can be purified by a method known in the field of organic synthetic chemistry, such as solvent extraction, recrystallization, chromatography or a method using an ion exchange resin.

Accordingly, the instant method is applicable to the synthesis of the compounds of the formulas (I-21) through (I-23).

(Method M)

Compound (XXX-1), Compound (XXX-2) and Compound (XXX-3) can be also produced by the following method.

A compound (XXVIII) and a compound of the formula (XXXII)



(XXXII)

wherein W, Y and Z are as defined above [hereinafter referred to as Compound (XXXII)] are condensed in the presence of a base to give a Compound (XXX-1), (XXX-2) or (XXX-3).

Examples of the solvent to be used for the condensation include water, methanol, ethanol, tert-butyl alcohol, tetrahydrofuran, diethyl ether, ethylene glycol dimethyl ether, dimethylformamide, dimethyl sulfoxide, benzene, toluene, xylene, dioxane, methylene chloride, chloroform, dichloroethane and acetonitrile.

Examples of the base to be used for the condensation include sodium hydroxide, sodium methoxide, sodium ethoxide, sodium hydride, potassium hydride, triethylamine, diisopropylethylamine and 1,8-diazabicyclo[5.4.0]undeca-7-ene.

The condensation generally proceeds at a temperature of from -20 °C to 150 °C and a temperature lower or higher than this temperature range may be selected on demand.

The condensation is generally carried out for 30 minutes to 2 days and the reaction period longer or shorter than the indicated period may be used as necessary.

After the condensation is carried out under the above-mentioned conditions or after removing the protecting group on demand, the Compound (XXX-1), (XXX-2) or (XXX-3) can be purified by a method known in the field of organic synthetic chemistry, such as solvent extraction, recrystallization, chromatography or a method using an ion exchange resin.

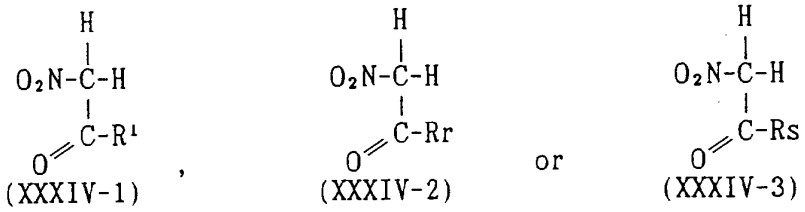
(Method N)

When W = nitro, Compound (XXXI-1), (XXXI-2) and (XXXI-3) can be also produced by the following method.

A compound (XXVIII-1), (XXVIII-2) or (XXVIII-3) and a compound (XXXIII)

CH_3NO_2 (XXXIII)

[hereinafter referred to as Compound (XXXIII)] are condensed in the presence of a base to give a compound of the formula (XXXIV)



(XXXIV-1), (XXXIV-2) or (XXXIV-3)

wherein R^1, Rr and Rs are as defined above [hereinafter referred to as Compound (XXXIV-1), Compound (XXXIV-2) or Compound (XXXIV-3)] and the obtained compound is condensed with formal in in the presence of a base and subjected to protection of hydroxyl as necessary to give a Compound (XXXI-1), (XXXI-2) or (XXXI-3).

Examples of the solvent to be used for the condensation include water, methanol, ethanol, tert-butyl alcohol, tetrahydrofuran, diethyl ether, ethylene glycol dimethyl ether, dimethylformamide, dimethyl sulfoxide, benzene, toluene, xylene, dioxane, methylene chloride, chloroform, dichloroethane and acetonitrile.

Examples of the base to be used for the condensation include sodium hydroxide, sodium methoxide, sodium ethoxide, sodium hydride, potassium hydride, triethylamine, diisopropylethylamine and 1,8-diazabicyclo[5.4.0]undeca-7-ene.

The condensation generally proceeds at a temperature of from -20 °C to 150 °C and a temperature lower or higher than this temperature range may be selected on demand.

The condensation is generally carried out for 30 minutes to 2 days and the reaction period longer or shorter than the indicated period may be used as necessary.

After the condensation is carried out under the above-mentioned conditions or after removing the protecting group on demand, the Compound (XXXIV-1), (XXXIV-2) or (XXXIV-3) can be purified by a method known in the field of organic synthetic chemistry, such as solvent extraction, recrystallization, chromatography or a method using an ion exchange resin.

Examples of the solvent to be used for the condensation with formalin include water, methanol, ethanol, tert-butyl alcohol, tetrahydrofuran, diethyl ether, ethylene glycol dimethyl ether, dimethylformamide, dimethyl sulfoxide, benzene, toluene, xylene, dioxane, methylene chloride, chloroform, dichloroethane and acetonitrile.

Examples of the base to be used for the condensation include sodium hydroxide, sodium methoxide, sodium ethoxide, sodium hydride, potassium hydride, triethylamine, diisopropylethylamine and 1,8-diazabicyclo[5.4.0]undeca-7-ene.

The condensation generally proceeds at a temperature of from -20 °C to 150 °C and a temperature lower or higher than this temperature range may be selected on demand.

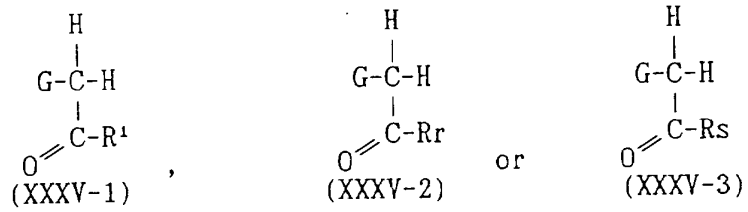
The condensation is generally carried out for 30 minutes to 2 days and the reaction period longer or shorter than the indicated period may be used as necessary.

After the condensation is carried out under the above-mentioned conditions or after removing the protecting group on demand, the Compound (XXXI-1), (XXXI-2) or (XXXI-3) can be purified by a method known in the field of organic synthetic chemistry, such as solvent extraction, recrystallization, chromatography or a method using an ion exchange resin.

(Method O)

Compound (XXXIV-1), Compound (XXXIV-2) and Compound (XXXIV-3) can be also produced by the following method.

A Compound (XVII) and a compound of the formula (XXXV)



(XXXV-1) , (XXXV-2) or (XXXV-3)

wherein R^1, Rr, Rs and G are as defined above [hereinafter referred to as Compound (XXXV-1), Compound (XXXV-2) or Compound (XXXV-3)] are condensed in the presence of a base to give a Compound (XXXIV-1), (XXXIV-2) or (XXXIV-3).

Examples of the solvent to be used for the condensation include water, methanol, ethanol, tert-butyl alcohol, tetrahydrofuran, diethyl ether, ethylene glycol dimethyl ether, dimethylformamide, dimethyl sulfoxide, benzene, toluene, xylene, dioxane, methylene chloride, chloroform, dichloroethane and acetonitrile.

Examples of the base to be used for the condensation include sodium hydroxide, sodium methoxide, sodium ethoxide, sodium hydride, potassium hydride, triethylamine, diisopropylethylamine and 1,8-diazabicyclo[5.4.0]undeca-7-ene.

The condensation generally proceeds at a temperature of from -20 °C to 150 °C and a temperature lower or higher than this temperature range may be selected on demand.

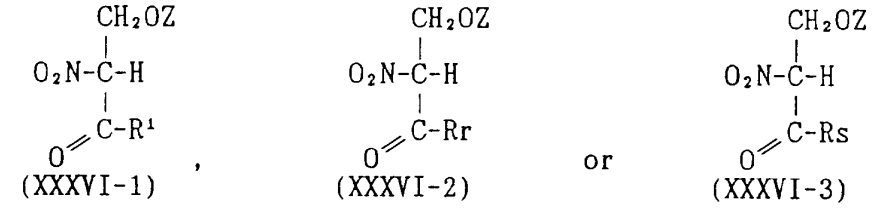
The condensation is generally carried out for 30 minutes to 2 days and the reaction period longer or shorter than the indicated period may be used as necessary.

After the condensation is carried out under the above-mentioned conditions or after removing the protecting group on demand, the Compound (XXXIV-1), (XXXIV-2) or (XXXIV-3) can be purified by a method known in the field of organic synthetic chemistry, such as solvent extraction, recrystallization, chromatography or a method using an ion exchange resin.

(Method P)

When W = nitro, Compound (XXXI-1), Compound (XXXI-2) and Compound (XXXI-3) can be also produced by the following method.

A Compound (XXV) and a Compound (XXVIII-1), (XXVIII-2) or (XXVIII-3) are condensed in the presence of a base to give a compound of the formula (XXXVI)



(XXXVI-1) , (XXXVI-2) or (XXXVI-3)

wherein R^1, Rr, Rs and Z are as defined above [hereinafter referred to as Compound (XXXVI-1), Compound (XXXVI-2) or Compound (XXXVI-3)]. The obtained compound is condensed with formal in in the presence of

a base and subjected to protection of hydroxyl as necessary to give a Compound (XXXI-1), (XXXI-2) or (XXXI-3).

Examples of the solvent to be used for the condensation include water, methanol, ethanol, tert-butyl alcohol, tetrahydrofuran, diethyl ether, ethylene glycol dimethyl ether, dimethylformamide, dimethyl sulfoxide, benzene, toluene, xylene, dioxane, methylene chloride, chloroform, dichloroethane and acetonitrile.

Examples of the base to be used for the condensation include sodium hydroxide, sodium methoxide, sodium ethoxide, sodium hydride, potassium hydride, triethylamine, diisopropylethylamine and 1,8-diazabicyclo[5.4.0]undeca-7-ene.

The condensation generally proceeds at a temperature of from -20 °C to 150 °C and a temperature lower or higher than this temperature range may be selected on demand.

The condensation is generally carried out for 30 minutes to 2 days and the reaction period longer or shorter than the indicated period may be used as necessary.

After the condensation is carried out under the above-mentioned conditions or after removing the protecting group on demand, the Compound (XXXVI-1), (XXXVI-2) or (XXXVI-3) can be purified by a method known in the field of organic synthetic chemistry, such as solvent extraction, recrystallization, chromatography or a method using an ion exchange resin.

Examples of the solvent to be used for the condensation with formal in include water, methanol, ethanol, tert-butyl alcohol, tetrahydrofuran, diethyl ether, ethylene glycol dimethyl ether, dimethylformamide, dimethyl sulfoxide, benzene, toluene, xylene, dioxane, methylene chloride, chloroform, dichloroethane and acetonitrile.

Examples of the base to be used for the condensation include sodium hydroxide, sodium methoxide, sodium ethoxide, sodium hydride, potassium hydride, triethylamine, diisopropylethylamine and 1,8-diazabicyclo[5.4.0]undeca-7-ene.

The condensation generally proceeds at a temperature of from -20 °C to 150 °C and a temperature lower or higher than this temperature range may be selected on demand.

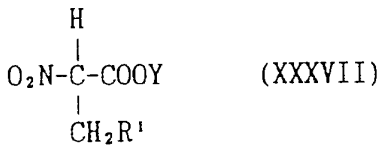
The condensation is generally carried out for 30 minutes to 2 days and the reaction period longer or shorter than the indicated period may be used as necessary.

After the condensation is carried out under the above-mentioned conditions or after removing the protecting group on demand, the Compound (XXXI-1), (XXXI-2) or (XXXI-3) can be purified by a method known in the field of organic synthetic chemistry, such as solvent extraction, recrystallization, chromatography or a method using an ion exchange resin.

(Method Q)

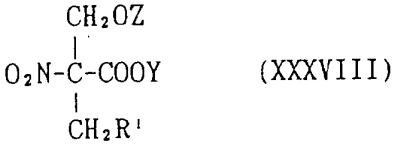
Compound (X) can be also produced by the following method.

A Compound (II) and a Compound (XXVII) (W = nitro) are condensed in the presence of a base to give a compound of the formula (XXXVII)



(XXXVII)

wherein R^1 and Y are as defined above [hereinafter referred to as Compound (XXXVII)]. The obtained compound is condensed with formal in in the presence of a base and subjected to protection of hydroxyl as necessary to give a compound of the formula (XXXVIII)



(XXXVIII)

wherein R^1, Y and Z are as defined above [hereinafter referred to as Compound (XXXVIII)] and the obtained compound is subjected to reduction of carboxyl with a suitable reducing agent and protection of hydroxyl as necessary to give a Compound (X).

Examples of the solvent to be used for the condensation include water, methanol, ethanol, tert-butyl alcohol, tetrahydrofuran, diethyl ether, ethylene glycol dimethyl ether, dimethylformamide, dimethyl sulfoxide, benzene, toluene, xylene, dioxane, methylene chloride, chloroform, dichloroethane and acetonitrile.

Examples of the base to be used for the condensation include sodium hydroxide, sodium methoxide, sodium ethoxide, sodium hydride, potassium hydride, triethylamine, diisopropylethylamine and 1,8-diazabicyclo[5.4.0]undeca-7-ene.

The condensation generally proceeds at a temperature of from -20 °C to 150 °C and a temperature lower or higher than this temperature range may be selected on demand.

The condensation is generally carried out for 30 minutes to 2 days and the reaction period longer or shorter than the indicated period may be used as necessary.

After the condensation is carried out under the above-mentioned conditions or after removing the protecting group on demand, the Compound (XXXVII) can be purified by a method known in the field of organic synthetic chemistry, such as solvent extraction, recrystallization, chromatography or a method using an ion exchange resin.

Examples of the solvent to be used for the condensation with formal in include water, methanol, ethanol, tert-butyl alcohol, tetrahydrofuran, diethyl ether, ethylene glycol dimethyl ether, dimethylformamide, dimethyl sulfoxide, benzene, toluene, xylene, dioxane, methylene chloride, chloroform, dichloroethane and acetonitrile.

Examples of the base to be used for the condensation include sodium hydroxide, sodium methoxide, sodium ethoxide, sodium hydride, potassium hydride, triethylamine, diisopropylethylamine and 1,8-diazabicyclo[5.4.0]undeca-7-ene.

The condensation generally proceeds at a temperature of from -20 °C to 150 °C and a temperature lower or higher than this temperature range may be selected on demand.

The condensation is generally carried out for 30 minutes to 2 days and the reaction period longer or shorter than the indicated period may be used as necessary.

After the condensation is carried out under the above-mentioned conditions or after removing the protecting group on demand, the Compound (XXXVIII) can be purified by a method known in the field of organic synthetic chemistry, such as solvent extraction, recrystallization, chromatography or a method using an ion exchange resin.

Examples of the reducing agent to be used for the reduction of carboxyl include metallic reducing reagent such as sodium borohydride, lithium borohydride or lithium aluminum hydride, and diborane.

Examples of the organic solvent to be used for the reduction of carboxyl include methanol, ethanol, tert-butyl alcohol, tetrahydrofuran, diethyl ether and ethylene glycol dimethyl ether.

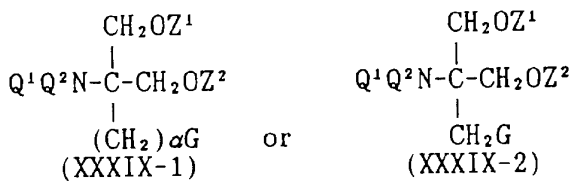
The reduction of carboxyl generally proceeds at a temperature of from -20 °C to 80 °C and a temperature lower or higher than this temperature range may be selected on demand.

The reduction of carboxyl is generally carried out for 30 minutes to 10 hours and the reaction period longer or shorter than the indicated period may be used as necessary.

After the reduction is carried out under the above-mentioned conditions or after removing the protecting group on demand, the Compound (X) can be purified by a method known in the field of organic synthetic chemistry, such as solvent extraction, recrystallization, chromatography or a method using an ion exchange resin.

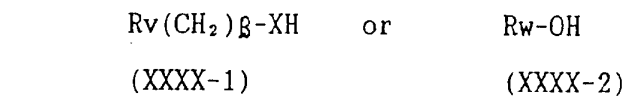
(Method R)

A compound of the formula (XXXIX)



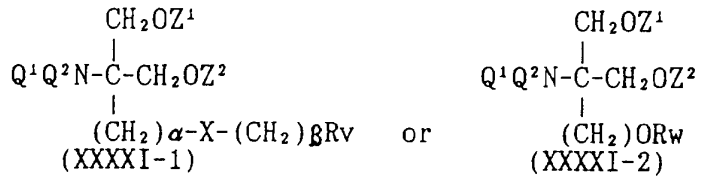
(XXXIX-1) or (XXXIX-2)

wherein Q^1, Q^2, Z^1, Z^2, G and α are as defined above [hereinafter referred to as Compound (XXXIX-1) or Compound (XXXIX-2)] and a compound of the formula (XXXX)



(XXXX-1) (XXXX-2)

wherein Rv, Rw, X and β are as defined above [hereinafter referred to as Compound (XXXX-1) or Compound (XXXX-2)] are condensed in the presence of a base to give a compound of the formula (XXXXI)



(XXXXI-1) (XXXXI-2)

wherein Rv, Rw, X, Q^1, Q^2, Z^1, Z^2, α and β are as defined above [hereinafter referred to as Compound (XXXXI-1) or Compound (XXXXI-2)] and the obtained compound is subjected to deprotection as necessary to give a compound (I-26) or (I-27).

Examples of the base to be used for the condensation include sodium hydroxide, sodium methoxide, sodium ethoxide, sodium hydride, potassium hydride, lithium diisopropylamide, butyl lithium, lithium hexamethyldisilazane, triethylamine, diisopropylethylamine and 1,8-diazabicyclo[5.4.0]undeca-7-ene.

Examples of the solvent to be used for the condensation include water, methanol, ethanol, tert-butyl alcohol, tetrahydrofuran, diethyl ether, ethylene glycol dimethyl ether, dimethylformamide, dimethyl sulfoxide, benzene, toluene, xylene, dioxane, methylene chloride, chloroform, dichloroethane and acetonitrile.

The condensation generally proceeds at a temperature of from -20 °C to 150 °C and a temperature lower or higher than this temperature range may be selected on demand.

The condensation is generally carried out for 30 minutes to 2 days and the reaction period longer or shorter than the indicated period may be used as necessary.

After the condensation is carried out under the above-mentioned conditions or after removing the protecting group on demand, the Compound (XXXXI-1) or (XXXXI-2) can be purified by a method known in the field of organic synthetic chemistry, such as solvent extraction, recrystallization, chromatography or a method using an ion exchange resin.

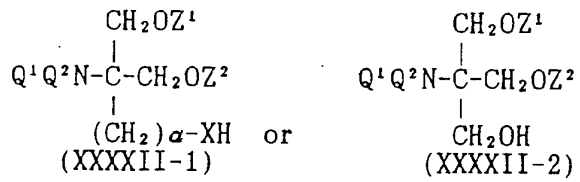
In the instant method, a compound wherein X is sulfinyl or sulfonyl can be obtained by oxidation of a compound wherein X is sulfur.

Accordingly, the instant method can be used for the synthesis of the compounds of the formulas (I-26) and (I-27). It is also applicable to the synthesis of the compounds (I-1), (I-2), (I-4), (I-5) and (I-7) through (I-11).

(Method S)

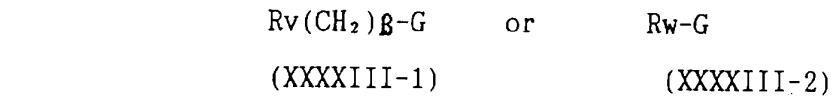
Compound (XXXXI-1) and Compound (XXXXI-2) can be also produced by the following method.

A compound of the formula (XXXXII)



(XXXXII-1) (XXXXII-2)

wherein Q^1, Q^2, Z^1, Z^2, X and α are as defined above [hereinafter referred to as Compound (XXXXII-1) or Compound (XXXXII-2)] and a compound of the formula (XXXXIII)



(XXXXIII-1) (XXXXIII-2)

wherein Rv, Rw, G and β are as defined above [hereinafter referred to as Compound (XXXXIII-1) or Compound (XXXXIII-2)] are condensed in the presence of a base and the obtained compound is subjected to deprotection on demand to give a Compound (XXXXI-1) or (XXXXI-2).

Examples of the base to be used for the condensation include sodium hydroxide, sodium methoxide, sodium ethoxide, sodium hydride, potassium hydride, lithium diisopropylamide, butyl lithium, lithium hexamethyldisilazane, triethylamine, diisopropylethylamine and 1,8-diazabicyclo[5.4.0]undeca-7-ene.

Examples of the solvent to be used for the condensation include water, methanol, ethanol, tert-butyl alcohol, tetrahydrofuran, diethyl ether, ethylene glycol dimethyl ether, dimethylformamide, dimethyl sulfoxide, benzene, toluene, xylene, dioxane, methylene chloride, chloroform, dichloroethane and acetonitrile.

The condensation generally proceeds at a temperature of from -20 °C to 150 °C and a temperature lower or higher than this temperature range may be selected on demand.

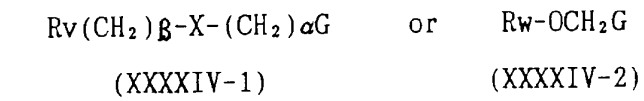
The condensation is generally carried out for 30 minutes to 2 days and the reaction period longer or shorter than the indicated period may be used as necessary.

After the condensation is carried out under the above-mentioned conditions or after removing the protecting group on demand, the Compound (XXXXI-1) or (XXXXI-2) can be purified by a method known in the field of organic synthetic chemistry, such as solvent extraction, recrystallization, chromatography or a method using an ion exchange resin.

(Method T)

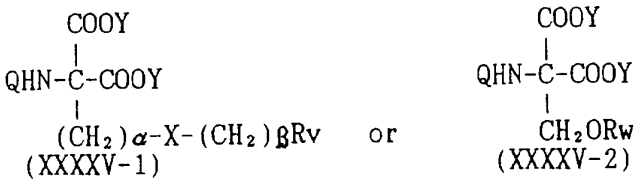
Compound (XXXXI-1) and Compound (XXXXI-2) can be also produced by the following method.

A compound of the formula (XXXXIV)



(XXXXIV-1) (XXXXIV-2)

wherein Rv, Rw, G, X, α and β are as defined above [hereinafter referred to as Compound (XXXXIV-1) or Compound (XXXXIV-2)] and a Compound (III) are condensed in the presence of a base to give a compound of the formula (XXXXV)



(XXXXV-1) (XXXXV-2)

wherein Rv, Rw, X, Q, Y, α and β are as defined above [hereinafter referred to as Compound (XXXXV-1) or Compound (XXXXV-2)]. The obtained compound is subjected to reduction with a suitable reducing agent and protection of hydroxyl and amino as necessary to give a compound (XXXXI-1) or (XXXXI-2).

Examples of the base to be used for the condensation include sodium hydroxide, sodium methoxide, sodium ethoxide, sodium hydride, potassium hydride, lithium diisopropylamide, butyl lithium, lithium hexamethyldisilazane, triethylamine, diisopropylethylamine and 1,8-diazabicyclo[5.4.0]undeca-7-ene.

Examples of the solvent to be used for the condensation include water, methanol, ethanol, tert-butyl alcohol, tetrahydrofuran, diethyl ether, ethylene glycol dimethyl ether, dimethylformamide, dimethyl sulfoxide, benzene, toluene, xylene, dioxane, methylene chloride, chloroform, dichloroethane and acetonitrile.

The condensation generally proceeds at a temperature of from -20 °C to 150 °C and a temperature lower or higher than this temperature range may be selected on demand.

The condensation is generally carried out for 30 minutes to 2 days and the reaction period longer or shorter than the indicated period may be used as necessary.

After the condensation is carried out under the above-mentioned conditions or after removing the protecting group on demand, the Compound (XXXXV-1) or (XXXXV-2) can be purified by a method known in the field of organic synthetic chemistry, such as solvent extraction, recrystallization, chromatography or a method using an ion exchange resin.

Examples of the reducing agent to be used for the reduction of carboxyl include metallic reducing reagent such as sodium borohydride, lithium borohydride or lithium aluminum hydride, and diborane.

Examples of the organic solvent to be used for the reduction of carboxyl include methanol, ethanol, tert-butyl alcohol, tetrahydrofuran, diethyl ether and ethylene glycol dimethyl ether.

The reduction of carboxyl generally proceeds at a temperature of from -20 °C to 80 °C and a temperature lower or higher than this temperature range may be selected on demand.

The reduction of carboxyl is generally carried out for 30 minutes to 10 hours and the reaction period longer or shorter than the indicated period may be used as necessary.

After the reduction is carried out under the above-mentioned conditions or after removing the protecting group on demand, the Compound (XXXXI-1) or (XXXXI-2) can be purified by a method known in the field of organic synthetic chemistry, such as solvent extraction, recrystallization,chromatography or a method using an ion exchange resin.

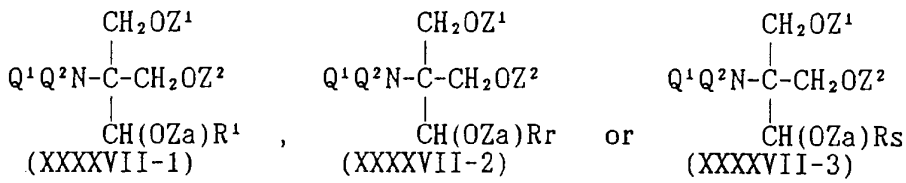
(Method U)

A Compound (XIV) is added with a compound of the formula (XXXXVI)

$$(R^1)nM \quad , \quad (Rr)nM \quad or \quad (Rs)nM$$

(XXXXVI-1) (XXXXVI-2) (XXXXVI-3)

wherein R^1, Rr, Rs, M and n are as defined above [hereinafter referred to as Compound (XXXXVI-1), Compound (XXXXVI-2) or Compound (XXXXVI-3)] and the mixture is subjected to protection of hydroxyl as necessary to give a compound of the formula (XXXXVII)



(XXXXVII-1) (XXXXVII-2) (XXXXVII-3)

wherein R^1, Rr, Rs, Q^1, Q^2, Z^1, Z^2 and Za are as defined above [hereinafter referred to as Compound (XXXXVII-1), Compound (XXXXVII-2) or Compound (XXXXVII-3)]. The obtained compound is subjected to deprotection on demand to give a Compound (XXII-1), (I-22) or (I-23).

Examples of the solvent to be used for the addition include tetrahydrofuran, diethyl ether, ethylene glycol dimethyl ether, dimethylformamide, dimethyl sulfoxide, benzene, toluene, xylene, dioxane, methylene chloride, chloroform, dichloroethane and acetonitrile.

The addition generally proceeds at a temperature of from -100 °C to 80 °C and a temperature lower or higher than this temperature range may be selected on demand.

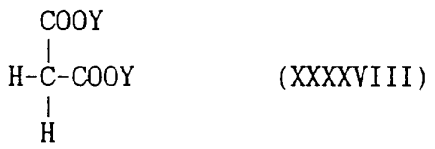
The addition is generally carried out for 30 minutes to 2 days and the reaction period longer or shorter than the indicated period may be used as necessary.

After the addition is carried out under the above-mentioned conditions or after removing the protecting group on demand, the Compound (XXXXVII-1), (XXXXVII-2) or (XXXXVII-3) can be purified by a method known in the field of organic synthetic chemistry, such as solvent extraction, recrystallization, chromatography or a method using an ion exchange resin.

Accordingly, the instant method can be used for the synthesis of the compounds of the formulas (I-21) through (I-23).

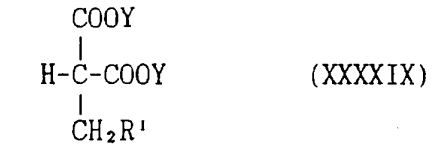
(Method V)

A compound of the formula (XXXXVIII)



(XXXXVIII)

wherein Y is as defined above [hereinafter referred to as Compound (XXXXVIII)] and a Compound (II) are condensed in the presence of a base to give a compound of the formula (XXXXIX)

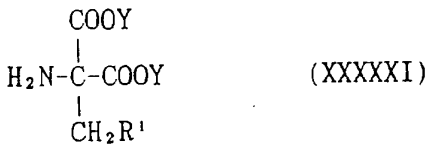


(XXXXIX)

wherein R^1 and Y are as defined above [hereinafter referred to as Compound (XXXXIX)] and the obtained compound is reacted with an amination agent of the formula (XXXXX)

H_2N-Le (XXXXX)

wherein Le means a leaving group such as 2,4-dinitrophenoxy, in the presence of a base to give a compound of the formula (XXXXXI)



(XXXXXI)

wherein R^1 and Y are as defined above [hereinafter referred to as Compound (XXXXXI)]. The obtained compound is subjected to reduction of carboxyl with a suitable reducing agent and deprotection as necessary to give a Compound (I-29).

Examples of the base to be used for the condensation include sodium hydroxide, sodium methoxide, sodium ethoxide, sodium hydride, potassium hydride, lithium diisopropylamide, butyl lithium, lithium hexamethyldisilazane, triethylamine, diisopropylethylamine and 1,8-diazabicyclo[5.4.0]undeca-7-ene.

Examples of the solvent to be used for the condensation include water, methanol, ethanol, tert-butyl alcohol, tetrahydrofuran, diethyl ether, ethylene glycol dimethyl ether, dimethylformamide, dimethyl sulfoxide, benzene, toluene, xylene, dioxane, methylene chloride, chloroform, dichloroethane and acetonitrile.

The condensation generally proceeds at a temperature of from -20 °C to 150 °C and a temperature lower or higher than this temperature range may be selected on demand.

The condensation is generally carried out for 30 minutes to 2 days and the reaction period longer or shorter than the indicated period may be used as necessary.

After the condensation is carried out under the above-mentioned conditions or after removing the protecting group on demand, the Compound (XXXXIX) can be purified by a method known in the field of organic synthetic chemistry, such as solvent extraction, recrystallization, chromatography or a method using an ion exchange resin.

Examples of the base to be used for the amination include sodium hydroxide, sodium methoxide, sodium ethoxide, sodium hydride, potassium hydride, lithium diisopropylamide, butyl lithium, lithium hexamethyldisilazane, triethylamine, diisopropylethylamine and 1,8-diazabicyclo[5.4.0]undeca-7-ene.

Examples of the solvent to be used for the amination include water, methanol, ethanol, tert-butyl alcohol, tetrahydrofuran, diethyl ether, ethylene glycol dimethyl ether, dimethylformamide, dimethyl sulfoxide, benzene, toluene, xylene, dioxane, methylene chloride, chloroform, dichloroethane and acetonitrile.

The amination generally proceeds at a temperature of from -20 °C to 150 °C and a temperature lower or higher than this temperature range may be selected on demand.

The amination is generally carried out for 30 minutes to 2 days and the reaction period longer or shorter than the indicated period may be used as necessary.

After the amination is carried out under the above-mentioned conditions or after removing the protecting group on demand, the Compound (XXXXXI) can be purified by a method known in the field of organic synthetic chemistry, such as solvent extraction, recrystallization, chromatography or a method using an ion exchange resin.

Examples of the reducing agent to be used for the reduction of carboxyl include metallic reducing reagent such as sodium borohydride, lithium borohydride or lithium aluminum hydride, and diborane.

Examples of the organic solvent to be used for the reduction of carboxyl include methanol, ethanol, tert-butyl alcohol, tetrahydrofuran, diethyl ether and ethylene glycol dimethyl ether.

The reduction of carboxyl generally proceeds at a temperature of from -20 °C to 80 °C and a temperature lower or higher than this temperature range may be selected on demand.

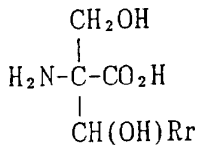
The reduction of carboxyl is generally carried out for 30 minutes to 10 hours and the reaction period longer or shorter than the indicated period may be used as necessary.

After the reduction is carried out under the above-mentioned conditions or after removing the protecting group on demand, the Compound (I-29) can be purified by a method known in the field of organic synthetic chemistry, such as solvent extraction, recrystallization, chromatography or a method using an ion exchange resin.

The instant method can be used for the synthesis of the compounds of the formulas (I-1) through (I-18), preferably for the synthesis of the compounds of the formulas (I-12) and (I-13).

(Method W)

Of the compounds of the formula (I) of the present invention, a compound wherein R is -CH(OH)Rr when it is a compound of the formula



(XXXXXII)

wherein Rr is as defined above [hereinafter referred to as Compound (XXXXXII)] or a derivative at carboxyl group thereof or a compound (XXXXXII) wherein the α-position of alkyl at Rr, which may have a double bond or carbonyl in the chain, is substituted by hydroxyl, can be produced by reduction, hydrogenation, ozonolysis or oxidation known per se, which may be used solely or in combination, of a corresponding lactone compound or a compound wherein amino or hydroxy of a Compound (XXXXXII) or lactone compound is protected by a protecting group.

Examples of the derivative at the carboxyl group of the Compound (XXXXXII) include ester (e.g. methyl ester, ethyl ester, benzyl ester, p-nitrobenzyl ester, trimethylsilyl ester, tert-butyldimethylsilyl ester), acid halide (e.g. acid chloride), acid anhydride and mixed acid anhydride.

A Compound (I) wherein Rr is an α-position hydroxyl-substituted alkyl is preferably produced by using the aforementioned lactone compound as a starting material.

Reduction proceeds in a solvent inert to the reaction and in the presence of a metal hydride complex at a temperature from under cooling to under refluxing. Examples of the metal hydride complex include

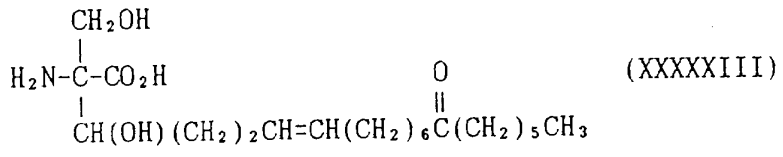
aluminum hydride, lithium aluminum hydride, lithium aluminum hydride-aluminum chloride, lithium trimethoxy aluminum hydride, sodium bis(2-methoxyethoxy)-aluminum hydride, diisobutyl aluminum hydride, sodium borohydride, sodium hydride, lithium borohydride and borohydride, and examples of the solvent include alcohol solvents such as methanol, ethanol, isopropanol and diethylene glycol, hydrocarbon solvents such as benzene, toluene and xylene, halohydrocarbon solvents such as methylene chloride, dichloroethane and chloroform, ether solvents such as diethyl ether, dipropyl ether, tetrahydrofuran and dioxane, dimethylformamide, and dimethyl sulfoxide, which may be used solely or in combination.

The reduction may be catalytic reduction using zinc-hydrochloric acid saturated acetic anhydride, copper-chromite catalyst, palladium-carbon, Raney nickel or rhenium oxide, or electroreduction. These reactions proceed in a manner similar to the reaction known per se.

The hydrogenation generally proceeds according to a method known per se using a conventional catalyst such as a palladium, nickel or platinum catalyst. In the reaction, a solvent inert to the reaction may be used and examples thereof are as mentioned above.

In the present invention, the compound obtained by the above-mentioned reactions can be used as a starting material.

Of the Compounds (XXXXXII), a compound wherein Rr is an α-position hydroxyl-substituted alkyl which may have a double bond or carbonyl in the chain and lactone compound thereof are known compounds reported in Japanese Patent Unexamined Publication Nos. 104087/1989 and 128347/1991 mentioned above and are produced according to the method described therein. Of the Compounds (XXXXXII), a compound wherein Rr is an alkyl which may have a double bond or carbonyl in the chain, such as heptadecyl, is produced, for example, by fermentation or by using a compound (XXXXXIII) produced by the fermentation and having the formula



(XXXXXIII)

as a starting meterial. Examples of the microorganism capable of producing the compound (XXXXXIII) include those belonging to *Ascomycetes* or *Fungi Imperfecti*, particularly the genera *Isaria* and *Mycelia* belonging to the *Fungi Imperfecti* and the genus *Myriococcum* (the genus *Thielavia*) belonging to *Ascomycetes*, which are respectively deposited at American Type Culture Collection as *Isaria sinclairii* ATCC No. 24400, *Myriococcum albomyces* ATCC No. 16425 and *Mycelia sterilia* ATCC No. 20349. Also, *Myriococcum albomyces* ATCC No. 16425 has been deposited at the Institute of Fermentation, Osaka as IFO32292.

Compound (XXXXXIII) can be produced, for example, by a mutant strain obtained by mutating the above-mentioned strain by a conventional artificial mutating method using ultraviolet rays, high frequency radiation, drug or the like.

The Compound (XXXXXIII)-producing cell may be cultured in various culture media containing conventional nutrition sources for mold. For example, a medium may contain glucose, starch, glycerin, sugar syrup, dextrin, molasses, maltose, xylose or the like as a carbon source and an inorganic or organic nitrogen compound such as corn steep liquor, peptone, yeast extract, potato brew, meat broth, soybean powder, wheat germ, potassium nitrate, sodium nitrate, ammonium sulfate, casein, gluten meal, cottonseed powder or feather powder as a nitrogen source. Besides these, there may be contained additives conventionally used for culture such as conventional inorganic salt, organic or inorganic substance which promotes the growth of cell and enhances production of the Compound (XXXXXIII), and antifoaming agent.

While the culture method is subject to no particular limitation, aerobic submerged culture is desirable. The temperature appropriate for the culture is 20-35 °C, preferably 25-30 °C for the microorganisms belonging to the genus *Isaria* and 30-50 °C, preferably 35-45 °C for the microorganisms belonging to the genus *Myriococcum* or *Mycelia*.

The Compound (XXXXXIII) produced in the culture medium is isolated therefrom by conventional steps such as extraction and adsorption which may be used in combination as necessary. For example, in the case of a microorganism belonging to the genus *Isaria* such as *Isaria sinclairii*, the Compound (XXXXXIII) is taken out from the culture by filtering off the insoluble matters such as cells from the culture, isolation by centrifugation, passing the culture filtrate through Amberlite XAD-2 (trade mark) and adsorbing Compound

(XXXXXIII). The Compound (XXXXXIII) thus obtained is eluted with, for example, methanol and the eluate is fractionated by reversed phase chromatography, whereby a highly purified product of Compound (XXXXXIII) can be obtained. In the case of a microorganism belonging to the genus *Myriococcum* or the genus *Mycelia*, such as *Myriococcum albomyces*, *Mycelia sterilia* or the like, cells are separated from the culture by filtration, centrifugation and the like and the culture filtrate is treated in the same manner as in the case of the microorganisms belonging to the genus *Isaria*. The Compound (XXXXXIII) is extracted from the separated cells by the use of methanol and the extract is treated with Amberlite XAD-2 in the same manner as with the filtrate above and purified by chromatography and recrystallization.

The 2-amino-1,3-propanediol compounds, isomers thereof and salts thereof of the present invention show superior immunosuppressive effect and are useful as a suppressant of rejection in organ or bone marrow transplantation in mammals inclusive of human, cow, horse, dog, mouse, rat etc., an agent for the prevention and treatment of autoimmune diseases such as rheumatoid arthritis, atopic eczema (atopic dermatitis), Behçet's disease, uvea diseases, systemic lupus erythematosus, Sjögren's syndrome, polysclerosis, myasthenia gravis, diabetes type I, endocrine eye disorders, primary biliary cirrhosis, Crohn's disease, glomerulonephritis, sarcoidosis, psoriasis, pemphigus, aplastic anemia, idiopathic thrombocytopenic purpura, allergy, polyarteritis nodosa, progressive systemic sclerosis, mixed connective-tissue disease, aortitis syndrome, polymyositis, dermatomyositis, Wegener's granulomatosis, ulcerative colitis, active chronic hepatitis, autoimmune hemolytic anemia, Evans syndrome, bronchial asthma, pollinosis and so on, and a reagent for use in medicine and pharmacy. Also, the compounds protected with a protecting group are useful as intermediates for the synthesis of the compounds having superior pharmacological actions as recited above.

When these compounds are used as pharmaceuticals, an effective amount thereof is generally admixed with carrier, excipient, diluent and so on and formulated into powder, capsule, tablet, injection or the like for the administration to patients. A lyophilized preparation may be produced by a method known per se.

While the dose of these compounds varies depending on disease, symptom, body weight, sex, age and so on, they are administered, for example, to an adult daily by 0.01-10 mg (potency) in a single to several times divided doses when suppressing rejection in kidney transplantation.

Moreover, the compounds of the present invention can be used in combination with other immunosuppressant such as cyclosporin, azathioprine, steroids or FK-506 (EP-A184162).

The present invention is hereinafter explained in detail by illustrating examples, to which the present invention is not limited.

Example 1

(1) Diethyl 2-acetamidomalonate (3.0 g) was dissolved in 50 ml of dry ethanol and 1.13 g of sodium ethoxide was added thereto. A solution of 4.7 g of tetradecyl bromide in 20 ml of ethanol was added to the mixed solution while stirring at room temperature. The inside of the reaction vessel was displaced with nitrogen and the mixture was refluxed for about 15 hours. Then, the mixture was neutralized with a 1N aqueous hydrochloric acid solution and concentrated. The concentrate was purified by silica gel column chromatography to give 3.5 g of diethyl 2-acetamido-2-tetradecylmalonate.

melting point = 58.5-60.5 °C

IR(KBr): 3280, 2970, 2930, 2860, 1750, 1655, 1525, 1480, 1220, 1030 cm^{-1}

(2) Diethyl 2-acetamido-2-tetradecylmalonate (3.40 g) was dissolved in 200 ml of dry tetrahydrofuran. The reaction vessel was equipped with a calcium chloride tube and 1.58 g of lithium aluminum hydride was added thereto in an ice water bath, followed by stirring. After stirring the mixture at room temperature for 30 minutes, 3.0 ml of water was added thereto to stop the reaction. The reaction mixture was concentrated under reduced pressure and 100 ml of acetic anhydride and 80 ml of pyridine were added to the concentrate. The mixture was stirred at room temperature overnight. The reaction mixture was poured into ice water to make the total amount 1600 ml and extracted three times with 500 ml of ethyl acetate. The ethyl acetate layers were combined and washed with a 1N aqueous hydrochloric acid solution, a saturated aqueous sodium hydrogencarbonate solution and a saturated aqueous sodium chloride solution in order. The mixture was dehydrated over anhydrous magnesium sulfate and concentrated. The concentrate was purified by silica gel column chromatography to give 1.35 g of 2-acetamido-1,3-diacetoxy-2-tetradecylpropane.

melting point = 84.0-85.5 °C

IR(KBr): 3310, 2950, 2920, 2840, 1750, 1655, 1550, 1470, 1375, 1255, 1230, 1035, 900 cm^{-1}

Example 2

2-Acetamido-1,3-diacetoxy-2-tetradecylpropane (1.25 g) was dissolved in 100 ml of methanol and 19.4 ml of a 1N aqueous sodium hydroxide solution was added thereto. The mixture was refluxed under heating for 6 hours. The mixture was neutralized with a 1N aqueous hydrochloric acid solution and concentrated under reduced pressure. The concentrate was washed with water and ethyl acetate:hexane = 1:1 in order to give 791 mg of 2-amino-2-tetradecyl-1,3-propanediol hydrochloride.
melting point = 96.5-98.5 °C
Rf: 0.55 (chloroform:methanol:water = 65:35:5)
IR(KBr): 3520, 3450, 3300, 3050, 2920, 2850, 1630, 1530, 1470, 1290, 1070, 1050 cm^{-1}

Example 3

(1) Diethyl 2-acetamidomalonate (3.0 g) was dissolved in 50 ml of dry ethanol and 1.13 g of sodium ethoxide was added thereto. A solution of 5.5 g of hexadecyl bromide in 20 ml of ethanol was added thereto at room temprature with stirring. The inside of the reaction vessel was displaced with nitrogen and the mixture was refluxed for about 15 hours. The mixture was neutralized with a 1N aqueous hydrochloric acid solution and concentrated. The concentrate was purified by silica gel column chromatography to give 4.37 g of diethyl 2-acetamido-2-hexadecylmalonate.
melting point = 65.0-67.0 °C
IR(KBr): 3300, 2920, 2850, 1745, 1650, 1515, 1210, 1020 cm^{-1}
(2) Diethyl 2-acetamido-2-hexadecylmalonate (4.30 g) was dissolved in 200 ml of dry tetrahydrofuran and the reaction vessel was equipped with a calcium chloride tube. Thereto was added 1.90 g of lithium aluminum hydride in an ice water bath and the mixture was stirred. After stirring the mixture at room temperature for 30 minutes, 3.6 ml of water was added thereto to stop the reaction. The reaction mixture was concentrated under reduced pressure and 100 ml of acetic anhydride and 80 ml of pyridine were added to the residue. The mixture was stirred at room temperature overnight. The reaction mixture was poured into ice water to make the total amount 1600 ml and extracted three times with 500 ml of ethyl acetate. The ethyl acetate layers were combined and washed with a 1N aqueous hydrochloric acid solution, a saturated aqueous sodium hydrogencarbonate solution and a saturated aqueous sodium chloride solution in order. The resultant mixture was dehydrated over anhydrous magnesium sulfate and concentrated. The concentrate was purified by silica gel column chromatography to give 1.83 g of 2-acetamido-1,3-diacetoxy-2-hexadecylpropane.
melting point = 84-86 °C
IR(KBr): 3300, 2920, 2850, 1740, 1655, 1560, 1390, 1270, 1240, 1055 cm^{-1}

Example 4

2-Acetamido-1,3-diacetoxy-2-hexadecylpropane (1.75 g) was dissolved in 100 ml of methanol and 23.8 ml of a 1N aqueous sodium hydroxide solution was added thereto. The mixture was refluxed under heating for 6 hours. The mixture was neutralized with a 1N aqueous hydrochloric acid solution and concentrated under reduced pressure. The concentrate was washed with water and ethyl acetate:hexane = 1:1 in order to give 892 mg of 2-amino-2-hexadecyl-1,3-propanediol hydrochloride.
melting point = 100.5-104.0 °C
Rf: 0.55 (chloroform:methanol:water = 65:35:5)
IR(KBr): 3350, 2920, 2850, 1590, 1470, 1050 cm^{-1}

Example 5

(1) Diethyl 2-acetamidomalonate (5.0 g) was dissolved in 64 ml of dry ethanol and 1.71 g of sodium ethoxide was added thereto. A solution of 8.4 g of octadecyl bromide in 20 ml of dry ethanol was added thereto while stirring at room temperature. The inside of the reaction vessel was displaced with nitrogen and the mixture was refluxed for about 15 hours. The mixture was neutralized with a 1N aqueous hydrochloric acid solution and concentrated. The concentrate was purified by silica gel column chromatography to give 6.4 g of diethyl 2-acetamido-2-octadecylmalonate.
melting point = 70-71 °C
^{1}H-NMR (200MHz, $CDCl_3$) δ:
6.77 (1H, br.s, -NH-), 4.24 (4H, q, J = 7.16Hz, $-OCH_2-$ × 2), 2.35-2.26

(2H, m, C_3-Ha, Hb), 2.03 (3H, s, CH_3CONH-), 1.25 (38H, m, O-CH_2 - CH_3 × 2, CH_2 × 16), 0.88 (3H, t, J = 6.47Hz, CH_3)

IR: 3260, 2910, 2850, 1745, 1640, 1515, 1210, 1020 cm^{-1}

(2) Diethyl 2-acetamido-2-octadecylmalonate (3.0 g) was dissolved in dry tetrahydrofuran and the reaction vessel was equipped with a calcium chloride tube. In an ice water bath, 1.2 g of lithium aluminum hydride was added thereto and the mixture was stirred. Then, the mixture was stirred at room temperature for 30 minutes and 2.31 g of water was added thereto to stop the reaction. The reaction mixture was concentrated under reduced pressure and 130 ml of acetic anhydride and 120 ml of pyridine were added to the concentrate. The mixture was stirred at room temperature overnight. The resultant mixture was poured into ice water to make the total amount 2200 ml and extracted three times with 700 ml of ethyl acetate. The ethyl acetate layers were combined and washed with a 1N aqueous hydrochloric acid solution, an aqueous sodium hydrogencarbonate solution and an aqueous sodium chloride solution in order. The mixture was dehydrated over anhydrous magnesium sulfate and concentrated. The concentrate was purified by silica gel column chromatography to give 1.7 g of 2-acetamido-1,3-diacetoxy-2-octadecylpropane.

melting point = 90-91 °C

^{1}H-NMR (200MHz, $CDCl_3$) δ:

5.64 (1H, br.s, -NH-), 4.30 (4H, s, -CH_2O- × 2), 2.09 (6H, s, $OCOCH_3$ × 2), 1.97 (3H, s, $NHCOCH_3$), 1.25 (34H, br.s, CH_2 × 17), 0.88 (3H, t, J = 6.47Hz, CH_3)

IR: 3280, 2920, 2850, 1750, 1735, 1645, 1565, 1385, 1270, 1240, 1045 cm^{-1}

Example 6

2-Acetamido-1,3-diacetoxy-2-octadecylpropane (1.00 g) was dissolved in 26 ml of methanol and 6.4 ml of a 1N aqueous sodium hydroxide solution was added thereto. The mixture was refluxed under heating for 6 hours. The mixture was neutralized with a 1N aqueous hydrochloric acid solution and concentrated under reduced pressure. The concentrate was washed with water and ethyl acetate:hexane = 1:1 in order to give 639 mg of 2-amino-2-octadecyl-1,3-propanediol hydrochloride.

melting point = 108.5-109.5 °C

^{1}H-NMR (200MHz, CD_3 OD) δ:

3.64 (2H, d, J = 11.48Hz, -CHa-O-), 3.57 (2H, d, J = 11.47Hz, -CHb-O-), 1.28 (34H, br.s, CH_2 × 17), 0.90 (3H, t, J = 6.35Hz, -CH_3)

IR: 3275, 2900, 2840, 1630, 1600, 1530, 1465, 1290, 1050 cm^{-1}

Example 7

2-Amino-2-octadecyl-1,3-propanediol hydrochloride (100 mg) as obtained in Example 5 was dissolved in 200 ml of methanol and the mixture was dropwise added to 50 ml of Diaion WA-10 (trade mark, anion exchange resin). The solvent of the eluate was distilled away to give 64 mg of 2-amino-2-octadecyl-1,3-propanediol.

melting point = 76.0-80.0 °C

IR: 3290, 3175, 2910, 2850, 1590, 1580, 1480, 1065, 1050, 1000 cm^{-1}

Example 8

(1) Diethyl 2-acetamidomalonate (3.0 g) was dissolved in 50 ml of dry ethanol and 1.3 g of sodium ethoxide was added thereto. A solution of 6.5 g of docosyl bromide in 20 ml of dry ethanol was added thereto while stirring at room temperature. The inside of the reaction vessel was displaced with nitrogen and the mixture was refluxed for about 15 hours. The mixture was neutralized with a 1N aqueous hydrochloric acid solution and concentrated. The concentrate was purified by silica gel column chromatography to give 4.2 g of diethyl 2-acetamido-2-docosylmalonate.

melting point = 79-80 °C

IR(KBr): 3300, 2925, 2860, 1750, 1655, 1520, 1220 cm^{-1}

(2) Diethyl 2-acetamido-2-docosylmalonate (4.15 g) was dissolved in dry tetrahydrofuran and the reaction vessel was eqipped with a calcium chloride tube. In an ice water bath, 1.4 g of lithium aluminum hydride was added thereto and the mixture was stirred. The mixture was stirred at room temperature for 30

minutes and 2.31 g of water was added thereto to stop the reaction. The reaction mixture was concentrated under reduced pressure and 130 ml of acetic anhydride and 120 ml of pyridine were added thereto. The mixture was stirred at room temperature overnight. The reaction mixture was poured into ice water to make the total amount 2200 ml and extracted three times with 700 ml of ethyl acetate. The ethyl acetate layers were combined and washed with a 1N aqueous hydrochloric acid solution, a saturated aqueous sodium hydrogencarbonate solution and a saturated aqueous sodium chloride solution in order. The mixture was dehydrated over anhydrous magnesium sulfate and concentrated. The concentrate was purified by silica gel column chromatography to give 1.8 g of 2-acetamido-1,3-diacetoxy-2-docosylpropane.

melting point = 94-95 °C

IR(KBr): 3280, 2920, 2850, 1750, 1655, 1520, 1480, 1220 cm^{-1}

Example 9

2-Acetamido-1,3-diacetoxy-2-docosylpropane (1.5 g) was dissolved in 40 ml of methanol and 9.6 ml of a 1N aqueous sodium hydroxide solution was added thereto. The mixture was refluxed under heating for 6 hours. The mixture was neutralized with a 1N aqueous hydrochloric acid solution and concentrated under reduced pressure. The concentrate was washed with water and ethyl acetate:hexane = 1:1 in order to give 846 mg of 2-amino-2-docosyl-1,3-propanediol hydrochloride.

melting point = 109.0-110.5 °C

Rf: 0.55 (chloroform:methanol:water = 65:35:5)

IR(KBr): 3500, 3450, 3290, 2920, 2850, 1640, 1530, 1470, 1060 cm^{-1}

Example 10

(1) Diethyl 2-acetamidomalonate (3.0 g) was dissolved in 50 ml of dry ethanol and 1.3 g of sodium ethoxide was added thereto. A solution of 6.0 g of icosyl bromide in 20 ml of dry ethanol was added thereto while stirring at room temperature. The inside of the reaction vessel was displaced with nitrogen and the mixture was refluxed for about 15 hours. The mixture was neutralized with a 1N aqueous hydrochloric acid solution and concentrated. The concentrate was purified by silica gel column chromatography to give 4 g of diethyl 2-acetamido-2-icosylmalonate.

melting point = 76.5-77.5 °C

IR(KBr): 2920, 2850, 1750, 1655, 1520, 1480, 1220 cm^{-1}

(2) Diethyl 2-acetamido-2-icosylmalonate (3.7 g) was dissolved in dry tetrahydrofuran. The reaction vessel was eqipped with a calcium chloride tube and the mixture was cooled to 0 °C. Lithium aluminum hydride (1.4 g) was added thereto and the mixture was stirred. The mixture was stirred at room temperature for 30 minutes and 2.31 g of water was added thereto to stop the reaction. The reaction mixture was concentrated under reduced pressure and 130 ml of acetic anhydride and 120 ml of pyridine were added thereto. The mixture was stirred at room temperature overnight. The reaction mixture was poured into ice water to make the total amount 2200 ml and extracted three times with 700 ml of ethyl acetate. The ethyl acetate layers were combined and washed with a 1N aqueous hydrochloric acid solution, a saturated aqueous sodium hydrogencarbonate solution and a saturated aqueous sodium chloride solution in order. The mixture was dehydrated over anhydrous magnesium sulfate and concentrated. The concentrate was purified by silica gel column chromatography to give 1.7 g of 2-acetamido-1,3-diacetoxy-2-icosylpropane.

melting point = 93-94 °C

IR(KBr): 3280, 2920, 2855, 1775, 1755, 1650, 1565, 1480, 1385, 1270, 1245, 1045 cm^{-1}

Example 11

2-Acetamido-1,3-diacetoxy-2-icosylpropane (1.5 g) was dissolved in 40 ml of methanol and 9.6 ml of a 1N aqueous sodium hydroxide solution was added thereto. The mixture was refluxed under heating for 6 hours. The mixture was neutralized with a 1N aqueous hydrochloric acid solution and the reaction mixture was concentrated under reduced pressure. The concentrate was washed with water and ethyl acetate:hexane = 1:1 in order to give 817 mg of 2-amino-2-icosyl-1,3-propanediol hydrochloride.

melting point = 109.5-111.0 °C

Rf: 0.55 (chloroform:methanol:water = 65:35:5)

IR(KBr): 3300, 2910, 2850, 1640, 1600, 1480, 1065, 1050 cm^{-1}

Example 12

(1) Diethyl 2-acetamidomalonate (15 g) was dissolved in 200 ml of dry ethanol and 5.6 g of sodium ethoxide was added thereto. To the reaction mixture, 22 g of 9-octadecenyl chloride was added while stirring at room temperature. The inside of the reaction vessel was displaced with nitrogen and the mixture was refluxed for about 15 hours. The mixture was neutralized with ethanol-concentrated hydrochloric acid (11:1) and concentrated. The concentrate was purified by silica gel column chromatography to give 1.3 g of diethyl 2-acetamido-2-(9-octadecenyl)malonate as a colorless, oily and viscous substance.

^{1}H-NMR (200MHz, $CDCl_3$) δ:

6.765 (1H, br.s, -NH-), 5.340-5.310 (2H, m, CH=CH), 4.240 (4H, q, J=7.4Hz, $-OCH_2-$ × 2), 2.032 (3H, s, CH_3 CON), 1.990 (4H, m, $CH_2CH=$ × 2), 1.252 (26H, m, CH_2 × 13), 1.252 (6H, t, J=7.2Hz, OCH_2 $-CH_3$ × 2), 0.880 (3H, t, J=6.5Hz, CH_3)

(2) Diethyl 2-acetamido-2-(9-octadecenyl)malonate (1.3 g) was dissolved in 30 ml of dry tetrahydrofuran and 450 mg of lithium aluminum hydride was added thereto under ice-cooling. The inside of the reaction vessel was displaced with dry nitrogen and the mixture was stirred. Then, the mixture was stirred at room temperature for 2 hours and 1 ml of water was added thereto to stop the reaction. The reaction mixture was concentrated under reduced pressure and 10 ml of acetic anhydride and 5 ml of pyridine were added thereto. The mixture was stirred at room temperature overnight. Water was added to the reaction mixture under ice-cooling to make the total amount about 100 ml and the mixture was extracted twice with 50 ml of ethyl acetate. The ethyl acetate layers were combined and washed with a 1N aqueous hydrochloric acid solution, a saturated aqueous sodium hydrogencarbonate solution and a saturated aqueous sodium chloride solution in order. The mixture was dehydrated over anhydrous magnesium sulfate and concentrated to give 430 mg of 2-acetamido-1,3-diacetoxy-2-(9-octadecenyl)-propane as a coloreless, oily and viscous substance.

IR($CHCl_3$): 3460, 3420, 3010, 2940, 2860, 1750, 1690, 1520, 1475, 1390, 1380, 1240(br), 1045, 990 cm^{-1}

Example 13

2-Acetamido-1,3-diacetoxy-2-(9-octadecenyl)propane (332 mg) was dissolved in 30 ml of methanol and 7.8 ml of a 1N aqueous sodium hydroxide solution was added thereto. The mixture was refluxed under heating overnight. The mixture was neutralized with methanol-concentrated hydrochloric acid (11:1) and concentrated under reduced pressure. The concentrate was dissolved in methanol-water (1:1) and subjected to reversed phase column chromatography [packing: Sep-Pak(C_{18})]. After washing, the mixture was eluted with methanol. The eluate was concentrated to give 209 mg of 2-amino-2-(9-octadecenyl)-1,3-propanediol hydrochloride as a colorless, oily and viscous substance.

^{1}H-NMR (200MHz, CD_3 OD) δ:

5.385-5.315 (2H, m, CH=CH), 3.616 (2H, d, J=11.4Hz, OCH_{2a} × 2), 3.548 (2H, d, J=11.4Hz, OCH_{2b} × 2), 2.071-1.957 (4H, m, $\underline{CH_2}CH=$ × 2), 1.665-1.580 (2H, m, CCH_2), 1.39-1.28 (24H, m, CH_2 × 12), 0.896 (3H, t, J=6Hz, CH_3)

IR: 3300(br), 2920, 2850, 1600, 1500, 1465, 1050, 965 cm^{-1}

Example 14

(1) Sodium (0.23 g) was added to 15 ml of absolute ethanol and the mixture was stirred at room temperature for 30 minutes in a nitrogen flow to give a 10 mmol solution of sodium ethoxide in ethanol. To this solution, 1.98 g of diethyl 2-acetamidomalonate was added and the mixture was heated at 50 °C for 30 minutes in a stream of nitrogen. 3-Phenylpropyl bromide was added thereto at room temperature and the mixture was refluxed under heating for 24 hours. The mixture was neutralized with dilute hydrochloric acid and ethanol was distilled away. The resultant residue was extracted with ethyl acetate. The ethyl acetate layer was washed with water and dried over anhydrous magnesium sulfate. The solvent was distilled away and the residue was purified by silica gel column chromatography (ethyl acetate:hexane = 1:4 - 1:1) and recrystallized from diisopropyl ether-hexane to give 800 mg of diethyl 2-acetamido-2-(3-phenylpropyl)malonate as white crystals.

melting point = 76-77 °C

Rf: 0.58 (ethyl acetate:hexane = 1:1)

^{1}H-NMR (90MHz, $CDCl_3$) δ:

1.22 (3H, t, J = 7Hz), 1.10-1.56 (4H, m), 2.02 (3H, s), 2.28-2.75 (2H, m), 4.21 (4H, q, J = 7Hz), 6.75 (1H, br.s), 7.02-7.42 (5H, m)

IRν : 3259, 2980, 2863, 1738, 1648 cm^{-1}

MS(EI): 335(M^+)

(2) A solution (50 ml) of 1.0 g of the above-mentioned compound and 136 mg of lithium borohydride in tetrahydrofuran was refluxed under heating for 1 hour in a nitrogen flow. The reaction mixture was poured into 100 ml of ice water and extracted with ethyl acetate. The extract was washed and dried, and the solvent was distilled away. The residue was purified by silica gel column chromatography (methanol:chloroform = 1:20) to give 720 mg of 2-acetamido-2-(3-phenylpropyl)-1,3-propanediol as a colorless, oily substance.

Rf: 0.30 (ethyl acetate)

^{1}H-NMR (90MHz, $CDCl_3$) δ:

1.47-1.89 (4H, m), 2.00 (3H, s), 2.44-2.84 (2H, m), 3.73 (4H, dd, J = 7Hz, 15Hz), 3.37-4.17 (2H, m), 5.51-5.97 (1H, m), 7.00-7.45 (5H, m)

IRν : 3294, 2938, 1652 cm^{-1}

MS(EI): 251(M^+)

Example 15

2-Acetamido-2-(3-phenylpropyl)-1,3-propanediol (600 mg) was dissolved in 25 ml of methanol and 11.9 ml of a 1N, aqueous sodium hydroxide solution was added thereto. The mixture was refluxed under heating for 6 hours. The mixture was poured into 30 ml of ice water and neutralized with dilute hydrochloric acid. The solvent was distilled away. Chloroform was added to the residue for extraction and the chloroform layer was washed and dried. The solvent was distilled away and the residue was purified by column chromatography (chloroform:methanol = 9:1 - 4:1) to give 250 mg of 2-amino-2-(3-phenylpropyl)-1,3-propanediol as a pale yellow, oily substance.

Rf: 0.22 (methanol:chloroform = 1:4)

^{1}H-NMR (90MHz, $CDCl_3$) δ:

1.11-1.98 (4H, m), 2.43-2.75 (2H, m), 3.15-4.03 (4H, m), 3.62 (4H, br.s), 7.19 (5H, s)

IRν : 3347, 3023, 2937, 1583 cm^{-1}

MS(EI): 209(M + 1)

Example 16

(1) A solution of 5.42 g of cinnamyl bromide, 5.43 g of diethyl 2-acetamidomalonate and 1.87 g of sodium ethoxide in 70 ml of ethanol was refluxed under heating for 2 hours under a nitrogen atmosphere. The mixture was poured into 200 ml of ice water and extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate and the solvent was distilled away. The residue was purified by silica gel chromatography (ethyl acetate:hexane = 1:10 - 1:3) to give 2.68 g of diethyl 2-acetamido-2-(3-phenyl-2-propenyl)malonate as white crystals.

melting point = 70-75 °C

Rf: 0.38 (ethyl acetate:hexane = 1:5)

^{1}H-NMR ($CDCl_3$/TMS) δ:

1.31 (6H, t, J = 7.5Hz), 1.56 (2H, s), 2.09 (3H, s), 4.28 (4H, q, J = 7.5Hz), 6.30-6.80 (2H, m), 7.27 (5H, s)

IR(KBr): 3280, 2990, 1740, 1640 cm^{-1}

(2) A solution (80 ml) of 2.50 g of the above-mentioned compound and 1.63 g of lithium borohydride in tetrahydrofuran was refluxed under heating for 2 hours under a nitrogen atmosphere. After the reaction, the solvent was distilled away and the residue was evaporated to dryness. Acetic anhydride (14 ml) and 50 ml of pyridine were added to the residue and the mixture was stirred at room temperature overnight. The mixture was poured into ice water and extracted with ethyl acetate. The extract was washed with 2N hydrochloric acid, a saturated aqueous sodium bicarbonate solution and saturated brine in order and dried. The solvent was distilled away and the residue was purified by silica gel column chromatography (ethyl acetate:hexane = 3:1) to give 200 mg of 2-acetamido-1,3-diacetoxy-2-(3-phenyl-2-propenyl)-

propane as white crystals.
melting point = 88-90 °C
Rf: 0.70 (ethyl acetate)
^{1}H-NMR ($CDCl_3$/TMS) δ:
1.96 (3H, s), 2.07 (6H, s), 2.82 (2H, d, J = 7.5Hz), 4.36 (4H, s)
IR(KBr): 3311, 3084, 1750, 1655, 1560 cm^{-1}
MS(EI): 333(M^+)

elemental analysis	calculated	C 64.85,	H 6.95,	N 4.20
	found	C 64.85,	H 6.88,	N 4.15

Example 17

2-Acetamido-1,3-diacetoxy-2-(3-phenyl-2-propenyl)propane (170 mg) was dissolved in 6 ml of methanol and 6 ml of a 1N aqueous sodium hydroxide solution was added thereto. The mixture was refluxed under heating for 3 hours. After the reaction, the solvent was distilled away and the residue was purified by silica gel column chromatography (methanol: chloroform = 1:30 - 1:6) to give 70 mg of 2-amino-2-(3-phenyl-2-propenyl)-1,3-propanediol as pale brown crystals.
Rf: 0.14 (methanol:chloroform = 1:10)
IR(KBr): 3367, 2935, 1556 cm^{-1}

Example 18

(1) 1-Phenyl-1-propyn-3-ol (5 g), 5.1 g of tosyl chloride and 20 ml of pyridine were stirred at room temperature for 1 hour. The reaction mixture was poured into 100 ml of ice water and extracted with ethyl acetate. The oil layer was washed with 1N hydrochloric acid and saturated brine and dried over anhydrous sodium sulfate. The solvent was distilled away. The residue was purified by silica gel column chromatography (ethyl acetate:hexane = 1:5) to give 2.54 g of 3-phenyl-2-propynyl chloride as a pale yellow, oily substance.
Rf: 0.81 (ethyl acetate:hexane = 1:2)
^{1}H-NMR ($CDCl_3$/TMS) δ:
4.37 (2H, s), 7.23-7.60 (5H, m)
IR(neat): 2222, 758, 690 cm^{-1}
MS(70eV): 150(M^+)
(2) A solution of 2.5 g of the above-mentioned compound, 3.79 g of dimethyl 2-acetamidomalonate and 1.43 g of sodium ethoxide in 50 ml of ethanol was refluxed under heating for 3 hours under a nitrogen atmosphere. Water (20 ml) was added thereto to stop the reaction and the mixture was extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate and the solvent was distilled away. The residue was purified by silica gel column chromatography (ethyl acetate: hexane = 1:7 - 1:2) to give 2.5 g of diethyl 2-acetamido-2-(3-phenyl-2-propynyl)malonate as white crystals.
melting point = 94-96.5 °C
Rf: 0.38 (ethyl acetate:hexane = 1:2)
^{1}H-NMR ($CDCl_3$/TMS) δ:
1.28 (6H, t, J = 7.5Hz), 2.08 (3H, s), 3.49 (2H, s), 4.30 (4H, q, J = 7.5Hz), 6.98 (1H, br.s), 7.16-7.49 (5H, m)
IR(KBr): 3260, 1747, 1643, 1197 cm^{-1}
MS(70eV): 331(M^+)
(3) A solution (50 ml) of 1.8 g of the above-mentioned compound and 0.47 g of lithium borohydride in tetrahydrofuran was refluxed under heating for 1.5 hours under a nitrogen atmosphere. After cooling, the mixture was neutralized with 8 ml of a 1N aqueous hydrochloric acid solution and evaporated to dryness. Acetic anhydride (4 ml) and 30 ml of pyridine were added to the residue and the mixture was stirred at room temperature for 2.5 hours. The reaction mixture was poured into ice water and extracted with chloroform. The extract was washed with 1N hydrochloric acid and saturated brine in order and dried. The solvent was distilled away and the residue was purified by silica gel column chromatography (ethyl acetate: hexane = 2:1) to give 430 mg of 2-acetamido-1,3-diacetoxy-2-(3-phenyl-2-propynyl)propane as a colorless, oily substance.

Rf: 0.64 (ethyl acetate)

^{1}H-NMR ($CDCl_3$/TMS) δ:

1.98 (3H, s), 2.07 (6H, s), 3.09 (2H, s), 4.47 (4H, s), 5.95 (1H, br.s), 7.18-7.48 (5H, m)

IR(neat): 3293, 2135, 1745, 1662 cm^{-1}

MS(70eV): 331(M^+)

Example 19

2-Acetamido-1,3-diacetoxy-2-(3-phenyl-2-propynyl)propane (430 mg) was dissolved in 8 ml of methanol and 8 ml of a 1N aqueous sodium hydroxide solution was added thereto. The mixture was refluxed under heating for 2 hours. The solvent was distilled away and the residue was purified by silica gel column chromatography (methanol:chloroform = 1:50 - 1:7) to give 230 mg of 2-amino-2-(3-phenyl-2-propynyl)-1,3-propanediol as a pale yellow, amorphous-like solid.

Rf: 0.20 (methanol:chloroform = 1:5)

IR(KBr): 3281, 2932, 1558, 1049 cm^{-1}

Example 20

(1) A solution of 1.1 g of 4-(4-butylphenyl)butanol, 1.05 g of tosyl chloride, 0.48 ml of pyridine and a catalytic amount of dimethylaminopyridine in dichloromethane was allowed to stand at room temperature overnight. The reaction mixture was poured into 50 ml of ice water and extracted with chloroform. The extract was dried over anhydrous sodium sulfate and the solvent was distilled away. The residue was purified by silica gel column chromatography (ethyl acetate:hexane = 1:6) to give 1.2814 g of 4-(4-butylphenyl)butyl p-toluenesulfonate as a colorless, oily substance.

^{1}H-NMR ($CDCl_3$/TMS) δ:

0.96 (3H, t, J = 7Hz), 1.50-2.00 (8H, m), 2.48 (3H, s), 2.40-2.75 (4H, m), 4.08 (2H, t, J = 6Hz), 7.07 (4H, m), 7.36 (2H, d, J = 8Hz), 7.83 (2H, d, J = 8Hz)

IR: 2956, 2929, 2858, 1361 cm^{-1}

MS: 360(M^+)

(2) The above-mentioned compound (1.2138 g) and 0.606 g of sodium iodide were dissolved in 34 ml of 2-butanone and the mixture was refluxed under heating for 4 hours. The mixture was poured into 100 ml of ice water and extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate and the solvent was distilled away. The residue was purified by silica gel column chromatography (ethyl acetate:hexane = 1:9) to give 0.953 g of 4-(4-butylphenyl)-1-iodobutane as a red, oily substance.

Rf: 0.75 (ethyl acetate:hexane = 1:5)

^{1}H-NMR ($CDCl_3$/TMS) δ:

0.92 (3H, t, J = 7Hz), 1.10-2.05 (8H, m), 2.59 (4H, t, J = 7.5Hz), 3.20 (2H, t, J = 7Hz), 7.07 (5H, s)

(3) A solution of 953.4 mg of the above-mentioned compound, 687.7 mg of diethyl 2-acetamidomalonate and 260 mg of sodium ethoxide in 10 ml of ethanol was refluxed under heating for 3 hours under a nitrogen atmosphere. The mixture was poured into 100 ml of ice water and extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate and the solvent was distilled away. The residue was purified by silica gel column chromatography (ethyl acetate:hexane = 1:3 - 1:2) to give 480 mg of diethyl 2-acetamido-2-[4-(4-butylphenyl)-butyl]malonate as white crystals.

melting point = 60-61 °C

Rf: 0.38 (ethyl acetate:hexane = 1:2)

^{1}H-NMR ($CDCl_3$/TMS) δ:

0.93 (3H, t, J = 6Hz), 1.24 (3H, t, J = 7Hz), 1.09-1.85 (8H, m), 2.02 (3H, s), 2.35 (2H, m), 2.58 (4H, t, J = 7.5Hz), 4.25 (2H, q, J = 6Hz), 6.75 (1H, br.s), 7.07 (4H, s)

IR: 3270, 2930, 2850, 1740, 1640 cm^{-1}

MS: 405(M^+), 290

elemental analysis	calculated found	C 68.12, C 68.25,	H 8.70, H 8.69,	N 3.45 N 3.55

(4) A solution (15 ml) of 450 mg of the above-mentioned compound and 100 mg of lithium borohydride in tetrahydrofuran was refluxed under heating for 2 hours under a nitrogen atmosphere. The mixture was neutralized with 2.5 ml of a 2N aqueous hydrochloric acid solution and dried to solidness. Acetic anhydride (2 ml) and 4 ml of pyridine were added to the residue and the mixture was stirred at room temperature overnight. The reaction mixture was poured into ice water and extracted with ethyl acetate. The extract was washed with 2N hydrochloric acid, a saturated sodium bicarbonate solution and saturated brine in order and dried. The solvent was distilled away and the residue was purified by silica gel column chromatography (ethyl acetate:hexane = 3:1) to give 72.4 mg of 2-acetamido-1,3-diacetoxy-2-[4-(4-butylphenyl)butyl]propane as white crystals.

melting point = 68-71 °C

Rf: 0.63 (ethyl acetate)

^{1}H-NMR ($CDCl_3$/TMS) δ:

0.91 (3H, t, J = 7Hz), 1.10-2.40 (10H, m), 1.93 (3H, s), 2.06 (6H, s), 2.58 (4H, t, J = 7.5Hz), 4.28 (4H, s), 5.62 (1H, br.s), 7.07 (4H, s)

IR: 3298, 3090, 2931, 2859, 1739, 1652, 1557 cm^{-1}

MS: 405(M^+)

elemental analysis	calculated found	C 68.12, C 67.95,	H 8.70, H 8.52,	N 3.45 N 3.44

Example 21

2-Acetamido-1,3-diacetoxy-2-[4-(4-butylphenyl)butyl]propane (66.2 mg) was dissolved in 2 ml of methanol and 2 ml of a 1N aqueous sodium hydroxide solution was added thereto. The mixture was refluxed under heating for 4 hours. The solvent was distilled away and the residue was purified by silica gel thin layer chromatography (methanol:chloroform = 1:4) to give 24.9 mg of 2-amino-2-[4-(4-butylphenyl)butyl]-1,3-propanediol as white crystals.

melting point = 92-94 °C

Rf: 0.15 (methanol:chloroform = 1:4)

IR: 3276, 2928, 2858, 1560 cm^{-1}

Example 22

(1) 4-(4-Hexylphenyl)butanol (5.0 g) was dissolved in 20 ml of pyridine and 4.88 g of tosyl chloride was added thereto. The reaction mixture was left standing at room temperature overnight. The reaction mixture was poured into ice water and extracted with ethyl acetate. The extract was washed with 2N hydrochloric acid, a saturated aqueous sodium bicarbonate solution and saturated brine in order and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate:hexane = 1:7) to give 2.21 g of 4-(4-hexylphenyl)butyl p-toluenesulfonate as a colorless, oily substance.

Rf: 0.35 (ethyl acetate:hexane = 1:5)

^{1}H-NMR ($CDCl_3$/TMS) δ:

0.90 (3H, t, J = 6Hz), 1.09-1.85 (12H, m), 2.46 (3H, s), 2.53 (4H, m), 4.06 (2H, t, J = 6Hz), 7.06 (4H, s), 7.34 (2H, d, J = 8Hz), 7.81 (2H, d, J = 8Hz)

IR: 2927, 2856, 1599 cm^{-1}

MS: 388(M^+), 216

elemental analysis	calculated found	C 71.10, C 71.35,	H 8.30 H 8.34

(2) The above-mentioned compound (2.21 g) and 1.02 g of sodium iodide were dissolved in 57 ml of 2-butanone and the mixture was refluxed under heating for 2 hours. The reaction mixture was poured into

ice water and extracted with ethyl acetate. The extract was washed with saturated brine, and dried and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate:hexane = 1:9) to give 1.765 g of 4-(4-hexylphenyl)-1-iodobutane as a colorless, oily substance.

Rf: 0.43 (ethyl acetate:hexane = 1:5)

^{1}H-NMR ($CDCl_3$/TMS) δ:

0.90 (3H, t, J = 6Hz), 1.05-2.05 (12H, m), 2.60 (4H, m), 3.21 (2H, t, J = 7Hz), 7.10 (4H, s)

MS: 344(M^+), 273, 175

elemental analysis	calculated	C 55.82,	H 7.32
	found	C 55.81,	H 7.32

(3) A solution of 1.6806 g of the above-mentioned compound, 1.1133 g of diethyl 2-acetamidomalonate and 523 mg of sodium ethoxide in 20 ml of ethanol was refluxed under heating for 4.5 hours under a nitrogen atmosphere. The reaction mixture was poured into ice water and extracted with ethyl acetate. The extract was dried and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate:hexane = 1:3) to give 870 mg of diethyl 2-acetamido-2-[4-(4-hexylphenyl)-butyl]malonate as white crystals.

melting point = 57-58 °C

Rf: 0.42 (ethyl acetate:hexane = 1:2)

^{1}H-NMR ($CDCl_3$/TMS) δ:

0.91 (3H, t, J = 6Hz), 1.24 (6H, t, J = 7Hz), 1.08-1.90 (12H, m), 2.02 (3H, s), 2.35 (2H, m), 2.58 (4H, t, J = 7Hz), 4.23 (4H, q, J = 7Hz), 6.74 (1H, br.s), 7.07 (4H, s)

IR: 3270, 2927, 2858, 1746, 1644, 1514 cm^{-1}

MS: 433(M^+), 360, 318

elemental analysis	calculated	C 69.25,	H 9.07,	N 3.23
	found	C 69.44,	H 8.97,	N 3.26

(4) A solution (20 ml) of 840 mg of the above-mentioned compound and 211 mg of lithium borohydride in tetrahydrofuran was refluxed under heating for 4 hours under a nitrogen atmosphere. The mixture was neutralized with 2N hydrochloric acid and the solvent was evaporated to dryness. Acetic anhydride (5.5 ml) and 16 ml of pyridine were added to the residue and the mixture was stirred at room temperature overnight. The reaction mixture was treated conventionally and the residue obtained was purified by silica gel column chromatography (ethyl acetate:hexane = 3:1) to give 244.5 mg of 2-acetamido-1,3-diacetoxy-2-[4-(4-hexylphenyl)butyl]propane as white crystals.

melting point = 61-64 °C

Rf: 0.71 (ethyl acetate)

^{1}H-NMR ($CDCl_3$/TMS) δ:

0.88 (3H, t, J = 6Hz), 1.10-1.90 (14H, m), 1.92 (3H, s), 2.04 (6H, s), 2.58 (4H, t, J = 7Hz), 4.28 (4H, s), 5.58 (1H, br.s), 7.06 (4H, s)

IR: 3313, 2928, 2856, 1750, 1656 cm^{-1}

MS: 433(M^+), 389, 373

elemental analysis	calculated	C 69.25,	H 9.07,	N 3.23
	found	C 69.26,	H 9.01,	N 3.22

Example 23

2-Acetamido-1,3-diacetoxy-2-[4-(4-hexylphenyl)butyl]propane (200.2 mg) was dissolved in 7 ml of methanol and 1N sodium hydroxide was added thereto. The mixture was refluxed under heating for 5 hours. The solvent was distilled away and the residue obtained was purified by silica gel thin layer chromatography (methanol:chloroform = 1:3) to give 79.7 mg of 2-amino-2-[4-(4-hexylphenyl)butyl]-1,3-propanediol as

white crystals.
melting point = 99-102 °C
Rf: 0.14 (methanol:chloroform = 1:4)
IR: 3286, 2927, 2858, 1562, 1514 cm^{-1}

Example 24

(1) Concentrated sulfuric acid (18.3 g) was gradually added dropwise to 13.94 g of concentrated nitric acid and the mixture was vigorously shaken for 10 minutes. To the mixed solution, 10 g of propyl bromide was gradually added dropwise at -20 °C and the mixture was stirred at -20 °C for 1 hour. The reaction mixture was poured into 500 ml of ice water and extracted with ether. The extract was washed and dried, and the solvent was distilled away. The residue was purified by silica gel column chromatography (ethyl acetate:hexane = 1:9) to give 4.5 g of 3-(4-nitrophenyl)propyl bromide as a colorless, oily substance. Rf: 0.33 (ethyl acetate:hexane = 1:15)
(2) Sodium (0.68 g) was added to 40 ml of absolute ethanol under ice-cooling. The mixture was stirred at room temperature for 30 minutes in a stream of nitrogen to give a sodium ethoxide solution. To this solution, 1.98 g of diethyl 2-acetamidomalonate was added and 4.8 g of the compound of (1) above was dropwise added thereto. The mixture was refluxed under heating for 6 hours. The reaction mixture was poured into 100 ml of ice water and extracted with ethyl acetate. The extract was washed and dried, and the solvent was distilled away. The residue was purified by silica gel column chromatography (ethyl acetate:hexane = 1:3 - 1:1) to give 3.0 g of diethyl 2-acetamido-2-[3-(4-nitrophenyl)propyl]malonate as a yellow, oily substance.
Rf: 0.51 (ethyl acetate:hexane = 1:1)
(3) A solution (50 ml) of 1.0 g of the compound of (2) above and 228 mg of lithium borohydride in tetrahydrofuran was refluxed under heating for 2 hours in a stream of nitrogen. The reaction mixture was poured into 100 ml of ice water and extracted with ethyl acetate. The extract was washed and dried, and the solvent was distilled away. The residue was purified by silica gel column chromatography (methanol: chloroform = 1:9) to give 400 mg of 2-acetamido-2-[3-(4-nitrophenyl)propyl]-1,3-propanediol as a yellow, oily substance.

Rf:	0.22 (ethyl acetate)
^{1}H-NMR (90MHz, $CDCl_3$) δ:	1.38-1.80 (4H, m), 2.00 (3H, s), 2.57-3.04 (2H, m), 3.39-4.28 (4H, m), 3.93 (2H, br.s), 6.23-6.58 (1H, m), 7.17-7.63 (2H, m), 7.75-8.20 (2H, m)
IRν :	3301, 2944, 1652, 1519 cm^{-1}
MS(EI):	296(M^+)

Example 25

2-Acetamido-2-[3-(4-nitrophenyl)propyl]-1,3-propanediol (400 mg) was dissolved in 50 ml of methanol and 6.7 ml of a 1N aqueous sodium hydroxide solution was added thereto. The mixture was refluxed under heating for 3 hours and neutralized with dilute hydrochloric acid. The solvent was distilled away and chloroform was added to the residue for extraction. The chloroform layer was washed and dried, and the solvent was distilled away. The residue was purified by silica gel column chromatography (methanol:chloroform = 1:4) to give 100 mg of 2-amino-2-[3-(4-nitrophenyl)propyl]-1,3-propanediol as a red, oily substance.

Rf:	0.13 (chloroform:methanol = 4:1)
^{1}H-NMR (90MHz, $CDCl_3$) δ:	1.10-2.05 (4H, m), 2.52-3.11 (2H, m), 3.19-3.86 (4H, m), 4.65 (4H, br.s), 7.08-7.65 (3H, m), 7.70-8.18 (1H, m)
IRν :	3359, 2936, 2866, 1524 cm^{-1}

Example 26

(1) A 15N aqueous sodium hydroxide solution (2 ml) and a solution (10 ml) of 8.0 g of undecyl bromide in ethanol was added to a solution (30 ml) of 4.56 g of 3-(3-hydroxyphenyl)-propanol in ethanol and the mixture was stirred at 70 °C for 12 hours. The solvent was distilled away and the residue was extracted with ethyl acetate. The extract was washed with saturated sodium hydrogencarbonate and brine, and

dried over magnesium sulfate. The solvent was distilled away and the residue was purified by silica gel column chromatography (ethyl acetate:hexane = 1:20 - 1:3) to give 7.37 g of 3-(3-undecyloxyphenyl)-propanol as a colorless, oily substance.

^{1}H-NMR (90MHz, $CDCl_3$) δ:

0.87 (3H, t, J = 6Hz), 1.10-2.08 (20H, m), 1.60 (1H, br.s), 2.69 (2H, t, J = 6Hz), 3.55-3.81 (2H, m), 3.94 (3H, t, J = 6Hz), 6.62-6.87 (3H, m), 7.06-7.23 (1H, m)

(2) Carbon tetrabromide (5.68 g) and 4.49 g of triphenylphosphine were added to a solution (100 ml) of 5 g of the above-mentioned compound in methylene chloride and the mixture was stirred at room temperature overnight. The reaction mixture was poured into ice water and extracted with methylene chloride. The organic layer was washed and dried, and the solvent was distilled away. Petroleum ether was added to the residue and insoluble matters were filtered off. The petroleum ether layer was distilled away and the residue was purified by silica gel column chromatography (ethyl acetate:hexane = 1:20) to give 4.6 g of 3-(3-undecyloxyphenyl)propyl bromide as a colorless, oily substance.

^{1}H-NMR (90MHz, $CDCl_3$) δ:

0.83 (3H, t, J = 7Hz), 1.04-1.53 (16H, m), 1.55-1.86 (2H, m), 2.14 (2H, m, J = 7Hz), 2.70 (2H, t, J = 7Hz), 3.34 (2H, t, J = 7Hz), 3.90 (2H, t, J = 7Hz), 6.73-6.85 (3H, m), 7.14-7.42 (1H, m)

IR: 2925, 2553, 1583, 1451, 1261 cm^{-1}

(3) Sodium (0.43 g) was added to absolute ethanol (40 ml) under ice-cooling and the mixture was stirred at room temperature for 30 minutes in a stream of nitrogen to give a 19 mmol solution of sodium ethoxide in ethanol. To this solution, 4.0 g of diethyl 2-acetamidomalonate was added and the mixture was stirred at 50 °C for 30 minutes in a stream of nitrogen. The compound (4.6 g) of (2) above was added thereto at room temperature and the mixture was refluxed under heating for 6 hours. After cooling to room temperature, the mixture was neutralized with dilute hydrochloric acid and ethanol was distilled away. The residue was extracted with ethyl acetate. The ethyl acetate layer was washed and dried, and the solvent was distilled away. The residue was purified by silica gel column chromatography (ethyl acetate:hexane = 1:5 - 1:1) to give 4.2 g of diethyl 2-acetamido-2-[3-(3-undecyloxyphenyl)-propyl]-malonate as white crystals.

melting point = 38-39 °C

^{1}H-NMR (90MHz, $CDCl_3$) δ:

0.88 (3H, t, J = 7Hz), 1.12-1.90 (27H, m), 2.03 (3H, s), 2.27-2.73 (4H, m), 3.93 (3H, t, J = 7Hz), 4.22 (4H, q, J = 7Hz), 6.61-6.87 (3H, m), 7.04-7.22 (1H, m)

IR: 3251, 2917, 1741, 1680 cm^{-1}

MS(EI): 505(M^+)

(4) A solution (20 ml) of 3.5 g of the compound of (3) above in anhydrous tetrahydrofuran was dropwise added to a solution (50 ml) of 1.08 g of lithium aluminum hydride in anhydrous tetrahydrofuran under ice-cooling and the mixture was stirred under ice-cooling for 1 hour. The excess lithium aluminum hydride was decomposed and filtered off. The filtrate was extracted with ethyl acetate. The ethyl acetate layer was washed and dried. The solvent was distilled away and the residue was purified by silica gel column chromatography (ethyl acetate, chloroform:methanol = 9:1) to give 1.6 g of 2-acetamido-2-[3-(3-undecyloxyphenyl)propyl]-1,3-propanediol as a colorless, oily substance.

^{1}H-NMR (90MHz, $CDCl_3$) δ:

0.86 (3H, t, J = 6Hz), 1.05-1.45 (16H, m), 1.45-1.87 (6H, m), 1.99 (3H, s), 2.47-2.70 (2H, m), 3.64 (4H, dd, J = 12Hz, 21Hz), 3.82 (2H, t, J = 6Hz), 3.79-4.10 (2H, m), 5.89 (1H, br.s), 6.60-6.82 (3H, m), 7.03-7.31 (1H, m)

IR: 3307, 2926, 2857, 1652 cm^{-1}

MS(EI): 421 [M + 1]

Example 27

2-Acetamido-2-[3-(3-undecyloxyphenyl)propyl]-1,3-propanediol (1.4 g) was dissolved in 50 ml of methanol and 16.6 ml of a 1N aqueous sodium hydroxide solution was added thereto. The mixture was refluxed under heating for 3 hours. The mixture was poured into ice water and neutralized with dilute hydrochloric acid. The solvent was distilled away and chloroform was added to the residue for extraction. The chloroform layer was washed and dried. The solvent was distilled away and the residue was recrystallized from

diisopropyl ether-hexane to give 0.9 g of 2-amino-2-[3-(3-undecyloxyphenyl)propyl]-1,3-propanediol as white crystals.

melting point = 71-72 °C

^{1}H-NMR (90MHz, $CDCl_3$) δ:

0.86 (3H, t, J = 6Hz), 1.14-1.91 (22H, m), 2.20 (4H, br.s), 2.60 (2H, t, J = 6Hz), 3.49 (4H, dd, J = 10Hz, 13Hz), 3.94 (2H, t, J = 6Hz), 6.62-6.86 (3H, m), 7.05-7.21 (1H, m)

IR: 3344, 3289, 3179, 2919, 1610 cm^{-1}

MS(EI): 379(M^+)

Example 28 : 2-Amino-2-[2-(4-octylphenyl)ethyl]-1,3-propanediol

(1) 2-(4-Octanoylphenyl)ethyl acetate

Aluminum chloride (111.8 g) was added to dichloroethane (500 ml) in a stream of nitrogen and the mixture was stirred at room temperature. Then, phenethyl acetate (91.8 g) and decanoyl chloride (100 g) were dropwise added thereto under ice-cooling and the mixture was stirred at room temperature overnight. The reaction mixture was poured into ice water and extracted with diethyl ether. The ether layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and the residue was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:20) to give 61.3 g of the subject compound (yield 38%) as an oily substance.

IRν Neat max : 2929, 1740, 1685, 1236 cm^{-1}

(2) 2-(4-Octylphenyl)ethyl acetate

Triethylsilane (28.8 ml) was added to a solution (86ml) of the above-mentioned compound (24.9 g) in trifluoroacetic acid under ice-cooling and the mixture was stirred at room temperature for 2 hours. The solvent was distilled away and thereto was added ice water and then a cool, saturated sodium hydrogencarbonate solution gradually. The mixture was extracted with ethyl acetate and the ethyl acetate layer was washed and dried over magnesium sulfate. The solvent was distilled away and the residue obtained was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:20) to give 20.5 g of the subject compound as an oily substance (yield 87%).

IRν Neat max : 2927, 2855, 1742, 1237 cm^{-1}

(3) 2-(4-Octylphenyl)ethyl alcohol

Sodium methoxide (11.9 g) was added to a solution of the above-mentioned compound (30.3 g) in methanol (300 ml) and the mixture was refluxed under heating for 3 hours. The reaction mixture was concentrated and ice water was added thereto. The mixture was extracted with ethyl acetate and the ethyl acetate layer was washed with a 5% aqueous HCl solution and saturated brine. The resultant mixture was dried over magnesium sulfate. The solvent was distilled away and the residue obtained was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:15, ethyl acetate) to give 25.0 g of the subject compound as an oily substance (yield 97%).

IRν Neat max : 3357, 2927, 2855, 1467 cm^{-1}

(4) 2-(4-Octylphenyl)ethyl methanesulfonate

Triethylamine (16.4 ml) was added to a solution (500 ml) of the above-mentioned compound (25 g) in dichloromethane and the mixture was ice-cooled. Methanesulfonyl chloride (13.4 g) was dropwise added thereto and the mixture was stirred at room temperature for 1 hour. The reaction mixture was poured into ice water and extracted with dichloromethane. The dichloromethane layer was washed with a saturated potassium hydrogencarbonate solution, a 1% saturated aqueous hydrochloric acid solution and saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and the residue was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:19) to give 31.6 g of the subject compound as an oily substance (yield 95%).

^{1}H-NMR ($CDCl_3$) δ:

0.86 (3H, t, J = 6Hz), 1.13-1.79 (12H, m), 2.58 (2H, t, J = 6Hz), 2.82 (3H, s), 3.01 (2H, t, J = 6Hz), 4.39 (2H, t, J = 6Hz), 7.12 (4H, s)

IRν Neat max : 2926, 1356, 1174 cm^{-1}

(5) 2-(4-Octylphenyl)ethyl iodide

Sodium iodide (18.13 g) was added to a solution (500 ml) of the above-mentioned compound (31.5 g) in 2-butanone and the mixture was refluxed under heating for 4 hours. The reaction mixture was concentrated and poured into ice water. The resultant mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and the residue obtained was purified by silica gel column chromatography (eluent; ethyl acetate: hexane = 1:20) to give 27.5 g of the subject compound as an oily substance (yield 80%).

^{1}H-NMR ($CDCl_3$) δ:
0.86 (3H, t, J = 6Hz), 1.07-1.79 (12H, m), 2.58 (2H, t, J = 6Hz), 3.01-3.57 (4H, m), 7.11 (4H, s)

IRν Neat max : 2925, 2853, 1168 cm^{-1}

(6) Diethyl 2-acetamido-2-(4-octylphenyl)ethyl malonate

A solution (80 ml) of sodium ethoxide (8.2 g) in absolute ethanol was dropwise added to diethyl acetamidomalonate (26 g) in a stream of nitrogen and the mixture was stirred at 65 °C for 30 minutes. Then, a solution of the above-mentioned compound (13.8 g) in anhydrous tetrahydrofuran was dropwise added thereto and the mixture was stirred at 65 °C for 30 minutes. The reaction mixture was concentrated and poured into ice water.

The resultant mixture was extracted with ethyl acetate. The extract was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and the residue was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:3) to give 10.6 g of the subject compound (yield 61%).

melting point = 49-51 °C

^{1}H-NMR ($CDCl_3$) δ:
0.86 (3H, t, J = 6Hz), 1.14 (6H, t, J = 6Hz), 1.20-1.73 (12H, m), 2.95 (3H, s), 2.30-2.83 (6H, m), 4.21 (4H, q, J = 6Hz), 6.74 (1H, s), 7.05 (4H, s)

IRν max : 3257, 2924, 1747, 1643 cm^{-1}

(7) 2-Amino-2-[2-(4-octylphenyl)ethyl]-1,3-propanediol

(a) A solution (100 ml) of the above-mentioned compound (11.55 g) in anhydrous tetrahydrofuran was dropwise added to a solution (260 ml) of lithium aluminum hydride (3.03 g) in anhydrous tetrahydrofuran under ice-cooling in a stream of nitrogen and the mixture was stirred at room temperature for 2 hours. A saturated aqueous sodium sulfate solution was added to the reaction mixture under ice-cooling. The resultant aluminum hydroxide was filtered off and the resultant mixture was dried over anhydrous sodium sulfate. The solvent was distilled away and pyridine (40 ml) was added to the residue. Acetic anhydride (30 ml) was added thereto under ice-cooling and the mixture was left standing at room temperature overnight. The reaction mixture was poured into water-cooled 5% hydrochloric acid and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and the residue was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 2:1) to give 8.25 g of 1,3-propanediyl-2-acetamido-2-[2-(4-octylphenyl)ethyl]ylidenediacetate as white crystals.

(b) An aqueous solution (100 ml) of lithium hydroxide (7.2 g) was added to a solution (100 ml) of the above-mentioned diacetate (8.25 g) in methanol and the mixture was refluxed under heating for 2 hours. The reaction mixture was concentrated and extracted with ethyl acetate. The extract was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and the residue was recrystallized from ethyl acetate to give 4 g of the subject compound, melting point 103-105 °C.

^{1}H-NMR (DMSO) δ:
0.86 (3H, t, J = 6Hz), 1.10-1.85 (14H, m), 2.38-2.79 (6H, m), 3.39 (4H, s), 7.06 (4H, s), 7.84 (2H, brs)

IRν : 3354, 2925, 1019 cm^{-1}

Example 29 : 2-Amino-2-[2-(4-octylphenyl)ethyl]-1,3-propanediol hydrochloride

2-Amino-2-[2-(4-octylphenyl)ethyl]-1,3-propanediol (7 g) was dissolved in ethanol (50 ml) and a 1N hydrochloric acid/ether solution (50 ml) was added thereto. The solvent was distilled away and the resultant crystals were recrystallized from ethanol to give 4.2 g of the subject compound.
melting point = 118-120 °C
^{1}H-NMR (DMSO) δ:
0.89 (3H, t, J = 6Hz), 1.07-1.77 (12H, m), 1.82-2.17 (2H, m), 2.42-2.95 (4H, m), 3.80 (4H, s), 5.03 (2H, brs), 7.11 (4H, s), 8.07 (3H, brs)
IRν : 3371, 3265, 2924, 1069 cm^{-1}

Example 30 : 2-Acetamido-1,3-diacetoxy-2-[2-(4-octylphenyl)-ethyl]-1,3-propanediol

A solution (100 ml) of diethyl 2-acetamido-2-[2-(4-octylphenyl)ethyl]malonate (11.55 g) in anhydrous tetrahydrofuran was dropwise added to a solution (260 ml) of lithium aluminum hydride (3.0 g) in anhydrous tetrahydrofuran under ice-cooling. The mixture was stirred for 1 hour under ice-cooling and then at room temperature for 2 hours. A saturated aqueous solution of sodium sulfate was dropwise added under ice-cooling to decompose lithium aluminum hydride, which was then filtered off. The resultant mixture was extracted with ethyl acetate and the ethyl acetate layer was washed and dried. The solvent was distilled away and the residue was purified by silica gel column chromatography (chloroform/methanol = 9/1) to give crystals of 2-acetamido-2-[2-(4-octylphenyl)ethyl]-1,3-propanediol, melting point 66-68 °C. The obtained compound was dissolved in pyridine (40 ml) and acetic anhydride (30 ml) was added thereto under ice-cooling. The mixture was left standing at room temperature overnight. The reaction mixture was poured into a 10% aqueous hydrochloric acid solution (500 ml) and extracted with ethyl acetate. The ethyl acetate layer was washed with an aqueous potassium hydrogencarbonate solution and saturated brine, and dried over anhydrous magnesium sulfate. The solvent was distilled away and the residue was purified by silica gel column chromatography (ethyl acetate/hexane = 2/1) to give 8.25 g of the subject compound.
yield 71%
melting point = 105-107 °C
^{1}H-NMR ($CDCl_3$) δ:
0.85 (3H, t), 1.22-1.29 (10H, m), 1.51-1.61 (2H, m), 1.93 (3H, s), 2.07 (6H, s), 2.17 (2H, t), 2.54 (2H, t), 2.55 (2H, t), 4.35 (4H, s), 5.61 (1H, brs), 7.07 (4H, s)
IR (Nujol)ν : 3310, 2920, 1738, 1652, 1556 cm^{-1}
In the same manner as in the above-mentioned Examples, the following compounds can be produced.

Example 31 : 2-Amino-2-hexyl-1,3-propanediol hydrochloride

Rf value : 0.47 ($CHCl_3$:MeOH:CH_3COOH:H_2O = 70:20:6:4)
IR(KBr): 3950, 1560, 1420, 1050 cm^{-1}

Example 32 : 2-Amino-2-octyl-1,3-propanediol hydrochloride

Rf value : 0.48 ($CHCl_3$:MeOH:CH_3COOH:H_2O = 70:20:6:4)
IR(KBr): 3190, 2930, 2850, 1630, 1560, 1410, 1100, 1060, 1020 cm^{-1}

Example 33 : 2-Amino-2-decyl-1,3-propanediol hydrochloride

Rf value : 0.49 ($CHCl_3$:MeOH:CH_3COOH:H_2O = 70:20:6:4)
IR(KBr): 3350, 2920, 2850, 1560, 1470, 1420, 1060 cm^{-1}

Example 34 : 2-Amino-2-dodecyl-1,3-propanediol hydrochloride

IR(KBr): 3260, 3050, 2920, 2850, 1590, 1520, 1470, 1260, 1070, 1050 cm^{-1}
melting point = 94.0-95.5 °C

Example 35 : 2-Amino-2-tridecyl-1,3-propanediol hydrochloride

IR(KBr): 3420, 3320, 2400, 2350, 1620, 1590, 1510, 1465, 1085, 1045, 1030, 1000 cm^{-1}
melting point = 103.0-104.0 °C

Example 36 : 2-Amino-2-pentadecyl-1,3-propanediol hydrochloride

IR(KBr): 3430, 3350, 3030, 2920, 2850, 1620, 1590, 1510, 1475, 1080, 1055, 1040 cm^{-1}

elemental analysis	calculated found	C 63.97, C 63.91,	H 11.93, H 11.96,	N 4.14, N 4.17,	O 9.47, O 9.45,	Cl 10.49 Cl 10.51

melting point = 106.5-108.0 °C

Example 37 : 2-Amino-2-(2-pentadecynyl)-1,3-propanediol hydrochloride

IR(KBr): 3400, 2920, 2850, 1500, 1470, 1060 cm^{-1}

elemental analysis	calculated found	C 64.74, C 64.34,	H 10.87, H 10.95,	N 4.19, N 4.13,	O 9.58, O 9.57,	Cl 10.62 Cl 10.66

melting point = 100.0-101.0 °C

The instant compound is produced according to the following steps (1) through (6).

(1) Propargyl alcohol (3.00 g) was portionwise added to a mixed solution of 2.256 g of sodium hydride and 30 ml of dry dimethylformamide under ice-cooling under a nitrogen atmosphere. The mixture was stirred at room temperature for 30 minutes. The mixture was ice-cooled again and 5.175 g of chloro methyl methyl ether was portionwise added thereto. The mixture was stirred at room temperature overnight. Then, 4.284 g of sodium hydride was added thereto under ice-cooling and the mixture was heated to room temperature, followed by stirring for 30 minutes. The reaction mixture was ice-cooled again and a solution of 26.68 g of lauryl bromide in 20 ml of dry dimethylformamide was portionwise added thereto. The mixture was stirred at room temperature overnight. The reaction mixture was poured into ice water and extracted three times with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over magnesium sulfate anhydride. The solvent was distilled away under reduced pressure and the residue was purified by silica gel column chromatography to give 12.374 g of 15-methoxymethoxy-13-pentadecyne.

IR(cm^{-1}): 2940, 2850, 1470, 1150, 1005, 1400, 1000, 930

^{1}H-NMR ($CDCl_3$) δ:

0.879 (3H, t, J = 6.74Hz, $CH_2\underline{CH_3}$), 1.257 (20H, br.s, CH_2 × 10), 2.213 (2H, tt, J = 6.96, 2.20Hz, C≡C-$\underline{CH_2}CH_2$), 3.380 (3H, s, OCH_3), 4.204 (2H, t, J = 2.20Hz, OCH_2C≡C), 4.711 (2H, s, OCH_2O)

(2) The compound (12.374 g) of (1) above was dissolved in a 1N solution (230 ml) of hydrochloric acid in methanol and the mixture was heated at 65 °C for 1.5 hours. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography to give 8.465 g of 2-pentadecynyl alcohol.

melting point = 41.5-42.5 °C

IR(cm^{-1}): 3300, 3200, 2960, 2930, 2850, 1480, 1030

^{1}H-NMR ($CDCl_3$) δ:

0.880 (3H, t, J = 6.74Hz, CH_3), 1.260 (20H, br.s, CH_2 × 10), 2.209 (2H, tt, J = 6.96, 2.12Hz, C≡CCH_2), 4.255 (2H, dd, J = 2.69, 2.44Hz, OCH_2)

(3) In a reaction vessel equipped with a calcium chloride tube, 8.465 g of the compound of (2) above was dissolved in 85 ml of dichloromethane and 15.683 g of carbon tetrabromide and 14.867 g of triphenylphosphine were added thereto under ice-cooling. The mixture was stirred at 0 °C for 5 minutes. The reaction mixture was concentrated under reduced pressure and the residue was extracted with hexane. The hexane extract obtained was concentrated under reduced pressure and the residue was purified by silica gel column chromatography to give 7.964 g of 2-pentadecynyl bromide.

IR(cm^{-1}): 2930, 2850, 1470, 1420

^{1}H-NMR ($CDCl_3$) δ:

0.880 (3H, t, J = 6.43Hz, CH_3), 1.261 (20H, br.s, CH_2 × 10), 2.232 (2H, tt, J = 6.96Hz, 2.36Hz, C≡C-CH_2),3.932 (2H, t, J = 2.32Hz, $BrCH_2$C≡C)

(4) Diethyl acetamidomalonate (3.327 g) and 1.137 g of sodium ethylate were dissolved in 50 ml of dry ethanol and the mixture was stirred at room temperature for 30 minutes under a nitrogen atmosphere. A solution of 4.000 g of the compound of (3) above in 30 ml of dry ethanol was added thereto and the mixture was refluxed for 15 hours. Methanol (50 ml) was added to the reaction mixture and the insoluble matters were removed. The solvent was distilled away under reduced pressure and the residue was purified by silica gel column chromatography to give 3.236 g of diethyl 2-acetamido-2-(2-pentadecynyl)-malonate.

melting point = 43.0-43.5 °C

IR(cm^{-1}): 3250, 2920, 2850, 1750, 1650, 1540, 1470, 1380, 1300, 1240, 1200, 1100, 1080, 1060, 1020, 865

^{1}H-NMR ($CDCl_3$) δ:

0.879 (3H, t, J = 6.35Hz, CH_3), 1.261 (20H, s, CH_2 × 10), 1.261 (6H, t, J = 7.21Hz, $OCH_2\underline{CH_3}$), 2.057 (3H, s, Ac), 2.123-2.077 (2H, m, C≡C$\underline{CH_2}CH_2$), 3.211 (2H, t, J = 2.32Hz, CCH_2-C≡C), 4.253 (2H, q, J = 7.08Hz, $O\underline{CH_2}CH_3$), 4.257 (2H, q, J = 7.08Hz, $O\underline{CH_2}CH_3$), 6.896 (1H, br.s, NH)

(5) In a reaction vessel equipped with a calcium chloride tube, 2.437 g of diethyl 2-acetamido-2-(pentadecynyl)malonate was dissolved in 80 ml of dry tetrahydrofuran and 0.898 g of lithium aluminum hydride was added thereto under ice-cooling. After heating to a room temperature, the mixture was stirred for 30 minutes. Water (3 ml) was added thereto under ice-cooling to stop the reaction and the solvent was distilled away under reduced pressure. Pyridine (70 ml) and 130 ml of acetic anhydride were added to the residue and the mixture was stirred at room temperature overnight. The reaction mixture was poured into ice water and extracted three times with ethyl acetate. The ethyl acetate layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine in order and dried over anhydrous magnesium sulfate. The solvent was distilled away under reduced pressure and the residue was purified by silica gel column chromatography and recrystallized from hexane to give 808 mg of 2-acetamido-1,3-diacetoxy-2-(2-pentadecynyl)propane.

melting point = 95.5-96.5 °C

IR(cm^{-1}): 3300, 2930, 2850, 1740, 1650, 1580, 1400, 1380, 1260, 1040

^{1}H-NMR ($CDCl_3$) δ:

0.879 (3H, t, J = 6.47Hz, CH_3), 1.225 (24H, br.s, CH_2 × 12), 1.980 (3H, s, NAc), 2.089 (6H, s, OAc × 2), 2.140 (2H, m, CH_2C≡C-$\underline{CH_2}CH_2$), 2.790 (2H, t, J = 2.32Hz, $\underline{CH_2}$C≡C-CH_2CH_2), 4.422 (4H, s, CH_2O × 2), 5.829 (1H, br.s, NH)

(6) 2-Acetamido-1,3-diacetoxy-2-(2-pentadecynyl)propane (600 mg) was dissolved in 28 ml of methanol and 7.09 ml of a 1N aqueous sodium hydroxide solution was added thereto. The mixture was refluxed for 6 hours. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in 20 ml of a solvent (methanol:water = 3:7). After adsorption onto Sep-Pak, the residue was eluted with methanol: water = 8:2 and the eluate was concentrated. The residue was dissolved in methanol and the mixture was acidified with hydrochloric acid. The solvent was distilled away under reduced pressure to give 343 mg of 2-amino-2-(2-pentadecynyl)-1,3-propanediol hydrochloride.

Example 38 : 2-Amino-2-(12-hydroxydodecyl)-1,3-propanediol hydrochloride

IR(KBr): 3350, 2920, 2850, 1500, 1470, 1080, 1050, 1040 cm^{-1}

melting point = 138.0-142.0 °C

The instant compound is produced according to the following steps (1) through (5).

(1) Dodecanediol (23.000 g) was dissolved in 230 ml of dry tetrahydrofuran and 40 ml of dichloromethane, and 10 mg of p-toluenesulfonic acid and 9.578 g of dihydropyran were added thereto. The mixture was stirred at room temperature for a day. Triethylamine (1.0 ml) was added thereto to stop the reaction and the reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 8.132 g of dodecanediol monotetrahydropyranyl ether.

IR(cm^{-1}): 3620, 3450, 2930, 2850, 1460, 1360, 1140, 1125, 1080, 1030

(2) The above-mentioned dodecanediol monotetrahydropyranyl ether (7.882 g) and 11.437 g of carbon tetrabromide were dissolved in 78 ml of dichloromethane. Triphenylphosphine (10.843 g) was added thereto under ice-cooling and the mixture was stirred at 0 °C for 5 minutes. The solvent was distilled away under reduced pressure and the residue was purified by silica gel column chromatography to give

4.029 g of 1-bromo-12-tetrahydropyranyloxydodecane.

IR(cm^{-1}): 2930, 2850, 1460, 1445, 1360, 1140, 1120, 1080, 1020, 980

^{1}H-NMR ($CDCl_3$) δ:

1.274 (16H, br.s), 1.611-1.554 (6H, m), 1.750-1.689 (1H, m), 1.888-1.802 (1H, m), 1.852 (2H, qui, J = 7.1Hz), 3.381 (1H, dt, J = 9.5, 6.9Hz), 3.407 (2H, t, J = 6.9Hz), 3.526-3.472 (1H, m), 3.728 (1H, dt, J = 9.5, 7.0Hz), 3.900-3.845 (1H, m), 4.574 (1H, dd, J = 4.4, 2.7Hz)

(3) Diethyl acetamidomalonate (6.996 g) and 3.189 g of sodium ethoxide were dissolved in 130 ml of dry ethanol and a solution of 10.698 g of 1-bromo-12-tetrahydropyranyloxydodecane in 200 ml of dry ethanol was added thereto. The mixture was refluxed under heating for 8 hours. The solvent was distilled away under reduced pressure and the residue was purified by silica gel column chromatography to give 5.837 g of diethyl 2-acetamido-2-(12-tetrahydropyranyloxydodecyl)malonate.

IR(cm^{-1}): 3450, 2930, 2850, 1740, 1680, 1500, 1380, 1285, 1020

^{1}H-NMR ($CDCl_3$) δ:

1.25 (6H, t, J = 7.1Hz), 1.25 (20H, br.s), 1.61-1.52 (6H, m), 1.83-1.71 (2H, m), 2.03 (3H, s), 3.87-3.35 (4H, m), 4.24 (4H, q, J = 7.1Hz), 4.58 (1H, d.d, J = 4.4, 2.4Hz), 6.77 (1H, br.s)

(4) Diethyl 2-acetamido-2-(12-tetrahydropyranyloxydodecyl)-malonate (5.837 g) was dissolved in 13.0 ml of methanol and 2.202 g of sodium borohydride was gradually added thereto under ice-cooling. The entire amount of sodium hydride was added thereto and the mixture was left standing at room temperature for 2 hours. Methanol (30 ml) was added thereto and the mixture was made to assume weak acidity with 2N hydrochloric acid. The solvent was distilled away under reduced pressure. Pyridine (100 ml) and acetic anhydride (200 ml) were added to the residue and the mixture was stirred at room temperature for day and night. The reaction mixture was poured into ice water and extracted with ethyl acetate. The ethyl acetate layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and a saturated aqueous sodium chloride solution in order. The mixture was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The concentrate was dissolved in 100 ml of methanol and 30 mg of p-toluenesulfonic acid was added thereto. The mixture was stirred at room temperature for 1 hour. Triethylamine (0.5 ml) was added thereto and the mixture was stirred for 10 minutes, followed by concentration under reduced pressure. The concentrate was purified by silica gel column chromatography to give 1.180 g of 2-acetamido-1,3-diacetoxy-2-(12-hydroxydodecyl)propane.

melting point = 75.0-76.5 °C

IR(cm^{-1}): 3350, 2930, 2850, 1740, 1630, 1550, 1375, 1270, 1240, 1040

^{1}H-NMR ($CDCl_3$) δ:

1.236 (22H, br.s, CH_2 × 11), 1.843-1.821 (2H, m, CH_2), 1.937 (3H, s, NAc), 2.056 (6H, s, OAc × 2), 3.608 (2H, br.s, $\underline{CH_2}OH$), 4.269 (4H, d.d, J = 14.0, 11.5Hz, $\underline{CH_2}OAc$ × 2), 5.607 (1H, br.s, NH)

(5) 2-Acetamido-1,3-diacetoxy-2-(12-hydroxydodecyl)propane (500 mg) was dissolved in 24 ml of methanol and 6.0 ml of a 1N aqueous sodium hydroxide solution was added thereto. The mixture was refluxed under heating for 6 hours. The reaction mixture was concentrated under reduced pressure and methanol was distilled away. The residue was extracted with ethyl acetate, and the extract was washed with water and dried over anydrous magnesium sulfate. The solvent was distilled away under reduced pressure and the residue was dissolved in methanol. The mixture was acidified with hydrochloric acid and the solvent was distilled away by concentration under reduced pressure. The residue was dried in vacuo to give 103 mg of 2-amino-2-(12-hydroxydodecyl)-1,3-propanediol hydrochloride.

^{1}H-NMR (DMSO) δ:

1.23 (22H, s, CH_2 × 11), 3.49-3.40 (6H, m, CH_2O × 3), 5.26 (3H, br.s, OH × 3)

elemental analysis	calculated found	C 56.94, C 56.73,	H 10.99, H 10.95,	N 4.43, N 4.32,	O 16.43, O 16.49,	Cl 11.21 Cl 11.51

Example 39 : 2-Acetamido-1,3-diacetoxy-2-hexylpropane

melting point = 55-56 °C

Example 40 : 2-Acetamido-1,3-diacetoxy-2-octylpropane

melting point = 79.5-82 °C

Example 41 : 2-Acetamido-1,3-diacetoxy-2-decylpropane

melting point = 70-72 °C

Example 42 : 2-Acetamido-1,3-diacetoxy-2-dodecylpropane

melting point = 75.5-76.5 °C

Example 43 : 2-Acetamido-1,3-diacetoxy-2-tridecylpropane

melting point = 77.0-78.0 °C

Example 44 : 2-Acetamido-1,3-diacetoxy-2-pentadecylpropane

melting point = 82.0-83.0 °C

Example 45 : 2-Acetamido-1,3-diacetoxy-2-(2-pentadecynyl)propane

IR(KBr): 3300, 2930, 2850, 1740, 1650, 1580, 1400, 1380, 1260, 1040 cm^{-1}
melting point = 95.5-96.5 °C

Example 46 : 2-Amino-2-tetradecyl-1,3-propanediol

IR(KBr): 3300, 3260, 3200, 2930, 2860, 1580, 1480, 1070, 105 cm^{-1}
melting point = 68.5-69.5 °C

Example 47 : 2-(N-Ethylamino)-2-octadecyl-1,3-propanediol

IR(KBr): 3360(br), 2920, 2850, 1470, 1070 cm^{-1}
^{1}H-NMR ($CDCl_3$/TMS) δ: 3.530 (2H, d, J = 11.4Hz), 3.472 (2H, d, J = 11.4Hz), 2.545 (2H, q, J = 7.2Hz), 2.5 (2H, br.s), 1.252 (34H, m), 1.121 (3H, t, J = 7.0Hz), 0.879 (3H, t, J = 6.6Hz)
melting point = 65.0-67.0 °C

Example 48 : 2-(N,N-Dimethylamino)-2-tetradecyl-1,3-propanediol

IR(KBr): 3530, 3050(br), 2920, 2850, 1470, 1060, 1040, 1030 cm^{-1}
melting point = 51-52 °C

Example 49 : 2-Amino-2-(4-tetradecenyl)-1,3-propanediol hydrochloride

The instant compound is produced by the following steps (1) through (6).
(1) Diethyl acetamidomalonate (6.0 g) was dissolved in 50 ml of dehydrated ethanol and 2.26 g of sodium ethoxide and 5.22 g of 5-bromo-1-pentene were added thereto. The mixture was refluxed under a nitrogen atmosphere overnight. The reaction mixture was neutralized and concentrated. The concentrate was purified by silica gel column chromatography using hexane-ethyl acetate (5:1 → 2:1) as an eluent to give 4.871 g of colorless, oily diethyl 2-acetamido-2-pentenylmalonate.
IRν max ($CHCl_3$): 3450, 3000, 2950, 1740, 1680, 1500, 1480, 1280, 1200, 1100, 1020, 920, 860 cm^{-1}
^{1}H-NMR ($CDCl_3$/TMS) δ:
1.25 (2H, m), 1.255 (6H, t, J = 7.2Hz), 2.044 (2H, m), 2.040 (3H, s), 2.336 (2H, m), 4.246 (4H, q, J = 7.2Hz), 4.990 (1H, dd, J = 1.8, 17.2Hz), 5.013 (1H, dd, J = 1.8, 10.6Hz), 5.758 (1H, ddt, J = 6.2, 10.6, 17.2Hz), 6.789 (1H,

s)

(2) Diethyl 2-acetamido-2-pentenylmalonate (4.0 g) was dissolved in 210 ml of acetone and 3.3 g of N-methylmorpholine-N-oxide and 36 ml of a 1% aqueous osmium tetraoxide solution were added thereto. The mixture was stirred at room temperature for 2 hours. A solution of 700 mg of sodium sulfite in 20 ml of water was added thereto and the mixture was stirred for 15 minutes. The reaction mixture was concentrated and subjected to silica gel column chromatography using chloroform/methanol (10:1) as an eluent and a fraction having an Rf value : 0.3 (chloroform:methanol = 10:1) was concentrated. The residue was dissolved in 630 ml of 1,4-dioxane and 70 ml of a 0.2 M aqueous meta-sodium periodate solution was added thereto. The mixture was stirred at room temperature for 2 hours. The reaction mixture was filtrated, concentrated, extracted with ethyl acetate and washed with water. The hexane layer was dehydrated and concentrated to give 4.17 g of colorless, oily diethyl 2-acetamido-2-(4-formylbutyl)-malonate.

Rf value = 0.4 (chloroform:methanol = 10:1)

(3) Decane bromide (7.0 g) and 10 g of triphenylphosphine were stirred at 120 °C under a nitrogen atmosphere for 8 hours. The mixture was recrystallized from acetone-ether to give 14.4 g of colorless, crystalline decyltriphenylphosphonium bromide.

IRν max ($CHCl_3$): 2920, 2850, 1440, 1120, 1000, 680 cm^{-1}

(4) Decyltriphenylphosphonium bromide (10.85 g) was dissolved in 100 ml of dry tetrahydrofuran. Under an argon atmosphere, 13 ml of a 1.6 M n-butyl lithium/hexane solution was dropwise added thereto and the mixture was stirred for 15 minutes. The mixture was cooled to -78 °C and a solution of diethyl 2-acetamido-2-(4-formylbutyl)malonate (4.17 g)/dry tetrahydrofuran (50 ml) was dropwise added thereto and the mixture was stirred at 78 °C for 40 minutes under an argon atmosphere. Under the same conditions, a solution of t-butanol (3.3 ml)/tetrahydrofuran (15 ml) was dropwise added thereto and the mixture was stirred at room temperature under an argon atmosphere for 1.5 hours. The reaction mixture was diluted with ether and washed with water. The organic layer was dehydrated and concentrated. The concentrate was purified by silica gel column chromatography using hexane-acetic acid (5:1→ 5:2) as an eluent to give 2.1 g of colorless, oily diethyl 2-acetamido-2-(4-tetradecenyl)malonate.

IRν max ($CHCl_3$): 3450, 2940, 2850, 1740, 1680, 1500, 1380, 1280, 1200, 1100, 1020, 860 cm^{-1}

^{1}H-NMR ($CDCl_3$/TMS) δ:

0.88 (3H, t, J = 6.6Hz), 1.257 (16H, m), 1.255 (6H, t, J = 7.08Hz), 2.010 (4H, m), 2.066 (3H, s), 2.334 (2H, m), 4.243 (4H, q, J = 7.08Hz), 5.273 (1H, dt, J = 5.4, 10.8Hz), 5.376 (1H, dt, J = 5.4, 10.8Hz), 6.775 (1H, s)

(5) Diethyl 2-acetamido-2-(4-tetradecenyl)malonate (807 mg) was dissolved in 25 ml of dry tetrahydrofuran and 297 mg of lithium aluminum hydride was added thereto under ice-cooling. The mixture was stirred at room temperature for 1.5 hours. Water (0.544 ml) was added thereto under ice-cooling and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was concentrated and an appropriate amount of pyridine-acetic anhydride was added to the residue. The mixture was stirred at room temperature overnight. The reaction mixture was added to ice, extracted with ethyl acetate and washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and a saturated aqueous sodium chloride solution. The ethyl acetate layer was dehydrated, concentrated and purified by silica gel column chromatography using hexane-ethyl acetate (3:1 → 2:1) as an eluent to give 537 mg of colorless, powdery 2-acetamido-1,3-diacetoxy-2-(4-tetradecenyl)propane.

IRν max ($CHCl_3$): 3430, 2920, 2850, 1740, 1680, 1500, 1370, 1280, 1180, 1090, 1010, 855 cm^{-1}

(6) 2-Acetamido-1,3-diacetoxy-2-(4-tetradecenyl)propane (450 mg) was dissolved in 27 ml of methanol and 9 ml of a 1N aqueous sodium hydroxide solution was added thereto. The mixture was refluxed under a nitrogen atmosphere for 8 hours. The reaction mixture was neutralized with hydrochloric acid and concentrated. Water was added to the concentrate and the mixture was subjected to chromatography using Sep-Pak(C_{18}) (trade mark) and elution with methanol. The methanol eluate was concentrated to give 332 mg of pale yellow, oily 2-amino-2-(4-tetradecenyl)1,3-propanediol hydrochloride.

IRν max (KBr): 3400(br), 2920, 2850, 1590, 1500, 1470, 1050, 1040 cm^{-1}

Rf value : 0.6 (chloroform:methanol:acetic acid:water = 70:20:6:4)

Example 50 : 2-Amino-1,3-diacetoxy-2-octadecylpropane

IR($CHCl_3$): 3400(br), 2930, 2850, 1740, 1470, 1380, 1240, 1040 cm^{-1}

^{1}H-NMR ($CDCl_3$/TMS) δ:

4.014 (2H, d, J = 11.0Hz), 3.938 (2H, d, J = 11.0Hz), 2.089 (6H, s), 1.255

(34H, m), 0.879 (3H, t, J = 6.6Hz)

The instant compound is produced as follows.

(1) 2-Amino-1,3-propanediol hydrochloride (7 g) was suspended in 150 ml of N,N-dimethylformamide, and 3.8 g of triethylamine and 5.4 g of di-t-butyldicarbonate were added thereto. The mixture was stirred at 50 °C for 5 hours. Under ice-cooling, water was added to the reaction mixture and the mixture was stirred. The resultant precipitate was collected by filtration. The precipitate was recrystallized from hexaneethyl acetate (5:1) to give 6.79 g of colorless, crystalline 2-octadecyl-2-(N-t-butoxycarbonylamino)-1,3-propanediol.

IRν max (KBr): 3400(br), 3300, 2920, 2850, 1680, 1560, 1300, 1180, 1020 cm^{-1}

(2) The compound (4 g) of (1) above was dissolved in 15 ml of pyridine and 50 ml of acetic anhydride and the mixture was refluxed at room temperature overnight. The reaction mixture was poured into ice water, extracted with ethyl acetate and washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and, a saturated aqueous sodium chloride solution. After dehydration, the reaction mixture was concentrated to give 4.8 g of colorless, oily 1,3-diacetoxy-2-(N-t-butoxycarbonylamino)propane.

IRν max ($CHCl_3$): 3460, 2930, 2850, 1740, 1690(sh), 1510, 1470, 1380, 1240, 1160, 1040 cm^{-1}

(3) The compound (4.8 g) of (2) above was dissolved in 10 ml of trifluoroacetic acid and the mixture was left standing at room temperature for 15 minutes. The reaction mixture was diluted with ethyl acetate and washed with a saturated aqueous sodium hydrogencarbonate solution and saturated sodium chloride. The ethyl acetate layer was dehydrated and concentrated to give 3.83 g of colorless, oily 2-amino-1,3-diacetoxy-2-octadecylpropane.

Example 51 : 1,3-Diacetoxy-2-octadecyl-2-(N-pentanoylamino)-propane

IR($CHCl_3$): 3450, 3400, 2920, 2850, 1740, 1680, 1520, 1460, 1380, 1240, 1020 cm^{-1}

^{1}H-NMR ($CDCl_3$/TMS) δ:

5.599 (1H, s), 4.330 (2H, d, J = 11.6Hz), 4.271 (2H, d, J = 11.6Hz), 2.150 (2H, t, J = 7.2Hz), 2.078 (6H, s), 1.6 (4H, m), 1.251 (34H, m), 0.918 (3H, t, J = 7.4Hz), 0.879 (3H, t, J = 6.8Hz)

Example 52 : 2-Octadecyl-2-(N-pentanoylamino)-1,3-propanediol

IR(KBr): 3420, 3350(br), 2920, 2850, 1650, 1520, 1460, 1030 cm^{-1}

^{1}H-NMR ($CDCl_3$/TMS) δ:

5.840 (1H, s), 4.021 (2H, br.s), 3.803 (2H, d, J = 11.4Hz), 3.559 (2H, t, J = 11.4Hz), 2.231 (2H, t, J = 7.8Hz), 1.6 (4H, m), 1.251 (34H, m), 0.928 (3H, t, J = 7.4Hz), 0.878 (3H, t, J = 6.6Hz)

melting point = 73.0-73.5 °C

The instant compound is produced as follows.

(1) 2-Amino-1,3-diacetoxy-2-octadecylpropane (1.0 g) was dissolved in 50 ml of dry ether and 425 mg of N,N-dimethylaniline and 500 mg of pentanoyl chloride were added thereto. The mixture was stirred at room temperature under a nitrogen atmosphere for 6 hours. The reaction mixture was diluted with ethyl acetate and washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and a saturated aqueous sodium chloride solution. The organic layer was dehydrated and the resultant mixture was concentrated. The concentrate was purified by silica gel column chromatography using hexane-ethyl acetate (5:1→ 2:1) as an eluent to give 1.036 g of colorless, oily 1,3-diacetoxy-2-octadecyl-2-(N-pentanoylamino)propane.

IRν max ($CHCl_3$): 3450, 3400, 2920, 2850, 1740, 1680, 1520, 1460, 1380, 1240, 1020 cm^{-1}

^{1}H-NMR ($CDCl_3$/TMS) δ:

0.879 (3H, t, J = 6.8Hz), 0.918 (3H, t, J = 7.4Hz), 1.251 (34H, m), 1.6 (4H, m), 2.078 (6H, s), 2.150 (2H, t, J = 7.2Hz), 4.271 (2H, d, J = 11.6Hz), 4.330 (2H, d, J = 11.6Hz), 5.599 (1H, s)

(2) 1,3-Diacetoxy-2-octadecyl-2-(N-pentanoylamino)propane (400 mg) was dissolved in 8 ml of methanol and 17 mg of a 28% sodium methoxide-methanol solution was added thereto. The mixture was stirred at room temperature for 1 hour. Concentrated hydrochloric acid-methanol (1:11, 0.088 ml) was added thereto and the mixture was concentrated. The concentrate was subjected to silica gel column chromatography using chloroform-methanol (30:1) as an eluent. The resultant crystals were recrystallized from chloroform-hexane to give 312 mg of colorless, crystalline 2-octadecyl-2-(N-pentanoylamino)-1,3-

propanediol.

Example 53 : 2-Octadecyl-2-(N-pentylamino)-1,3-propanediol

IR(KBr): 3470(br), 2930, 2850, 1480, 1060 cm^{-1}

^{1}H-NMR ($CDCl_3$/TMS) δ:

3.990 (3H, br.s), 3.707 (2H, d, J = 12.8Hz), 3.643 (2H, d, J = 12.8Hz), 2.686 (2H, t, J = 7.8Hz), 1.252 (40H, m), 0.908 (3H, t, J = 7.0Hz), 0.879 (3H, t, J = 6.6Hz)

melting point = 53.0-54.0 °C

The instant compound is produced as follows.

1,3-Diacetoxy-2-octadecyl-2-(N-pentanoylamino)propane (400 mg) was dissolved in 30 ml of dry ether and 150 mg of lithium aluminum hydride was added thereto under ice-cooling. The mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated and 20 ml of dry tetrahydrofuran was added thereto. Under ice-cooling, 0.15 ml of water, 0.15 ml of a 15% aqueous sodium hydroxide solution and 0.45 ml of water were added in order and the reaction mixture was filtered. The filtrate was concentrated and purified by silica gel column chromatography using chloroform-methanol-acetic acid (19:1:0.1 → 10:1:0.05) as an eluent to give 153 mg of colorless, powdery 2-octadecyl-2-(N-pentylamino)-1,3-propanediol.

Example 54 : 2-(N-Decanoylamino)-1,3-diacetoxy-2-octadecylpropane

^{1}H-NMR ($CDCl_3$/TMS) δ:

5.594 (1H, s), 4.828 (2H, d, J = 12.0Hz), 4.269 (2H, d, J = 12.0Hz), 2.140 (2H, t, J = 7.2Hz), 1.6 (2H, m), 1.252 (46H, m), 0.878 (6H, t, J = 6.8Hz)

Rf value : 0.5 ($EtOAc:C_6H_{14}$ = 1:2)

Example 55 : 2-(N-Decanoylamino)-2-octadecyl-1,3-propanediol

IR(KBr): 3350, 3100, 2920, 2850, 1640, 1560, 1480, 1080 cm^{-1}

melting point = 71.5-72.5 °C

Example 56 : 2-(N-Decylamino)-2-octadecyl-1,3-propanediol

IR(KBr): 3350(br), 2920, 2850, 1470, 1060 cm^{-1}

^{1}H-NMR ($CDCl_3$/TMS) δ:

3.562 (2H, d, J = 12.8Hz), 3.498 (2H, d, J = 12.8Hz), 2.741 (3H, br.s), 2.536 (2H, t, J = 7.2Hz), 1.525 (2H, m), 1.251 (48H, m), 0.879 (6H, t, J = 6.8Hz)

melting point = 48.0-49.5 °C

Example 57 : 1,3-Diacetoxy-2-(N,N-dimethylamino)-2-octadecylpropane

^{1}H-NMR ($CDCl_3$/TMS) δ:

4.208 (2H, d, J = 11.4Hz), 4.071 (2H, d, J = 11.4Hz), 2.359 (6H, s), 2.070 (6H, s), 1.252 (34H, m), 0.878 (3H, t, J = 6.8Hz)

Rf value : 0.4 ($EtOAc:C_6H_{14}$ = 3:2)

Example 58 : 2-(N,N-Dimethylamino)-2-octadecyl-1,3-propanediol

IR(KBr): 3540, 3100(br), 2920, 2850, 1470, 1060, 1040 cm^{-1}

^{1}H-NMR ($CDCl_3$/TMS) δ:

3.715 (2H, d, J = 10.8Hz), 3.632 (2H, d, J = 10.8Hz), 3.040 (2H, br.s), 2.412 (6H, s), 1.253 (34H, m), 0.880 (3H, t, J = 6.8Hz)

melting point = 63.5-64.5 °C

The instant compound is produced as follows.

(1) 2-Amino-1,3-diacetoxy-2-octadecylpropane (700 mg) was dissolved in 35 ml of acetonitrile and 1.38 g of 37% formaldehyde and 330 mg of sodium cyanoborohydride were added thereto. The mixture was stirred at room temperature for 1 hour. Acetic acid (0.265 ml) was added thereto and the mixture was

stirred at room temperature for 1 hour. The reaction mixture was concentrated and purified by silica gel column chromatography using hexane-ethyl acetate (4:1 → 3:1) as an eluent to give 436 mg of colorless, oily 1,3-diacetoxy-2-(N,N-dimethylamino)-2-octadecylpropane.

^{1}H-NMR ($CDCl_3$/TMS) δ:

0.878 (3H, t, J = 6.8Hz), 1.252 (34H, m), 2.070 (6H, s) 2.359 (6H, s), 4.071 (2H, d, J = 11.4Hz), 4.208 (2H, d, J = 11.4Hz)

Rf value : 0.4 (ethyl acetate:hexane = 3:2)

(2) The compound (436 mg) of (1) above was dissolved in 15 ml of, methanol and 37 mg of a 28% sodium methoxide methanol solution was added thereto. The mixture was stirred at room temperature for 6 hours. The reaction mixture was concentrated and water was added thereto. The resultant precipitate was collected by filtration and recrystallized from chloroformhexane to give 295 mg of colorless, crystalline 2-(N,N-dimethylamino)-2-octadecyl-1,3-propanediol.

Example 59 : 2-Amino-2-(cis- or trans-4-tetradecenyl)-1,3-propanediol hydrochloride

Example 60 : 2-Amino-2-(3-dodecylthiopropyl)-1,3-propanediol hydrochloride

IR(KBr): 3510, 3450, 3380, 3020, 2920, 2850, 1630, 1530, 1460, 1070, 1050 cm^{-1}

^{1}H-NMR ($CDCl_3$-$DMSOd_6$/TMS) δ:

3.78 (2H, d, J = 11.8Hz), 3.68 (2H, d, J = 11.8Hz), 2.5 (4H, m), 1.26 (24H, m), 0.88 (3H, t, J = 7.1Hz)

melting point = 76-78 °C

The subject compound was prepared as follows:

(1) Dodecylthiol (5 g) was dissolved in 50 ml of dry N,N-dimethylformamide and 1 g of 60% sodium hydride was added thereto under ice-cooling. The mixture was stirred at room temperature for 1 hour. Further, a solution of 3.45 g of 3-bromopropanol in 10 ml of dry N,N-dimethylformamide was dropwise added thereto under ice-cooling and the mixture was stirred at room temperature for 3 hours. The reaction mixture was poured into ice, extracted with ether and washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and a saturated aqueous sodium chloride solution. The ether layer was dehydrated and concentrated. The resultant mixture was purified by silica gel column chromatography using hexane-ethyl acetate (10:1 → 3:1) as an eluent to give 6.071 g of 3-dodecylthiopropanol as a colorless powder.

IRν max ($CHCl_3$): 3450(br), 2930, 2850, 1460, 1050 cm^{-1}

(2) 3-Dodecylthiopropanol (3.0 g) was dissolved in 60 ml of dichloromethane and 7.66 g of carbon tetrabromide and 5.44 g of triphenylphosphine were added thereto under ice-cooling. The mixture was stirred under ice-cooling for 15 minutes. The reaction mixture was concentrated, and the residue was extracted with hexane. The extract was concentrated and purified by silica gel column chromatography using hexane as an eluent to give 3.255 g of pale yellow, oily 3-bromopropyldodecyl sulfide.

Rf value = 0.4 (hexane)

(3) Diethyl acetamidomalonate (1.6 g) was dissolved in 30 ml of dehydrated ethanol and 505 mg of sodium ethoxide and 2 g of 3-bromopropyldodecyl sulfide were added thereto. The mixture was refluxed under a nitrogen atmosphere overnight. The reaction mixture was neutralized with concentrated hydrochloric acid-ethanol (1:11) and concentrated. The concentrate was purified by silica gel column chromatography using hexane-ethyl acetate (5:1 → 5:2) as an eluent to give 1.722 g of colorless, powdery diethyl 2-acetamido-2-(3-dodecylthiopropyl)malonate.

IRν max ($CHCl_3$): 3440, 2930, 2850, 1740, 1680, 1500, 1380, 1260, 1100, 1020, 860 cm^{-1}

^{1}H-NMR ($CDCl_3$/TMS) δ:

0.88 (3H, t, J = 7.4Hz), 1.26 (18H, m), 1.26 (6H, t, J = 7.3Hz), 1.57 (4H, m), 2.04 (3H, s), 2.42 (2H, m), 2.47 (2H, t, J = 7.3Hz), 2.48 (2H, t, J = 7.3Hz), 4.25 (4H, q, J = 7.4Hz), 6.78 (1H, s)

(4) Diethyl 2-acetamido-2-(3-dodecylthiopropyl)malonate (1.5 g) was dissolved in 30 ml of dry tetrahydrofuran and 500 mg of lithium aluminum hydride was added thereto under ice-cooling. The mixture was stirred under ice-cooling for 30 minutes and at room temperature for 1 hour. To the reaction mixture was added 1.0 ml of water under ice-cooling and the mixture was stirred for 1 hour and concentrated. Pyridine (5 ml) and 10 ml of acetic anhydride were added to the residue, and the mixture was stirred at room temperature overnight. The reaction mixture was poured to ice, extracted with ethyl acetate and washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution

and a saturated aqueous sodium chloride solution. The ethyl acetate layer was dehydrated and concentrated. The concentrate was subjected to silica gel column chromatography using hexane-ethyl acetate (3: 1 → 1:1) as an eluent and recrystallized from hexane to give 852 mg of 2-acetamido-1,3-diacetoxy-2-(3-dodecylthiopropyl)-propane.

^{1}H-NMR ($CDCl_3$/TMS) δ:
0.88 (3H, t, J = 6.8Hz), 1.26 (24H, m), 1.96 (3H, s), 2.09 (6H, s), 2.5 (4H, m), 4.30 (4H, s), 5.67 (1H, s)

Rf value = 0.4 (ethyl acetate:hexane = 7:3)

(5) 2-Acetamido-1,3-diacetoxy-2-(3-dodecylthiopropyl)-propane (750 mg) was dissolved in 30 ml of methanol and 10 ml of a 1N aqueous sodium hydroxide solution was added thereto. The mixture was refluxed under a nitrogen atmosphere for 6 hours. The reaction mixture was cooled with ice and the resultant precipitate was collected by filtration. The precipitate was dissolved in methanol and 3 ml of concentrated hydrochloric acid-methanol (1:11) was added thereto. The mixture was concentrated and recrystallized from ethyl acetate-hexane to give 449 mg of colorless, crystalline 2-amino-2-(3-dodecylthiopropyl)-1,3-propanediol hydrochloride.

Example 61 : 2-Acetamido-1,3-diacetoxy-2-(3-dodecylthiopropyl)propane

^{1}H-NMR ($CDCl_3$/TMS) δ:
5.67 (1H, s), 4.30 (4H, s), 2.5 (4H, m), 2.09 (6H, s), 1.96 (3H, s), 1.26 (24H, m), 0.88 (3H, t, J = 6.8Hz)

Rf value : 0.4 ($EtOAc:C_6H_{14}$ = 7:3)

Example 62 : 2-Amino-2-(3,7,11-trimethyldodecyl)-1,3-propanediol hydrochloride

Example 63 : 2-Amino-2-(3,7,11-trimethyl-2,6,10-tridecenyl)-1,3-propanediol hydrochloride

Example 64 : 2-Amino-2-(8-oxotetradecyl)-1,3-propanediol hydrochloride

Example 65 : 2-Amino-2-(8-hydroxytetradecyl)-1,3-propanediol hydrochloride

Example 66 : 2-Amino-2-(2-dodecylaminoethyl)-1,3-propanediol hydrochloride

Example 67 : 2-Amino-2-(2-dodecanoylaminoethyl)-1,3-propanediol hydrochloride

Example 68 : 2-Amino-2-(11-carboxyundecyl)-1,3-propanediol hydrochloride

Example 69 : 2-Amino-2-(11-methoxycarbonylundecyl)-1,3-propanediol hydrochloride

Example 70 : 2-Amino-2-(12-acetoxydodecyl)-1,3-propanediol hydrochloride

Example 71 : 2-Acetamido-1,3-diacetoxy-2-(3,7,11-trimethyldodecyl)propane

Example 72 : 2-Acetamido-1,3-diacetoxy-2-(3,7,11-trimethyl-2,6,10-tridecenyl)propane

Example 73 : 2-Acetamido-1,3-diacetoxy-2-(8-oxotetradecyl)propane

Example 74 : 2-Acetamido-1,3-diacetoxy-2-(8-hydroxytetradecyl)propane

Example 75 : 2-Acetamido-1,3-diacetoxy-2-(11-methoxycarbonylundecyl)propane

Example 76 : 2-Amino-2-(2-propynyl)-1,3-propanediol

Example 77 : 2-Amino-2-(2-propenyl)-1,3-propanediol

Example 78 : 2-(N-Methylamino)-2-octadecyl-1,3-propanediol

Example 79 : 2-(N,N-Dimethylamino)-2-octadecyl-1,3-propanediol

Example 80 : 2-(N-Octadecylamino)-2-octadecyl-1,3-propanediol

Example 81 : 2-(N,N-Dioctadecylamino)-2-octadecyl-1,3-propanediol

Example 82 : 2-(N-Octadecanoylamino)-2-octadecyl-1,3-propanediol

Example 83 : 2-Amino-2-decyl-1,3-propanediol

Example 84 : 2-Amino-2-dodecyl-1,3-propanediol

Example 85 : 2-Acetamido-2-octadecyl-1,3-propanediol

Example 86 : 2-Amino-2-(2-octadecynyl)-1,3-propanediol

Example 87 : 2-Amino-2-(2-octadecenyl)-1,3-propanediol

Example 88 : 2-Amino-2-(4-phenylbutyl)-1,3-propanediol

Example 89 : 2-Amino-2-(5-phenylpentyl)-1,3-propanediol

Example 90 : 2-Amino-2-(2-phenylpropyl)-1,3-propanediol

Example 91 : 2-Amino-2-[8-(4-hexylphenyl)octyl]-1,3-propanediol

Example 92 : 2-Amino-2-[4-(4-decylphenyl)butyl]-1,3-propanediol

Example 93 : 2-Amino-2-[4-(4-pentyloxyphenyl)butyl]-1,3-propanediol

Example 94 : 2-Amino-2-[4-(4-bromophenyl)butyl]-1,3-propanediol

Example 95 : 2-Amino-2-[3-(2,4-dinitrophenyl)propyl]-1,3-propanediol

Example 96 : 2-Amino-2-[3-(4-aminophenyl)propyl]-1,3-propanediol

Example 97 : 2-Amino-2-[3-(4-decyloxyphenyl)-2-propenyl]-1,3-propanediol

Example 98 : 2-Amino-2-(14-fluorotetradecyl)-1,3-propanediol hydrochloride, melting point = 92-94 °C

Example 99 : 2-Acetamido-1,3-diacetoxy-2-(14-fluorotetradecyl)propane, melting point = 82-84 °C

Example 100 : 2-Amino-2-(9-pentyloxynonyl)-1,3-propanediol 1/5 hydrate, melting point = 32-33 °C

Example 101 : 2-Acetamido-1,3-diacetoxy-2-(9-pentyloxynonyl)propane, melting point = 62-64 °C

Example 102 : 2-Amino-2-(8-hexyloxyoctyl)-1,3-propanediol hydrochloride, melting point = 66-67 °C

Example 103 : 2-Acetamido-1,3-diacetoxy-2-(8-hexyloxyoctyl)propane, melting point = 66-69 °C

Example 104 : 2-Amino-2-(7-heptyloxyheptyl)-1,3-propanediolhydrochloride, melting point = 59-61 °C

Example 105 : 2-Acetamido-1,3-diacetoxy-2-(7-heptyloxyheptyl)propane, melting point = 53-55 °C

Example 106 : 2-Amino-2-(6-octyloxyhexyl)-1,3-propanediol hydrochloride, melting point = 58-62 °C

Example 107 : 2-Acetamido-1,3-diacetoxy-2-(6-octyloxyhexyl)propane, melting point = 47-50 °C

Example 108 : 2-Amino-2-(2-phenylethyl)-1,3-propanediol hydrochloride, melting point = 156-157 °C

Example 109 : 2-Acetamido-1,3-diacetoxy-2-(2-phenylethyl)propane, melting point = 116-117 °C

Example 110 : 2-Amino-2-(3-phenylbutyl)-1,3-propanediol hydrochloride 1/5 hydrate, melting point = 111-118 °C

Example 111 : 2-Acetamido-1,3-diacetoxy-2-(3-phenylbutyl)propane, melting point = 98-99 °C

Example 112 : 2-Amino-2-(6-phenylhexyl)-1,3-propanediol, melting point = 77-79 °C

Example 113 : 2-Acetamido-1,3-diacetoxy-2-(6-phenylhexyl)propane, melting point = 58-59 °C

Example 114 : 2-Amino-2-(10-phenyldecyl)-1,3-propanediol, melting point = 87-88.5 °C

Example 115 : 2-Acetamido-1,3-diacetoxy-2-(10-phenyldecyl)propane,

IR ; 3301, 2928, 2855, 1747, 1661, 1552 cm^{-1}

Example 116 : 2-Amino-2-[6-(3-phenylpropyloxy)hexyl]-1,3-propanediol 1/4 hydrate, melting point = 66-67 °C

Example 117 : 2-Acetamido-1,3-diacetoxy-2-[6-(3-phenylpropyloxy)hexyl]propane,

IR ; 3418, 1735, 1655, 1026 cm^{-1}

Example 118 : 2-Amino-2-[8-(phenylmethyloxy)octyl]-1,3-propanediol hydrochloride, melting point = 87-88 °C

Example 119 : 2-Acetamido-1,3-diacetoxy-2-[8-(phenylmethyloxy)octyl]propane,

IR ; 3308, 1740, 1660, 1240 cm^{-1}

Example 120 : 2-Amino-2-[3-(4-heptylcyclohexyl)propyl]-1,3-propanediol, melting point = 65-66 °C

Example 121 : 2-Acetamido-1,3-diacetoxy-2-[3-(4-heptylcyclohexyl)propyl]propane, melting point = 53-55 °C

Example 122 : 2-Amino-2-[4-(4-butylcyclohexyl)butyl]-1,3-propanediol hydrochloride 1/5 hydrate, melting point = 96-99 °C

Example 123 : 2-Acetamido-1,3-diacetoxy-2-[4-(4-butylcyclohexyl)butyl]propane, melting point = 66-69 °C

Example 124 : 2-Amino-2-(4-nonylphenylmethyl)-1,3-propanediol, melting point = 112-113 °C

Example 125 : 2-Acetamido-1,3-diacetoxy-2-(4-nonylphenylmethyl)propane, melting point = 85-89 °C

Example 126 : 2-Amino-2-[3-(4-heptylphenyl)propyl]-1,3-propanediol 1/2 hydrate, melting point = 78-80 °C

Example 127 : 2-Acetamido-1,3-diacetoxy-2-[3-(4-heptylphenyl)propyl]propane, melting point = 62-64 °C

Example 128 : 2-Amino-2-[3-(4-undecylphenyl)propyl]-1,3-propanediol, melting point = 89-91 °C

Example 129 : 2-Acetamido-1,3-diacetoxy-2-[3-(4-undecylphenyl)propyl]propane, melting point = 64-67 °C

Example 130 : 2-Amino-2-[4-(4-octylphenyl)butyl]-1,3-propanediol hydrochloride, melting point = 108-110 °C

Example 131 : 2-Acetamido-1,3-diacetoxy-2-[4-(4-octylphenyl)butyl]propane, melting point = 64-67 °C

Example 132 : 2-Amino-2-[6-(4-butylphenyl)hexyl]-1,3-propanediol, melting point = 70-71 °C

Example 133 : 2-Acetamido-1,3-diacetoxy-2-[6-(4-butylphenyl)hexyl]propane,

IR ; 3300, 2930, 2858, 1748, 1660 cm^{-1}

Example 134 : 2-Amino-2-[8-(4-ethylphenyl)octyl]-1,3-propanediol hydrochloride 1 hydrate, melting point = 47-48 °C

Example 135 : 2-Acetamido-1,3-diacetoxy-2-[8-(4-ethylphenyl)octyl]propane, melting point = 58-60 °C

Example 136 : 2-Amino-2-(4-octyloxyphenylmethyl)-1,3-propanediol, melting point = 119-120 °C

Example 137 : 2-Acetamido-1,3-diacetoxy-2-(4-octyloxyphenylmethyl)propane, melting point = 77-78 °C

Example 138 : 2-Amino-2-(4-decyloxyphenylmethyl)-1,3-propanediol hydrochloride, melting point = 100-102 °C

Example 139 : 2-Acetamido-1,3-diacetoxy-2-(4-decyloxyphenylmethyl)propane, melting point = 74-77 °C

Example 140 : 2-Amino-2-[2-(4-pentyloxyphenyl)ethyl]-1,3-propanediol hydrochloride, melting point = 134-137 °C

Example 141 : 2-Acetamido-1,3-diacetoxy-2-[2-(4-pentyloxyphenyl)ethyl]propane, melting point = 93-95 °C

Example 142 : 2-Amino-2-[3-(4-hexyloxyphenyl)propyl]-1,3-propanediol, melting point = 70-71 °C

Example 143 : 2-Acetamido-1,3-diacetoxy-2-[3-(4-hexyloxyphenyl)propyl]propane, melting point = 70-72.5 °C

Example 144 : 2-Amino-2-[3-(4-heptyloxyphenyl)propyl]-1,3-propanediol hydrochloride 1/6 hydrate, melting point = 111-113 °C

Example 145 : 2-Acetamido-2-[3-(4-heptyloxyphenyl)propyl]-1,3-propanediol, melting point = 93-95 °C

Example 146 : 2-Amino-2-[3-(4-octyloxyphenyl)propyl]-1,3-propanediol, melting point = 73-75 °C

Example 147 : 2-Acetamido-1,3-diacetoxy-2-[3-(4-octyloxyphenyl)propyl]propane, melting point = 66-69 °C

Example 148 : 2-Amino-2-[4-(4-decyloxyphenyl)propyl]-1,3-propanediol, melting point = 60-62 °C

Example 149 : 2-Acetamido-1,3-diacetoxy-2-[4-(4-decyloxyphenyl)propyl]propane, melting point = 66-67 °C

Example 150 : 2-Amino-2-[3-(3-heptyloxyphenyl)propyl]-1,3-propanediol hydrochloride, melting point = 102-103 °C

Example 151 : 2-Acetamido-2-[3-(3-heptyloxyphenyl)propyl]-1,3-propanediol,

IR ; 3305, 2932, 1652, 1376 cm^{-1}

Example 152 : 2-Amino-2-[4-(4-pentyloxyphenyl)butyl]-1,3-propanediol, melting point = 79-80 °C

Example 153 : 2-Acetamido-1,3-diacetoxy-2-[4-(4-pentyloxyphenyl)butyl]propane, melting point = 83-84 °C

Example 154 : 2-Amino-2-[4-(4-hexyloxyphenyl)butyl]-1,3-propanediol hydrochloride, melting point = 99-100 °C

Example 155 : 2-Acetamido-1,3-diacetoxy-2-[4-(4-hexyloxyphenyl)butyl]propane, melting point = 83-87 °C

Example 156 : 2-Amino-2-[5-(4-butoxyphenyl)pentyl]-1,3-propanediol hydrochloride, melting point = 79-80 °C

Example 157 : 2-Acetamido-1,3-diacetoxy-2-[5-(4-butoxyphenyl)pentyl]propane, melting point = 71-73 °C

Example 158 : 2-Amino-2-[8-(4-methoxyphenyl)octyl]-1,3-propanediol, melting point = 69-70 °C

Example 159 : 2-Acetamido-1,3-diacetoxy-2-[8-(4-methoxyphenyl)octyl]propane,

IR ; 3301, 1745, 1662, 1246 cm^{-1}

Example 160 : 2-Amino-2-[4-(4-chlorophenyl)butyl]-1,3-propanediol, melting point = 75-79 °C

Example 161 : 2-Acetamido-1,3-diacetoxy-2-[4-(4-chlorophenyl)butyl]propane, melting point = 82-84 °C

Example 162 : 2-Amino-2-[3-(4-decanoylaminophenyl)propyl]-1,3-propanediol 1/4 hydrate, melting point = 112-113 °C

Example 163 : 2-t-Butoxycarbonylamino-2-[3-(4-decanoylaminophenyl)propyl]propane, melting point = 93-94 °C

Example 164 : 2-Amino-2-[3-(4-decylaminophenyl)propyl]-1,3-propanediol 1/2 hydrate, melting point = 100-102 °C

Example 165 : 2-Amino-2-{7-[2-(4-hexylphenyl)-1,3-dioxolan-2-yl]heptyl}-1,3-propanediol 1/2 hydrate hydrochloride,

IR ; 3346, 1610, 1510, 1047 cm^{-1}

Example 166 : 2-Acetamido-1,3-diacetoxy-2-{7-[2-(4-hexylphenyl)-1,3-dioxolan-2-yl]heptyl}propane,

IR ; 3308, 1745, 1660, 1238, 1043 cm^{-1}

Example 167 : 2-Amino-2-[7-(4-hexylbenzoyl)heptyl]-1,3-propanediol hydrochloride, melting point = 114-115 °C

Example 168 : 2-Amino-2-[8-(4-hexylphenyl)octyl]-1,3-propanediol, melting point = 71-73 °C

Example 169 : 2-Acetamido-1,3-diacetoxy-2-[8-(4-hexylphenyl)octyl]propane,

IR ; 3306, 1745, 1660, 1240 cm^{-1}

Example 170 : 2-Amino-2-{3-[4-(2-decyl-1,3-dioxolan-2-yl)phenyl]propyl}-1,3-propanediol 2/3 hydrate,

IR ; 3346, 1037 cm^{-1}

Example 171 : 2-Acetamido-1,3-diacetoxy-2-{3-[4-(2-decyl-1,3-dioxolan-2-yl)phenyl]propyl}propane, melting point = 45-47 °C

Example 172 : 2-Acetamido-1,3-diacetoxy-2-{3-[4-(2-hexyl-1,3-dioxolan-2-yl)phenyl]propyl}propane 3/5 hydrate, melting point = 48-50 °C

Example 173 : 2-Amino-2-[3-(4-decanoylphenyl)propyl]-1,3-propanediol hydrochloride, melting point = 126-127 °C

Example 174 : 2-Amino-2-[3-(4-heptanoylphenyl)propyl]-1,3-propanediol hydrochloride, melting point = 129-130 °C

Example 175 : 2-Amino-2-{2-[4-(5-phenylpentyloxymethyl)phenyl]ethyl}-1,3-propanediol hydrochloride 3/2 hydrate, melting point = 105-108 °C

Example 176 : 2-Acetamido-1,3-diacetoxy-2-{2-[4-(5-phenylpentyloxymethyl)phenyl]ethyl}propane,

IR ; 3308, 1738, 1651, 1226 cm^{-1}

Example 177 : 2-Amino-2-[6-(4-hexyloxyphenyloxy)hexyl]-1,3-propanediol hydrochloride 5/4 hydrate, melting point = 90-95 °C

Example 178 : 2-Acetamido-2-[6-(4-hexyloxyphenyloxy)hexyl]-1,3-propanediol, melting point = 81-83 °C

Example 179 : 2-Amino-2-[6-(2-phenyloxyethyloxy)hexyl]-1,3-propanediol, melting point = 90-93 °C

Example 180 : 2-Acetamido-1,3-diacetoxy-2-[6-(2-phenyloxyethyloxy)hexyl]propane,

IR ; 2935, 2864, 1744, 1660, 1245 cm^{-1}

Example 181 : 2-Acetamido-2-(12-phenyloxydodecyl)-1,3-propanediol, melting point = 76-77 °C

Example 182 : 2-Amino-2-(12-phenyloxydodecyl)-1,3-propanediol hydrochloride

Example 183 : 2-(N,N-Dimethylamino)-2-[2-(4-octylphenyl)ethyl]-1,3-propanediol

Example 184 : 2-Amino-2-[2-(4-hexyloxyphenyl)ethyl]-1,3-propanediol

Example 185 : 2-Acetamido-1,3-diacetoxy-2-[2-(4-hexyloxyphenylethyl]propane

Example 186 : 2-Amino-2-{2-[4-(8-fluorooctyl)phenyl]ethyl}-1,3-propanediol

Example 187 : 2-Acetamido-1,3-diacetoxy-2-{2-[4-(8-fluorooctyl)phenyl]ethyl}propane

Example 188 : 2-Amino-2-{2-[4-(7-fluoroheptyloxy)phenyl]ethyl}-1,3-propanediol

white amorphous-like solid
Rf value = 0.09 (chloroform:methanol = 9:1)
^{1}H-NMR (DMSO-d_6) δ;
1.26-1.64 (14H, m), 3.50 (4H, s), 3.90 (2H, t, J=6.3Hz), 4.42 (2H, td, J=47.4Hz, 6.3Hz), 5.48 (2H, br.s), 6.83 (2H, d, J=8.8Hz), 7.09 (2H, d, J=8.8Hz), 7.86 (3H, br.s)
IR(KBr) 3391, 1612, 1581, 1249, 831 cm^{-1}

elemental analysis calculated	C 56.61,	H 8.71,	N 3.67
found	C 57.00,	H 8.58,	N 3.69

Example 189 : 2-Acetamido-1,3-diacetoxy-2-{2-[4-(7-fluoroheptyloxy)phenyl]ethyl}propane, colorless liquid

Rf value = 0.70 (ethyl acetate)
IR(neat) 3310, 1738, 1651, 1614, 1514, 1244, 815 cm^{-1}

Example190 : 2-Amino-2-{2-[4-(1,1-difluorooctyl)phenyl]ethyl}-1,3-propanediol

Example 191 : 2-Acetamido-1,3-diacetoxy-2-{2-[4-(1,1-difluorooctyl)phenyl]ethyl}propane

Example 192 : 2-Amino-2-{2-[4-(1,1-difluoroheptyloxy)phenyl]ethyl}-1,3-propanediol

Example 193 : 2-Acetamido-1,3-diacetoxy-2-{2-[4-(1,1-difluoroheptyloxy)phenyl]ethyl}propane

Example 194 : 2-Amino-2-{2-[4-(4-methylpentyl)phenyl]ethyl}-1,3-propanediol

Example 195 : 2-Acetamido-1,3-diacetoxy-2-{2-[4-(4-methylpentyl)phenyl]ethyl}propane

Example 196 : 2-Amino-2-[2-(4-fluorophenyl)ethyl]-1,3-propanediol hydrochloride, melting point = 169-170 °C

Example 197 : 2-Acetamido-2-[2-(4-fluorophenyl)ethyl]-1,3-propanediol, melting point = 63-65 °C

Example 198 : 2-Acetamido-1,3-diacetoxy-2-[2-(4-fluorophenyl)ethyl]propane

Example 199 : 2-Amino-2-[2-(3-fluoro-4-octylphenyl)ethyl]-1,3-propanediol

Example 200 : 2-Acetamido-1,3-diacetoxy-2-[2-(3-fluoro-4-octylphenyl)ethyl]propane

Example 201 : 2-Amino-2-[2-(2-ethyl-4-octylphenyl)ethyl]-1,3-propanediol

Example 202 : 2-Acetamido-1,3-diacetoxy-2-[2-(2-ethyl-4-octylphenyl)ethyl]propane

Example 203 : 2-Amino-2-[2-(3-methyl-4-octylphenyl)ethyl]-1,3-propanediol

Example 204 : 2-Acetamido-1,3-diacetoxy-2-[2-(3-methyl-4-octylphenyl)ethyl]propane

Example 205 : 2-Amino-2-[2-(4-heptyloxy-3-methoxyphenyl)ethyl]-1,3-propanediol 1/2 hydrate hydrochloride, melting point = 126-129 °C

^{1}H-NMR ($CDCl_3$) δ:
0.80 (3H, t, J = 6Hz), 1.22-1.36 (8H, m), 1.70-1.76 (2H, m), 1.83-1.91 (2H, m), 2.50-2.54 (2H, m), 3.30 (3H, s), 3.77 (4H, s), 3.89 (2H, t, J = 8Hz), 6.63-6.72 (3H, m)
IRν 3179, 2931, 1617, 1518, 1240, 1036 cm^{-1}

Example 206 : 2-Acetamido-1,3-diacetoxy-2-[2-(4-heptyloxy-3-methoxyphenyl)ethyl]propane, melting point = 138-139 °C

^{1}H-NMR ($CDCl_3$) δ:
0.88 (3H, t, J = 6Hz), 1.30-1.56 (10H, m), 1.96 (3H, s), 2.09 (6H, s), 2.18-2.22 (2H, m), 2.53-2.57 (2H, m), 3.86 (3H, s), 3.97 (2H, t, J = 6Hz), 4.35 (4H, s), 5.65 (1H, s), 6.70-6.80 (3H, m)
IRν 3291, 2930, 1738, 1258 cm^{-1}

elemental analysis	calculated found	C 64.49, C 64.32,	H 8.44, H 8.33,	N 3.01 N 3.03

Example 207 : 2-Amino-2-[2-(4-heptyloxy-3-methylphenyl)ethyl]-1,3-propanediol

Example 208 : 2-Acetamido-1,3-diacetoxy-2-[2-(4-heptyloxy-3-methylphenyl)ethyl]propane

Example 209 : 2-Amino-2-[2-(4-phenylmethyloxyphenyl)ethyl]-1,3-propanediol 1/5 hydrate hydrochloride melting point = 207-210 °C

^{1}H-NMR ($CDCl_3$) δ:
1.90-1.95 (2H, m), 2.59-2.63 (2H, m), 3.71 (4H, q, J = 12Hz), 5.04 (2H, s), 6.91 (2H, d, J = 8Hz), 7.13 (2H, d, J = 8Hz), 7.37-7.44 (5H, m)

IRν 3422, 1617, 1508, 1245 cm^{-1}

Example 210 : 2-Acetamido-1,3-diacetoxy-2-[2-(4-phenylmethyloxyphenyl)ethyl]propane, melting point = 150-153 °C

^{1}H-NMR ($CDCl_3$) δ:
1.95 (3H, s), 2.09 (6H, s), 2.15-2.20 (2H, m), 2.53-2.58 (2H, m), 4.34 (4H, s), 5.04 (2H, s), 5.64 (1H, s), 6.90 (2H, d, J = 8Hz), 7.10 (2H, d, J = 8Hz), 7.36-7.43 (5H, m)

IRν 3318, 1763, 1736, 1654, 1250 cm^{-1}

elemental analysis	calculated found	C 67.43, C 67.47,	H 6.84, H 6.96,	N 3.28 N 3.19

Example 211 : 2-Amino-2-[2-(4-hydroxyphenyl)ethyl]-1,3-propanediol, melting point = 180-185 °C

^{1}H-NMR ($CDCl_3$) δ:
1.61-1.66 (2H, m), 2.52-2.57 (2H, m), 3.57 (4H, s), 6.74 (2H, d, J = 8Hz), 7.03 (2H, d, J = 8Hz)

IRν 3355, 2923, 1602, 1474, 1232 cm^{-1}

elemental analysis	calculated found	C 62.54, C 62.45,	H 8.11, H 8.07,	N 6.63 N 6.68

Example 212 : 2-Acetamido-1,3-diacetoxy-2-[2-(4-hydroxyphenyl)ethyl]propane, melting point = 100-105 °C

^{1}H-NMR ($CDCl_3$) δ:
1.98 (3H, s), 2.10 (6H, s), 2.17-2.22 (2H, m), 2.52-2.56 (2H, m), 4.34 (4H, s), 5.73 (1H, s), 6.76 (2H, d, J = 9Hz), 7.03 (2H, d, J = 9Hz)

IRν 3590, 1741, 1577, 1243 cm^{-1}

Example 213 : 2-Amino-2-(9-phenyloxynonyl)-1,3-propanediol hydrochloride, melting point = 103-104 °C

elemental analysis	calculated found	C 62.50, C 62.21,	H 9.32, H 9.39,	N 4.05 N 3.95

Example 214 : 2-Acetamido-2-(9-phenyloxynonyl)-1,3-propanediol melting point = 71-73 °C

elemental analysis	calculated	C 68.34,	H 9.46,	N 3.99
	found	C 68.34,	H 9.44,	N 3.01

Example 215 : 2-Acetamido-1,3-diacetoxy-2-(9-phenyloxynonyl)propane

Example 216 : 2-Amino-2-(12-fluorododecyl)-1,3-propanediol 1/10 hydrate hydrochloride, melting point = 87-89 °C

Example217 : 2-Acetamido-1,3-diacetoxy-2-(12-fluorododecyl)propane, melting point = 57-59 °C

Example 218: 2-Amino-2-(13-fluorotridecyl)-1,3-propanediol

Example 219 : 2-Acetamido-1,3-diacetoxy-2-(13-fluorotridecyl)propane

Example 220 : 2-Ainino-2-{2-[4-(N-decyl-N-methylamino)phenyl]ethyl}-1,3-propanediol

Example 221 : 2-Acetamido-1,3-diacetoxy-2-{2-[4-(N-decyl-N-methylamino)phenyl]ethyl}propane

Example 222 : 2-Amino-2-[2-(4-heptylthiophenyl)ethyl]-1,3-propanediol

Example 223 : 2-Acetamido-1,3-diacetoxy-2-[2-(4-heptylthiophenyl)ethyl]propane

Example 224 : 2-Amino-2-[2-(4-heptylphenyl)ethyl]-1,3-propanediol

Example 225 : 2-Acetamido-1,3-diacetoxy-2-[2-(4-heptylphenyl)ethyl]propane

Example 226 : 2-Amino-2-[2-(4-heptylphenyl)-2-oxoethyl]-1,3-propanediol

Example 227 : 2-Acetamido-1,3-diacetoxy-2-[2-(4-heptylphenyl)-2-oxoethyl]propane

Example 228 : 2-Amino-2-[2-(4-heptylphenyl)-2-hydroxyethyl]-1,3-propanediol

Example 229 : 2-Acetamido-1,3-diacetoxy-2-[2-(4-heptylphenyl)-2-hydroxyethyl]propane

Example 230 : 2-Amino-2-{2-[2-(4-heptylphenyl)-1,3-dioxolan-2-yl]ethyl}-1,3-propanediol

Example 231 : 2-Acetamido-1,3-diacetoxy-2-{2-[2-(4-heptylphenyl)-1,3-dioxolan-2-yl]ethyl}propane

Example 232 : 2-Amino-2-[2-(4-octylphenyl)-2-oxoethyl]-1,3-propanediol

Example 233 : 2-Acetamido-1,3-diacetoxy-2-[2-(4-octylphenyl)-2-oxoethyl]propane

Example 234 : 2-Amino-2-[2-(4-octylphenyl)-2-hydroxyethyl]-1,3-propanediol

Example 235 : 2-Acetamido-1,3-diacetoxy-2-[2-(4-octylphenyl)-2-hydroxyethyl]propane

Example 236 : 2-Amino-2-{2-[2-(4-octylphenyl)-1,3-dioxolan-2-yl]ethyl}-1,3-propanediol

Example 237 : 2-Acetamido-1,3-diacetoxy-2-{2-[2-(4-octylphenyl)-1,3-dioxolan-2-yl]ethyl}propane

Example 261 : 2-Amino-2-(8-hydroxytetradecyl)-1,3-propanediol hydrochloride

(1) 2-Acetamido-3-acetoxy-2-acetoxymethyl-14-oxoicosa-6-enoic acid-δ-lactone

Acetic anhydride (200 ml) and pyridine (20 ml) were added to 2-amino-3,4-dihydroxy-2-dihydroxymethyl-14-oxoicosa-6-enoic acid (20 g) and the mixture was stirred at room temperature overnight. The reaction mixture was poured into ice water and extracted with ethyl acetate. The ethyl acetate layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine in order. The resultant mixture was dried over magnesium sulfate and the solvent was distilled away to give the subject compound (22.9 g).

(2) 14-Hydroxy-2-acetamido-3-acetoxy-2-acetoxymethyl-14-oxoicosa-6-enoic acid-δ-lactone

Deionized water (150 ml) was added to a solution of the above-mentioned compound (12.8 g) in dioxane. The mixture was stirred in an ice bath for about 30 minutes while bubbling carbon dioxide to saturation, thereby to make the solution weak acidic. Sodium borohydride (2.41 g) was added thereto and the mixture was stirred for 1 hour. The reaction mixture was acidified with 1N hydrochloric acid and made weak acidic with 1N sodium hydroxide. The resultant mixture was concentrated and extracted with ethyl acetate. The ethyl acetate layer was washed with a saturated sodium hydrogencarbonate solution and saturated brine in order and dried over magnesium sulfate. The solvent was distilled away and the residue obtained was purified by silica gel column chromatography (eluent; chloroform: methanol = 50:1) to give the subject compound (7.49 g).

IR : 3440, 2920, 2850, 1750, 1680 cm^{-1}

(3) 14-t-Butyldimethylsilyloxy-2-acetamido-3-acetoxy-2-acetoxymethyl-14-oxoicosa-6-enoic acid-δ-lactone

Imidazole (4.97 g) and t-butyldimethylsilyl chloride (5.50 g) were added to a solution of the compound (7.49 g) as mentioned above in N,N-dimethylformamide (75 ml) and the mixture was stirred at 60 °C for 1 hour. Deionized water was added to the reaction mixture under ice-cooling and the mixture was stirred for 30 minutes and then at room temperature for 30 minutes. Deionized water was added thereto and the mixture was extracted with diethyl ether. The diethyl ether layer was concentrated and dried over magnesium sulfate. The solvent was distilled away and the residue obtained was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:2) to give the subject compound (8.50 g).

IR : 3440, 2920, 2850, 1750, 1680, 830 cm^{-1}

(4) 5,6-Dihydroxy-14-t-butyldimethylsilyloxy-2-acetamido-3-acetoxy-2-acetoxymethyl-14-oxoicosa-6-enoic acid-δ-lactone

N-Methylmorpholine-N-oxide (3.19 g) and a 1% aqueous osmium solution (34.5 ml) were added to a solution of the compound (8.50 g) as mentioned above in acetone (207 ml) and the mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated and extracted with ethyl acetate. The ethyl acetate layer was washed with a saturated sodium sulfite solution, 1N hydrochloric acid, a saturated sodium hydrogencarbonate solution and saturated brine in order and dried over magnesium sulfate. The solvent was distilled away to give the subject compound (8.05 g).

IR : 3440, 2920, 2850, 1750, 1680, 830 cm^{-1}

(5) 8-t-Butyldimethylsilyloxytetradecanal

A 0.2N aqueous sodium periodate solution (183 ml) was added to a solution of the compound (8.05 g) as mentioned above in dioxane (610 ml) and the mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated and extracted with hexane. The hexane layer was dried over magnesium sulfate and the solvent was distilled away to give the subject compound (4.1 g, yield 98.4%).

IR : 2920, 2850, 1720, 830 cm^{-1}

(6) 8-t-Butyldimethylsilyloxytetradecanol

Deionized water (40 ml) was added to a solution of the compound (4.1 g) as mentioned above in dioxane (120 ml) and sodium borohydride (1.15 g) was added thereto under ice-cooling. The mixture was stirred at room temperature for 30 minutes. The reaction mixture was concentrated and extracted with ethyl acetate. The ethyl acetate layer was washed with 1N hydrochloric acid, a saturated sodium hydrogencarbonate solution and saturated brine in order, and dried over magnesium sulfate. The solvent was distilled away and the residue obtained was purified by silica gel column chromatography (eluent; ethyl ace-

tate:hexane = 1:10) to give the subject compound (3.74 g).
IR : 2920, 2850, 1710, 830 cm^{-1}

(7) 1-Iodo-8-t-butyldimethylsilyloxytetradecane

Imidazole (1.85 g), triphenylphosphine (7.14 g) and iodine (5.53 g) were added to a solution of the compound (3.74 g) as mentioned above in benzene (200 ml) and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was extracted with ethyl acetate and washed with a saturated sodium sulfite solution and saturated brine in order. The ethyl acetate layer was dried over magnesium sulfate and the solvent was distilled away. The residue obtained was purified by silica gel column chromatography (eluent; hexane) to give the subject compound (4.42 g).
IR : 2920, 2850, 830 cm^{-1}

(8) Diethyl 2-acetamido-2-(8-t-butyldimethylsilyloxytetradecyl)malonate

Diethyl acetamidomalonate (2.54 g) and sodium ethoxide (0.80 g) were added to a solution of the compound (4.42 g) as mentioned above in dehydrated ethanol (200ml) and the mixture was refluxed under heating in a stream of nitrogen overnight. The reaction mixture was concentrated and the residue obtained was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:10) to give the subject compound (2.81 g).
^{1}H-NMR ($CDCl_3$) δ:
0.03 (6H, s), 0.84 (9H, m), 1.23 (18H, m), 1.23 (3H, t, J = 7.0Hz), 1.35 (3H, m), 2.01 (3H, s), 2.28 (2H, m), 3.57 (1H, q, J = 6.0Hz), 4.215 (2H, q, J = 7Hz), 6.74 (1H, s)
IR : 3440, 2920, 2850, 1740, 1680, 830 cm^{-1}

(9) 2-Acetamido-1,3-diacetoxy-2-(8-t-butyldimethylsilyloxytetradecyl)propane

Sodium borohydride (1.77 g) was added to a solution of the compound (3.38 g) as mentioned above in methanol (13 ml) and the mixture was allowed to stand at room temperature for 1 hour. The reaction mixture was extracted with ethyl acetate and washed with 1N hydrochloric acid, a saturated sodium hydrogencarbonate solution and saturated brine in order. The ethyl acetate layer was dried over magnesium sulfate and the solvent was distilled away. Acetic anhydride (19.6 ml) and pyridine (1.96 ml) were added to the residue obtained and the mixture was stirred at room temperature overnight. The reaction mixture was poured into ice water and extracted with ethyl acetate. The ethyl acetate layer was washed with 1N hydrochloric acid, a saturated sodium hydrogencarbonate solution and saturated brine in order and dried over magnesium sulfate. The solvent was distilled away and the residue obtained was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:2) to give the subject compound (2.04 g).
^{1}H-NMR ($CDCl_3$) δ:
0.009 (6H, s), 0.86 (3H, t), 0.86 (9H, s), 1.24 (18H, m), 1.36 (4H, m), 1.82 (2H, m), 1.94 (3H, s), 2.06 (6H, s), 3.58 (1H, q, J = 8Hz), 4.26 (2H, d, J = 11.2Hz), 4.29 (2H, d, J = 11.3Hz), 5.59 (1H, s)
IR : 3440, 2920, 2850, 1740, 1680, 830 cm^{-1}

(10) 2-Acetamido-1,3-diacetoxy-2-(8-hydroxytetradecyl)propane

A solution of the compound (2.04 g) as mentioned above in 0.01N hydrochloric acid-methanol (37.6 ml) was allowed to stand at room temperature for 3 hours. Deionized water was added thereto and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with a saturated sodium hydrogencarbonate solution and a saturated sodium chloride solution in order and dried over magnesium sulfate. The solvent was distilled away and the residue obtained was purified by silica gel column chromatography (eluent; ethyl acetate: hexane = 1:1) to give the subject compound (1.15 g).
melting point = 82-84 °C
^{1}H-NMR ($CDCl_3$) δ:
0.85 (3H, t, J = 6.9Hz), 1.26 (18H, m), 1.40 (4H, m), 1.82 (2H, m), 1.93 (3H, s), 2.05 (6H, s), 3.55 (1H, m), 4.25 (2H, d, J = 11.2Hz), 4.28 (2H, d, J = 11.7Hz), 5.59 (1H, s)
IR : 3440, 2920, 2850, 1720, 1680 cm^{-1}

(11) 2-Amino-2-(8-hydroxytetradecyl)-1,3-propanediol hydrochloride

1N Sodium hydroxide was added to a solution of the compound (300 mg) as mentioned above in methanol (12.6 ml) and the mixture was refluxed under heating in a stream of nitrogen for 6 hours. The reaction mixture was concentrated and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over magnesium sulfate. The solvent was distilled away. 1N Hydrochloric acid-methanol (1.4 ml) was added to the residue obtained and the mixture was concentrated to give the subject compound (230 mg).
melting point = 106-108 °C
^{1}H-NMR ($CDCl_3$) δ:
0.84 (3H, t, J = 6.8Hz), 1.22 (22H, m), 1.48 (2H, d, J = 10.3Hz), 3.40 (2H, d, J = 10.3Hz), 3.44 (2H, d, J = 12.2Hz), 4.21 (1H, m), 5.28 (2H, br.s), 7.74 (3H, br.s)
IR : 3350, 2900, 2850 cm^{-1}

Example 262 : 2-Amino-2-(8-oxotetradecyl-1,3-propanediol hydrochloride

(1) 2-Acetamido-1,3-diacetoxy-2-(8-oxotetradecyl)propane

Pyridinium chlorochromate (301.5 mg) was added to a solution of 2-acetamido-1,3-diacetoxy-2-(8-hydroxtetradecyl)propane (300 mg) in dichloromethane (19 ml) and the mixture was stirred at room temperature for 2 hours in a stream of nitrogen. Ether (38 ml) and magnesium sulfate (appropriate amount) were added thereto and the mixture was stirred for 10 minutes. The reaction mixture was suction-filtered and the filtrate was concentrated. The concentrate was extracted with ethyl acetate and the ethyl acetate layer was washed with 1N hydrochloric acid, a saturated sodium hydrogencarbonate solution and saturated brine in order. The resultant mixture was dried over magnesium sulfate. The solvent was distilled away to give the subject compound (290 mg).
melting point = 88-89 °C
^{1}H-NMR ($CDCl_3$) δ:
0.88 (3H, t, J = 7.1Hz), 1.27 (14H, m), 1.55 (4H, m), 1.84 (2H, dd, J = 8.8, 15.6Hz), 2.08 (6H, s), 2.38 (4H, t, J = 7.4Hz), 4.28 (2H, d, J = 11.3Hz), 4.31 (2H, d, J = 11.2Hz), 5.63 (1H, s)
IR : 2920, 2850, 1740-1680 cm^{-1}

(2) 2-Amino-2-(8-oxotetradecyl)-1,3-propanediol hydrochloride

1N Sodium hydroxide (4.1 ml) was added to a solution of the compound (290 mg) as mentioned above in methanol (12.2 ml) and the mixture was refluxed under heating in a nitrogen flow for 6 hours. The reaction mixture was concentrated and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over magnesium sulfate. The solution was distilled away and 1N hydrochloric acid-methanol (1.2 ml) was added to the residue obtained. The mixture was concentrated and the residue obtained was recrystallized from ethyl acetate to give the subject compound (176 mg).
melting point = 121-122 °C
^{1}H-NMR ($CDCl_3$) δ:
0.614 (3H, t, J = 6.3Hz), 1.03 (18H, m), 1.28 (4H, m), 1.41 (2H, m), 2.12 (4H, t, J = 7.3Hz), 3.38 (2H, d, J = 12.2Hz), 3.48 (2H, d, J = 12.2Hz), 4.71 (2H, br.s), 7.65 (3H, br.s)
IR : 3420-3340, 3030, 2920, 2850, 1700 cm^{-1}

Example 263 : 2-Amino-2-(2-N-dodecylaminoethyl)-1,3-propanediol hydrochloride

(1) Diethyl aminomalonate hydrochloride (10 g) was dissolved in 100 ml of N,N-dimethylformamide, and 6.3 g of triethylamine and 12.1 g of di-t-butyldicarbonate were added thereto. The mixture was stirred at 60 °C for 1 hour. Water was added to the reaction mixture under ice-cooling and the mixture was stirred at room temperature. The reaction mixture was extracted with ether, dehydrated and concentrated. The resultant mixture was purified by silica gel column chromatography using hexane-ethyl acetate (10:1 → 5:1) as an eluent to give 13 g of colorless, oily diethyl N-t-butoxycarbonylaminomalonate.
IRν_{max} ($CHCl_3$) : 3450, 2970, 1740(sh), 1710, 1490, 1375, 1340, 1160, 1060, 1020, 860 cm^{-1}

(2) Diethyl N-t-butoxycarbonylaminomalonate (5 g) was dissolved in 100 ml of dehydrated ethanol, and 1.53 g of sodium ethoxide and 2.7 g of aryl bromide were added thereto. The mixture was refluxed under a nitrogen atmosphere for 12 hours. The reaction mixture was concentrated and purified by silica gel column chromatography using hexane-ethyl acetate (20:1 → 10: 1 → 8:1) to give 4.8 g of colorless, oily diethyl 2-aryl-N-t-butoxycarbonylaminomalonate.

IRν_{max} ($CHCl_3$) : 3450, 2980, 2860, 1740(sh), 1710, 1480, 1400, 1370, 1310, 1160, 1080, 1060, 1020, 915, 860 cm^{-1}

(3) Diethyl 2-aryl-N-t-butoxycarbonylaminomalonate (4.8 g) was dissolved in 30 ml of methanol and 4.34 g of sodium borohydride was added thereto. The mixture was allowed to stand at room temperature for 2 hours. Ethyl acetate was added to the reaction mixture and the mixture was washed with a 1N aqueous hydrochloric acid solution, a saturated aqueous sodium hydrogencarbonate solution and a saturated aqueous sodium chloride solution. The resultant mixture was dehydrated and concentrated. The residue was dissolved in 32 ml of N,N-dimethylformamide, and 5.72 g of imidazole and 6.33 g of t-butyldimethylsilyl chloride were added thereto. The mixture was stirred at 60 °C for 1 hour.

Water was added to the reaction mixture under ice-cooling and the mixture was stirred at room temperature. The resultant mixture was extracted with ether, dehydrated and concentrated. The concentrate was purified by silica gel column chromatography using hexane-ethyl acetate (10:1) as an eluent to give 3.8 g of colorless, oily 2-aryl-2-(N-t-butoxycarbonylam ino)-1,3-propanediol bis-t-butyldimethylsilyl ether. Rf value = 0.7 (hexane-ethyl acetate = 10:1)

(4) 2-Aryl-2-(N-t-butoxycarbonylamino)-1,3-propanediol bis-t-butyldimethylsilyl ether (3.8 g) was dissolved in 300 ml of acetone, and 2.45 g of N-methylmorpholine-N-oxide and 43 ml of a 1% aqueous osmium tetraoxide solution were added thereto. The mixture was stirred at room temperature for 4 hours. The reaction mixture was concentrated and ethyl acetate was added thereto. The mixture was washed with a saturated aqueous sodium sulfite solution, a 1N aqueous hydrochloric acid solution, a saturated aqueous sodium hydrogencarbonate solution and a saturated aqueous sodium chloride solution. After dehydration, the resultant mixture was concentrated to give 4.3 g of colorless, oily 2-(2,3-dihydroxypropyl)-2-(N-t-butoxycarbonylamino)-1,3-propanediol bis-t-butyldimethylsilyl ether.

IRν_{max} ($CHCl_3$) : 3450(br), 2940, 2850, 1710, 1500, 1470, 1400, 1370, 1260, 1160, 1080(br), 840 cm^{-1}

(5) 2-(2,3-Dihydroxypropyl)-2-(N-t-butoxycarbonylamino)-1,3-propanediol bis-t-butyldimethylsilyl ether (4.3 g) was dissolved in 600 ml of 1,4-dioxane and a solution of 3.8 g of meta-sodium periodate in 90 ml of water was added thereto. The mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated and hexane was added thereto. After washing with water, the resultant mixture was dehydrated and concentrated to give 3.76 g of colorless, oily 2-(N-t-butoxycarbonylamino)-2-(2-formylethyl)-1,3-propanediol bis-t-butyldimethylsilyl ether.

Rf value = 0.7 (hexane-ethyl acetate = 5:1)

(6) 2-(N-t-Butoxycarbonylamino)-2-(2-formylethyl)-1,3-propanediol bis-t-butyldimethylsilyl ether (1.2 g) was dissolved in 20 ml of methanol and a solution of 2.89 g of dodecylamine in 5.2 ml of concentrated hydrochloric acid-methanol (1:11) and 245 mg of sodium cyanoborohydride were added thereto. The mixture was stirred at room temperature overnight. The reaction mixture was concentrated and ethyl acetate was added thereto. A 1N aqueous hydrochloric acid solution was added until the aqueous layer assumed acidity; a 1N aqueous sodium hydroxide solution was added until the aqueous layer assumed weak acidity; and the solution was partitioned. The ethyl acetate layer was washed with a saturated aqueous sodium chloride solution, dehydrated and concentrated. The resultant mixture was purified by silica gel column chromatography using hexane-ethyl acetate (3:1 → 2:1 → 1:1) as an eluent to give 956 mg of colorless, oily 2-(2-N-dodecylaminoethyl)-2-(butoxycarbonylamino)-1,3-propanediol bis-t-butyldimethylsilyl ether.

IRν_{max} ($CHCl_3$) : 3450, 2920, 2850, 1710, 1500, 1460, 1400, 1370, 1260, 1160, 1100(br), 840 cm^{-1}

^{1}H-NMR ($CDCl_3$) δ:

5.31 (1H, s, NHBoc), 3.69 (2H, d, J = 8Hz, OCH_{2a} × 2), 3.61 (2H, d, J = 8Hz, OCH_{2b} × 2), 2.66 (2H, t, J = 8Hz, H_2C-N), 2.55 (2H, t, J = 8Hz, N-CH_2), 1.85 (2H, t, J = 8Hz, -C-CH_2), 1.40 (9H, s, Boc.-t-Bu), 1.24 (20H, m, CH_2 × 10), 0.85 (21H, m, Si-tBu × 2 and CH_2CH_3), 0.03 (12H, s, Si-CH_3 × 4)

(7) 2-(2-N-Dodecylaminoethyl)-2-(N-t-butoxycarbonylamino)-1,3-propanediol bis-t-butyldimethylsilyl ether (100 mg) was dissolved in 2 ml of methanol and 1.6 ml of concentrated hydrochloric acid-methanol (1:11) was added thereto. The mixture was warmed at 40 °C for 3 hours. The reaction mixture was concentrated to give 58 mg of pale yellow, oily 2-amino-2-(2-N-dodecylaminoethyl)-1,3-propanediol

hydrochloride.

IRν_{max} (KBr) : 3350(br), 2920, 2850, 1600, 1460, 1060 cm^{-1}

^{1}H-NMR (DMSO-d_6) δ:

9.00 (2H, br.s, $^+NH_2Cl^-$), 8.04 (3H, br.s, $^+NH_3Cl^-$), 5.51 (2H, s, OH × 2), 3.47 (2H, s, OCH_2), 3.45 (2H, s, OCH_2), 2.99 (2H, m, H_2CN), 2.81 (2H, m, NCH_2), 1.96 (2H, m, -C-CH_2), 1.23 (20H, m, CH_2 × 10), 0.84 (3H, t, 6.8Hz, CH_3)

Example 264 : 2-Amino-2-(11-methoxycarbonylundecyl)-1,3-propanediol hydrochloride

2-Acetamido-1,3-diacetoxy-2-(12-hydroxydodecyl)propane (426 mg) was dissolved in 2.7 ml of dry dimethylformamide and 1.345 g of pyridinium dichromate was added thereto. The mixture was stirred at room temperature day and night under a nitrogen atmosphere. The reaction mixture was poured into water and extracted twice with ether. The ether layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away under reduced pressure and 17 ml of methanol and 4.23 ml of a 1N aqueous sodium hydroxide solution were added to the residue. The mixture was refluxed under heating under a nitrogen atmosphere for 6 hours. The reaction mixture was passed through a strongly acidic ion exchange resin, Amberlite IR-120B column, and the eluate was concentrated. The concentrate was dissolved in methanol and the mixture was acidified with hydrochloric acid. The solvent was distilled away under reduced pressure to give 122 mg of the subject compound.

melting point = 100.0-104.0 °C

IR(cm^{-1}) : 3370, 2920, 2850, 1740, 1500, 1470, 1170, 1080

NMR (DMSO) δ:

7.684 (3H, br.s), 5,275 (2H, br.s), 3.563 (3H, s), 3.441 (1H, d, J = 11.2Hz), 3.430 (1H, d, J = 11.2Hz), 3.402 (1H, d, J = 11.7Hz), 3.390 (1H, d, J = 11.2Hz), 2.272 (2H, t, J = 7.3Hz), 1.229 (20H, s)

Example 265 : 2-Amino-2-(11-carboxyundecyl)-1,3-propanediolhydrochloride

2N Hydrochloric acid (0.5 ml) was added to 10 mg of 2-amino-2-(11-methoxycarbonylundecyl)-1,3-propanediol hydrochloride and the mixture was heated at 90 °C for 1 hour. The solvent was distilled away under reduced pressure to give 10 mg of the subject compound.

NMR (DMSO) δ:

11.992 (1H, br.s, COOH), 7.771 (3H, br.s, $^+NH_3$), 5.292 (2H, t, J = 4.9Hz, OH × 2), 3.417 (4H, ddd, J = 16.5, 11.7, 5.0Hz, CH_2O × 2), 2.168 (2H, t, J = 7.4Hz, CH_2COO), 1.224 (20H, s, CH_2 × 10)

Example 266 : 2-Acetamido-1,3-diacetoxy-2-(8-acetoxytetradecyl)propane

^{1}H-NMR ($CDCl_3$) δ:

0.85 (3H, t, J = 6.8Hz), 1.24 (18H, m), 1.47 (4H, m), 1.82 (2H, m), 1.94 (3H, s), 2.05 - 2.01 (9H, s), 4.25 (2H, d, J = 11.7Hz), 4.29 (2H, d, J = 11.7Hz), 4.83 (1H, q, J = 6.3Hz), 5.62 (1H, s)

IR : 3400, 2920, 2850, 1720, 1680 cm^{-1}

Example 267 : 2-Acetamido-1,3-diacetoxy-2-(3,7,11-trimethyldodecyl)propane

^{1}H-NMR ($CDCl_3$) δ:

5.589 (1H, br.s), 4.293 (4H, dd, J = 13.7, 12.3Hz), 2.073 (6H, s), 1.956 (3H, s), 1.857 (1H, qui, J = 13.7Hz), 1.844 (1H, qui, J = 13.3Hz), 1.513 (1H, septet, J = 6.6Hz), 1.345 - 1.040 (16H, m), 0.857 (6H, d, J = 6.4Hz), 0.848 (3H, d, J = 6.4Hz), 0.831 (3H, d, J = 6.8Hz)

Example 268 : 2-Acetamido-1,3-diacetoxy-(3,7,11-trimethyl-2,6,10-tridecenyl)propane

^{1}H-NMR ($CDCl_3$) δ:

5.57 (1H, br.s), 5.07 (3H, m), 4.28 (4H, s), 2.60 (2H, d, J = 7.8Hz), 2.01 (6H, s), 2.05 - 1.94 (8H, m), 1.94 (3H, s), 1.70 - 1.57 (12H, m)

Example 269 : 2-Acetamido-1,3-diacetoxy-2-(11-methoxycarbonylundecyl)propane

melting point = 49.5-51.5 °C
IRν : 3300, 2930, 2850, 1740, 1655, 1580, 1475, 1390, 1240, 1060 cm^{-1}
^{1}H-NMR ($CDCl_3$) δ:
5.61 (1H, br.s), 4.265 (4H, dd, J = 13.6Hz, 11.2Hz), 3.635 (3H, s), 2.272 (2H, t, J = 7.6Hz), 2.051 (6H, s), 1.934 (3H, s), 1.836 - 1.817 (2H, m), 1.225 (18H, br.s)

Example 270 : 2-Acetamido-1,3-diacetoxy-(12-acetoxydodecyl)propane

melting point = 67.5-69.0 °C
^{1}H-NMR ($CDCl_3$) δ:
5.607 (1H, br.s), 4.267 (4H, dd, J = 13.7, 11.3Hz), 4.021 (2H, t, J = 6.9Hz), 2.052 (6H, s), 2.017 (3H, s), 1.934 (3H, s), 1.840 - 1.819 (2H, m), 1.225 (20H, br.s)

Example 271 : 2-Amino-2-(1,2,12-trihydroxyoctadecyl)-1,3-propanediol

^{1}H-NMR (400MHz, in CD_3OD) δ:
3.85 - 3.73 (7H, m), 1.60 (2H, m), 1.45 - 1.25 (26H, m), 0.90 (3H, t)
IRν_{max} (KBr): 3350(br), 2920, 2850, 1560, 1480, 1420, 1060 cm^{-1}

Example 272 : 2-Amino-2-(1,2-dihydroxy-12-oxooctadecyl)-1,3-propanediol

^{1}H-NMR (400MHz, in CD_3OD) δ:
5.48 (2H, m), 3.86 - 3.72 (6H, m), 2.44 (4H, t), 2.29 (2H, t), 2.02 (2H, t), 1.53 (4H, quintet), 1.29 (12H, br.s), 0.89 (3H, t)
IRν_{max} ($CHCl_3$): 3300, 2925, 2850, 1710, 1560, 1420, 1060, 980 cm^{-1}

Example 273 : 2-Amino-2-(1,2-dihydroxy-12-hydroxyiminooctadecyl)-1,3-propanediol

^{1}H-NMR (400MHz, in CD_3OD) δ:
3.85 - 3.73 (4H, m), 2.42 (2H, t), 2.15 (2H, t), 1.62 - 1.32 (24H, m)-,0.89 (3H, t)
IRν_{max} ($CHCl_3$): 3300(br), 2920, 2850, 1560, 1420, 1050 cm^{-1}

Example 274 : 2-Amino-2-(1,2,12-trihydroxy-4-octadecenyl)-1,3-propanediol

A lactone compound (2.00 g) of 2-amino-3-hydroxy-2-(1,2-dihydro-12-oxo-4-octadecenyl)propionic acid was dissolved in 66 ml of dry tetrahydrofuran and 800 mg of lithium aluminum hydride was portionwise added thereto at room temperature with stirring. The mixture was stirred at room temperature for 40 minutes and 0.8 ml of water, 0.8 ml of a 15% aqueous sodium hydroxide solution and 2.4 ml of water were added thereto in order. The insoluble matters were filtered off. The filtrate obtained was concentrated under reduced pressure, and the residue was washed with water and dried under reduced pressure to give 408 mg of the subject compound.
IRν_{max} (KBr): 3280, 2920, 2850, 1640, 1470, 1400, 1075, 970cm^{-1}
^{1}H-NMR (300MHz, in CD_3OD, Ref:TMS) δ:
5.57 (1H, dt, J = 15.3 and 6.6Hz), 5.43 (1H, dt, J = 15.3 and 6.9Hz), 3.85 (1H, dt, J = 6.9 and 1.0Hz), 3.84 - 3.73 (5H, m), 3.67 (1H, d, J = 1.0Hz), 2.31 (2H, br.t, J = 6.7Hz), 2.02 (2H, br.q, J = 6.4Hz), 1.42 - 1.31 (20H, m), 0.90 (3H, t, J = 6.8Hz)

Example 275 : 2-Amino-2-(1,2-dihydroxy-4-octadecenyl)-1,3-propanediol

A lactone compound (978 mg) of 2-amino-3-hydroxy-2-(1,2-dihydroxy-4-octadecenyl)propionic acid and 403 mg of lithium aluminum hydride were reacted in 33 ml of dry tetrahydrofuran according to the method of Example 274 to give 222 mg of the subject compound.
IRν_{max} (KBr) cm^{-1}: 3300, 2920, 2850, 1575, 1480, 1390, 1060, 1105, 975

^{1}H-NMR (200MHz, in CD_3OD, Ref:TMS) δ:
5.57 (1H, dt, J = 15.4 and 6.4Hz), 5.42 (1H, dt, J = 15.4 and 6.5Hz), 3.88 - 3.66 (6H, m), 2.31 (2H, t, J = 6.7Hz), 2.04 - 1.93 (2H, m), 1.28 (22H, br.s), 0.90 (t, J = 6.5Hz)

Example 276 : 2-Amino-2-(1,2-dihydroxyoctadecyl)-1,3-propanediol

2-Amino-2-(1,2-dihydroxy-4-octadecenyl)-1,3-propanediol (68.0 mg) was dissolved in 14 ml of methanol and 6.8 mg of 5% palladium-carbon was added thereto. The catalytic reduction was conducted at ordinary temperature and at atmospheric pressure day and night. After the reaction, the catalyst was filtered off and the filtrate was concentrated under reduced pressure to give 34.3 mg of the subject compound.

IRν_{max} (KBr) cm^{-1}: 3300, 2920, 2850, 1575, 1460, 1370, 1060

^{1}H-NMR (200MHz, in CD_3OD, Ref :TMS) δ:
3.77 (6H, m), 1.65 (2H, m), 1.27 (28H, br.s), 0.89 (3H, t, J = 6.5Hz)

Example 277 : 2-Amino-2-(1,12-dihydroxy-4-octadecenyl)-1,3-propanediol

According to the method of Example 274, 35.0 mg of 2-amino-3-hydroxy-2-(1-hydroxy-12-oxo-4-octadecenyl)propionic acid and 14.4 mg of lithium aluminum hydride were reacted in 2.0 ml of dry tetrahydrofuran to give 8.9 mg of the subject compound.

IRν_{max} (KBr) cm^{-1}: 3300, 2920, 2850, 1640, 1400, 970

^{1}H-NMR (200MHz, in CD_3OD, Ref:TMS) δ:
5.40 (2H, m), 3.97 - 3.70 (5H, m), 3.58 (1H, m), 1.94 (4H, m), 1.70 - 1.21 (22H, m), 0.88 (3H, t, J = 6.5Hz)

In the same manner as above, the following compounds are obtained.

Example 278 : 2-Amino-2-(1,2,12-trihydroxyoctadecyl)-1,3-propanediol

Example 279 : 2-Amino-2-(1,12-dihydroxyoctadecyl)-1,3-propanediol

Example 280 : 2-Amino-2-[2-(4-heptyloxyphenyl)ethyl]-1,3-propanediol

(1) 2-(4-Heptyloxyphenyl)ethanol

2-(4-Hydroxyphenyl)ethanol (10.0 g) and sodium methoxide (4.30 g) were added to methanol (120 ml) and the mixture was refluxed under heating for 30 minutes. A solution of heptyl bromide (14.2 g) in methanol (30 ml) was dropwise added thereto and the mixture was refluxed under heating for 6 hours with stirring. The reaction mixture was concentrated and the concentrate was poured into ice water. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over magnesium sulfate. The solvent was distilled away and the resultant residue was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:2) to give the subject compound (10.81 g).

melting point = 37-39 °C

Rf value : 0.44 (ethyl acetate:n-hexane = 1:2)

^{1}H-NMR ($CDCl_3$) δ:
0.89 (3H, t, J = 6.0Hz), 1.10-1.99 (11H, m), 2.81 (2H, t, J = 6.25Hz), 3.68-4.05 (4H, m), 6.85 (2H, d, J = 8.7Hz), 7.15 (2H, d, J = 8.7Hz)

IR : 3312, 1610, 1514, 1249 cm^{-1}

MS(EI): 236(M^+)

(2) 2-(4-Heptyloxyphenyl)ethylmethanesulfonate

Triethylamine (4.2 g) was added to a solution of the above-mentioned compound (10.81 g) in tetrahydrofuran (300 ml) and the mixture was cooled with ice. Methanesulfonyl chloride (5.23 g) was dropwise added thereto and the mixture was stirred at room temperature for 2 hours. The reaction mixture was poured into ice water and extracted with dichloromethane. The dichloromethane layer was washed with a saturated potassium hydrogencarbonate solution, a 1% aqueous hydrochloric acid solution and saturated brine and dried over magnesium sulfate. The solvent was distilled away and the resultant residue was

purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:5) to give the subject compound (11.32 g). melting point = 35-36 °C

Rf value : 0.33 (ethyl acetate:n-hexane = 1:2)

^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, t, J = 6.0Hz), 1.10-1.95 (10H, m), 2.86 (3H, s), 3.00 (2H, t, J = 7.5Hz), 3.94 (2H, t, J = 6.3Hz), 4.39 (2H, t, J = 7.0Hz), 6.85 (2H, d, J = 8.7Hz), 7.15 (2H, d, J = 8.7Hz)

IR : 1354, 1516, 1249cm^{-1}

MS(EI): 314(M^+)

(3) 2-(4-Heptyloxyphenyl)ethyl iodide

Sodium iodide (10 g) was added to a solution of the above-mentioned compound (11.32 g) in 2-butanone (400 ml) and the mixture was refluxed under heating for 4 hours. The reaction mixture was concentrated and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over magnesium sulfate. The solvent was distilled away and the residue obtained was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:5) to give the subject compound (9.07 g).

Rf value : 0.80 (ethyl acetate:n-hexane = 1:2)

^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, J = 6.0Hz), 1.10-1.96 (10H, m), 2.98-3.48 (4H, m), 3.94 (2H, t, J = 6.3Hz), 6.84 (2H, d, J = 8.7Hz), 7.11 (2H, d, J = 8.7Hz)

IR : 1610, 1512, 1246 cm^{-1}

MS(EI): 346(M^+)

(4) Diethyl 2-acetamido-2-(4-heptyloxyphenyl)ethylmalonate

A solution of sodium ethoxide (4.99 g) in absolute ethanol (60 ml) was dropwise added to diethyl acetamidomalonate (15 g) in a stream of nitrogen and the mixture was stirred at 65 °C for 30 minutes. A solution of the above-mentioned compound (8.0 g) in tetrahydrofuran (30 ml) was dropwise added thereto and the mixture was stirred at 65 °C for 6 hours. The reaction mixture was concentrated, poured into ice water and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and the resultant residue was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:5) to give the subject compound (6.50 g).

melting point = 77-80 °C

Rf value : 0.44 (chloroform:methanol = 9:1)

^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, J = 6.0Hz), 1.05-1.90 (16H, m), 1.98 (3H, s), 2.10-2.85 (4H, m), 3.92 (2H t, J = 7.0Hz), 4.21 (4H, q, J = 7.5Hz), 6.65 (1H, br.s), 6.79 (2H, d, J = 8.7Hz), 7.05 (2H, d, J = 8.7Hz)

IR : 3242, 1745, 1641, 1614, 1512, 1296 cm^{-1}

MS(EI): 435(M^+)

(5) 1,3-Propanediyl-2-acetamido-2-[2-(4-heptyloxyphenyl)ethyl]ylidenediacetate

A solution (50 ml) of the above-mentioned compound (6.50 g) in anhydrous tetrahydrofuran was dropwise added to a solution (150 ml) of lithium aluminum hydride (1.70 g) in anhydrous tetrahydrofuran under ice-cooling in a stream of nitrogen and the mixture was stirred at room temperature for 2 hours. A saturated aqueous sodium sulfate solution was added to the reaction mixture under ice-cooling and aluminum hydroxide produced was filtered off. The solvent was distilled away and pyridine (66 ml) was added to the residue. Acetic anhydride (14 ml) was added thereto under ice-cooling and the mixture was allowed to stand at room temperature overnight. The reaction mixture was poured into ice-cooled 5% hydrochloric acid and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and the residue obtained was purified by silica gel column chromatography (eluent; ethyl acetate) to give the subject compound (4.54 g) as white crystals.

melting point = 89-91 °C

Rf value : 0.35 (chloroform:methanol = 9:1)

^{1}H-NMR ($CDCl_3$) δ:
0.89 (3H, t, J = 6.0Hz), 1.05-2.72 (14H, m), 1.95 (3H, s), 2.08 (6H, s), 3.92 (2H, t, J = 7.0Hz), 4.34 (4H, s), 5.65 (1H, br.s), 6.80 (2H, d, J = 8.7Hz), 7.10 (2H, d, J = 8.7Hz)
IR : 3308, 1739, 1651, 1614, 1514, 1246 cm^{-1}
MS(EI): 435(M^+)

(6) 2-Amino-2-[2-(4-heptyloxyphenyl)ethyl]-1,3-propanediol hydrochloride

An aqueous solution (100 ml) of lithium hydroxide (3.93 g) was added to a solution of the above-mentioned compound (4.54 g) in methanol (70 ml)-tetrahydrofuran (70 ml) and the mixture was refluxed under heating for 3 hours. The reaction mixture was concentrated and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and the resultant mixture was recrystallized from ethyl acetate. A 1M hydrochloric acid-ether solution (43 ml) was added to a solution of the resultant crystals in tetrahydrofuran (28 ml)-methanol (28 ml). The solvent was distilled away and the crystals precipitated were recrystallized from ethyl acetate to give the subject compound (1.30 g).
melting point = 111-112 °C
Rf value : 0.20 (chloroform:methanol = 5:1)
^{1}H-NMR ($CDCl_3$) δ:
0.88 (3H, t, J = 5.5Hz), 1.10-1.91 (14H, m), 3.56 (4H, t, J = 5.0Hz), 5.36 (2H, t, J = 4.5Hz), 6.84 (2H, d, J = 8.7Hz), 7.13 (2H, d, J = 8.7Hz), 7.85 (2H, br.s)
IR : 3279, 1610, 1514, 1246 cm^{-1}
MS(EI): 309(M^+)

elemental analysis	calculated	C 62.50,	H 9.32,	N 4.05
	found	C 62.06,	H 9.11,	N 4.13

Example 281 : 2-Amino-2-[2-(4-nonyloxyphenyl)ethyl]-1,3-propanediol

(1) 2-(4-Nonyloxyphenyl)ethanol

2-(4-Hydroxyphenyl)ethanol (10.0 g) and sodium methoxide (4.30 g) were added to methanol (120 ml) and the mixture was refluxed under heating for 30 minutes. A solution of nonyl bromide (33 g) in methanol (20 ml) was dropwise added thereto and the mixture was refluxed under heating for 6 hours. The reaction mixture was concentrated, poured into ice water and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over magnesium sulfate. The solvent was distilled away and the residue obtained was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:3) to give the subject compound (20 g).
Rf value : 0.46 (ethyl acetate:n-hexane = 1:2)

(2) 2-(4-Nonyloxyphenyl)ethylmethanesulfonate

Triethylamine (8.8 g) was added to a solution of the above-mentioned compound (20 g) in tetrahydrofuran (500 ml) and the mixture was cooled with ice. Methanesulfonyl chloride (9.17 g) was dropwise added thereto and the mixture was stirred at room temperature for 4 hours. The reaction mixture was poured into ice water and extracted with dichloromethane. The dichloromethane layer was washed with a saturated potassium hydrogencarbonate solution, a 1% aqueous hydrochloric acid solution and saturated brine and dried over magnesium sulfate. The solvent was distilled away and the residue obtained was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:3) to give the subject compound (19.6 g).
melting point = 37-42 °C
Rf value : 0.45 (ethyl acetate:n-hexane = 1:2)
^{1}H-NMR ($CDCl_3$) δ:
0.89 (3H, t, J = 6.9Hz), 1.05-1.90 (16H, m), 2.82 (3H, s), 2.99 (2H, t, J = 6.1Hz), 3.90 (2H, t, J = 6.9Hz), 4.35 (2H, t, J = 6.9Hz), 6.78 (2H, d, J = 8.3Hz), 7.06 (2H, d,

J = 8.3Hz)
IR : 1354, 1251 cm^{-1}
MS(EI): 342(M^+)

(3) 2-(4-Nonyloxyphenyl)ethyl iodide

Sodium iodide (17 g) was added to a solution of the above-mentioned compound (19.6 g) in 2-butanone (650 ml) and the mixture was refluxed under heating for 4 hours. The reaction mixture was concentrated and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over magnesium sulfate. The solvent was distilled away and the residue obtained was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:3) to give the subject compound (18.08 g) as an oily substance.

Rf value : 0.69 (ethyl acetate:n-hexane = 1:2)
^{1}H-NMR ($CDCl_3$) δ:
0.90 (3H, t, J = 5.5Hz), 1.05-1.90 (14H, m), 2.90-3.40 (4H, m), 3.90 (2H, t, J = 6.9Hz), 6.76 (2H, d, J = 8.3Hz), 7.02 (2H, d, J = 8.3Hz)
IR : 1610, 1512, 1246 cm^{-1}
MS(EI): 374(M^+)

(4) Diethyl 2-acetamido-2-(4-nonyloxyphenyl)ethylmalonate

A solution of sodium ethoxide (10.4 g) in absolute ethanol (135 ml) was dropwise added to diethyl acetamidomalonate (31 g) in a stream of nitrogen and the mixture was stirred at 65 °C for 30 minutes. A solution of the above-mentioned compound (18 g) in tetrahydrofuran (63 ml) was dropwise added thereto and the mixture was stirred at 65 °C for 6 hours. The reaction mixture was concentrated, poured into ice water and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and the residue obtained was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:3) to give the subject compound (8.78 g).

melting point = 76-77 °C
Rf value : 0.38 (ethyl acetate:n-hexane = 1:2)
^{1}H-NMR ($CDCl_3$) δ:
0.89 (3H, t, J = 6.8Hz), 1.05-1.80 (20H, m), 1.99 (3H, s), 2.20-2.75 (4H, m), 3.88 (2H, t, J = 6.2Hz), 4.15 (4H, q, J = 6.9Hz), 6.70 (1H, br.s), 6.72 (2H, d, J = 8.3Hz), 6.99 (2H, d, J = 8.3Hz)
IR : 3281, 1743, 1645, 1512, 1246 cm^{-1}
MS(EI): 463(M^+)

(5) 1,3-Propanediyl-2-acetamido-2-[2-(4-nonyloxyphenyl)ethyl]ylidenediacetate

A solution (50 ml) of the above-mentioned compound (8.78 g) in anhydrous tetrahydrofuran was dropwise added to a solution (150 ml) of lithium aluminum hydride (1.79 g) in anhydrous tetrahydrofuran under ice-cooling in a stream of nitrogen and the mixture was stirred at room temperature for 2 hours. A saturated aqueous sodium sulfate solution was added to the reaction mixture under ice-cooling and aluminum hydroxide produced was filtered off. The solvent was distilled away and pyridine (84 ml) was added to the residue. Acetic anhydride (18 ml) was added thereto under ice-cooling and the mixture was allowed to stand at room temperature overnight. The reaction mixture was poured into ice-cooled 5% hydrochloric acid and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and the residue obtained was purified by silica gel column chromatography (eluent; ethyl acetate) to give the subject compound (5.62 g) as white crystals.

melting point = 88-94 °C
Rf value : 0.50 (chloroform:methanol = 9:1)
^{1}H-NMR ($CDCl_3$) δ:
0.89 (3H, t, J = 6.9Hz), 1.05-2.30 (18H, m), 1.93 (3H, s), 2.06 (6H, s), 3.89 (2H, t, J = 7.0Hz), 4.30 (4H, s), 5.60 (1H, br.s), 6.72 (2H, d, J = 8.2Hz), 7.01 (2H, d, J = 8.2Hz)
IR : 3308, 1738, 1651, 1614, 1514, 1246 cm^{-1}

MS(EI): 463(M^+)

elemental analysis	calculated	C 67.36,	H 8.91,	N 3.02
	found	C 67.35,	H 8.77,	N 3.05

(6) 2-Amino-2-[2-(4-nonyloxyphenyl)ethyl]-1,3-propanediol hydrochloride

An aqueous solution (54 ml) of lithium hydroxide (4.57 g) was added to a solution of the above-mentioned compound (5.62 g) in methanol (86 ml)-tetrahydrofuran (86 ml) and the mixture was refluxed under heating for 3 hours. The reaction mixture was concentrated and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and the residue was crystallized from ethyl acetate. A 1M hydrochloric acid/ether solution (20 ml) was added to a solution of the resultant crystals in tetrahydrofuran (40 ml)-methanol (40 ml). The solvent was distilled away and crystals precipitated were recrystallized from ethyl acetate to give the subject compound (2.10 g).

melting point = 106-108 °C

Rf value : 0.14 (chloroform:methanol = 5:1)

^{1}H-NMR ($CDCl_3$) δ:

0.85 (3H, t, J = 4.1Hz), 1.10-1.90 (18H, m), 3.50 (4H, d, J = 4.7Hz), 3.88 (2H, t, J = 5.4Hz), 5.32 (2H, t, J = 4.9Hz), 6.75 (2H, d, J = 8.2Hz), 7.02 (2H, d, J = 8.2Hz), 7.81 (2H, br.s)

IR : 3277, 1610, 1514, 1248 cm^{-1}

MS(EI): 337(M^+)

elemental analysis	calculated	C 64.24,	H 9.70,	N 3.75
	found	C 64.16,	H 9.51,	N 3.70

Example 282 : 2-Amino-2-[2-(4-(N-heptyl-N-methylamino)phenyl)ethyl]-1,3-propanediol

(1) 2-(4-Heptanoylaminophenyl)ethanol

2-(p-Aminophenyl)ethyl alcohol (13.8 g) and triethylamine (10.8 g) were added to tetrahydrofuran (300 ml) and the mixture was stirred for 30 minutes under ice-cooling. Heptanoyl chloride (15 g) was dropwise added thereto, and the mixture was stirred for 30 minutes under ice-cooling and then at room temperature for 3 hours. The reaction mixture was poured into ice water and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over magnesium sulfate. The solvent was distilled away and the residue obtained was recrystallized from ethyl acetate-isopropyl alcohol to give the subject compound (13.15 g).

melting point = 105-110 °C

Rf value : 0.41 (ethyl acetate:n-hexane = 1:2 → 1:1)

^{1}H-NMR ($CDCl_3$) δ:

0.89 (3H, t, J = 6.8Hz), 1.31-1.42 (8H, m), 1.70 (2H, tt, J = 7.3Hz, J = 7.8Hz), 2.35 (2H, t, J = 7.3Hz), 2.83 (2H, t, J = 6.4Hz), 3.84 (2H, dd, J = 6.3Hz, J = 5.8Hz), 7.12 (1H, br.s), 7.18 (2H, d, J = 8.3Hz), 7.45 (2H, d,J = 8.3Hz)

IR : 3302, 1660, 1593, 1412 cm^{-1}

MS(EI): 249(M^+1)

elemental analysis	calculated	C 70.97,	H 9.33,	N 5.52
	found	C 71.30,	H 9.26,	N 5.66

(2) 2-(4-Heptanoylaminophenyl)ethoxytetrahydropyran

The above-mentioned compound (7.0 g), 3,4-dihydro-2H-pyran (3.08 g) and p-toluenesulfonic acid (180 mg) were added to tetrahydrofuran (50 ml) and dichloromethane (50 ml), and the mixture was stirred at room temperature for 7 hours. Triethylamine (0.5 ml) was added thereto and the solvent was distilled away. The resultant residue was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:1) to give the subject compound (11 g).

melting point = 66-68 °C

Rf value : 0.72 (ethyl acetate:n-hexane = 1:1)

^{1}H-NMR ($CDCl_3$) δ:

0.89 (3H, t, J = 6.4Hz), 1.31-2.05 (14H, m), 2.34 (2H, t, J = 7.3Hz), 2.87 (2H, t, J = 6.4Hz), 3.47 (2H, t, J = 6.4Hz), 3.47 (2H, dt, J = 7.3Hz, J = 9.7Hz), 3.77 (1H, m), 3.92 (1H, dt, J = 7.3Hz, J = 9.8Hz), 4.58 (1H, t, J = 3.9Hz), 7.19 (2H, d, J = 8.3Hz), 7.42 (2H, d, J = 8.3Hz)

IR : 3273, 1655, 1599, 1033 cm^{-1}

MS(EI): 333(M^+)

(3) 2-(4-(N-Heptanoyl-N-methylamino)phenyl)ethoxytetrahydropyran

The above-mentioned compound (7.0 g) and potassium-t-butoxide (5.18 g) were added to ethylene glycol dimethyl ether (120 ml) and the mixture was stirred at 60 °C for 30 minutes. A solution of methyl iodide (16.39 g) in ethylene glycol dimethyl ether (4 ml) was added thereto and the mixture was stirred at 60 °C for 1 hour. The solvent was distilled away and the residue obtained was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:7) to give the subject compound (5.95 g).

Rf value : 0.23 (ethyl acetate:n-hexane = 1:5)

^{1}H-NMR ($CDCl_3$) δ:

0.83 (3H, t, J = 6.8Hz), 1.17-1.26 (6H, m), 1.42-1.60 (4H, m), 1.63-1.90 (4H, m), 2.04 (2H, t, J = 6.4Hz), 3.47 (2H, t, J = 6.4Hz), 3.47 (2H, dt, J = 7.3Hz, J = 9.7Hz), 3.77 (1H, m), 3.92 (1H, dt, J = 7.3Hz, J = 9.8Hz), 4.58 (1H, t, J = 3.9Hz), 7.19 (2H, d, J = 8.3Hz), 7.42 (2H, d, J = 8.3Hz)

IR : 3273, 1655, 1599, 1033 cm^{-1}

MS(EI): 333(M^+)

(4) 2-(4-(N-Heptyl-N-methylamino)phenyl)ethoxytetrahydropyran

A solution of the above-mentioned compound (5.95 g) in tetrahydrofuran (90 ml) was cooled to 5 °C and a diboranetetrahydrofuran complex (tetrahydrofuran 1M solution : 32.2 ml) was added thereto. The mixture was stirred at 5 °C for 3 hours and methanol (60 ml) was added thereto. The solvent was distilled away and the residue obtained was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:7) to give the subject compound (3.6 g).

Rf value : 0.49 (ethyl acetate:n-hexane = 1:2)

^{1}H-NMR ($CDCl_3$) δ:

0.88 (3H, t, J = 7.3Hz), 1.22-1.40 (8H, m), 1.42-1.62 (8H, m), 1.68-1.84 (2H, m), 2.81 (2H, t, J = 7.3Hz), 2.89 (3H, s), 3.26 (2H, t, J = 7.8Hz), 3.46 (1H, m), 3.57 (1H, dt, J = 7.4Hz, J = 7.8Hz), 3.81 (1H, m), 3.89 (1H, dt, J = 7.3Hz, J = 7.8Hz), 4.60 (1H, t, J = 3.0Hz), 6.63 (2H, d, J = 8.8Hz), 7.08 (2H, d, J = 8.8Hz)

IR : 1616, 1365, 1030 cm^{-1}

MS(EI): 333(M^+)

(5) 2-(4-(N-Heptyl-N-methylamino)phenyl)ethyl alcohol

p-Toluenesulfonic acid (3.10 g) was added to a solution of the above-mentioned compound (3.36 g) in methanol (60 ml) and the mixture was stirred at room temperature for 3 hours. Triethylamine (3 ml) was added thereto and the solvent was distilled away. The residue obtained was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:12) to give the subject compound (3.22 g).

Rf value : 0.31 (methanol:chloroform = 1:9)

^{1}H-NMR ($CDCl_3$) δ:

0.88 (3H, t, J = 6.9Hz), 1.22-1.38 (10H, m), 2.77 (2H, t, J = 6.4Hz), 2.90 (3H, s),

3.27 (2H, t, J = 7.4Hz), 3.80 (1H, t, J = 6.4Hz), 6.66 (2H, d, J = 8.7Hz), 7.08 (2H, d, J = 8.7Hz)

IR : 3368, 1369 cm^{-1}

MS(EI): 249(M^+)

(6) 2-(4-(N-Heptyl-N-methylamino)phenyl)ethylmethanesulfonate

Triethylamine (2.22 g) was added to a solution of the above-mentioned compound (3.65 g) in tetrahydrofuran (60 ml) and the mixture was cooled with ice. Methanesulfonyl chloride (3.01 g) was dropwise added thereto and the mixture was stirred at room temperature for 2 hours. The reaction mixture was poured into ice water and extracted with dichloromethane. The dichloromethane layer was washed with a saturated potassium hydrogencarbonate solution, a 1% aqueous hydrochloric acid solution and saturated brine and dried over magnesium sulfate. The solvent was distilled away and the residue obtained was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:5) to give the subject compound (4.02 g).

Rf value : 0.56 (ethyl acetate:n-hexane = 1:5)

^{1}H-NMR ($CDCl_3$) δ:

0.88 (3H, t, J = 6.4Hz), 1.24-1.29 (10H, m), 2.84 (3H, s), 2.90 (3H, s), 2.96 (2H, t, J = 6.8Hz), 3.27 (2H, t, J = 7.3Hz), 4.36 (2H, t, J = 6.9Hz), 6.64 (2H, d, J = 8.3Hz), 7.07 (2H, d, J = 8.3Hz)

(7) 2-(4-(N-heptyl-N-methylamino)phenyl)ethyl iodide

Sodium iodide (3.66 g) was added to a solution of the above-mentioned compound (4.00 g) in 2-butanone (200 ml) and the mixture was refluxed under heating for 2 hours. The reaction mixture was concentrated and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over magnesium sulfate. The solvent was distilled away and the resultant residue was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:10) to give the subject compound (2.58 g) as an oily substance.

Rf value : 0.78 (ethyl acetate:n-hexane = 1:10)

^{1}H-NMR ($CDCl_3$) δ:

0.88 (3H, t, J = 7.3Hz), 1.22-1.40 (10H, m), 2.90 (2H, s), 3.07 (2H, t, J = 7.8Hz), 3.63 (2H, t, J = 5.9Hz), 3.65 (2H, t, J = 7.3Hz), 6.62 (2H, d, J = 8.3Hz), 7.04 (2H, d, J = 8.3Hz)

IR : 1614, 1521, 1371, 804 cm^{-1}

MS(EI): 359(M^+)

(8) Diethyl 2-acetamide-2-(4-(N-heptyl-N-methylamino)phenyl)ethylmalonate

A solution of sodium ethoxide (1.54 g) in absolute ethanol (18 ml) was dropwise added to diethyl acetamidomalonate (4.63 g) in a stream of nitrogen and the mixture was stirred at 60 °C for 30 minutes. A solution of the above-mentioned compound (18 g) in tetrahydrofuran (7 ml) was dropwise added thereto and the mixture was stirred at 60 °C for 6 hours. The reaction mixture was concentrated, poured into ice water and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and the residue obtained was purified by silica gel column chromatography (eluent, ethyl acetate:hexane = 1 : 2) to give the subject compound (1.92 g) as an oily substance.

Rf value : 0.49 (ethyl acetate:n-hexane = 1:2)

^{1}H-NMR ($CDCl_3$) δ:

0.88 (3H, t, J = 6.8Hz), 1.23-1.29 (10H, m), 1.24 (6H, t, J = 7.4Hz), 1.99 (3H, s), 2.38 (2H, m), 2.63 (2H, m), 2.88 (3H, s), 3.25 (2H, t, J = 7,3Hz), 4.21 (4H, q, J = 7.4Hz), 6.60 (2H, d, J = 8.3Hz), 6.76 (1H, br.s), 6.99 (2H,d, J = 8.3Hz)

IR : 3285, 1739, 1682, 1616, 1371 cm^{-1}

MS(EI): 448(M^+)

(9) 1,3-Propanediyl-2-acetamide-2-[2(4-(N-heptyl-N-methylamino)phenyl)ethyl]ylidenediacetate

A solution (20 ml) of the above-mentioned compound (1.92 g) in anhydrous tetrahydrofuran was added dropwise to a solution (35 ml) of lithium aluminum hydride (0.49 g) in anhydrous tetrahydrofuran under ice-cooling in a stream of nitrogen. The mixture was stirred at room temperature for 2 hours. A saturated aqueous sodium sulfate solution was added to the reaction mixture under ice-cooling and aluminum hydroxide produced was filtered off. The solvent was distilled away and pyridine (84 ml) was added to the residue. Acetic anhydride (19 ml) was added thereto under ice-cooling and the mixture was allowed to stand at room temperature overnight. The reaction mixture was poured into ice-cooled 5% hydrochloric acid and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and the residue obtained was purified by silica gel column chromatography (eluent; ethyl acetate) to give the subject compound (1.2 g) as an oily substance.

melting point = 88-94 °C

Rf value : 0.50 (chloroform:methanol = 9:1)

^{1}H-NMR ($CDCl_3$) δ:

0.88 (3H, t, J = 6.9Hz), 1.24-1.29 (10H, m), 1.94 (3H, s), 2.08 (6H, s), 2.15 (2H, m), 2.51 (2H, m), 2.89 (3H, s), 3.26 (2H, t, J = 7.8Hz), 4.36 (4H, s), 5.60 (1H, br.s), 6.63 (2H, d, J = 8.3Hz), 7.03 (2H, d, J = 8.3Hz)

IR : 3314, 1739, 1651, 1616, 1386 cm^{-1}

MS(EI): 448(M^+)

(10) 2-Amino-2-[2-(4-(N-heptyl-N-methylamino)phenyl)ethyl]-1,3-propanediol hydrochloride

An aqueous solution (12 ml) of lithium hydroxide (1.01g) was added to a solution of the above-mentioned compound (1.20 g) in methanol (18 ml)-tetrahydrofuran (18 ml) and the mixture was refluxed under heating for 3 hours. The reaction mixture was concentrated and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and the residue was recrystallized from ethyl acetate. A 1M hydrochloric acid/ether solution (14 ml) was added to a solution of the resultant crystals in tetrahydrofuran (7 ml)-methanol (7 ml). The solvent was distilled away and the crystals precipitated were recrystallized from ethyl acetate to give the subject compound (0.11 g).

melting point = 128-129 °C

Rf value : 0.20 (chloroform:methanol = 9:1)

^{1}H-NMR ($CDCl_3$) δ:

0.84 (3H, t, J = 6.8Hz), 1.25-1.46 (10H, m), 1.70-1.74 (2H, m), 2.42-2.46 (2H, m), 2.81 (3H, s), 3.23 (2H, t, J = 7.4Hz), 3.49 (4H, d, J = 5.3Hz), 5.35 (2H, t, J = 4.9Hz), 6.59 (2H, d, J = 8.3Hz), 6.97 (2H, d, J = 8.3Hz)

IR : 3277, 1610, 1514, 1248 cm^{-1}

MS(EI): 322(M^+)

elemental analysis	calculated found	C 59.13, C 59.23,	H 9.92, H 9.39,	N 72.26 (1.5H_2O) N 7.14

Example 283 : 2-Amino-2-[2-(4-heptanoylaminophenyl)ethyl]-1,3-propanediol

(1) 2-(4-Heptanoylaminophenyl)ethanol

2-(p-Aminophenyl)ethyl alcohol (13.8 g) and triethylamine (10.8 g) were added to tetrahydrofuran (300 ml) and the mixture was stirred under ice-cooling for 30 minutes. Heptanoyl chloride (15 g) was dropwise added thereto and the mixture was stirred under ice-cooling for 30 minutes and then at room temperature for 3 hours. The reaction mixture was poured into ice water and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over magnesium sulfate. The solvent was distilled away and the resultant residue was recrystallized from ethyl acetate-isopropyl alcohol to give the subject compound (13.15 g).

melting point = 105-110 °C

Rf value : 0.41 (ethyl acetate:n-hexane = 1:2 → 1:1)

^{1}H-NMR ($CDCl_3$) δ:

0.89 (3H, t, J = 6.8Hz), 1.31-1.42 (8H, m), 1.70 (2H, tt, J = 7.3Hz, J = 7.8Hz), 2.35 (2H, t, J = 7.3Hz), 2.83 (2H, t, J = 6.4Hz), 3.84 (2H, dd, J = 6.3Hz, J = 5.8Hz), 7.12 (1H, br.s), 7.18 (2H, d, J = 8.3Hz), 7.45 (2H, d,J = 8.3Hz)

IR : 3302, 1660, 1593, 1412 cm^{-1}

MS(EI): 249(M^+1)

elemental analysis	calculated found	C 70.97, C 71.30,	H 9.33, H 9.26,	N 5.52 N 5.66

(2) 2-(4-Heptanoylaminophenyl)ethylmethanesulfonate

Triethylamine (3.67 g) was added to the above-mentioned compound (6.00 g) in tetrahydrofuran (100 ml) and the mixture was cooled with ice. Methanesulfonyl chloride (5.00 g) was dropwise added thereto and the mixture was stirred at room temperature for 2 hours. The reaction mixture was poured into ice water and extracted with dichloromethane. The dichloromethane layer was washed with a saturated potassium hydrogencarbonate solution, a 1% aqueous hydrochloric acid solution and saturated brine and dried over magnesium sulfate. The solvent was distilled away and the residue obtained was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:1) to give the subject compound (6.02 g).

melting point = 103-105 °C

Rf value : 0.56 (ethyl acetate:n-hexane = 1:5)

^{1}H-NMR ($CDCl_3$) δ:

0.89 (3H, t, J = 6.4Hz), 1.22-1.40 (6H, m), 1.72 (2H, t, J = 7.3Hz), 2.35 (2H, t, J = 7.3Hz), 2.87 (3H, s), 3.02 (2H, t, J = 7.3Hz), 4.39 (2H, t, J = 6.4Hz), 7.13 (1H, br.s), 7.19 (2H, d, J = 8.3Hz), 7.48 (2H, d, J = 8.3Hz)

IR : 3307. 1659, 1337 cm^{-1}

MS(EI): 327(M^+)

elemental analysis	calculated found	C 70.97, C 71.30,	H 9.33, H 9.26,	N 5.52 N 5.66

(3) 2-(4-Heptanoylaminophenyl)ethyl iodide

Sodium iodide (5.51 g) was added to a solution of the above-mentioned compound (6.02 g) in 2-butanone (300 ml) and the mixture was refluxed under heating for 2 hours. The reaction mixture was concentrated and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over magnesium sulfate. The solvent was distilled away and the residue obtained was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:5) to give the subject compound (5.31 g) as an oily substance.

melting point = 82-86 °C

Rf value : 0.33 (ethyl acetate:n-hexane = 1:5)

^{1}H-NMR ($CDCl_3$) δ:

0.87 (3H, t, J = 6.9Hz), 1.21-1.40 (6H, m), 1.70 (2H, t, J = 7.3Hz), 2.32 (2H, t, J = 7.3Hz), 3.12 (2H, t, J = 7.8Hz), 3.30 (2H, t, J = 7.4Hz), 7.05 (1H, br.s), 7.12 (2H, d, J = 8.3Hz), 7.44 (2H, d, J = 8.3Hz)

IR : 3450, 1660, 1595, 709 cm^{-1}

MS(EI): 359(M^+)

elemental analysis	calculated found	C 50.15, C 50.11,	H 6.17, H 6.06,	N 3.96 N 3.96

(4) Diethyl-2-tert-butoxycarbonylamino-2-(4-heptanoylaminophenyl)ethyl malonate

A solution of sodium ethoxide (3.19 g) in absolute ethanol (40 ml) was dropwise added to diethyl 2-tert-butoxycarbonylaminomalonate (12.12 g) in a stream of nitrogen and the mixture was stirred at 50 °C for 30 minutes. A solution of the above-mentioned compound (5.31 g) in tetrahydrofuran (20 ml) was dropwise added thereto and the mixture was stirred at 60 °C for 5 hours. The reaction mixture was concentrated, poured into ice water and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and the residue obtained was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:7) to give the subject compound (4.29 g).

Rf value : 0.49 (ethyl acetate:n-hexane = 1:2)

^{1}H-NMR ($CDCl_3$) δ:

0.82 (3H, t, J = 6.9Hz), 1.18 (6H, t, J = 6.8Hz), 1.21-1.40 (6H, m), 1.37 (9H, s), 1.64 (2H, t, J = 7.4Hz), 2.27 (2H, t, J = 7.3Hz), 2.42 (2H, m), 2.51 (2H, m), 4.05-4.25 (4H, m), 5.92 (1H, br.s), 7.00 (1H, br.s), 7.03 (2H, d, J = 8.3Hz), 7.33 (2H, d, J = 8.3Hz)

IR : 3319, 1772, 1739, 1666 cm^{-1}

MS(EI): 506(M^+)

(5) 1,3-Propanediyl-2-tert-butoxycarbonylamino-2-[2-(4-heptanoylaminophenyl)ethyl]ylidenediacetate

Sodium borohydride (0.32 g) was added to a solution of the above-mentioned compound (4.29 g) in methanol in a stream of nitrogen. The residue was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 2:1) to give the subject compound (0.56 g) as an oily substance.

Rf value : 0.31 (acetic acid:n-hexane = 2:1)

^{1}H-NMR ($CDCl_3$) δ:

0.89 (3H, t, J = 6.8Hz), 1.21-1.46 (10H, m), 1.45 (9H, s), 1.70-1.90 (4H, m), 2.34 (2H, t, J = 7.3Hz), 2.59 (2H, t, J = 8.7Hz), 3.61-3.64 (2H, m), 3.85-3.89 (2H, m), 5.03 (1H, br.s), 7.13 (2H, d, J = 8.3Hz), 7.42 (2H, d, J = 8.3Hz)

IR : 3310, 1668, 1602 cm^{-1}

MS(EI): 422(M^+)

(6) 2-Amino-2-[2-(4-heptanoylaminophenyl)ethyl]-1,3-propanediol

A solution of the above-mentioned compound (0.56 g) in trifluoroacetic acid (4 ml) was stirred under ice-cooling for 4 hours. The reaction mixture was concentrated and ethyl acetate (110 ml) was added thereto. The mixture was washed with a saturated aqueous sodium hydrogencarbonate solution and dried over anhydrous magnesium sulfate. The solvent was distilled away and the residue was recrystallized from methanol-ethyl acetate to give the subject compound (0.14 g) as white crystals. melting point = 133-135 °C

Rf value : 0.47 (chloroform:methanol = 5:1)

^{1}H-NMR (DMSO-d_6) δ:

0.85 (3H, t, J = 6.4Hz), 1.26-1.57 (12H, m), 2.25 (2H, t, J = 3.9Hz), 3.17-3.25 (4H, m), 4.43 (2H, t, J = 4.9Hz), 7.07 (2H, d, J = 8.8Hz), 7.45 (2H, d,J = 8.7Hz), 9.73 (1H, br.s),

IR : 3317, 1653, 1601 cm^{-1}

MS(EI): 322(M^+)

elemental analysis	calculated found	C 67.05, C 66.95,	H 9.38, H 9.08,	N 8.69 (1.5H_2O) N 8.25

Example 284 : 2-Amino-2-[2-(4-octylphenyl)ethyl]-1,3-propanediol

(1) Ethyl 2-ethoxycarbonyl-4-(4-octylphenyl)butyrate

Sodium (2.67 g) was dissolved in absolute ethanol (100 ml) and diethyl malonate (18.6 g) was dropwise added thereto at 27 - 30 °C for 3 minutes. The mixture was stirred at 40 °C for 40 minutes and 2-(4-octylphenyl)ethyl iodide (40 g) was dropwise added to the reaction mixture at 44 - 45 °C over 10 minutes.

The mixture was refluxed at 50 °C for 1 hour and stirred under heating for 1.5 hours. The reaction mixture was cooled and the solvent was distilled away under reduced pressure. Water was added thereto and extracted with ethyl acetate. The extract was washed with water and dried over magnesium sulfate. The solvent was distilled away under reduced pressure and the residue obtained was subjected to silica gel column chromatography to give the subject compound (28.8 g).

IR : 2920, 2850, 1745, 1725, 1240, 1140, 1040 cm^{-1}

(2) Ethyl 2-amino-2-ethoxycarbonyl-4-(4-octylphenyl)butyrate

60% Sodium hydride (0.38 g) was suspended in dry dimethylformamide (30 ml) and ethyl 2-ethoxycarbonyl-4-(4-octylphenyl)butyrate (3.0 g) was added thereto. The mixture was stirred at room temperature for 2 hours. O-(2,4-Dinitrophenyl)hydroxylamine (1.14 g) was added thereto and the mixture was stirred at room temperature for 5 hours. The reaction mixture was poured into cool water and extracted with toluene. The extract was washed with aqueous sodium chloride and dried over magnesium sulfate. The solvent was distilled away under reduced pressure to give 3 g of the subject compound.

IR : 3380, 3320, 2930, 2850, 1730, 1180 cm^{-1}

(3) 2-Amino-2-[2-(4-octylphenyl)ethyl]-1,3-propanediol

A suspension of sodium borohydride (0.60 g) and lithium bromide (1.66 g) in ethanol (17 ml) was stirred at room temperature for 25 minutes. Ethyl 2-amino-2-ethoxycarbonyl-4-(4-octylphenyl)butyrate (1.24 g) was dropwise added thereto over 3 minutes and the mixture was stirred at room temperature for 5 hours. Water (40 ml) was added to the reaction mixture and the mixture was stirred for 40 minutes. The crystals precipitated was collected by filtration and dried to give 0.68 g of the subject compound, melting point = 125-126 °C. Treatment of the subject compound with hydrochloric acid-ethanol gives the corresponding hydrochloride.

Example 285 : 2-Amino-2-{2-[4-(7-octenyloxy)phenyl]ethyl}-1,3-propanediol

(1) 2-[4-(7-Octenyloxy)phenyl]ethyl alcohol

Sodium ethoxide (4.98 g) was added to a solution (240 ml) of 2-(4-hydroxyphenyl)ethyl alcohol (8.68 g) in absolute ethanol and the mixture was stirred at 50 °C for 30 minutes. A solution of 7-octenyl bromide (10 g) in anhydrous tetrahydrofuran was dropwise added thereto and the mixture was stirred at 50 °C for 6 hours. The reaction mixture was concentrated, poured into ice water and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and the residue was purified by silica gel chromatography (eluent; ethyl acetate:hexane = 1:5) to give the subject compound (10.76 g) as an oily substance.

^{1}N-NMR (DMSO) δ:

1.35 (6H, s), 1.50 - 2.16 (4H, m), 2.62 (2H, t, J = 6Hz), 3.41 - 3.65 (2H, m), 3.88 (2H, t, J = 6Hz), 4.63 (1H, t, J = 5Hz), 4.95 (2H, t × t, J = 7Hz, 2Hz), 5.66 - 5.96 (1H, m), 6.74 (2H, d, J = 9Hz), 7.04 (2H, d, J = 9Hz)

IRν $NEAT_{max}$: 3445, 2251, 1028, 823, 761cm^{-1}

MS 248 (M^+)

(2) 2-[4-(7-Octenyloxy)phenyl]ethyl iodide

Triethylamine (7.25 ml) was added to a solution (100 ml) of the above-mentioned compound (10.76 g) in dichloromethane and the mixture was cooled with ice. Methanesulfonyl chloride (3.69 ml) was dropwise added thereto and the mixture was stirred at room temperature for 1 hour. The reaction mixture was poured into ice water and extracted with chloroform. The chloroform layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and sodium iodide (7.78 g) was added to a solution (200 ml) of the residue in 2-butanone. The mixture was refluxed under heating for 5 hours. The reaction mixture was concentrated, poured into ice water and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and the residue was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:3) to give the subject compound (13.72 g) as an oily substance.

^{1}H-NMR ($CDCl_3$) δ:

1.53 (6H, s), 1.68 - 2.07 (4H, m), 2.96 - 3.18 (4H, m), 3.90 (2H, t, J = 6Hz), 4.92 (2H, m), 5.56 - 5.96 (1H, m), 6.76 (2H, d, J_H = 9Hz), 7.03 (2H, d, J_H = 9Hz)

IRν NEAT$_{max}$: 2930, 1511, 1246cm^{-1}

MS 358 (M^+)

(3) Diethyl 2-acetamido-2-[4-(7-octenyloxy)phenyl]ethylmalonate

Sodium ethoxide (5.72 g) was added to a solution (100 ml) of diethyl acetamidomalonate (16.60 g) in absolute ethanol and the mixture was stirred at 65 °C for 30 minutes. A solution (100 ml) of the above-mentioned compound (13.69 g) in absolute ethanol was dropwise added thereto and the mixture was stirred at 65 °C for 3 hours. The reaction mixture was concentrated, poured into ice water and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and the residue was purified by silica gel chromatography (eluent; ethyl acetate:hexane = 1:2) to give the subject compound (4.60 g).

melting point = 50-53 °C

^{1}H-NMR ($CDCl_3$) δ:

1.25 (8H, t), 1.30 - 1.49 (6H, m), 1.72 - 1.79 (2H, m), 2.00 (3H, s), 2.63 - 2.67 (2H, m), 3.91 (2H, t, J = 6Hz), 4.15 - 4.25 (4H, m), 4.92 - 5.03 (2H, m), 5.76 - 5.86 (1H, m), 6.79 (2H, d, J = 8Hz), 7.04 (2H, d, J = 8Hz)

IRν_{max} : 3251, 2931, 1743, 1515, 1247, 1186cm^{-1}

MS 447 (M^+)

(4) 2-Acetamido-2-[2-{4-(7-octenyloxy)phenyl}ethyl]-1,3-propanediol diacetate

A solution (70 ml) of the above-mentioned compound (4.47 g) in anhydrous tetrahydrofuran was dropwise added to a solution (50 ml) of lithium aluminum hydride (1.52 g) in anhydrous tetrahydrofuran under ice-cooling. The mixture was heated to room temperature and stirred for 3 hours. A saturated aqueous sodium sulfate solution was dropwise added thereto under ice-cooling to decompose lithium aluminum hydride and the same was filtered off. The reaction mixture was dried over anhydrous sodium sulfate and the solvent was distilled away. Pyridine (19.8 ml) was added to the residue. Acetic anhydride (18.4 ml) was added thereto under ice-cooling and the mixture was allowed to stand at room temperature overnight. The reaction mixture was poured into ice water and extracted with ethyl acetate. The ethyl acetate layer was washed with 7% hydrochloric acid and saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and the residue was purified by silica gel chromatography (eluent; ethyl acetate:hexane = 1:2) to give the subject compound (2.23 g) as white crystals.

melting point = 88-90 °C

MS 447 (M^+)

^{1}H-NMR ($CDCl_3$) δ:

1.54 - 1.57 (8H, m), 1.76 (2H, m), 1.96 (3H, s), 2.03 - 2.09 (8H, m), 2.52 - 2.57 (2H, m), 3.92 (2H, t, J = 6Hz), 4.34 (4H, s), 4.93 - 5.02 (2H, m), 5.64 (1H, s), 5.64 - 5.86 (1H, m), 6.81 (2H, d, J = 4Hz), 7.08 (2H, d, J = 4Hz)

IRν : 3308, 1738, 1652, 1247, 1227 cm^{-1}

(5) 2-Amino-2-{2-[4-(7-octenyloxy)phenyl]ethyl}-1,3-propanediol

An aqueous solution (20 ml) of lithium hydroxide (0.84 g) was added to a solution (20 ml) of the above-mentioned compound (1.01 g) in methanol and the mixture was refluxed under heating for 2 hours. The reaction mixture was concentrated and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and the residue was recrystallized from ethyl acetate to give the subject compound (0.32 g), melting point 95 - 98 °C.

^{1}H-NMR ($CDCl_3$) δ:

1.36 - 1.48 (8H, m), 1.73 - 1.78 (2H, m), 2.06 (2H, q, J = 8Hz), 2.59 (2H, t, J = 8Hz), 3.56 (4H, q, J = 12Hz), 3.91 (2H, q, J = 8Hz), 4.93 - 5.02 (2H, m), 5.76 - 5.86 (1H, m), 6.82 (2H, d, J = 10Hz), 7.09 (2H, t, J = 10Hz)

IRν : 3350, 2938, 1512, 1245, 1021cm^{-1}

Example 286 : 2-Amino-2-[2-(4-octyloxyphenyl)ethyl]-1,3-propanediol hydrochloride

(1) 2-Acetamido-2-[2-(4-octyloxyphenyl)ethyl]-1,3-propanediol diacetate

10% Palladium carbon (0.1 g) was added to a solution (30 ml) of 2-acetamido-2-[2-{4-(7-octenyloxy)-phenyl}ethyl]-1,3-propanediol diacetate (1.27 g) in ethanol and the mixture was stirred at ordinary temperature and at atmospheric pressure for 6 hours under a hydrogen atmosphere. The catalyst was filtered off and the filtrate was concentrated. The residue was collected by filtration to give the subject compound (1.18 g).

melting point = 99-102 °C

^{1}H-NMR ($CDCl_3$) δ:

0.86 (3H, t, J = 8Hz), 1.26 - 1.56 (12H, m), 1.94 (3H, s), 2.07 (6H, s), 2.12 - 2.17 (2H, m), 2.50 - 2.55 (2H, m), 3.89 (2H, t, J = 6Hz), 4.32 (4H, s), 5.62 (1H, s), 6.79 (2H, d, J = 8Hz), 7.06 (2H, d, J = 8Hz)

IRν : 3311, 2917, 1738, 1651, 1247 cm^{-1}

(2) 2-Amino-2-{2-(4-octyloxyphenyl)ethyl}-1,3-propanediol hydrochloride

An aqueous solution (20 ml) of lithium hydroxide (0.94 g) was added to a solution (20 ml) of the above-mentioned compound (1.13 g) in ethanol and the mixture was refluxed under heating for 3 hours. The reaction mixture was concentrated and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and the residue was dissolved in methanol (10 ml). A solution (10 ml) of 1M hydrochloric acid in ether was added thereto and the crystals precipitated were collected by filtration to give the subject compound (0.60 g, 65.2%).

melting point = 59-61 °C

^{1}H-NMR ($CDCl_3$) δ:

0.88 (3H, t, J = 4Hz), 1.28 - 1.41 (12H, m), 1.73 - 1.75 (2H, m), 1.95(2H, m), 2.60 (2H, s), 3.78 - 3.92 (6H, m), 6.80 (2H, m), 7.10 (2H, m)

IRν : 3354, 1609, 1513, 1247 cm^{-1}

Example 287 : 2-Amino-2-(13-phenyltridecyl)-1,3-propanediol

(1) 12-(Tetrahydropyran-2-yloxy)dodecanol

1,12-Dodecanediol (25 g) was dissolved in dichloromethane (200 ml) and tetrahydrofuran (200 ml), and a catalytic amount of p-toluenesulfonic acid and 3,4-dihydro-2H-pyran (14 ml) were added thereto. The mixture was allowed to stand at room temperature for 2 hours and the reaction was stopped by triethylamine. The solvent was distilled away and the residue obtained was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:2) to give the subject compound (15.46 g) as a colorless, oily substance.

Rf value : 0.39 (ethyl acetate:hexane = 1:2)

^{1}H-NMR ($CDCl_3$/TMS) δ:

1.28 (16H, m), 1.62 (10H, m), 3.65 (6H, m), 4.59 (1H, br.s)

IR(neat): 3417, 2927, 2854, 1034cm^{-1}

MS(EI): 285 (M^+-1)

(2) 12-(Tetrahydropyran-2-yloxy)dodecanal

Oxalyl chloride (6.9 ml) was slowly added dropwise to a solution (85 ml) of dimethyl sulfoxide (11.3 ml) in dichloromethane at -78 °C under a nitrogen atmosphere. The mixture was stirred at -78 °C for 20 minutes and a solution of the above-mentioned compound (15.25 g) in dichloromethane (130 ml) was gradually added thereto over 30 minutes. The mixture was stirred at -78 °C for 20 minutes and triethylamine (37 ml) was added thereto. The reaction was stopped with 150 ml of water and the reaction mixture was extracted twice with 150 ml of chloroform. The chloroform layer was dried and the solvent was distilled away. The residue obtained was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:3) to give the subject compound (13.54 g) as a slightly yellow, oily substance.

Rf value : 0.63 (ethyl acetate:hexane = 1:2)

^{1}H-NMR ($CDCl_3$/TMS) δ:
1.29 (14H, m), 1.58 (10H, m), 2.43 (2H, dt, J = 2 & 6Hz), 3.26 - 4.20 (4H, m), 4.59 (1H, br.s), 9.79 (1H, t, J = 2Hz)
IR(neat): 2929, 2855, 1727cm^{-1}
MS(EI): 284 (M^+)

(3) 1-Phenyl-13-(tetrahydropyran-2-yloxy)-1-tridecene

A solution (31 ml) of 1.6M butyl lithium in hexane was added to a suspension of benzyltriphenylphosphonium chloride (19.44 g) in tetrahydrofuran (100 ml) under ice-cooling and a solution of the above-mentioned compound (13.54 g) in tetrahydrofuran (30 ml) was dropwise added thereto under ice-cooling. The mixture was stirred for 3 hours. The reaction mixture was concentrated and the concentrate was poured into 200 ml of ice water. The mixture was extracted twice with 150 ml of ethyl acetate and the extract was dried and concentrated. The residue obtained was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:9) to give the subject compound (2.60 g).
Rf value : 0.66 (ethyl acetate:hexane = 1:5)
^{1}H-NMR ($CDCl_3$/TMS) δ:
1.30 (14H, m), 1.58 (10H, m), 2.22 (2H, m), 3.60 & 3.80 (4H, 2m), 4.59 (1H, br.s), 6.19 - 6.53 (2H, m), 7.30 (5H, m)
IR(neat): 2927, 2854, 1466, 1034 cm^{-1}
MS(EI): 358 (M^+)

(4) 13-Phenyl-1-(tetrahydropyran-2-yloxy)tridecane

10% Palladium carbon (260 mg) was added to a solution of the above-mentioned compound (2.63 g) in ethanol (80 ml) and the mixture was stirred at room temperature for 3 hours under a hydrogen atmosphere. The catalyst was filtered through Celite and the filtrate was concentrated. The residue obtained was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:9) to give the subject compound (2.67 g) as a colorless, oily substance.
Rf value : 0.60 (ethyl acetate:hexane = 1:5)
^{1}H-NMR ($CDCl_3$/TMS) δ:
1.27 (18H, m), 1.60 (10H, m), 2.62 (2H, t, J = 7Hz), 3.45 & 3.80 (4H, 2m), 4.59 (1H, br.s), 7.21 (5H, m)
IR(neat): 2927, 2854, 1453 cm^{-1}
MS(EI): 360 (M^+)

(5) 13-Phenyltridecanol

A solution of the above-mentioned compound (2.63 g) and a catalytic amount of p-toluenesulfonic acid in methanol (30 ml) and tetrahydrofuran (8 ml) was allowed to stand at room temperature overnight. Triethylamine (0.5 ml) was added thereto and the mixture was concentrated. The residue obtained was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:5) to give the subject compound (1.78 g) as white crystals.
melting point = 34-36 °C
Rf value : 0.24 (ethyl acetate:hexane = 1:5)
^{1}H-NMR ($CDCl_3$/TMS) δ:
1.28 & 1.57 (23H, 2br.s), 2.62 (2H, t, J = 7.5Hz), 3.65 (2H, t, J = 6Hz), 7.23 (5H, m)
IR(KBr): 3344, 3259, 2918, 2848, 1468 cm^{-1}
MS(EI): 276 (M^+)

(6) 13-Phenyltridecylmethanesulfonate

Triethylamine (1.2 ml) was added to a solution of the above-mentioned compound (1.73 g) in dichloromethane (30 ml) and the mixture was cooled with ice. Methanesulfonyl chloride (0.58 ml) was dropwise added thereto and the mixture was stirred at room temperature for 2 hours. The reaction mixture was poured into ice water and extracted with dichloromethane. The dichloromethane layer was washed with a saturated potassium hydrogencarbonate solution, a 1% aqueous hydrochloric acid solution and saturated

brine and dried over magnesium sulfate. The solvent was distilled away and the residue obtained was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:5) to give the subject compound (2.12 g) as white crystals.

melting point = 45-47 °C

Rf value : 0.39 (ethyl acetate:hexane = 1:1)

^{1}H-NMR ($CDCl_3$/TMS) δ: 1.28 & 1.70 (22H, 2m), 2.62 (2H, t, J = 7.5Hz), 3.01 (3H, s), 4.23 (2H, t, J = 6Hz), 7.22 (5H, m)

IR(KBr): 2920, 2851, 1474, 1344 cm^{-1}

MS(EI): 354 (M^+)

elemental analysis	calculated	C 67.75,	H 9.67
	found	C 67.70,	H 9.48

(7) 13-Phenyltridecyl iodide

Sodium iodide (1.165 g) was added to a solution of the above-mentioned compound (2.12 g) in 2-butanone (60 ml) and the mixture was refluxed under heating for 2 hours. The reaction mixture was concentrated and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over magnesium sulfate. The solvent was distilled away and the residue obtained was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:9) to give the subject compound (2.19 g) as white crystals.

melting point = 19-22 °C

Rf value : 0.88 (ethyl acetate:hexane = 1:2)

^{1}H-NMR ($CDCl_3$/TMS) δ: 1.27 & 1.70 (22H, 2m), 2.61 (2H, t, J = 7.5Hz), 3.19 (2H, t, J = 6.5Hz), 7.21 (5H, m)

IR(KBr): 2917, 2851, 1472 cm^{-1}

MS(EI): 386 (M^+)

elemental analysis	calculated	C 75.63,	H 9.91
	found	C 75.22,	H 9.92

(8) Diethyl 2-acetamido-2-(13-phenyltridecyl)malonate

A solution of sodium ethoxide (0.764 g) in absolute ethanol (22 ml) was dropwise added to diethyl acetamidomalonate (2.38 g) in a stream of nitrogen and the mixture was stirred at 65 °C for 30 minutes. A solution of the above-mentioned compound (2.11 g) in tetrahydrofuran (5 ml) was dropwise added thereto and the mixture was stirred at 65 °C for 6 hours. The reaction mixture was concentrated, poured into ice water and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and the residue obtained was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:3) to give the subject compound (2.06 g) as a colorless, oily substance.

Rf value : 0.41 (ethyl acetate:hexane = 1:2)

^{1}H-NMR ($CDCl_3$/TMS) δ: 1.25 (20H, m), 1.58 (2H, m), 2.02 (3H, s), 2.30 (2H, m), 2.61 (2H, t, J = 7.5Hz), 4.23 (4H, q, J = 6Hz), 6.76 (1H, br.s), 7.21 (5H, m)

IR(Neat): 3416, 3312, 2925, 2854, 1741, 1671 cm^{-1}

MS(EI): 475 (M^+)

(9) 2-Acetamido-1,3-diacetoxy-2-(13-phenyltridecyl)propane

A solution (20 ml) of the above-mentioned compound (1.90 g) in anhydrous tetrahydrofuran was added dropwise to a solution (40 ml) of lithium aluminum hydride (0.56 g) in anhydrous tetrahydrofuran under ice-

cooling in a stream of nitrogen and the mixture was stirred at room temperature for 2 hours. A saturated aqueous sodium sulfate solution was added to the reaction mixture under ice-cooling and aluminum hydroxide produced was filtered off. The solvent was distilled away and pyridine (8 ml) was added to the residue. Acetic anhydride (5 ml) was added thereto under ice-cooling and the mixture was allowed to stand at room temperature overnight. The reaction mixture was poured into 5% hydrochloric acid under ice-cooling and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and the residue obtained was purified by silica gel column chromatography (eluent; ethyl acetate) to give the subject compound (1.01 g) as white crystals.

melting point = 42-45 °C

Rf value : 0.24 (ethyl acetate:hexane = 1:1)

^{1}H-NMR ($CDCl_3$/TMS) δ:

1.26 & 1.61 (22H, 2m), 1.96 (3H, s), 2.08 (6H, s), 2.62 (2H, t, J = 7.5Hz), 4.30 (4H, s), 5.61 (1H, br.s), 7.21 (5H, m)

IR(KBr): 3295, 2926, 2854, 1748, 1660, 1553 cm^{-1}

MS(EI): 475 (M^+)

elemental analysis	calculated found	C 70.70, C 70.96,	H 9.54, H 9.52,	N 2.94 N 2.96

(10) 2-Amino-2-(13-phenyltridecyl)-1,3-propanediol 1/4 hydrate

An aqueous solution (11.5 ml) of lithium hydroxide (0.88 g) was added to a solution of the above-mentioned compound (0.90 g) in methanol (11.5 ml) and the mixture was refluxed under heating for 3 hours. The reaction mixture was concentrated and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and the residue was recrystallized from ethyl acetate to give the subject compound (170 mg) as white crystals.

melting point = 61-64 °C

^{1}H-NMR ($CDCl_3$/TMS) δ:

1.27 & 1.60 (24H, 2m), 2.00 (4H, m), 2.62 (2H, t, J = 7.5Hz), 3.50 (4H, m), 7.22 (5H, m)

IR(KBr): 3342, 3290, 3157, 2916, 2849, 1581, 1472 cm^{-1}

MS(EI): 349 (M^+)

elemental analysis	calculated found	C 74.63, C 74.88,	H 11.24, H 10.94,	N 3.96 N 3.92

Example 288 : 2-Amino-2-{2-[4-(6-phenylhexyloxy)phenyl]ethyl}-1,3-propanediol

(1) 6-Phenylhexylmethanesulfonate

Triethylamine (5.09 ml) was added to a solution of 6-phenylhexanol (5.0 g) in dichloromethane (140 ml) and the mixture was cooled with ice. Methanesulfonyl chloride (2.50 ml) was dropwise added thereto and the mixture was stirred at room temperature for 2 hours. The reaction mixture was poured into ice water and extracted with chloroform. The chloroform layer was washed with a saturated potassium hydrogencarbonate solution, a 1% aqueous hydrochloric acid solution and saturated brine and dried over magnesium sulfate. The solvent was distilled away and the residue obtained was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:2) to give the subject compound (8.08 g) as a colorless, oily substance.

Rf value : 0.45 (ethyl acetate:hexane = 1:2)

^{1}H-NMR ($CDCl_3$/TMS) δ:

1.15 - 1.95 (8H, m), 2.65 (2H, t, J = 7.5Hz), 2.99 (3H, s), 4.22 (2H, t, J = 6Hz), 7.22 (5H, m)

IR(neat): 3027, 2937, 2858, 1497cm^{-1}

(2) 6-Phenylhexyl iodide

Sodium iodide (5.33 g) was added to a solution of the above-mentioned compound (7.93 g) in 2-butanone (150 ml) and the mixture was refluxed under heating for 2 hours. The reaction mixture was concentrated and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over magnesium sulfate. The solvent was distilled away and the residue obtained was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:19) to give the subject compound (7.62 g) as a colorless, oily substance.

Rf value : 0.78 (ethyl acetate:hexane = 1:5)

^{1}H-NMR ($CDCl_3$/TMS) δ: 1.20 - 2.00 (8H, m), 2.60 (2H, t, J = 7.5Hz), 3.17 (2H, t, J = 6.5Hz), 7.15 (5H, m)

IR(neat): 3026, 2930, 2855, 1496, 1453 cm^{-1}

MS(EI): 288 (M^+)

(3) 2-[4-(6-Phenylhexyloxy)phenyl]ethanol

2-(4-Hydroxyphenyl)ethanol (3.97 g) and sodium ethoxide (2.30 g) were added to ethanol (130 ml) and the mixture was refluxed under heating for 30 minutes. A solution of the above-mentioned compound (7.53 g) in tetrahydrofuran (30 ml) was dropwise added thereto and the mixture was stirred under reflux under heating for 6 hours. The reaction mixture was concentrated, poured into ice water and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over magnesium sulfate. The solvent was distilled away and the residue obtained was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:3) to give the subject compound (5.49 g) as a colorless, oily substance.

Rf value : 0.50 (ethyl acetate:hexane = 1:2)

^{1}H-NMR ($CDCl_3$/TMS) δ: 1.24 - 1.89 (8H, m), 2.59 (2H, t, J = 7.5Hz), 2.76 (2H, t, J = 5Hz), 3.76 (2H, t, J = 6.5Hz), 3.89 (2H, t, J = 5Hz), 6.76 (2H, d, J = 8.5Hz), 7.06 (2H, d, J = 8.5Hz), 7.13 (5H, m)

IR(neat): 3355, 2933, 2858, 1613, 1512 cm^{-1}

MS(EI): 298 (M^+)

(4) 2-[4-(6-Phenylhexyloxy)phenyl]ethylmethanesulfonate

Triethylamine (3.3 ml) was added to a solution of the above-mentioned compound (5.40 g) in dichloromethane (100 ml) and the mixture was cooled with ice. Methanesulfonyl chloride (1.7 ml) was dropwise added thereto and the mixture was stirred at room temperature for 2 hours. The reaction mixture was poured into ice water and extracted with dichloromethane. The dichloromethane layer was washed with a saturated potassium hydrogencarbonate solution, a 1% aqueous hydrochloric acid solution and saturated brine and dried over magnesium sulfate. The solvent was distilled away and the residue obtained was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:2) to give the subject compound (6.99 g) as a colorless, oily substance.

Rf value : 0.39 (ethyl acetate:hexane = 1:2)

^{1}H-NMR ($CDCl_3$/TMS) δ: 1.30 - 1.92 (8H, m), 2.75 (2H, t, J = 7.5Hz), 2.81 (3H, s), 2.96 (2H, t, J = 7Hz), 3.89 (2H, t, J = 6Hz), 4.33 (2H, t, J = 7Hz), 6.80 (2H, d, J = 8.5Hz), 7.06 (2H, d, J = 8.5Hz), 7.15 (5H, m)

IR(neat): 2936, 2858, 1513 cm^{-1}

MS(EI): 376 (M^+)

(5) 2-[4-(6-Phenylhexyloxy)phenyl]ethyl iodide

Sodium iodide (3.29 g) was added to a solution of the above-mentioned compound (6.88 g) in 2-butanone (180 ml) and the mixture was refluxed under heating for 4 hours. The reaction mixture was concentrated and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over magnesium sulfate. The solvent was distilled away and the residue obtained was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:9) to give the subject compound (6.25 g) as a colorless, oily substance.

Rf value : 0.81 (ethyl acetate:hexane = 1:2)

^{1}H-NMR ($CDCl_3$/TMS) δ:

1.18 - 1.92 (8H, m), 2.60 (2H, t, J = 7.5Hz), 3.18 (4H, m), 3.90 (2H, t, J = 6Hz), 6.75 (2H, d, J = 8.5Hz), 7.06 (2H, d, J = 8.5Hz), 7.10 (5H, m)

IR(neat): 2932, 2856, 1611, 1511 cm^{-1}

MS(EI): 408 (M^+)

elemental analysis	calculated found	C 58.83, C 58.88,	H 6.17 H 6.53

(6) Diethyl 2-acetamido-2-{2-[4-(6-phenylhexyl)phenyl]ethyl}malonate

A solution of sodium ethoxide (3.20 g) in absolute ethanol (40 ml) was dropwise added to diethyl acetamidomalonate (9.89 g) in a stream of nitrogen and the mixture was stirred at 65 °C for 30 minutes. A solution of the above-mentioned compound (6.20 g) in tetrahydrofuran (15 ml) was dropwise added thereto and the mixture was stirred at 65 °C for 6 hours. The reaction mixture was concentrated, poured into ice water and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and the residue obtained was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:3) to give the subject compound (4.04 g) as white crystals.

melting point = 53-55 °C

Rf value : 0.18 (ethyl acetate:hexane = 1:2)

^{1}H-NMR ($CDCl_3$/TMS) δ:

1.84 (6H, t, J = 7Hz), 1.11 - 1.88 (10H, m), 1.97 (3H, s), 2.24 - 2.76(6H, m), 3.87 (2H, t, J = 6Hz), 4.16 (4H, q, J = 7Hz), 6.70 (1H, s), 6.74 (2H, d, J = 8.5Hz), 6.97 (2H, d, J = 8.5Hz), 7.15 (5H, m)

IR(neat): 3233, 2933, 1747, 1639, 1511 cm^{-1}

MS(EI): 497 (M^+)

elemental analysis	calculated found	C 70.00, C 69.83,	H 7.90, H 7.91,	N 2.81 N 2.90

(7) 2-Acetamido-1,3-diacetoxy-2-{2-[4-(6-phenylhexyloxy)phenyl]ethyl}propane

A solution (10 ml) of the above-mentioned compound (3.79 g) in anhydrous tetrahydrofuran was dropwise added to a solution (60 ml) of lithium aluminum hydride (0.87 g) in anhydrous tetrahydrofuran under ice-cooling in a stream of nitrogen and the mixture was stirred at room temperature for 2 hours. A saturated aqueous sodium sulfate solution was added thereto under ice-cooling and aluminum hydroxide produced was filtered off. The solvent was distilled away and pyridine (15 ml) was added to the residue. Acetic anhydride (10 ml) was added thereto under ice-cooling and the mixture was allowed to stand at room temperature overnight. The reaction mixture was poured into ice-cooled 5% hydrochloric acid and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and the residue obtained was purified by silica gel column chromatography (eluent; ethyl acetate) to give the subject compound (1.80 g) as white crystals.

melting point = 68-70 °C

Rf value : 0.66 (ethyl acetate)

^{1}H-NMR ($CDCl_3$/TMS) δ:

1.24 - 1.88 (8H, m), 1.94 (3H, s), 2.06 (6H, s), 2.10 (2H, m), 2.56 (4H, m), 3.88 (2H, t, J = 7Hz), 4.30 (4H, s), 5.60 (1H, s), 6.72 (2H, d, J = 8.5Hz), 7.02 (2H, d, J = 8.5Hz), 7.13 (5H, m)

IR(KBr): 3319, 2934, 1739, 1652 cm^{-1}

MS(EI): 497 (M^+)

elemental analysis	calculated found	C 70.00, C 70.34,	H 7.90, H 7.93,	N 2.81 N 2.86

(8) 2-Amino-2-{2-[4-(6-phenylhexyloxy)phenyl]ethyl}-1,3-propanediol hydrochloride

An aqueous solution (17 ml) of lithium hydroxide (1.33 g) was added to a solution of the above-mentioned compound (1.75 g) in methanol (25 ml) and the mixture was refluxed under heating for 3 hours. The reaction mixture was concentrated and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and the residue obtained was recrystallized from ethyl acetate. A solution (10 ml) of 1M hydrochloric acid in ether was added to a solution of the resultant crystals in methanol (10 ml). The solvent was distilled away and the crystals precipitated were recrystallized from ethyl acetate to give the subject compound (0.90 g) as white crystals.

melting point = 89-91 °C

Rf value : 0.41 (chloroform:methanol:acetic acid:water = 70:20:6:4)

^{1}H-NMR ($CDCl_3$) δ: 1.33 (4H, m), 1.59 (6H, m), 1.91 (1H, br.s), 2.36 (1H, br.s), 2.55 (2H, t, J = 7.8Hz), 3.72 (4H, m), 4.98 (1H; br.s), 6.66 (2H, d, J = 8.8Hz), 7.03 (2H, d, J = 8.8Hz), 7.12 (3H, m), 7.22 (2H, m), 7.85 (1H, br.s)

IR(KBr): 3275, 3028, 2934, 2858, 1513 cm^{-1}

MS(EI): 371 (M^+)

elemental analysis	calculated found	C 67.71, C 67.61,	H 8.40, H 8.30,	N 3.43 N 3.42

Example 289 : 2-Amino-2-[2-(4-undecyloxyphenyl)ethyl]-1,3-propanediol

(1) 2-(4-Undecyloxyphenyl)ethanol

A solution (300 ml) of 2-(4-hydroxyphenyl)ethanol (15.5 g), undecyl bromide (25 ml) and sodium ethoxide (8.40 g) in ethanol was refluxed under heating for 5 hours. The solvent was distilled away and water (200 ml) and ethyl acetate (200 ml) were added thereto. The aqueous layer was extracted with ethyl acetate (200 ml). The combined extract was dried and filtered. The solvent was distilled away and the residue obtained was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:3) to give 23.37 g of the subject compound as white crystals.

melting point = 47-50 °C

Rf value : 0.40 (ethyl acetate:hexane = 1:2)

^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t, J = 7.5Hz), 1.10-1.58 (16H, m), 1.87 (2H, m), 2.78 (2H,t, J = 7.5Hz), 3.78 (2H, t, J = 7Hz), 3.89 (2H, t, J = 7Hz), 6.82 (2H, d, J = 9Hz), 7.09 (2H, d, J = 9Hz)

IR(KBr): 3250, 2919, 2850, 1513, 1251 cm^{-1}

MS(EI): 292(M^+)

(2) 2-(4-Undecyloxyphenyl)ethyl methanesulfonate

To a solution (400 ml) of the compound obtained above (23.24 g) in dichloromethane was added triethylamine (14.4 ml). Methanesulfonyl chloride (7.1 ml) was added to the mixture under ice-cooling and the mixture was stirred at room temperature for 2 hours. Then, the reaction mixture was poured into 200 ml of ice water and extracted twice with dichloromethane (200 ml). The extract was dried and concentrated, and the residue obtained was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:3) to give the subject compound (28.07 g) as white crystals.

melting point = 43-44 °C

Rf value : 0.51 (ethyl acetate:hexane = 1:2)

^{1}H-NMR ($CDCl_3$/TMS) δ:
0.88 (3H, t, J = 7.5Hz), 1.25 (16H, m), 1.75 (2H, m), 2.81 (3H, s), 2.96 (2H, t, J = 7Hz), 3.90 (2H, t, J = 6Hz), 4.35 (2H, t, J = 7Hz), 6.75 (2H, d, J = 9Hz), 7.05 (2H, d, J = 9Hz)
IR(KBr): 2919, 2851, 1515, 1352 cm^{-1}
MS(EI): 370(M^+)

elemental analysis	calculated	C 64.83,	H 9.25
	found	C 64.78,	H 9.17

(3) 2-(4-Undecyloxyphenyl)ethyl iodide

A solution (350 ml) of the compound obtained above (27.95 g) and sodium iodide (13.00 g) in 2-butanone was refluxed under heating for 3 hours. The solvent was distilled away and water (200 ml) was added thereto. The mixture was extracted twice with ethyl acetate (200 ml) and dried. The solvent was distilled away and the residue obtained was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:19) to give the subject compound (26.45 g) as white crystals.
melting point = 22-23 °C
Rf value : 0.79 (ethyl acetate:hexane = 1:5)
^{1}H-NMR ($CDCl_3$/TMS) δ:
0.88 (3H, t, J = 7Hz), 1.30 (16H, m), 1.75 (2H, m), 2.90-3.40 (4H, m), 3.90 (2H, t, J = 7Hz), 6.76 (2H, d, J = 9Hz), 7.02 (2H, d, J = 9Hz),
IR(KBr): 2920, 2852, 1609, 1509, 1247 cm^{-1}
MS(EI): 402(M^+)

(4) Diethyl 2-acetamido-2-[2-(4-undecyloxyphenyl)ethyl]malonate

A solution of sodium ethoxide (13.37 g) in absolute ethanol (400 ml) was dropwise added to diethyl acetamidomalonate (42.68 g) in a stream of nitrogen and the mixture was stirred at 65 °C for 30 minutes. A solution of the compound obtained above (26.35 g) in tetrahydrofuran (50 ml) was dropwise added thereto and the mixture was stirred at 65 °C for 6 hours. The reaction mixture was concentrated, poured into ice water and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and the residue obtained was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:5) to give the subject compound (13.94 g).
melting point = 63-65 °C
Rf value : 0.24 (ethyl acetate:hexane = 1:2)
^{1}H-NMR ($CDCl_3$/TMS) δ:
0.86 (3H, t, J = 7.1Hz), 1.24 (20H, m), 1.41 (2H, m), 1.73 (2H, m), 1.97 (3H, s), 2.39 (2H, m), 2.62 (2H, m), 3.89 (2H, t, J = 6.3Hz), 4.18 (4H, m), 6.74 (1H, s), 6.77 (2H, d, J = 8.3Hz), 7.02 (2H, d, J = 8.3Hz)
IR(KBr): 3286, 2917, 2851, 1746, 1647, 1513 cm^{-1}
MS(EI): 491(M^+)

elemental analysis	calculated	C 68.40,	H 9.22,	N 2.85
	found	C 68.15,	H 9.23,	N 2.80

(5) 2-Acetamido-1,3-diacetoxy-2-[2-(4-undecyloxyphenyl)ethyl]propane

A solution (60 ml) of the compound obtained above (13.02 g) in anhydrous tetrahydrofuran was dropwise added to a solution (200 ml) of lithium aluminum hydride (3.0 g) in anhydrous tetrahydrofuran in a stream of nitrogen under ice-cooling and the mixture was stirred at room temperature for 2 hours. A saturated aqueous sodium sulfate solution was added to the reaction mixture under ice-cooling and the resultant aluminum hydroxide was filtered off. The solvent was distilled away and pridine (40 ml) was added

to the residue. Thereto was added acetic anhydride (30 ml) under ice-cooling and the mixture was allowed to stand at room temperature overnight. The reaction mixture was poured into ice-cooled 5% hydrochloric acid and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and the residue obtained was purified by silica gel column chromatography (eluent; ethyl acetate) to give the subject compound (7.18 g) as white crystals.

melting point = 82-85 °C

Rf value : 0.6 (ethyl acetate)

^{1}H-NMR ($CDCl_3$/TMS) δ: 0.86 (3H, t, J=6.4Hz), 1.24 (14H, m), 1.41 (2H, m), 1.75 (2H, m), 1.94 (3H, s), 2.07 (6H, s), 2.14 (2H, m), 2.53 (2H, m), 3.89 (2H, t, J=6.6Hz), 4.32 (4H, s), 5.62 (1H, s), 6.79 (2H, d, J=8.8Hz), 7.06 (2H, d, J=8.8Hz)

IR(KBr): 3314, 2918, 2851, 1737, 1653 cm^{-1}

MS(EI): 491 (M^+)

elemental analysis	calculated found	C 68.40, C 68.36,	H 9.22, H 9.19,	N 2.85 N 2.85

(6) 2-Amino-2-[2-(4-undecyloxyphenyl)ethyl]-1,3-propanediol hydrochloride

To a solution of the compound obtained above (7.16 g) in methanol (70 ml) was added an aqueous solution (70 ml) of lithium hydroxide (5.50 g) and the mixture was refluxed under heating for 3 hours. The reaction mixture was concentrated and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and the residue was recrystallized from ethyl acetate. To a solution of the thus obtained crystals in tetrahydrofuran (20 ml)-methanol (20 ml), 1M hydrochloric acid in ether (30 ml) was added. The solvent was distilled away and the precipitated crystals were recrystallized from ethyl acetate to give the subject compound (1.90 g).

melting point = 88-91 °C

^{1}H-NMR ($CDCl_3$-CD_3OD/TMS) δ: 0.80 (3H, t, J=6.9Hz), 1.19 (14H, m), 1.36 (2H, m), 1.68 (2H, m), 1.85 (2H, m), 2.53 (2H, m), 3.65 (4H, m), 3.84 (2H, t, J=6.4Hz), 6.74 (2H, d, J=8.3Hz), 7.04 (2H, d, J=8.3Hz)

IR(KBr): 3274, 2921, 2852, 1613, 1513, 1247 cm^{-1}

MS(EI): 365(M^+)

elemental analysis	calculated found	C 65.73, C 65.53,	H 10.03, H 9.82,	N 3.48 N 3.42

Example 290 : 2-Amino-2-[2-(4-dodecylphenyl)ethyl]-1,3-propanediol

(1) 2-(4-Dodecanoylphenyl)ethyl acetate

Aluminum chloride (48.2 g) was added to dichloroethane (400ml) in a stream of nitrogen and the mixture was stirred at room temperature. Then, phenethyl acetate (39.6 g) and undecanoyl chloride (52.7 g) were dropwise added thereto under ice-cooling and the mixture was stirred at room temperature overnight. The reaction mixture was poured into ice water and extracted with diethyl ether. The ether layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and the residue obtained was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:20) to give the subject compound (34.5 g) as pale yellow crystals.

melting point = 32-33 °C

IR(neat)$_{max}$: 2921, 2852, 1738, 1686, 1240 cm^{-1}

(2) 2-(4-Dodecylphenyl)ethanol

To a solution (50 ml) of the compound obtained above (34.5 g) in trifluoroacetic acid was added triethylsilane (22.7 ml) under ice-cooling and the mixture was stirred at room temperature for 3 hours. The solvent was distilled away and ice water was poured to the residue. A cold, saturated aqueous sodium hydrogencarbonate solution was slowly added to the mixture. The mixture was extracted with ethyl acetate, and the ethyl acetate layer was washed and dried over magnesium sulfate. The solvent was distilled away and methanol (250 ml) was added to the residue to give a methanol solution. To the solution was added sodium methoxide (10.2 g) and the mixture was refluxed under heating for 4 hours. The reaction mixture was concentrated and ice water was poured to the residue. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with a 5% aqueous hydrochloric acid solution and saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away to give the subject compound (27.1 g) as an oily substance.

Rf : 0.21 (ethyl acetate:hexane = 1:3)

(3) 2-(4-Dodecylphenyl)ethyl iodide

To a solution (500 ml) of the compound obtained above (27.1 g) in dichloromethane was added triethylamine (14.4 ml) and the mixture was stirred at room temperature for 3 hours. The reaction mixture was poured into ice water and the mixture was extracted with dichloromethane. The dichloromethane layer was washed with a saturated aqueous potassium hydrogencarbonate solution, a 1% aqueous hydrochloric acid solution and saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and 2-butanone (500 ml) was added to the residue. Thereto was added sodium iodide (12.2 g) and the mixture was refluxed under heating for 3 hours. The reaction mixture was poured into ice water and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and the residue was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:20) to give the subject compound (18.6 g) as an oily substance.

^{1}H-NMR ($CDCl_3$) δ:
0.37 (3H, t, J = 6Hz), 0.66-0.86 (18H, m), 1.05-1.10 (2H, m), 2.06(2H, t, J = 6Hz), 2.63 (2H, t, J = 4Hz), 2.83 (2H, t, J = 4Hz), 6.60 (4H, dd, J = 4Hz, 8Hz)

IR(neat)$_{max}$: 2919, 1513, 1467, 1168 cm^{-1}

(4) Diethyl 2-acetamido-2-[2-(4-dodecylphenyl)ethyl]malonate

A solution (100 ml) of sodium ethoxide (6.3 g) in absolute ethanol was dropwise added to diethyl acetamidomalonate (20.2 g) in a stream of nitrogen and the mixture was stirred at 65 °C for 30 minutes. Then, a solution (50 ml) of the compound obtained above (18.6 g) in anhydrous tetrahydrofuran was dropwise added thereto and the mixture wad stirred at 65 °C for 3 hours. The reaction mixture was concentrated, poured into ice water and extracted with ethyl acetate. The extract was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and the residue was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:3) to give the subject compound (8.9 g).

melting point = 60-62 °C

^{1}H-NMR ($CDCl_3$) δ:
0.86 (3H, t, J = 6Hz), 1.24 (6H, t, J = 6Hz), 1.23-1.59 (18H, m), 1.54-1.59 (2H, m), 1.97 (3H, s), 2.45 (3H, t, J = 6Hz), 2.54 (3H, t, J = 6Hz), 2.67 (3H, t, J = 6Hz), 4.15-4.24 (4H, m), 6.75 (1H, br.s), 7.06 (4H, dd, J = 6Hz, 6Hz)

IR(KBr)$_{max}$: 3253, 2920, 2850, 1747, 1644, 1517 cm^{-1}

(5) 2-Acetamido-1,3-diacetoxy-2-[2-(4-dodecylphenyl)ethyl]propane

A solution (50 ml) of the compound obtained above (8.9 g) in anhydrous tetrahydrofuran was dropwise added to a solution (200 ml) of lithium aluminum hydride (1.38 g) in anhydrous tetrahydrofuran in a stream of nitrogen under ice-cooling, and the mixture was stirred at room temperature for 2 hours. A saturated aqueous sodium sulfate solution was added to the reaction mixture under ice-cooling and the resultant aluminum hydroxide was filtered off. The resultant mixture was dried over anhydrous sodium sulfate and the solvent was distilled away. Pyridine (28.7 ml) was added to the residue. Thereto was added acetic

anhydride (18.5 ml) under ice-cooling and the mixture was allowed to stand at room temperature overnight. The reaction mixture was poured into ice-cooled 5% hydrochloric acid and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and the residue was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:2) to give the subject compound (2.5 g) as white crystals.

melting point = 111-113 °C

^{1}H-NMR ($CDCl_3$) δ: 0.86 (3H, t, J = 6Hz), 1.24-1.31 (18H, m), 1.53-1.58 (4H, m), 1.95 (3H, s), 2.09 (6H, s), 2.56 (2H, t, J = 6Hz), 2.58 (2H, t, J = 6Hz), 4.35 (4H, s), 5.62 (1H, br.s), 7.09 (4H, s)

IR(KBr): 3309, 2918, 2850, 1738, 1651 cm^{-1}

(6) 2-Amino-2-[2-(4-dodecylphenyl)ethyl]-1,3-propanediol hydrochloride

An aqueous solution (25 ml) of lithium hydroxide (1.7 g) was added to a solution (25 ml) of the compound obtained above (2.5 g) in methanol and the mixture was refluxed under heating for 3 hours. The reaction mixture was concentrated and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and a 26% hydrochloric acid - ethanol solution was added thereto, followed by stirring. The solvent was distilled away and the residue was recrystallized from ethanol to give the subject compound (770 mg) as white crystals.

^{1}H-NMR (DMSO) δ: 0.88 (3H, t, J = 6Hz), 1.25-1.30 (18H, m), 1.52-1.58 (2H, m), 1.94-2.02 (2H, m), 2.56-2.60 (2H, m), 2.64-2.68 (2H, m), 3.81 (4H, dd, J = 11, 26Hz), 4.79 (2H, br.s), 7.09 (4H, dd, J = 6, 26Hz), 8.07 (3H, br.s)

IR(KBr): 2921, 2852, 1738, 1686, 1240 cm^{-1}

Exmaple 291 : 2-Amino-2-[2-(2-octylphenyl)ethyl]-1,3-propanediol

(1) 1-(2-Bromophenyl)octanol

Magnesium pieces (6.56 g) were added to anhydrous tetrahydrofuran (10 ml) in a stream of nitrogen and the mixture was stirred at room temperature. A solution (200 ml) of 1-bromoheptane (48.4 g) in anhydrous tetrahydrofuran was dropwise added thereto while heating gradually and the mixture was stirred at 40 °C for 1 hour. Thereto was dropwise added a solution (100 ml) of 2-bromobenzaldehyde (25 g) in anhydrous tetrahydrofuran at room temperature and the mixture was stirred for 1 hour. The reaction mixture was poured into a saturated, aqueous ammonium chloride solution and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and the residue was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:8) to give the subject compound (18.9 g) as an oily substance.

^{1}H-NMR ($CDCl_3$) δ: 0.85 (3H, t, J = 6Hz), 1.24-1.58 (10H, m), 1.61-1.79 (2H, m), 5.05(1H, m, J = 4Hz), 7.08-7.12 (1H, m, J = 6Hz), 7.29-7.31 (1H, m, J = 6Hz), 7.50-7.54 (2H, m, J = 4Hz)

IRν (neat): 3350, 2927, 1466, 1023 cm^{-1}

(2) trans-2-(1-Octenyl)bromobenzene

Diphosphorus pentaoxide (7.1 g) was added to a solution (200 ml) of the compound obtained above (2.85 g) in benzene and the mixture was refluxed under heating for 2 hours. The diphosphorus pentaoxide was filtered off and the solvent was distilled away. Ice water was added to the residue. The mixture was extracted with ethyl acetate, and the ethyl acetate layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and the residue was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:15) to give the subject compound (2.4 g) as an oily substance.

^{1}H-NMR ($CDCl_3$) δ: 0.86 (3H, t, J = 7Hz), 1.18-1.45 (6H, m), 1.46-1.55 (2H, m), 2.24 (2H, m, J = 1Hz, 7Hz), 6.16 (1H, m, J = 7Hz), 6.72 (1H, d, J = 16Hz), 7.02-7.08 (1H, m), 7.19-7.33 (1H, m), 7.46-7.55 (2H, m)

IRν (neat): 2957, 2855, 1466, 1023cm^{-1}

(3) trans-2-(1-Octenyl)-benzaldehyde

Magnesium pieces (3.74 g) were added to anhydrous tetrahydrofuran (10 ml) in a stream of nitrogen and the mixture was stirred at room temperature. A solution (100 ml) of the compound obtained above (37.4 g) in anhydrous tetrahydrofuran was dropwise added thereto while heating gradually and the reaction mixture was stirred at 60 °C for 1.5 hours. Thereto was dropwise added a solution (100 ml) of dimethylformamide (11.5 ml) in anhydrous tetrahydrofuran at room temperature and the mixture was stirred overnight. The reaction mixture was poured into a saturated aqueous ammonium chloride solution and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and the residue was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:15) to give the subject compound (26.7 g) as an oily substance.

^{1}H-NMR ($CDCl_3$) δ:
0.88 (3H, t, J = 6Hz), 1.22-1.38 (6H, m), 1.45-1.52 (2H, m), 2.24-2.36 (2H, m), 6.11-6.18 (1H, m), 7.15 (1H, d, J = 18Hz), 7.33-7.37 (1H, m), 7.48-7.53 (2H, m), 7.58 (1H, d, J = 4Hz), 10.31 (1H, s)

IRν (neat): 2927, 2855, 1699, 1597 cm^{-1}

(4) 2-Octylbenzaldehyde

To a solution (200 ml) of the compound obtained above (26.7 g) in methanol was added a solution (20 ml) of 10% palladium carbon (1 g) in methanol and the mixture was stirred at ordinary temperature and at atmospheric pressure in a stream of hydrogen for 14 hours for catalytic reduction. The 10% palladium carbon was filtered off and the solvent was distilled away. The residue was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:20) to give the subject compound (22 g) as an oil.

^{1}H-NMR ($CDCl_3$) δ:
0.86 (3H, t, J = 7Hz), 1.25-1.38 (10H, m), 1.54-1.63 (2H, m), 3.00 (2H, t, J = 7Hz), 7.24-7.26 (1H, m), 7.31-7.35 (1H, m), 7.46-7.50 (1H, m), 7.80-7.83 (1H, m), 10.28 (1H, s)

IRν (neat): 3335, 2926, 1701, 1601cm^{-1}

(5) Ethyl (2-octylphenyl)acetate

Methyl methylsulfinylmethyl sulfide (12.4 g) and Triton B (9.16 ml) were added to a solution (100 ml) of the compound obtained above (22 g) in dioxane at room temperature and the mixture was refluxed under heating for 2 hours. The solvent was distilled away and ethyl acetate was added to the residue. The ethyl acetate layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and ethanol (200 ml) was added to the residue. Thereto was added a 26% hydrochloric acid-ethanol solution and the mixture was stirred at room temperature for 30 minutes. The solvent was distilled away and ice water was poured to the residue. The mixture was extracted with ethyl acetate. The extract was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and the residue was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:30) to give the subject compound (20.2 g) as an oily substance.

^{1}H-NMR ($CDCl_3$) δ:
0.86 (3H, t, J = 5Hz), 1.19-1.38 (10H, m), 1.24 (3H, t, J = 5Hz), 1.49-1.62 (2H, m), 2.59 (2H, t, J = 6Hz), 3.85 (2H, s), 4.13 (2H, q, J = 5Hz), 7.10-7.35 (4H, m)

(6) 2-(2-Octylphenyl)ethyl alcohol

A solution (50 ml) of the compound obtained above (20.2 g) in anhydrous tetrahydrofuran was dropwise added to a solution (200 ml) of lithium aluminum hydride (3.04 g) in anhydrous tetrahydrofuran in stream of nitrogen under ice-cooling and the mixture was stirred at room temperature for 2 hours. A saturated aqueous sodium sulfate solution was added to the reaction mixture under ice-cooling and the resultant aluminum hydroxide was filtered off. The filtrate was dried over anhydrous sodium sulfate and the solvent was distilled away. The residue was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:30) to give the subject compound (10.2 g) as an oily substance.

^{1}H-NMR ($CDCl_3$) δ:
0.87 (3H, t, J = 6Hz), 1.21-1.46 (10H, m), 1.47-1.62 (2H, m), 2.61(2H, t, J = 6Hz), 2.96 (3H, t, J = 6Hz), 3.82 (2H, dd, J = 6Hz, 12Hz), 7.14-7.24 (4H, m)
IRν (neat): 3335, 2926, 2854, 1467cm^{-1}

(7) 2-(2-Octylphenyl)ethyl methanesulfonate

Triethylamine (7.37 ml) was added to a solution (250 ml) of the compound obtained above (10.2 g) in dichloromethane and the mixture was cooled with ice. Thereto was dropwise added methanesulfonyl chloride (6.04 g) and the mixture was stirred at room temperature for 2 hours. The reaction mixture was poured into ice water and extracted with dichloromethane. The dichloromethane layer was washed with a saturated aqueous potassium hydrogencarbonate solution, a 1% aqueous hydrochloric acid solution and saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and the residue was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:8) to give the subject compound (13.4 g) as an oily substance.
^{1}H-NMR ($CDCl_3$) δ:
0.86 (3H, t, J = 6Hz), 1.22-1.41 (10H, m), 1.51-1:59 (2H, m), 2.60 (2H, t, J = 6Hz), 2.84 (3H, s), 3.09 (2H, t, J = 6Hz), 4.38 (2H, t, J = 6Hz), 7.10-7.20 (4H, m)
IR(neat): 2929, 1467, 1357, 1174 cm^{-1}

(8) 2-(2-Octylphenyl)ethyl iodide

To a solution of the compound obtained above (13.4 g) in 2-butanone (300 ml) was added sodium iodide (7.7 g) and the mixture was refluxed under heating for 2 hours. The reaction mixture was poured into ice water and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and the residue was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:30) to give the subject compound (11.9 g).
^{1}H-NMR ($CDCl_3$) δ:
0.87 (3H, t, J = 6Hz), 1.18-1.74 (10H, m), 1.50-1.59 (2H, m), 2.57 (2H, t, J = 6Hz), 3.18 (2H, t, J = 6Hz), 3.28 (2H, t, J = 6Hz), 7.10-7.25 (4H, m)
IR(neat): 2923, 2854, 1490, 1468 cm^{-1}

(9) Diethyl 2-acetamido-2-[2-(2-octylphenyl)ethyl]malonate

A solution (50 ml) of sodium ethoxide (6.39 g) in anhydrous ethanol was dropwise added to diethyl acetamidomalonate (20.4 g) in a stream of nitrogen and the mixture was stirred at 65 °C for 1.5 hours. A solution of the compound obtained above (10.8 g) in tetrahydrofuran was dropwise added thereto and the mixture was refluxed under heating for 7 hours. The reaction mixture was concentrated, poured into ice water and extracted with ethyl acetate. The extract was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and the residue was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:3) to give the subject compound (5.8 g) as white crystals. melting point = 37-38 °C
^{1}H-NMR ($CDCl_3$) δ:
0.86 (3H, t, J = 6Hz), 1.21-1.36 (10H, m), 1.25 (6H, t, J = 6Hz), 1.46-1.57 (2H, m), 2.03 (3H, s), 2.38-2.47 (2H, m), 2.51 (2H, t, J = 6Hz), 2.55-2.63 (2H, m, J = 6Hz), 4.16-4.41 (4H, m), 6.82 (2H, br.s), 7.05-7.15 (4H, m)
IR(KBr): 3415, 2977, 2855, 1741, 1683, 1492 cm^{-1}

(10) 2-Acetamido-1,3-diacetoxy-2-[2-(2-octylphenyl)ethyl]propane

A solution (50 ml) of the compound obtained above (4.3 g) in anhydrous tetrahydrofuran was dropwise added to a solution (200 ml) of lithium aluminum hydride (0.76 g) in anhydrous tetrahydrofuran in a stream of nitrogen under ice-cooling, and the mixture was stirred at room temperature for 2 hours. A saturated aqueous sodium sulfate solution was added to the reaction mixture under ice-cooling and the resultant aluminum hydroxide was filtered off. The filtrate was dried over anhydrous sodium sulfate and the solvent was distilled away. Pyridine (10 ml) was added to the residue and then, acetic anhydride (13 ml) was added thereto, and the mixture was allowed to stand at room temperature overnight. The reaction mixture was

poured into ice-cooled 5% hydrochloric acid and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and the residue was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 1:3) to give the subject compound (2.2 g) as an oily substance.

^{1}H-NMR ($CDCl_3$) δ:
0.86 (3H, t, J = 6Hz), 1.21-1.38 (12H, m), 1.47-1.58 (2H, m), 1.97 (3H, s), 2.08 (6H, s), 2.56 (2H, t, J = 6Hz), 2.58 (2H, t, J = 6Hz), 4.35 (4H, s), 5.66 (1H, br.s), 7.09-7.13 (4H, m)

IR(neat): 3295, 2927, 1747, 1660, 1256 cm^{-1}

(11) 2-Amino-2-[2-(2-octylphenyl)ethyl]-1,3-propanediol hydrochloride

An aqueous solution (20 ml) of lithium hydroxide (1.7 g) was added to a solution of the compound obtained above (2.2 g) in methanol (20 ml) and the mixture was refluxed under heating for 4 hours. The reaction mixture was concentrated and extracted with ethyl acetate. The extract was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and a 26% hydrochloric acid-ethanol solution was added to the residue. The solvent was distilled away and the residue was recrystallized from ethanol to give hydrochloride of the subject compound (800 mg). melting point = 168-170 °C

^{1}H-NMR (DMSO) δ:
0.85 (3H, t, J = 7Hz), 1.22-1.37 (10H, m), 1.43-1.54 (2H, m), 1.68-1.78 (2H, m), 2.52-2.63 (4H, m), 3.49-3.59 (4H, m), 5.40 (2H, t, J = 4Hz), 7.05-7.17 (4H, m), 7.89 (3H, br.s)

IRν (KBr): 3385, 3272, 2925, 1519, 1069 cm^{-1}

Example 292 : 2-Amino-2-(4-octylthiobenzyl-)1,3-propanediolhydrochloride 1/2 hydrate

(1) 4-(Methylthio)benzyl alcohol

Sodium borohydride (3.78 g) was added to isopropyl alcohol (50 ml) and the mixture was stirred under ice-cooling. Thereto was dropwise added 4-(methylthio)benzaldehyde (15 g) and the mixture was stirred at room temperature for 30 minutes. The solvent was distilled away and water was added to the residue. The mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. The solvent was distilled away and the residue obtained was recrystallized from hexane-ethyl acetate to give the subject compound (15 g) as white crystals.
melting point = 41-43 °C

^{1}H-NMR ($CDCl_3$) δ:
2.40 (3H, s), 4.43 (2H, s), 7.10 (4H, s), 3.36 (1H, br.s)

elemental analysis($C_8H_{10}OS$)	calculated	C 62.30,	H 6.54
	found	C 61.90,	H 6.55

MS: 154 (M^+)

(2) 4-(Methylsulfinyl)benzyl alcohol

m-Chloroperbenzoic acid (content 50%, 35 g) was added to a solution (100 ml) of the compound obtained above (15 g) in chloroform under ice-cooling and the mixture was stirred for 1 hour. Thereto was added calcium hydroxide (37 g) and the mixture was stirred at room temperature for 1 hour. The insoluble matters were filtered off, and the filtrate was washed with saturated brine and dried over anhydrous sodium sulfate. The solvent was distilled away and the residue obtained was purified by silica gel column chromatography (eluent; chloroform:methanol = 20:1) to give the subject compound (15.56 g) as an oily substance.

^{1}H-NMR ($CDCl_3$) δ:
2.73 (3H, s), 3.28 (1H, br.s), 4.45 (2H, s), 7.52 (4H, s)

IR(neat): 3364, 1409, 1303, 1148, 1031 cm^{-1}

elemental analysis($C_8H_{10}O_2S$)	calculated found	C 56.45, C 56.51,	H 5.92 H 5.87

MS: 170 (M^+)

(3) 4-(Methylsulfinyl)benzyl methanesulfonate

Triethylamine (14 ml) was added to a solution (100 ml) of the compound obtained above (13.88 g) in dichloromethane under ice-cooling. Thereto was dropwise added methanesulfonyl chloride (6.2 ml) and the mixture was stirred for 30 minutes. The reaction mixture was poured into ice water and extracted with dichloromethane. The organic layer was washed with a saturated aqueous sodium hydrogencarbonate solution, 0.1N hydrochloric acid and saturated brine and dried over anhydrous sodium sulfate. The solvent was distilled away and the residue obtained was purified by silica gel column chromatography (eluent; chloroform:methanol = 10:1) to give the subject compound (15.38 g) as white crystals.
melting point = 63-65 °C
^{1}H-NMR($CDCl_3$) δ:
2.74 (3H, s), 3.0 (3H, s), 5.22 (2H, s), 7.52 (2H, d, J = 8Hz), 7.63 (2H, d, J = 8Hz)
IR(KBr): 3015, 1349, 1172, 1040, 951 cm^{-1}

elemental analysis($C_9H_{12}O_4S_2$)	calculated found	C 43.53, C 43.51,	H 4.87 H 4.82

MS: 248 (M^+)

(4) 4-(Methylsulfinyl)benzyl iodide

To a solution (100 ml) of the compound obtained above (8.25 g) in 2-butanone was added sodium iodide (7.5 g) and the mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated, poured into ice water and extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. The solvent was distilled away and the residue was purified by silica gel column chromatography (eluent; chloroform:methanol = 10:1) to give the subject compound (8.65 g) as yellow crystals.
melting point = 80-81 °C
^{1}H-NMR ($CDCl_3$) δ:
2.70 (3H, s), 4.42 (3H, s), 7.50 (4H, s)
IR(KBr): 1399, 1153, 1038, 837, 565 cm^{-1}

elemental analysis(C_8H_9OSI)	calculated found	C 34.30, C 34.17,	H 3.24 H 3.21

MS: 280 (M^+)

(5) Diethyl 2-acetamido-2-(4-methylsulfinylbenzyl)malonate

Sodium ethoxide (4 g) was added to a solution (200 ml) of diethyl acetamidomalonate (13 g) in absolute ethanol in a stream of nitrogen and the mixture was stirred at 65 °C for 1 hour. A solution of the compound obtained above (8.4 g) in absolute ethanol was dropwise added thereto and the mixture was stirred at 65 °C for 1 hour. The reaction mixture was concentrated, poured into ice water and extracted with ethyl acetate. The extract was washed with saturated brine and dried over anhydrous sodium sulfate. The solvent was distilled away and the residue was purified by silica gel column chromatography (eluent; chloroform:methanol = 20:1) to give the subject compound (8.2 g) as crystals.
melting point = 135-136 °C
^{1}H-NMR ($CDCl_3$) δ:
1.28 (6H, t, J = 7Hz), 2.02 (3H, s), 2.70 (3H, s), 3.70 (2H, s), 4.25 (4H, m), 6.52 (1H, s), 7.15 (2H, d, J = 8Hz), 7.53 (2H, d, J = 8Hz)

IR(KBr): 3253, 2986, 1748, 1642, 1198, 1039 cm^{-1}

elemental analysis($C_{17}H_{23}NO_5S$) :			
calculated	C 55.27,	H 6.27,	N 3.79
found	C 55.09,	H 6.25,	N 3.78

(6) Diethyl 2-acetamido-2-(4-mercaptobenzyl)malonate

The compound obtained above (6.22 g) was added to trifluoroacetic anhydride (50 ml) under ice-cooling and the mixture was stirred for 1 hour. The trifluoroacetic anhydride was removed, and ethanol (100 ml) and triethylamine (100 ml) were added thereto. The mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated and chloroform (200 ml) was added thereto. Then, the mixture was washed with a saturated aqueous ammonium chloride solution and dried over anhydrous sodium sulfate. The solvent was distilled away and the residue was purified by silica gel column chromatography (eluent; chloroform:methanol = 10:1) to give the subject compound (4.26 g) as crystals.

melting point = 125-128 °C

^{1}H-NMR ($CDCl_3$) δ:

1.27 (6H, t, J = 7Hz), 2.00 (3H, s), 3.38 (1H, s), 3.57 (2H, s), 4.24 (4H, m), 6.50 (1H, s), 6.85 (2H, d, J = 8Hz), 7.14 (2H, d, J = 8Hz)

IR(KBr): 3398, 2986, 2547, 1736, 1665, 1212, 1018 cm^{-1}

elemental analysis($C_{16}H_{21}NO_5S$)			
calculated	C 56.62,	H 6.24,	N 4.13
found	C 56.61,	H 6.20,	N 4.09

MS: 339 (M^+)

(7) Diethyl 2-acetamido-2-(4-octylthiobenzyl)malonate

1-Bromooctane (0.58 g) and potassium carbonate (0.5 g) were added to a solution (10 ml) of the compound obtained above (1 g) in dimethylformamide and the mixture was stirred at room temperature for 5 hours. The reaction mixture was poured into ice water and extracted with ethyl acetate. The organic layer was washed with a saturated aqueous ammonium chloride solution and dried over anhydrous sodium sulfate. The solvent was distilled away and the residue was purified by silica gel column chromatography (eluent; chloroform:methanol = 25:1) to give the subjected compound (1.16 g) as crystals.

melting point = 82-84 °C

^{1}H-NMR ($CDCl_3$) δ:

0.85 (3H, t, J = 7Hz), 1.27 (14H, m), 1.40 (2H, quint, J = 7Hz), 1.61 (2H, quint, J = 7Hz), 2.01 (3H, s), 2.86 (2H, t, J = 7Hz), 3.58 (2H, s),4.25 (4H, m), 6.51 (1H, s), 6.89 (2H, d, J = 8Hz), 7.17 (2H, d, J = 8Hz)

IR(KBr) : 3255, 2952, 1747, 1644, 1298, 1274, 1220 cm^{-1}

elemental analysis($C_{24}H_{37}NO_5S$)			
calculated	C 63.83,	H 8.26,	N 3.10
found	C 63.33,	H 8.14,	N 3.06

MS: 451 (M^+)

(8) 2-Acetamido-2-(4-octylthiobenzyl)-1,3-propanediol

A solution (10 ml) of the compound obtained above (1 g) in anhydrous tetrahydrofuran was dropwise added to a solution of lithium aluminum hydride (0.26 g) in anhydrous tetrahydrofuran (10 ml) under ice-cooling. The mixture was stirred under ice-cooling for 1 hour and at room temperature for 1 hour. Then,

thereto was dropwise added a saturated aqueous sodium sulfate solution to decompose the lithium aluminum hydride. The insoluble matters were filtered off and the filtrate was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. The solvent was distilled away and the residue obtained was purified by silica gel column chromatography (eluent; chloroform:methanol = 10:1) to give the subjected compound (0.6 g) as crystals.

melting point = 76-78 °C

^{1}H-NMR ($CDCl_3$) δ:

0.86 (3H, t, J = 7Hz), 1.25 (8H, m), 1.40 (2H, quint, J = 7Hz), 1.61 (2H, quint, J = 7Hz), 1.99 (3H, s), 2.87 (2H, t, J = 7Hz), 2.89 (2H, s), 3.50 (2H, m), 3.70 (2H, m), 3.73 (2H, m, -OH × 2), 5.79 (1H, s, -NH), 7.14 (2H, d, J = 8Hz), 7.25 (2H, d, J = 8Hz)

IR(KBr): 3422, 3347, 3192, 2942, 1654, 1550, 1055 cm^{-1}

elemental analysis($C_{20}H_{33}NO_3S$)			
calculated	C 65.36,	H 9.05,	N 3.81
found	C 65.29,	H 9.11,	N 3.75

MS: 367 (M^+)

(9) 2-Amino-2-(4-octylthiobenzyl)-1,3-propanediol hydrochloride

An aqueous solution (5 ml) of lithium hydroxide (380 mg) was added to a solution (5ml) of the compound obtained above (400 mg) in methanol and the mixture was refluxed under heating for 4 hours. The reaction mixture was concentrated and extracted with ethyl acetate. The extract was washed with saturated brine and dried over anhydrous sodium sulfate. The solvent was distilled away to give white powder. The thus-obtained powder was dissolved in ethanol (2 ml) and thereto was added a 26% hydrochloric acid-ethanol solution(1 ml). The solvent was distilled away and the precipitated crystals were recrystallized from hexane-ethyl acetate to give the subjected compound (80 mg).

melting point = 100-102 °C

^{1}H-NMR (CD_3OD) δ:

0.76 (3H, t, J = 7Hz), 1.16 (8H, m), 1.30 (2H, m), 1.53 (2H, quint, J = 7Hz), 2.79 (2H, t, J = 7Hz), 2.86 (2H, s), 3.43 (2H, m), 3.62 (3H, m), 7.06 (2H, d, J = 8Hz), 7.15 (2H, d, J = 8Hz)

IR(KBr): 3363, 3286, 2924, 1516, 1494, 1072 cm^{-1}

elemental analysis($C_{18}H_{31}NO_2S$ HCl 1/2H_2O)			
calculated	C 58.28,	H 8.97,	N 3.78
found	C 58.44,	H 9.02,	N 3.68

Example 293 : 2-Amino-2-[2-(5-octyl-2-thienyl)ethyl]-1,3-propanediol hydrochloride

(1) 2-(2-Thienylethyl)-2-tetrahydropyranyl ether

To a solution (100 ml) of 2-(2-thienyl)ethanol (12.85 g) in dichloromethane, 3,4-dihydro-2H-pyran (9.25 g) and p-toluenesulfonic acid (2 g) were added. The mixture was stirred at room temperature for 4 hours. The solvent was distilled away and ethyl acetate was added thereto. The mixture was washed with saturated brine and dried over anhydrous sodium sulfate. The solvent was distilled away and the oily substance obtained was purified by distillation to give 13.52 g of the subject compound as an oily substance.

boiling point = 107-108 °C/1 mmHg

^{1}H-NMR ($CDCl_3$) δ:

1.50 (4H, m), 1.70 (1H, m), 1.82 (1H, m), 3.11 (2H, t, J = 7Hz), 3.47 (1H, m), 3.60 (1H, dt, J = 10, 7Hz), 3.79 (1H, m), 3.95 (1H, dt, J = 10,7Hz), 4.61 (1H, t, J = 3.5Hz), 6.83 (1H, dd, J = 1, 3.4Hz), 6.90 (1H, dd, J = 3.4, 5.4Hz), 7.11 (1H, dd, J = 1, 5.4Hz)

IR(neat): 2930, 1250, 1120, 1030, 870 cm^{-1}

elemental analysis $C_{11}H_{16}O_2S$	calculated	C 62.23,	H 7.60
	found	C 62.83,	H 7.01

MS: 212 (M^+)

(2) 2-(5-Octyl-2-thienyl)ethyl 2-tetrahydropyranyl ether

A solution (100 ml) of the above-mentioned compound (8.5 g) in anhydrous tetrahydrofuran was cooled to -78 °C and a solution (1.63 mol/l, 30 ml) of n-butyl lithium in hexane was dropwise added thereto. The mixture was stirred under ice-cooling for 30 minutes and then at room temperature for 30 minutes. A solution (15 ml) of 1-bromooctane (10 g) in anhydrous tetrahydrofuran was dropwise added thereto and the mixture was stirred at room temperature for 7 hours. The reaction mixture was poured into ice water and extracted with ethyl acetate. The organic layer was washed with a saturated aqueous ammonium chloride solution and dried over anhydrous sodium sulfate. The solvent was distilled away and the residue obtained was purified by silica gel column chromatography (eluent; hexane:ethyl acetate = 20:1) to give 6.6 g of the subject compound as an oily substance.

^{1}H-NMR ($CDCl_3$) δ:

0.85 (3H, t, 7Hz), 1.25 (10H, m), 1.53 (4H, m), 1.62 (2H, m), 1.72 (1H, m), 1.83 (1H, m), 2.71 (2H, t, J = 7Hz), 3.02 (2H, t, J = 7Hz), 3.46 (1H, m), 3.60 (1H, dt, J = 10, 7Hz), 3.80 (1H, m), 3.92 (1H, dt, J = 10, 7Hz), 4.61 (1H, t, J = 3.5Hz), 6.54 (1H, d, J = 3.4Hz), 6.61 (1H, d, J = 3.4Hz)

IR(neat): 2927, 2854, 1135, 1120, 1033 cm^{-1}

elemental analysis $C_{19}H_{32}O_2S$	calculated	C 70.32,	H 9.94
	found	C 70.12,	H 10.03

MS: 324 (M^+)

(3) 2-(5-Octyl-2-thienyl)ethanol

Tetrahydrofuran (20 ml) and p-toluenesulfonic acid (0.3 g) were added to a solution (80 ml) of the above-mentioned compound (6.5 g) in methanol and the mixture was stirred at room temperature for 1 hour. The solvent was distilled away and ethyl acetate was added to the resulting mixture. The mixture was washed with saturated brine and dried over anhydrous sodium sulfate. The solvent was distilled away and the residue obtained was purified by silica gel column chromatography (eluent; hexane:ethyl acetate = 5:1) to give 4 g of the subject compound as an oil.

^{1}H-NMR ($CDCl_3$) δ:

0.86 (3H, t, J = 7Hz), 1.27 (10H, m), 1.62 (2H, quint, J = 7Hz), 2.73 (2H, t, J = 7Hz), 3.00 (2H, t, J = 6Hz), 3.80 (2H, t, J = 6Hz), 6.58 (1H, d, J = 3.4Hz), 6.64 (1H, d, J = 3.4Hz)

IR(neat): 3348, 2927, 2854, 1466, 1047, 797 cm^{-1}

elemental analysis $C_{14}H_{24}OS \cdot 0.1H_2O$	calculated	C 69.43,	H 10.07
	found	C 69.34,	H 10.17

MS: 240 (M^+)

(4) 2-(5-Octyl-2-thienyl)ethyl methanesulfonate

Triethylamine (3 ml) was added to a solution (50 ml) of the above-mentioned compound (4 g) in dichloromethane. Methanesulfonyl chloride (1.5 ml) was dropwise added thereto and the mixture was stirred for 30 minutes. The reaction mixture was poured into ice water and extracted with dichloromethane. The organic layer was washed with a saturated aqueous sodium hydrogencarbonate solution, 0.1N hydrochloric

acid and saturated brine, and dried over anhydrous sodium sulfate. The solvent was distilled away and the residue obtained was purified by silica gel column chromatography (eluent; chloroform:methanol = 20:1) to give 5 g of the subject compound as an oily substance.

^{1}H-NMR ($CDCl_3$) δ:

0.86 (3H, t, J = 7Hz), 1.27 (10H, m), 1.61 (2H, quint, J = 7Hz), 2.72 (2H, t, J = 7.5Hz), 2.91 (3H, s), 3.17 (2H, t, J = 3.4Hz), 4.37 (2H, t, J = 6.5Hz), 6.58 (1H, d, J = 3.4Hz), 6.67 (1H, d, J = 3.4Hz)

IR(neat): 2927, 2854, 1357, 1176, 959, 802 cm^{-1}

elemental analysis $C_{15}H_{26}O_3S_2$	calculated	C 56.57,	H 8.23
	found	C 56.19,	H 8.10

MS: 318 (M^+)

(5) 2-(5-Octyl-2-thienyl)ethyl iodide

Sodium iodide (4.5 g) was added to a solution (50 ml) of the above-mentioned compound (4.8 g) in 2-butanone and the mixture was stirred at room temperature for 17 hours. The reaction mixture was concentrated, poured into ice water and extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. The solvent was distilled away and the residue was purified by silica gel column chromatography (eluent; hexane:ethyl acetate = 20:1) to give 4.9 g of the subject compound as an oily substance.

^{1}H-NMR ($CDCl_3$) δ:

0.86 (3H, t, J = 7Hz), 1.28 (10H, m), 1.62 (2H, quint, J = 7Hz), 2.72 (2H, t, J = 7.5Hz), 3.30 (4H, m), 6.57 (1H, d, J = 3.4Hz), 6.63 (1H, d, J = 3.4Hz)

IR(neat): 2926, 2853, 1466, 1168, 796 cm^{-1}

elemental analysis $C_{14}H_{23}SI$	calculated	C 48.00,	H 6.62
	found	C 48.29,	H 6.99

MS: 350 (M^+)

(6) Diethyl 2-acetamido-2-[2-(5-octyl-2-thienyl)ethyl]malonate

60% Oily sodium hydride (0.33 g) was suspended in anhydrous dimethylformamide (20 ml) and diethyl acetamidomalonate (1.82 g) was added thereto. The mixture was stirred at room temperature for 1 hour. Then, a solution (10 ml) of the above-mentioned compound (2.7 g) in anhydrous dimethylformamide was dropwise added thereto and the mixture was stirred at room temperature for 10 hours. The reaction mixture was poured into ice water and extracted with ethyl acetate. The extract was washed with a saturated aqueous ammonium chloride solution and dried over anhydrous sodium sulfate. The solvent was distilled away and the residue was purified by silica gel column chromatography (eluent; hexane:ethyl acetate = 2:1) to give 1.4 g of the subject compound as crystals.

melting point = 57-58 °C

^{1}H-NMR ($CDCl_3$) δ:

0.86 (3H, t, J = 7Hz), 1.25 (16H, m), 1.57 (2H, quint, J = 7Hz), 2.0 (3H, s), 2.61 (2H, m), 2.70 (4H, m), 4.20 (4H, m), 6.52 (1H, d, J = 3.4Hz), 6.53 (1H, d, J = 3.4Hz), 6.75 (1H, s)

IR(neat): 3278, 2923, 2852, 1746, 1647, 1211, 1195 cm^{-1}

elemental analysis $C_{23}H_{37}NO_5S$	calculated	C 62.84,	H 8.48,	N 3.19
	found	C 62.80,	H 8.42,	N 2.94

MS: 439 (M^+)

(7) 2-Acetamido-2-[2-(5-octyl-2-thienyl)ethyl]-1,3-propanediol

A solution (15 ml) of the above-mentioned compound (1.3 g) in anhydrous tetrahydrofuran was dropwise added to a solution (15 ml) of lithium aluminum hydride (0.38 g) in anhydrous tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 1 hour, the mixture was stirred at room temperature for 1 hour. A saturated aqueous sodium sulfate solution was dropwise added under ice-cooling to decompose lithium aluminum hydride. The insoluble matters were filtered off and the filtrate was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. The solvent was distilled away and the residue obtained was purified by silica gel column chromatography (eluent; chloroform:methanol = 15:1) to give 0.5 g of the subject compound as crystals.

melting point = 58-60 °C

^{1}H-NMR ($CDCl_3$) δ:

0.86 (3H, t, J = 7Hz), 1.27 (10H, m), 1.60 (2H, m), 1.94 (3H, s), 2.02 (2H, m), 2.71 (2H, t, J = 7Hz), 2.82 (2H, t, J = 7Hz), 3.57 (2H, dd, J = 6, 12Hz), 3.71 (2H, br.s, OH × 2), 3.80 (2H, dd, J = 6, 12Hz), 5.88 (1H, s), 6.54 (1H, d, J = 3.4Hz), 6.58 (1H, d, J = 3.4Hz)

IR(KBr): 3277, 2924, 2852, 1626, 1560, 1236, 1064, 1036 cm^{-1}

elemental analysis $C_{19}H_{33}NO_3S$	calculated	C 64.19,	H 9.36,	N 3.94
	found	C 63.75,	H 9.17,	N 3.68

MS: 355 (M^+)

(8) 2-Amino-2-[2-(5-octyl-2-thienyl)ethyl]-1,3-propanediol hydrochloride

A aqueous solution (5 ml) of lithium hydroxide (380 mg) was added to a solution (5 ml) of the above-mentioned compound (500 mg) in methanol and the mixture was refluxed under heating for 5 hours. The reaction mixture was concentrated and extracted with ethyl acetate. The extract was washed with saturated brine and dried over anhydrous sodium sulfate. The solvent was distilled away, whereby a powder was obtained. The powder was dissolved in ethanol (3 ml) and a 26% solution (2 ml) of hydrochloric acid in ethanol was added thereto. The solvent was distilled away and the precipitated crystals were recrystallized from hexane-ethyl acetate to give 150 mg of the subject compound.

melting point = 63-65 °C

^{1}H-NMR (CD_3OD) δ:

0.79 (3H, t, J = 7Hz), 1.18 (10H, m), 1.53 (2H, m), 1.96 (2H, m), 2.63 (2H, t, J = 7.5Hz), 2.74 (2H, m), 3.61 (2H, d, J = 12.2Hz), 3.67 (2H, d, J = 12.2Hz), 6.47 (1H, d, J = 3.4Hz), 6.54 (1H, d, J = 3.4Hz)

IR(KBr): 3482, 3265, 1631, 1530, 1468, 1059, 811 cm^{-1}

elemental analysis $C_{17}H_{31}NO_2S$ HCl	calculated	C 58.35,	H 9.22,	N 4.00
	found	C 58.12,	H 9.25,	N 4.03

MS: 313 (M^+)

Example 294 : 2-Amino-2-(4-octylsulfinylbenzyl)-1,3-propanediol

(1) 2-Acetamido-1,3-diacetoxy-2-(4-octylthiobenzyl)propane

Acetic anhydride (0.67 ml) was added to a solution (30 ml) of 2-acetamido-2-(4-octylthiobenzyl)-1,3-propanediol (1.04 g) in pyridine and the mixture was stirred at room temperature for 4 hours. The reaction mixture was concentrated and a 5% aqueous ammonium chloride solution was added thereto. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and dried over anhydrus magnesium sulfate. The solvent was distilled away and the residue was purified by silica gel column chromatography (eluent; ethyl acetate:hexane = 4:1) to give 0.73 g of the subject compound.

melting point = 71-74 °C

^{1}H-NMR ($CDCl_3$) δ:

0.85 (3H, t, J = 6.9Hz), 1.10-1.85 (12H, m), 1.94 (3H, s), 2.06 (6H, s), 2.28 (2H, t, J = 7.8Hz), 3.19 (2H, s), 4.26 (4H, dd, J = 11.2, 17.6Hz), 5.48 (1H, br.s), 7.03 (2H, d, J = 8.3Hz), 7.20 (2H, d, J = 8.3Hz)

IR(KBr): 3295, 2924, 1739 cm^{-1}

MS: 451 (M^+)

elemental analysis	calculated found	C 63.83, C 64.00,	H 8.26, H 8.32,	N 3.10 N 3.12

(2) 2-Acetamido-1,3-diacetoxy-2-(4-octylsulfinylbenzyl)propane

To a solution (15 ml) of the above-mentioned compound (0.73 g) in chloroform was added m-chloroperbenzoic acid (0.56 g) and the mixture was stirred for 40 minutes. Calcium hydroxide (0.23 g) was added to the reaction mixture and the mixture was stirred at room temperature for 1 hour. The insoluble matters were filtered off and the solvent was distilled away. The residue was purified by silica gel column chromatography (eluent; dichloromethane:methanol = 30:1) to give 0.66 g of the subject compound.

melting point = 70-72 °C

^{1}H-NMR ($CDCl_3$) δ:

0.85 (3H, t, J = 7.3Hz), 1.10-1.80 (12H, m), 1.95 (3H, s), 2.07 (6H,s), 2.76 (2H, m), 3.33 (2H, s), 4.09-4.16 (4H, m), 5.54 (1H, s), 7.29 (2H, d, J = 8.3Hz), 7.54 (2H, d, J = 8.3Hz)

IR(KBr): 3278, 3081, 2928, 1746, 1672, 1218 cm^{-1}

MS: 467 (M^+)

elemental analysis	calculated found	C 61.65, C 61.36,	H 7.97, H 7.90,	N 3.00 N 2.93

(3) 2-Amino-2-(4-octylsulfinylbenzyl)-1,3-propanediol

An aqueous solution (3 ml) of lithium hydroxide (242 mg) was added to a solution (3 ml) of the above-mentioned compound (300 mg) in methanol and the mixture was stirred at 50 °C for 5 hours. After concentration, the reaction mixture was extracted with ethyl acetate and washed with water. The mixture was dried over anhydrous magnesium sulfate and the solvent was distilled away. The residue was recrystallized from ethyl acetate-hexane to give 81.5 mg of the subject compound.

melting point = 80-82 °C

^{1}H-NMR ($CDCl_3$) δ:

0.85 (3H, t, J = 6.8Hz), 1.20-1.80 (16H, m), 2.70-2.90 (4H, m), 3.44 (4H, dd, J = 10.3, 17.1Hz), 7.38 (2H, d, J = 7.8Hz), 7.55 (2H, d, J = 7.8Hz)

IR(KBr): 3339, 2915, 2758, 1033 cm^{-1}

MS: 342 (M^+)

elemental analysis	calculated found	C 63.31, C 62.62,	H 9.15, H 9.04,	N 4.10 N 3.91

Example 295 : 2-Amino-2-(4-octylsulfonylbenzyl)-1,3-propanediol

(1) 2-Acetamido-1,3-diacetoxy-2-(4-octylsulfonylbenzyl)propane

To a solution (10 ml) of 2-acetamido-1,3-diacetoxy-2-(4-octylsulfinylbenzyl)propane (330 mg) in chloroform was added m-chloroperbenzoic acid (244 mg) under ice-cooling. The mixture was stirred for 2.5 hours and then at room temperature for 1.5 hours. Calcium hydroxide (0.1 g) was added to the reaction mixture and the mixture was stirred at room temperature for 45 minutes. The insoluble matters were filtered

off and the filtrate was concentrated under reduced pressure. The residue was recrystallized from hexane-ethyl acetate to give 162 mg of the subject compound.
melting point = 98-100 °C
^{1}H-NMR ($CDCl_3$) δ:
0.84 (3H, t, J = 7.3Hz), 1.10-1.80 (12H, m), 1.96 (3H, s), 2.07 (6H, s), 3.06 (2H, m), 3.38 (2H, s), 4.25 (4H, dd, J = 11.7, 25.8Hz), 5.54 (1H, s), 7.34 (2H, d, J = 8.2Hz), 7.81 (2H, d, J = 8.2Hz)
IR(KBr) : 3317, 2921, 2853, 1749, 1654, 1313, 1141 cm^{-1}
MS: 483 (M^+)

elemental analysis	calculated found	C 59.61, C 59.50,	H 7.71, H 7.60,	N 2.90 N 2.85

(2) 2-Amino-2-(4-octylsulfonylbenzyl)-1,3-propanediol

An aquous solution (2.5 ml) of lithium hydroxide (109 mg) was added to a solution (2.5 ml) of the above-mentioned compound (140 mg) in methanol and the mixture was stirred at 50 °C for 4 hours. The reaction mixture was extracted with ethyl acetate and the extract was washed with water. The mixture was dried over anhydrous magnesium sulfate and the solvent was distilled away. The residue was recrystallized from hexaneethyl acetate to give 45 mg of the subject compound.
melting point = 108-109 °C
^{1}H-NMR ($CDCl_3$) δ:
0.84 (3H, t, J = 7.3Hz), 1.10-1.86 (16H, m), 2.83 (2H, s), 3.06 (2H, m), 3.43 (2H, s), 3.44 (2H, s), 7.43 (2H, d, J = 7.8Hz), 7.82 (2H, d, J = 7.8Hz)
IR(KBr): 3343, 2915, 1299, 1147 cm^{-1}
MS: 357 (M^+)

elemental analysis	calculated (0.1H_2O) found	C 60.17, C 59.89,	H 8.75, H 8.79,	N 3.90 N 3.91

Example 296 : 2-Amino-2-[2-(3-octylphenyl)ethyl]-1,3-propanediol and hydrochloride thereof

(1) 1-(3-Bromophenyl)octanol

A small amount of iodine was added to a solution (100 ml) of magnesium (9.8 g) in anhydrous tetrahydrofuran and the mixture was stirred at 50 °C until the color of the iodine disappeared. A solution of heptyl bromide in anhydrous tetrahydrofuran (200 ml) was dropwise added thereto over 1 hour. The mixture was stirred at 65 °C for 1 hour and a solution of m-bromobenzaldehyde in anhydrous tetrahydrofuran (200 ml) was dropwise added thereto under ice-cooling. The mixture was stirred at room temperature for 30 minutes. Under ice-cooling, a saturated aqueous ammonium chloride solution (7.3 ml) was added thereto and the mixture was stirred for 1 hour. The insoluble matters were filtered off and the filtrate was concentrated. The concentrate was dissolved in ethyl acetate and the mixture was washed with water. The mixture was dried over magnesium sulfate and the solvent was distilled away. The residue obtained was purified by silica gel column chromatography (eluent; hexane:ethyl acetate = 10:1) to give 50.9 g of the subject compound as an oily substance.
^{1}H-NMR ($CDCl_3$) δ:
0.85 (3H, t, J = 6.8Hz), 1.20-1.90 (13H, m), 4.61 (1H, m), 7.1-7.3 (2H, m), 7.36 (1H, dt, J = 1.5, 7.8Hz), 7.49 (1H, m)
IR(neat): 3346, 2922, 2853cm^{-1}
MS: 285 (M^+)

elemental analysis	calculated found	C 58.96, C 58.92,	H 7.42, H 7.36,	N 0.00 N 0.00

(2) trans-1-(3-Bromophenyl)-1-octene

Phosphorus pentaoxide (24.9 g) was added to a solution of the above-mentioned compound (10 g) in benzene (500 ml) and the mixture was refluxed under heating for 1.5 hours. The insoluble matters were filtered off, and the filtrate was washed with water and dried over anhydrous magnesium sulfate. The solvent was distilled away and the residue was purified by silica gel column chromatography (eluent; hexane:ethyl acetate = 20:1) to give 9 g of the subject compound as an oily substance.

^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.9Hz), 1.20-1.50 (8H, m), 2.19 (2H, dt, J=6.3, 6.5Hz), 6.21 (1H, td, J=6.3, 16.1Hz), 6.28 (1H, d, J=16.1Hz), 7.13 (1H, t, J=7.9Hz), 7.21 (1H, m), 7.28 (1H, m), 7.47 (1H, m)

IR(neat): 3439, 3063 cm^{-1}

MS: 267 (M^+)

(3) trans-1-(3-Formylphenyl)-1-octene

A small amount of iodine was added to a solution of magnesium (1.38 g) in anhydrous tetrahydrofuran (30 ml) and the mixture was stirred at 50°C until the color of the iodine disappeared. A solution of the above-mentioned compound (13.8 g) in anhydrous tetrahydrofuran (40 ml) was dropwise added thereto over 30 minutes. The mixture was stirred at 55°C for 1 hour and a solution of dimethylformamide (4 ml) in anhydrous tetrahydrofuran (30 ml) was dropwise added thereto over 1 hour. The mixture was stirred at room temperature for 2 hours. Under ice-cooling, a saturated aqueous ammonium chloride solution was added thereto and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and dried over magnesium sulfate. The solvent was distilled away and the residue obtained was purified by silica gel column chromatography (eluent; hexane:ethyl acetate = 30:1) to give 7.12 g of the subject compound as an oily substance.

^{1}H-NMR ($CDCl_3$) δ: 0.86 (3H, t, J=6.8Hz), 1.20-1.60 (8H, m), 2.22 (2H, dt, J=6.8, 6.9Hz), 6.32 (1H, td, J=6.8, 15.7Hz), 6.41 (1H, d, J=15.7Hz), 7.43 (1H, t, J=7.8Hz), 7.57 (1H, m), 7.68 (1H, m), 7.83 (1H, s), 9.99 (1H, s)

IR(neat): 2956, 2927, 2855, 1699 cm^{-1}

MS: 216 (M^+)

elemental analysis	calculated found	C 83.29, C 83.50,	H 9.32 H 9.29

(4) 3-(trans-1-Octenyl)-β-methylsulfinyl-β-methyl thiostyrene

Methyl methyl sulfinyl methyl sulfide (3 ml) and a solution (2.6 ml) of trimethylbenzyl ammonium hydroxide in methanol were added to a solution of the above-mentioned compound (6.17 g) in dioxane (30 ml) and the mixture was stirred at 80°C for 2 hours. The reaction mixture was concentrated, dissolved in ethyl acetate and washed with water. The mixture was dried over anhydrous magnesium sulfate. The solvent was distilled away and the residue obtained was purified by silica gel column chromatography (eluent; hexane:ethyl acetate = 4:1) to give 6.48 g of the subject compound as an oily substance.

^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t, J=6.8Hz), 1.20-1.55 (8H, m), 2.12 (2H, dt, J=6.8, 6.9Hz), 2.30 (3H, s), 2.75 (3H, s), 6.25 (1H, td, J=6.8, 16.1Hz), 6.37 (3H, t, J=16.1Hz), 7.30-7.40 (2H, m), 7.60 (1H, s), 7.72 (1H, m), 7.81 (1H, s)

IR(neat): 2955, 2925, 1068 cm^{-1}

MS: 322 (M^+)

(5) Ethyl 3-(trans-1-octenyl)phenylacetate

A solution of 26% hydrogen chloride in ethanol (48 ml) was added to a solution of the above-mentioned compound (6.48 g) in ethanol (40 ml) and the mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated and the residue was purified by silica gel column chromatography (eluent; hexane:ethyl acetate = 20:1) to give 5.11 g of the subject compound as an oily substance.

^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t, J = 6.8Hz), 1.18-1.50 (11H, m), 2.19 (2H, dt, J = 6.8, 6.9Hz), 3.57 (2H, s), 4.13 (2H, q, J = 7.3Hz), 6.22 (1H, td, J = 6.8, 16.1Hz), 6.33 (1H, d, J = 16.1Hz), 7.10-7.25 (4H, m)

IR(neat): 2957, 2927, 2855, 1737 cm^{-1}

MS: 274 (M^+)

(6) 2-[3-(trans-1-Octenyl)phenyl]ethanol

Lithium aluminum hydride (1.22 g) was suspended in anhydrous tetrahydrofuran (150 ml) and thereto was added the above-mentioned compound (5.89 g) under ice-cooling. The mixture was stirred for 1 hour. Under ice-cooling, ethanol and water were added thereto and the insoluble matters were filtered off. The filtrate was dried over anhydrous sodium sulfate and the solvent was distilled away. The residue was purified by silica gel column chromatography (eluent; hexane: ethyl acetate = 5:1) to give 4.22 g of the subject compound as an oily substance.

^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t, J = 6.8Hz), 1.10-1.50 (8H, m), 2.19 (2H, dt, J = 6.8, 6.9Hz), 2.83 (2H, t, J = 6.3Hz), 3.85 (2H, dt, J = 6.2, 6.3Hz), 6.20 (1H, td, J = 6.8, 16.1Hz), 6.34 (1H, d, J = 16.1Hz), 7.03 (1H, m), 7.18-7.27(3H, m)

IR(neat): 3348, 2956, 2926, 2854 cm^{-1}

MS: 232 (M^+)

(7) 2-[3-(trans-1-Octenyl)phenyl]ethylmethanesulfonate

Triethylamine (2.8 ml) was added to a solution (60 ml) of the above-mentioned compound (4.19 g) in dichloromethane and the mixture was ice-cooled. Thereto was dropwise added methanesulfonyl chloride (14 ml) and the mixture was stirred at room temperature for 1.5 hours. The reaction mixture was poured into ice water and extracted with dichloromethane. The dichloromethane layer was washed with a saturated potassium hydrogencarbonate solution, a 1% aqueous hydrochloric acid solution and saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and the residue was purified by silica gel column chromatography (eluent; hexane: ethyl acetate = 5:1) to give 5.55 g of the subject compound as an oily substance.

^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t, J = 6.8Hz), 1.20-1.50 (8H, m), 2.19 (2H, dt, J = 6.8, 6.9Hz), 2.83 (3H, s), 3.02 (2H, t, J = 6.8Hz), 4.40 (2H, t, J = 6.8Hz), 6.22 (1H, td, J = 6.8, 15.6Hz), 6.33 (1H, d, J = 15.6Hz), 7.03 (1H, m), 7.18-7.24 (3H, m)

IR(neat): 2956, 2927, 2855 cm^{-1}

MS: 310 (M^+)

(8) 2-[3-(trans-1-Octenyl)phenyl]ethyl iodide

Sodium iodide (3.99 g) was added to a solution of the above-mentioned compound (5.51 g) in 2-butanone (60 ml) and the mixture was stirred at 45 °C for 3 hours. The reaction mixture was concentrated, poured into ice water and extracted with ethyl acetate. The extract was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and the residue was purified by silica gel column chromatography (eluent; hexane:ethyl acetate = 100:1) to give 4.75 g of the subject compound as an oily substance.

^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t, J = 6.8Hz), 1.20-1.50 (8H, m), 2.19 (2H, dt, J = 6.8, 6.9Hz), 3.14 (2H, t, J = 7.4Hz), 3.34 (2H, t, J = 7.4Hz), 6.21 (1H, td, J = 6.8, 18.1Hz), 6.34 (1H, d, J = 18.1Hz), 7.00 (1H, m), 7.14-7.24 (3H, m)

IR(neat): 2956, 2925, 2853 cm^{-1}

MS: 342 (M^+)

(9) Diethyl 2-acetamido-2-[2-[3-(trans-1-octenyl)phenyl)ethyl]malonate

Sodium ethoxide (7.62 g) was added to a solution of diethyl acetamidomalonate (7.62 g) in ethanol (30 ml) and the mixture was stirred at 60 °C for 45 minutes. Thereto was dropwise added a solution of the above-mentioned compound (4 g) in ethanol (20 ml) and the mixture was refluxed under heating for 5 hours. The reaction mixture was concentrated, poured into ice water and extracted with ethyl acetate. The extract was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and the residue was purified by silica gel column chromatography (eluent; hexane:ethyl acetate = 3:1) to give 2.46 g of the subject compound as an oily substance.

^{1}H-NMR ($CDCl_3$) δ:
0.87 (3H, t, J = 6.9Hz), 1.22 (6H, t, J = 6.8Hz), 1.22-1.50 (8H, m), 1.97 (3H, s), 2.17 (2H, dt, J = 6.8, 6.9Hz), 2.43 (2H, m), 2.67 (2H, m), 4.11-4.23 (4H, m), 6.18 (1H, td, J = 6.8, 16.1Hz), 6.31 (1H, d, J = 16.1Hz), 6.74 (1H, s), 6.94 (1H, d, J = 6.8Hz), 7.09-7.18 (3H, m)

IR(neat): 3413, 2957, 2927, 1741, 1683 cm^{-1}

MS: 431 (M^+)

elemental analysis calculated (1/10 H_2O)			
found	C 69.29, C 69.04,	H 8.65, H 8.75,	N 3.23 N 3.26

(10) 2-Acetamido-1,3-diacetoxy-2-[2-(3-(trans-1-octenyl)phenyl)ethyl]propane

The above-mentioned compound (2.8 g) in anhydrous tetrahydrofuran (20 ml) was dropwise added to a solution of lithium aluminum hydride (0.74 g) in anhydrous tetrahydrofuran (40 ml) in a stream of nitrogen under ice-cooling and the mixture was stirred at room temperature for 2 hours. Under ice-cooling, ethanol and water were added to the reaction mixture and the insoluble matters were filtered off. The filtrate was dried over anhydrous magnesium sulfate and the solvent was distilled away to give a yellow, oily substance (2.34 g). This substance was dissolved in pyridine (60 ml) and thereto was added acetic anhydride (1.6 ml) under ice-cooling. The mixture was stirred at room temperature for 2.5 hours. The reaction mixture was concentrated and the residue was dissolved in ethyl acetate. The mixture was washed with a saturated aqueous ammonium chloride and saturated brine and dried over anhydrous magnesium sulfate. The solvent was distilled away and the residue was purified by silica gel column chromatography (eluent; hexane:ethyl acetate = 4:1) to give 1.8 g of the subject compound as white crystals.

melting point = 84-86 °C

^{1}H-NMR ($CDCl_3$) δ:
0.87 (3H, t, J = 6.8Hz), 1.10-1.50 (8H, m), 1.94 (3H, s), 2.07 (6H, s), 2.15-2.21 (4H, m), 2.57 (2H, m), 4.33 (4H, s), 5.62 (1H, s), 6.19 (1H, dt, J = 6.8, 16.1Hz), 6.33 (1H, d, J = 16.1Hz), 6.99 (1H, d, J = 6.8Hz), 7.13-7.21 (3H, m)

IR(KBr): 3311, 2961, 2926, 1738, 1652 cm^{-1}

MS: 431 (M^+)

elemental analysis	calculated found	C 69.58, C 69.85,	H 8.64, H 8.74,	N 3.25 N 3.35

(11) 2-Acetamido-1,3-diacetoxy-2-[2-(3-(octylphenyl)ethyl]propane

A suspension of 10% palladium carbon (150 mg) in methanol (10 ml) was added to a solution of the above-mentioned compound (1.41 g) in methanol (10 ml) and the mixture was stirred under hydrogen pressurization (10 atm) for 2 hours. The inside of the reaction vessel was displaced with nitrogen and the insoluble matters were filtered off. The solvent was distilled away and the residue was purified by silica gel column chromatography (eluent; hexane:ethyl acetate = 2:1) to give 1.05 g of the subject compound as

white crystals.
melting point = 86-87 °C
^{1}H-NMR ($CDCl_3$) δ:
0.86 (3H, t, J = 6.9Hz), 1.10-1.60 (12H, m), 1.93 (3H, s), 2.07 (6H, s), 2.18 (2H, m), 2.52 (2H, t, J = 6.8Hz), 2.56 (2H, t, J = 6.8Hz), 4.33 (4H, s), 5.61 (1H, s), 6.95-7.05 (3H, m), 7.17 (1H, t, J = 7.8Hz)
IR(KBr): 3313, 2960, 2925, 2854, 1738, 1651 cm^{-1}

(12) 2-Amino-2-[2-(3-octylphenyl)ethyl]-1,3-propanediol

An aqueous solution (10 ml) of lithium hydroxide (1 g) was added to a solution of the above-mentioned compound (1.04 g) in methanol (10 ml) and the mixture was refluxed under heating for 5 hours. The reaction mixture was concentrated, exctracted with ethyl acetate and washed with saturated brine. The mixture was dried over anhydrous magnesium sulfate and the solvent was distilled away. The residue was purified by silica gel column chromatography (eluent; chloroform:methanol = 5:1) to give 0.46 g of the subject compound as white crystals.
melting point = 89-92 °C
^{1}H-NMR ($CDCl_3$) δ:
0.85 (3H, t, J = 6.4Hz), 1.20-1.35 (12H, m), 1.55 (2H, m), 1.83 (2H, m), 2.51 (2H, t, J = 7.2Hz), 2.60 (2H, m), 2.98 (2H, br.s), 3.68 (2H, t, J = 11.2Hz), 3.71 (2H, t, J = 11.2Hz), 6.97 (3H, m), 7.12 (1H, t, J = 7.3Hz)
IR(KBr): 3396, 3257, 2925, 2854 cm^{-1}

(13) 2-Amino-2-[3-(3-octylphenyl)ethyl]-1,3-propanediol hydrochloride

The above-mentioned compound (0.45 g) was dissolved in ethanol (20 ml) and thereto was added a 26% solution (1 ml) of hydrochloric acid in ethanol. The solvent was distilled away and the precipitated crystals were recrystallized from ethyl acetate:methanol = 30:1 to give 0.33 g of the subject compound.
melting point = 99-101 °C
^{1}H-NMR (DMSO) δ:
0.84 (3H, t, J = 6.8Hz), 1.20-1.35 (12H, m), 1.53 (2H, m), 1.74 (2H, m), 2.40-2.60 (2H, m), 3.45 (4H, s), 5.33 (2H, br.s), 6.98-7.00 (3H, m), 7.18 (1H, t, J = 7.3Hz), 7.70 (3H, br.s)
IR(KBr): 3178, 2924, 2853 cm^{-1}

Example 297 : 2-Amino-2-(4-decylphenyl)-1,3-propanediol

(1) 4-Bromomethyldecylbenzene

4-Decylphenylmethanol (3.91 g) was dissolved in toluene (40 ml) and thereto was added 48% hydrobromic acid (40 ml). The mixture was refluxed under heating at 90 °C for 6 hours. After cooling, the organic layer was separated and washed with saturated brine and a sodium hydrogencarbonate solution. The mixture was dried over anhydrous sodium sulfate and the solvent was distilled away to give 4.9 g of the oily subject compound.
^{1}H-NMR ($CDCl_3$) δ:
0.86 (3H, t, J = 6.6Hz), 1.2-1.3 (14H, m), 1.5-1.6 (2H, m), 2.57 (2H, t, J = 7.6Hz), 4.47 (2H, s), 7.13 (2H, d, J = 8.1Hz), 7.28 (2H, d, J = 8.0Hz)

(2) 4-Decylphenylnitromethane

Silver nitrite (4.15 g) and dry ether (20 ml) were placed in a flask and cooled with ice. Thereto was dropwise added a solution of 4-bromomethyldecylbenzene (5.5 g) in ether (10 ml) with stirring. After the dropwise addition, the mixture was stirred under ice-cooling for 4 hours and the insoluble matters were filtered off. The solvent in the filtrate was distilled away and the residue was crystallized from pentane to give 1.44 g of the subject compound as pale yellow crystals.
melting point = 50 °C
^{1}H-NMR ($CDCl_3$) δ:
0.88 (3H, t, J = 6Hz), 1.2-1.3 (14H, m), 1.5-1.6 (2H, m), 2.62 (2H, t, J = 8Hz), 5.41

(2H, s), 7.24 (2H, d, J = 8Hz), 7.28 (2H, d, J = 8Hz)

(3) 2-(4-Decylphenyl)-2-nitro-1,3-propanediol

4-Decylphenylnitromethane (555 mg) was dissolved in ethanol (5 ml) and thereto were added a 1N aqueous sodium hydroxide solution (0.02 ml) and 37% formalin (0.45 ml). The mixture was heated at 50 °C for 6 hours. The solvent was distilled away and the residue was extracted with ethyl acetate. The extract was washed with saturated brine and dried over anhydrous sodium sulfate. The solvent was distilled away and the residue was crystallized from hexane to give 1.75 g of the colorless, scale-like subject compound.
melting point = 80-81 °C
^{1}H-NMR ($CDCl_3$) δ:
0.88 (3H, t, J = 6Hz), 1.2-1.3 (14H, m), 1.5-1.6 (2H, m), 2.59 (2H, t, J = 8Hz), 2.77 (2H, m), 4.35 (2H, m), 4.60 (2H, m), 7.17 (2H, d, J = 10Hz), 7.21 (2H, d, J = 10Hz)

(4) 2-Amino-2-(4-decylphenyl)-1,3-propanediol

2-(4-Decylphenyl)-2-nitro-1,3-propanediol (170 mg) was dissolved in ethanol (30 ml) and the mixture was subjected to catalytic reduction in the presence of 5% palladium carbon (40 mg) under hydrogen pressure of 20 atm. After stirring the mixture for 8 hours, the insoluble matters were filtered off and the filtrate was concentrated. The residue was purified by preparative thin layer chromatography (silica gel) to give 8.9 mg of the subject compound.
melting point = 136-137 °C
^{1}H-NMR ($CDCl_3$-CD_3OD) δ:
0.88 (3H, t, J = 8Hz), 1.1-1.4 (14H, m), 1.4-1.8 (2H, m), 2.3-2.7 (6H, m), 3.5-4.2 (4H, m), 7.2 (2H, d, J = 10Hz), 7.33 (2H, d, J = 10Hz)
melting point of hydrochloride = 113-114 °C (recrystallized from isopropyl alcohol)

Example 298 : 2-Acetylamino-2-(4-decylphenyl)-1,3-propanediol

2-Amino-2-(4-decylphenyl)-1,3-propanediol (313 mg) was dissolved in a mixed solvent of ethanol (20 ml) and chloroform (5 ml). Thereto was added triethylamine (0.4 ml) and the mixture was cooled to -60 °C with dry ice-methanol. Thereto was dropwise added a solution of acetyl chloride (0.12 ml) in dichloromethane (5 ml) under ice-cooling and the mixture was heated to room temperature. The solvent was distilled away and the residue was dissolved in ethyl acetate. The mixture was washed with brine, an aqueous dilute hydrochloric acid solution and an aqueous sodium hydrogencarbonate solution. The resultant mixture was dried over anhydrous sodium sulfate and the solvent was distilled away. The residue was purified by preparative thin layer chromatography (silica gel) and recrystallized from hexane to give 130 mg of the colorless, crystalline subject compound.
melting point = 112-113 °C
^{1}H-NMR ($CDCl_3$) δ:
0.88 (3H, t, J = 6.9Hz), 1.2-1.4 (14H, m), 1.5-1.7 (2H, m), 2.17 (3H, s), 2.58 (2H, t, J = 7.9Hz), 3.66 (2H, dd, J = 7.7Hz, 6Hz), 3.88 (2H, dd, J = 12Hz, 7.6Hz), 4.05 (2H, dd, J = 11.9Hz, 6Hz), 6.37 (1H, bs), 7.20 (2H, d, J = 8.6Hz), 7.25 (2H, d, J = 8.6Hz)

Example 299 : 5-Acetamido-5-(4-decylphenyl)-2,2-dimethyl-1,3-dioxane

2-Acetylamino-2-(4-decylphenyl)-1,3-propanediol (224 mg) and 2,2-dimethoxypropane (0.3 ml) were dissolved in benzene (5 ml) and the mixture was refluxed under heating in the presence of a catalytic amount of toluenesulfonic acid. After cooling, the reaction mixture was washed with an aqueous sodium hydrogencarbonate solution and dried over sodium sulfate. The solvent was distilled away and the residue was purified by preparative thin layer chromatography (silica gel) to give 99 mg of the amorphous subject compound.
^{1}H-NMR ($CDCl_3$) δ:
0.88 (3H, t, J = 6.6Hz), 1.2-1.4 (14H, m), 1.48 (3H, s), 1.51 (3H, s), 1.5-1.7 (2H, m), 2.06 (3H, s), 2.56 (2H, t, J = 7.8Hz), 4.14 (4H, s), 6.23 (1H, bs), 7.15 (2H, d, J = 8.3Hz), 7.22 (2H, d, J = 8.3Hz)

Example 300 : 2-Amino-2-(8-phenyloctyl)-1,3-propanediol

Example 301 : 2-Amino-2-(9-phenylnonyl)-1,3-propanediol

Example 302 : 2-Amino-2-(11-phenylundecyl)-1,3-propanediol

Example 303 : 2-Amino-2-(12-phenyldodecyl)-1,3-propanediol

Example 304 : 2-Amino-2-(14-phenyltetradecyl)-1,3-propanediol

Example 305 : 2-Amino-2-(15-phenylpentadecyl)-1,3-propanediol

Example 306 : 2-Amino-2-(16-phenylhexadecyl)-1,3-propanediol

Example 307 : 2-Amino-2-[2-(4-tridecylphenyl)ethyl]-1,3-propanediol

Example 308 : 2-Amino-2-[2-(4-tetradecylphenyl)ethyl]-1,3-propanediol

Example 309 : 2-Amino-2-[2-(4-hexyloxyphenyl)ethyl]-1,3-propanediol

Example 310 : 2-Amino-2-[2-(4-decyloxyphenyl)ethyl]-1,3-propanediol

Example 311 : 2-Amino-2-[2-(4-dodecyloxyphenyl)ethyl]-1,3-propanediol

Example 312 : 2-Amino-2-[2-(4-tridecyloxyphenyl)ethyl]-1,3-propanediol

Example 313 : 2-Amino-2-[2-(4-(8-fluorooctyl)phenyl)ethyl]-1,3-propanediol

Example 314 : 2-Amino-2-[2-(4-(12-fluorododecyl)phenyl)ethyl]-1,3-propanediol

Example 315 : 2-Amino-2-[2-(4-(7-fluoroheptyloxy)phenyl)ethyl]-1,3-propanediol

Example 316 : 2-Amino-2-[2-(4-(11-fluoroundecyloxy)phenyl)ethyl]-1,3-propanediol

Example 317 : 2-Amino-2-[2-(4-phenylmethyloxyphenyl)ethyl]-1,3-propanediol

Example 318 : 2-Amino-2-[2-(4-(2-phenylethyloxy)phenyl)ethyl]-1,3-propanediol

Example 319 : 2-Amino-2-[2-(4-(3-phenylpropyloxy)phenyl)ethyl]-1,3-propanediol

Example 320 : 2-Amino-2-[2-(4-(4-phenylbutyloxy)phenyl)ethyl]-1,3-propanediol

Example 321 : 2-Amino-2-[2-(4-(5-phenylpentyloxy)phenyl)ethyl]-1,3-propanediol

Example 322 : 2-Amino-2-[2-(4-(7-phenylheptyloxy)phenyl)ethyl]-1,3-propanediol

Example 323 : 2-Amino-2-[2-(4-(8-phenyloctyloxy)phenyl)ethyl]-1,3-propanediol

Example 324 : 2-Amino-2-[4-(6-(4-fluorophenyl)hexyloxy)phenyl)ethyl]-1,3-propanediol

Example 325 : 2-Amino-2-[2-(4-(4-phenoxybutyloxy)phenyl)ethyl]-1,3-propanediol

Example 326 : 2-Amino-2-[2-(4-(5-phenoxypentyloxy)phenyl)ethyl]-1,3-propanediol

Example 327 : 2-Amino-2-[2-(4-(6-phenoxyhexyloxy)phenyl)ethyl]-1,3-propanediol

Example 328 : 2-Amino-2-[2-(4-(7-phenoxyheptyloxy)phenyl)ethyl]-1,3-propanediol

Example 329 : 2-Amino-2-[2-(4-(4-phenoxybutyl)phenyl)ethyl]-1,3-propanediol

Example 330 : 2-Amino-2-[2-(4-(5-phenoxypentyl)phenyl)ethyl]-1,3-propanediol

Example 331 : 2-Amino-2-[2-(4-(6-phenoxyhexyl)phenyl)ethyl]-1,3-propanediol

Example 332 : 2-Amino-2-[2-(4-(7-phenoxyheptyl)phenyl)ethyl]-1,3-propanediol

Example 333 : 2-Amino-2-[2-(4-octylcyclohexyl)ethyl]-1,3-propanediol

Example 334 : 2-Amino-2-[2-(4-nonylcyclohexyl)ethyl]-1,3-propanediol

Example 335 : 2-Amino-2-[2-(4-dodecylcyclohexyl)ethyl]-1,3-propanediol

Example 336 : 2-Amino-2-[2-(1-octylpiperidin-4-yl)ethyl]-1,3-propanediol

Example 337 : 2-Amino-2-[2-(1-dodecylpiperidin-4-yl)ethyl]-1,3-propanediol

Example 338 : 2-Amino-2-[2-(5-nonyl-2-thienyl)ethyl]-1,3-propanediol

Example 339 : 2-Amino-2-[2-(5-decyl-2-thienyl)ethyl]-1,3-propanediol

Example 340 : 2-Amino-2-[2-(5-dodecyl-2-thienyl)ethyl]-1,3-propanediol

Example 341 : 2-Amino-2-[13-(2-thienyl)tridecyl]-1,3-propanediol

Example 342 : 2-Amino-2-[2-(5-octyl-2-pyridyl)ethyl]-1,3-propanediol

Example 343 : 2-Amino-2-[2-(5-decyl-2-pyridyl)ethyl]-1,3-propanediol

Example 344 : 2-Amino-2-[13-(2-pyridyl)tridecyl]-1,3-propanediol

Example 345 : 2-Amino-2-[2-(2-octyl-5-pyridyl)ethyl]-1,3-propanediol

Example 346 : 2-Amino-2-[2-(2-decyl-5-pyridyl)ethyl]-1,3-propanediol

Example 347 : 2-Amino-2-[13-(3-pyridyl)tridecyl]-1,3-propanediol

Example 348 : 2-Amino-2-(4-decylphenyl)-1,3-propanediol

Example 349 : 2-Amino-2-(4-dodecylphenyl)-1,3-propanediol

Example 350 : 2-Amino-2-(4-tetradecylphenyl)-1,3-propanediol

Example 351 : 2-Amino-2-(4-hexadecylphenyl)-1,3-propanediol

Example 352 : 2-Amino-2-[1-hydroxy-2-(4-octylphenyl)ethyl]-1,3-propanediol

Example 353 : 2-Amino-2-[2-(4-dodecylphenyl)-1-hydroxyethyl]-1,3-propanediol

Example 354 : 2-Amino-2-[2-(4-heptyloxyphenyl)-1-hydroxyethyl]-1,3-propanediol

Example 355 : 2-Amino-2-[1-hydroxy-2-(4-undecyloxyphenyl)ethyl]-1,3-propanediol

Example 356 : 2-Amino-2-[2-(4-(8-fluorooctyl)phenyl)-1-hydroxyethyl]-1,3-propanediol

Example 357 : 2-Amino-2-[2-(4-(12-fluorododecyl)phenyl)-1-hydroxyethyl]-1,3-propanediol

Example 358 : 2-Amino-2-[2-(4-(7-fluoroheptyloxy)phenyl)-1-hydroxyethyl]-1,3-propanediol

Example 359 : 2-Amino-2-[1-hydroxy-2-(4-(11-fluoroundecyloxy)phenyl)ethyl]-1,3-propanediol

Example 360 : 2-Amino-2-[2-(4-octylphenyl)ethenyl]-1,3-propanediol

Example 361 : 2-Amino-2-[2-(4-decylphenyl)ethenyl]-1,3-propanediol

Example 362 : 2-Amino-2-[2-(4-dodecylphenyl)ethenyl]-1,3-propanediol

Example 363 : 2-Amino-2-[2-(4-tetradecylphenyl)ethenyl]-1,3-propanediol

Example 364 : 2-Amino-2-(4-octylphenoxymethyl)-1,3-propanediol

Example 365 : 2-Amino-2-(4-decylphenoxymethyl)-1,3-propanediol

Example 366 : 2-Amino-2-(4-dodecylphenoxymethyl)-1,3-propanediol

Example 367 : 2-Amino-2-(4-tetradecylphenoxymethyl)-1,3-propanediol

Example 368 : 2-Amino-2-(1-hydroxy-2-phenylethyl)-1,3-propanediol hydrochloride

melting point = 188-190 °C
^{1}H-NMR (DMSO-d_6) δ(ppm): 2.57 (1H, dd, J = 10.7, 14.2Hz), 2.88 (1H, d, J = 14.2Hz), 3.63 (4H, m)-,3.85 (1H, d, J = 10.7Hz), 5.16 (1H, br.s), 5.28 (2H, br.s), 7.25 (5H, m), 7.77 (3H, br.s)
IRν $(KBr)_{max}$: 3156, 2814, 1626, 1550, 1080, 1056, 743, 702 cm^{-1}

Example 369 : 2-Acetamido-1,3-diacetoxy-2-(1-acetoxy-2-phenylethyl)propane, transparent oil

^{1}H-NMR ($CDCl_3$) δ(ppm): 1.89 (3H,s), 1.94 (3H, s), 2.08 (3H, s), 2.13 (3H, s), 2.83 (1H, dd,J = 10.3, 14.2Hz), 3.05 (1H, dd, J = 3.4, 14.2Hz), 4.46 (1H, d, J = 11.7Hz), 4.48 (1H, d, J = 11.7Hz), 4.55 (1H, d, J = 11.7Hz), 4.71 (1H, d, J = 11.7Hz), 5.66 (1H, dd, J = 3, 4, 10.3Hz), 5.86 (1H, s, -NH), 7.22 (5H, m)

Example 370 : (Z)-2-Amino-2-styryl-1,3-propanediol

^{1}H-NMR ($CDCl_3$) δ(ppm): 2,62 (4H, br.s), 3.47 (2H, d, J = 11Hz), 3.55 (2H, d, J = 11Hz), 5.55 (1H, d, J = 12.7Hz), 6.74 (1H, d, J = 12.7Hz), 7.27 (5H, m)

Example 371 : (E)-2-Amino-2-styryl-1,3-propanediol

^{1}H-NMR (CD_3OD) δ(ppm): 3.51 (2H, d, J = 11Hz), 3.63 (2H, d, J = 11Hz), 6.10 (1H, d, J = 16.4Hz), 6.55 (1H, d, J = 16.4Hz), 7.23 (5H, m)

Example 372 : 2-Acetamido-2-[2-(4-decylphenyl)ethyl]-1,3-propanediol diacetate

melting point = 101-104 °C
^{1}H-NMR ($CDCl_3$) δ(ppm): 0.88 (3H, t, J = 6Hz), 1.26-1.29 (16H, m), 1.95 (3H, s), 2.09 (6H, s), 2.17-2.21 (2H, m), 2.54-2.60 (4H, m), 4.35 (4H, s), 5.63 (1H, s), 7.09 (4H, s)
IRν : 3310, 2919, 1735, 1654, 1231, 1058 cm^{-1}

Example 373 : 2-Amino-2-[2-(4-decylphenyl)ethyl]-1,3-propanediol hydrochloride

melting point = 111-115 °C
^{1}H-NMR ($CDCl_3$) δ (ppm):
0.88 (3H, t, J = 6Hz), 1.26-1.29 (16H, s), 1.92-1.96 (2H, m), 2.56 (2H, t, J = 8Hz), 2.61-2.65 (2H, m), 3.71 (4H, q, J = 12Hz), 7.11 (4H, s)
IRν : 3373, 2923, 1603, 1518, 1070 cm^{-1}

Example 374 : 2-Acetamido-2-[2-(4-(4-methylpentyloxy)phenyl)ethyl]-1,3-propanediol diacetate

melting point = 83-87 °C
^{1}H-NMR ($CDCl_3$) δ (ppm):
0.91 (6H, d, J = 6Hz), 1.57 (4H, s), 1.96 (3H, s), 2.09 (6H, s), 2.15-2.19 (2H, m), 2.51-2.58 (2H, m), 3.91 (2H, t, J = 6Hz), 4.34 (4H, s),6.81 (2H, d, J = 4Hz), 7.08 (2H, d, J = 4Hz)
IRν : 3310, 2954, 1735, 1649 cm^{-1}

elemental analysis	calculated found	C 65.54, C 65.60,	H 8.37, H 8.40,	N 3.32 N 3.43

Example 375 : 2-Amino-2-(2-(4-(4-methylpentyloxy)phenyl)ethyl]-1,3-propanediol 1/10 hydrate

melting point = 125-128 °C
^{1}H-NMR ($CDCl_3$) δ(ppm):
0.83 (6H, d, J = 6Hz), 1.25 (2H, t, J = 6Hz), 1.54-1.58 (3H, m), 1.66-1.72 (2H, m), 2.47-2.51 (2H, m), 3.39-3.50 (4H, m), 3.81-3.85 (2H, m), 6.73 (2H, d, J = 12Hz), 7.02 (2H, d, J = 12Hz)
IRν : 3324, 2951, 1513, 1247, 1026 cm^{-1}

Example 376 : 2-Acetamido-2-(2-pyridylmethyl)-1,3-propanediol

^{1}H-NMR (400MHz, $CDCl_3$) δ (ppm):
1.66 (2H, br.s, OH), 1.94 (3H, s, CH_3), 3.26 (2H, s, CH_2), 3.56 (4H,dd, J = 72, 12Hz, CH_2 × 2), 6.97 (1H, br.s, NH), 7.23 (1H, dd, J = 8.0, 4.0Hz, ArH), 7.33 (1H, d, J = 8.0Hz, ArH), 7.69 (1H, dt, J = 8.0, 4.0Hz,ArH), 8.49 (1H, d, J = 4.0Hz, ArH)

Example 377 : 2-Acetamido-2-(2-pyridylmethyl)-1,3-diacetoxypropane

^{1}H-NMR (400MHz, $CDCl_3$) δ (ppm):
1.96 (3H, s, CH_3), 2.05 (6H, s, CH_3 × 2), 3.13 (2H, s, CH_2), 4.47 (4H, dd, J = 40, 12Hz, CH_2 × 2),
7.15 (1H, d, J = 8.0Hz, ArH), 7.21 (1H, dd, J = 8.0, 4.0Hz, ArH), 7.48 (1H, s, NH), 7.65 (1H, dt, J = 8.0, 4.0Hz, ArH), 8.55 (1H, d, J = 4.0Hz, ArH)
IRν (KBr)$_{max}$: 3320(NH), 1748 (CO), 1654, 1533, 1248 cm^{-1}
MS: 308 ($M^+ + 1$)
melting point = 109-110 °C

Example 378 : 2-Amino-2-(2-pyridylmethyl)-1,3-propanediol 3/4 hydrate 2 hydrochloride

^{1}H-NMR (400MHz, CD_3OD) δ (ppm):
3.53 (2H, s, $ArCH_2$), 3.65 (4H, ddd, J = 24, 12, 4.0Hz, CH_2 × 2), 4.88 (6H, br.s, OH × 2, N^+H_3, N^+), 8.02 (1H, t, J = 8.0Hz, ArH), 8.09 (1H, d, J = 8.0Hz, ArH), 8.57-8.61 (1H, m, ArH), 8.81 (1H, d, J = 4.0Hz, ArH)

IRν (KBr)$_{max}$: 3385, 3070, 3059, 2945, 2897, 1621, 1066 cm^{-1}
MS: 183 (M^+)
melting point = 165-170 °C

Example 379 : 2-Acetamido-2-[2-(5-butylpyridyl)methyl]-1,3-propanediol

^{1}H-NMR (400MHz, $CDCl_3$) δ (ppm):
0.94 (3H, t, d = 8.0Hz, CH_3), 1.26 (2H, t, J = 8.0Hz, CH_2), 1.36 (2H, m,CH_2), 1.59 (2H, br.s, OH × 2), 1.93 (3H, s, CH_3), 2.58-2.62 (2H, m,CH_2), 3.21 (2H, s, CH_2), 3.55 (4H, dd, J = 72, 12Hz, CH_2 × 2), 6.97 (1H, br.s, NH), 7.22 (1H, d, J = 8.0Hz, ArH), 8.45-8.50 (1H, m, ArH), 8.31 (1H, br.s, ArH)
IRν (neat)$_{max}$: 3378(OH), 2958, 2933, 2862, 1738(CO), 1658 cm^{-1} oil

Example 380 : 2-Acetamido-2-[2-(5-butylpyridyl)methyl]-1,3-diacetoxypropane

^{1}H-NMR (400MHz, $CDCl_3$) δ (ppm):
0.94 (3H, t, J = 8.0Hz, CH_3), 1.33-1.42 (2H, m, CH_2), 1.56-1.64 (2H, m, CH_2), 1.96 (3H, s, CH_3), 2.05 (6H, s, CH_3 × 2), 2.60 (2H, t, J = 8.0Hz, CH_2), 3.08 (2H, s, CH_2), 4.46 (4H, dd, J = 40, 12Hz, CH_2 × 2), 7.05 (1H, d, J = 8.0Hz, ArH), 7.44-7.46 (1H, m, ArH), 7.56 (1H, s, NH), 8.35-8.37 (1H, m, ArH)
IRν (KBr)$_{max}$: 3371, 3290, 2959, 2934, 1745(CO), 1681, 1240 cm^{-1} oil

Example 381 : 2-Amino-2-[2-(5-butylpyridyl)methyl]-1,3-propanediol

^{1}H-NMR (400MHz, $CDCl_3$) δ (ppm):
0.94 (3H, t, J = 8.0Hz, CH_3), 1.36 (2H, dt, J = 16, 8.0Hz, CH_2), 1.59 (2H, dt, J = 16, 8.0Hz, CH_2), 2.60 (2H, t, J = 8.0Hz, CH_2), 2.92 (2H, s, CH_2), 1.20-3.00 (4H, m, OH × 2, NH_2), 3.39 (4H, dd, J = 36, 12Hz, CH_2 × 2), 7.13 (1H, d, J = 8.0Hz, ArH), 7.48 (1H, dd, J = 8.0, 2.0Hz, ArH), 8.33 (1H, d, J = 2.0Hz, ArH)
IRν (KBr)$_{max}$: 3339, 3269, 2923, 2857, 1595, 1033 cm^{-1}
melting point = 63-65 °C

Example 382 : 2-Acetamido-1,3-diacetoxy-2-[2-(1-octylpiperidin-4-yl)ethyl]propane

melting point = 93-95 °C
^{1}H-NMR ($CDCl_3$) δ (ppm):
0.85 (3H, t, J = 6.4Hz), 1.19-1.36 (15H, m), 1.50 (2H, br.s), 1.64 (2H, d, J = 11.8Hz), 1.85-1.97 (3H, m), 1.93 (3H, s), 2.05 (6H, s), 2.33 (2H, br.s), 2.97 (2H, br.s), 4.25 (4H, s), 5.61 (1H, s)
IRν (KBr)$_{max}$: 3302, 1739, 1654, 1560 cm^{-1}

Example 383 : 2-Acetamido-2-(2-propenyl)-1,3-propanediol pale yellow liquid

Rf value : 0.55 (chloroform:methanol = 5:1)
^{1}H-NMR ($CDCl_3$-CD_3OD) δ (ppm):
1.95 (3H, s), 2.33 (2H, d, J = 7.3Hz), 3.49 (2H, d, J = 11.7Hz), 3.64 (2H, d, J = 11.7Hz), 5.07-5.10 (2H, m), 5.66-5.90 (1H, m)
IRν (neat): 3310, 1641 cm^{-1}
MS(EI): 174 (M + 1)

Example 384 : 2-Amino-2-(2-propenyl)-1,3-propanediol 8/5 hydrate hydrochloride

brown liquid
^{1}H-NMR ($CDCl_3$) δ (ppm):
2.33 (2H, d, J = 10.7Hz), 3.56 (4H, dd, J = 3.0Hz, J = 19.0Hz), 3.39 (11H,

br.s), 5.14-5.22 (2H, m), 5.62-5.23 (1H, m)
IRν (neat): 3445, 1614, 1516 cm^{-1}
MS(EI): 132 (M + 1)

elemental analysis	calculated found	C 36.68, C 36.27,	H 8.82, H 8.47,	N 7.13 N 7.26

Example 385 : 2-Amino-2-phenylmethyloxymethyl-1,3-propanediol1/10 hydrate hydrochloride

melting point = 113-114 °C

Example 386 : 2-Acetamido-1,3-diacetoxy-2-phenylmethyloxymethyl propane

IRν (neat): 3307, 2934, 1743, 1662, 1549 cm^{-1}

Example 387 : 2-Amino-2-[2-(4-nonylphenyl)ethyl]-1,3-propanediol 1/3 hydrate hydrochloride

melting point = 95-97 °C

elemental analysis	calculated found	C 66.00, C 66.19,	H 10.15, H 10.24,	N 3.85 N 3.86

Example 387 : 2-Acetamido-1,3-diacetoxy-2-[2-(4-nonylphenyl)ethyl]propane

melting point = 95-98 °C

Example 388 : 2-Acetamido-2-[2-(4-undecylphenyl)ethyl]-1,3-propanediol

melting point = 90-91 °C

Example 389 : 2-Amino-2-[2-(4-undecylphenyl)ethyl]-1,3-propanediol

melting point = 105-107 °C
^{1}H-NMR ($CDCl_3$) δ(ppm):
0.88 (3H, t, J = 6.8Hz), 1.20-1.80 (24H, m), 2.56 (2H, t, J = 7.8Hz), 2.61 (2H, m), 3.51 (2H, d, J = 10.8Hz), 3.61 (2H, d, J = 10.8Hz), 7.10 (4H, s)

Example 390 : 2-Acetamido-4-(4-heptylphenyl)-2-hydroxymethyl-1,4-butanediol

melting point = 117-118 °C

Example 391 : 2-Acetamido-4-(4-octylphenyl)-2-hydroxymethyl-1,4-butanediol

melting point = 118-119 °C

Example 392 : 2-Acetamido-2-[2-(4-heptylphenyl)ethyl]-1,3-propanediol

melting point = 89-90 °C

Example 393 : 2-Acetamido-2-1,3-propanediyl-[2-(4-heptylphenyl)ethyl]ylidene diacetate

melting point = 108-109 °C

Example 394 : 2-Amino-2-[2-(4-heptylphenyl)ethyl]-1,3-propanediol hydrochloride

melting point = 134-135 °C
^{1}H-NMR (DMSO only) δ (ppm):
0.83 (3H, t, J = 6Hz), 1.17-2.33 (8H, m), 1.45-1.58 (2H, m), 1.69-1.79 (2H, m), 2.48-2.62 (4H, m), 3.34 (2H, br.s), 3.48 (4H, s), 7.08 (4H, s), 7.47 (3H, br.s)
IRν (KBr)$_{max}$: 3369, 2926, 1515, 1467, 1059 cm^{-1}

Example 395 : 2-Acetamido-1,3-propanediyl-2-[2-(4-tetradecylphenyl)ethyl]ylidene diacetate

melting point = 125-126 °C

Example 396 : 2-Amino-2-[2-(4-tetradecylphenyl)ethyl]-1,3-propanediol hydrochloride

melting point = 123-124 °C
^{1}H-NMR (DMSO-$CDCl_3$) δ(ppm):
0.80 (3H, t, J = 6Hz), 1.02-1.24 (22H, m), 1.45-1.53 (2H, m), 1.88 (2H, m, J = 4Hz), 2.46 (2H, t, J = 6Hz), 2.56-2.62 (2H, m), 3.56 (2H, dd, J = 12Hz, 31Hz), 3.57 (2H, dd, J = 12Hz, 31Hz), 4.90 (2H, br.s), 7.01 (4H, dd, J = 7Hz, 12Hz), 7.99 (3H, br.s)
IRν (KBr)$_{max}$: 3374, 3268, 2922, 1516, 1469, 1069 cm^{-1}

Example 397 N-Methylamino-2-[2-(4-octylphenyl)ethyl]-1,3-propanediol

^{1}H-NMR ($CDCl_3$) δ(ppm):
0.80 (3H, t, J = 7Hz), 1.09-1.39 (10H, m), 1.45-1.56 (2H, m), 1.56-1.76 (2H, m), 2.41 (3H, s), 2.44-2.61 (4H, m), 3.32 (3H, br.s), 3.47-3.81 (4H, m), 7.01 (4H, s)
IRν (neat): 3386, 2927, 1467, 1058, 909 cm^{-1}

Example 398 : 2-Amino-4-(4-heptylphenyl)-2-hydroxymethyl-1,4-butanediol hydrochloride

melting point = 105-108 °C
^{1}H-NMR (DMSO) δ(ppm):
0.86 (3H, t, J = 7Hz), 1.17-1.36 (8H, m), 1.46-1.63 (2H, m), 1.76 (2H, dd, J = 7Hz, 18Hz), 2.54 (2H, t, J = 7Hz), 3.34 (3H, br.s), 3.58 (4H, dd, J = 11Hz, 35Hz), 4.83-4.92 (1H, m), 6.99 (3H, br. s), 7.18 (4H, dd, J = 7Hz, 37Hz)
IRν (KBr)$_{max}$: 3388, 2928, 1610, 1511, 1063 cm^{-1}

Example 399 : 2-Amino-4-(4-ocfylphenyl)-2-hydroxymethyl-1,4-butanediol 1/4 hydrate

^{1}H-NMR ($CDCl_3$) δ (ppm):
0.86 (3H, t, J = 7Hz), 1.22-1.38 (10H, m), 1.54-1.68 (3H, m), 1.68-1.79 (1H, m), 2.59 (2H, t, J = 7Hz), 3.40 (3H, br.s), 3.50 (4H, dd, J = 8Hz, 38Hz), 3.63 (2H, br.s), 4.91 (1H, m), 7.20 (4H, dd, J = 6Hz, 30Hz)
IRν (neat): 3340, 3286, 2925, 1465, 1027 cm^{-1}

The action and effect of the present invention are explained in detail by illustrating experimental examples in the following.

For determining the immunosuppressive activity, various immune reactions using lymphocytes of mouse, rat or human are usable. It may be determined with high sensitivity, for example, by an allogenic mixed lymphocyte reaction (allogenic MLR) of mouse, rat or human.

The allogenic MLR is a blastogenesis of lymphocytes induced by a mixed culture of lymphocytes derived from two kinds of cells which are allogenic but have different major histocompatibility antigens, such as spleen cells, lymph node cells and peripheral blood lymphocytes. The allogenic MLR is a phenomenon induced by and reflects the difference in major histocompatibility antigens of the donors of the lymphocytes, and a blastogenesis phenomenon of the lymphocytes is not developed by a mixed culture of the lymphocytes from monozygotic twins. Accordingly, allogenic MLR is widely used for the donor-recipient

selection in organ transplantations.

When allogenic MLR is desired, one way-MLR, wherein the lymphocytes of one of them are used as stimulator cells upon X-ray irradiation or treatment with mitomycin C to inhibit proliferation and the blastogenesis of the other lymphocytes (responder cells) is determined, may be used.

Further, the immunosuppressive activity may be determined as an activity to inhibit induction of cytotoxic T cells having the major histocompatibility antigen restrictive property during allogenic MLR.

Also, the immunosuppressive activity may be determined, besides allogenic MLR, as an activity to inhibit the blastogenesis of the lymphocytes induced by the stimulation of of various mitogens such as concanavalin A, phytohemaggulutinin and pokeweed mitogen or as an activity to inhibit the proliferation of the lymphocytes induced by a cytokine (e.g. interleukin 1, 2, 3, 4, 5 or 6) having an activity to reinforce the proliferation or promote the differentiation of the lymphocytes such as T cells or B cells, or manifestation of such function. In addition, it is possible to evaluate the immunosuppressive activity according to the inhibition of the production of these cytokines from T cells or macrophages.

Alternatively, the activity may be evaluated as an activity to inhibit induction of allogenic cells-specific cytotoxic T cells induced in spleen cells of mouse previously immunized with, for example, allogenic cells by intraperitoneally, orally, intravenously, intradermally, subcutaneously or intramuscularly administering a compound to mice; as an activity to inhibit the production of an allogenic cells-specific antibody produced in the blood serum of mouse immunized with allogenic cells or the like; or as an activity to inhibit rejection on organ transplantation between allogenic mice, rats, dogs and so on, graft-versus-host reaction, or delayed type allergy and adjuvant arthritis.

Moreover, the immunosuppressive activity may be evaluated as an activity to inhibit, for example, production of an anti-DNA antiboty, production of a rheumatoid factor, nephritis, abnormal proliferation of lymphocytes or urinary protein; or a macrobiotic effect by the administration of the compound to MRL/lpr mouse, NZB/WF_1 mouse, BXSB mouse, NOD mouse and the like which are model animals with autoimmune diseases.

Experimental Example 1 (inhibition of allogenic mixed lymphocyte reaction in mouse)

The mouse allogenic mixed lymphocyte reaction (hereinafter referred to as mouse allogenic MLR) is carried out by a mixed culture of spleen cells of BALB/c mouse as responder cells and spleen cells of C57BL/6 mouse treated with mitomycin C as stimulator cells at the same ratio.

The reaction cells are prepared as follows. A spleen is removed from a 5-6 weeks old BALB/c mouse and a single cell suspension of spleen cells is obtained by the use of an RPMI1640 medium (containing kanamycin sulfate 60 μg/ml, penicillin G potassium 100 units/ml, N-2-hydroxyethylpiperazine-N'-2-ethanesulfonate 10 mM, 0.1% sodium hydrogencarbonate and L-glutamine 2 mM) supplemented with 5% heat-inactivated fetal calf serum (hereinafter referred to as FCS). After hemolysis treatment, the suspension is adjusted to a concentration of 10^7 cells/ml by the use of an RPMI1640 medium containing 10^{-4} M 2-mercaptoethanol and 10% FCS and used as a reaction cell suspension.

The stimulator cells are prepared as follows. A spleen is removed from a 5-6 weeks old C57BL/6 mouse and a single cell suspension of spleen cell is obtained by the use of an RPMI1640 medium. After hemolysis treatment, the suspension is treated with 40 μg/ml mitomycin C at 37 °C for 60 minutes. After washing three times, the suspension is adjusted to a concentration of 10^7 cells/ml by the use of an RPMI1640 medium containing 10^{-4} M 2-mercaptoethanol and 10% FCS and used as a stimulator cell suspension.

The responder cell suspension (50 μl) prepared by the method described above, the stimulator cell suspension (50 μl) prepared by the method described above and a test sample (100 μl) prepared by the use of an RPMI1640 medium containing 10% FCS are placed in a 96 well flat-bottomed micro testplate and cultured at 37 °C under 5% CO_2-95% air for 4 days.

The blastogenesis reaction of lymphocytes in mouse allogenic MLR is determined by a method using ^{3}H-thymidine uptake as an index. Namely, after the culture, ^{3}H-thymidine 18.5 KBq/well is added and the cells are cultured for 4 hours. The cells are collected by a cell harvester and the radioactivity incorporated into the cells is determined by a liquid scintillation counter and used as an index for the lymphocyte blastogenesis in mouse allogenic MLR. The inhibition of mouse allogenic MLR is calculated by the formula below and evaluated accordingly.

Of the compounds of the present invention, the preferred show an IC_{50} value (a concentration to inhibit by 50%) of from about 1 nM to about 50 nM in a mouse allogenic mixed lymphocyte reaction.

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$$\text{Inhibition (\%)} = \left\{ 1 - \frac{\left(\begin{array}{c}\text{cpm of MLR}\\ \text{with test sample}\end{array}\right) - \left(\begin{array}{c}\text{cpm of responder}\\ \text{cells alone}\end{array}\right)}{\left(\begin{array}{c}\text{cpm of MLR with-}\\ \text{out test sample}\end{array}\right) - \left(\begin{array}{c}\text{cpm of responder}\\ \text{cells alone}\end{array}\right)} \right\} \times 100$$

Experimental Example 2 [Inhibition of proliferation of interleukin 2 (IL-2)-dependent mouse T cell line CTLL-2 induced by IL-2]

An IL-2-dependent mouse T cell line CTLL-2 is prepared to a concentration of 2×10^5 cell/ml in an RPMI1640 medium containing 10% FCS. A cell suspension thereof (50 μl), recombinant human IL-2 (rh-IL-2) 40 U/ml (50 μl) and a test sample (100 μl) prepared by the use of an RPMI1640 medium containing 10% FCS are placed in a 96 well flat-bottomed micro testplate and cultured at 37 °C under 5% CO_2-95% air for 68 hours. After the culture, 100 μl of the supernatant of each well is removed and a 5 mg/ml MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] solution is added to each well by 20 μl and the cells are incubated at 37 °C for 4 hours. Then, 0.01N hydrochloric acid solution (100 μl) containing 10% sodium dodecyl sulfate is added thereto and the cells are incubated at 37 °C overnight. The purple formazan crystals produced are dissolved and the absorbance at 570 nm is measured using a microplate absorbance photometer and used as an index of the proliferation of the IL-2-dependent CTLL-2 cells. The inhibition (%) of the IL-2 dependent proliferation is calculated by the following formula.

Of the compounds of the present invention, the preferred show an IC_{50} value (a concentration to inhibit by 50%) of from about 1 nM to about 50 nM in the IL-2-dependent proliferation of mouse T cell line CTLL-2.

$$\text{Inhibition (\%)} = \left\{ 1 - \frac{\left(\begin{array}{c}\text{absorbance when}\\ \text{test sample and}\\ \text{rh-IL-2 are added}\end{array}\right) - \left(\begin{array}{c}\text{absorbance when}\\ \text{rh-IL-2 is}\\ \text{not added}\end{array}\right)}{\left(\begin{array}{c}\text{absorbance when}\\ \text{rh-IL-2 alone}\\ \text{is added}\end{array}\right) - \left(\begin{array}{c}\text{absorbance when}\\ \text{rh-IL-2 is}\\ \text{not added}\end{array}\right)} \right\} \times 100$$

Experimental Example 3 (take-prolonging effect on allogenic skin graft in rat)

A full-thickness graft (1.5 × 1.5 cm) of a 4 weeks-old male WKAH rat or LEW rat is grafted to a graft floor on the back of a 4 weeks-old male F344 rat by suture. The graft is covered with a sterile gauze and bound. The bandage is removed 5 days after the grafting and the skin graft is observed daily until it is rejected. The skin graft is considered to be rejected when 90% or more of the epithelium of the skin graft showed necrosis and turned brown. The number of days from the grafting to rejection is taken as a graft taking days. A test compound is intraperitoneally, intravenously or orally administered once a day and 10 times from the grafting day to day 9.

When a test compound is not administered, an average taking days for grafting the skin of a WKAH rat to an F344 rat was 6.6±0.5 and that for grafting the skin of an LEW rat to an F344 rat was 8.2±0.4.

Of the compounds of the present invention, a preferred compound showed, when administered at 0.1-10 mg/kg, an average taking days of not less than 10 for grafting the skin of a WKAH rat to an F344 rat and not less than 20 for grafting the skin of an LEW rat to an F344 rat, thus showing a take-prolonging effect statistically significant as compared with the group without administration of the test compound.

Experimental Example 4 (Inhibition of adjuvant arthritis in rat)

Dead tuberclosis bacterium (R35H5v-1 strain, 0.5 mg) was suspended as an adjuvant in 1.0 ml of liquid paraffin and innoculated to the tail head of a 10 weeks-old male LEW rat to cause adjuvant arthritis. After the innoculation of the adjuvant, the rats are observed daily to determine the onset of arthritis, ratio of the onset cases and body weight changes. At day 21, swelling of the hind limbs and the weight of the organs are measured. A test compound is intravenously or orally administered from the adjuvant innoculation day once a day and 22 times up to day 21.

When the test compound was not administered, arthritis was found in all 7 rats innoculated with adjuvant at day 9.6±0.5, along with swelling and destruction of the bone of the hind limbs. Along with the onset of the adjuvant arthritis, decrease in body weight, increase in the weights of kidney and adrenal and decrease in the thymus weight were found.

Of the compounds of the present invention, a preferred compound delayed the onset of and decreased the ratio of the onset cases of the adjuvant arthritis to a statistically significant degree and significantly suppressed swelling and bone destruction of the hind limbs by the administration of 0.1-10 mg/kg thereof. In addition, decrease in body weight, increase in the weights of kidney and adrenal and decrease in the thymus weight, which accompany onset of adjuvant arthritis, were significantly reduced.

As is evident from the various experiments inclusive of phamacological experiments as noted above, the compounds of the present invention and salts thereof have superior immunosuppressive action and are useful as pharmaceuticals.

Formulation Examples

(1) Soft capsules (per capsule)	
Compound of the invention	30 mg
Polyethylene glycol 300	300 mg
Polysolbate 80	20 mg
Total	350 mg

Production method

Polyethylene glycol 300 and Polysorbate 80 are added to a compound of the present invention and the mixture is packed in a soft capsule.

(2) Injections (per 10 ml in one ampoule)	
Compound of the invention	0.3%
Polyethylene glycol 300	20 %
Ethanol	60 %
Injectable distilled water	amount to make the total 10 ml

Production method

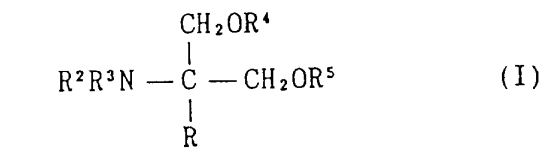
Ethanol and polyethylene glycol 300 are added to a compound of the present invention and injectable distilled water is added to reach the total amount.

Injections containing 30 ml of the compound of the present invention in one ampoule (10 ml) are thus obtained.

While the present invention has been described in detail by the specification including examples, the present invention is subject to various modifications and changes insofar as they are within the spirit and scope of the present invention.

Claims

1. A 2-amino-1,3-propanediol compound of the formula



(I)

wherein

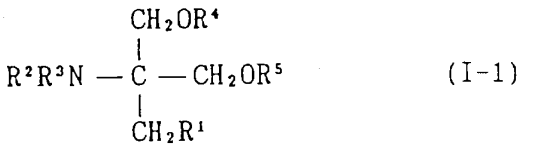
R is an optionally substituted straight- or branched carbons chain which may have, in the chain, a bond, a hetero atom or a group selected from the group consisting of a double bond, a triple bond, oxygen, sulfur, sulfinyl, sulfonyl, -N-(R^6)- where R^6 is hydrogen, alkyl, aralkyl, acyl or alkoxycarbonyl, carbonyl, optionally substituted arylene, optionally substituted cycloalkylene, optionally substituted heteroarylene and an alicycle thereof, and which may be substituted, at the chain end thereof, by a double bond, a triple bond, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted heteroaryl or an alicycle thereof; an optionally substituted aryl, an optionally substituted cycloalkyl, an optionally substituted heteroaryl or an alicycle thereof; and

R^2, R^3, R^4 and R^5 are the same or different and each is a hydrogen, an alkyl, an aralkyl, an acyl or an alkoxycarbonyl, or R^4 and R^5 may be bonded to form an alkylene chain which may be substituted by alkyl, aryl or aralkyl;

wherein the optionally substituted straight- or branched carbon chain may have a substituent selected from the group consisting of alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, alkylenedioxy, acyl, alkylamino, alkylthio, acylamino, alkoxycarbonyl, alkoxycarbonylamino, acyloxy, alkylcarbamoyl, haloalkyl, haloalkoxy, nitro, halogen, amino, hydroxyimino, hydroxy, carboxy, optionally substituted aryl, optionally substituted aryloxy, optionally substituted cycloalkyl, optionally substituted heteroaryl and an alicycle thereof; the aforementioned optionally substituted arylene, optionally substituted cycloalkylene, optionally substituted heteroarylene and an alicycle thereof may have a substituent selected from the group consisting of alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, alkylenedioxy, acyl, alkylamino, alkylthio, acylamino, alkoxycarbonyl, alkoxycarbonylamino, acyloxy, alkylcarbamoyl, haloalkyl, haloalkoxy, nitro, halogen, amino, hydroxy and carboxy; and the optionally substituted aryl, optionally substituted aryloxy, optionally substituted cycloalkyl, optionally substituted heteroaryl and an alicycle thereof may have a substituent selected from the group consisting of alkyl, alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, alkylenedioxy, acyl, alkylamino, alkylthio, acylamino, alkoxycarbonyl, alkoxycarbonylamino, acyloxy, alkylcarbamoyl, haloalkyl, haloalkoxy, nitro, halogen, amino, hydroxy and carboxy;

provided that when R is C1-C5 alkyl, the alkyl should be substituted and when R is furylmethyl, phenylmethyl or phenylmethyl substituted by lower alkyl, lower alkoxy, chloro, hydroxy or amino, one of R^2 and R^3 is not methyl or ethyl; or a pharmaceutically acceptable salt thereof.

2. A 2-amino-1,3-propanediol compound of Claim 1, having the formula



(I-1)

wherein

R^1 is an optionally substituted straight- or branched carbon chain which may

have, in the chain, a bond, a hetero atom or a group selected from the group consisting of a double bond, a triple bond, oxygen, sulfur, sulfinyl, sulfonyl, -N-(R^6)- where R^6 is hydrogen, alkyl, aralkyl, acyl or alkoxycarbonyl, carbonyl, optionally substituted arylene, optionally substituted cycloalkylene, optionally substituted heteroarylene and an alicycle thereof, and which may be substituted, at the chain end (ω-position) thereof, by a double bond, a triple bond, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted heteroaryl or an alicycle thereof; an optionally substituted aryl, an optionally substituted cycloalkyl, an optionally substituted heteroaryl or an alicycle thereof; and

R^2, R^3, R^4 and R^5

are the same or different and each is a hydrogen, an alkyl, an aralkyl, an acyl or an alkoxycarbonyl, or R^4 and R^5 may be bonded to form an alkylene chain which may be substituted by alkyl, aryl or aralkyl;

wherein the optionally substituted straight- or branched carbon chain may have a substituent selected from the group consisting of alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, alkylenedioxy, acyl, alkylamino, alkylthio, acylamino, alkoxycarbonyl, alkoxycarbonylamino, acyloxy, alkylcarbamoyl, haloalkyl, haloalkoxy, nitro, halogen, amino, hydroxyimino, hydroxy, carboxy, optionally substituted aryl, optionally substituted aryloxy, optionally substituted cycloalkyl, optionally substituted heteroaryl and an alicycle thereof; and the aforementioned optionally substituted arylene, optionally substituted cycloalkylene, optionally substituted heteroarylene, an alicycle thereof, optionally substituted aryl, optionally substituted aryloxy, optionally substituted cycloalkyl, optionally substituted heteroaryl and an alicycle thereof may have a substituent selected from the group consisting of alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, alkylenedioxy, acyl, alkylamino, alkylthio, acylamino, alkoxycarbonyl, alkoxycarbonylamino, acyloxy, alkylcarbamoyl, haloalkyl, haloalkoxy, nitro, halogen, amino, hydroxy and carboxy;

provided that when R^1 is C1-C4 alkyl, the alkyl should be substituted and when R^1 is furyl, phenyl or phenyl substituted by lower alkyl, lower alkoxy, chloro, hydroxy or amino, one of R^2 and R^3 is not methyl or ethyl; or a pharmaceutically acceptable salt thereof.

3. A 2-amino-1,3-propanediol compound of Claim 1 or 2, having the formula

$$R^2aR^3aN-\underset{\displaystyle CH_2R^1a}{\overset{\displaystyle CH_2OR^4a}{\overset{|}{\underset{|}{C}}}}-CH_2OR^5a \qquad (I\text{-}2)$$

wherein

R^1a is an optionally substituted straight- or branched carbon chain which may have, in the chain, a bond, a hetero atom or a group selected from the group consisting of a double bond, a triple bond, oxygen, sulfur, sulfinyl, sulfonyl, -N(R^6)- where R^6 is hydrogen, alkyl, aralkyl, acyl or alkoxycarbonyl, carbonyl, optionally substituted phenylene and optionally substituted cycloalkylene; an optionally substituted phenyl or an optionally substituted cycloalkyl; and

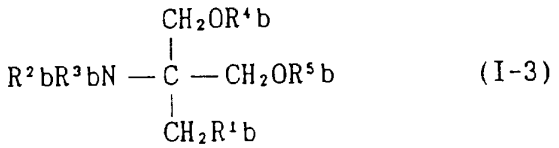
R^2a, R^3a, R^4a and R^5a

are the same or different and each is a hydrogen, an alkyl, an acyl or an alkoxycarbonyl;

wherein the optionally substituted phenyl and optionally substituted cycloalkyl may have a substituent selected from the group consisting of optionally substituted straight- or branched carbon chain which may have, in the chain, a bond, a hetero atom or a group selected from the group consisting of a double bond, a triple bond, oxygen, sulfur, sulfinyl, sulfonyl, -N(R^6)- where R^6 is hydrogen, alkyl, aralkyl, acyl or alkoxycarbonyl, carbonyl, optionally substituted phenylene and optionally substituted cycloalkylene; alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, alkylenedioxy, acyl, alkylamino, alkylthio, acylamino, alkoxycarbonyl, alkoxycarbonylamino, acyloxy, alkylcarbamoyl, haloalkyl, nitro, halogen, amino, hydroxy, carboxy, optionally substituted phenyl, optionally substituted phenoxy and optionally

substituted cycloalkyl; the optionally substituted carbon chain may have a substituent selected from the group consisting of alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, alkylenedioxy, acyl, alkylamino, alkylthio, acylamino, alkoxycarbonyl, alkoxycarbonylamino, acyloxy, alkylcarbamoyl, haloalkyl, nitro, halogen, amino, hydroxy, carboxy, optionally substituted phenyl, optionally substituted phenoxy and optionally substituted cycloalkyl; and the aforementioned optionally substituted phenylene, optionally substituted cycloalkylene, optionally substituted phenyl, optionally substituted phenoxy and optionally substituted cycloalkyl may have a substituent selected from the group consisting of alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, alkylenedioxy, acyl, alkylamino, alkylthio, acylamino, alkoxycarbonyl, alkoxycarbonylamino, acyloxy, alkylcarbamoyl, haloalkyl, nitro, halogen, amino, hydroxy and carboxy;
provided that when R^1a is C1-C4 alkyl, the alkyl should be substituted and when R^1a is furyl, phenyl or phenyl substituted by lower alkyl, lower alkoxy, chloro, hydroxy or amino, one of R^2a and R^3a is not methyl or ethyl; or a pharmaceutically acceptable salt thereof.

4. A 2-amino-1,3-propanediol compound of Claim 3, having the formula



(I-3)

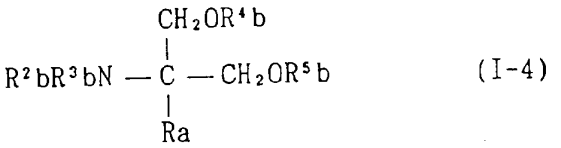
wherein

R^1b is an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted phenyl or an optionally substituted cycloalkyl, and

R^2b, R^3b, R^4b and R^5b are the same or different and each is a hydrogen, an alkyl or an acyl;

wherein the optionally substituted alkyl, optionally substituted alkenyl and optionally substituted alkynyl may have a substituent selected from the group consisting of alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, acyl, alkylamino, alkylthio, acylamino, alkoxycarbonyl, alkoxycarbonylamino, acyloxy, alkylcarbamoyl, nitro, halogen, amino, hydroxy, carboxy, optionally substituted phenyl and optionally substituted cycloalkyl; and the aforementioned optionally substituted phenyl and optionally substituted cycloalkyl may have 1 to 3 substituents selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, acyl, alkylamino, alkylthio, acylamino, alkoxycarbonyl, alkoxycarbonylamino, acyloxy, alkylcarbamoyl, haloalkyl, nitro, halogen, amino, hydroxy and carboxy; provided that when R^1b is C1-C4 alkyl, the alkyl should be substituted and when R^1b is furyl, phenyl or phenyl substituted by lower alkyl, lower alkoxy, chloro, hydroxy or amino, one of R^2b and R^3b is not methyl or ethyl; or a pharmaceutically acceptable salt thereof.

5. A 2-amino-1,3-propanediol compound of any one of Claims 1, 2, 3 and 4, having the formula



(I-4)

wherein

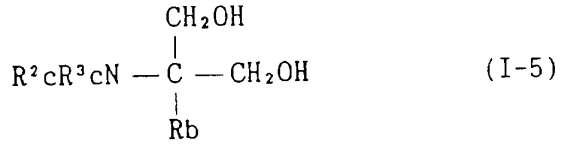
Ra is a straight- or branched chain alkyl having 12 to 22 carbon atoms, which may have, in the chain, a bond or a hetero atom selected from the group consisting of a double bond, a triple bond, oxygen, sulfur, sulfinyl, sulfonyl, -N(R^6)- where R^6 is hydrogen, alkyl, aralkyl, acyl or alkoxycarbonyl, and carbonyl, and which may have, as a substituent, alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, acyl, alkylamino, alkylthio, acylamino,

alkoxycarbonyl, alkoxycarbonylamino, acyloxy, alkylcarbamoyl, nitro, halogen, amino, hydroxyimino, hydroxy or carboxy, and

R^2b, R^3b, R^4b and R^5b

are the same or different and each is a hydrogen, an alkyl or an acyl; or a pharmaceutically acceptable salt thereof.

6. A 2-amino-1,3-propanediol compound of Claim 5, having the formula



(I-5)

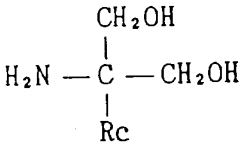
wherein

Rb is a straight- or branched chain alkyl having 13 to 20 carbon atoms, which may have, in the chain, an oxygen atom and which may have, as a substituent, nitro, halogen, amino, hydroxy or carboxy, and

R^2c and R^3c

are the same or different and each is a hydrogen or an alkyl, or a pharmaceutically acceptable salt thereof.

7. A 2-amino-1,3-propanediol compound of Claim 5 or 6, having the formula



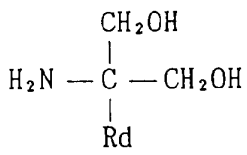
(I-6)

wherein

Rc is a straight- or branched chain alkyl having 13 to 20 carbon atoms or a straight- or branched chain alkyl having 13 to 20 carbon atoms which is substituted by halogen, or a pharmaceutically acceptable salt thereof.

8. A 2-amino-1,3-propanediol compound of any one of Claims 5, 6 and 7, which is selected from the group consisting of
2-amino-2-tridecyl-1,3-propanediol,
2-amino-2-tetradecyl-1,3-propanediol,
2-amino-2-pentadecyl-1,3-propanediol,
2-amino-2-hexadecyl-1,3-propanediol,
2-amino-2-heptadecyl-1,3-propanediol,
2-amino-2-octadecyl-1,3-propanediol,
2-amino-2-nonadecyl-1,3-propanediol,
2-amino-2-icosyl-1,3-propanediol,
2-amino-2-(12-fluorododecyl)-1,3-propanediol and
2-amino-2-(14-fluorotetradecyl)-1,3-propanediol, or a pharmaceutically acceptable salt thereof.

9. A 2-amino-1,3-propanediol compound of any one of Claims 1, 2, 3 and 4, having the formula



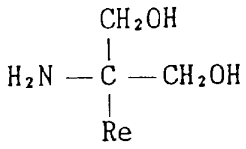
(I-7)

wherein

Rd is a phenylalkyl, a substituted phenylalkyl, a cycloalkylalkyl, a substituted cycloalkylalkyl, a heteroarylalkyl, a substituted heteroarylalkyl, a heterocyclic alkyl or a substituted heterocyclic alkyl,

wherein the alkyl moiety may have, in the carbon chain, a bond or a hetero atom selected from the group consisting of a double bond, a triple bond, oxygen, sulfur, sulfinyl, sulfonyl, -N(R^6)- where R^6 is hydrogen, alkyl, aralkyl, acyl or alkoxycarbonyl, and carbonyl, and may have, as a substituent, alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, acyl, alkylamino, alkylthio, acylamino, alkoxycarbonyl, alkoxycarbonylamino, acyloxy, alkylcarbamoyl, nitro, halogen, amino, hydroxy or carboxy; and the substituted phenylalkyl, substituted cycloalkylalkyl, substituted heteroarylalkyl and substituted heterocyclic alkyl may have a substituent selected from the group consisting of alkyl, alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, haloaralkyloxy, aralkyloxyalkyl, phenoxyalkyl, phenoxyalkoxy, alkylenedioxy, acyl, alkylamino, alkylthio, acylamino, alkoxycarbonyl, alkoxycarbonylamino, acyloxy, alkylcarbamoyl, haloalkyl, haloalkoxy, nitro, halogen, amino, hydroxy and carboxy; or a pharmaceutically acceptable salt thereof.

10. A 2-amino-1,3-propanediol compound of Claim 9, having the formula



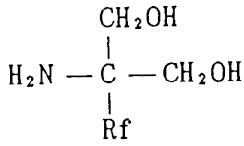
(I-8)

wherein

Re is a phenylalkyl wherein the alkyl moiety is a straight- or branched chain having 6 to 20 carbon atoms; a phenylalkyl which may be substituted by a straight- or branched chain C6-C20 alkyl optionally substituted by halogen, a straight- or branched chain C6-C20 alkoxy optionally substituted by halogen, a straight- or branched chain C6-C20 alkenyloxy, phenylalkoxy, halophenylalkoxy, phenylalkoxyalkyl, phenoxyalkoxy or phenoxyalkyl; a cycloalkylalkyl wherein the alkyl moiety is a straight- or branched chain having 6 to 20 carbon atoms; a cycloalkylalkyl substituted by a straight- or branched chain alkyl having 6 to 20 carbon atoms; a heteroarylalkyl wherein the alkyl moiety is a straight- or branched chain having 6 to 20 carbon atoms; a heteroarylalkyl substituted by a straight- or branched chain alkyl having 6 to 20 carbon atoms; a heterocyclic alkyl wherein the alkyl moiety is a straight- or branched chain having 6 to 20 carbon atoms, or a heterocyclic alkyl substituted by a straight- or branched chain alkyl having 6 to 20 carbon atoms;

wherein the alkyl moiety may have, in the carbon chain, a bond or a hetero atom selected from the group consisting of a double bond, a triple bond, oxygen, sulfur, sulfinyl, sulfonyl, -N(R^6)- where R^6 is hydrogen, alkyl, aralkyl, acyl or alkoxycarbonyl, and carbonyl, and may have, as a substituent, alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, acyl, alkylamino, alkylthio, acylamino, alkoxycarbonyl, alkoxycarbonylamino, acyloxy, alkylcarbamoyl, nitro, halogen, amino, hydroxy or carboxy; or a pharmaceutically acceptable salt thereof.

11. A 2-amino-1,3-propanediol compound of Claim 9 or 10, having the formula



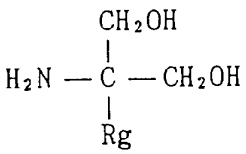
(I-9)

wherein

Rf is a phenylalkyl wherein the alkyl moiety is a straight- or branched chain having 6 to 20 carbon atoms which may have, in the carbon chain, one or two oxygen atoms; a phenylalkyl which may be substituted by a straight- or branched chain C6-C20 alkyl optionally substituted by halogen, a straight- or branched chain C6-C20 alkoxy optionally substituted by halogen, a straight- or branched chain C6-C20 alkenyloxy, phenylalkoxy, halophenylalkoxy, phenylalkoxyalkyl, phenoxyalkoxy or phenoxyalkyl; a cycloalkylalkyl wherein the alkyl moiety is a straight- or branched chain having 6 to 20 carbon atoms which may have, in the carbon chain, one or two oxygen atoms; a cycloalkylalkyl substituted by a straight- or branched chain alkyl having 6 to 20 carbon atoms; a heteroarylalkyl wherein the alkyl moiety is a straight- or branched chain having 6 to 20 carbon atoms which may have, in the carbon chain, one or two oxygen atoms; a heteroarylalkyl substituted by a straight- or branched chain alkyl having 6 to 20 carbon atoms; a heterocyclic alkyl wherein the alkyl moiety is a straight- or branched chain having 6 to 20 carbon atoms which may have, in the carbon chain, one or two oxygen atoms, or a heterocyclic alkyl substituted by a straight- or branched chain alkyl having 6 to 20 carbon atoms;

wherein the alkyl moiety may have, in the carbon chain, a substituent selected from the group consisting of alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, acyl, alkylamino, alkylthio, acylamino, alkoxycarbonyl, alkoxycarbonylamino, acyloxy, alkylcarbamoyl, nitro, halogen, amino, hydroxy and carboxy; or a pharmaceutically acceptable salt thereof.

12. A 2-amino-1,3-propanediol compound of any one of Claims 9, 10 and 11, having the formula

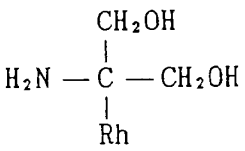


(I-10)

wherein

Rg is a phenylalkyl wherein the alkyl moiety is a straight- or branched chain having 6 to 20 carbon atoms which may have, in the carbon chain, one or two oxygen atoms; a phenylalkyl which may be substituted by a straight- or branched chain C6-C14 alkyl optionally substituted by halogen, a straight- or branched chain C6-C14 alkoxy optionally substituted by halogen, a straight- or branched chain C6-C14 alkenyloxy, phenylalkoxy, halophenylalkoxy, phenylalkoxyalkyl, phenoxyalkoxy or phenoxyalkyl; a cycloalkylalkyl wherein the alkyl moiety has 6 to 20 carbon atoms; a cycloalkylalkyl substituted by a straight- or branched chain alkyl having 6 to 14 carbon atoms; a heteroarylalkyl wherein the alkyl moiety has 6 to 20 carbon atoms; a heteroarylalkyl substituted by a straight- or branched chain alkyl having 6 to 14 carbon atoms; a heterocyclic alkyl wherein the alkyl moiety has 6 to 20 carbon atoms, or a heterocyclic alkyl substituted by a straight- or branched chain alkyl having 6 to 14 carbon atoms; or a pharmaceutically acceptable salt thereof.

13. A 2-amino-1,3-propanediol compound of Claim 12, having the formula



(I-11)

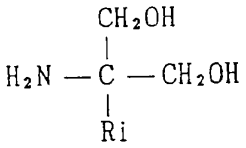
wherein

Rh is a phenylalkyl wherein the alkyl moiety has 6 to 20 carbon atoms, a phenylalkoxyalkyl wherein the alkyl moiety and alkoxy moiety have 6 to 20 carbon atoms in total, a phenoxyalkyl wherein the alkyl moiety has 6 to 20 carbon atoms or a phenoxyalkoxyalkyl wherein the alkyl moiety and alkoxy moiety have 6 to 20 carbon atoms in total, or a pharmaceutically acceptable salt thereof.

14. A 2-amino-1,3-propanediol compound of Claim 13, which is selected from the group consisting of
2-amino-2-(8-phenyloctyl)-1,3-propanediol,
2-amino-2-(9-phenylnonyl)-1,3-propanediol,
2-amino-2-(10-phenyldecyl)-1,3-propanediol,
2-amino-2-(11-phenylundecyl)-1,3-propanediol,
2-amino-2-(12-phenyldodecyl)-1,3-propanediol,
2-amino-2-(13-phenyltridecyl)-1,3-propanediol,
2-amino-2-(14-phenyltetradecyl)-1,3-propanediol,
2-amino-2-(15-phenylpentadecyl)-1,3-propanediol,
2-amino-2-(16-phenylhexadecyl)-1,3-propanediol,
2-amino-2-[6-(8-phenyloctyloxy)hexyl]-1,3-propanediol,
2-amino-2-(8-phenylmethyloxyoctyl)-1,3-propanediol,
2-amino-2-(9-phenoxynonyl)-1,3-propanediol,
2-amino-2-(12-phenoxydodecyl)-1,3-propanediol and
2-amino-2-[6-(2-phenoxyethyloxy)hexyl]-1,3-propanediol, or a pharmaceutically acceptable salt thereof.

15. A 2-amino-1,3-propanediol compound of Claim 13, which is selected from the group consisting of
2-amino-2-(10-phenyldecyl)-1,3-propanediol,
2-amino-2-(13-phenyltridecyl)-1,3-propanediol,
2-amino-2-[6-(8-phenyloctyloxy)hexyl]-1,3-propanediol,
2-amino-2-(8-phenylmethyloxyoctyl)-1,3-propanediol,
2-amino-2-(9-phenoxynonyl)-1,3-propanediol,
2-Amino-2-(12-phenoxydodecyl)-1,3-propanediol and
2-amino-2-[6-(2-phenoxyethyloxy)hexyl]-1,3-propanediol, or a pharmaceutically acceptable salt thereof.

16. A 2-amino-1,3-propanediol compound of Claim 12, having the formula



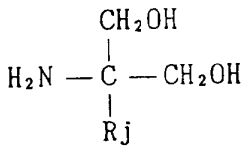
(I-12)

wherein

Ri is a phenylalkyl substituted by a straight- or branched chain C6-C14 alkyl optionally substituted by halogen, a straight- or branched chain C6-C14 alkoxy optionally substituted by halogen or a straight- or branched chain C6-C14 alkenyloxy,

wherein the alkyl moiety of phenylalkyl may be substituted by hydroxy, or a pharmaceutically acceptable salt thereof.

17. A 2-amino-1,3-propanediol compound of Claim 16, having the formula



(I-13)

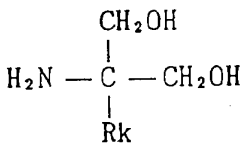
wherein

Rj is a phenylalkyl substituted by a straight- or branched chain C6-C14 alkyl optionally substituted by halogen, a straight- or branched chain C6-C14 alkoxy optionally substituted by halogen or a straight- or branched chain C6-C14 alkenyloxy, wherein the alkyl moiety is a C2-C6 alkyl optionally substituted by hydroxy, or a pharmaceutically acceptable salt thereof.

18. A 2-amino-1,3-propanediol compound of Claim 16 or 17, which is selected from the group consisting of
2-amino-2-[2-(4-heptylphenyl)ethyl]-1,3-propanediol,
2-amino-2-[2-(4-octylphenyl)ethyl]-1,3-propanediol,
2-amino-2-[2-(4-nonylphenyl)ethyl]-1,3-propanediol,
2-amino-2-[2-(4-decylphenyl)ethyl]-1,3-propanediol,
2-amino-2-[2-(4-undecylphenyl)ethyl]-1,3-propanediol,
2-amino-2-[2-(4-dodecylphenyl)ethyl]-1,3-propanediol,
2-amino-2-[2-(4-tridecylphenyl)ethyl]-1,3-propanediol,
2-amino-2-[2-(4-tetradecylphenyl)ethyl]-1,3-propanediol,
2-amino-2-[2-(4-hexyloxyphenyl)ethyl]-1,3-propanediol,
2-amino-2-[2-(4-heptyloxyphenyl)ethyl]-1,3-propanediol,
2-amino-2-[2-(4-octyloxyphenyl)ethyl)-1,3-propanediol,
2-amino-2-[2-(4-nonyloxyphenyl)ethyl]-1,3-propanediol,
2-amino-2-[2-(4-decyloxyphenyl)ethyl]-1,3-propanediol,,
2-amino-2-[2-(4-undecyloxyphenyl)ethyl]-1,3-propanediol,
2-amino-2-[2-(4-dodecyloxyphenyl)ethyl]-1,3-propanediol,
2-amino-2-[2-(4-tridecyloxyphenyl)ethyl]-1,3-propanediol,
2-amino-2-[2-(4-(8-fluorooctyl)phenyl)ethyl]-1,3-propanediol,
2-amino-2-[2-(4-(12-fluorododecyl)phenyl)ethyl]-1,3-propanediol,
2-amino-2-[2-(4-(7-fluoroheptyloxy)phenyl)ethyl]-1,3-propanediol,
2-amino-2-[2-(4-(11-fluoroundecyloxy)phenyl)ethyl]-1,3-propanediol and
2-amino-2-[2-(4-(7-octenyloxy)phenyl)ethyl]-1,3-propanediol, or a pharmaceutically acceptable salt thereof.

19. A 2-amino-1,3-propanediol compound of Claim 16 or 17, which is selected from the group consisting of
2-amino-2-[2-(4-heptylphenyl)ethyl]-1,3-propanediol,
2-amino-2-[2-(4-octylphenyl)ethyl]-1,3-propanediol,
2-amino-2-[2-(4-nonylphenyl)ethyl]-1,3-propanediol,
2amino-2-[2-(4-decylphenyl)ethyl]-1,3-propanediol,
2-amino-2-[2-(4-undecylphenyl)ethyl]-1,3-propanediol,
2-amino-2-[2-(4-dodecylphenyl)ethyl]-1,3-propanediol,
2-amino-2-[2-(4-heptyloxyphenyl)ethyl]-1,3-propanediol,
2-amino-2-[2-(4-octyloxyphenyl)ethyl]-1,3-propanediol,
2-amino-2-[2-(4-nonyloxyphenyl)ethyl]-1,3-propanediol,
2-amino-2-[2-(4-undecyloxyphenyl)ethyl]-1,3-propanediol and
2-amino-2-[2-(4-(7-octenyloxy)phenyl)ethyl]-1,3-propanediol, or a pharmaceutically acceptable salt thereof.

20. A 2-amino-1,3-propanediol compound of Claim 12, having the formula

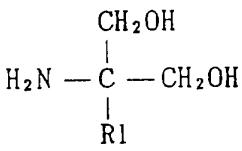


(I-14)

wherein

Rk is a phenylalkyl substituted by phenylalkoxy, halophenylalkoxy, phenylalkoxyalkyl, phenoxyalkoxy or phenoxyalkyl, or a pharmaceutically acceptable salt thereof.

21. A 2-amino-1,3-propanediol compound of Claim 20, having the formula



(I-15)

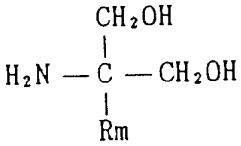
wherein

Rl is a phenylalkyl substituted by phenylalkoxy wherein the alkoxy moiety has 2 to 8 carbon atoms, halophenylalkoxy wherein the alkoxy moiety has 2 to 8 carbon atoms, phenylalkoxyalkyl wherein the alkoxy moiety and alkyl moiety have 2 to 8 carbon atoms in total, phenoxyalkoxy wherein the alkoxy moiety has 2 to 8 carbon atoms or phenoxyalkyl wherein the alkyl moiety has 2 to 8 carbon atoms, where the alkyl moiety has 2 to 6 carbon atoms, or a pharmaceutically acceptable salt thereof.

22. A 2-amino-1,3-propanediol compound of Claim 20 or 21, which is selected from the group consisting of
2-amino-2-[2-(4-phenylmethyloxyphenyl)ethyl]-1,3-propanediol,
2-amino-2-[2-(4-(2-phenylethyloxy)phenyl)ethyl]-1,3-propanediol,
2-amino-2-[2-(4-(3-phenylpropyloxy)phenyl)ethyl]-1,3-propanediol,
2-amino-2-[2-(4-(4-phenylbutyloxy)phenyl)ethyl]-1,3-propanediol,
2-amino-2-[2-(4-(5-phenylpentyloxy)phenyl)ethyl]-1,3-propanediol,
2-amino-2-[2-(4-(6-phenylhexyloxy)phenyl)ethyl]-1,3-propanediol,
2-amino-2-[2-(4-(7-phenylheptyloxy)phenyl)ethyl]-1,3-propanediol,
2-amino-2-[2-(4-(8-phenyloctyloxy)phenyl)ethyl]-1,3-propanediol,
2-amino-2-[4-(6-(4-fluorophenyl)hexyloxy)phenyl)ethyl]-1,3-propanediol, 2-amino-2-[2-(4-(5-phenylpentyloxymethyl)phenyl)ethyl]-1,3-propanediol,
2-amino-2-[2-(4-(4-phenoxybutyloxy)phenyl)ethyl]-1,3-propanediol,
2-amino-2-[2-(4-(5-phenoxypentyloxy)phenyl)ethyl]-1,3-propanediol,
2-amino-2-[2-(4-(6-phenoxyhexyloxy)phenyl)ethyl]-1,3-propanediol,
2-amino-2-[2-(4-(7-phenoxyheptyloxy)phenyl)ethyl]-1,3-propanediol,
2-amino-2-[2-(4-(4-phenoxybutyl)phenyl)ethyl]-1,3-propanediol,
2-amino-2-[2-(4-(5-phenoxypentyl)phenyl)ethyl]-1,3-propanediol,
2-amino-2-[2-(4-(6-phenoxyhexyl)phenyl))ethyl]-1,3-propanediol, and
2-amino-2-[2-(4-(7-phenoxyheptyl)phenyl)ethyl]-1,3-propanediol, or a pharmaceutically acceptable salt thereof.

23. A 2-amino-1,3-propanediol compound of Claim 20 or 21, which is selected from the group consisting of 2-amino-2-[2-(4-(6-phenylhexyloxy)phenyl)ethyl]-1,3-propanediol and 2-amino-2-[2-(4-(5-phenylpentyloxymethyl)phenyl))ethyl]-1,3-propanediol, or a pharmaceutically acceptable salt thereof.

24. A 2-amino-1,3-propanediol compound of Claim 12, having the formula



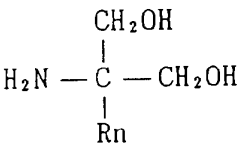
(I-16)

wherein

Rm is an alkyl-substituted cycloalkylalkyl wherein the alkyl moiety has 6 to 20 carbon atoms in total, or a pharmaceutically acceptable salt thereof.

25. A 2-amino-1,3-propanediol compound of Claim 24, which is selected from the group consisting of
2-amino-2-[3-(4-heptylcyclohexyl)propyl]-1,3-propanediol,
2-amino-2-[4-(4-butylcyclohexyl)butyl]-1,3-propanediol,
2-amino-2-[2-(4-octylcyclohexyl)ethyl]-1,3-propanediol,
2-amino-2-[2-(4-nonylcyclohexyl))ethyl]-1,3-propanediol and
2-amino-2-[2-(4-dodecylcyclohexyl))ethyl]-1,3-propanediol, or a pharmaceutically acceptable salt thereof.

26. A 2-amino-1,3-propanediol compound of Claim 12, having the formula



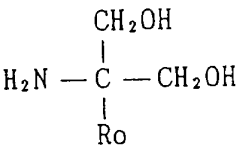
(I-17)

wherein

Rn is a 1-alkyl-substituted piperidin-4-ylalkyl wherein the alkyl moiety has 6 to 20 carbon atoms in total, or a pharmaceutically acceptable salt thereof.

27. A 2-amino-1,3-propanediol compound of Claim 26, which is selected from the group consisting of 2-amino-2-[2-(1-octylpiperidin-4-yl)ethyl]-1,3-propanediol, and 2-amino-2-[2-(1-dodecylpiperidin-4-yl)-ethyl]-1,3-propanediol,or a pharmaceutically acceptable salt thereof.

28. A 2-amino-1,3-propanediol compound of Claim 12, having the formula



(I-18)

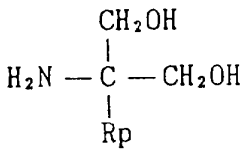
wherein

Ro is a thienylalkyl wherein the alkyl moiety has 6 to 20 carbon atoms, an alkyl-substituted thienylalkyl wherein the alkyl moiety has 6 to 20 carbon atoms in total, a pyridylalkyl wherein the alkyl moiety has 6 to 20 carbon atoms or an alkyl-substituted pyridylalkyl wherein the alkyl moiety has 6 to 20 carbon atoms in total, or a pharmaceutically acceptable salt thereof.

29. A 2-amino-1,3-propanediol compound of Claim 28, which is selected from the group consisting of
2-amino-2-[2-(5-octyl-2-thienyl)ethyl]-1,3-propanediol,
2-amino-2-[2-(5-nonyl-2-thienyl)ethyl]-1,3-propanediol,
2-amino-2-[2-(5-decyl-2-thienyl)ethyl]-1,3-propanediol,

2-amino-2-[2-(5-dodecyl-2-thienyl)ethyl]-1,3-propanediol,
2-amino-2-[13-(2-thienyl)tridecyl]-1,3-propanediol,
2-amino-2-[2-(5-octyl-2-pyridyl)ethyl]-1,3-propanediol,
2-amino-2-[2-(5-decyl-2-pyridyl)ethyl]-1,3-propanediol,
2-amio-2-[13-(2-pyridyl)tridecyl]-1,3-propanediol,
2-amino-2-[2-(2-octyl-5-pyridyl)ethyl]-1,3-propanediol,
2-amino-2-[2-(2-decyl-5-pyridyl)ethyl]-1,3-propanediol and
2-amino-2-[13-(3-pyridyl)tridecyl]-1,3-propanediol, or a pharmaceutically acceptable salt thereof.

30. A 2-amino-1,3-propanediol compound of Claim 1 or 2, having the formula

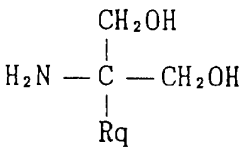


(I-19)

wherein

Rp is a phenyl substituted by C6-C18 alkyl, a cycloalkyl, a heteroaryl or a heterocycle, or a pharmaceutically acceptable salt thereof.

31. A 2-amino-1,3-propanediol compound of Claim 30, having the formula



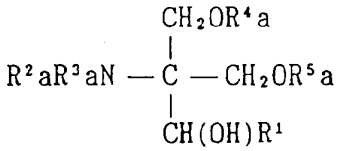
(I-20)

wherein

Rq is a phenyl substituted by C6-C18 alkyl, or a pharmaceutically acceptable salt thereof.

32. A 2-amino-1,3-propanediol compound of Claim 30 or 31, which is selected from the group consisting of
2-amino-2-(4-decylphenyl)-1,3-propanediol,
2-amino-2-(4-dodecylphenyl)-1,3-propanediol,
2-amino-2-(4-tetradecylphenyl)-1,3-propanediol and
2-amino-2-(4-hexadecylphenyl)-1,3-propanediol, or a pharmaceutically acceptable salt thereof.

33. A 2-amino-1,3-propanediol compound of Claim 1 or 2, having the formula



(I-21)

wherein

R^1 is an optionally substituted straight- or branched carbon chain which may have, in the chain, a bond, a hetero atom or a group selected from the group consisting of a double bond, a triple bond, oxygen, sulfur, sulfinyl, sulfonyl, -N(R^6)- where R^6 is hydrogen, alkyl, aralkyl, acyl or alkoxycarbonyl, and carbonyl, optionally substituted arylene, optionally substituted

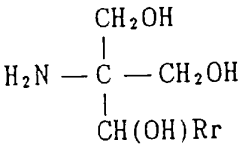
cycloalkylene, optionally substituted heteroarylene and an alicycle thereof, and which may be substituted, at the chain end (ω-position) thereof, by a double bond, a triple bond, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted heteroaryl or an alicycle thereof, an optionally substituted aryl, an optionally substituted cycloalkyl, an optionally substituted heteroaryl or an alicycle thereof, and

R^2a, R^3a, R^4a and R^5a

are the same or different and each is a hydrogen, an alkyl, an acyl or an alkoxycarbonyl;

wherein the optionally substituted straight- or branched carbon chain may have a substituent selected from the group consisting of alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, alkylenedioxy, acyl, alkylamino, alkylthio, acylamino, alkoxycarbonyl, alkoxycarbonylamino, acyloxy, alkylcarbamoyl, haloalkyl, haloalkoxy, nitro, halogen, amino, hydroxyimino, hydroxy, carboxy, optionally substituted aryl, optionally substituted aryloxy, optionally substituted cycloalkyl, optionally substituted heteroaryl and an alicycle thereof; and the aforementioned optionally substituted arylene, optionally substituted cycloalkylene, optionally substituted heteroarylene, an alicycle thereof, optionally substituted aryl, optionally substituted aryloxy, optionally substituted cycloalkyl, optionally substituted heteroaryl and an alicycle thereof may have a substituent selected from the group consisting of alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, alkylenedioxy, acyl, alkylamino, alkylthio, acylamino, alkoxycarbonyl, alkoxycarbonylamino, acyloxy, alkylcarbamoyl, haloalkyl, haloalkoxy, nitro, halogen, amino, hydroxy and carboxy; or a pharmaceutically acceptable salt thereof.

34. A 2-amino-1,3-propanediol compound of Claim 33, having the formula



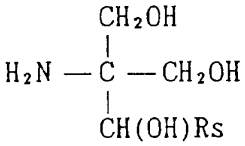
(I-22)

wherein

Rr is an alkyl optionally substituted by hydroxy and/or hydroxyimino which may have, in the chain, a double bond or carbonyl, or a pharmaceutically acceptable salt thereof.

35. A 2-amino-1,3-propanediol compound of Claim 33 or 34, which is selected from the group consisting of
2-amino-2-(1,2,12-trihydroxy-4-octadecenyl)-1,3-propanediol,
2-amino-2-(1,2-dihydrory-4-octadecenyl)-1,3-propanediol,
2-amino-2-(1,2-dihydroxyoctadecyl)-1,3-propanediol,
2-amino-2-(1,12-dihydroxy-4-octadecenyl)-1,3-propanediol,
2-amino-2-(1,2,4-trihydroxybutyl)-1,3-propanediol,
2-amino-2-(1,2,12-trihydroxyoctadecyl)-1,3-propanediol and
2-amino-2-(1,12-dihydroxyoctadecyl)-1,3-propanediol, or a pharmaceutically acceptable salt thereof.

36. A 2-amino-1,3-propanediol compound of Claim 33, having the formula



(I-23)

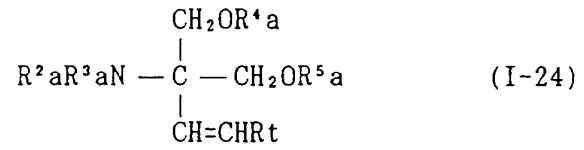
wherein

Rs is a phenylalkyl substituted by a straight- or branched chain C6-C14 alkyl optionally substituted by halogen, a straight- or branched chain C6-C14 alkoxy optionally substituted by

halogen or a straight- or branched chain C6-C14 alkenyloxy, or a pharmaceutically acceptable salt thereof.

37. A 2-amino-1,3-propanediol compound of Claim 36, which is selected from the group consisting of
2-amino-2-[1-hydroxy-2-(4-octylphenyl)ethyl]-1,3-propanediol,
2-amino-2-[2-(4-dodecylphenyl)-1-hydroxyethyl]-1,3-propanediol,
2-amino-2-[2-(4-heptyloxyphenyl)-1-hydroxyethyl]-1,3-propanediol,
2-amino-2-[1-hydroxy-2-(4-undecyloxyphenyl)ethyl]-1,3-propanediol,
2-amino-2-[2-(4-(8-fluorooctyl)phenyl)-1-hydroxyethyl]-1,3-propanediol,
2-amino-2-[2-(4-(12-fluorododecyl)phenyl)-1-hydroxyethyl]-1,3-propanediol,
2-amino-2-[2-(4-(7-fluoroheptyloxy)phenyl)-1-hydroxyethyl]-1,3-propanediol and
2-amino-2-[1-hydroxy-2-(4-(11-fluoroundecyloxy)phenyl)ethyl]-1,3-propanediol, or a pharmaceutically acceptable salt thereof.

38. A 2-amino-1,3-propanediol compound of Claim 1 or 2, having the formula



(I-24)

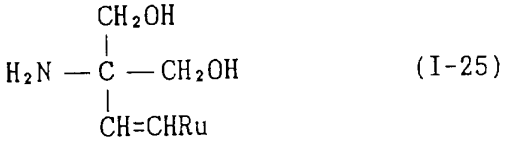
wherein

Rt is an optionally substituted straight- or branched carbon chain which may have, in the chain, a bond, a hetero atom or a group selected from the group consisting of a double bond, a triple bond, oxygen, sulfur, sulfinyl, sulfonyl, -N(R^6)- where R^6 is hydrogen, alkyl, aralkyl, acyl or alkoxycarbonyl, carbonyl, optionally substituted arylene, optionally substituted cycloalkylene, optionally substituted heteroarylene and an alicycle thereof, an optionally substituted aryl, an optionally substituted cycloalkyl, an optionally substituted heteroaryl or an alicycle thereof, and

R^2a, R^3a, R^4a and R^5a are the same or different and each is a hydrogen, an alkyl, an acyl or an alkoxycarbonyl;

wherein the optionally substituted straight- or branched carbon chain may have a substituent selected from the group consisting of alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, alkylenedioxy, acyl, alkylamino, alkylthio, acylamino, alkoxycarbonyl, alkoxycarbonylamino, acyloxy, alkylcarbamoyl, haloalkyl, haloalkoxy, nitro, halogen, amino, hydroxy, carboxy, optionally substituted aryl, optionally substituted aryloxy, optionally substituted cycloalkyl, optionally substituted heteroaryl and an alicycle thereof; and the aforementioned optionally substituted arylene, optionally substituted cycloalkylene, optionally substituted heteroarylene, an alicycle thereof, optionally substituted aryl, optionally substituted aryloxy, optionally substituted cycloalkyl, optionally substituted heteroaryl and an alicycle thereof may have a substituent selected from the group consisting of alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, alkylenedioxy, acyl, alkylamino, alkylthio, acylamino, alkoxycarbonyl, alkoxycarbonylamino, acyloxy, alkylcarbamoyl, haloalkyl, haloalkoxy, nitro, halogen, amino, hydroxy and carboxy; or a pharmaceutically acceptable salt thereof.

39. A 2-amino-1,3-propanediol compound of Claim 38, having the formula



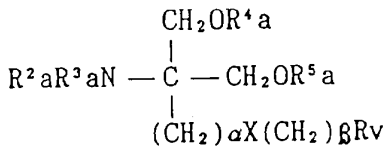
(I-25)

wherein

Ru is a phenyl substituted by alkyl having 4 to 16 carbon atoms, or a pharmaceutically acceptable salt thereof.

40. A 2-amino-1,3-propanediol compound of Claim 38 or 39, which is selected from the group consisting of
2-amino-2-[2-(4-octylphenyl)ethenyl]-1,3-propanediol,
2-amino-2-[2-(4-decylphenyl)ethenyl]-1,3-propanediol,
2-amino-2-[2-(4-dodecylphenyl)ethenyl]-1,3-propanediol and
2-amino-2-[2-(4-tetradecylphenyl)ethenyl]-1,3-propanediol, or a pharmaceutically acceptable salt thereof.

41. A 2-amino-1,3-propanediol compound of Claim 1 or 2, having the formula



(I-26)

wherein

Rv is an optionally substituted aryl, an optionally substituted cycloalkyl, an optionally substituted heteroaryl or an alicycle thereof;

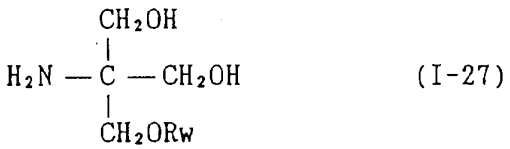
R^2a, R^3a, R^4a and R^5a are the same or different and each is a hydrogen, an alkyl, an acyl or an alkoxycarbonyl;

X is an oxygen, a sulfur, a sulfinyl, a sulfonyl, -N(R^6)-where R^6 is hydrogen, alkyl, aralkyl, acyl or alkoxycarbonyl; and

α and β are 0 or an integer of 1-20 provided that $\alpha + \beta$ = 5-20,

wherein the optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted heteroaryl and an alicycle thereof may have a substituent selected from the group consisting of alkyl, alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, alkylenedioxy, acyl, alkylamino, alkylthio, acylamino, alkoxycarbonyl, alkoxycarbonylamino, acyloxy, alkylcarbamoyl, haloalkyl, haloalkoxy, nitro, halogen, amino, hydroxy and carboxy; or a pharmaceutically acceptable salt thereof.

42. A 2-amino-1,3-propanediol compound of Claim 41, having the formula



(I-27)

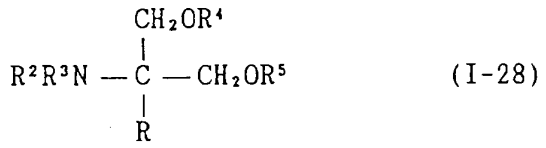
wherein

Rw is a phenyl substituted by C4-C16 alkyl, or a pharmaceutically acceptable salt thereof.

43. A 2-amino-1,3-propanediol compound of Claim 41 or 42, which is selected from the group consisting of
2-amino-2-(4-octylphenoxymethyl)-1,3-propanediol,
2-amino-2-(4-decylphenoxymethyl)-1,3-propanediol,
2-amino-2-(4-dodecylphenoxymethyl)-1,3-propanediol and
2-amino-2-(4-tetradecylphenoxymethyl)-1,3-propanediol, or a pharmaceutically acceptable salt thereof.

44. A pharmaceutical composition comprising any one of the compounds claimed in Claims 1 to 4.

45. An immunosuppressant comprising a 2-amino-1,3-propanediol compound of the formula



(I-28)

wherein

R is an optionally substituted straight- or branched carbon chain which may have, in the chain, a bond, a hetero atom or a group selected from the group consisting of a double bond, a triple bond, oxygen, sulfur, sulfinyl, sulfonyl, -N-(R^6)- where R^6 is hydrogen, alkyl, aralkyl, acyl or alkoxycarbonyl, carbonyl, optionally substituted arylene, optionally substituted cycloalkylene, optionally substituted heteroarylene and an alicycle thereof, and which may be substituted, at the chain end thereof, by a double bond, a triple bond, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted heteroaryl or an alicycle thereof, an optionally substituted aryl, an optionally substituted cycloalkyl, an optionally substituted heteroaryl or an alicycle thereof, and

R^2, R^3, R^4 and R^5 are the same or different and each is a hydrogen, an alkyl, an aralkyl, an acyl or an alkoxycarbonyl, or R^4 and R^5 may be bonded by an alkylene chain which may be substituted by alkyl, aryl or aralkyl;

wherein the optionally substituted straight- or branched carbon chain may have a substituent selected from the group consisting of alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, alkylenedioxy, acyl, alkylamino, alkylthio, acylamino, alkoxycarbonyl, alkoxycarbonylamino, acyloxy, alkylcarbamoyl, haloalkyl, haloalkoxy, nitro, halogen, amino, hydroxyimino, hydroxy, carboxy, optionally substituted aryl, optionally substituted aryloxy, optionally substituted cycloalkyl, optionally substituted heteroaryl and an alicycle thereof; the aforementioned optionally substituted arylene, optionally substituted cycloalkylene, optionally substituted heteroarylene and an alicycle thereof may have a substituent selected from the group consisting of alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, alkylenedioxy, acyl, alkylamino, alkylthio, acylamino, alkoxycarbonyl, alkoxycarbonylamino, acyloxy, alkylcarbamoyl, haloalkyl, haloalkoxy, nitro, halogen, amino, hydroxy and carboxy; and the optionally substituted aryl, optionally substituted aryloxy, optionally substituted cycloalkyl, optionally substituted heteroaryl and an alicycle thereof may have a substituent selected from the group consisting of alkyl, alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, alkylenedioxy, acyl, alkylamino, alkylthio, acylamino, alkoxycarbonyl, alkoxycarbonylamino, acyloxy, alkylcarbamoyl, haloalkyl, haloalkoxy, nitro, halogen, amino, hydroxy and carboxy; or a pharmaceutically acceptable salt thereof.

46. An immunosuppressant comprising a 2-amino-1,3-propanediol compound or a pharmaceutically acceptable salt thereof of any one of Claims 1 to 43.

47. A pharmaceutical agent according to Claim 45 or 46, wherein the immunosuppressant is an agent for suppressing rejection.

48. A pharmaceutical agent according to Claim 45 or 46, wherein the immunosuppressant is an agent for the prevention and treatment of autoimmune diseases.

49. A pharmaceutical agent of Claim 48, wherein the agent for the prevention and treatment of autoimmune diseases is an agent for the prevention and treatment of rheumatism.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP93/01515

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl^5 C07C215/10, C07C233/18, C07C215/24, C07C215/28, C07C323/25, C07C225/06, C07C229/22, C07C219/04,

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int. Cl^5 C07C215/02-215/40, C07C217/28-217/40, C07C219/04-219/16 C07C225/02-225/18, C07C229/22, C07C233/18, C07C323/25,

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	"Merck Index" 11th Edition (1989) Merck & Co., Inc., p. 1536-1537 [9684. Tromethamine]	1
X	JP, A, 63-2904 (SS Pharmaceutical Co., Ltd.), January 7, 1988 (07. 01. 88), Page 5,(Family: none)	1
X	JP, A, 57-156459 (Mitsui Toatsu Chemicals, Inc.), September 27, 1982 (27. 09. 82), Page 5, (Family: none)	1
X	JP, A, 58-101108 (Unitika, Ltd.), June 16, 1983 (16. 06. 83), (Family: none)	1
X	JP, A, 4-173723 (Kao Corp.), June 22, 1992 (22. 06. 92), (Family: none)	1
X	JP, A, 63-43140 (Fuji Photo Film Co., Ltd.), February 24, 1988 (24. 02. 88), Page 3, (Family: none)	1

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
January 10, 1994 (10. 01. 94)	February 1, 1994 (01. 02. 94)
Name and mailing address of the ISA/ Japanese Patent Office Facsimile No.	Authorized officer Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP93/01515

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JP, A, 4-69320 (Kao Corp.), March 4, 1992 (04. 03. 92), (Family: none)	1
X	JP, A, 51-54565 (Toa Eiyo K.K.), May 13, 1976 (13. 05. 76), Page 3, (Family: none)	1
X	JP, A, 4-9309 (Kao Corp.), January 14, 1992 (14. 01. 92) & EP, A2, 450527	1
X	JP, A, 57-21366 (Mitsui Toatsu Chemicals, Inc.), February 4, 1982 (04. 02. 82), Page 5 & EP, A2, 44203	1
X	US, A, 3660488 (Phillips Petroleum Company), May 2, 1972 (02. 05. 72), (Family: none)	1
X	US, A, 3432603 (Sterling Drug Inc.), March 11, 1969 (11. 03. 69), (Family: none)	1
X	US, A, 3426042 (Union Carbide Corporation), February 4, 1969 (04. 02. 69), (Family: none)	1
X	US, A, 3324043 (Sterling Drug Inc.), June 6, 1967 (06. 06. 67), (Family: none)	1
P	JP, A, 5-78294 (Kao Corp), March 30, 1993 (30. 03. 93), (Family: none)	1
X	JP, A, 4-224548 (Kao Corp.), August 13, 1992 (13. 08. 92), (Family: none)	1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP93/01515

A(Continuation). CLASSIFICATION OF SUBJECT MATTER

C07C217/28, A61K31/13, A61K31/195, A61K31/215, A61K31/24

B(Continuation). FIELDS SEARCHED

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(74) Agents: **REID, Scott, W.** et al.; The Genomics Institute of the Novartis Research Foundation, 10675 John Jay Hopkins Drive, San Diego, CA 92121 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*

— *of inventorship (Rule 4.17(iv)) for US only*

Published:

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: IMMUNOSUPPRESSANT COMPOUNDS AND COMPOSITIONS

(57) Abstract: The present invention relates to immunosuppressant, process for their production, their uses and pharmaceutical compositions containing them. The invention provides a novel class of compounds useful in the treatment or prevention of diseases or disorders mediated by lymphocyte interactions, particularly diseases associated with EDG receptor mediated signal transduction.

WO 2004/103306 A2

IMMUNOSUPPRESSANT COMPOUNDS AND COMPOSITIONS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of priority to U.S. Provisional Patent Application Number 60/471,931 (filed 19 May 2003) and U.S. Provisional Patent Application Number 60/561,968 (filed 14 April 2004). The full disclosures of these applications are incorporated herein by reference in their entirety and for all purposes.

BACKGROUND OF THE INVENTION

Field of the Invention

The invention provides a novel class of immunosuppressant compounds useful in the treatment or prevention of diseases or disorders mediated by lymphocyte interactions, particularly diseases associated with EDG receptor mediated signal transduction.

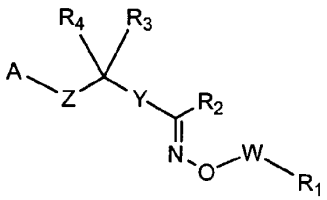
Background

EDG receptors belong to a family of closely related, lipid activated G-protein coupled receptors. EDG-1, EDG-3, EDG-5, EDG-6, and EDG-8 (also respectively termed S1P1, S1P3, S1P2, S1P4, and S1P5) are identified as receptors specific for sphingosine-1-phosphate (S1P). EDG2, EDG4, and EDG7 (also termed LPA1, LPA2, and LPA3, respectively) are receptors specific for lysophosphatidic (LPA). Among the S1P receptor isotypes, EDG-1, EDG-3 and EDG-5 are widely expressed in various tissues, whereas the expression of EDG-6 is confined largely to lymphoid tissues and platelets, and that of EDG-8 to the central nervous system. EDG receptors are responsible for signal transduction and are thought to play an important role in cell processes involving cell development, proliferation, maintenance, migration, differentiation, plasticity and apoptosis. Certain EDG receptors are associated with diseases mediated by lymphocyte interactions, for example, in transplantation rejection, autoimmune diseases, inflammatory diseases, infectious diseases and cancer. An alteration in EDG receptor activity contributes to the

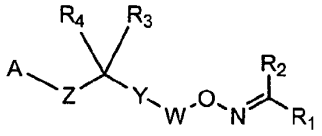
pathology and/or symptomology of these diseases. Accordingly, molecules that themselves alter the activity of EDG receptors are useful as therapeutic agents in the treatment of such diseases.

SUMMARY OF THE INVENTION

This application relates to compounds selected from Formula Ia and Ib:



Ia



Ib

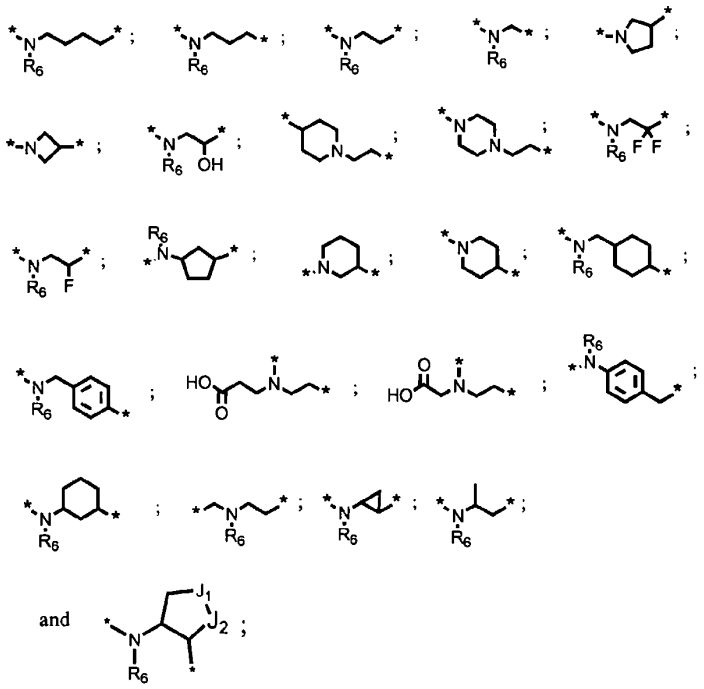
in which:

A is chosen from $-C(O)OR_5$, $-OP(O)(OR_5)_2$, $-P(O)(OR_5)_2$, $-S(O)_2OR_5$, $-P(O)(R_5)OR_5$ and 1*H*-tetrazol-5-yl; wherein each R_5 is independently chosen from hydrogen and C_{1-6}alkyl;

W is chosen from a bond, C_{1-3}alkylene, C_{2-3}alkenylene;

Y is chosen from C_{6-10}aryl and C_{2-9}heteroaryl; wherein any aryl or heteroaryl of Y can be optionally substituted with 1 to 3 radicals chosen from halo, hydroxy, nitro, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted C_{1-6}alkyl and halo-substituted C_{1-6}alkoxy;

Z is chosen from:



wherein the left and right asterisks of Z indicate the point of attachment between –$C(R_3)(R_4)$– and A of Formula Ia or Ib, respectively; R_6 is chosen from hydrogen and C_{1-6}alkyl; and J_1 and J_2 are independently methylene or a heteroatom chosen from S, O and NR_5; wherein R_5 is chosen from hydrogen and C_{1-6}alkyl; and any alkylene of Z can be further substituted by one to three radicals chosen from halo, hydroxy, C_{1-6}alkyl; or R_6 can be attached to a carbon atom of Y to form a 5-7 member ring;

R_1 is chosen from C_{6-10}aryl and C_{2-9}heteroaryl; wherein any aryl or heteroaryl of R_1 is optionally substituted by a radical chosen from C_{6-10}arylC_{0-4}alkyl, C_{2-9}heteroarylC_{0-4}alkyl, C_{3-8}cycloalkylC_{0-4}alkyl, C_{3-8}heterocycloalkylC_{0-4}alkyl or C_{1-6}alkyl; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl group of R_1 can be optionally substituted by one to five radicals chosen from halo, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl and halo-substituted-C_{1-6}alkoxy; and any alkyl group of R_1 can optionally have a methylene replaced by an atom or group chosen from –S–, –S(O)–, –$S(O)_2$–, –NR_5– and –O–; wherein R_5 is chosen from hydrogen or C_{1-6}alkyl;

R_2 is chosen from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl and halo substituted C_{1-6}alkyl;

R_3 and R_4 are independently chosen from hydrogen, C_{1-6}alkyl, halo, hydroxy, C_{1-6}alkoxy, halo-substituted C_{1-6}alkyl and halo-substituted C_{1-6}alkoxy; and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates (e.g. hydrates) of such compounds.

A second aspect of the invention is a pharmaceutical composition which contains a compound of Formula Ia or Ib or an N-oxide derivative, individual isomer or mixture of isomers thereof, or a pharmaceutically acceptable salt thereof, in admixture with one or more suitable excipients.

A third aspect of the invention is a method for treating a disease in an animal in which alteration of EDG receptor mediated signal transduction can prevent, inhibit or ameliorate the pathology and/or symptomology of the disease, which method comprises administering to the animal a therapeutically effective amount of a compound of Formula Ia or Ib or a N-oxide derivative, individual isomer or mixture of isomers thereof; or a pharmaceutically acceptable salt thereof.

A fourth aspect of the invention is the use of a compound of Formula Ia or Ib in the manufacture of a medicament for treating a disease in an animal in which alteration of EDG receptor mediated signal transduction contributes to the pathology and/or symptomology of the disease.

A fifth aspect of the invention is a process for preparing compounds of Formula Ia or Ib and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts thereof.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The invention provides compounds that are useful in the treatment and/or prevention of diseases or disorders mediated by lymphocyte interactions. Also provided are methods for treating such diseases or disorders.

Definitions

In this specification, unless otherwise defined:

"Alkyl" as a group and as a structural element of other groups, for example halo-substituted-alkyl, alkoxy, acyl, alkylthio, alkylsulfonyl and alkylsulfinyl, can be either

straight-chained or branched. "Alkenyl" as a group and as a structural element of other groups contains one or more carbon-carbon double bonds, and can be either straight-chain, or branched. Any double bonds can be in the cis- or trans- configuration. "Alkynyl" as a group and as structural element of other groups and compounds contains at least one C ≡C triple bond and can also contain one or more C=C double bonds, and can, so far as possible, be either straight-chain or branched. Any cycloalkyl group, alone or as a structural element of other groups can contain from 3 to 8 carbon atoms, preferably from 3 to 6 carbon atoms. "Alkylene" and "alkenylene" are divalent radicals derived from "alkyl" and "alkenyl" groups, respectively. In this application, any alkyl group of R^1 can be optionally interrupted by a member of the group selected from –S–, –S(O)–, –$S(O)_2$–, –NR^{20}– and –O– (wherein R^{20} is hydrogen or C_{1-6}alkyl). These groups include –CH_2–O–CH_2–, –CH_2–$S(O)_2$–CH_2–, –$(CH_2)_2$–NR^{20}–CH_2–, –CH_2–O–$(CH_2)_2$–, and the like.

"Aryl" means a monocyclic or fused bicyclic aromatic ring assembly containing six to ten ring carbon atoms. For example, C_{6-12}aryl can be phenyl, biphenyl or naphthyl, preferably phenyl. A fused bicyclic ring can be partially saturated, for example, 1,2,3,4-tetrahydro-naphthalene, and the like. "Arylene" means a divalent radical derived from an aryl group. For example, arylene as used in this application can be phenylene, biphenylene, naphthylene and the like.

"Halo" or "halogen" means F, Cl, Br or I, preferably F or Cl. Halo-substituted alkyl groups and compounds can be partially halogenated or perhalogenated, whereby in the case of multiple halogenation, the halogen substituents can be identical or different. A preferred perhalogenated alkyl group is for example trifluoromethyl or trifluoromethoxy.

"Heteroaryl" means aryl, as defined in this application, with the addition of at least one heteroatom moiety selected from N, O or S, and each ring is comprised of 5 to 6 ring atoms, unless otherwise stated. For example, C_2heteroaryl includes oxadiazole, triazole, and the like. C_9heteroaryl includes quinoline, 1,2,3,4-tetrahydro-quinoline, and the like. C_{2-9}heteroaryl as used in this application includes thienyl, pyridinyl, furanyl, isoxazolyl, benzoxazolyl or benzo[1,3]dioxolyl, preferably thienyl, furanyl or pyridinyl. "Heteroarylene" means heteroaryl, as defined in this application, provided that the ring assembly comprises a divalent radical. A fused bicyclic heteroaryl ring system can be

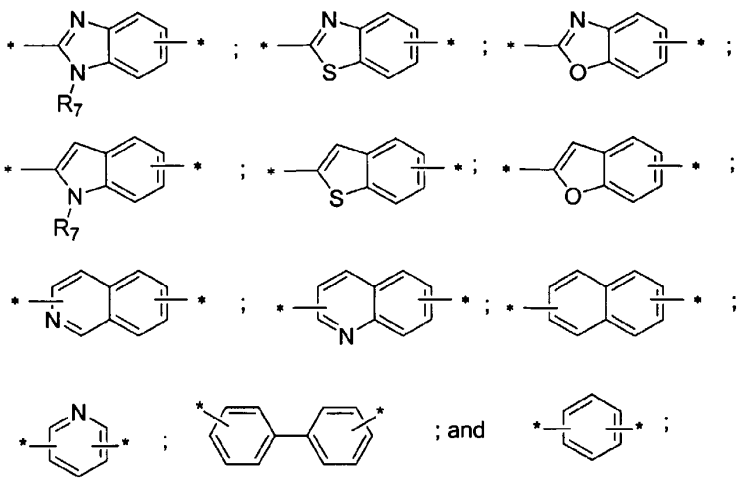
partially saturated, for example, 2,3-dihydro-1H-isoindole, 1,2,3,4-tetrahydro-quinoline, and the like.

As used in the present invention, an EDG-1 selective compound (agent or modulator) has a specificity that is selective for EDG-1 over EDG-3 and over one or more of EDG-5, EDG-6, and EDG-8. As used herein, selectivity for one EDG receptor (a "selective receptor") over another EDG receptor (a "non-selective receptor") means that the compound has a much higher potency in inducing activities mediated by the selective EDG receptor (e.g., EDG-1) than that for the non-selective S1P-specific EDG receptor. If measured in a GTP-γS binding assay (as described in the Example below), an EDG-1 selective compound typically has an EC50 (effective concentration that causes 50% of the maximum response) for a selective receptor (EDG-1) that is at least 5, 10, 25, 50, 100, 500, or 1000 fold lower than its EC50 for a non-selective receptor (e.g., one or more of EDG-3, EDG-5, EDG-6, and EDG-8).

Detailed Description of the Invention

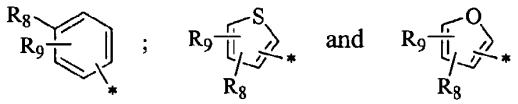
The invention provides compounds that are useful for treating or preventing diseases or disorders that are mediated by lymphocyte interactions. In one embodiment, for compounds of Formula Ia or Ib, R_1 is phenyl, naphthyl or thienyl optionally substituted by C_{6-10}arylC_{0-4}alkyl, C_{2-9}heteroarylC_{0-4}alkyl, C_{3-8}cycloalkylC_{0-4}alkyl, C_{3-8}heterocycloalkylC_{0-4}alkyl or C_{1-6}alkyl; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl group of R_1 can be optionally substituted by one to five radicals chosen from halo, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl and halo-substituted-C_{1-6}alkoxy; and any alkyl group of R^1 can optionally have a methylene replaced by an atom or group chosen from –S–, –S(O)–, –$S(O)_2$–, –NR_5– and –O–; wherein R_5 is hydrogen or C_{1-6}alkyl.

In another embodiment, Y is chosen from:



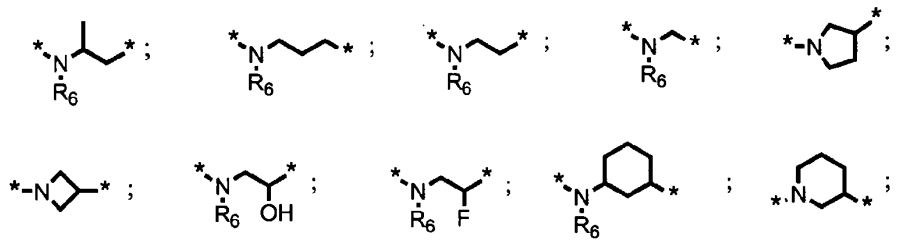
wherein R_7 is hydrogen or C_{1-6}alkyl; and the left and right asterisks of Y indicate the point of attachment a) either between $-C(R_2)=NOWR_1$ and the $-CR_3R_4-$, or between $-CR_3R_4-$ and $-C(R_2)=NOWR_1$ of Formula Ia, respectively, or b) either between $-CR_3R_4-$ and W or between W and $-CR_3R_4-$ of Formula Ib, respectively; wherein any aryl or heteroaryl of Y can be optionally substituted with 1 to 3 radicals chosen from halo, hydroxy, nitro, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted C_{1-6}alkyl and halo-substituted C_{1-6}alkoxy.

In a further embodiment, R_1 is chosen from:



wherein the asterisk is the point of attachment of R_1 with W; R_8 is C_{6-10}arylC_{0-4}alkyl, C_{2-9}heteroarylC_{0-4}alkyl, C_{3-8}cycloalkylC_{0-4}alkyl, C_{3-8}heterocycloalkylC_{0-4}alkyl or C_{1-6}alkyl; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl group of R_8 can be optionally substituted by one to three radicals chosen from halo, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl and halo-substituted-C_{1-6}alkoxy; and any alkyl group of R_8 can optionally have a methylene replaced by an atom or group chosen from –S–, –S(O)–, –$S(O)_2$–, $-NR_5-$ and –O–; wherein R_5 is hydrogen or C_{1-6}alkyl; and R_9 is chosen from halo, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl and halo-substituted-C_{1-6}alkoxy.

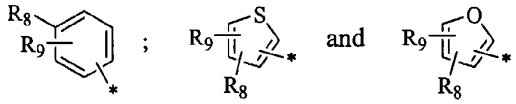
In another embodiment, A is –C(O)OH; Z is chosen from:



wherein the left and right asterisks of Z indicate the point of attachment between –$C(R_3)(R_4)$– and A of Formula Ia or Ib, respectively; R_6 is chosen from hydrogen and C_{1-6}alkyl; and R_3 and R_4 are both hydrogen.

In a further embodiment, Y is chosen from phenyl, pyridinyl, thienyl and furanyl; wherein any phenyl, pyridinyl, thienyl or furanyl of Y is optionally substituted with 1 to 3 radicals chosen from methyl, ethyl, cyclopropyl, chloro, bromo, fluoro and methoxy; or where Y is phenyl, R_6 can be attached to a carbon atom of Y to form 3,4-dihydro-1H-isoquinolin-2-yl.

In another embodiment, W is a bond or methylene; R_1 is chosen from:



wherein R_8 is chosen from phenyl, cyclohexyl, thienyl, 3,3-dimethyl-butyl, pyridinyl, cyclopentyl and piperidinyl; wherein R_8 can be optionally substituted by 1 to 3 radicals chosen from trifluoromethyl, methoxy, fluoro, triflouromethoxy and methyl; and R_9 is chosen from trifluoromethyl, fluoro, methyl, chloro, methoxy and ethyl.

Preferred compounds of the invention include: 3-{4-[1-(2-Trifluoromethyl-biphenyl-4-ylmethoxyimino)-ethyl]-benzylamino}-propionic acid, 3-{4-[1-(4-Cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzylamino}-propionic acid, 1-{4-[1-(4-Cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, 3-({2-Chloro-6-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-pyridin-3-ylmethyl}-amino)-propionic acid, 3-({6-[1-(4-Cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-pyridin-3-ylmethyl}-amino)-propionic acid, 3-{4-[1-(Biphenyl-4-ylmethoxyimino)-ethyl]-benzylamino}-propionic acid, 4-{4-[1-(Biphenyl-4-

ylmethoxyimino)-ethyl]-benzylamino}-butyric acid, 1-{4-[1-(Biphenyl-4-ylmethoxyimino)-ethyl]-benzyl}-azetidine-3-carboxylic acid, 1-{4-[1-(Biphenyl-4-ylmethoxyimino)-ethyl]-benzyl}-piperidine-3-carboxylic acid, {4-[1-(Biphenyl-4-ylmethoxyimino)-ethyl]-benzylamino}-acetic acid, 3-{4-[1-(Biphenyl-4-ylmethoxyimino)-ethyl]-benzylamino}-cyclopentanecarboxylic acid, 3-{4-[1-(4'-Trifluoromethyl-biphenyl-4-ylmethoxyimino)-ethyl]-benzylamino}-propionic acid, 3-{4-[1-(5-Phenyl-furan-2-ylmethoxyimino)-ethyl]-benzylamino}-propionic acid, 3-{4-[1-(3'-Trifluoromethyl-biphenyl-4-ylmethoxyimino)-ethyl]-benzylamino}-propionic acid, 3-{4-[1-(3-Trifluoromethyl-biphenyl-4-ylmethoxyimino)-ethyl]-benzylamino}-propionic acid, 3-{4-[1-(4'-Methoxy-biphenyl-4-ylmethoxyimino)-ethyl]-benzylamino}-propionic acid, 3-{4-[1-(Biphenyl-3-ylmethoxyimino)-ethyl]-benzylamino}-propionic acid, 3-{4-[1-(4-Thiophen-2-yl-benzyloxyimino)-ethyl]-benzylamino}-propionic acid, 3-{4-[1-(4-Thiophen-2-yl-3-trifluoromethyl-benzyloxyimino)-ethyl]-benzylamino}-propionic acid, 3-{4-[1-(4'-Fluoro-biphenyl-4-ylmethoxyimino)-ethyl]-benzylamino}-propionic acid, 3-{4-[1-(4'-Trifluoromethoxy-biphenyl-4-ylmethoxyimino)-ethyl]-benzylamino}-propionic acid, 3-{4-[1-(3'-Trifluoromethoxy-biphenyl-4-ylmethoxyimino)-ethyl]-benzylamino}-propionic acid, 1-{4-[1-(2-Trifluoromethyl-biphenyl-4-ylmethoxyimino)-ethyl]-benzyl}-azetidine-3-carboxylic acid, 1-{4-[1-(2-Trifluoromethyl-biphenyl-4-ylmethoxyimino)-ethyl]-benzyl}-pyrrolidine-3-carboxylic acid, 1-{4-[1-(2-Trifluoromethyl-biphenyl-4-ylmethoxyimino)-ethyl]-benzyl}-piperidine-3-carboxylic acid, 3-{4-[1-(3'-Methoxy-biphenyl-4-ylmethoxyimino)-ethyl]-benzylamino}-propionic acid, 2-Hydroxy-3-{4-[1-(2-trifluoromethyl-biphenyl-4-ylmethoxyimino)-ethyl]-benzylamino}-propionic acid, 3-{4-[1-(4'-Methyl-biphenyl-4-ylmethoxyimino)-ethyl]-benzylamino}-propionic acid, 3-{4-[1-(4-Phenyl-thiophen-2-ylmethoxyimino)-ethyl]-benzylamino}-propionic acid, 1-{4-[1-(Biphenyl-4-ylmethoxyimino)-ethyl]-benzyl}-pyrrolidine-3-carboxylic acid, 3-{4-[1-(4-Furan-3-yl-benzyloxyimino)-ethyl]-benzylamino}-propionic acid, 3-{4-[1-(4-Thiophen-3-yl-3-trifluoromethyl-benzyloxyimino)-ethyl]-benzylamino}-propionic acid, 3-{4-[1-(4-Thiophen-3-yl-2-trifluoromethyl-benzyloxyimino)-ethyl]-benzylamino}-propionic acid, 2-Fluoro-3-{4-[1-(2-trifluoromethyl-biphenyl-4-ylmethoxyimino)-ethyl]-benzylamino}-propionic acid, 3-{4-[1-(2-Trifluoromethyl-biphenyl-4-ylmethoxyimino)-ethyl]-benzylamino}-butyric acid, 3-{4-[1-(5-Phenyl-thiophen-2-ylmethoxyimino)-ethyl]-

benzylamino}-propionic acid, 3-{4-[1-(4-Cyclohexyl-benzyloxyimino)-ethyl]-benzylamino}-propionic acid, 3-{4-[1-(3-Fluoro-biphenyl-4-ylmethoxyimino)-ethyl]-benzylamino}-propionic acid, 3-{4-[1-(4'-Fluoro-2-trifluoromethyl-biphenyl-4-ylmethoxyimino)-ethyl]-benzylamino}-propionic acid, 3-{4-[1-(4'-Methyl-2-trifluoromethyl-biphenyl-4-ylmethoxyimino)-ethyl]-benzylamino}-propionic acid, 3-{4-[1-(4-Furan-2-yl-3-trifluoromethyl-benzyloxyimino)-ethyl]-benzylamino}-propionic acid, 3-{4-[1-(2'-Fluoro-2-trifluoromethyl-biphenyl-4-ylmethoxyimino)-ethyl]-benzylamino}-propionic acid, 3-(4-{1-[4-(3,3-Dimethyl-butyl)-3-trifluoromethyl-benzyloxyimino]-ethyl}-benzylamino)-propionic acid, 3-{4-[1-(4-Furan-3-yl-3-trifluoromethyl-benzyloxyimino)-ethyl]-benzylamino}-propionic acid, 3-{4-[1-(4-Pyridin-3-yl-benzyloxyimino)-ethyl]-benzylamino}-propionic acid, 3-{4-[1-(4-Pyridin-4-yl-benzyloxyimino)-ethyl]-benzylamino}-propionic acid, 3-{4-[1-(2-Fluoro-biphenyl-4-ylmethoxyimino)-ethyl]-benzylamino}-propionic acid, 3-({2-Methoxy-6-[1-(2-trifluoromethyl-biphenyl-4-ylmethoxyimino)-ethyl]-pyridin-3-ylmethyl}-amino)-propionic acid, 3-{4-[1-(4-Cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzylamino}-propionic acid, 3-{4-[1-(4-Cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-benzylamino}-propionic acid, 3-{2-Bromo-4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-benzylamino}-propionic acid, 3-{4-[1-(4-Cyclopentyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-benzylamino}-propionic acid, 3-{2-Chloro-4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-benzylamino}-propionic acid, 3-({6-[1-(4-Cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-pyridin-3-ylmethyl}-amino)-propionic acid, 3-({5-[1-(4-Cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-thiophen-2-ylmethyl}-amino)-propionic acid, 3-({5-[1-(4-Cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-pyridin-2-ylmethyl}-amino)-propionic acid, 3-({5-[1-(4-Cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-furan-2-ylmethyl}-amino)-propionic acid, 3-({2-[1-(4-Cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-pyridin-4-ylmethyl}-amino)-propionic acid, 3-{4-[1-(4-Cyclohexyl-3-fluoro-benzyloxyimino)-ethyl]-benzylamino}-propionic acid, 3-{2-Chloro-4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-benzylamino}-propionic acid, 1-{6-[1-(4-Cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-pyridin-3-ylmethyl}-azetidine-3-carboxylic acid, 3-{2-Ethyl-4-[1-(4-piperidin-1-yl-3-trifluoromethyl-benzyloxyimino)-ethyl]-benzylamino}-propionic acid, 3-{4-[1-(4-

Cyclohexyl-3-methyl-benzyloxyimino)-ethyl]-2-ethyl-benzylamino}-propionic acid, 3-{4-[1-(3-Chloro-4-cyclohexyl-benzyloxyimino)-ethyl]-2-ethyl-benzylamino}-propionic acid, 3-{4-[1-(4-Cyclohexyl-3-methoxy-benzyloxyimino)-ethyl]-2-ethyl-benzylamino}-propionic acid, 1-{4-[1-(4-Cyclohexyl-3-methoxy-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, 3-{4-[1-(4-Cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-methyl-benzylamino}-propionic acid, 1-{4-[1-(4-Cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-methyl-benzyl}-azetidine-3-carboxylic acid, 3-{4-[1-(4-Cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-cyclopropyl-benzylamino}-propionic acid, 1-{4-[1-(4-Cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-cyclopropyl-benzyl}-azetidine-3-carboxylic acid, 3-{2-Ethyl-4-[1-(2-trifluoromethyl-biphenyl-4-ylmethoxyimino)-ethyl]-benzylamino}-propionic acid, 1-{4-[1-(4-Cyclohexyl-3-ethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, 1-{4-[1-(4-Cyclohexyl-3-methyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, 1-{2-Chloro-4-[1-(4-cyclohexyl-3-ethyl-benzyloxyimino)-ethyl]-benzyl}-azetidine-3-carboxylic acid, 3-{2-Chloro-4-[1-(4-cyclohexyl-3-ethyl-benzyloxyimino)-ethyl]-benzylamino}-propionic acid, 3-{4-[1-(4-Cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-fluoro-benzylamino}-propionic acid, 1-{4-[1-(4-Cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-fluoro-benzyl}-azetidine-3-carboxylic acid, 3-{6-[1-(4-Cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-3,4-dihydro-1H-isoquinolin-2-yl}-propionic acid, 3-{6-[1-(4-Cyclohexyl-3-ethyl-benzyloxyimino)-ethyl]-3,4-dihydro-1H-isoquinolin-2-yl}-propionic acid, 3-{4-[1-(2-Trifluoromethyl-biphenyl-4-yl)-ethylideneaminooxymethyl]-benzylamino}-propionic acid, 3-{4-[1-(4-Cyclohexyl-3-trifluoromethyl-phenyl)-ethylideneaminooxymethyl]-benzylamino}-propionic acid, 3-{4-[1-(4-Cyclohexyl-3-trifluoromethyl-phenyl)-ethylideneaminooxymethyl]-2-ethyl-benzylamino}-propionic acid, 1-{4-[1-(4-Cyclohexyl-3-trifluoromethyl-phenyl)-ethylideneaminooxymethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid and 1-{4-[1-(4-Cyclohexyl-3-ethyl-phenyl)-ethylideneaminooxymethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid. Further, preferred compounds are also shown in the examples and table 1, *infra*.

The invention provides forms of the compound that have the hydroxyl or amine group present in a protected form; these function as prodrugs. Prodrugs are compounds that

are converted into an active drug form after administration, through one or more chemical or biochemical transformations. Forms of the compounds of the present invention that are readily converted into the claimed compound under physiological conditions are prodrugs of the claimed compounds and are within the scope of the present invention. Examples of prodrugs include forms where a hydroxyl group is acylated to form a relatively labile ester such as an acetate ester, and forms where an amine group is acylated with the carboxylate group of glycine or an L-amino acid such as serine, forming an amide bond that is particularly susceptible to hydrolysis by common metabolic enzymes.

Compounds of Formula Ia or Ib can exist in free form or in salt form, e.g. addition salts with inorganic or organic acids. Where hydroxyl groups are present, these groups can also be present in salt form, e.g. an ammonium salt or salts with metals such as lithium, sodium, potassium, calcium, zinc or magnesium, or a mixture thereof. Compounds of Formula Ia or Ib and their salts in hydrate or solvate form are also part of the invention.

When the compounds of Formula Ia or Ib have asymmetric centers in the molecule, various optical isomers are obtained. The present invention also encompasses enantiomers, racemates, diastereoisomers and mixtures thereof. Moreover, when the compounds of Formula Ia or Ib include geometric isomers, the present invention embraces cis-compounds, trans-compounds and mixtures thereof. Similar considerations apply in relation to starting materials exhibiting asymmetric carbon atoms or unsaturated bonds as mentioned above.

Methods and Pharmaceutical Compositions for Treating Immunomodulatory Conditions

The compounds of Formula Ia or Ib in free form or in pharmaceutically acceptable salt form, exhibit valuable pharmacological properties, e.g. lymphocyte recirculation modulating properties, for example, as indicated by the *in vitro* and *in vivo* tests of Example 6 and are therefore indicated for therapy. Compounds of Formula Ia or Ib preferably show an EC_{50} in the range of 1×10^{-11} to 1×10^{-5} M, preferably less than 50nM. The compounds exhibit selectivity for one or more EDG/S1P receptors, preferably EDG-1/S1P-1. EDG-1/S1P-1 selective modulators of the present invention can be identified by assaying a compound's binding to EDG-1/S1P-1 and one or more of the other EDG/S1P receptors (e.g., EDG-3/S1P-3, EDG-5/S1P-2, EDG-6/S1P-4, and EDG-8/S1P-5). An EDG-1/S1P-1 selective modulator usually has an EC50 for the EDG-1/S1P-1 receptor in the range of 1 x

10^{-11} to 1 x 10^{-5} M, preferably less than 50 nM, more preferably less than 5 nM. It also has an EC50 for one or more of the other EDG/S1P receptors that is at least 5, 10, 25, 50, 100, 500, or 1000 fold higher than its EC50 for EDG-1/S1P-1. Thus, some of the EDG-1/S1P-1 modulatory compounds will have an EC50 for EDG-1/S1P-1 that is less than 5 nM while their EC50 for one or more of the other EDG/S1P receptors are at least 100 nM or higher. Other than assaying binding activity to the EDG/S1P receptors, EDG-1/S1P-1 selective agents can also be identified by examining a test agent's ability to modify a cellular process or activity mediated by an EDG/S1P receptor.

The compounds of Formula Ia or Ib are, therefore, useful in the treatment and/or prevention of diseases or disorders mediated by lymphocytes interactions, for example in transplantation, such as acute or chronic rejection of cell, tissue or organ allo- or xenografts or delayed graft function, graft versus host disease, autoimmune diseases, e.g. rheumatoid arthritis, systemic lupus erythematosus, hashimoto's thyroidis, multiple sclerosis, myasthenia gravis, diabetes type I or II and the disorders associated therewith, vasculitis, pernicious anemia, Sjoegren syndrome, uveitis, psoriasis, Graves ophthalmopathy, alopecia areata and others, allergic diseases, e.g. allergic asthma, atopic dermatitis, allergic rhinitis/conjunctivitis, allergic contact dermatitis, inflammatory diseases optionally with underlying aberrant reactions, e.g. inflammatory bowel disease, Crohn's disease or ulcerative colitis, intrinsic asthma, inflammatory lung injury, inflammatory liver injury, inflammatory glomerular injury, atherosclerosis, osteoarthritis, irritant contact dermatitis and further eczematous dermatitises, seborrhoeic dermatitis, cutaneous manifestations of immunologically-mediated disorders, inflammatory eye disease, keratoconjunctivitis, myocarditis or hepatitis, ischemia/reperfusion injury, e.g. myocardial infarction, stroke, gut ischemia, renal failure or hemorrhage shock, traumatic shock, T cell lymphomas or T cell leukemias, infectious diseases, e.g. toxic shock (e.g. superantigen induced), septic shock, adult respiratory distress syndrome or viral infections, e.g. AIDS, viral hepatitis, chronic bacterial infection, or senile dementia. Examples of cell, tissue or solid organ transplants include e.g. pancreatic islets, stem cells, bone marrow, corneal tissue, neuronal tissue, heart, lung, combined heart-lung, kidney, liver, bowel, pancreas, trachea or oesophagus. For the above uses the required dosage will of course vary depending on the mode of administration, the particular condition to be treated and the effect desired.

Furthermore, the compounds of Formula Ia or Ib are useful in cancer chemotherapy, particularly for cancer chemotherapy of solid tumors, e.g. breast cancer, or as an anti-angiogenic agent.

The required dosage will of course vary depending on the mode of administration, the particular condition to be treated and the effect desired. In general, satisfactory results are indicated to be obtained systemically at daily dosages of from about 0.03 to 2.5 mg/kg per body weight. An indicated daily dosage in the larger mammal, e.g. humans, is in the range from about 0.5 mg to about 100 mg, conveniently administered, for example, in divided doses up to four times a day or in retard form. Suitable unit dosage forms for oral administration comprise from ca. 1 to 50 mg active ingredient.

The compounds of Formula Ia or Ib can be administered by any conventional route, in particular enterally, for example, orally, e.g. in the form of tablets or capsules, or parenterally, for example, in the form of injectable solutions or suspensions, topically, e.g. in the form of lotions, gels, ointments or creams, or in a nasal or a suppository form. Pharmaceutical compositions comprising a compound of Formula Ia or Ib in free form or in pharmaceutically acceptable salt form in association with at least one pharmaceutical acceptable carrier or diluent can be manufactured in conventional manner by mixing with a pharmaceutically acceptable carrier or diluent.

The compounds of Formula Ia or Ib can be administered in free form or in pharmaceutically acceptable salt form, for example, as indicated above. Such salts can be prepared in a conventional manner and exhibit the same order of activity as the free compounds.

In accordance with the foregoing the present invention further provides:

1.1 A method for preventing or treating disorders or diseases mediated by lymphocytes, e.g. such as indicated above, in a subject in need of such treatment, which method comprises administering to said subject an effective amount of a compound of Formula Ia or Ib or a pharmaceutically acceptable salt thereof;

1.2 A method for preventing or treating acute or chronic transplant rejection or T-cell mediated inflammatory or autoimmune diseases, e.g. as indicated above, in a subject in need of such treatment, which method comprises administering to said subject an effective amount of a compound of Formula Ia or Ib or a pharmaceutically acceptable salt thereof;

1.3 A method for inhibiting or controlling deregulated angiogenesis, e.g. sphingosine-1-phosphate (S1P) mediated angiogenesis, in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of a compound of Formula Ia or Ib or a pharmaceutically acceptable salt thereof.

1.4 A method for preventing or treating diseases mediated by a neo-angiogenesis process or associated with deregulated angiogenesis in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of a compound of Formula Ia or Ib or a pharmaceutically acceptable salt thereof.

2. A compound of Formula Ia or Ib, in free form or in a pharmaceutically acceptable salt form for use as a pharmaceutical, e.g. in any of the methods as indicated under 1.1 to 1.4 above.

3. A pharmaceutical composition, e.g. for use in any of the methods as in 1.1 to 1.4 above comprising a compound of Formula Ia or Ib in free form or pharmaceutically acceptable salt form in association with a pharmaceutically acceptable diluent or carrier therefor.

4. A compound of Formula Ia or Ib or a pharmaceutically acceptable salt thereof for use in the preparation of a pharmaceutical composition for use in any of the method as in 1.1 to 1.4 above.

The compounds of Formula Ia or Ib may be administered as the sole active ingredient or in conjunction with, e.g. as an adjuvant to, other drugs e.g. immunosuppressive or immunomodulating agents or other anti-inflammatory agents, e.g. for the treatment or prevention of allo- or xenograft acute or chronic rejection or inflammatory or autoimmune disorders, or a chemotherapeutic agent, e.g. a malignant cell anti-proliferative agent. For example the compounds of Formula Ia or Ib may be used in combination with a calcineurin inhibitor, e.g. cyclosporin A or FK 506; a mTOR inhibitor, e.g. rapamycin, 40-O-(2-hydroxyethyl)-rapamycin, CCI779, ABT578 or AP23573; an ascomycin having immunosuppressive properties, e.g. ABT-281, ASM981, etc.; corticosteroids; cyclophosphamide; azathioprene; methotrexate; leflunomide; mizoribine; mycophenolic acid; mycophenolate mofetil; 15-deoxyspergualine or an immunosuppressive homologue, analogue or derivative thereof; immunosuppressive monoclonal antibodies, e.g. monoclonal antibodies to leukocyte receptors, e.g. MHC, CD2, CD3, CD4, CD7, CD8, CD25, CD28,

CD40. CD45, CD58, CD80, CD86 or their ligands; other immunomodulatory compounds, e.g. a recombinant binding molecule having at least a portion of the extracellular domain of CTLA4 or a mutant thereof, e.g. an at least extracellular portion of CTLA4 or a mutant thereof joined to a non-CTLA4 protein sequence, e.g. CTLA4Ig (for ex. designated ATCC 68629) or a mutant thereof, e.g. LEA29Y ; adhesion molecule inhibitors, e.g. LFA-1 antagonists, ICAM-1 or -3 antagonists, VCAM-4 antagonists or VLA-4 antagonists; or a chemotherapeutic agent.

By the term "chemotherapeutic agent" is meant any chemotherapeutic agent and it includes but is not limited to,

i. an aromatase inhibitor,

ii. an anti-estrogen, an anti-androgen (especially in the case of prostate cancer) or a gonadorelin agonist,

iii. a topoisomerase I inhibitor or a topoisomerase II inhibitor,

iv. a microtubule active agent, an alkylating agent, an antineoplastic antimetabolite or a platin compound,

v. a compound targeting/decreasing a protein or lipid kinase activity or a protein or lipid phosphatase activity, a further anti-angiogenic compound or a compound which induces cell differentiation processes,

vi. a bradykinin 1 receptor or an angiotensin II antagonist,

vii. a cyclooxygenase inhibitor, a bisphosphonate, a histone deacetylase inhibitor, a heparanase inhibitor (prevents heparan sulphate degradation), e.g. PI-88, a biological response modifier, preferably a lymphokine or interferons, e.g. interferon □, an ubiquitination inhibitor, or an inhibitor which blocks anti-apoptotic pathways,

viii. an inhibitor of Ras oncogenic isoforms, e.g. H-Ras, K-Ras or N-Ras, or a farnesyl transferase inhibitor, e.g. L-744,832 or DK8G557,

ix. a telomerase inhibitor, e.g. telomestatin,

x. a protease inhibitor, a matrix metalloproteinase inhibitor, a methionine aminopeptidase inhibitor, e.g. bengamide or a derivative thereof, or a proteosome inhibitor, e.g. PS-341, and/or

xi. a mTOR inhibitor.

The term "aromatase inhibitor" as used herein relates to a compound which inhibits the estrogen production, i.e. the conversion of the substrates androstenedione and testosterone to estrone and estradiol, respectively. The term includes, but is not limited to steroids, especially atamestane, exemestane and formestane and, in particular, non-steroids, especially aminoglutethimide, roglethimide, pyridoglutethimide, trilostane, testolactone, ketokonazole, vorozole, fadrozole, anastrozole and letrozole. A combination of the invention comprising a chemotherapeutic agent which is an aromatase inhibitor is particularly useful for the treatment of hormone receptor positive tumors, e.g. breast tumors.

The term "anti-estrogen" as used herein relates to a compound which antagonizes the effect of estrogens at the estrogen receptor level. The term includes, but is not limited to tamoxifen, fulvestrant, raloxifene and raloxifene hydrochloride. A combination of the invention comprising a chemotherapeutic agent which is an anti-estrogen is particularly useful for the treatment of estrogen receptor positive tumors, e.g. breast tumors.

The term "anti-androgen" as used herein relates to any substance which is capable of inhibiting the biological effects of androgenic hormones and includes, but is not limited to, bicalutamide.

The term "gonadorelin agonist" as used herein includes, but is not limited to abarelix, goserelin and goserelin acetate.

The term "topoisomerase I inhibitor" as used herein includes, but is not limited to topotecan, irinotecan, 9-nitrocamptothecin and the macromolecular camptothecin conjugate PNU-166148 (compound A1 in WO99/17804).

The term "topoisomerase II inhibitor" as used herein includes, but is not limited to the anthracyclines such as doxorubicin, daunorubicin, epirubicin, idarubicin and nemorubicin, the anthraquinones mitoxantrone and losoxantrone, and the podophillotoxines etoposide and teniposide.

The term "microtubule active agent" relates to microtubule stabilizing and microtubule destabilizing agents including, but not limited to taxanes, e.g. paclitaxel and docetaxel, vinca alkaloids, e.g., vinblastine, especially vinblastine sulfate, vincristine especially vincristine sulfate, and vinorelbine, discodermolides and epothilones and derivatives thereof, e.g. epothilone B or a derivative thereof.

The term "alkylating agent" as used herein includes, but is not limited to busulfan, chlorambucil, cyclophosphamide, ifosfamide, melphalan or nitrosourea (BCNU or Gliadel™).

The term "antineoplastic antimetabolite" includes, but is not limited to 5-fluorouracil, capecitabine, gemcitabine, cytarabine, fludarabine, thioguanine, methotrexate and edatrexate.

The term "platin compound" as used herein includes, but is not limited to carboplatin, cis-platin and oxaliplatin.

The term "compounds targeting/decreasing a protein or lipid kinase activity or further anti-angiogenic compounds" as used herein includes, but is not limited to protein tyrosine kinase and/or serine and/or threonine kinase inhibitors or lipid kinase inhibitors, e.g. compounds targeting, decreasing or inhibiting the activity of the epidermal growth factor family of receptor tyrosine kinases (EGFR, ErbB2, ErbB3, ErbB4 as homo- or heterodimers), the vascular endothelial growth factor family of receptor tyrosine kinases (VEGFR), the platelet-derived growth factor-receptors (PDGFR), the fibroblast growth factor-receptors (FGFR), the insulin-like growth factor receptor 1 (IGF-1R), the Trk receptor tyrosine kinase family, the Axl receptor tyrosine kinase family, the Ret receptor tyrosine kinase, the Kit/SCFR receptor tyrosine kinase, members of the c-Abl family and their gene-fusion products (e.g. BCR-Abl), members of the protein kinase C (PKC) and Raf family of serine/threonine kinases, members of the MEK, SRC, JAK, FAK, PDK or PI(3) kinase family, or of the PI(3)-kinase-related kinase family, and/or members of the cyclin-dependent kinase family (CDK) and anti-angiogenic compounds having another mechanism for their activity, e.g. unrelated to protein or lipid kinase inhibition.

Compounds which target, decrease or inhibit the activity of VEGFR are especially compounds, proteins or antibodies which inhibit the VEGF receptor tyrosine kinase, inhibit a VEGF receptor or bind to VEGF, and are in particular those compounds, proteins or monoclonal antibodies generically and specifically disclosed in WO 98/35958, e.g. 1-(4-chloroanilino)-4-(4-pyridylmethyl)phthalazine or a pharmaceutically acceptable salt thereof, e.g. the succinate, in WO 00/27820, e.g. a N-aryl(thio) anthranilic acid amide derivative e.g. 2-[(4-pyridyl)methyl]amino-N-[3-methoxy-5-(trifluoromethyl)phenyl]benzamide or 2-[(1-oxido-4-pyridyl)methyl]amino-N-[3-trifluoromethylphenyl]benzamide, or in WO 00/09495,

WO 00/59509, WO 98/11223, WO 00/27819 and EP 0 769 947; those as described by M. Prewett et al in Cancer Research 59 (1999) 5209-5218, by F. Yuan et al in Proc. Natl. Acad. Sci. USA, vol. 93, pp. 14765-14770, Dec. 1996, by Z. Zhu et al in Cancer Res. 58, 1998, 3209-3214, and by J. Mordenti et al in Toxicologic Pathology, Vol. 27, no. 1, pp 14-21, 1999; in WO 00/37502 and WO 94/10202; Angiostatin™, described by M. S. O'Reilly et al, Cell 79, 1994, 315-328; Endostatin™, described by M. S. O'Reilly et al, Cell 88, 1997, 277-285; anthranilic acid amides; ZD4190; ZD6474; SU5416; SU6668; or anti-VEGF antibodies or anti-VEGF receptor antibodies,e.g. RhuMab.

By antibody is meant intact monoclonal antibodies, polyclonal antibodies, multispecific antibodies formed from at least 2 intact antibodies, and antibody fragments so long as they exhibit the desired biological activity.

Compounds which target, decrease or inhibit the activity of the epidermal growth factor receptor family are especially compounds, proteins or antibodies which inhibit members of the EGF receptor tyrosine kinase family, e.g. EGF receptor, ErbB2, ErbB3 and ErbB4 or bind to EGF or EGF related ligands, or which have a dual inhibiting effect on the ErbB and VEGF receptor kinase and are in particular those compounds, proteins or monoclonal antibodies generically and specifically disclosed in WO 97/02266, e.g. the compound of ex. 39, or in EP 0 564 409, WO 99/03854, EP 0520722, EP 0 566 226, EP 0 787 722, EP 0 837 063, US 5,747,498, WO 98/10767, WO 97/30034, WO 97/49688, WO 97/38983 and, especially, WO 96/30347 (e.g. compound known as CP 358774), WO 96/33980 (e.g. compound ZD 1839) and WO 95/03283 (e.g. compound ZM105180) or PCT/EP02/08780; e.g. trastuzumab (Herpetin®), cetuximab, Iressa, OSI-774, CI-1033, EKB-569, GW-2016, E1.1, E2.4, E2.5, E6.2, E6.4, E2.11, E6.3 or E7.6.3.

Compounds which target, decrease or inhibit the activity of PDGFR are especially compounds which inhibit the PDGF receptor, e.g. a N-phenyl-2-pyrimidine-amine derivative, e.g. imatinib.

Compounds which target, decrease or inhibit the activity of c-AbI family members and their gene fusion products are, e.g. a N-phenyl-2-pyrimidine-amine derivative, e.g. imatinib; PD180970; AG957; or NSC 680410.

Compounds which target, decrease or inhibit the activity of protein kinase C, Raf, MEK, SRC, JAK, FAK and PDK family members, or PI(3) kinase or PI(3) kinase-related

family members, and/or members of the cyclin-dependent kinase family (CDK) are especially those staurosporine derivatives disclosed in EP 0 296 110, e.g. midostaurin; examples of further compounds include e.g. UCN-01, safingol, BAY 43-9006, Bryostatin 1, Perifosine; Ilmofosine; RO 318220 and RO 320432; GO 6976; Isis 3521; or LY333531/LY379196.

Further anti-angiogenic compounds are e.g. thalidomide (THALOMID) and TNP-470.

Compounds which target, decrease or inhibit the activity of a protein or lipid phosphatase are, e.g. inhibitors of phosphatase 1, phosphatase 2A, PTEN or CDC25, e.g. okadaic acid or a derivative thereof.

Compounds which induce cell differentiation processes are, e.g. retinoic acid, α-, γ- or δ-tocopherol or α-, γ- or δ-tocotrienol.

The term cyclooxygenase inhibitor as used herein includes, but is not limited to, e.g. celecoxib (Celebrex^R), rofecoxib (Vioxx^R), etoricoxib, valdecoxib or a 5-alkyl-2-arylaminophenylacetic acid, e.g. 5-methyl-2-(2'-chloro-6'-fluoroanilino)phenyl acetic acid.

The term "histone deacetylase inhibitor" as used herein includes, but is not limited to MS-27-275, SAHA, pyroxamide, FR-901228 or valproic acid.

The term "bisphosphonates" as used herein includes, but is not limited to, etridonic, clodronic, tiludronic, pamidronic, alendronic, ibandronic, risedronic and zoledronic acid.

The term "matrix metalloproteinase inhibitor" as used herein includes, but is not limited to collagen peptidomimetic and non-petidomimetic inhibitors, tetracycline derivatives, e.g. hydroxamate peptidomimetic inhibitor batimastat and its orally bioavailable analogue marimastat, prinomastat, BMS-279251, BAY 12-9566, TAA211 or AAJ996.

The term "mTOR inhibitor" as used herein includes, but is not limited to rapamycin (sirolimus) or a derivative thereof, e.g. 32-deoxorapamycin, 16-pent-2-ynyloxy-32-deoxorapamycin, 16-pent-2-ynyloxy-32(S)-dihydro-rapamycin, 16-pent-2-ynyloxy-32(S)-dihydro-40-O-(2-hydroxyethyl)-rapamycin and, more preferably, 40-0-(2-hydroxy-ethyl)-rapamycin. Further examples of rapamycin derivatives include e.g. CCI779 or 40- [3-hydroxy-2-(hydroxymethyl)-2-methylpropanoate]-rapamycin or a pharmaceutically acceptable salt thereof, as disclosed in USP 5,362,718, ABT578 or 40-(tetrazolyl)-

rapamycin, particularly 40-epi-(tetrazolyl)-rapamycin, e.g. as disclosed in WO 99/15530, or rapalogs as disclosed e.g. in WO 98/02441 and WO01/14387, e.g. AP23573.

Where the compounds of Formula Ia or Ib are administered in conjunction with other immunosuppressive / immunomodulatory, anti-inflammatory or chemotherapeutic therapy, dosages of the co-administered immunosuppressant, immunomodulatory, anti-inflammatory or chemotherapeutic compound will of course vary depending on the type of co-drug employed, e.g. whether it is a steroid or a calcineurin inhibitor, on the specific drug employed, on the condition being treated and so forth.

In accordance with the foregoing the present invention provides in a yet further aspect:

5. A method as defined above comprising co-administration, e.g. concomitantly or in sequence, of a therapeutically effective non-toxic amount of a compound of Formula Ia or Ib and at least a second drug substance, e.g. an immunosuppressant, immunomodulatory, anti-inflammatory or chemotherapeutic drug, e.g. as indicated above.

6. A pharmaceutical combination, e.g. a kit, comprising a) a first agent which is a compound of Formula Ia or Ib as disclosed herein, in free form or in pharmaceutically acceptable salt form, and b) at least one co-agent, e.g. an immunosuppressant, immunomodulatory, anti-inflammatory or chemotherapeutic drug, e.g. as disclosed above. The kit may comprise instructions for its administration.

The terms "co-administration" or "combined administration" or the like as utilized herein are meant to encompass administration of the selected therapeutic agents to a single patient, and are intended to include treatment regimens in which the agents are not necessarily administered by the same route of administration or at the same time.

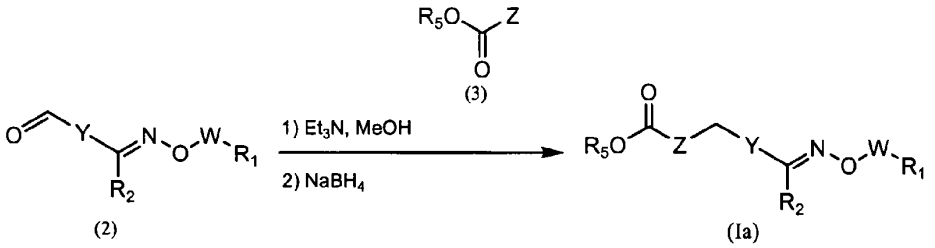
The term "pharmaceutical combination" as used herein means a product that results from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term "fixed combination" means that the active ingredients, e.g. a compound of Formula Ia or Ib and a co-agent, are both administered to a patient simultaneously in the form of a single entity or dosage. The term "non-fixed combination" means that the active ingredients, e.g. a compound of Formula Ia or Ib and a co-agent, are both administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific time limits, wherein such

administration provides therapeutically effective levels of the 2 compounds in the body of the patient. The latter also applies to cocktail therapy, e.g. the administration of 3 or more active ingredients.

Methods for Preparing Compounds of the Invention

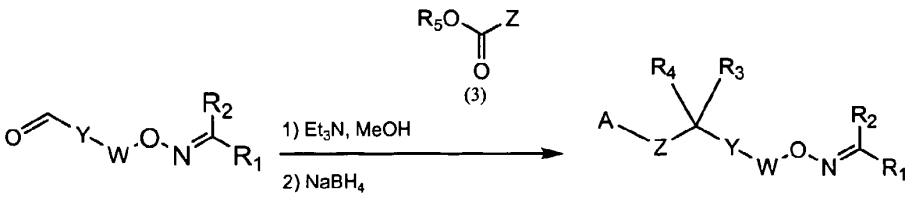
The present invention also includes processes for the preparation of immunomodulatory compounds of the invention. In the reactions described, it can be necessary to protect reactive functional groups, for example hydroxy, amino, imino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups can be used in accordance with standard practice, for example, see T.W. Greene and P. G. M. Wuts in "Protective Groups in Organic Chemistry", John Wiley and Sons, 1991.

Compounds of Formula Ia, in which A is $R_5OC(O)$- and R_3 and R_4 are hydrogen, can be prepared by proceeding as in the following reaction scheme:



in which W, Y, Z, R_1, R_2, and R_5 are as defined for Formula Ia above. Compounds of Formula I can be prepared by reacting a compound of formula 2 with a compound of formula 3 in the presence of a suitable solvent (e.g. methanol, and the like), a suitable base (e.g. triethylamine, and the like) and a suitable reducing agent (e.g. sodium borohydride). The reaction proceeds at a temperature of about 0 to about 60°C and can take up to about 48 hours to complete.

Compounds of Formula Ib, in which A is $R_5OC(O)$- and R_3 and R_4 are hydrogen, can be prepared by proceeding as in the following reaction scheme:



in which W, Y, Z, R_1, R_2, and R_5 are as defined for Formula Ib above. Compounds of Formula I can be prepared by reacting a compound of formula 4 with a compound of formula 3 in the presence of a suitable solvent (e.g. methanol, and the like), a suitable base (e.g. triethylamine, and the like) and a suitable reducing agent (e.g. sodium borohydride). The reaction proceeds at a temperature of about 0 to about 60°C and can take up to about 48 hours to complete.

Additional Processes for Preparing Compounds of the Invention:

A compound of the invention can be prepared as a pharmaceutically acceptable acid addition salt by reacting the free base form of the compound with a pharmaceutically acceptable inorganic or organic acid. Alternatively, a pharmaceutically acceptable base addition salt of a compound of the invention can be prepared by reacting the free acid form of the compound with a pharmaceutically acceptable inorganic or organic base. Alternatively, the salt forms of the compounds of the invention can be prepared using salts of the starting materials or intermediates.

The free acid or free base forms of the compounds of the invention can be prepared from the corresponding base addition salt or acid addition salt from, respectively. For example a compound of the invention in an acid addition salt form can be converted to the corresponding free base by treating with a suitable base (e.g., ammonium hydroxide solution, sodium hydroxide, and the like). A compound of the invention in a base addition salt form can be converted to the corresponding free acid by treating with a suitable acid (e.g., hydrochloric acid, etc.).

Compounds of the invention in unoxidized form can be prepared from N-oxides of compounds of the invention by treating with a reducing agent (e.g., sulfur, sulfur dioxide, triphenyl phosphine, lithium borohydride, sodium borohydride, phosphorus trichloride,

tribromide, or the like) in a suitable inert organic solvent (e.g. acetonitrile, ethanol, aqueous dioxane, or the like) at 0 to 80°C.

Prodrug derivatives of the compounds of the invention can be prepared by methods known to those of ordinary skill in the art (e.g., for further details see Saulnier et al., (1994), Bioorganic and Medicinal Chemistry Letters, Vol. 4, p. 1985). For example, appropriate prodrugs can be prepared by reacting a non-derivatized compound of the invention with a suitable carbamylating agent (e.g., 1,1-acyloxyalkylcarbanochloridate, para-nitrophenyl carbonate, or the like).

Protected derivatives of the compounds of the invention can be made by means known to those of ordinary skill in the art. A detailed description of techniques applicable to the creation of protecting groups and their removal can be found in T W. Greene, "Protecting Groups in Organic Chemistry", 3rd edition, John Wiley and Sons, Inc., 1999.

Compounds of the present invention can be conveniently prepared, or formed during the process of the invention, as solvates (e.g., hydrates). Hydrates of compounds of the present invention can be conveniently prepared by recrystallization from an aqueous/organic solvent mixture, using organic solvents such as dioxin, tetrahydrofuran or methanol.

Compounds of the invention can be prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to forma pair of diastereoisomeric compounds, separating the diastereomers and recovering the optically pure enantiomers. While resolution of enantiomers can be carried out using covalent diastereomeric derivatives of the compounds of the invention, dissociable complexes are preferred (e.g., crystalline diastereomeric salts). Diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and can be readily separated by taking advantage of these dissimilarities. The diastereomers can be separated by chromatography, or preferable, by separation/resolution techniques based upon differences in solubility. The optically pure enantiomer is then recovered, along with the resolving agent, by any practical means that would not result in racemization. A more detailed description of the techniques applicable to the resolution of stereoisomers of compounds from the their racemic mixture can be found in Jean Jacques, Andre Collet,

Samuel H. Wilen, "Enantiomers, Racemates and Resolutions", John Wiley And Sons, Inc., 1981.

In summary, the compounds of Formula Ia or Ib can be made by a process, which involves:

(a) reacting a compound of formula 2 or 4 with a compound of formula 3; and

(b) optionally converting a compound of the invention into a pharmaceutically acceptable salt;

(c) optionally converting a salt form of a compound of the invention to a non-salt form;

(d) optionally converting an unoxidized form of a compound of the invention into a pharmaceutically acceptable N-oxide;

(e) optionally converting an N-oxide form of a compound of the invention to its unoxidized form;

(f) optionally resolving an individual isomer of a compound of the invention from a mixture of isomers;

(g) optionally converting a non-derivatized compound of the invention into a pharmaceutically acceptable prodrug derivative; and

(h) optionally converting a prodrug derivative of a compound of the invention to its non-derivatized form.

Insofar as the production of the starting materials is not particularly described, the compounds are known or can be prepared analogously to methods known in the art or as disclosed in the Examples hereinafter.

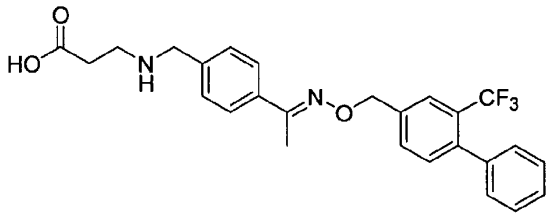
One of skill in the art will appreciate that the above transformations are only representative of methods for preparation of the compounds of the present invention, and that other well known methods can similarly be used.

EXAMPLES

The following examples provide detailed descriptions of the preparation of representative compounds and are offered to illustrate, but not to limit the present invention.

Example 1

3-{4-[1-(2-Trifluoromethyl-biphenyl-4-ylmethoxyimino)-ethyl]-benzylamino}-propionic acid



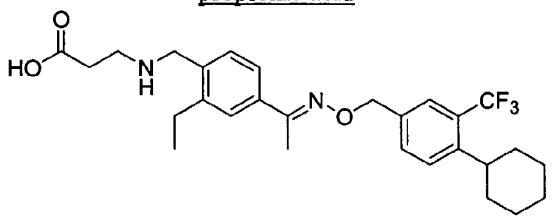
To a solution of 1-(4-hydroxymethyl-phenyl)-ethanone (1 eq) in methanol is added *O*-(4-chloro-3-trifluoromethyl-benzyl)-hydroxylamine (1 eq) followed by the addition of acetic acid (0.05 eq). The mixture is stirred at room temperature for 5 hours. After concentrated, the residue is purified by column chromatography (30% EtOAc in hexane) to give 1-(4-hydroxymethyl-phenyl)-ethanone *O*-(4-chloro-3-trifluoromethyl-benzyl)-oxime as an oil [MS: (ES^+) 358.1 $(M+1)^+$].

A mixture of 1-(4-hydroxymethyl-phenyl)-ethanone *O*-(4-chloro-3-trifluoromethyl-benzyl)-oxime (1 eq), phenyl boronic acid (1.5 eq), $Pd(OAc)_2$ (0.03 eq), phosphine ligand (0.06 eq) and KF (3 eq) in dry THF is heated at 100 ^{0}C in microwave for 30 minutes. The resulting mixture is diluted with EtOAc and washed with brine. The organic layer is dried over Na_2SO_4. After concentration, the residue is purified by column chromatography (30% EtOAc in hexane) to give 1-(4-hydroxymethyl-phenyl)-ethanone *O*-(2-trifluoromethyl-biphenyl-4-ylmethyl)-oxime as a white solid [MS: (ES^+) 400.1 $(M+1)^+$].

To a suspension of MnO_2 (10 eq) in dioxane is added 1-(4-hydroxymethyl-phenyl)-ethanone *O*-(2-trifluoromethyl-biphenyl-4-ylmethyl)-oxime (1 eq). The resulting mixture is refluxed for 10 minutes. After filtration and concentration, the residue is dissolved in MeOH and treated with β-alanine (2 eq) and Et_3N (1.5 eq). The resulting mixture is heated at 50 ^{0}C for 30 minutes. After cooling to room temperature, $NaBH_4$ (3 eq) is added in portions. Purification by preparative LCMS results in 3-{4-[1-(2-trifluoromethyl-biphenyl-4-ylmethoxyimino)-ethyl]-benzylamino}-propionic acid; ^{1}H NMR (400 MHz, CD_3OD) δ 2.28 (s, 3H), 2.75 (t, J = 6.8 Hz, 2H), 3.26 (t, J = 6.8 Hz, 2H), 4.22 (s, 2H), 5.30 (s, 2H), 7.26-7.77 (m, 12H). MS: (ES^+): 471.1 $(M+1)^+$.

Example 2

3-{4-[1-(4-Cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzylamino}-propionic acid



A mixture of 4-amino-3-ethyl-benzonitrile (5 mmol) and water (10 mL) is placed in a flask equipped with a magnetic stirrer and a thermometer probe. Concentrated hydrochloric acid (1.2 mL) is added slowly. After most of the solid is dissolved, ice (20 g) is added and the temperature is kept at 0°C using an ice-salt bath. To the stirred mixture is added a solution of sodium nitrite (5 mmol) in water (2.5 mL), dropwise. The mixture is stirred at 0°C for 30 minutes. A solution of hydrated sodium acetate in water is added to adjust the pH to neutral.

In a separate flask, a mixture of formaldoxime trimer hydrochloride (7.5 mmol), hydrated cupric sulfate (0.52 mmol), sodium sulfite (0.15 mmol) and a solution of sodium acetate (20 mmol) is prepared, and is cooled to 0°C.

The mixture of the diazonium salt is slowly added to the above mixture. After addition, the mixture is stirred at 0°C for 1.5 hours, treated with concentrated hydrochloric acid (4.4 mL) and heated to reflux overnight.

The mixture is cooled to room temperature, and extracted with ethyl acetate. The combined ethyl acetate layers are washed with a saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated to give dark oil. 3-Ethyl-4-formyl-benzonitrile is isolated by column chromatography (EtOAc/Hexane gradient).

To a solution of 3-ethyl-4-formyl-benzonitrile (1.7 mmol) in ethanol (10 mL) at 0°C is added $NaBH_4$ (1.7 mmol). The mixture is stirred at 0°C for 0.5 hour, 5% citric acid (5 mL) is added and the solvent is removed under reduced pressure. The mixture is dissolved in EtOAc (50 mL), washed with saturated aqueous $NaHCO_3$, and brine. The separated organic layer is dried over $MgSO_4$, filtered and concentrated. 3-Ethyl-4-hydroxymethyl-benzonitrile is purified by column chromatography.

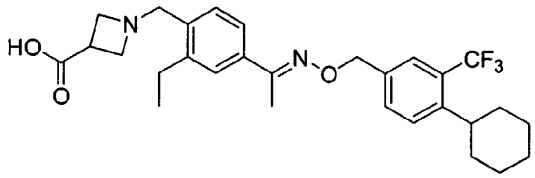
To a solution of 3-ethyl-4-hydroxymethyl-benzonitrile (1.21 mmol) in dry THF under N_2 is added methyl magnesium bromide (3.63 mmol, 3.0 M in diethyl ether). The mixture is heated to reflux overnight. The mixture is cooled, concentrated HCl (10 mL) is added and the mixture is extracted with EtOAc. The combined EtOAc layers are washed with saturated aqueous $NaHCO_3$ and brine. The organic layer is separated, dried over $MgSO_4$, filtered and concentrated. The crude product 1-(3-ethyl-4-hydroxymethyl-phenyl)-ethanone is carried to the next step without further purification.

To a solution of 1-(3-ethyl-4-hydroxymethyl-phenyl)-ethanone (1 eq) in methanol is added *O*-(4-cyclohexyl-3-trifluoromethyl-benzyl)-hydroxylamine (1 eq) followed by the addition of acetic acid (0.05 eq). The mixture is stirred at room temperature for 12 hours. After concentration, the residue is purified by column chromatography (30% EtOAc in hexane) to give 1-(3-ethyl-4-hydroxymethyl-phenyl)-ethanone *O*-(4-cyclohexyl-3-trifluoromethyl-benzyl)-oxime as an oil [MS: (ES^+) 434.2 $(M+1)^+$].

To a suspension of MnO_2 (10 eq) in dioxane is added 1-(3-ethyl-4-hydroxymethyl-phenyl)-ethanone *O*-(4-cyclohexyl-3-trifluoromethyl-benzyl)-oxime (1 eq). The resulting mixture is refluxed for 10 minutes. After filtration and concentration, the residue is dissolved in MeOH and treated with β-alanine (2 eq) and Et_3N (1.5 eq). The resulting mixture is heated at 50^0C for 30 minutes. After cooling to room temperature, $NaBH_4$ (3 eq) is added in portions. Purification by preparative LCMS results in 3-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzylamino}-propionic acid; ^1H NMR (400 MHz, CD_3OD) δ 1.25 (t, 3H), 1.45 (m, 5H), 1.85 (m, 5H), 2.28 (s, 3H), 2.79 (m, 4H), 2.95 (m, 1H), 3.36 (t, 2H), 4.31 (s, 2H), 5.26 (s, 2H) 7.42-7.68 (m, 6H). MS: (ES^+): 505.3 $(M+1)^+$.

Example 3

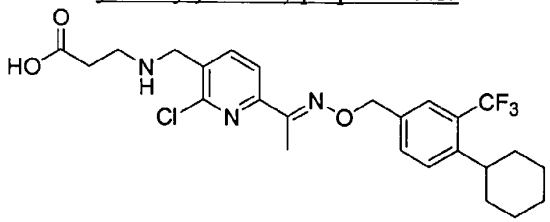
1-{4-[1-(4-Cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid



To a suspension of MnO_2 (10 eq) in dioxane is added 1-(3-ethyl-4-hydroxymethyl-phenyl)-ethanone *O*-(4-cyclohexyl-3-trifluoromethyl-benzyl)-oxime (1 eq). The resulting mixture is refluxed for 10 minutes. After filtration and concentration, the residue is dissolved in MeOH and treated with azetidine-3-carboxylic acid (2 eq) and Et_3N (1.5 eq). The resulting mixture is heated at 50^0C for 30 minutes. After cooling to room temperature, $NaBH_3CN$ (3 eq) is added in portions. Purification by preparative LCMS results in 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid; ^{1}H NMR (400 MHz, CD_3OD) δ 1.24 (t, 3H), 1.30-1.60 (m, 5H), 1.74-1.92 (m, 5H), 2.28 (s, 3H), 2.79 (q, 2H), 2.92 (m, 1H), 3.68 (m, 1H), 4.32 (m, 4H), 4.51 (s, 2H) 5.22 (s, 2H), 7.38 (d, 1H), 7.50-7.68 (m, 5H). MS: (ES^+): 517.3 $(M+1)^+$.

Example 4

3-({2-Chloro-6-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-pyridin-3-ylmethyl}-amino)-propionic acid



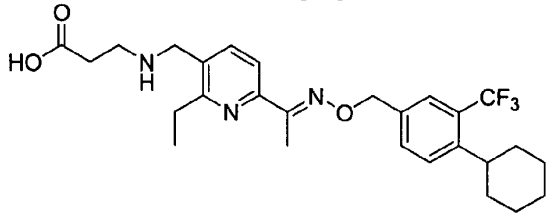
To a solution of 1-(6-chloro-5-methyl-pyridin-2-yl)-ethanone (1 eq) in CCl_4 is added NBS (1 eq) and BPO (0.1 eq). The mixture is refluxed for 12 hours. After concentration, 1-(5-bromomethyl-6-chloro-pyridin-2-yl)-ethanone is isolated by flash column chromatography. MS: (ES^+): 247.9 $(M+1)^+$.

To a solution of 3-amino-propionic acid tert-butyl ester hydrochloride (1.5 eq) in DMF is added NaH (3.5 eq). The resulting mixture is stirred at room temperature for 15 minutes and a solution of 1-(5-bromomethyl-6-chloro-pyridin-2-yl)-ethanone (1 eq) in DMF is then added. After stirring for 3 hours, it is partitioned with 20% EtOAc/hexane and H_2O. The organic layer is washed with brine and dried. After concentration, 3-[(6-acetyl-2-chloro-pyridin-3-ylmethyl)-amino]-propionic acid tert-butyl ester is isolated by flash column chromatography. MS: (ES^+): 313.1 $(M+1)^+$.

To a solution of 3-[(6-acetyl-2-chloro-pyridin-3-ylmethyl)-amino]-propionic acid tert-butyl ester (1 eq) in methanol is added *O*-(4-chloro-3-trifluoromethyl-benzyl)-hydroxylamine (1 eq) followed by the addition of acetic acid (0.05 eq). The mixture is stirred at room temperature for 5 hours. After concentration, the residue is purified by column chromatography to give 3-({2-chloro-6-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-pyridin-3-ylmethyl}-amino)-propionic acid tert-butyl ester. MS: (ES^+) 568.3 $(M+1)^+$. The tert-butyl group is subsequently removed by treatment with TFA/DCM (1/1) at room temperature. The final compound 3-({2-chloro-6-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-pyridin-3-ylmethyl}-amino)-propionic acid is purified by preparative LCMS. ^1H NMR (400 MHz, CD_3OD) δ 1.28-1.60 (m, 5H), 1.71-1.92 (m, 5H), 2.30 (s, 3H), 2.79 (t, 2H), 2.90 (m, 1H), 3.38 (t, 2H), 4.42 (s, 2H), 5.29 (s, 2H), 7.38 (d, 1H), 7.50-7.68 (m, 3H), 7.94 (s, 2H). MS: (ES^+): 512.2 $(M+1)^+$.

Example 5

3-({6-[1-(4-Cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-pyridin-3-ylmethyl}-amino)-propionic acid



A mixture of 3-[(6-acetyl-2-chloro-pyridin-3-ylmethyl)-amino]-propionic acid tert-butyl ester (1 eq), tributyl-vinyltin (1.2 eq), $Pd(PPh_3)_4$ (0.05 eq), and LiCl (3 eq) in dioxane is heated at 100^0C for 12 hours. The reaction mixture is diluted with EtOAc and stirred

together with aqueous KF for 10 minutes. It is then filtered through celite and the organic layer is washed with brine. After concentration, the residue is purified by flash column chromatography to give 3-[(6-cetyl-2-vinyl-pyridin-3-ylmethyl)-amino]-propionic acid tert-butyl ester. MS: (ES^+): 305.2 $(M+1)^+$.

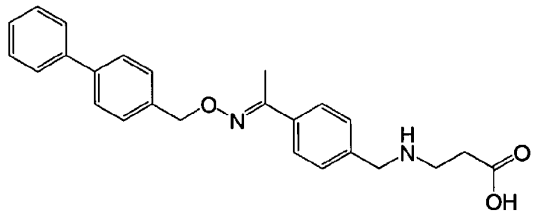
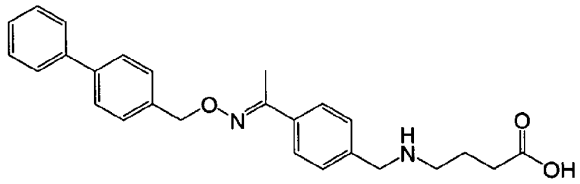
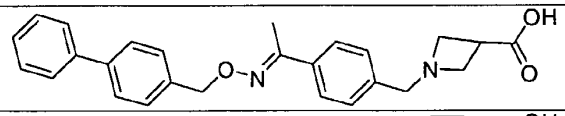
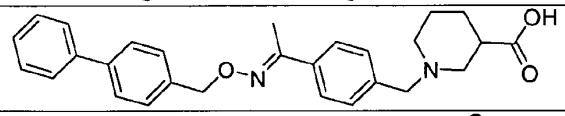
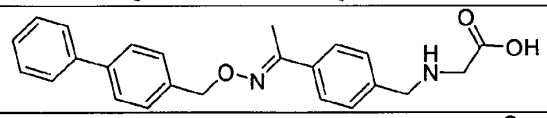
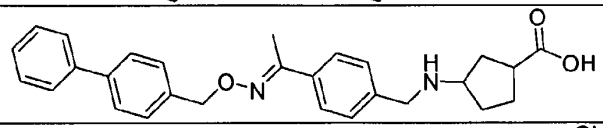
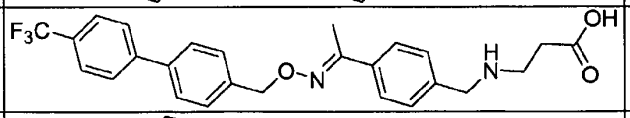
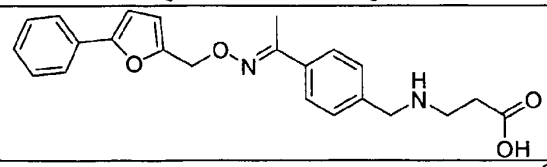
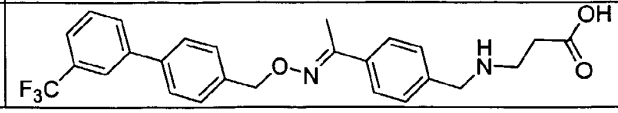
The above compound is dissolved in EtOH and hydrogenated in the presence of 10% Pd-C. After filtration and concentration, the crude product 3-[(6-acetyl-2-ethyl-pyridin-3-ylmethyl)-amino]-propionic acid tert-butyl ester is used directly in the next step without further purification.

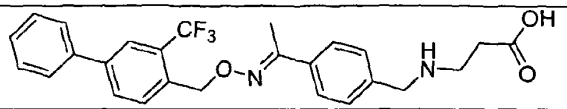
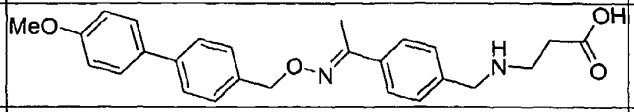
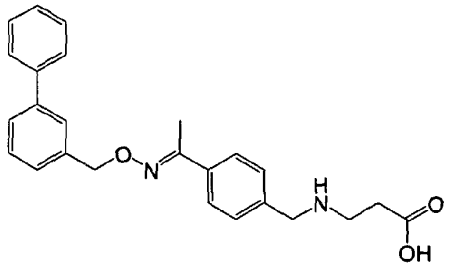
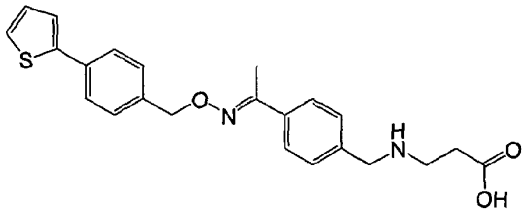
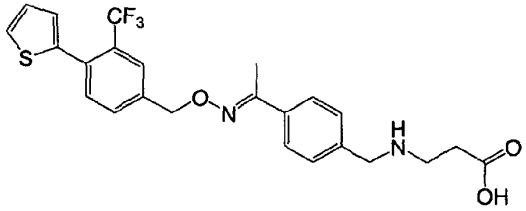
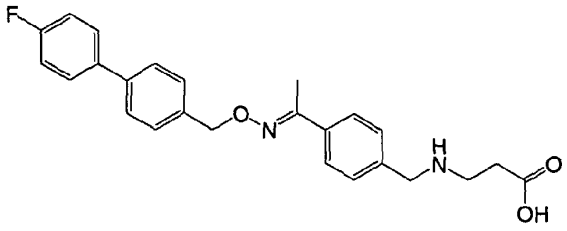
To a solution of 3-[(6-acetyl-2-ethyl-pyridin-3-ylmethyl)-amino]-propionic acid tert-butyl ester (1 eq) in methanol is added *O*-(4-chloro-3-trifluoromethyl-benzyl)-hydroxylamine (1 eq) followed by the addition of acetic acid (0.05 eq). The mixture is stirred at room temperature for 5 hours. After concentration, the residue is purified by column chromatography to give 3-({6-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-pyridin-3-ylmethyl}-amino)-propionic acid tert-butyl ester. MS: (ES^+) 562.3 $(M+1)^+$. The tert-butyl group is subsequently removed by treatment with TFA/DCM (1/1) at room temperature. The final compound 3-({6-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-pyridin-3-ylmethyl}-amino)-propionic acid is purified by preparative LCMS. ^1H NMR (400 MHz, CD_3OD) δ 1.30-1.62 (m, 8H), 1.72-1.91 (m, 5H), 2.36 (s, 3H), 2.78 (t, 2H), 2.94 (m, 3H), 3.37 (t, 2H), 4.42 (s, 2H), 5.29 (s, 2H), 7.51-7.80 (m, 5H). MS: (ES^+): 506.3 $(M+1)^+$.

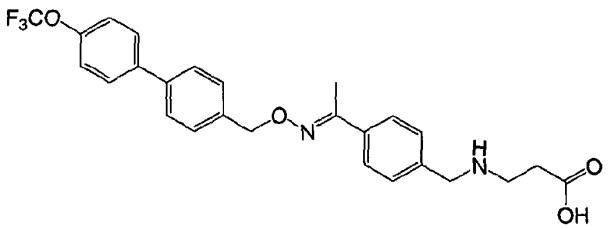
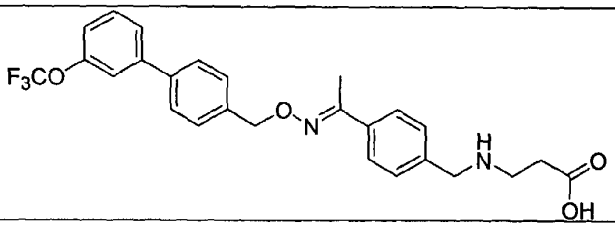
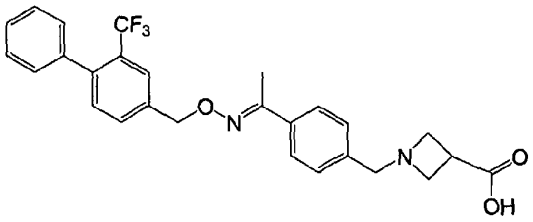
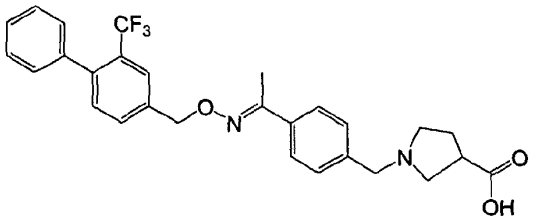
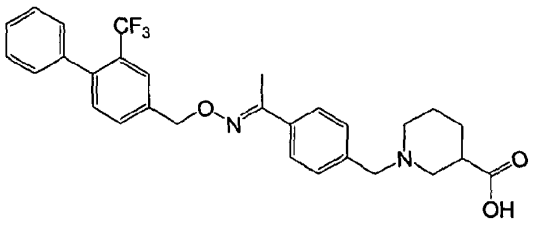
By repeating the procedure described in the above examples, using appropriate starting materials, the following compounds of Formula Ia or Ib can be synthesized (Table 1).

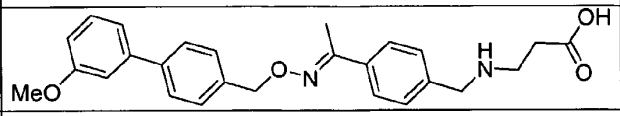
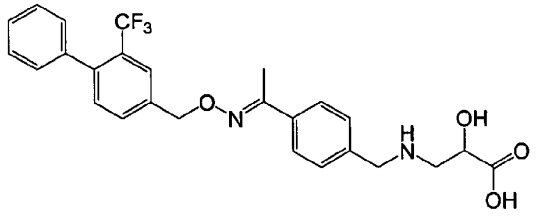
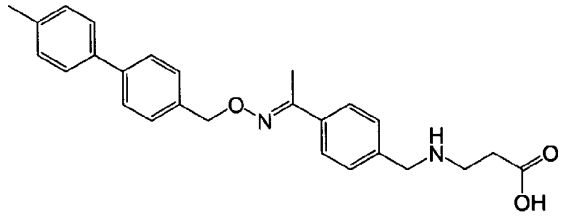
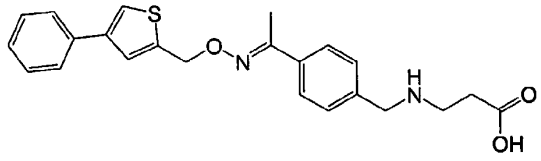
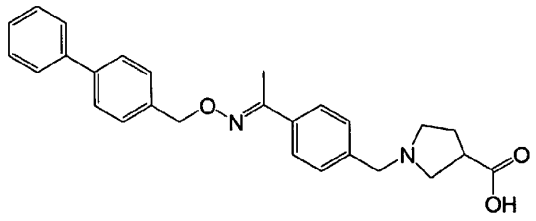
TABLE 1

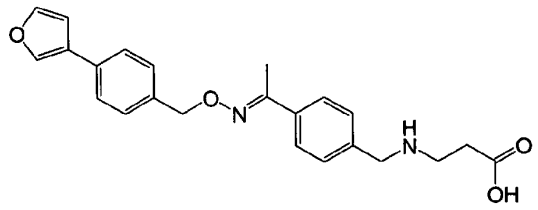
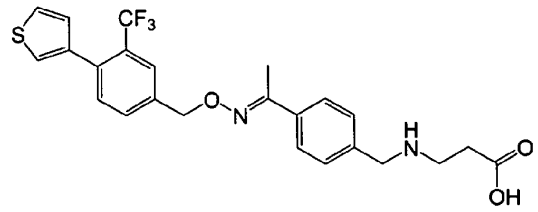
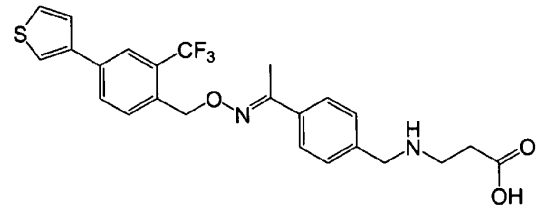
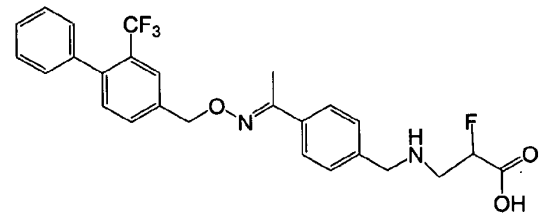
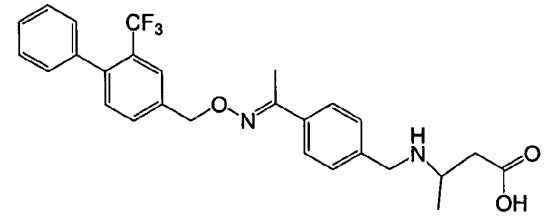
Compound	Structure	Physical Data MS ES (M+1)

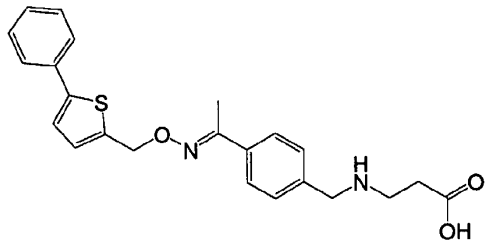
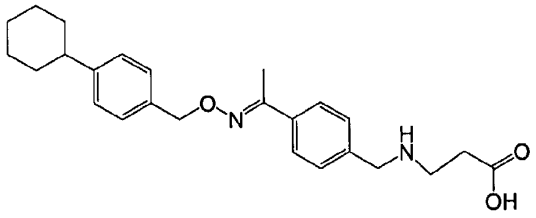
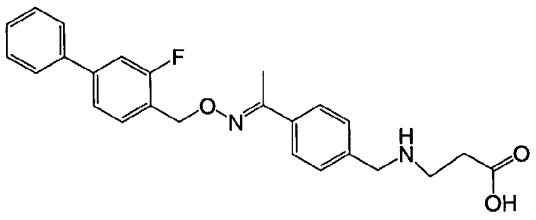
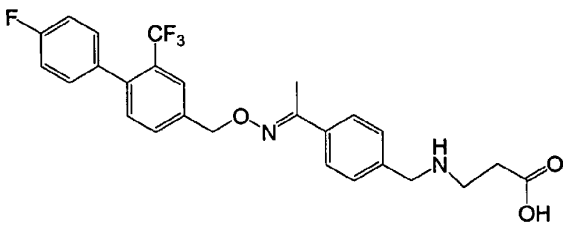
Compound	Structure	Physical Data MS ES (M+1)
6		403.2
7		417.2
8		415.2
9		443.2
10		389.2
11		443.2
12		471.2
13		393.2
14		471.2

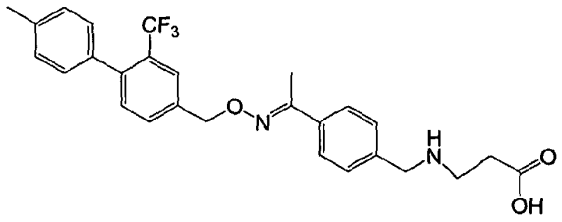
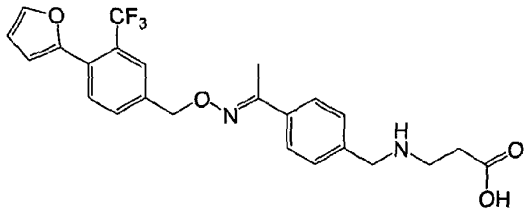
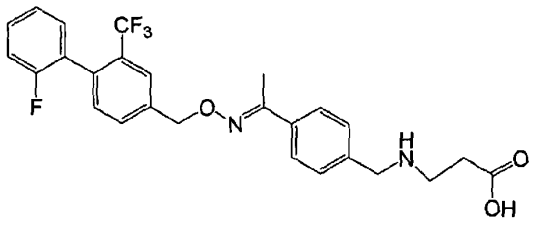
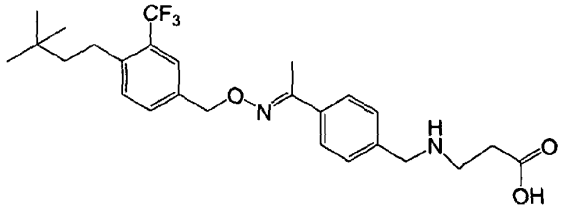
Compound	Structure	Physical Data MS ES (M+1)
15		471.2
16		433.2
17		403.2
18		409.2
19		477.2
20		421.1

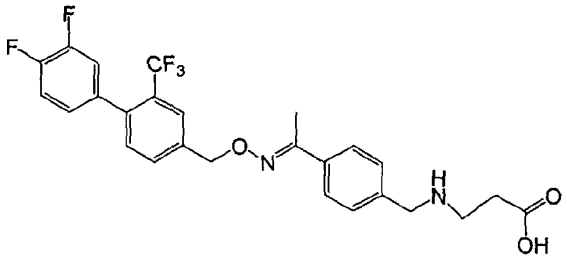
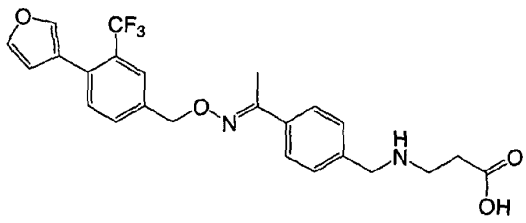
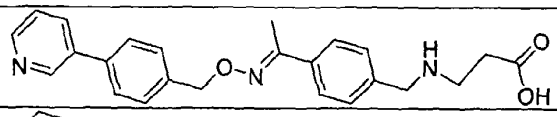
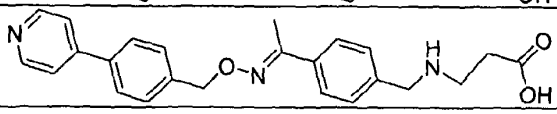
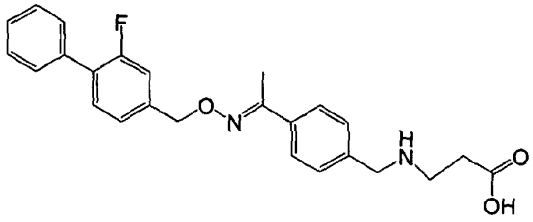
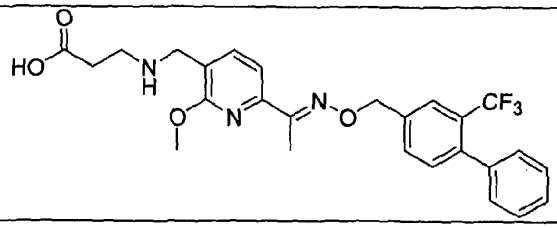
Compound	Structure	Physical Data MS ES (M+1)
21		487.2
22		487.2
23		483.1
24		497.2
25		511.2

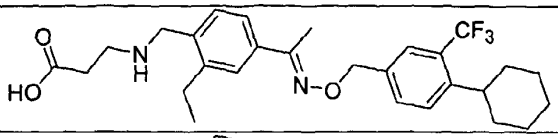
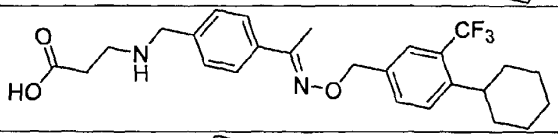
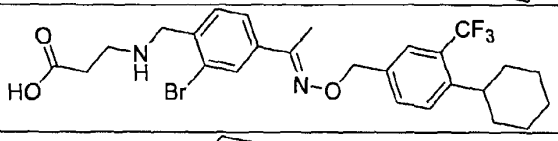
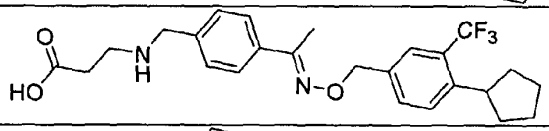
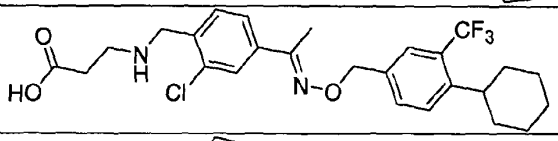
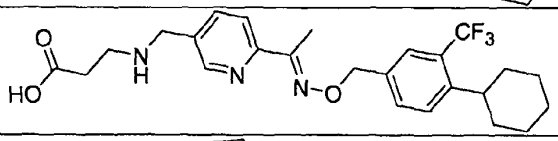
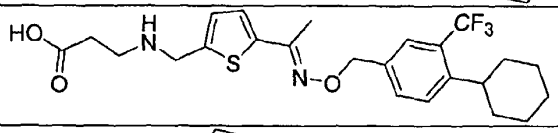
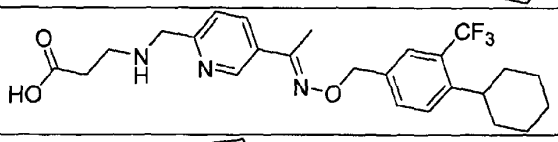
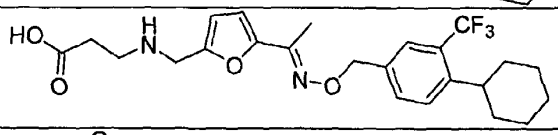
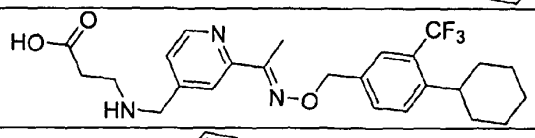
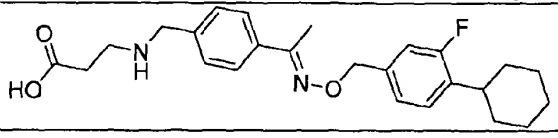
Compound	Structure	Physical Data MS ES (M+1)
26		433.2
27		31.9
28		417.2
29		409.2
30		429.2

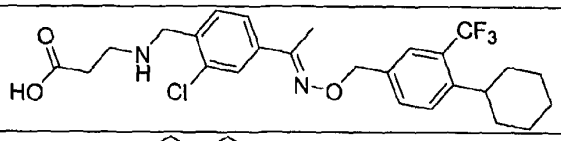
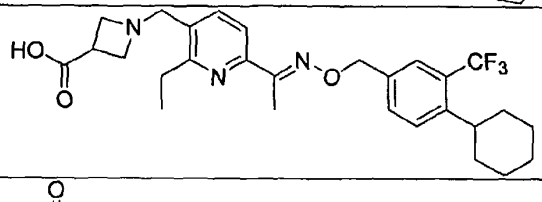
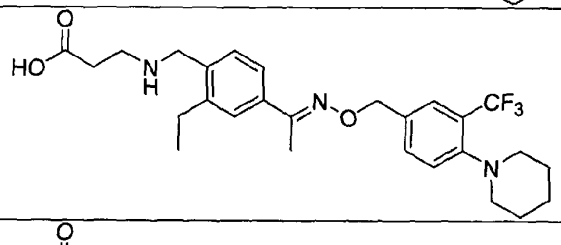
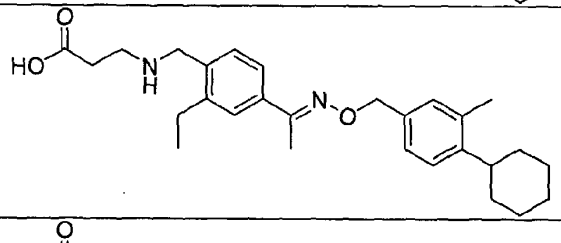
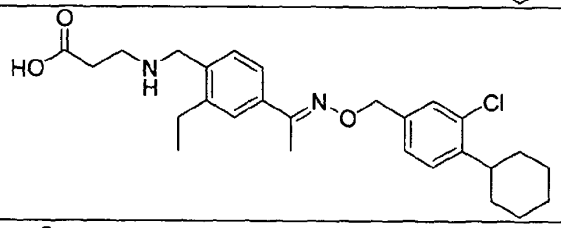
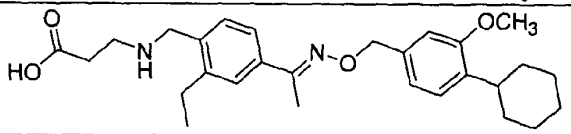
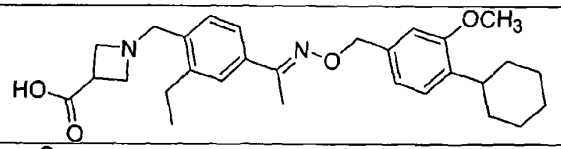
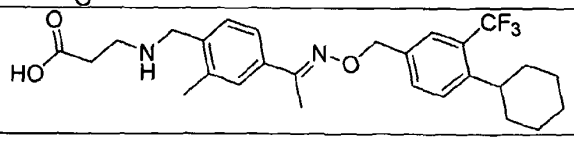
Compound	Structure	Physical Data MS ES (M+1)
31		393.2
32		477.2
33		477.2
34		489.2
35		485.2

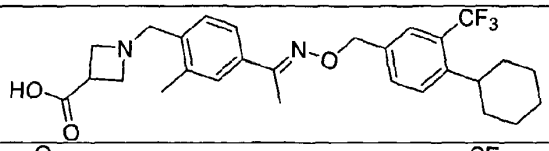
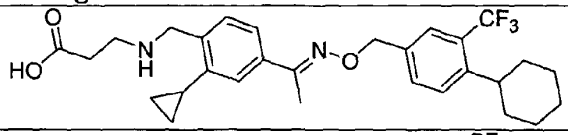
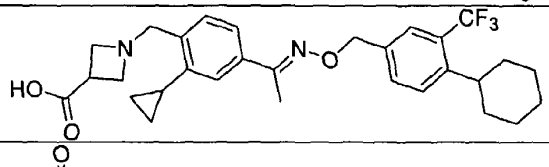
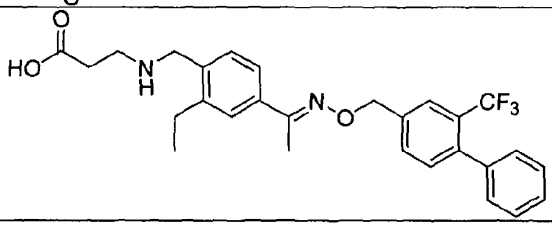
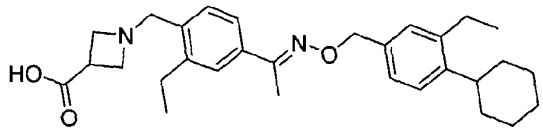
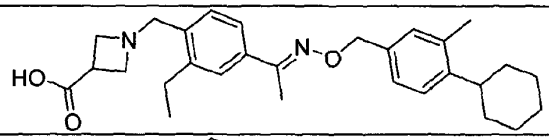
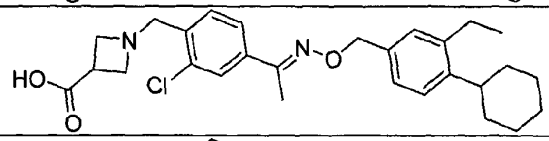
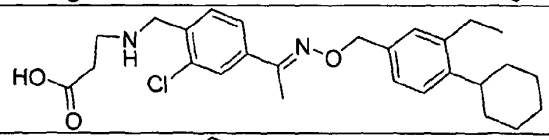
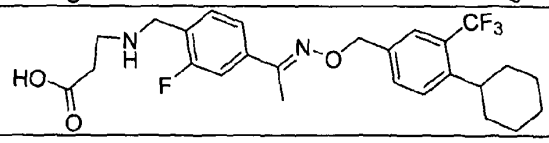
Compound	Structure	Physical Data MS ES (M+1)
36		409.2
37		409.2
38		421.2
39		489.2

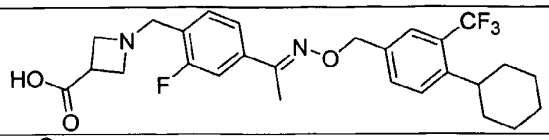
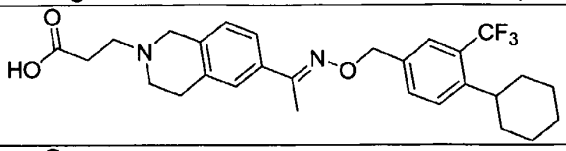
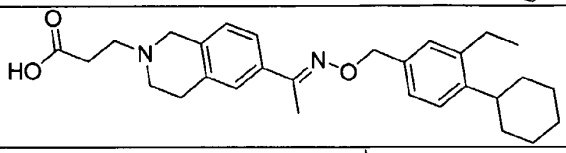
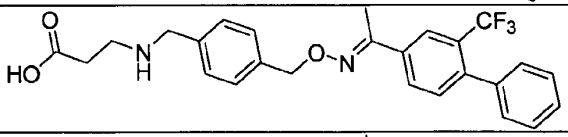
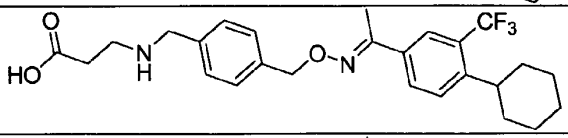
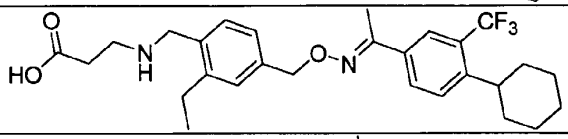
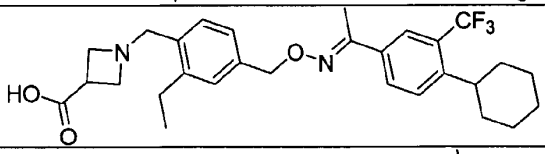
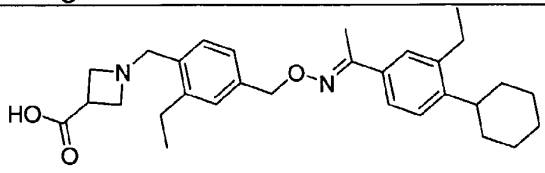
Compound	Structure	Physical Data MS ES (M+1)
40		485.2
41		461.2
42		489.2
43		479.2

Compound	Structure	Physical Data MS ES (M+1)
44		507.2
45		461.2
46		404.2
47		404.2
48		421.2
49		502.2

Compound	Structure	Physical Data MS ES (M+1)
50		505.3
51		477.2
52		555.1
53		463.2
54		511.2
55		478.2
56		483.2
57		478.2
58		467.2
59		478.2
60		427.2

Compound	Structure	Physical Data MS ES (M+1)
61		512.2
62		518.3
63		506.3
64		451.3
65		471.2
66		467.3
67		479.3
68		491.3

Compound	Structure	Physical Data MS ES (M+1)
69		503.2
70		517.3
71		529.3
72		499.2
73		477.3
74		463.3
75		483.2
76		471.2
77		495.2

Compound	Structure	Physical Data MS ES (M+1)
78		507.2
79		503.2
80		463.3
81		
82		
83		
84		
85		

Example 6

Compounds of Formula Ia or Ib Exhibit Biological Activity

A. In vitro: GPCR activation assay measuring GTP [γ-^{35}S] binding to membranes prepared from CHO cells expressing human EDG receptors

EDG-1 ($S1P_1$) GTP [γ-^{35}S] binding assay: Homogenized membranes are prepared from CHO cell clones stably expressing a human EDG-1 N-terminal c-myc tag. Cells are grown in suspension in two 850 cm^2 roller bottles for three or fours days before harvesting. The cells are centrifuged down, washed once with cold PBS, and resuspended in ≤20 ml of Buffer A (20 mM HEPES, pH 7.4, 10 mM EDTA, EDTA-free complete protease inhibitor cocktail [1 tablet/25 ml]). The cell suspension is homogenized on ice, using a Polytron homogenizer at 30000 rpm at three intervals of 15 seconds each. The homogenate is first centrifuged at 2000 rpm on a tabletop low speed centrifuge for 10 minutes. The supernatant, after passing through a cell strainer, is then re-centrifuged at 50,000 x g for 25 minutes at 4°C. The pellet is resuspended into buffer B (15% glycerol, 20 mM HEPES, pH 7.4, 0.1 mM EDTA, EDTA-free complete protease inhibitor cocktail [1 tablet/10 ml]). Protein concentration of the prep is determined using the BCA Protein Assay kit (Pierce) using BSA as standard. The membranes are aliquoted and kept frozen at -80°C.

Solutions of test compounds ranging from 10mM to 0.01nM are prepared in DMSO. S1P is diluted in 4% BSA solution as positive controls. The desired amount of membrane prep is diluted with ice-cold assay buffer (20 mM HEPES, pH 7.4, 100 mM NaCl, 10 mM $MgCl_2$, 0.1% Fatty acid-free BSA, 5 μM GDP) and vortexed well. 2 μl or less of compound is distributed into each well of a round-bottom 96-well polystyrene assay plate, followed by addition of 100 μl of diluted membranes (3-10 μg/well) and kept on ice until the addition of hot GTPγS. [^{35}S]-GTPγS is diluted 1:1000 (v/v) with cold assay buffer and 100 μl is added into each well. The reaction is carried out at room temperature for 90 minutes before the membranes are harvested onto Perkin-Elmer Unifilter® GF/B-96 filter plate using a Packard Filtermate Harvester. After several washes with wash buffer (20 mM HEPES, pH 7.4, 100 mM NaCl, 10 mM $MgCl_2$), and a rinse with 95% ethanol, the filter is dried in a 37°C oven for 30 minutes. MicroScint-20 is added and the plate sealed for scintillation counting on TopCount. EC50 values are obtained by fitting the GTP [γ-^{35}S] binding curves (raw data) with the dose response curve-fitting tool of GraphPad Prism. Six or twelve different concentrations are used to generate a concentration response curve (using three data points per concentration).

EDG-3,-5,-6 and -8 GTP [γ-^{35}S] binding assays are carried out in a comparable manner to the EDG-1 GTP [γ-^{35}S] binding assay using membranes from CHO cells stably expressing c-terminal c-myc tagged or untagged receptors. For each membrane preparation, titration experiments are first run with S1P control to determine the optimal amount of membranes to be added per assay well. Compounds of the invention were tested according to the above assay and were observed to exhibit selectivity for the EDG-1 receptor. For example, 3-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzylamino}-propionic acid (example 2) has an EC_{50} of 0.8 nM in the above assay and is at least 1000 fold selective for EDG-1 compared to one or more of the other receptors including EDG-3, EDG-5, EDG-6 and EDG-8. Similarly, 1-{4-[1-(4-Cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid (example 3) has an EC_{50} of 0.2 nM in the above assay and is at least 1000 fold selective for EDG-1 compared to one or more of the other receptors including EDG-3, EDG-5, EDG-6 and EDG-8.

B. In vitro: FLIPR calcium flux assay

Compounds of the invention are tested for agonist activity on EDG-1, EDG-3, EDG-5, and EDG-6 with a FLIPR calcium flux assay. Briefly, CHO cells expressing an EDG receptor are maintained in F-12K medium (ATCC), containing 5% FBS, with 500ug/ml of G418. Prior to the assay, the cells are plated in 384 black clear bottom plates at the density of 10,000 cells/well/25µl in the medium of F-12K containing 1% FBS. The second day, the cells are washed three times (25 µl/each) with washing buffer. About 25 µl of dye are added to each well and incubated for 1 hour at 37°C and 5% CO_2. The cells are then washed four times with washing buffer (25 µl/each). The calcium flux is assayed after adding 25 µl of SEQ2871 solution to each well of cells. The same assay is performed with cells expressing each of the different EDG receptors. Titration in the FLIPR calcium flux assay is recorded over a 3-minute interval, and quantitated as maximal peak height percentage response relative to EDG-1 activation.

C. In vivo: Screening Assays for measurement of blood lymphocyte depletion and assessment of heart effect

Measurement of circulating lymphocytes: Compounds are dissolved in DMSO and diluted to obtain a final concentration of 4% DMSO (v/v, final concentration) and then further diluted in a constant volume of Tween80 25%/H2O, v/v. Tween80 25%/H2O (200 µl), 4% DMSO, and FTY720 (10µg) are included as negative and positive controls, respectively. Mice (C57bl/6 male, 6-10 week-old) are administered 250-300 µL of compound solution orally by gavages under short isoflurane anesthesia.

Blood is collected from the retro-orbital sinus 6 and 24 hours after drug administration under short isoflurane anesthesia. Whole blood samples are subjected to hematology analysis. Peripheral lymphocyte counts are determined using an automated analyzer. Subpopulations of peripheral blood lymphocytes are stained by fluorochrome-conjugated specific antibodies and analyzed using a fluorescent activating cell sorter (Facscalibur). Two mice are used to assess the lymphocyte depletion activity of each compound screened. The result is an ED_{50}, which is defined as the effective dose required displaying 50 % of blood lymphocyte depletion. Compounds of the invention were tested according to the above assay and were preferably found to exhibit an ED_{50} of less than 1mg/kg, more preferably an ED_{50} of less than 0.5 mg/kg. For example, 3-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzylamino}-propionic acid (example 2) exhibits an ED50 of 0.07 mg/kg. Further, 1-{4-[1-(4-Cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid (example 3) exhibits and ED50 of 0.1 mg/kg.

Assessment of Heart Effect: The effects of compounds on cardiac function are monitored using the AnonyMOUSE ECG screening system. Electrocardiograms are recorded in conscious mice (C57bl/6 male, 6-10 week-old) before and after compound administration. ECG signals are then processed and analyzed using the e-MOUSE software. 90 µg of compound further diluted in 200µl water, 15% DMSO are injected IP. Four mice are used to assess the heart effect of each compound.

D: In vivo: Anti-angiogenic Activity

Porous chambers containing (i) sphingosine-1-phosphate (5 μM/chamber) or (ii) human VEGF (1 μg/chamber) in 0.5 ml of 0.8% w/v agar (containing heparin, 20 U/ml) are implanted subcutaneously in the flank of mice. S1P or VEGF induces the growth of vascularized tissue around the chamber. This response is dose-dependent and can be quantified by measuring the weight and blood content of the tissue. Mice are treated once a day orally or intravenously with a compound of Formula Ia or Ib starting 4-6 hours before implantation of the chambers and continuing for 4 days. The animals are sacrificed for measurement of the vascularized tissues 24 hours after the last dose. The weight and blood content of the vascularized tissues around the chamber is determined. Animals treated with a compound of Formula Ia or Ib show reduced weight and/or blood content of the vascularized tissues compared to animals treated with vehicle alone. Compounds of Formula Ia or Ib are anti-angiogenic when administered at a dose of about 0.3 to about 3mg/kg.

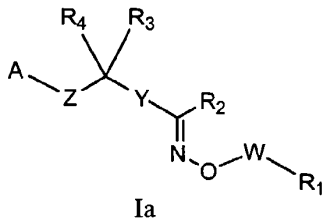
E: In vitro: Antitumor Activity

A mouse breast cancer cell line originally isolated from mammary carcinomas is used, e.g. JygMC(A). The cell number is adjusted to $5x10^5$ for plating in fresh medium before the procedure. Cells are incubated with fresh medium containing 2.5mM of thymidine without FCS for 12 hours and then washed twice with PBS, followed by addition of fresh medium with 10% FCS and additionally incubated for another 12 hours. Thereafter the cells are incubated with fresh medium containing 2.5mM of thymidine without FCS for 12 hours. To release the cells from the block, the cells are washed twice with PBS and replated in fresh medium with 10% FCS. After synchronization, the cells are incubated with or without various concentrations of a compound of Formula Ia or Ib for 3, 6, 9, 12, 18 or 24 hours. The cells are harvested after treatment with 0.2% EDTA, fixed with ice-cold 70% ethanol solution, hydrolyzed with 250μg/ml of RNaseA (type 1-A: Sigma Chem. Co.) at 37°C for 30 minutes and stained with propidium iodide at 10mg/ml for 20 minutes. After the incubation period, the number of cells is determined both by counting cells in a Coulter counter and by the SRB colorimetric assay. Under these conditions compounds of Formula Ia or Ib inhibit the proliferation of the tumor cells at concentrations ranging from 10^{-12} to 10^{-6} M.

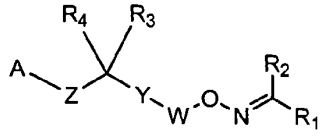
It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and understanding of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference for all purposes.

WE CLAIM

1. A compound selected from Formula Ia and Ib:



Ia



Ib

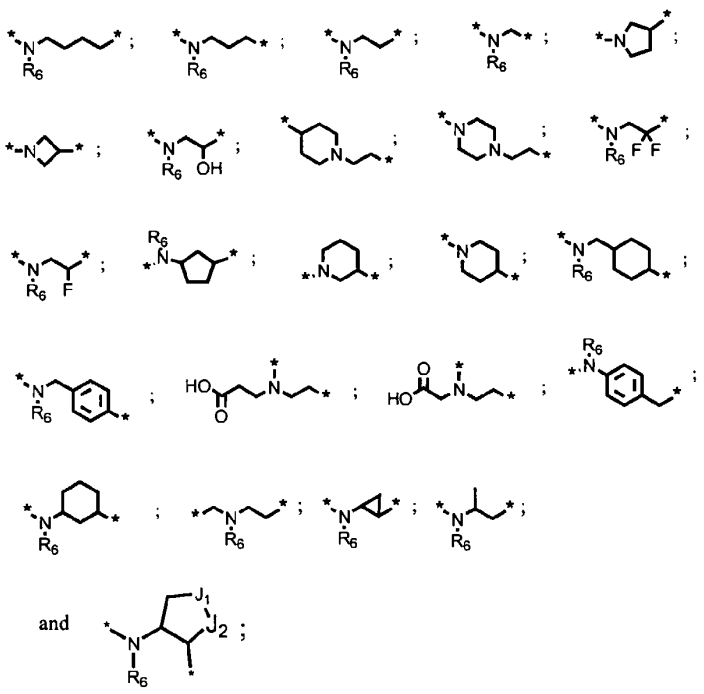
in which:

A is chosen from $-C(O)OR_5$, $-OP(O)(OR_5)_2$, $-P(O)(OR_5)_2$, $-S(O)_2OR_5$, $-P(O)(R_5)OR_5$ and 1*H*-tetrazol-5-yl; wherein each R_5 is independently chosen from hydrogen and C_{1-6}alkyl;

W is chosen from a bond, C_{1-3}alkylene, C_{2-3}alkenylene;

Y is chosen from C_{6-10}aryl and C_{2-9}heteroaryl; wherein any aryl or heteroaryl of Y can be optionally substituted with 1 to 3 radicals chosen from halo, hydroxy, nitro, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted C_{1-6}alkyl and halo-substituted C_{1-6}alkoxy;

Z is chosen from:



wherein the left and right asterisks of Z indicate the point of attachment between –$C(R_3)(R_4)$– and A of Formula Ia or Ib, respectively; R_6 is chosen from hydrogen and C_{1-6}alkyl; and J_1 and J_2 are independently methylene or a heteroatom chosen from S, O and NR_5; wherein R_5 is chosen from hydrogen and C_{1-6}alkyl; and any alkylene of Z can be further substituted by one to three radicals chosen from halo, hydroxy, C_{1-6}alkyl; or R_6 can be attached to a carbon atom of Y to form a 5-7 member ring;

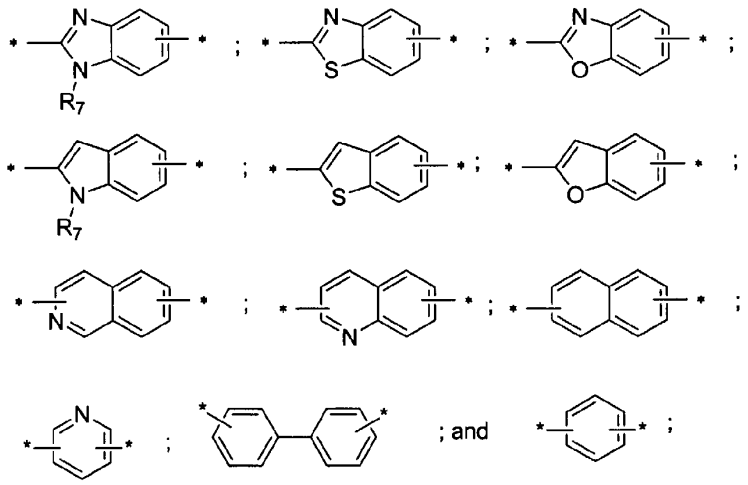
R_1 is chosen from C_{6-10}aryl and C_{2-9}heteroaryl; wherein any aryl or heteroaryl of R_1 is optionally substituted by a radical chosen from C_{6-10}arylC_{0-4}alkyl, C_{2-9}heteroarylC_{0-4}alkyl, C_{3-8}cycloalkylC_{0-4}alkyl, C_{3-8}heterocycloalkylC_{0-4}alkyl or C_{1-6}alkyl; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl group of R_1 can be optionally substituted by one to five radicals chosen from halo, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl and halo-substituted-C_{1-6}alkoxy; and any alkyl group of R_1 can optionally have a methylene replaced by an atom or group chosen from –S–, –S(O)–, –$S(O)_2$–, –NR_5– and –O–; wherein R_5 is chosen from hydrogen or C_{1-6}alkyl;

R_2 is chosen from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl and halo substituted C_{1-6}alkyl;

R_3 and R_4 are independently chosen from hydrogen, C_{1-6}alkyl, halo, hydroxy, C_{1-6}alkoxy, halo-substituted C_{1-6}alkyl and halo-substituted C_{1-6}alkoxy; and the pharmaceutically acceptable salts, hydrates, solvates, isomers and prodrugs thereof.

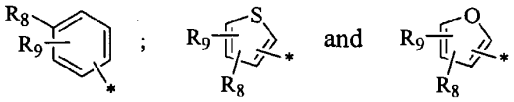
2. The compound of claim 1 in which R_1 is phenyl, naphthyl or thienyl optionally substituted by C_{6-10}arylC_{0-4}alkyl, C_{2-9}heteroarylC_{0-4}alkyl, C_{3-8}cycloalkylC_{0-4}alkyl, C_{3-8}heterocycloalkylC_{0-4}alkyl or C_{1-6}alkyl; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl group of R_1 can be optionally substituted by one to five radicals chosen from halo, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl and halo-substituted-C_{1-6}alkoxy; and any alkyl group of R^1 can optionally have a methylene replaced by an atom or group chosen from –S–, –S(O)–, –S(O)$_2$–, –NR$_5$– and –O–; wherein R_5 is hydrogen or C_{1-6}alkyl.

3. The compound of claim 1 in which Y is chosen from:



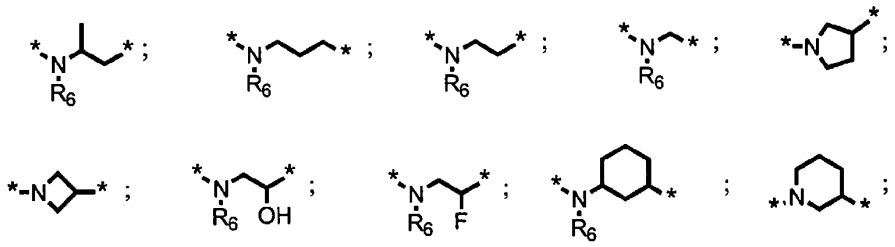
wherein R_7 is hydrogen or C_{1-6}alkyl; and the left and right asterisks of Y indicate the point of attachment a) either between –C(R_2)=NOWR_1 and the –CR_3R_4–, or between –CR_3R_4– and –C(R_2)=NOWR_1 of Formula Ia, respectively, or b) either between –CR_3R_4– and W or between W and –CR_3R_4– of Formula Ib, respectively; wherein any aryl or heteroaryl of Y can be optionally substituted with 1 to 3 radicals chosen from halo, hydroxy, nitro, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted C_{1-6}alkyl and halo-substituted C_{1-6}alkoxy.

4. The compound of claim 1 in which R_1 is chosen from:



wherein the asterisk is the point of attachment of R_1 with W; R_8 is $C_{6-10}arylC_{0-4}alkyl$, $C_{2-9}heteroarylC_{0-4}alkyl$, $C_{3-8}cycloalkylC_{0-4}alkyl$, $C_{3-8}heterocycloalkylC_{0-4}alkyl$ or $C_{1-6}alkyl$; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl group of R_8 can be optionally substituted by one to three radicals chosen from halo, $C_{1-6}alkyl$, $C_{1-6}alkoxy$, halo-substituted-$C_{1-6}alkyl$ and halo-substituted-$C_{1-6}alkoxy$; and any alkyl group of R_8 can optionally have a methylene replaced by an atom or group chosen from –S–, –S(O)–, –$S(O)_2$–, –NR_5– and –O–; wherein R_5 is hydrogen or $C_{1-6}alkyl$; and R_9 is chosen from halo, $C_{1-6}alkyl$, $C_{1-6}alkoxy$, halo-substituted-$C_{1-6}alkyl$ and halo-substituted-$C_{1-6}alkoxy$.

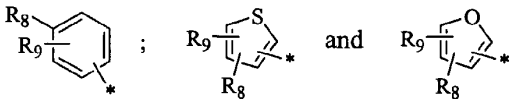
5. The compound of claim 1 in which A is –C(O)OH; Z is chosen from:



wherein the left and right asterisks of Z indicate the point of attachment between –$C(R_3)(R_4)$– and A of Formula Ia or Ib, respectively; R_6 is chosen from hydrogen and $C_{1-6}alkyl$; and R_3 and R_4 are both hydrogen.

6. The compound of claim 5 in which Y is chosen from phenyl, pyridinyl, thienyl and furanyl; wherein any phenyl, pyridinyl, thienyl or furanyl of Y is optionally substituted with 1 to 3 radicals chosen from methyl, ethyl, cyclopropyl, chloro, bromo, fluoro and methoxy; or where Y is phenyl, R_6 can be attached to a carbon atom of Y to form 3,4-dihydro-1H-isoquinolin-2-yl.

7. The compound of claim 6 in which W is a bond or methylene; R_1 is chosen from:



wherein R_8 is chosen from phenyl, cyclohexyl, thienyl, 3,3-dimethyl-butyl, pyridinyl, cyclopentyl and piperidinyl; wherein R_8 can be optionally substituted by 1 to 3 radicals chosen from trifluoromethyl, methoxy, fluoro, triflouromethoxy and methyl; and R_9 is chosen from trifluoromethyl, fluoro, methyl, chloro, methoxy and ethyl.

8. The compound of claim 6 chosen from: 3-{4-[1-(2-Trifluoromethyl-biphenyl-4-ylmethoxyimino)-ethyl]-benzylamino}-propionic acid, 3-{4-[1-(4-Cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzylamino}-propionic acid, 1-{4-[1-(4-Cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, 3-({2-Chloro-6-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-pyridin-3-ylmethyl}-amino)-propionic acid, 3-({6-[1-(4-Cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-pyridin-3-ylmethyl}-amino)-propionic acid, 3-{4-[1-(Biphenyl-4-ylmethoxyimino)-ethyl]-benzylamino}-propionic acid, 4-{4-[1-(Biphenyl-4-ylmethoxyimino)-ethyl]-benzylamino}-butyric acid, 1-{4-[1-(Biphenyl-4-ylmethoxyimino)-ethyl]-benzyl}-azetidine-3-carboxylic acid, 1-{4-[1-(Biphenyl-4-ylmethoxyimino)-ethyl]-benzyl}-piperidine-3-carboxylic acid, {4-[1-(Biphenyl-4-ylmethoxyimino)-ethyl]-benzylamino}-acetic acid, 3-{4-[1-(Biphenyl-4-ylmethoxyimino)-ethyl]-benzylamino}-cyclopentanecarboxylic acid, 3-{4-[1-(4'-Trifluoromethyl-biphenyl-4-ylmethoxyimino)-ethyl]-benzylamino}-propionic acid, 3-{4-[1-(5-Phenyl-furan-2-ylmethoxyimino)-ethyl]-benzylamino}-propionic acid, 3-{4-[1-(3'-Trifluoromethyl-biphenyl-4-ylmethoxyimino)-ethyl]-benzylamino}-propionic acid, 3-{4-[1-(3-Trifluoromethyl-biphenyl-4-ylmethoxyimino)-ethyl]-benzylamino}-propionic acid, 3-{4-[1-(4'-Methoxy-biphenyl-4-ylmethoxyimino)-ethyl]-benzylamino}-propionic acid, 3-{4-[1-(Biphenyl-3-ylmethoxyimino)-ethyl]-benzylamino}-propionic acid, 3-{4-[1-(4-Thiophen-2-yl-benzyloxyimino)-ethyl]-benzylamino}-propionic acid, 3-{4-[1-(4-Thiophen-2-yl-3-

trifluoromethyl-benzyloxyimino)-ethyl]-benzylamino}-propionic acid, 3-{4-[1-(4'-Fluoro-biphenyl-4-ylmethoxyimino)-ethyl]-benzylamino}-propionic acid, 3-{4-[1-(4'-Trifluoromethoxy-biphenyl-4-ylmethoxyimino)-ethyl]-benzylamino}-propionic acid, 3-{4-[1-(3'-Trifluoromethoxy-biphenyl-4-ylmethoxyimino)-ethyl]-benzylamino}-propionic acid, 1-{4-[1-(2-Trifluoromethyl-biphenyl-4-ylmethoxyimino)-ethyl]-benzyl}-azetidine-3-carboxylic acid, 1-{4-[1-(2-Trifluoromethyl-biphenyl-4-ylmethoxyimino)-ethyl]-benzyl}-pyrrolidine-3-carboxylic acid, 1-{4-[1-(2-Trifluoromethyl-biphenyl-4-ylmethoxyimino)-ethyl]-benzyl}-piperidine-3-carboxylic acid, 3-{4-[1-(3'-Methoxy-biphenyl-4-ylmethoxyimino)-ethyl]-benzylamino}-propionic acid, 2-Hydroxy-3-{4-[1-(2-trifluoromethyl-biphenyl-4-ylmethoxyimino)-ethyl]-benzylamino}-propionic acid, 3-{4-[1-(4'-Methyl-biphenyl-4-ylmethoxyimino)-ethyl]-benzylamino}-propionic acid, 3-{4-[1-(4-Phenyl-thiophen-2-ylmethoxyimino)-ethyl]-benzylamino}-propionic acid, 1-{4-[1-(Biphenyl-4-ylmethoxyimino)-ethyl]-benzyl}-pyrrolidine-3-carboxylic acid, 3-{4-[1-(4-Furan-3-yl-benzyloxyimino)-ethyl]-benzylamino}-propionic acid, 3-{4-[1-(4-Thiophen-3-yl-3-trifluoromethyl-benzyloxyimino)-ethyl]-benzylamino}-propionic acid, 3-{4-[1-(4-Thiophen-3-yl-2-trifluoromethyl-benzyloxyimino)-ethyl]-benzylamino}-propionic acid, 2-Fluoro-3-{4-[1-(2-trifluoromethyl-biphenyl-4-ylmethoxyimino)-ethyl]-benzylamino}-propionic acid, 3-{4-[1-(2-Trifluoromethyl-biphenyl-4-ylmethoxyimino)-ethyl]-benzylamino}-butyric acid, 3-{4-[1-(5-Phenyl-thiophen-2-ylmethoxyimino)-ethyl]-benzylamino}-propionic acid, 3-{4-[1-(4-Cyclohexyl-benzyloxyimino)-ethyl]-benzylamino}-propionic acid, 3-{4-[1-(3-Fluoro-biphenyl-4-ylmethoxyimino)-ethyl]-benzylamino}-propionic acid, 3-{4-[1-(4'-Fluoro-2-trifluoromethyl-biphenyl-4-ylmethoxyimino)-ethyl]-benzylamino}-propionic acid, 3-{4-[1-(4'-Methyl-2-trifluoromethyl-biphenyl-4-ylmethoxyimino)-ethyl]-benzylamino}-propionic acid, 3-{4-[1-(4-Furan-2-yl-3-trifluoromethyl-benzyloxyimino)-ethyl]-benzylamino}-propionic acid, 3-{4-[1-(2'-Fluoro-2-trifluoromethyl-biphenyl-4-ylmethoxyimino)-ethyl]-benzylamino}-propionic acid, 3-(4-{1-[4-(3,3-Dimethyl-butyl)-3-trifluoromethyl-benzyloxyimino]-ethyl}-benzylamino)-propionic acid, 3-{4-[1-(4-Furan-3-yl-3-trifluoromethyl-benzyloxyimino)-ethyl]-benzylamino}-propionic acid, 3-{4-[1-(4-Pyridin-3-yl-benzyloxyimino)-ethyl]-benzylamino}-propionic acid, 3-{4-[1-(4-Pyridin-4-yl-benzyloxyimino)-ethyl]-benzylamino}-propionic acid, 3-{4-[1-(2-Fluoro-biphenyl-4-ylmethoxyimino)-ethyl]-

benzylamino}-propionic acid, 3-({2-Methoxy-6-[1-(2-trifluoromethyl-biphenyl-4-ylmethoxyimino)-ethyl]-pyridin-3-ylmethyl}-amino)-propionic acid, 3-{4-[1-(4-Cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzylamino}-propionic acid, 3-{4-[1-(4-Cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-benzylamino}-propionic acid, 3-{2-Bromo-4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-benzylamino}-propionic acid, 3-{4-[1-(4-Cyclopentyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-benzylamino}-propionic acid, 3-{2-Chloro-4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-benzylamino}-propionic acid, 3-({6-[1-(4-Cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-pyridin-3-ylmethyl}-amino)-propionic acid, 3-({5-[1-(4-Cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-thiophen-2-ylmethyl}-amino)-propionic acid, 3-({5-[1-(4-Cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-pyridin-2-ylmethyl}-amino)-propionic acid, 3-({5-[1-(4-Cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-furan-2-ylmethyl}-amino)-propionic acid, 3-({2-[1-(4-Cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-pyridin-4-ylmethyl}-amino)-propionic acid, 3-{4-[1-(4-Cyclohexyl-3-fluoro-benzyloxyimino)-ethyl]-benzylamino}-propionic acid, 3-{2-Chloro-4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-benzylamino}-propionic acid, 1-{6-[1-(4-Cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-pyridin-3-ylmethyl}-azetidine-3-carboxylic acid, 3-{2-Ethyl-4-[1-(4-piperidin-1-yl-3-trifluoromethyl-benzyloxyimino)-ethyl]-benzylamino}-propionic acid, 3-{4-[1-(4-Cyclohexyl-3-methyl-benzyloxyimino)-ethyl]-2-ethyl-benzylamino}-propionic acid, 3-{4-[1-(3-Chloro-4-cyclohexyl-benzyloxyimino)-ethyl]-2-ethyl-benzylamino}-propionic acid, 3-{4-[1-(4-Cyclohexyl-3-methoxy-benzyloxyimino)-ethyl]-2-ethyl-benzylamino}-propionic acid, 1-{4-[1-(4-Cyclohexyl-3-methoxy-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, 3-{4-[1-(4-Cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-methyl-benzylamino}-propionic acid, 1-{4-[1-(4-Cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-methyl-benzyl}-azetidine-3-carboxylic acid, 3-{4-[1-(4-Cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-cyclopropyl-benzylamino}-propionic acid, 1-{4-[1-(4-Cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-cyclopropyl-benzyl}-azetidine-3-carboxylic acid, 3-{2-Ethyl-4-[1-(2-trifluoromethyl-biphenyl-4-ylmethoxyimino)-ethyl]-benzylamino}-propionic acid, 1-{4-[1-(4-Cyclohexyl-3-ethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, 1-{4-[1-(4-

Cyclohexyl-3-methyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, 1-{2-Chloro-4-[1-(4-cyclohexyl-3-ethyl-benzyloxyimino)-ethyl]-benzyl}-azetidine-3-carboxylic acid, 3-{2-Chloro-4-[1-(4-cyclohexyl-3-ethyl-benzyloxyimino)-ethyl]-benzylamino}-propionic acid, 3-{4-[1-(4-Cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-fluoro-benzylamino}-propionic acid, 1-{4-[1-(4-Cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-fluoro-benzyl}-azetidine-3-carboxylic acid, 3-{6-[1-(4-Cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-3,4-dihydro-1H-isoquinolin-2-yl}-propionic acid, 3-{6-[1-(4-Cyclohexyl-3-ethyl-benzyloxyimino)-ethyl]-3,4-dihydro-1H-isoquinolin-2-yl}-propionic acid, 3-{4-[1-(2-Trifluoromethyl-biphenyl-4-yl)-ethylideneaminooxymethyl]-benzylamino}-propionic acid, 3-{4-[1-(4-Cyclohexyl-3-trifluoromethyl-phenyl)-ethylideneaminooxymethyl]-benzylamino}-propionic acid, 3-{4-[1-(4-Cyclohexyl-3-trifluoromethyl-phenyl)-ethylideneaminooxymethyl]-2-ethyl-benzylamino}-propionic acid, 1-{4-[1-(4-Cyclohexyl-3-trifluoromethyl-phenyl)-ethylideneaminooxymethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid and 1-{4-[1-(4-Cyclohexyl-3-ethyl-phenyl)-ethylideneaminooxymethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid.

9. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Claim 1 in combination with a pharmaceutically acceptable excipient.

10. A method for treating a disease in an animal in which alteration of EDG/S1P receptor mediated signal transduction can prevent, inhibit or ameliorate the pathology and/or symptomology of the disease, which method comprises administering to the animal a therapeutically effective amount of a compound of Claim 1.

11. A method for preventing or treating disorders or diseases mediated by lymphocytes, for preventing or treating acute or chronic transplant rejection or T-cell mediated inflammatory or autoimmune diseases, for inhibiting or controlling deregulated angiogenesis, or for preventing or treating diseases mediated by a neo-angiogenesis process or associated with deregulated angiogenesis in a subject comprising administering to the

subject in need thereof an effective amount of a compound of claims1, or a pharmaceutically acceptable salt thereof.

12. The use of a compound of claim 1 in the manufacture of a medicament for treating a disease in an animal in which alteration of EDG/S1P receptor mediated signal transduction contributes to the pathology and/or symptomology of the disease.

Electronic Patent Application Fee Transmittal	
Application Number:	11720205
Filing Date:	25-May-2007
Title of Invention:	DOSAGE REGIMEN OF AN S1P RECEPTOR AGONIST
First Named Inventor/Applicant Name:	John M. Kovarik
Filer:	Karen DeBenedictis/Denise Cooper
Attorney Docket Number:	34053-US-PCT
Filed as Large Entity	

U.S. National Stage under 35 USC 371 Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**180**

Electronic Acknowledgement Receipt	
EFS ID:	11222298
Application Number:	11720205
International Application Number:	
Confirmation Number:	5868
Title of Invention:	DOSAGE REGIMEN OF AN S1P RECEPTOR AGONIST
First Named Inventor/Applicant Name:	John M. Kovarik
Customer Number:	1095
Filer:	Karen DeBenedictis/Denise Cooper
Filer Authorized By:	Karen DeBenedictis
Attorney Docket Number:	34053-US-PCT
Receipt Date:	19-OCT-2011
Filing Date:	25-MAY-2007
Time Stamp:	16:59:36
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$180
RAM confirmation Number	3600
Deposit Account	190134
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		34053_IDS.pdf	278260 ec879355a28c24858f2344f6c7b2342ea43d506e	yes	4
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Transmittal Letter		1	2	
	Information Disclosure Statement (IDS) Form (SB08)		3	4	
Warnings:					
Information:					
2	Foreign Reference	EP1431275.pdf	2323710 e57878eee030b6d327b70f36e0693986f0e2ce8f	no	66
Warnings:					
Information:					
3	Foreign Reference	EP1431284A1.pdf	1311340 9311d8be6c6ca6ef52b5014c2272d186ff3c6c47	no	37
Warnings:					
Information:					
4	Foreign Reference	EP627406A1.pdf	12298139 2f88f38b1dd8d4af611b360d5dee61e10773732f	no	258
Warnings:					
Information:					
5	Foreign Reference	WO04103306_A.pdf	5938402 6d0b6d7b9f9d8898437929946936521 7dee77e1c	no	58
Warnings:					
Information:					
6	Non Patent Literature	Vyshkovski_A.pdf	29267 27e56e806ccbc695edc8da0f8f554570217de69d	no	1
Warnings:					
Information:					
7	Non Patent Literature	Okoto_A.pdf	47802 8a29958ae0f1798b1d27ecfc12a303131a1859da	no	6
Warnings:					
Information:					

8	Non Patent Literature	Mikhailov_A.pdf	23540 9e7f830671580c34f292beca57a41f52c99f5bb9	no	1
Warnings:					
Information:					
9	Fee Worksheet (SB06)	fee-info.pdf	30603 c708a0d437ada82f84b84e75c1c6f8be4d17d39b	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	22281063		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Case PAT034053-US-PCT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE PCT NATIONAL STAGE APPLICATION OF
Kovarik, John M. et al.
INTERNATIONAL APPLICATION NO: PCT/US2005/43044
FILED: November 28, 2005
U.S. APPLICATION NO: 11/720205
35 USC §371 DATE: May 25, 2007
FOR: Dosage Regimen of an S1P Receptor Agonist

Art Unit: 1614
Examiner: Blakely III, Nelson

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT

Sir:

This paper is being filed:

☒ supplemental to the Information Disclosure Statements filed May 25, 2007 and March 15, 2011.

In accordance with 37 C.F.R. §1.56, applicants wish to call the Examiner's attention to the references cited on the attached form(s) PTO/SB/08A/B.

☒ Copies of the references are enclosed herewith.

The Examiner is requested to consider the foregoing information in relation to this application and indicate that each reference was considered by returning a copy of the initialed PTO/SB/08A/B form(s).

Please charge Deposit Account No. 19-0134 in the name of Novartis in the amount of $180 for payment of the fee pursuant to 37 CFR §1.17(p) for the submission of an Information Disclosure Statement under 37 CFR §1.97(c). The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment, to Account No. 19-0134 in the name of Novartis.

Respectfully submitted,

Karen DeBenedictis
Attorney for Applicant
Reg. No. 32,977

Novartis Pharmaceuticals Corporation
One Health Plaza, Bldg. 101
East Hanover, NJ 07936
(862) 778-3785
Date: 10/19/2011

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/720,205	05/25/2007	John M. Kovarik	34053-US-PCT	5868

1095 7590 05/25/2011

NOVARTIS
CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 101/2
EAST HANOVER, NJ 07936-1080

EXAMINER	
BLAKELY III, NELSON CLARENCE	
ART UNIT	PAPER NUMBER
1629	

MAIL DATE	DELIVERY MODE
05/25/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	11/720,205	KOVARIK ET AL.	
	Examiner	Art Unit	
	NELSON BLAKELY III	1629	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 March 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 8-20* is/are pending in the application.

4a) Of the above claim(s) *9-11 and 18-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,8 and 12-17* is/are rejected.

7)☒ Claim(s) *4,8,13 and 14* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *03/15/2011*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application Status

New claims 17-20 are presented. Claims 1-4 and 8-20 of the instant application are pending. Claims 9-11 and 18-20 are withdrawn pursuant to Applicant's Response, filed 03/15/2011. Accordingly, instant claims 1-4, 8 and 12-17 are presented for examination on their merits.

Applicant's Arguments, filed 03/15/2011, have been fully considered. Rejections/objections not reiterated from previous Office Actions are hereby ***withdrawn***. The following rejections/objections are either reiterated or newly applied. They constitute the complete set of rejections/objections presently being applied to the instant application.

Information Disclosure Statement

The Information Disclosure Statement, filed 05/25/2007, is acknowledged and considered. Typographical errors have been corrected on the aforementioned statement.

Applicant's Amendment

Applicant's Amendment, filed 03/15/2011, is acknowledged.

Claim Objections

Claims 4, 8, 13 and 14 are objected to for the following informalities:

With regard to instant claim 4, Applicant is encouraged to replace the recitation "4 to 5 days" with "four to five days" for the accuracy and consistency of the claim language. See, for example, instant claims 1-3.

With regard to instant claim 8, Applicant is required to insert a ". (period)" at the end of the claim.

With regard to instant claim 13, Applicant is encouraged to insert a ", (comma)" after the claim number, e.g., "The method of claim 1, ...," in line 1. Further, Applicant is encouraged to insert a ", (comma)" and space after the recitation "2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol," in lines 2 and 3.

With regard to instant claim 14, it is noted that the recitation "2-5, 5-10, 10-15 and 15-20 mg, respectively, during the initial period of four days" is added to the claim in the instant amendment; however, the aforementioned recitation is not underlined. Amendments should be indicated as such to avoid new matter issues.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation "the daily dosage" in line 5. There is insufficient antecedent basis for this limitation in the claim.

Claim 15 recites the limitation "0.1-0.5 mg" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 17 is rejected under 35 U.S.C. 112, fourth paragraph, as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claims, or amend the claims to place the claims in proper dependent form, or rewrite the claims in independent form. Instant claim 8, from which instant claim 17 depends, is amended to recite “wherein the loading regimen is administered during the initial three to six days in a dosage that is increased stepwise up to a dosage that is 3- to 21-fold relative to the standard daily dosage of said S1P receptor modulator or agonist,” and instant claim 17 recites “during the loading regimen, the dosage of said S1P receptor modulator or agonist is increased incrementally up to a dosage that is 3- to 21-fold relative to the standard daily dosage of the S1P receptor modulator or agonist.” Instant claim 17 does not further limit the subject matter of instant claim 8.

Response to Arguments

Applicant's Arguments, with respect to claims 1-4, 8 and 12-16, have been considered, but are moot in view of the new grounds of rejection.

Claim Rejections - 35 USC § 103 (New Grounds of Rejection)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4, 8 and 12-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fujii *et al.* (U.S. Patent No. 6,197,829B1), in view of Brinkmann *et al.* (The Journal of Biological Chemistry, Vol. 277, No. 24, Issue of June 14, pages 21453-

21457; 2002), Quesniaux *et al.* (Transplant Immunology, Vol. 7, pages 149-157; 1999) and Chiba *et al.* (U.S. Patent Application Publication No. 2002/0102279A1; cited in a previous Office Action).

With regard to instant claims 1-4, 8 and 12-17, Fujii *et al.* disclose, in reference claim 2, a method for treating a disease or disorder selected from autoimmune diseases, e.g., multiple sclerosis (See column 7, lines 59-62), in a subject comprising administering a therapeutically effective amount of a composition of 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol (or FTY720) or a pharmaceutically acceptable acid addition salt thereof. In column 1, lines 26-29, Fujii *et al.* disclose wherein the route of administration may be oral. Further, in column 2, lines 27-35, Fujii *et al.* disclose wherein the amount of the compound of the reference invention may be mixed with a carrier, and may vary depending on the host to be treated, and a specified dosage form. The dose of the specified patient should be determined depending on the various factors such as age, body weight, the whole condition of health, sex, meal, time for administration, administration route, rate of excretion, combination of drug and the severity of the specified diseases under treatment.

It is noted wherein Fujii *et al.* disclose a list of autoimmune diseases, in addition to multiple sclerosis, in column 7, lines 59-66. However, Brinkmann *et al.* disclose, in the Introduction, page 21453, first paragraph, left column, wherein FTY720 is efficacious in a variety of transplant and autoimmune models without inducing a generalized immunosuppressed state and is effective in kidney transplantation. In the instant excerpt, Brinkmann *et al.* further disclose wherein FTY720 is phosphorylated by

sphingosine kinase, and wherein the phosphorylated compound is a potent agonist at four sphingosine-1-phosphage (S1P) receptors and represents the therapeutic principle in a rodent model of multiple sclerosis. On page 21453, in the paragraph bridging columns 1 and 2, Brinkmann *et al.* disclose wherein FTY720 does not inhibit T cell activation and proliferation and in rodent models does not impair immunity to systemic viral infection. Brinkmann *et al.* disclose, in the last paragraph, page 21457, wherein FTY720 is the first in a class of new immune system modulators that may allow both better management of allograft recipients and more effective treatment of patients with autoimmune disorders, which is a substantially unmet medical need. In the instant excerpt, Brinkmann *et al.* further disclose wherein the activity of FTY720 in models of autoimmune disorders such as EAE (experimental autoimmune encephalomyelitis), a model of human multiple sclerosis, is very encouraging. See instant claims 12, 13 and 16.

Fujii *et al.* fail to disclose specifically wherein a steady-state of the S1P receptor modulator or agonist blood levels is attained in the subject in less than a week (instant claims 1 and 2), wherein the dosage of said S1P receptor or agonist during the initial three to six days of treatment is increased stepwise up to a dosage that is 3- to 21-fold relative to the standard daily dosage of said S1P receptor agonist (instant claims 1-4, 8 and 17), wherein thereafter the treatment is continued at a dosage lower than the standard daily dosage (instant claims 2 and 8), or wherein the dosage is 2-5, 5-10, 10-15 and 15-20 mg, respectively during the initial period of four days (instant claim 14) or 0.1-0.5 mg (instant claim 15). However, Quesniaux *et al.* disclose, in the abstract,

wherein FTY720 was administered orally to Chacma baboons at 0.3 or 0.1 mg/kg/day for 3 days or at 0.03 mg/kg/day for 10 days. In the instant excerpt, Quesniaux *et al*. further disclose wherein the pharmacokinetic and pharmacodynamic profiles of FTY720 in baboons suggest the use of high induction doses to optimize immediate response followed by a reduced dose regimen for drug maintenance. On page 154, right column, first full paragraph, Quesniaux *et al*. disclose wherein the concentrations of FTY720 stabilized on days 7-9 for low dose FTY720 0.03 mg/kg/day administration. Further, it is not inventive to discover the optimum ranges or regimens by routine experimentation when general conditions of a claim are disclosed in the prior art. See *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) and MPEP §2144.05(II). As recited *supra*, Quesniaux *et al*. disclose the administration of 0.3 or 0.1 mg/kg/day for 3 days or at 0.03 mg/kg/day for 10 days. It is noted wherein 0.3 mg/kg/day is three times (or 3-fold) 0.1 mg/kg/day, and ten times (10-fold) 0.03 mg/kg/day. Additionally, in the abstract, Quesniaux *et al*. disclose "the use of high induction doses to optimize immediate response followed by a reduced dose regimen for drug maintenance." One of ordinary skill in the art, at the time of the invention, would have construed wherein the use of high induction dose<u>s</u> (plural) to optimize immediate response would reasonably encompass the instantly claimed stepwise administration. Even further, a skilled artisan would have conceived varying the dosage amounts to yield stabilized concentrations, as disclosed by Quesniaux *et al*., prior to days 7-9, or less than a week, as instantly claimed. Therefore, the determination of the optimum characterization of the dosage

amounts would have been a matter well within the purview of one of ordinary skill in the art, at the time of the invention, through no more than routine experimentation.

Fujii *et al*. fail to disclose wherein the dosage is 2-5, 5-10, 10-15 and 15-20 mg, respectively during the initial period of four days (instant claim 14). However, in view of the use of high induction doses to optimize an immediate response, as disclosed by Quesniaux *et al*., Chiba *et al*. disclose, in reference claims 1-5, 8 and 9, page 14, a method of suppressing the immune response in a mammal comprising accelerating lymphocyte homing (ALH) to any of the mesenteric or peripheral lymph tissues, for example, by administering an ALH-immunosuppressive compound or composition, wherein the compound or composition comprises 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol hydrochloride (FTY720). In the instant excerpt, Chiba *et al*. disclose wherein the therapeutic treatment comprises the treatment of an autoimmune disease, e.g., multiple sclerosis. In paragraph **[0051]**, page 5, Chiba *et al*. disclose that while the dose of the compound used in the composition varies depending on the disease, symptom, body weight, sex, age, and so on, it may be administered to an adult daily by 0.01-10 mg in a single dose, or in several divided doses.

Therefore, a skilled artisan would have envisaged the instantly claimed method for treating an autoimmune disease, e.g., multiple sclerosis, in a subject in need thereof, comprising administering to the subject a S1P receptor modulator or agonist, e.g., FTY720, as disclosed by Fujii *et al*. and Brinkmann *et al*., wherein the dosage amounts and regimen are modified to achieve a desired pharmacological response, as disclosed by Quesniaux *et al*. and Chiba *et al*. One of ordinary skill in the art would have been

motivated to combine the teachings of the aforementioned references when seeking a method of treating multiple sclerosis a dose-dependent manner, which provides for sustained treatment, as well as decreased instances of viral infection due to an impaired immune system. It would have been obvious to one of ordinary skill in the art, at the time of the invention, because the combined teachings of the prior art are suggestive of the claimed invention.

Accordingly, the instant invention, as claimed in claims 1-4, 8 and 12-17, is *prima facie* obvious over the combination of the aforementioned teachings.

Unexpected Results

On page 8 of Applicant's Remarks, filed 03/15/2011, Applicant alleges that there is an unexpected advantage to having patients attain a steady state blood level earlier because it is known that the first administration of FTY720 may induce a negative effect on the heart rate. Further, Applicant alleges that, advantageously, when patients are at steady state, they can restart treatment with FTY720 after a 1-2 week period without any negative effect on heart rate. However, a review of the specification, specifically, pages 18 and 19, recites procedures, e.g., loading regimen, but fails to provide data to support the allegation of unexpected results. Allegations without factual support are insufficient to support a finding of non-obviousness. Accordingly, the instant claims are rejected as set forth *supra*.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to NELSON BLAKELY III whose telephone number is (571)270-3290. The Examiner can normally be reached on Mon - Thurs, 7:00 am - 5:30 pm (EST).

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Jeffrey S. Lundgren can be reached on (571) 272-5541. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Phyllis G. Spivack/
Primary Examiner, Art Unit 1629
May 22, 2011

/N. B. III/
Examiner, Art Unit 1629

Notice of References Cited	Application/Control No. 11/720,205	Applicant(s)/Patent Under Reexamination KOVARIK ET AL.	
	Examiner NELSON BLAKELY III	Art Unit 1629	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-6,197,829	03-2001	Fujii et al.	514/653
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Brinkmann et al. (The Journal of Biological Chemistry, Vol. 277, No. 24, Issue of June 14, pages 21453-21457; 2002).
	V	Quesniaux et al. (Transplant Immunology, Vol. 7, pages 149-157; 1999).
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11720205	KOVARIK ET AL.
	Examiner	Art Unit
	NELSON C BLAKELY III	1629

SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
EAST Database Search	09/10/2010	NCB III
NPL	09/10/2010	NCB III
PALM Inventor Search	09/10/2010	NCB III
STN Database Search	09/10/2010	NCB III
Updated EAST Database Search	03/15/2011	NCB III
NPL	03/15/2011	NCB III
Updated PALM Inventor Search	03/15/2011	NCB III
Updated STN Database Search	03/15/2011	NCB III

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

/NELSON C BLAKELY III/ Examiner.Art Unit 1629	

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S1	0	("2003003099").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2010/01/20 16:07
S2	1	("20030003099").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2010/01/20 16:07
S3	1	("20050070506").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2010/09/10 13:56
S4	702	fty720	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2010/09/10 14:52
S5	437	S4 AND "multiple sclerosis"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2010/09/10 14:52
S6	0	S4 AND "multiple sclerosis"".CLM"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2010/09/10 14:52
S7	120	S4 AND "multiple sclerosis".CLM.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2010/09/10 14:53
S8	23	S7 AND FTY720.CLM.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2010/09/10 14:53
S9	5	((JOHN) NEAR2 (KOVARIK)).INV.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2010/09/10 15:04

S10	3	((SILKE) NEAR2 (APPEL)).INV.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2010/09/10 15:04
S11	3	((SILKE) NEAR2 (DINGEMANSE)).INV.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2010/09/10 15:05
S12	0	S10 NOT S9	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2010/09/10 15:05
S13	3	(("6197829") or ("6277888") or ("6476004")).PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2011/05/18 11:05
S14	9	((JOHN) NEAR2 (KOVARIK)).INV.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2011/05/18 11:20
S15	3	((SILKE) NEAR2 (APPEL)).INV.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2011/05/18 11:20
S16	2	(("5952316") or ("5604229")).PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2011/05/18 11:24
S17	1	("20020102279").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2011/05/18 14:10
S18	615	("fty720" fingolimod) AND "multiple sclerosis"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2011/05/18 14:56
S19	182	S18 AND "multiple sclerosis".CLM.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2011/05/18 14:56

S20	28	("fty720" fingolimod). CLM. AND "multiple sclerosis".CLM.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2011/05/18 14:57
S21	1	("6197829").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2011/05/19 11:30
S22	1	("6476004").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2011/05/19 12:00

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Receipt date: 03/15/2011

PTO/SB/08a (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 4

Complete if Known	
Application Number	11/720205
Filing Date	November 28, 2005
First Named Inventor	Kovarik, John M. et al.
Art unit	~~1614~~ 1629
Examiner Name	Blakely III, Nelson
Attorney Docket Number	PAT034053-US-PCT

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		US-6197829	03-06-2001	Tsuneo Fujii et al.	
		US-6277888 B1	08-21-2001	Atsushi Sakai et al	
		US-6476004 B1	11-05-2002	Atsushi Sakai et al	
		US-			
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FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
		WO 03/061567	07-31-~~2003~~ 2003	Merck & Co.		☐
		WO 03/062252	07-31-2003	Merck & Co.		☐
		WO 02/100148	12-19-2002	Novartis AG et al		☐
						☐
						☐
						☐

Examiner Signature	/Nelson Blakely III/	Date Considered	05/18/2011

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw a line through citation if not in conformance and not considered. Include copy of this form with the next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kind Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /N.B./

0454

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE PCT NATIONAL STAGE APPLICATION OF
Kovarik, John M. et al.

Art Unit: 1614
Examiner: Blakely III, Nelson
Conf. No.: 5868

INTERNATIONAL APPLICATION NO: PCT/US2005/43044
FILED: November 28, 2005
U.S. APPLICATION NO: 11/720205
35 USC §371 DATE: May 25, 2007
FOR: Dosage Regimen of an S1P Receptor Agonist

MS: Amendment
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

AMENDMENT

Sir:

This Amendment is being submitted in response to the Office Action in the above application that was mailed to Applicants' attorney on September 15, 2010 (the "Office Action"). Accompanying this Amendment is a Petition for Extension of Time, requesting that the allowable period for responding to the Office Action be extended by 3 months, so that it does not expire until March 15, 2011.

Amendments to the Claims are reflected in the listing of the claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 6 of this paper.

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

Claim 1. (Currently amended) A method for inhibiting graft rejection or treating an inflammatory or autoimmune disease or disorder in a subject in need thereof, comprising administering to the subject a S1P receptor modulator or agonist in such a pharmaceutically effective amount that a steady-state of the S1P receptor modulator or agonist blood levels is attained in the subject in less than a week~~:~~, wherein the daily dosage of said S1P receptor modulator or agonist during the initial three to six days of treatment is increased stepwise up to a dosage that is 3- to 21-fold relative to the standard daily dosage of said S1P receptor modulator or agonist.

Claim 2. (Currently amended) A method for inhibiting graft rejection or treating an inflammatory or autoimmune disease or disorder in a subject in need thereof, comprising administering to the subject an S1P receptor modulator or agonist in such a pharmaceutically effective amount that a steady-state of the S1P receptor modulator or agonist blood levels is attained in less than a week, and thereafter the treatment is continued at a dosage lower than the standard daily dosage, wherein the daily dosage of said S1P receptor modulator or agonist during the initial three to six days of treatment is increased stepwise up to a dosage that is 3- to 21-fold relative to the standard daily dosage of said S1P receptor modulator or agonist.

Claim 3. (Currently amended) The method of claim 1, ~~wherein the S1P receptor modulator or agonist is administered in a pharmaceutically effective amount such that a steady-state of the S1P receptor modulator or agonist blood levels is attained in the subject in a period of from 3 three to 6 six days, and~~ wherein the daily dosage of said ~~S1 P~~ S1P receptor modulator or agonist during the initial ~~3~~ three to ~~6~~ six days of treatment is increased stepwise up to ~~the 3- to 21-fold~~ a dosage that is 4- to 12-fold relative to the standard daily dosage of said S1P receptor agonist.

Claim 4. (Currently amended) The method of claim 1, wherein the initial period during which the daily dosage of said S1P receptor modulator or agonist is increased stepwise is ~~S1P receptor modulator or agonist is administered in a pharmaceutically effective amount such that a steady-state of the S1P receptor modulator or agonist blood levels is attained in the subject in~~ a period of from 4 to 5 days.

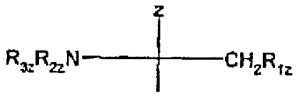
Claim 5 - 7. (Cancelled)

Claim 8. (Currently amended) A method for inhibiting graft rejection or treating an inflammatory or autoimmune disease in a subject in need thereof, comprising administering to the subject, after a loading regimen, a S1P receptor modulator or agonist at a daily dosage which is lower than the standard daily dosage~~.~~, wherein the loading regimen is administered during the initial three to six days in a dosage that is increased stepwise up to a dosage that is 3- to 21-fold relative to the standard daily dosage of said S1P receptor modulator or agonist

Claim 9. (Previously presented) A kit containing daily units of medication of an S1P receptor modulator or agonist of varying daily dosage, whereby the daily dosage of said S1P receptor modulator or agonist for the initial 3 to 6 days of treatment is incrementally increased so that the total amount present in the daily units corresponds to the R-fold standard daily dosage of said S1P receptor modulator or agonist for this initial time period.

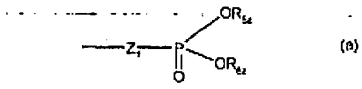
Claim 10. (Previously presented) A kit containing daily units of medication of an S1P receptor modulator or agonist of varying daily dosage, whereby the daily dosage of S1P receptor modulator or agonist for the initial 4 days of treatment is ¼; ½; and ¾ of the highest installment dose of the S1P receptor modulator or agonist; and 4x the maintenance dose of the S1P receptor modulator or agonist, respectively.

Claim 11. (Currently amended) The method of claim 1, wherein the S1P receptor modulator or agonist comprises a group of formula X



(X)

wherein Z is H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, phenyl, phenyl substituted by OH, C_{1-6} alkyl substituted by 1 to 3 substituents selected from the group consisting of halogen, C_{3-8} cycloalkyl, phenyl and phenyl substituted by OH, or CH_2-R_{4Z} wherein R_{4Z} is OH, acyloxy or a residue of formula (a)



(a)

wherein Z_1 is a direct bond or O, preferably O; each of R_{5Z} and R_{6Z}, independently, is H, or C_{1-4}alkyl optionally substituted by 1, 2 or 3 halogen atoms;
R_{1Z} is OH, acyloxy or a residue of formula (a); and each of R_{2Z} and R_{3Z} independently, is H, C_{1-4}alkyl or acyl; in free form or the isomers, phosphates~~, prodrugs~~ or pharmaceutically acceptable salts thereof.

Claim 12. (Currently amended) The method of claim 1, ~~[[13]]~~ wherein the S1P receptor modulator or agonist is 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol, 2-amino-2-[4-(3-benzyloxyphenoxy)-2-chlorophenyl]ethyl-1,3-propane-diol, 2-amino-2-[4-(benzyloxyphenylthio)-2-chlorophenyl]ethyl-1,3-propane-diol or 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, in free form or the isomers, phosphates~~,~~ ~~prodrugs~~ or pharmaceutically acceptable salts thereof.

Claim 13. (Currently amended) The method of claim 1 wherein the S1P receptor modulator or agonist is 2-amino-2-tetradecyl-1,3-propanediol, 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol2-amino-2-{2-[4-(1-oxo-5-phenylpentyl)phenyl]ethyl}propane-1,3-diol, 2-amino-4-(4-heptyloxyphenyl)-2-methyl-butanol, phosphoric acid mono-[(R)-2~amino-2-methyl-4-(4-pentyloxy-phenyl)-butyl]ester, (2R)~2-amino-~~4~~-[3-(4-cyclohexyloxybutyl)- benzo[b]thien-6-yl]-2-methylbutan-1-ol, 1-{~~4~~-[1-(4-cyclohexyl-3-trifluoromethyl- benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, in free form or the isomers, phosphates~~, prodrugs~~ or pharmaceutically acceptable salts thereof.

Claim 14. (Currently amended) The method of claim 1, wherein the S1P receptor modulator or agonist is 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol or a pharmaceutically acceptable salt thereof, and the dosage is ~~from 0.1 – 20 mg~~ 2 – 5, 5 – 10, 10 – 15 and 15 – 20 mg, respectively, during the initial period of four days.

Claim 15. (Currently amended) The method of claim ~~1~~ 14, wherein said ~~the~~ dosage is from 0.1 - 0.5 mg.

Claim 16. (Previously presented) The method of claim 1, wherein the autoimmune disease is selected from the group consisting of multiple sclerosis, lupus nephritis, rheumatoid arthritis, inflammatory bowel diseases and psoriasis.

Claim 17. (New) A method according to claim 8, wherein, during the loading regimen, the dosage of said S1P receptor modulator or agonist is increased incrementally up to a dosage that is 3- to 21-fold relative to the standard daily dosage of the S1P receptor modulator or agonist.

Claim 18. (New) A kit comprising daily units of medication, wherein said medication is an S1P receptor modulator or agonist, and wherein the daily dosages of said medication vary, and wherein the daily dosages of said S1P receptor modulator or agonist for the initial four days of treatment are, respectively, 1-fold, 1.5 to 2-fold; 2 to 3-fold and 3 to 4-fold relative to the standard daily dosage of the S1P receptor modulator or agonist.

Claim 19. (New) A kit according to claim 18, further comprising daily units of medication for treatment after the initial four day period, wherein the dosage of said daily units of medication for

treatment after the initial four day period subsubsequent treatment is lower than the standard dialy dosage for said S1P receptor modulator or agonist.

Claim 20. (New) A kit according to claim 18, wherein said S1P receptor modulator or agonist is 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol or a pharmaceutically acceptable salt thereof.

Remarks/Arguments

Reconsideration of the above application is respectfully requested.

There are 16 claims pending in this application. These are claims 1 – 16. By the amendments submitted in this paper, Applicants have cancelled claims 5 – 7, amended claims 1 – 4, 8, and 11 – 15, and added new claims 17 – 20. The above amendments add no new matter to this application. Support for the amendments to claims 1 – 4 and 8, and for new claim 17, can be found on page 14 of the specification. Support for the amendments to claims 11 – 13 can be found in claims 11 – 13, as presented in the Amendment filed on July 29, 2010. Support for new claims 18 -20 can be found on page 17 of the specification.

In the Office Action, the Examiner stated that certain references identified in the Information Disclosure Statement that Applicants submitted on 5/25/2007 were not supplied with such ISD. Applicants are enclosing the references WO03/061567, WO03/062252 and WO02/100148 with this paper. Applicants wish to thank the Examiner for supplying a copy of the Skerjanec *et al.* reference.

In the Office Action, on page 6, the Examiner made several objections to the claims. Applicants submit that the above amendments overcome all of these objections.

In the Office Action, the Examiner required that Applicants provide an Abstract that complies with the Office's language and format requirements. Applicants have enclosed such an abstract with this paper.

In the Office Action, the Examiner rejected claims 12 - 14 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement due to recitation of term "prodrugs" in claim 12 and 13 and the recitation of "0.1 – 20 mg" in claim 14. Applicants submit that claim 12 and 13, as amended, do not refer to "prodrugs" and that claim 14, as amended, does not recite the range "0.1 – 20 mg". Applicants therefore submit that the forgoing rejection has been overcome and they respectfully request that it be withdrawn.

The Examiner also rejected claims 1, 2, 4, 8, and 12 – 15 under 35 U.S.C. §103(a) as being unpatentable over Lake *et al.* (U.S. Patent Application Publication No. 2003/0003099A1 (hereinafter "Lake") in view of Skerjanec *et al.* (Am. J Transplant, Vol. 2, Suppl. 3, Abstract 964:2002 (hereinafter "Skerjanec"). For the reasons that follow, Applicants traverse this rejection, as applied to the pending claims, as amended, and they respectfully request that such rejection be withdrawn.

As mentioned by the Examiner, Lake refers to a method for inhibiting graft rejection comprising co-administering to the recipient an effective amount of an accelerated lymphocyte

homing ("ALH") agent and one or more compounds of reference claim 15, wherein the ALH agent is 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol ("FTY720") or a pharmaceutically acceptable salt thereof. Also, as the Examiner mentioned, Lake teaches that a preferred daily dosage range for the ALH agent is from about 0.03-2.5 mg/kg/day, as a single dose or in divided doses. However, Lake fails to disclose any loading regimen. There is no teaching or suggestion in Lake regarding how to increase stepwise the dosage of a S1P receptor modulator or agonist during the initial days of treatment, let alone during a specific initial time period of 3 to 6 days. Moreover, nothing in Lake would teach or suggest to one of skill in the art a dosing regimen that would result in steady-state blood levels of the S1P receptor modulator or agonist in less than a week, after which the S1P receptor modulator or agonist can be administered at a dosage less than the standard daily dosage. The statement in Lake that the daily dosages of the therapeutic agents discussed therein will vary depending on the severity of the condition being treated, the ALH agent employed, the host and the mode of administration adds nothing to the above recited disclosures of Lake stated that would motivate on of skill in the art to conceive of the dosing regimen of the present claims, with its unexpected advantages. Lake provides no guidance to those skilled in the art with respect to any specific dosing regimen, let alone that of the present claims.

The Examiner states that Skerjanec discloses that adult *de novo* renal transplanted patients were randomized within 24 hours of transplantation to FTY720 with a loading dose of 1, 2 or 4 mg followed by a once daily maintenance dose of 0.25, 0.5, 1 or 2.5 mg. Applicant respectfully disagrees. Skerjanec merely discloses a **single** loading dose of FTY720 (of 1, 2, **or** 4 mg) followed by once daily maintenance dose (0.25, 0.5, 1 **or** 2.5 mg) for treating graft rejection. Skerjanec does not disclose or suggest a dosing regimen wherein the drug, for example FTY720, is administered at a dosage that is **increased stepwise** before the standard dosage is given, *i.e.,* wherein the drug is administered at different dosages before the standard dosage is given.

Even combining the teaching of Lake *et al.* and Skerjanec *et al.*, the person skilled in the art would not arrive at the specific methods of treatment claimed in the present application. The combined teachings of the prior art are not suggestive of the claimed invention. There is nothing in the prior art that would have guided or even motivated the person skilled in the art to try a step-wise approach as claimed in the present application. There was, in particular, no teaching provided nor was it suggested in the above cited documents that by step-wise increasing the concentration of a S1P receptor modulator or agonist from 4- to 12-fold the standard daily dosage of said S1P receptor modulator or agonist during the initial 3 to 6 days of treatment, a steady-state of the S1P receptor modulator or agonist blood levels can be attained in less than a week. There is no indication and no suggestion that the methods of treatment of the present

invention can effectively be used to expedite steady-state blood levels and achieve the advantages conferred by an early attainment of such blood levels.

There is an unexpected advantage to having patients to attain a steady state blood level earlier. It is known that the first administration of FTY720 may induce a negative effect on the heart rate. This effect is a well-characterized pharmacodynamic effect consistently seen in all FTY720-treated populations. This effect may also occur when the patients have interrupted the treatment during a period of at least 1 or 2 weeks and restart the medication. Advantageously, Applicant has shown that when the patients are at steady state, they can restart treatment with FTY720 after a 1-2 week period without any negative effect on heart rate.

The Examiner also rejected claims 3, 5 and 7 under 35 U.S.C. §103(a) as being unpatentable over Lake in view of Skerjanec, and further in view of Galinski, "Basic Pharmacokinetics and Pharmacodynamics", in Remington: The Science and Practice of Pharmacy, Baltimore, Lippincoltt, Williams & Wilkins, 2006, p. 1171, (hereinafter "Galinski"). By the above amendments, claims 5 and 7 have been cancelled. For the reasons that follow, Applicants traverse this rejection, as applied to claim 3, as amended, and they respectfully request that such rejection be withdrawn.

Galinsky is a basic review on pharmacokinetics and pharmacodymanics. This document does not refer to specific loading regimens. Furthermore, it is completely silent regarding S1P receptor modulator or agonist. The teaching of Galinsky is too vague to provide the guidance necessary to motivate one of skill in the art to conceive of the dosing regimen of the above rejected claims. Applicants submit that much more than routine experimentation would be required of the skilled artisan to arrive to conceive of such claimed dosing regimens from the disclosure of Galinski.

The Examiner further rejected claim 16 under 35 U.S.C. §103(a) as being unpatentable over Lake in view of Skerjanec, and further in view of Chiba *et al.* (U.S. Patent Application Publication No. 2002/0102279A1, hereinafter "Chiba"). For the reasons that follow, Applicants traverse this rejection, as applied to the pending claims, as amended, and they respectfully request that such rejection be withdrawn. Applicant incorporates herein the above discussions of the Lake and Skerjanec references.

Chiba *et al.* refers to therapeutic methods involving accelerate lymphocyte homing immunosuppressive compounds such as FTY720. Chiba is silent regarding the possibility of administering the drug through a loading regimen, let alone as used in the methods of treatment of the present application. The skilled artisan could not arrive at the present invention even if combining the teaching of Lake, Skerjanec and Chiba.

Skerjanec concludes in stating that "the incidence of rejection is not predicted by differential exposure to the drug, suggesting that monitoring of FTY720 trough blood concentrations would likely not yield additional value to the clinical usage of this drug" [emphasis added]. Skerjanec further indicates that the effect of the drug in preventing rejection is independent of systemic exposure to the drug. Therefore, Skerjanec does not suggest to modify the exposure to the drug, for example, to achieve a steady state more quickly. There is no suggestion to provide a loading dosage over a longer period of time before administering the maintenance therapy. On the contrary, Skerjanec suggests that there is no correlation between drug exposure and drug efficacy in transplantation and there would be no value in modifying the dosing regimen. If anything, Skerjanec teaches away from the presently claimed invention.

In view of the above, Applicants submit that all pending claims, as amended, are patentable, and they respectfully request that these claims be allowed to issue.

Respectfully submitted,

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Attorney for Applicant
Reg. No. 32,977

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East Hanover, NJ 07936
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Date: 3/15/11

Abstract

This invention relates to a dosing regime for administering S1P receptor modulators or agonists whereby during the initial 3 to 6 days of treatment the daily dosage is increased stepwise so that in total the R-fold (R=accumulation factor) standard daily dosage is administered and thereafter continued at the standard daily dosage or at a daily dosage lower than the standard daily dosage.

CASE PAT034053-US-PCT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE PCT NATIONAL STAGE APPLICATION OF
Kovarik, John M. et al.
INTERNATIONAL APPLICATION NO: PCT/US2005/43044
FILED: November 28, 2005
U.S. APPLICATION NO: 11/720205
35 USC §371 DATE: May 25, 2007
FOR: Dosage Regimen of an S1P Receptor Agonist

Art Unit: 1614
Examiner: Blakely III, Nelson

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

PETITION FOR EXTENSION OF TIME

Sir:

The Office Action of September 15, 2010 has a shortened statutory time set to expire on December 15, 2010. A three-month extension is hereby requested pursuant to 37 CFR §1.136(a).

Please charge Deposit Account No. 19-0134 in the name of Novartis in the amount of $1110 for payment of the extension fee. The Commissioner is hereby authorized to charge any additional fees under 37 CFR §1.17 which may be required, or credit any overpayment, to Account No. 19-0134 in the name of Novartis.

Respectfully submitted,

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Attorney for Applicant
Reg. No. 32,977

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East Hanover, NJ 07936
(862) 778-3785

Date: 3/15/11

Case PAT034053-US-PCT

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Kovarik, John M. et al.
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Art Unit: 1614
Examiner: Blakely III, Nelson

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT

Sir:

This paper is being filed:

☒ supplemental to the Information Disclosure Statement filed May 25, 2007.

If a fee is deemed to be required, the Commissioner is hereby authorized to charge such fee to Deposit Account No. 19-0134 in the name of Novartis.

☒ A letter for payment of fee set forth in 37 C.F.R. §1.17(p) is enclosed.

In accordance with 37 C.F.R. §1.56, applicants wish to call the Examiner's attention to the references cited on the attached form(s) PTO/SB/08A/B.

☒ Copies of the references are enclosed herewith except for the US patents/applications .

The Examiner is requested to consider the foregoing information in relation to this application and indicate that each reference was considered by returning a copy of the initialed PTO/SB/08A/B form(s).

Respectfully submitted,

Karen DeBenedictis
Attorney for Applicant
Reg. No. 32,977

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Date: 3/15/11

CASE PAT034053-US-PCT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE PCT NATIONAL STAGE APPLICATION OF
Kovarik, John M. et al.
INTERNATIONAL APPLICATION NO: PCT/US2005/43044
FILED: November 28, 2005
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35 USC §371 DATE: May 25, 2007
FOR: Dosage Regimen of an S1P Receptor Agonist

Art Unit: 1614
Examiner: Blakely III, Nelson

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

FEE LETTER FOR INFORMATION DISCLOSURE STATEMENT

Sir:

Please charge Deposit Account No. 19-0134 in the name of Novartis in the amount of $180 for payment of the fee pursuant to 37 CFR §1.17(p) for the submission of an Information Disclosure Statement under 37 CFR §1.97(c).

The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment, to Account No. 19-0134 in the name of Novartis.

Respectfully submitted,

Karen DeBenedictis
Attorney for Applicant
Reg. No. 32,977

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Date: 3/15/11

PTO/SB/08a (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet	1	of	4

Complete if Known	
Application Number	11/720205
Filing Date	November 28, 2005
First Named Inventor	Kovarik, John M. et al.
Art unit	1614
Examiner Name	Blakely III, Nelson
Attorney Docket Number	PAT034053-US-PCT

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		US-6197829	03-06-2001	Tsuneo Fujii et al.	
		US-6277888 B1	08-21-2001	Atsushi Sakai et al	
		US-6476004 B1	11-05-2002	Atsushi Sakai et al	
		US-			
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		US-			
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		US-			

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
		WO 03/061567	07-31-2033	Merck & Co.		☐
		WO 03/062252	07-31-2003	Merck & Co.		☐
		WO 02/100148	12-19-2002	Novartis AG et al		☐
						☐
						☐
						☐

Examiner Signature		**Date Considered**	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw a line through citation if not in conformance and not considered. Include copy of this form with the next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kind Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

Electronic Patent Application Fee Transmittal

Application Number:	11720205
Filing Date:	25-May-2007
Title of Invention:	DOSAGE REGIMEN OF AN S1P RECEPTOR AGONIST
First Named Inventor/Applicant Name:	John M. Kovarik
Filer:	Karen DeBenedictis/Denise Cooper
Attorney Docket Number:	34053-US-PCT

Filed as Large Entity

U.S. National Stage under 35 USC 371 Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 3 months with $0 paid	1253	1	1110	1110

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**1290**

Electronic Acknowledgement Receipt	
EFS ID:	9664663
Application Number:	11720205
International Application Number:	
Confirmation Number:	5868
Title of Invention:	DOSAGE REGIMEN OF AN S1P RECEPTOR AGONIST
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Customer Number:	01095
Filer:	Karen DeBenedictis/Denise Cooper
Filer Authorized By:	Karen DeBenedictis
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Payment was successfully received in RAM	$1290
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The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. 1.492 (National application filing, search, and examination fees) Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)	

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

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Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Foreign Reference	WO0361567A.pdf	7380055 0efd2554e189b9d6a64d1f8ffec032a7de83274a	no	202
Warnings:					
Information:					
2	Foreign Reference	WO0362252A.pdf	4069379 c26f55b3afd85b3a9bc1d2bf2cac5bf114f557b3	no	112
Warnings:					
Information:					
3	Foreign Reference	WO02100148A.pdf	3030322 988a1aa90c1782c3230127e8a2f38f6d967fd783	no	16
Warnings:					
Information:					
4		34053_US_Amend.pdf	553148 9bb45c7798676f8cf3763d0e93c09cf59f70199a	yes	14

Multipart Description/PDF files in .zip description

Document Description	Start	End
Amendment/Req. Reconsideration-After Non-Final Reject	1	9
Abstract	10	10
Extension of Time	11	11
Transmittal Letter	12	12
Miscellaneous Incoming Letter	13	13
Information Disclosure Statement (IDS) Filed (SB/08)	14	14

Warnings:					
Information:					
5	Fee Worksheet (PTO-875)	fee-info.pdf	32570 42b06eda1b0ba92782625c796af7c3c83fcb8972	no	2

Warnings:	
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Total Files Size (in bytes):	15065474

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New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **DOHERTY, George, A.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **FORREST, Michael, J.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **HAJDU, Richard** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **HALE, Jeffrey, J.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **LI, Zhen** [CN/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **MANDALA, Suzanne, M.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **MILLS, Sander, G.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **ROSEN, Hugh** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **SCOLNICK, Edward, M.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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Published:

— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/061567 A2

(54) Title: SELECTIVE S1P1/EDG1 RECEPTOR AGONISTS

(57) Abstract: The present invention encompasses a method of treating an immunoregulatory abnormality in a mammalian patient in need of such treatment comprising administering to said patient a compound which is an agonist of the S1P1/Edg1 receptor in an amount effective for treating said immunoregulatory abnormality, wherein said compound possesses a selectivity for the S1P1/Edg1 receptor over the S1PR3/Edg3 receptor, said compound administered in an amount effective for treating said immunoregulatory abnormality. Pharmaceutical compositions are included. The invention also encompasses a method of identifying candidate compounds that are agonists of the S1P1/Edg1 receptor and which possesses a selectivity for the S1P1/Edg1 receptor over the S1PR3/Edg3 receptor. The invention further encompasses a method of treating a respiratory disease or condition in a mammalian patient in need of such treatment comprising administering to said patient a compound which is an agonist of the S1P1/Edg1 receptor in an amount effective for treating said respiratory disease or condition, wherein said compound possesses a selectivity for the S1P1/Edg1 receptor over the S1PR3/Edg3 receptor.

TITLE OF THE INVENTION
SELECTIVE S1P1/EDG1 RECEPTOR AGONISTS

BACKGROUND OF THE INVENTION

The present invention is related to compounds that are selective $S1P_1$/Edg1 receptor agonists and thus have immunosuppressive activities by producing lymphocyte sequestration in secondary lymphoid tissues. The invention is also directed to pharmaceutical compositions containing such compounds and methods of treatment or prevention.

Immunosuppressive agents have been shown to be useful in a wide variety of autoimmune and chronic inflammatory diseases, including systemic lupus erythematosis, chronic rheumatoid arthritis, type I diabetes mellitus, inflammatory bowel disease, biliary cirrhosis, uveitis, multiple sclerosis and other disorders such as Crohn's disease, ulcerative colitis, bullous pemphigoid, sarcoidosis, psoriasis, autoimmune myositis, Wegener's granulomatosis, ichthyosis, Graves ophthalmopathy, atopic dermatitis and asthma. They have also proved useful as part of chemotherapeutic regimens for the treatment of cancers, lymphomas and leukemias.

Although the underlying pathogenesis of each of these conditions may be quite different, they have in common the appearance of a variety of autoantibodies and/or self-reactive lymphocytes. Such self-reactivity may be due, in part, to a loss of the homeostatic controls under which the normal immune system operates. Similarly, following a bone-marrow or an organ transplantation, the host lymphocytes recognize the foreign tissue antigens and begin to produce both cellular and humoral responses including antibodies, cytokines and cytotoxic lymphocytes which lead to graft rejection.

One end result of an autoimmune or a rejection process is tissue destruction caused by inflammatory cells and the mediators they release. Anti-inflammatory agents such as NSAIDs act principally by blocking the effect or secretion of these mediators but do nothing to modify the immunologic basis of the disease. On the other hand, cytotoxic agents, such as cyclophosphamide, act in such a nonspecific fashion that both the normal and autoimmune responses are shut off. Indeed, patients treated with such nonspecific immunosuppressive agents are as likely to succumb to infection as they are to their autoimmune disease.

Cyclosporin A is a drug used to prevent rejection of transplanted organs. FK-506 is another drug approved for the prevention of transplant organ rejection, and in particular, liver transplantation. Cyclosporin A and FK-506 act by inhibiting the body's immune system from mobilizing its vast arsenal of natural protecting agents to reject the transplant's foreign protein. Cyclosporin A was approved for the treatment of severe psoriasis and has been approved by European regulatory agencies for the treatment of atopic dermatitis.

Though they are effective in delaying or suppressing transplant rejection, Cyclosporin A and FK-506 are known to cause several undesirable side effects including nephrotoxicity, neurotoxicity, and gastrointestinal discomfort. Therefore, an immunosuppressant without these side effects still remains to be developed and would be highly desirable.

The immunosuppressive compound FTY720 is a lymphocyte sequestration agent currently in clinical trials. FTY720 is metabolized in mammals to a compound that is a potent agonist of sphingosine 1-phosphate receptors. Agonism of sphingosine 1-phosphate receptors induces the sequestration of lymphocytes (T-cells and B-cells) in lymph nodes and Peyer's patches without lymphodepletion. Such immunosuppression is desirable to prevent rejection after organ transplantation and in the treatment of autoimmune disorders.

Sphingosine 1-phosphate is a bioactive sphingolipid metabolite that is secreted by hematopoietic cells and stored and released from activated platelets. Yatomi, Y., T. Ohmori, G. Rile, F. Kazama, H. Okamoto, T. Sano, K. Satoh, S. Kume, G. Tigyi, Y. Igarashi, and Y. Ozaki. 2000. *Blood.* 96:3431-8. It acts as an agonist on a family of G protein-coupled receptors to regulate cell proliferation, differentiation, survival, and motility. Fukushima, N., I. Ishii, J.J.A. Contos, J.A. Weiner, and J. Chun. 2001. Lysophospholipid receptors. Annu. Rev. Pharmacol. Toxicol. 41:507-34; Hla, T., M.-J. Lee, N. Ancellin, J.H. Paik, and M.J. Kluk. 2001. Lysophospholipids - Receptor revelations. *Science.* 294:1875-1878; Spiegel, S., and S. Milstien. 2000. Functions of a new family of sphingosine-1-phosphate receptors. *Biochim. Biophys. Acta.* 1484:107-16; Pyne, S., and N. Pyne. 2000. Sphingosine 1-phosphate signalling via the endothelial differentiation gene family of G-protein coupled receptors. *Pharm. & Therapeutics.* 88:115-131. Five sphingosine 1-phosphate receptors have been identified ($S1P_1$, $S1P_2$, $S1P_3$, $S1P_4$, and $S1P_5$, also

known as endothelial differentiation genes Edg1, Edg5, Edg3, Edg6, Edg8), that have widespread cellular and tissue distribution and are well conserved in human and rodent species (see Table). Binding to S1P receptors elicits signal transduction through Gq-, Gi/o, G12-, G13-, and Rho-dependent pathways. Ligand-induced activation of $S1P_1$ and $S1P_3$ has been shown to promote angiogenesis, chemotaxis, and adherens junction assembly through Rac- and Rho-, *see* Lee, M.-J., S. Thangada, K.P. Claffey, N. Ancellin, C.H. Liu, M. Kluk, M. Volpi, R.I. Sha'afi, and T. Hla. 1999. *Cell.* 99:301-12, whereas agonism of $S1P_2$ promotes neurite retraction, *see* Van Brocklyn, J.R., Z. Tu, L.C. Edsall, R.R. Schmidt, and S. Spiegel. 1999. *J. Biol. Chem.* 274:4626-4632, and inhibits chemotaxis by blocking Rac activation, *see* Okamoto, H., N. Takuwa, T. Yokomizo, N. Sugimoto, S. Sakurada, H. Shigematsu, and Y. Takuwa. 2000. *Mol. Cell. Biol.* 20:9247-9261. S1P4 is localized to hematopoietic cells and tissues, *see* Graeler, M.H., G. Bernhardt, and M. Lipp. 1999. *Curr. Top. Microbiol. Immunol.* 246:131-6, whereas $S1P_5$ is primarily a neuronal receptor with some expression in lymphoid tissue, *see* Im, D.S., C.E. Heise, N. Ancellin, B.F. O'Dowd, G.J. Shei, R.P. Heavens, M.R. Rigby, T. Hla, S. Mandala, G. McAllister, S.R. George, and K.R. Lynch. 2000. *J. Biol. Chem.* 275:14281-6. Administration of sphingosine 1-phosphate to animals induces systemic sequestration of peripheral blood lymphocytes into secondary lymphoid organs, stimulates FGF-mediated blood vessel growth and differentiation, *see* Lee, et al., supra, but also has cardiovascular effects that limit the utility of sphingosine 1-phosphate as a therapeutic agent, *see* Sugiyama, A., N.N. Aye, Y. Yatomi, Y. Ozaki, and K. Hashimoto. 2000. *Jpn. J. Pharmacol.* 82:338-342. The reduced heart rate and blood pressure measured with sphingosine 1-phosphate is associated with its non-selective, potent agonist activity on all S1P receptors.

The present invention is directed towards compounds which are selective agonists of the $S1P_1$/Edg1 receptor while having the specified window of selectivity as agonists of, or alternately antagonists or inverse agonists of the $S1P_3$/Edg3 receptor. An $S1P_1$/Edg1 receptor selective agonist has advantages over current therapies and extends the therapeutic window of lymphocytes sequestration agents, allowing better tolerability with higher dosing and thus improving efficacy as monotherapy. Receptor agonists selective for $S1P_1$/Edg1 over $S1P_3$/Edg3 having enhanced cardiovascular tolerability in rats are exemplified.

While the main use for immunosuppressants is in treating bone marrow, organ and transplant rejection, other uses for such compounds include the treatment of arthritis, in particular, rheumatoid arthritis, insulin and non-insulin dependent diabetes, multiple sclerosis, psoriasis, inflammatory bowel disease, Crohn's disease, lupus erythematosis and the like.

Thus, the present invention is focused on providing immunosuppressant compounds that are safer and more effective than prior compounds. These and other objects will be apparent to those of ordinary skill in the art from the description contained herein.

Summary of S1P receptors

Name	Synonyms	Coupled G proteins	mRNA expression
$S1P_1$	Edg1, LP_{B1}	$G_{i/o}$	Widely distributed, endothelial cells
$S1P_2$	Edg5, LP_{B2}, AGR16, H218	$G_{i/o}$, G_q, $G_{12/13}$	Widely distributed, vascular smooth muscle cells
$S1P_3$	Edg3, LP_{B3}	$G_{i/o}$, G_q, $G_{12/13}$	Widely distributed, endothelial cells
$S1P_4$	Edg6, LP_{C1}	$G_{i/o}$	Lymphoid tissues, lymphocytic cell lines
$S1P_5$	Edg8, LP_{B4}, NRG1	$G_{i/o}$	Brain, spleen

SUMMARY OF THE INVENTION

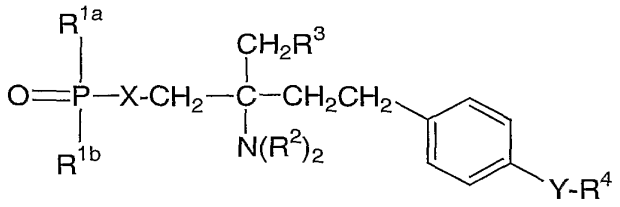
The present invention encompasses a method of treating an immunoregulatory abnormality in a mammalian patient in need of such treatment comprising administering to said patient a compound which is an agonist of the $S1P_1$/Edg1 receptor in an amount effective for treating said immunoregulatory abnormality, wherein said compound possesses a selectivity for the S1P1/Edg1

receptor over the S1PR3/Edg3 receptor, said compound administered in an amount effective for treating said immunoregulatory abnormality. Pharmaceutical compositions are included. The invention also encompasses a method of identifying candidate compounds that are agonists of the $S1P_1$/Edg1 receptor and which possesses a selectivity for the S1P1/Edg1 receptor over the S1PR3/Edg3 receptor. The invention further encompasses a method of treating a respiratory disease or condition in a mammalian patient in need of such treatment comprising administering to said patient a compound which is an agonist of the $S1P_1$/Edg1 receptor in an amount effective for treating said respiratory disease or condition, wherein said compound possesses a selectivity for the S1P1/Edg1 receptor over the S1PR3/Edg3 receptor.

DETAILED DESCRIPTION OF THE INVENTION

The present invention encompasses a method of treating an immunoregulatory abnormality in a mammalian patient in need of such treatment comprising administering to said patient a compound which is an agonist of the $S1P_1$/Edg1 receptor in an amount effective for treating said immunoregulatory abnormality, wherein said compound possesses a selectivity for the S1P1/Edg1 receptor over the S1PR3/Edg3 receptor of at least 20 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay and wherein said compound possesses an EC_{50} for binding to the $S1P_1$/Edg1 receptor of 100 nM or less as evaluated by the ^{35}S-GTPγS binding assay,

with the proviso that the compound does not fall within formula A:



A

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

X is O, S, NR^1 or $(CH_2)_{1-2}$, optionally substituted with 1-4 halo groups;

R^1 is H, C_{1-4}alkyl or haloC_{1-4} alkyl;

R^{1a} is H, OH, C_{1-4}alkyl, or OC_{1-4} alkyl, the alkyl and alkyl portions being optionally substituted with 1-3 halo groups;

R^{1b} represents H, OH, C_{1-4} alkyl or haloC_{1-4} alkyl;

each R^2 is independently selected from the group consisting of: H, C_{1-4} alkyl and haloC_{1-4} alkyl,

R^3 is H, OH, halo, C_{1-4}alkyl, OC_{1-4}alkyl, O-haloC_{1-4}alkyl or hydroxyC_{1-4}alkyl,

Y is selected from the group consisting of: $-CH_2-$, -C(O)-, -CH(OH)-, -C(=NOH)-, O and S, and

R^4 is selected from the group consisting of: C_{4-14}alkyl and C_{4-14}alkenyl.

An embodiment of the invention encompasses the above method wherein the compound has a selectivity for the $S1P_1$/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 100 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

Another embodiment of the invention encompasses the above method wherein the compound has a selectivity for the $S1P_1$/Edg1 receptor over the

$S1P_3$/Edg3 receptor of at least 200 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

Another embodiment of the invention encompasses the above method wherein the compound has a selectivity for the $S1P_1$/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 500 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

Another embodiment of the invention encompasses the above method wherein the compound has a selectivity for the $S1P_1$/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 2000 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

The invention also encompasses a method of treating an immunoregulatory abnormality in a mammalian patient in need of such treatment comprising administering to said patient a compound which is an agonist of the $S1P_1$/Edg1 receptor in an amount effective for treating said immunoregulatory abnormality, wherein said compound possesses a selectivity for the S1P1/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 100 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay and wherein said compound possesses an EC_{50} for binding to the $S1P_1$/Edg1 receptor of 10 nM or less as evaluated by the ^{35}S-GTPγS binding assay.

Within this embodiment is encompassed the above method wherein the compound possesses an EC_{50} for binding to the $S1P_1$/Edg1 receptor of 1 nM or less as evaluated by the ^{35}S-GTPγS binding assay.

Also within this embodiment is encompassed the above method wherein the compound has a selectivity for the $S1P_1$/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 200 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

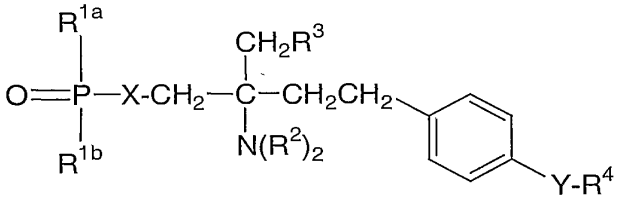
Also within this embodiment is encompassed the above method wherein the compound has a selectivity for the $S1P_1$/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 500 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

Also within this embodiment is encompassed the above method wherein the compound has a selectivity for the $S1P_1$/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 1000 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1PR_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

Also within this embodiment is encompassed the above method wherein the compound has a selectivity for the $S1P_1$/Edg1 receptor over the $S1PR_3$/Edg3 receptor of at least 2000 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

The invention also encompasses a pharmaceutical composition comprised of a compound which is an agonist of the $S1P_1$/Edg1 receptor in an amount effective for treating said immunoregulatory abnormality, wherein said compound possesses a selectivity for the $S1P_1$/Edg1 receptor over the $S1PR_3$/Edg3 receptor of at least 20 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay and wherein said compound possesses an EC_{50} for binding to the $S1P_1$/Edg1 receptor of 100 nM or less as evaluated by the ^{35}S-GTPγS binding assay,

with the proviso that the compound does not fall within formula A:



A

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

X is O, S, NR^1 or $(CH_2)_{1-2}$, optionally substituted with 1-4 halo groups;

R^1 is H, C_{1-4}alkyl or haloC_{1-4} alkyl;

R^{1a} is H, OH, C_{1-4}alkyl, or OC_{1-4} alkyl, the alkyl and alkyl portions being optionally substituted with 1-3 halo groups;

R^{1b} represents H, OH, C_{1-4} alkyl or haloC_{1-4} alkyl;

each R^2 is independently selected from the group consisting of: H, C_{1-4} alkyl and haloC_{1-4} alkyl,

R^3 is H, OH, halo, C_{1-4}alkyl, OC_{1-4}alkyl, O-haloC_{1-4}alkyl or hydroxyC_{1-4}alkyl,

Y is selected from the group consisting of: $-CH_2-$, -C(O)-, -CH(OH)-, -C(=NOH)-, O and S, and

R^4 is selected from the group consisting of: C_{4-14}alkyl and C_{4-14}alkenyl,

in combination with a pharmaceutically acceptable carrier.

The present invention also encompasses a pharmaceutical composition comprised of a compound which is an agonist of the $S1P_1$/Edg1 receptor in an amount effective for treating said immunoregulatory abnormality, wherein said compound possesses a selectivity for the S1P1/Edg1 receptor over the S1PR3/Edg3 receptor of at least 100 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay and wherein said compound possesses an EC_{50} for binding to the $S1P_1$/Edg1 receptor of 10 nM or less as evaluated by the ^{35}S-GTPγS binding assay, in combination with a pharmaceutically acceptable carrier.

For purposes of this specification, when a compound is said to be evaluated by the ^{35}S-GTPγS binding assay, this means said compound is evaluated following the procedures described herein under the heading ^{35}S-GTPγS binding assay.

The present invention is directed towards compounds which are selective agonists of the $S1P_1$/Edg1 receptor while having the specified window of selectivity as agonists of, or alternately antagonists or inverse agonists of the $S1P_3$/Edg3 receptor. The invention also encompasses compounds that are agonists of the $S1P_1$/Edg1 receptor while having the specified window of selectivity as non-modulators of the $S1P_3$/Edg3 receptor.

A further embodiment of the invention encompasses the concomitant administration of an $S1P_1$/Edg1 receptor in combination with an antagonist or inverse agonist of the $S1P_3$/Edg3 receptor, such that the combined therapy possesses a selectivity for the S1P1/Edg1 receptor over the S1PR3/Edg3 receptor of at least 20 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay and wherein said compound possesses an EC_{50} for binding to the $S1P_1$/Edg1 receptor of 100 nM or less as evaluated by the ^{35}S-GTPγS binding assay,

The invention also encompasses the above method wherein the immunoregulatory abnormality is an autoimmune or chronic inflammatory disease selected from the group consisting of: systemic lupus erythematosis, chronic rheumatoid arthritis, type I diabetes mellitus, inflammatory bowel disease, biliary

cirrhosis, uveitis, multiple sclerosis, Crohn's disease, ulcerative colitis, bullous pemphigoid, sarcoidosis, psoriasis, autoimmune myositis, Wegener's granulomatosis, ichthyosis, Graves ophthalmopathy and asthma.

The invention also encompasses the above method wherein the immunoregulatory abnormality is bone marrow or organ transplant rejection or graft-versus-host disease.

The invention also encompasses the above method wherein the immunoregulatory abnormality is selected from the group consisting of: transplantation of organs or tissue, graft-versus-host diseases brought about by transplantation, autoimmune syndromes including rheumatoid arthritis, systemic lupus erythematosus, Hashimoto's thyroiditis, multiple sclerosis, myasthenia gravis, type I diabetes, uveitis, posterior uveitis, allergic encephalomyelitis, glomerulonephritis, post-infectious autoimmune diseases including rheumatic fever and post-infectious glomerulonephritis, inflammatory and hyperproliferative skin diseases, psoriasis, atopic dermatitis, contact dermatitis, eczematous dermatitis, seborrhoeic dermatitis, lichen planus, pemphigus, bullous pemphigoid, epidermolysis bullosa, urticaria, angioedemas, vasculitis, erythema, cutaneous eosinophilia, lupus erythematosus, acne, alopecia areata, keratoconjunctivitis, vernal conjunctivitis, uveitis associated with Behcet's disease, keratitis, herpetic keratitis, conical cornea, dystrophia epithelialis corneae, corneal leukoma, ocular pemphigus, Mooren's ulcer, scleritis, Graves' opthalmopathy, Vogt-Koyanagi-Harada syndrome, sarcoidosis, pollen allergies, reversible obstructive airway disease, bronchial asthma, allergic asthma, intrinsic asthma, extrinsic asthma, dust asthma, chronic or inveterate asthma, late asthma and airway hyper-responsiveness, bronchitis, gastric ulcers, vascular damage caused by ischemic diseases and thrombosis, ischemic bowel diseases, inflammatory bowel diseases, necrotizing enterocolitis, intestinal lesions associated with thermal burns, coeliac diseases, proctitis, eosinophilic gastroenteritis, mastocytosis, Crohn's disease, ulcerative colitis, migraine, rhinitis, eczema, interstitial nephritis, Goodpasture's syndrome, hemolytic-uremic syndrome, diabetic nephropathy, multiple myositis, Guillain-Barre syndrome, Meniere's disease, polyneuritis, multiple neuritis, mononeuritis, radiculopathy, hyperthyroidism, Basedow's disease, pure red cell aplasia, aplastic anemia, hypoplastic anemia, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, agranulocytosis, pernicious anemia, megaloblastic

anemia, anerythroplasia, chronic lymphocytic leukemia, osteoporosis, sarcoidosis, fibroid lung, idiopathic interstitial pneumonia, dermatomyositis, leukoderma vulgaris, ichthyosis vulgaris, photoallergic sensitivity, cutaneous T cell lymphoma, arteriosclerosis, atherosclerosis, aortitis syndrome, polyarteritis nodosa, myocardosis, scleroderma, Wegener's granuloma, Sjogren's syndrome, adiposis, eosinophilic fascitis, lesions of gingiva, periodontium, alveolar bone, substantia ossea dentis, glomerulonephritis, male pattern alopecia or alopecia senilis by preventing epilation or providing hair germination and/or promoting hair generation and hair growth, muscular dystrophy, pyoderma and Sezary's syndrome, Addison's disease, ischemia-reperfusion injury of organs which occurs upon preservation, transplantation or ischemic disease, endotoxin-shock, pseudomembranous colitis, colitis caused by drug or radiation, ischemic acute renal insufficiency, chronic renal insufficiency, toxinosis caused by lung-oxygen or drugs, lung cancer, pulmonary emphysema, cataracta, siderosis, retinitis pigmentosa, senile macular degeneration, vitreal scarring, corneal alkali burn, dermatitis erythema multiforme, linear IgA ballous dermatitis and cement dermatitis, gingivitis, periodontitis, sepsis, pancreatitis, diseases caused by environmental pollution, aging, carcinogenesis, metastasis of carcinoma and hypobaropathy, disease caused by histamine or leukotriene-C_4 release, Behcet's disease, autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis, partial liver resection, acute liver necrosis, necrosis caused by toxin, viral hepatitis, shock, or anoxia, B-virus hepatitis, non-A/non-B hepatitis, cirrhosis, alcoholic cirrhosis, hepatic failure, fulminant hepatic failure, late-onset hepatic failure, "acute-on-chronic" liver failure, augmentation of chemotherapeutic effect, cytomegalovirus infection, HCMV infection, AIDS, cancer, senile dementia, trauma, and chronic bacterial infection.

The invention also encompasses the above method wherein the immunoregulatory abnormality is multiple sclerosis.

The invention also encompasses the above method wherein the immunoregulatory abnormality is rheumatoid arthritis.

The invention also encompasses the above method wherein the immunoregulatory abnormality is systemic lupus erythematosus.

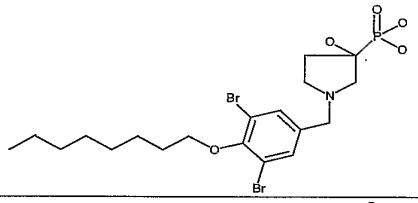
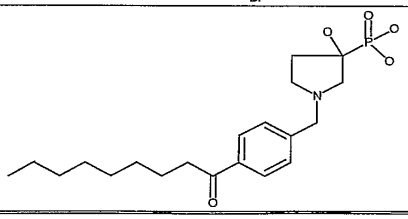
The invention also encompasses the above method wherein the immunoregulatory abnormality is psoriasis.

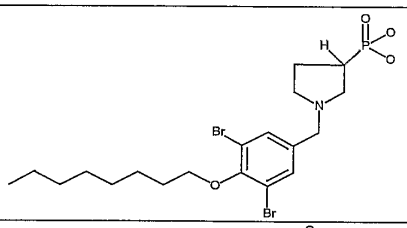
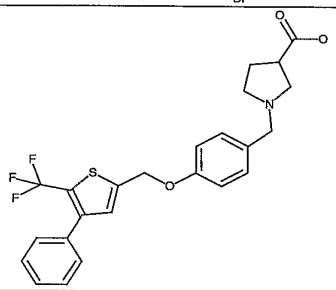
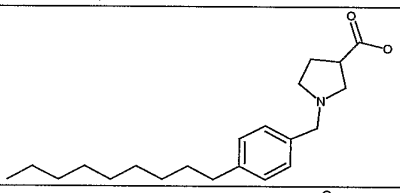
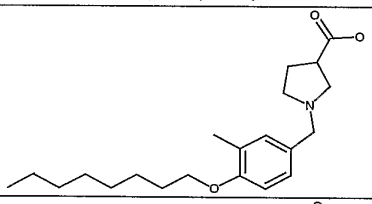
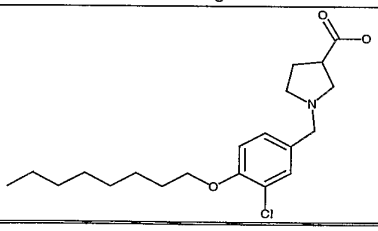
The invention also encompasses the above method wherein the immunoregulatory abnormality is rejection of transplanted organ or tissue.

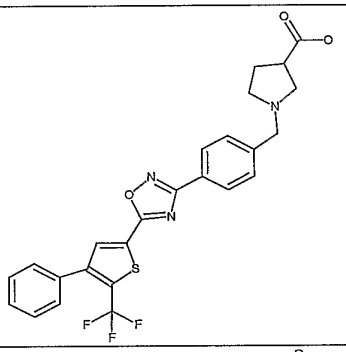
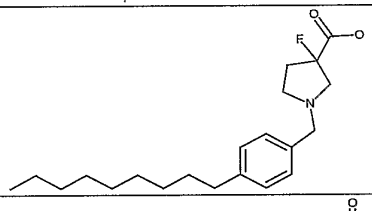
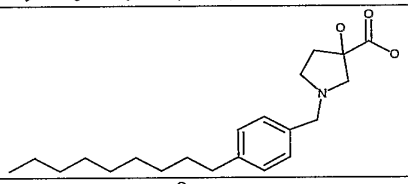
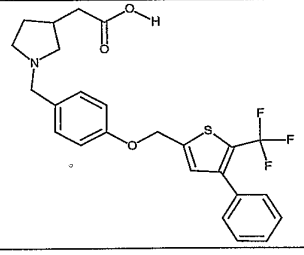
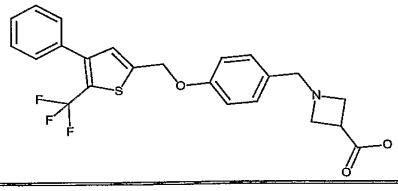
The invention also encompasses the above method wherein the immunoregulatory abnormality is inflammatory bowel disease.

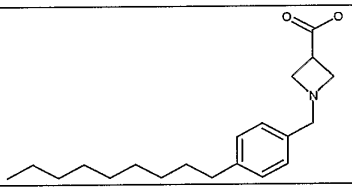
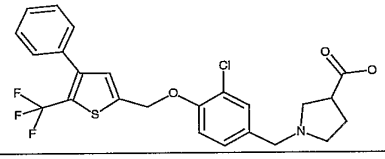
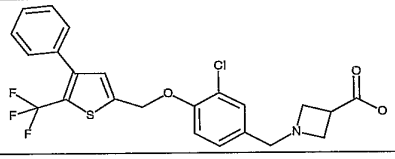
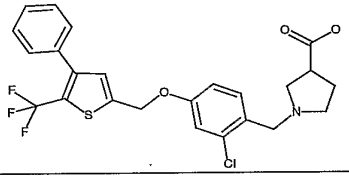
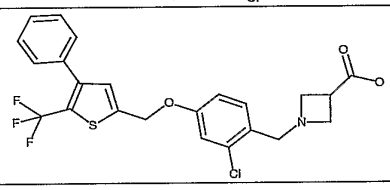
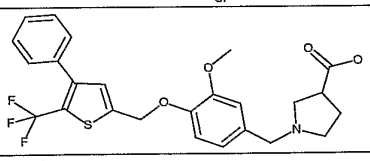
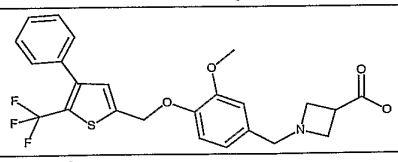
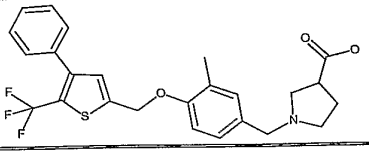
The invention also encompasses the above method wherein the immunoregulatory abnormality is a malignancy of lymphoid origin, such as acute and chronic lymphocytic leukemias and lymphomas.

Exemplifying the invention are the following compounds, which possess a selectivity for the $S1P_1$/Edg1 receptor over the S1PR3/Edg3 receptor of at least 20 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay and which possesses an EC_{50} for binding to the $S1P_1$/Edg1 receptor of 100 nM or less as evaluated by the ^{35}S-GTPγS binding assay:

Example No.	Structure
VII	
VIII	

Example No.	Structure
XV + XVI	
XVIII	
XIX	
XXIII	
XXVI	

Example No.	Structure
XXVIII	
XXXV	
XXXVI	
XXXVIII	
XL	

Example No.	Structure
XLI	
XLVI	
XLVII	
XLVIII	
XLIX	
L	
LI	
LII	

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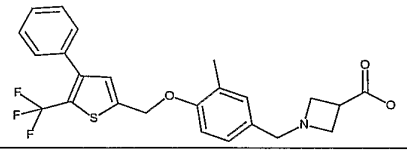
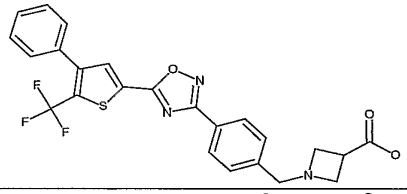
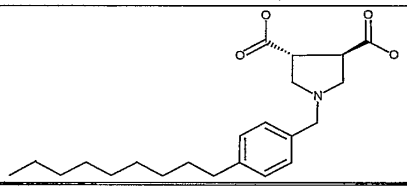
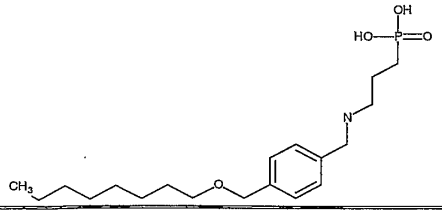
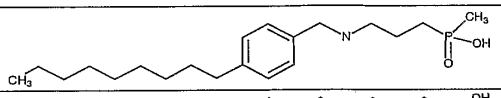
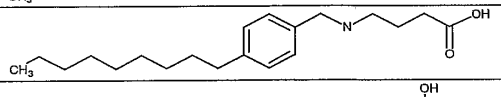
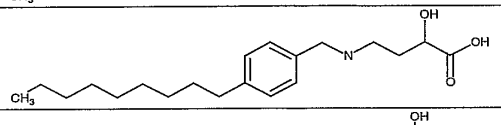
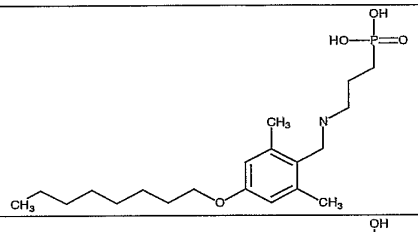
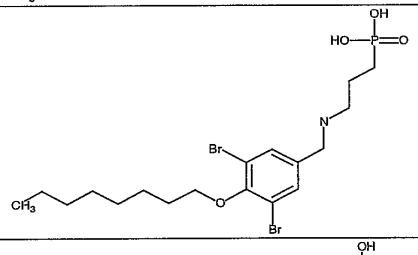
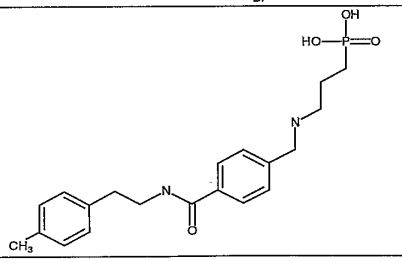
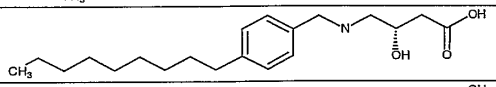
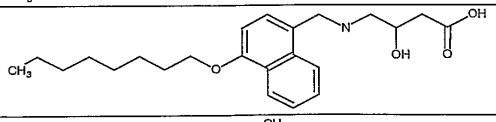
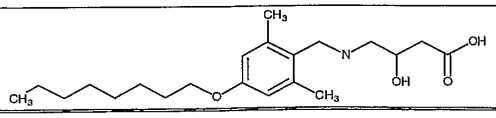
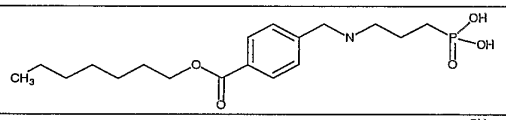
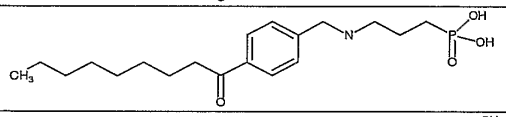
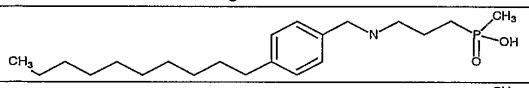
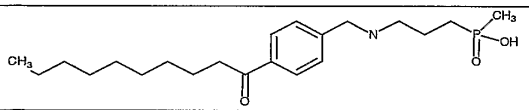
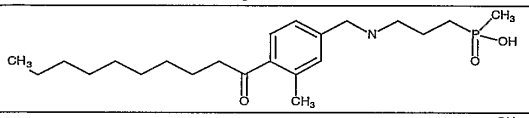
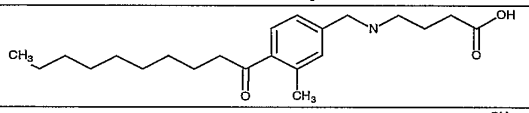
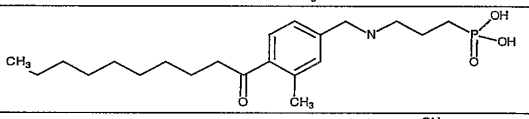
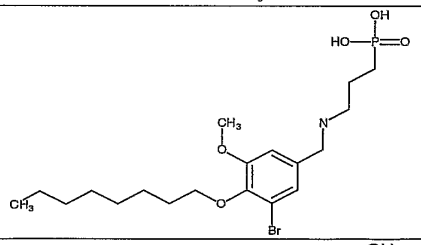
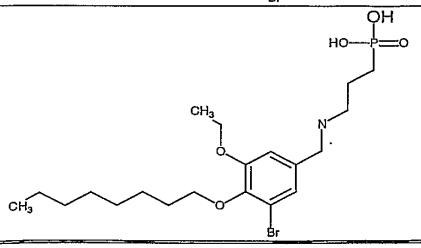
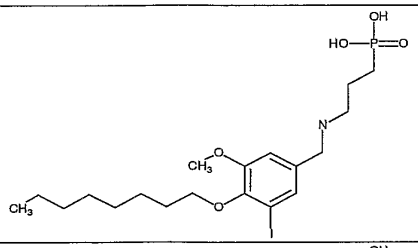
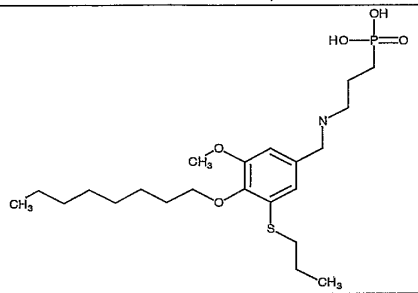
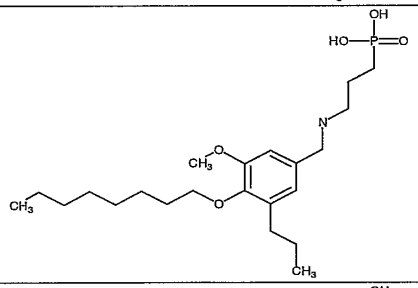
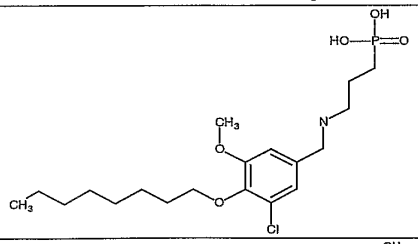
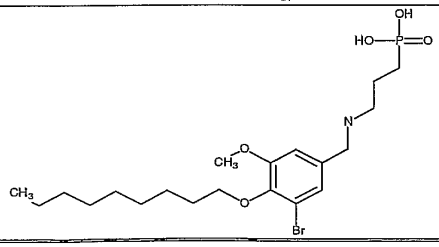
LIII	
LIV	
LVII	

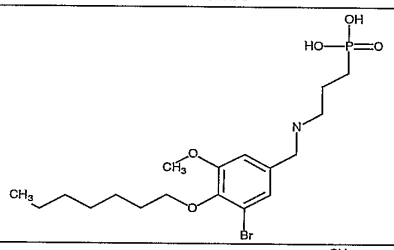
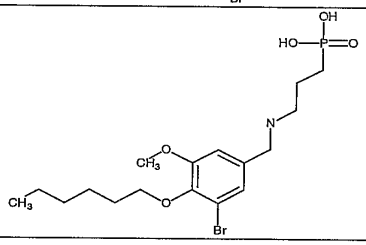
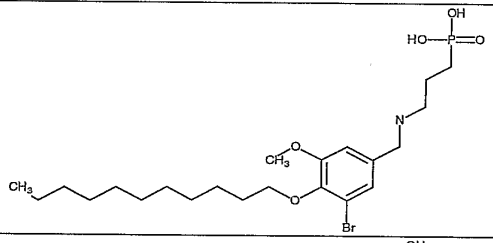
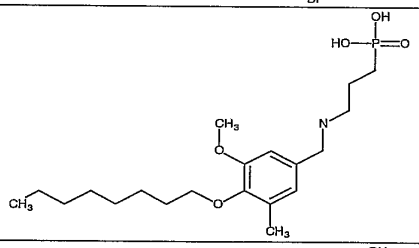
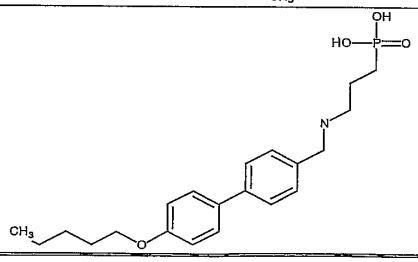
Further exemplifying the invention are the following compounds, which possess a selectivity for the S1P1/Edg1 receptor over the S1PR3/Edg3 receptor of at least 20 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the S1P3/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay and which possesses an EC_{50} for binding to the $S1P_1$/Edg1 receptor of 100 nM or less as evaluated by the ^{35}S-GTPγS binding assay:

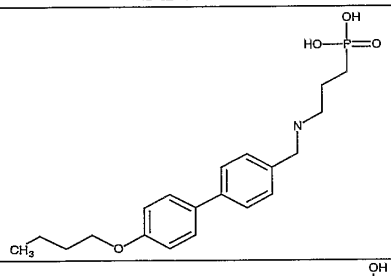
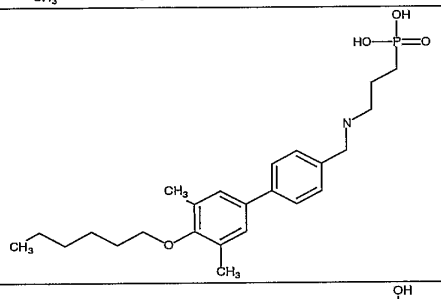
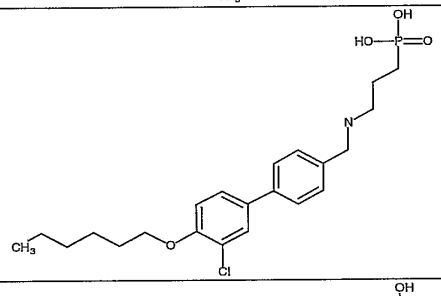
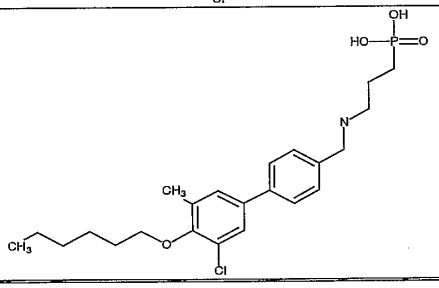
Example Number	Structure
6	

Example Number	Structure
12	
15	
16	
24	
25	
34	
41	
43	
44	

Example Number	Structure
45	
47	
48	
51	
53	
54	
55	
58	
59	

Example Number	Structure
66	
67	
68	
70	
71	

Example Number	Structure
72	
77	
78	
81	
84	

Example Number	Structure
85	
88	
89	
91	

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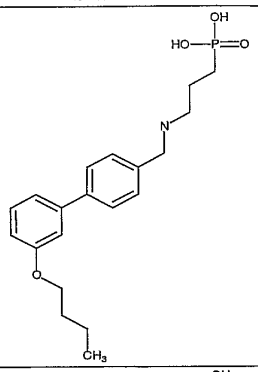
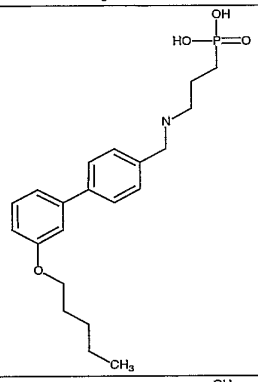
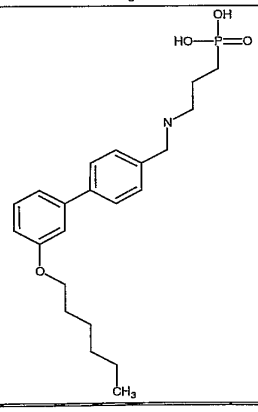
93	
94	
95	

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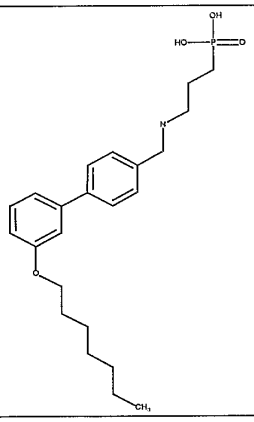
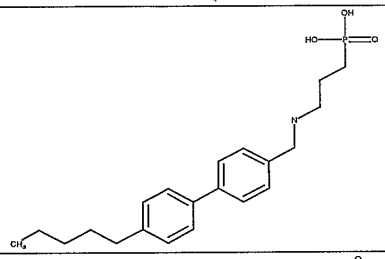
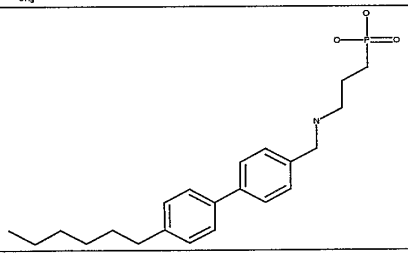
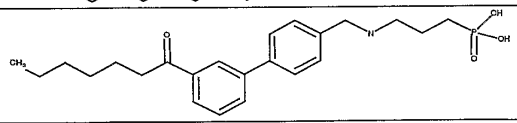
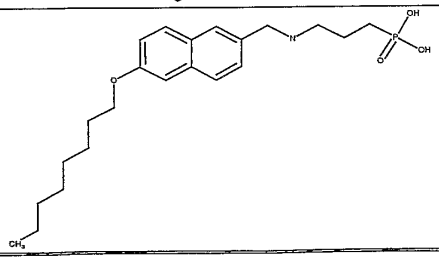
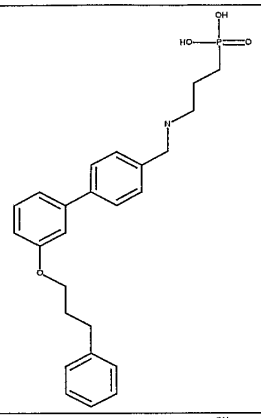
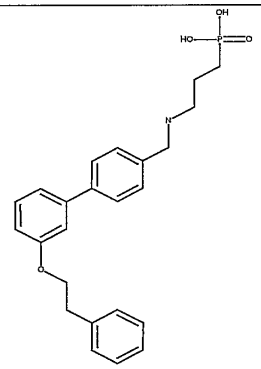
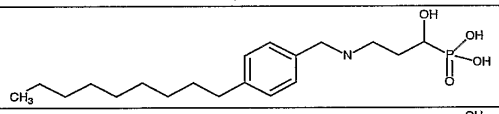
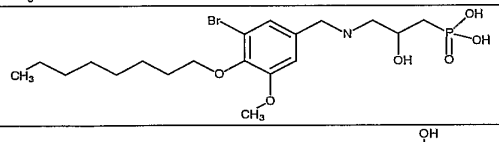
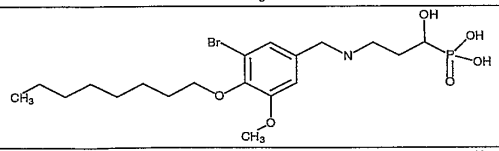
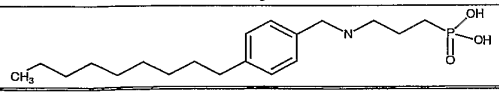
98	
99	
100	
103	
105	

Example Number	Structure
106	
107	
108	
110	
111	
112	

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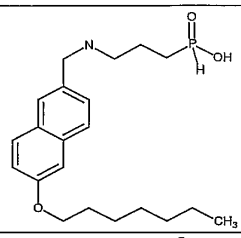
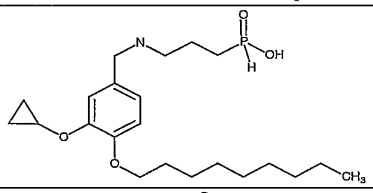
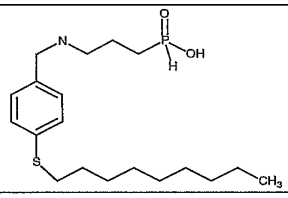
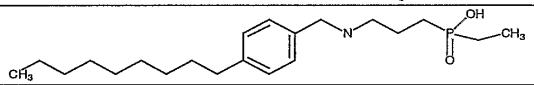
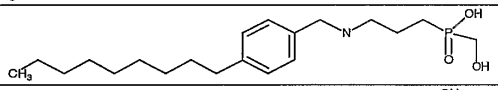
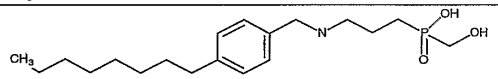
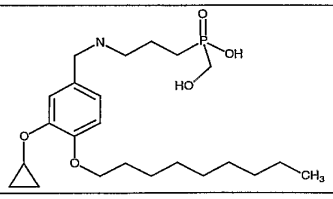
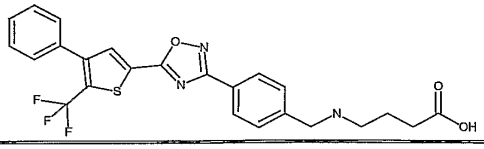
122	
123	
124	
125	
128	
134	
135	
141	

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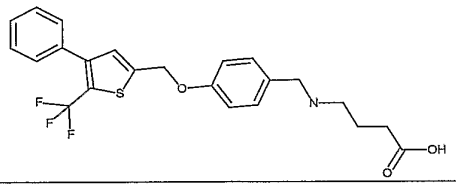
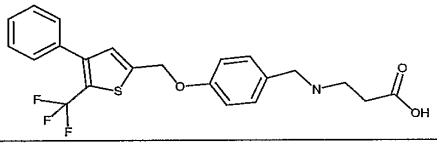
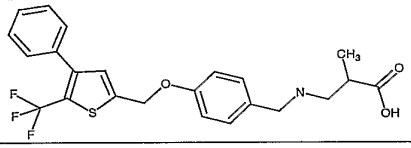
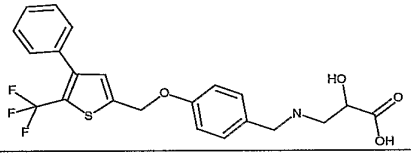
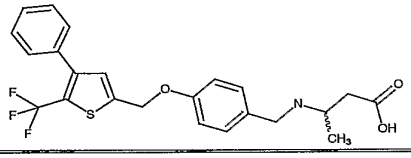
143	
144	
145	
146	
149	

The invention is described using the following definitions unless otherwise indicated.

The term "halogen" or "halo" includes F, Cl, Br, and I.

The term "alkyl" means linear or branched structures and combinations thereof, having the indicated number of carbon atoms. Thus, for example, C_{1-6}alkyl includes methyl, ethyl, propyl, 2-propyl, s- and t-butyl, butyl, pentyl, hexyl, 1,1-dimethylethyl, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term "haloalkyl" means alkyl as defined above substituted with at least one halo group, as defined above, and being optionally substituted with halo up to the maximum number of substituable positions.

The term "hydroxyalkyl" means alkyl as defined above substituted with at least one hydroxy group, and being optionally substituted with hydroxyup to the maximum number of substituable positions.

The term "alkoxy" means alkoxy groups of a straight, branched or cyclic configuration having the indicated number of carbon atoms. C_{1-6}alkoxy, for example, includes methoxy, ethoxy, propoxy, isopropoxy, and the like.

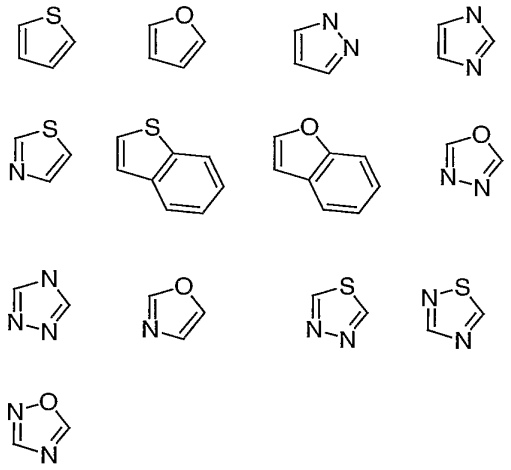
The term "alkylthio" means alkylthio groups having the indicated number of carbon atoms of a straight, branched or cyclic configuration. C_{1-6}alkylthio, for example, includes methylthio, propylthio, isopropylthio, and the like.

The term "alkenyl" means linear or branched structures and combinations thereof, of the indicated number of carbon atoms, having at least one carbon-to-carbon double bond, wherein hydrogen may be replaced by an additional carbon-to-carbon double bond. C_{2-6}alkenyl, for example, includes ethenyl, propenyl, 1-methylethenyl, butenyl and the like.

The term "alkynyl" means linear or branched structures and combinations thereof, of the indicated number of carbon atoms, having at least one carbon-to-carbon triple bond. C_{3-6}alkynyl, for example, includes , propenyl, 1-methylethenyl, butenyl and the like.

The term "HET" is defined as a 5- to 10-membered aromatic, partially aromatic or non-aromatic mono- or bicyclic ring, containing 1-5 heteroatoms selected from O, S and N, and optionally substituted with 1-2 oxo groups. Preferably, "HET" is a 5- or 6-membered aromatic or non-aromatic monocyclic ring containing 1-3 heteroatoms selected from O, S and N, for example, pyridine, pyrimidine, pyridazine, furan, thiophene, thiazole, oxazole, isooxazole and the like, or heterocycle is a 9- or 10-membered aromatic or partially aromatic bicyclic ring containing 1-3 heteroatoms selected from O, S, and N, for example, benzofuran, benzothiophene, indole, pyranopyrrole, benzopyran, quionoline, benzocyclohexyl, naphtyridine and the like. "HET" also includes the following: benzimidazolyl, benzofuranyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, indolazinyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthyridinyl, oxadiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridopyridinyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, thiadiazolyl, thiazolyl, thienyl, triazolyl,

azetidinyl, 1,4-dioxanyl, hexahydroazepinyl, piperazinyl, piperidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, dihydrobenzimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidinyl, methylenedioxybenzoyl, tetrahydrofuranyl, and tetrahydrothienyl. A preferred group of HET is as follows:



The term "treating" encompasses not only treating a patient to relieve the patient of the signs and symptoms of the disease or condition but also prophylactically treating an asymptomatic patient to prevent the onset or progression of the disease or condition. The term "amount effective for treating" is intended to mean that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, a system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician. The term also encompasses the amount of a pharmaceutical drug that will prevent or reduce the risk of occurrence of the biological or medical event that is sought to be prevented in a tissue, a system, animal or human by a researcher, veterinarian, medical doctor or other clinician.

The invention described herein includes pharmaceutically acceptable salts and hydrates. Pharmaceutically acceptable salts include both the metallic

(inorganic) salts and organic salts; a list of which is given in *Remington's Pharmaceutical Sciences*, 17th Edition, pg. 1418 (1985). It is well known to one skilled in the art that an appropriate salt form is chosen based on physical and chemical stability, flowability, hydroscopicity and solubility. As will be understood by those skilled in the art, pharmaceutically acceptable salts include, but are not limited to salts of inorganic acids such as hydrochloride, sulfate, phosphate, diphosphate, hydrobromide, and nitrate or salts of an organic acid such as malate, maleate, fumarate, tartrate, succinate, citrate, acetate, lactate, methanesulfonate, p-toluenesulfonate or pamoate, salicylate and stearate. Similarly pharmaceutically acceptable cations include, but are not limited to sodium, potassium, calcium, aluminum, lithium and ammonium (especially ammonium salts with secondary amines). Preferred salts of this invention for the reasons cited above include potassium, sodium, calcium and ammonium salts. Also included within the scope of this invention are crystal forms, hydrates and solvates of the compounds of the present invention.

For purposes of this Specification, "pharmaceutically acceptable hydrate" means the compounds of the instant invention crystallized with one or more molecules of water to form a hydrated form.

The invention also includes the compounds falling within the present invention in the form of one or more stereoisomers, in substantially pure form or in the form of a mixture of stereoisomers. All such isomers are encompassed within the present invention.

The compounds disclosed herein are selective agonists of the $S1P_1$/Edg1 receptor while having the specified window of selectivity as agonists of, or alternately antagonists or inverse agonists of the $S1P_3$/Edg3 receptor. An Edg1 selective agonist has advantages over current therapies and extends the therapeutic window of lymphocytes sequestration agents, allowing better tolerability of higher dosing and thus improving efficacy as monotherapy. The compounds disclosed herein are useful to suppress the immune system in instances where immunosuppression is in order, such as in bone marrow, organ or transplant rejection, autoimmune and chronic inflammatory diseases, including systemic lupus erythematosis, chronic rheumatoid arthritis, type I diabetes mellitus, inflammatory bowel disease, biliary cirrhosis, uveitis, multiple sclerosis, Crohn's disease, ulcerative colitis, bullous pemphigoid,

sarcoidosis, psoriasis, autoimmune myositis, Wegener's granulomatosis, ichthyosis, Graves ophthalmopathy and asthma.

More particularly, the compounds disclosed herein are useful to treat or prevent a disease or disorder selected from the group consisting of: transplantation of organs or tissue, graft-versus-host diseases brought about by transplantation, autoimmune syndromes including rheumatoid arthritis, systemic lupus erythematosus, Hashimoto's thyroiditis, multiple sclerosis, myasthenia gravis, type I diabetes, uveitis, posterior uveitis, allergic encephalomyelitis, glomerulonephritis, post-infectious autoimmune diseases including rheumatic fever and post-infectious glomerulonephritis, inflammatory and hyperproliferative skin diseases, psoriasis, atopic dermatitis, contact dermatitis, eczematous dermatitis, seborrhoeic dermatitis, lichen planus, pemphigus, bullous pemphigoid, epidermolysis bullosa, urticaria, angioedemas, vasculitis, erythema, cutaneous eosinophilia, lupus erythematosus, acne, alopecia areata, keratoconjunctivitis, vernal conjunctivitis, uveitis associated with Behcet's disease, keratitis, herpetic keratitis, conical cornea, dystrophia epithelialis corneae, corneal leukoma, ocular pemphigus, Mooren's ulcer, scleritis, Graves' opthalmopathy, Vogt-Koyanagi-Harada syndrome, sarcoidosis, pollen allergies, reversible obstructive airway disease, bronchial asthma, allergic asthma, intrinsic asthma, extrinsic asthma, dust asthma, chronic or inveterate asthma, late asthma and airway hyper-responsiveness, bronchitis, gastric ulcers, vascular damage caused by ischemic diseases and thrombosis, ischemic bowel diseases, inflammatory bowel diseases, necrotizing enterocolitis, intestinal lesions associated with thermal burns, coeliac diseases, proctitis, eosinophilic gastroenteritis, mastocytosis, Crohn's disease, ulcerative colitis, migraine, rhinitis, eczema, interstitial nephritis, Goodpasture's syndrome, hemolytic-uremic syndrome, diabetic nephropathy, multiple myositis, Guillain-Barre syndrome, Meniere's disease, polyneuritis, multiple neuritis, mononeuritis, radiculopathy, hyperthyroidism, Basedow's disease, pure red cell aplasia, aplastic anemia, hypoplastic anemia, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, agranulocytosis, pernicious anemia, megaloblastic anemia, anerythroplasia, osteoporosis, sarcoidosis, fibroid lung, idiopathic interstitial pneumonia, dermatomyositis, leukoderma vulgaris, ichthyosis vulgaris, photoallergic sensitivity, cutaneous T cell lymphoma, arteriosclerosis, atherosclerosis, aortitis syndrome, polyarteritis nodosa, myocardosis, scleroderma, Wegener's granuloma,

Sjogren's syndrome, adiposis, eosinophilic fascitis, lesions of gingiva, periodontium, alveolar bone, substantia ossea dentis, glomerulonephritis, male pattern alopecia or alopecia senilis by preventing epilation or providing hair germination and/or promoting hair generation and hair growth, muscular dystrophy, pyoderma and Sezary's syndrome, Addison's disease, ischemia-reperfusion injury of organs which occurs upon preservation, transplantation or ischemic disease, endotoxin-shock, pseudomembranous colitis, colitis caused by drug or radiation, ischemic acute renal insufficiency, chronic renal insufficiency, toxinosis caused by lung-oxygen or drugs, lung cancer, pulmonary emphysema, cataracta, siderosis, retinitis pigmentosa, senile macular degeneration, vitreal scarring, corneal alkali burn, dermatitis erythema multiforme, linear IgA ballous dermatitis and cement dermatitis, gingivitis, periodontitis, sepsis, pancreatitis, diseases caused by environmental pollution, aging, carcinogenesis, metastasis of carcinoma and hypobaropathy, disease caused by histamine or leukotriene-C_4 release, Behcet's disease, autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis, partial liver resection, acute liver necrosis, necrosis caused by toxin, viral hepatitis, shock, or anoxia, B-virus hepatitis, non-A/non-B hepatitis, cirrhosis, alcoholic cirrhosis, hepatic failure, fulminant hepatic failure, late-onset hepatic failure, "acute-on-chronic" liver failure, augmentation of chemotherapeutic effect, cytomegalovirus infection, HCMV infection, AIDS, cancer, senile dementia, trauma, and chronic bacterial infection.

Also embodied within the present invention is a method of preventing or treating resistance to transplantation or transplantation rejection of organs or tissues in a mammalian patient in need thereof, which comprises administering a therapeutically effective amount of the compounds of the present invention.

A method of suppressing the immune system in a mammalian patient in need thereof, which comprises administering to the patient an immune system suppressing amount of the compounds of the present invention is yet another embodiment.

Most particularly, the method described herein encompasses a method of treating or preventing bone marrow or organ transplant rejection which is comprised of admininstering to a mammalian patient in need of such treatment or prevention a compound of the present invention, or a pharmaceutically acceptable salt

or hydrate thereof, in an amount that is effective for treating or preventing bone marrow or organ transplant rejection.

A pharmaceutical formulation of the present invention comprises a pharmaceutically acceptable carrier and a compound disclosed herein or a pharmaceutically acceptable salt or hydrate thereof. A preferred embodiment of the formulation is one where a second immunosuppressive agent is also included. Examples of such second immunosuppressive agents are, but are not limited to azathioprine, brequinar sodium, deoxyspergualin, mizaribine, mycophenolic acid morpholino ester, cyclosporin, FK-506, rapamycin and FTY720.

The present compounds, including salts and hydrates thereof, are useful in the treatment of autoimmune diseases, including the prevention of rejection of bone marrow transplant, foreign organ transplants and/or related afflictions, diseases and illnesses.

The compounds disclosed herein can be administered by any means that effects contact of the active ingredient compound with the site of action in the body of a warm-blooded animal. For example, administration, can be oral, topical, including transdermal, ocular, buccal, intranasal, inhalation, intravaginal, rectal, intracisternal and parenteral. The term "parenteral" as used herein refers to modes of administration which include subcutaneous, intravenous, intramuscular, intraarticular injection or infusion, intrasternal and intraperitoneal.

The compounds can be administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in a combination of therapeutic agents. They can be administered alone, but are generally administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage administered will be dependent on the age, health and weight of the recipient, the extent of disease, kind of concurrent treatment, if any, frequency of treatment and the nature of the effect desired. Usually, a daily dosage of active ingredient compound will be from about 0.1-2000 milligrams per day. Ordinarily, from 1 to 100 milligrams per day in one or more applications is effective to obtain desired results. These dosages are the effective amounts for the treatment of autoimmune diseases, the prevention of rejection of foreign organ transplants and/or related afflictions, diseases and illnesses.

The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets, troches, dragées, granules and powders, or in liquid dosage forms, such as elixirs, syrups, emulsions, dispersions, and suspensions. The active ingredient can also be administered parenterally, in sterile liquid dosage forms, such as dispersions, suspensions or solutions. Other dosages forms that can also be used to administer the active ingredient as an ointment, cream, drops, transdermal patch or powder for topical administration, as an ophthalmic solution or suspension formation, i.e., eye drops, for ocular administration, as an aerosol spray or powder composition for inhalation or intranasal administration, or as a cream, ointment, spray or suppository for rectal or vaginal administration.

Gelatin capsules contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene gycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propylparaben, and chlorobutanol.

Suitable pharmaceutical carriers are described in *Remington's Pharmaceutical Sciences*, A. Osol, a standard reference text in this field.

For administration by inhalation, the compounds disclosed herein may be conveniently delivered in the form of an aerosol spray presentation from pressurized packs or nebulisers. The compounds may also be delivered as powders

which may be formulated and the powder composition may be inhaled with the aid of an insufflation powder inhaler device. The preferred delivery system for inhalation is a metered dose inhalation (MDI) aerosol, which may be formulated as a suspension or solution of a compound of the present invention in suitable propellants, such as fluorocarbons or hydrocarbons.

For ocular administration, an ophthalmic preparation may be formulated with an appropriate weight percent solution or suspension of the compounds of the present invention in an appropriate ophthalmic vehicle, such that the compound is maintained in contact with the ocular surface for a sufficient time period to allow the compound to penetrate the corneal and internal regions of the eye.

Useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

CAPSULES

A large number of unit capsules are prepared by filling standard two-piece hard gelatin capsules each with 100 milligrams of powdered active ingredient, 150 milligrams of lactose, 50 milligrams of cellulose, and 6 milligrams magnesium stearate.

SOFT GELATIN CAPSULES

A mixture of active ingredient in a digestible oil such as soybean oil, cottonseed oil or olive oil is prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 100 milligrams of the active ingredient. The capsules are washed and dried.

TABLETS

A large number of tablets are prepared by conventional procedures so that the dosage unit is 100 milligrams of active ingredient, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 milligrams of microcrystalline cellulose, 11 milligrams of starch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

INJECTABLE

A parenteral composition suitable for administration by injection is prepared by stirring 1.5% by weight of active ingredient in 10% by volume propylene glycol. The solution is made to volume with water for injection and sterilized.

SUSPENSION

An aqueous suspension is prepared for oral administration so that each 5 milliliters contain 100 milligrams of finely divided active ingredient, 100 milligrams of sodium carboxymethyl cellulose, 5 milligrams of sodium benzoate, 1.0 grams of sorbitol solution, U.S.P., and 0.025 milliliters of vanillin.

The same dosage forms can generally be used when the compounds of this invention are administered stepwise or in conjunction with another therapeutic agent. When drugs are administered in physical combination, the dosage form and administration route should be selected depending on the compatibility of the combined drugs. Thus the term coadministration is understood to include the administration of the two agents concomitantly or sequentially, or alternatively as a fixed dose combination of the two active components.

Methods for preparing the compounds of this invention are illustrated in the following schemes and examples. Alternative routes will be easily discernible to practitioners in the field.

In the tables that follow, any NMR data follows the compounds:

PREPARATION OF N-BENZYL PYRROLIDINE AND N-BENZYL AZETIDINE CARBOXYLATES, PHOSPHINATES AND PHOSPHANATES

Examples I-LVIII have the following structures:

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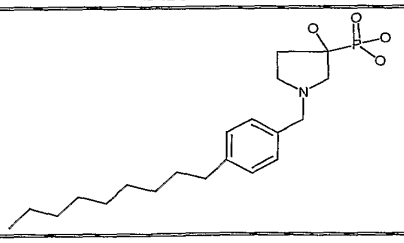
I	

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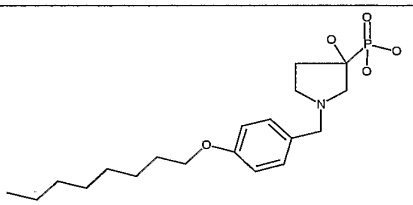
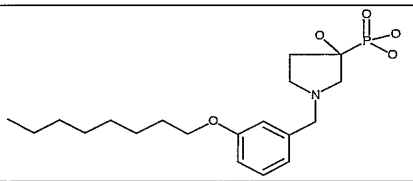
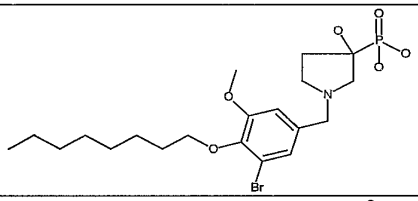
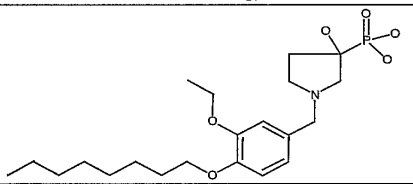
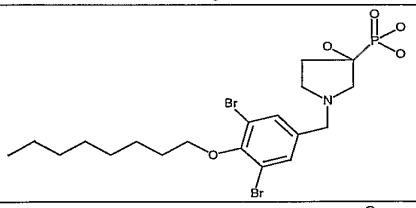
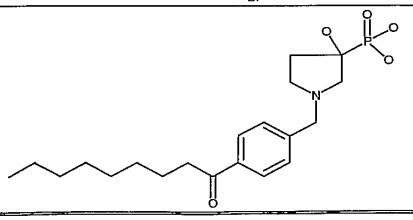
II	
III	
IV	
V + VI	
VII	
VIII	

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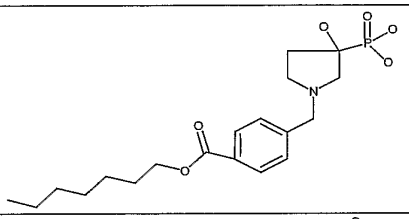
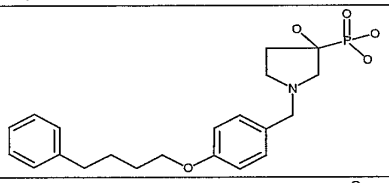
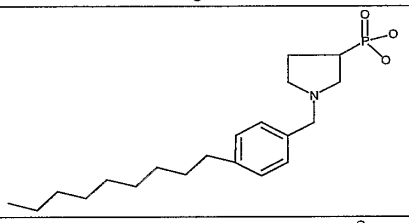
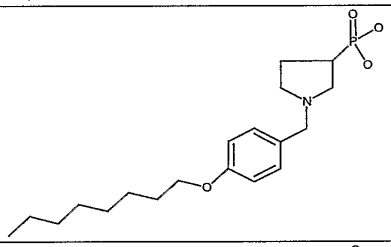
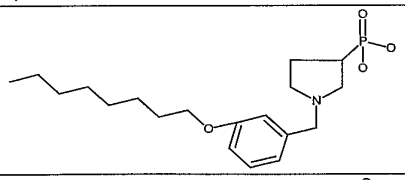
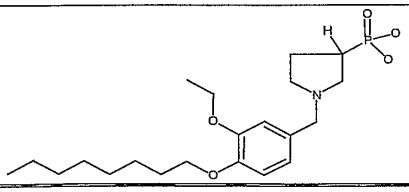
IX	
X	
XI	
XII	
XIII	
XIV	

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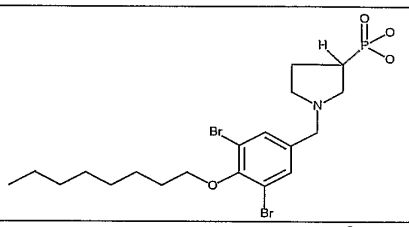
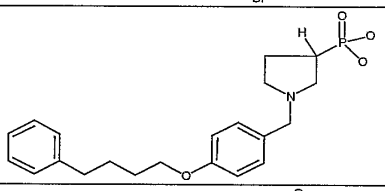
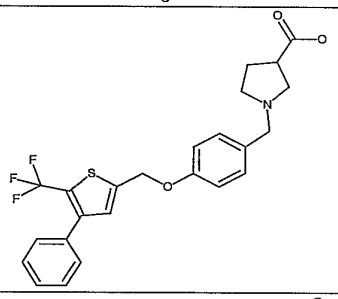
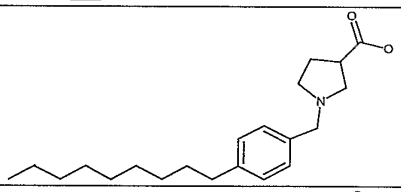
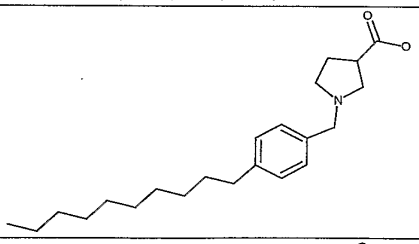
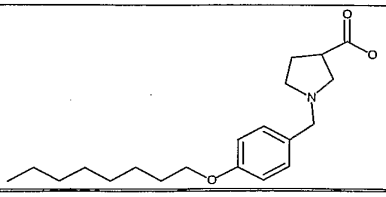
XV + XVI	
XVII	
XVIII	
XIX	
XX	
XXI	

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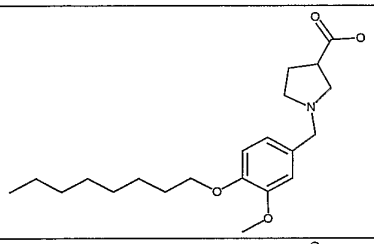
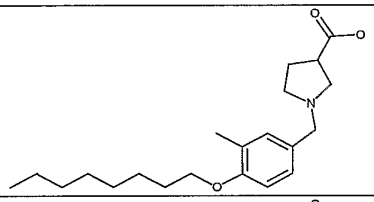
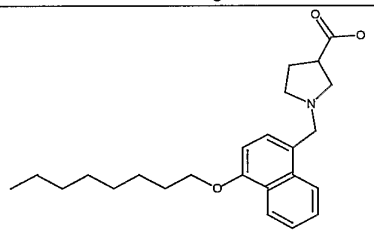
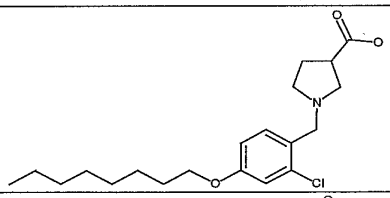
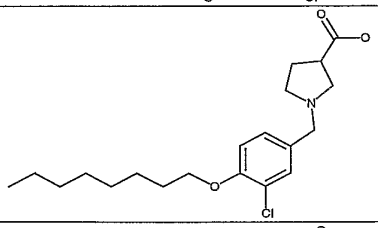
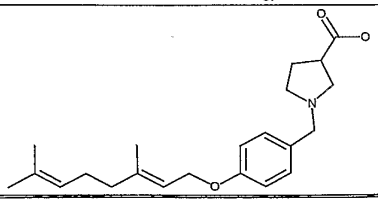
XXII	
XXIII	
XXIV	
XXV	
XXVI	
XXVII	

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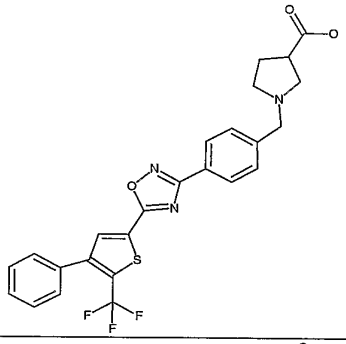
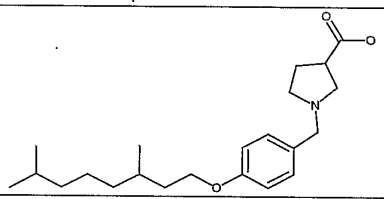
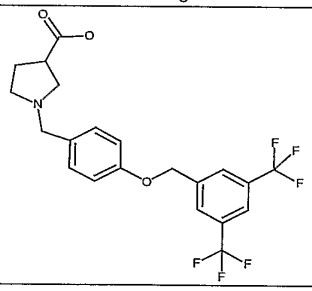
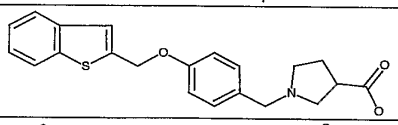
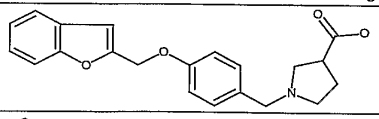
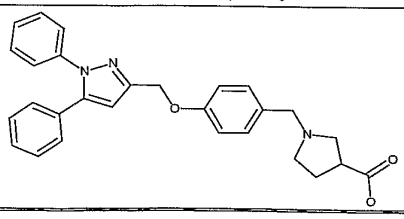
XXVIII	
XXIX	
XXX	
XXXI	
XXXII	
XXXIII	

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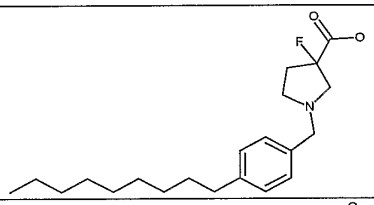
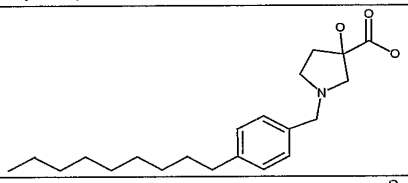
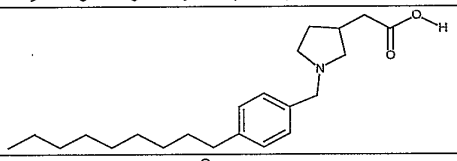
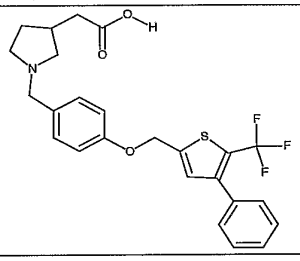
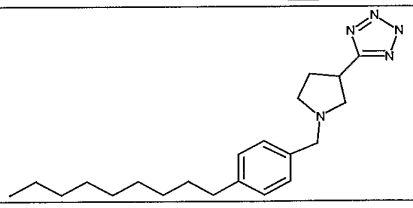
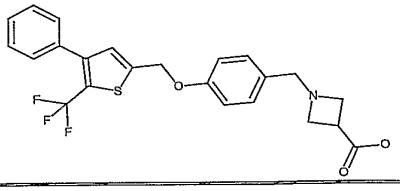
XXXV	
XXXVI	
XXXVII	
XXXVIII	
XXXIX	
XL	

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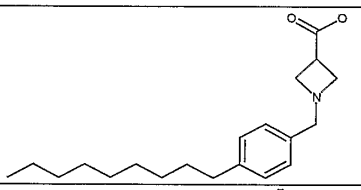
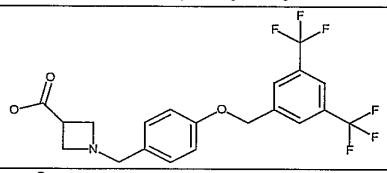
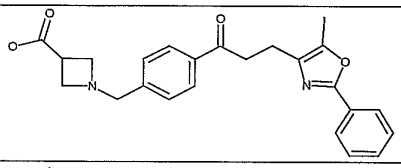
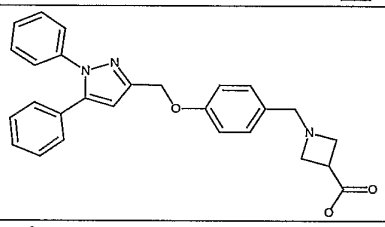
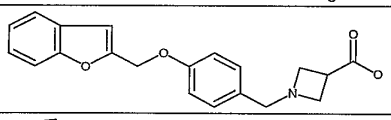
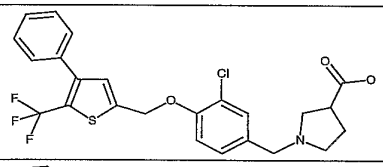
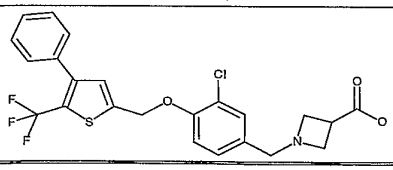
XLI	
XLII	
XLIII	
XLIV	
XLV	
XLVI	
XLVII	

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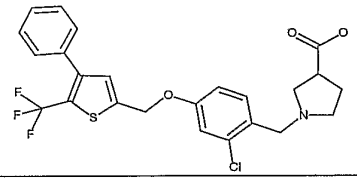
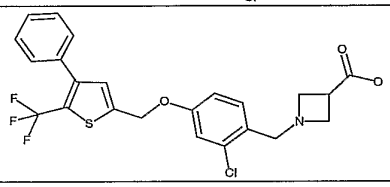
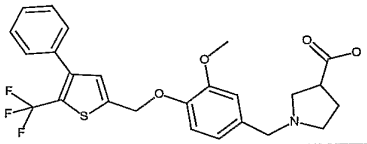
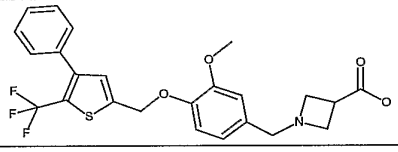
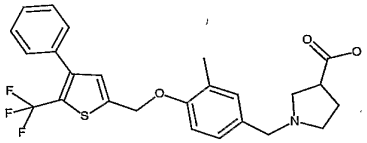
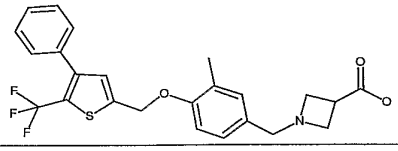
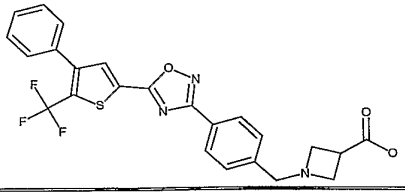
XLVIII	
XLIX	
L	
LI	
LII	
LIII	
LIV	

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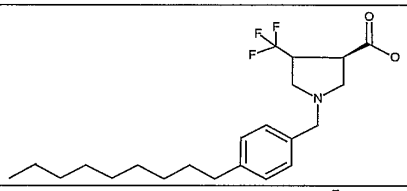
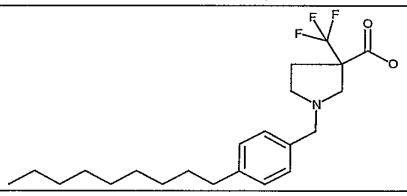
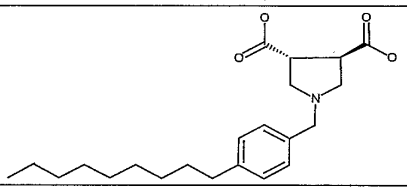
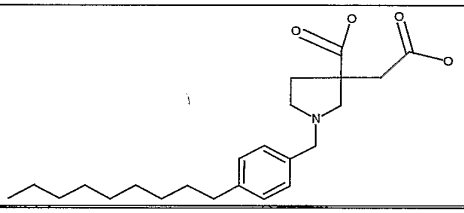
LV	
LVI	
LVII	
LVIII	

GENERAL

Concentration of solutions was carried out on a rotary evaporator under reduced pressure. Conventional flash chromatography was carried out on silica gel (230-400 mesh). Flash chromatography was also carried out using a Biotage Flash Chromatography apparatus (Dyax Corp.) on silica gel (32-63 mM, 60 Å pore size) in pre-packed cartridges of the size noted. NMR spectra were obtained in $CDCl_3$ solution unless otherwise noted. Coupling constants (J) are in hertz (Hz). Abbreviations: diethyl ether (ether), triethylamine (TEA), N,N-diisopropylethylamine (DIEA) sat'd aqueous (sat'd), rt (rt), hour(s) (h), minute(s) (min).

HPLC CONDITIONS

LC-1: Waters Xterra MS C18, 5 μ, 4.6 x 50 mm column, 10:90 to 95:5 v/v CH_3CN/H_2O + 0.05% TFA over 4.5 min, hold 1 min, PDA detection 200-600 nm, flow rate = 2.5 mL/min.

LC-2: Analytical Sales and Service Armor C8 5 μ 20 x 100 mm column, 10:90 to 90:10 v/v CH_3CN/H_2O + 0.05% TFA over 12 min, hold 4 min, UV detection at either 210 or 254 nM, flow rate = 10 mL/min.

PREPARATION OF ALDEHYDE INTERMEDIATES

Aldehyde I

4-Nonylbenzaldehyde

A solution of 2.0 g (7.5 mmol) of 4-nonylbenzoyl chloride in 75 mL of THF at –78 °C was treated with 7.5 mL (7.5 mmol) of 1M lithium tri-(tert-butoxy) aluminum hydride in THF. After 30 min at –78 °C, the reaction was quenched with 2N HCl and was allowed to warm to rt. The mixture was poured into Et_2O and washed with 2N HCl, sat'd $NaHCO_3$ and sat'd NaCl. The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified on a 40M Biotage column using 100:1 v/v hexane/Et_2O as the eluant to afford 708 mg (41%) of the title compound: ^{1}H-NMR (500 MHz) δ 0.87 (t, J = 7.0, 3H), 1.26-1.31 (m, 12H), 1.60-1.66 (m, 2H), 2.68 (t, J = 7.8, 2H), 7.32 (d, J = 8.0, 2H), 7.79 (d, J = 8.0, 2H), 9.97 (s, 1H).

Aldehyde II

4-Decylbenzaldehyde

The title compound was prepared using a procedure analogous to Aldehyde II substituting 4-decylbenzoyl chloride for 4-nonylbenzoyl chloride: ^{1}H-NMR (500 MHz) δ 0.87 (t, J = 6.9, 3H), 1.25-1.31 (m, 14H), 1.60-1.66 (m, 2H), 2.68 (t, J = 7.7, 2H), 7.33 (d, J = 8.0, 2H), 7.79 (d, J = 8.0, 2H), 9.97 (s, 1H).

Aldehyde III

3-(Octyloxy)benzaldehyde

A mixture of 1.00 g (0.82 mmol) of 3-hydroxybenzaldehyde, 1.70 g (12.2 mmol) of potassium carbonate and 2.16 g (9.00 mmol) of 1-iodooctane were warmed in acetonitrile at 80 °C for 16 h. The reaction was cooled, filtered and concentrated. The residue was purified using flash chromatography using 20:1 v/v hexane/ethyl acetate to afford 1.63 g of the title compound as a colorless oil: ^{1}H-NMR (500 MHz) δ 0.89 (t, J = 6.9, 3H), 1.24-1.39 (m, 8H), 1.42-1.50 (m, 2H), 1.80 (m, 2H), 4.01 (t, J = 6.6, 2H), 7.19 (m, 1H), 7.40 (s, 1H), 7.44-7.46 (m, 2H), 9.99 (s, 1H).

Aldehyde IV

4-(Octyloxy)benzaldehyde

The title compound was prepared using a procedure analogous to Aldehyde III substituting 4-hydroxybenzaldehyde for 3-hydroxybenzaldehyde: ^{1}H NMR (500 MHz) δ 0.91 (t, J = 6.9, 3H), 1.29-1.41 (m, 8H), 1.46-1.52 (m, 2H), 1.71-1.86 (m, 2H), 4.06 (t, J = 6.6, 2H), 7.01 (d, J = 8.7, 2H), 7.85 (d, J = 8.7, 2H), 9.90 (s, 1H).

Aldehyde V

3-Bromo-5-methoxy-4-octyloxybenzaldehyde

The title compound was prepared using a procedure analogous to Aldehyde III substituting 3-bromo-4-hydroxy-5-methoxybenzaldehyde for 3-hydroxybenzaldehyde: ESI-MS: 343 (M+H)

Aldehyde VI

3-Ethoxy-4-(octyloxy)benzaldehyde

The title compound was prepared using a procedure analogous to Aldehyde III substituting 3-ethoxy-4-hydroxybenzaldehyde for 3-hydroxybenzaldehyde: ^{1}H-NMR (500 MHz) δ 0.88-0.98 (m, 3H), 1.30-1.41 (m, 8H), 1.46-1.51 (m, 5H), 1.85-1.91 (m, 2H), 4.06-4.18 (m, 4H), 6.97 (d, J = 8.0, 1H), 7.39-7.44 (m, 2H), 9.84 (s, 1H); ESI-MS 279.1 (M+H).

Aldehyde VII

3,5-Dibromo-4-(octyloxy)benzaldehyde

The title compound was prepared using a procedure analogous to Aldehyde III substituting 3,5-dibromo-4-hydroxybenzaldehyde for 3-hydroxybenzaldehyde.

Aldehyde VIII

3-Methoxy-4-(octyloxy)benzaldehyde

The title compound was prepared using a procedure analogous to Aldehyde III substituting 3-methoxy-4-hydroxybenzaldehyde for 3-hydroxybenzaldehyde: ESI-MS 265.2 (M+H)

Aldehyde IX

3-Methyl-4-(octyloxy)benzaldehyde

The title compound was prepared using a procedure analogous to Aldehyde III substituting 3-methyl-4-hydroxybenzaldehyde for 3-hydroxybenzaldehyde.

Aldehyde X

4-(Octyloxy)-1-naphthaldehyde

The title compound was prepared using a procedure analogous to Aldehyde III substituting 4-hydroxy-1-naphthaldehyde for 3-hydroxybenzaldehyde.

Aldehyde XI

2-Chloro-4-(octyloxy)benzaldehyde

The title compound was prepared using a procedure analogous to Aldehyde III substituting 2-chloro-4-hydroxybenzaldehyde for 3-hydroxybenzaldehyde: ESI-MS 269.0 (M+H)

Aldehyde XII

3-Chloro-4-(octyloxy)benzaldehyde

The title compound was prepared using a procedure analogous to Aldehyde III substituting 3-chloro-4-hydroxybenzaldehyde for 3-hydroxybenzaldehyde.

Aldehyde XIII

4-(*trans*-3,7-Dimethyl-2,6-octadien-1-yloxy)benzaldehyde

The title compound was prepared using a procedure analogous to Aldehyde III using 4-hydroxybenzaldehyde and geranyl bromide: R_F: 0.29 (19:1 v/v hexane/EtOAc); ^{1}H-NMR (500 MHz) δ 1.58-1.83 (m, 9H), 2.00-2.16 (m, 4H), 4.65 (d, J = 6.6, 2H), 5.10 (m, 1H), 5.50 (m, 1H), 7.02 (d, J = 8.7, 2H), 7.85 (d, J = 8.7, 2H), 9.90 (s, 1H).

Aldehyde XIV

4-[Bis(3,5-trifluoromethyl)benzyloxy]benzaldehyde

The title compound was prepared using a procedure analogous to Aldehyde III using 4-hydroxybenzaldehyde and bis(3,5-trifluoromethyl)benzyl bromide: R_F: 0.28 (9:1 v/v hexane/EtOAc); ^{1}H-NMR (500 MHz) δ 5.28 (s, 2H), 7.14 (d, J = 8.7, 2H), 7.91-7.95 (m, 5H), 9.95 (s, 1H).

Aldehyde XV

3-(4-(Formyl)phenyl)-5-(4-phenyl-5-trifluoromethyl-2-thienyl)-1,2,4-oxadiazole

Step A: (E/Z)-2-Phenyl-3-chloro-4,4,4-trifluoro-2-butanal

Phosphorous oxychloride (7.5 mL, 80 mmol) was added to 15 mL of DMF at 0 °C. The resulting mixture was warmed to rt and stirred for 1 h. A solution of 5.0 g (26.6 mmol) of 1,1,1-trifluoromethyl-3-phenyl-2-propanone in 1 mL of DMF was added and the resulting mixture was stirred at 70 °C for 20 h. The reaction mixture was cooled to rt, poured onto 150 g of ice and stirred at ambient temperature for 1 h. The quenched mixture was extracted with 200 mL of ether. The extract was washed with 200 mL of water, dried and concentrated. Chromatography on a Biotage 40 M cartridge using hexanes (4L) as the eluant afforded 5.1 g (82%) of the title compound.

Step B: Ethyl (4-phenyl-5-trifluoromethyl)thiophene-2-carboxylate

Ethyl mercaptoacetate (2.75 mL, 25.0 mmol) was added to a suspension of 600 mg (25 mmol) of NaH in 45 mL of THF maintaining the internal temperature at 25 °C. A solution of 5.10 g (21.7 mmol) of (E/Z)-2-phenyl-3-chloro-4,4,4-trifluoro-2-butanal (from Step A) was added and the resulting mixture was stirred at rt for 20 h. The reaction was quenched with 50 mL of sat'd NH_4Cl and the resulting mixture was partitioned between 250 mL of ether and 100 mL of water. The organic layer was separated, dried and concentrated. Chromatography on a Biotage 40 M cartridge using hexanes (1L), then 4:1 v/v hexanes/CH_2Cl_2 (1L) as the eluant afforded 5.10 g (78%) of the title compound: ^1H NMR (400 Mhz) δ 1.40 (t, J= 7.2, 3H), 4.39 (q, J= 7.2, 2H), 7.42 (app s, 5H), 7.74 (q, J=1.6, 1H).

Step C: (4-Phenyl-5-trifluoromethyl)thiophene-2-carboxylic acid

A solution of 5.10 g (17.0 mmol) of ethyl 4-phenyl-5-trifluoromethyl-thiophene-2-carboxylate (from Step B) in 20 mL of EtOH was treated with 10 mL of 5.0 N NaOH and stirred at rt for 30 min. The EtOH was removed in vacuo. The residual aqueous mixture was acidified to pH 2 with 1 N HCl, then extracted with 300 mL of 1:1 v/v EtOAc/ether. The extract was separated, dried and concentrated. Recrystallization from 200 mL of 20:1 v/v hexanes/ether afforded 4.30 g (93%) of the title compound: ^1H NMR (500 Mhz) δ 7.43 (app s, 5H), 7.84 (app s, 1H); ^{13}C NMR ($CDCl_3$, 125 Mhz) δ 121.7 (q, J= 269), 128.5, 128.6, 128.8, 132.5 (q, J= 36), 133.3, 133.8, 137.5, 144.8, 167.0.

Step D: 3-[4-(Carbomethoxy)phenyl]-5-(4-phenyl-5-trifluoromethyl-2-thienyl)-1,2,4-oxadiazole

A solution of 408 mg (1.5 mmol) of 4-phenyl-5-trifluoromethyl-thiophene-2-carboxylic acid and 1 mL of oxalyl chloride in 5 mL of CH_2Cl_2 was treated with 5 drops of DMF. The resulting mixture was stirred at rt for 1 h, then concentrated. The crude acid chloride and 291 mg (1.5 mmol) of 4-(carbomethoxy)benzamidoxime were dissolved in 7 mL of 6:1 v/v xylenes/pyridine. The resulting solution was heated at 140 °C for 1 h, then cooled. The mixture was partitioned between 50 mL of 1:1 EtOAc/ether and 50 mL of 1 N HCl. The organic layer was separated, washed with 3 x 50 mL of 1 N HCl, 50 mL of sat'd $NaHCO_3$, dried and concentrated. Chromatography on a Biotage 40 M cartridge using hexanes

(1L), then 20:1 v/v hexanes/EtOAc (1L) as the eluant afforded 423 mg (65%) of the title compound: ^{1}H NMR (500 Mhz) δ 3.97 (s, 3H), 7.48 (app s, 5H), 7.92 (s, 1H), 8.18 (app d, J= 8.5, 2H), 8.23 (app d, J= 8.5, 2H).

Step E: 3-[4-(Hydroxymethyl)phenyl]-5-(4-phenyl-5-trifluoromethyl-2-thienyl)-1,2,4-oxadiazole

A solution of 390 mg (0.91 mmol) of 3-[4-(carbomethoxy)phenyl]-5-(4-phenyl-5-trifluoromethyl-2-thienyl)-1,2,4-oxadiazole (from Step D) in 10 mL of CH_2Cl_2 at –78 °C was treated with 2.7 mL of 1.0 M DIBALH solution in CH_2Cl_2. The resulting solution was stirred cold for 1 h, then quenched with 5 mL of sat'd Rochelle salt solution. The mixture was partitioned between 100 mL CH_2Cl_2 and 50 mL of 1 N NaOH. The organic layer was separated, dried and concentrated. Chromatography on a Biotage 40 S cartridge using 4:1 v/v hexanes/EtOAc (1L) as the eluant afforded 325 mg (89%) of the title compound: ^{1}H NMR (500 Mhz) δ 1.80 (app s, 1H), 4.80 (d, J= 4.0, 2H), 7.46-7.48 (5H), 7.52 (d, J= 8.0, 2H), 7.91 (q, J= 1.5, 1H), 8.14 (d, J= 8.0, 2H).

Step F: 3-[4-(Formyl)phenyl]-5-(4-phenyl-5-trifluoromethyl-2-thienyl)-1,2,4-oxadiazole

A mixture of 310 mg (0.77 mmol) of 3-[4-(hydroxymethyl)phenyl]-5-(4-phenyl-5-trifluoromethyl-2-thienyl)-1,2,4-oxadiazole (from Step E), 527 mg (1.5 mmol) of 4-methylmorpholine N-oxide and 500 mg of 4 A molecular sieves in 15 mL of CH_3CN was treated with 12 mg (0.034 mmol) of tetrapropylammonium perruthnate and the resulting mixture was stirred ar rt for 2 h. The solids were filtered and the filtrated was concentrated. Chromatography on a Biotage 40 S cartridge using 9:1 v/v hexanes/EtOAc (1L) as the eluant afforded 205 mg (66%) of the title compound: ^{1}H NMR (500 Mhz) δ 7.48 (app s, 5H), 7.93 (app s, 1H), 8.03 (d, J= 8.5, 2H), 8.33 (d, J= 8.5, 2H), 10.1 (s, 1H).

Aldehyde XVI

4-[(4-Phenyl-5-trifluoromethyl-2-thienyl)methoxy]benzaldehyde

Step A: 2-Hydroxymethyl-4-phenyl-5-trifluoromethyl-thiophene

A solution of 2.10 g (7.7 mmol) of 4-phenyl-5-trifluoromethyl-thiophene-2-carboxylic acid (from Aldehyde XV, Step C) in 20 mL of THF was treated with 5.0 mL of 2.0 M borane dimethylsulfide complex in THF. The resulting solution was heated at reflux for 3 h, cooled to rt, quenched with 10 mL of MeOH and concentrated. Chromatography on a Biotage 40M cartridge using 9:1 v/v hexanes/EtOAc as the eluant afforded 1.95 g (98%) of the title compound: ^{1}H NMR (500 Mhz) δ 2.05 (app s, 1H), 4.87 (s, 2H), 6.99 (s, 1H), 7.41 (app s, 5H).

Step B: 4-((4-Phenyl-5-trifluoromethyl-2-thienyl)methoxy)benzaldehyde

A solution of 1.95 g (7.5 mmol) of 2-hydroxymethyl-4-phenyl-5-trifluoromethyl-thiophene (from Step A), 925 mg (7.6 mmol) of 4-hydroxybenzaldehyde and 3.0 g (11.4 mmol) of triphenylphosphene in 40 mL of THF at 0 °C was treated with 2.0 g (11.4 mmol) of diethylazodicarboxylate. The resulting mixture was warmed to rt, stirred for 2 h, then concentrated. Chromatography on a Biotage 75S cartridge using 9:1 v/v heptane/EtOAc as the eluant afforded 2.5 g of impure title compound. Chromatography on a Biotage 40M cartridge using 19:1 v/v hexanes/EtOAc (1L), then 4:1 v/v hexanes/EtOAc (1L) as the eluant afforded 1.65 g (60%) of the title compound: ^{1}H NMR (500 Mhz) δ 5.32 (s, 2H), 7.10 (d, J= 8.5, 2H), 7.12 (s, 1H), 7.41-7.43 (5H), 7.85-7.90 (2H), 9.92 (s, 1H).

Aldehydes 17-21 were prepared using procedures analogous to those described in Aldehyde 16 substituting the appropriately substituted benzaldehyde for 4-(hydroxy)benzaldehyde in Step B:

Aldehyde XVII

3-((4-Phenyl-5-trifluoromethyl-2-thienyl)methoxy)benzaldehyde

Aldehyde XVIII

2-Chloro-4-((4-phenyl-5-trifluoromethyl-2-thienyl)methoxy)benzaldehyde

Aldehyde XIX

3-Chloro-4-((4-phenyl-5-trifluoromethyl-2-thienyl)methoxy)benzaldehyde

Aldehyde XX

3-Methyl-4-((4-phenyl-5-trifluoromethyl-2-thienyl)methoxy)benzaldehyde

Aldehyde XXI

3-Methoxy-4-((4-phenyl-5-trifluoromethyl-2-thienyl)methoxy)benzaldehyde

Aldehyde XXII

4-(4-Phenylbutoxy)benzaldehyde

The title compound was prepared using a procedure analogous to Aldehyde IV substituting 4-(iodobutyl)benzene for 1-iodooctane: ESI-MS 255.2 (M+H)

Aldehyde XXIII

4-(Non-1-oyl)benzaldehyde

Step A: 4-(1-Hydroxynon-1-yl)benzaldehyde

Terephthaldicarboxaldehyde (2.00 g, 14.91 mmol) was dissolved in tetrahydrofuran (25 ml) and cooled to 0°C. Octylmagnesium chloride (7.5 ml, 2.0M in THF, 15 mmol) was added dropwise. After 15 minutes, the reaction was quenched with 2N aqueous hydrochloric acid (50 ml) and diluted with ethyl acetate (50 ml). The organic layer was separated, washed with sat'd NaCl (50 ml), dried over magnesium sulfate and concentrated . Silica gel chromatography eluting with 91:9 v/v hexane/EtOAc gave 0.19 g (0.77 mmol, 5.1%) of the title compound: ^{1}H NMR (500 MHz) δ 10.0 (s, 1H), 7.87 (d, J = 8.0, 2H), 7.52 (d, J = 8.3, 2H), 4.75-4.80 (m, 1H), 1.68-1.82 (m, 2H), 1.22-1.45 (m, 12H), 0.91 (t, J = 7.0, 3H).

Step B: 4-(Non-1-oyl)benzaldehyde

Dess-Martin periodinane (0.268 g, 0.632 mmol) was added to a solution of 4-(1-hydroxynon-1-yl)benzaldehyde (0.125 g, 0.505 mmol) from Step A in CH_2Cl_2 (3.0 ml). After 1 h, the reaction was filtered and concentrated. Silica gel chromatography eluting with 19:1 v/v hexane/EtOAc gave 0.107 g (0.446 mmol, 88%) of the title compound: ^{1}H NMR (500 MHz) δ 10.1 (s, 1H), 8.10 (d, J = 8.2,

2H), 7.97 (d, J = 8.2, 2H), 3.00 (t, J = 7.3, 2H), 1.70-1.8 (m, 2H), 1.22-1.42 (m, 10H), 0.88 (t, J = 7.0, 3H).

Aldehyde XXIV

Heptyl 4-(formyl)benzoate

The title compound was prepared through a condensation between 1-heptanol and 4-formylbenzoic acid. ^{1}H NMR (500 MHz , $CDCl_3$): δ 10.10 (s, 1H), 8.20 (d, J = 8.2, 2H), 7.95 (d, J = 8.2, 2H), 4.35 (t, J = 6.8, 2H), 1.75-1.85 (m, 2H), 1.40-1.50 (m, 2H), 1.25-1.40 (m, 6H), 0.89 (t, J = 7.0, 3H).

Aldehydes XXV and XXVI were prepared using procedures analogous to those described in Aldehyde 16 substituting the appropriately substituted alcohol for 2-hydroxymethyl-4-phenyl-5-trifluoromethyl-thiophene in Step B:

Aldehyde XXV

4-[(Benzothien-2-yl)methoxy]benzaldehyde

^{1}H NMR (500 MHz) δ 5.34 (s, 2H), 7.04 (d, J = 8.7, 2H), 7.18 (s, 1H), 7.25-7.30 (m, 4H), 7.76 (d, J = 8.7, 2H), 9.82 (s, 1H).

Aldehyde XXVI

4-[(2,3-Diphenyl-2H-pyrazol-5-yl)methoxy]benzaldehyde

^{1}H NMR (500 MHz) δ 5.21 (s, 2H), 6.55 (s, 1H), 7.10 (d, J = 8.7, 2H), 7.14-7.17 (m, 5H), 7.21-7.30 (m, 5H), 7.79 (d, J = 8.7, 2H), 9.82 (s, 1H).

PREPARATION OF EXAMPLES

EXAMPLE I

(R/S)-1-(4-(Nonyl)phenyl)methyl-3-hydroxy-pyrrolidin-3-yl)phosphonic acid

Step A: (R/S)-1-tert-Butoxycarbonyl-3-hydroxypyrrolidine

A solution of 2.5 g (28.7 mmol) of (R/S)-3-hydroxypyrrolidine in 10 mL of CH_2Cl_2 at 0 °C was treated with 6.89 g (31.6 mmol) of di-tert-butyl-dicarbonate in 2 mL CH_2Cl_2 and 0.35 g (2.8 mmol) of 4-(N,N-dimethylamino) pyridine. After stirring for 10 min, the reaction was warmed to rt and stirred overnight. The reaction was diluted with 100 mL of CH_2Cl_2 and washed with 100 mL of 1N HCl and 100 mL of 1N $NaHCO_3$. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified on a 40M Biotage column using 7:3 v/v hexane/acetone as the eluant to afford 5.3 g (99%) of the title compound: R_F: 0.26 (7:3 v/v hexane/acetone); ^{1}H-NMR (500 MHz) δ 1.45 (s, 9H), 1.88-2.00 (m, 2H), 2.52 (br s, 1H), 3.29-3.50 (m, 4H), 4.42 (m, 1H).

Step B: 1-tert-Butoxycarbonyl-3-oxo-pyrrolidine

A solution of 2.3 mL (26 mmol) of oxalyl chloride in 80 mL of CH_2Cl_2 at -78 °C was treated with 3.8 mL (53 mmol) of DMSO in 5 mL of CH_2Cl_2. The resulting mixture was stirred cold for 5 min. A solution of 2.0 g (10.7 mmol) of (R/S)-1-tert-butoxycarbonyl-3-hydroxypyrrolidine (from Step A) in 10 mL of CH_2Cl_2 was added. The resulting mixture was stirred for 30 min, treated with 18.7 mL (107 mmol) of DIEA and warmed to 0 °C. After stirring for 45 min, the reaction was quenched with H_2O and poured into 100 mL of 1N HCl. After separating the layers, the organic layer was washed with 100 mL sat'd NaCl, dried over Na_2SO_4 and concentrated. The residue was purified on a 40M Biotage column using 4:1 v/v hexane/acetone as the eluant to afford 1.9 g (96%) of the title compound: R_F: 0.49 (7:3 v/v hexane/acetone); ^{1}H-NMR (500 MHz) δ 1.48 (s, 9H), 2.58 (t, J = 7.9, 2H), 3.71-3.78 (m, 4H).

Step C: (R/S)-1-tert-Butoxycarbonyl-3-hydroxy-pyrrolidin-3-yl phosphonic acid, diethyl ester

A mixture of 1.9 g (10.3 mmol) of 1-tert-butoxycarbonyl-3-oxopyrrolidine (from Step B), 1.3 mL (10.3 mmol) of diethyl phosphite and 1.4 mL (10.3 mmol) of TEA was stirred at 100 °C for 1.5 h. Volatiles were removed under reduced pressure. The residue was purified on a 40M Biotage column using 13:7 v/v hexane/acetone as the eluant to afford 1.78 g (53%) of the title compound as a yellow

oil: R_F: 0.16 (7:3 v/v hexane/acetone); ^{1}H-NMR (500 MHz) δ 1.33 (t, J = 7.0, 6H), 1.45 (s, 9H), 2.08 (m, 1H), 2.18 (m, 1H), 3.47-3.64 (m, 4H), 4.13-4.22 (m, 4H).

Step D: (R/S)-3-Hydroxy-pyrrolidin-3-yl phosphonic acid, diethyl ester

A solution of 1.78 g (5.5 mmol) of (R/S)-1-tert-butoxycarbonyl-3-hydroxy-pyrrolidin-3-yl phosphonic acid, diethyl ester (from Step C) in 2N HCl in EtOH was stirred at rt for 5.5 h. The reaction was concentrated from CH_2Cl_2 several times. The crude product was partitioned between aqueous NH_4OH and $CHCl_3$/isopropanol (3:1 v/v). After separating phases, the aqueous layer was extracted with 3X $CHCl_3$/isopropanol (3:1 v/v). The combined organics were dried over Na_2SO_4 and concentrated. The residue was purified on a 40S Biotage column using 90:10:1 v/v/v CH_2Cl_2/MeOH/NH_4OH as the eluant to afford the title compound as a light brown oil: ^{1}H-NMR (500 MHz) δ 1.35 (t, J = 7.0, 6H), 1.92 (m, 1H), 2.20 (m, 1H), 2.78-2.99 (m, 3H), 3.06 (dd, J = 12.7, 3.7, 1H), 3.13 (dd, J = 12.7, 6.2, 1H), 3.20 (m, 1H), 4.16-4.23 (m, 4H).

Step E: (R/S)-1-(4-(Nonylphenyl)methyl-3-hydroxy-pyrrolidin-3-yl phosphonic acid, diethyl ester

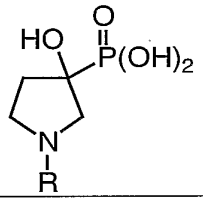
A solution of 60 mg (0.23 mmol) of (R/S)-3-hydroxypyrrolidin-3-ylphosphonic acid, diethyl ester (from Step D) and 54 mg (0.23 mmol) of Aldehyde I in 1.5 mL of CH_2Cl_2 was treated with 73 mg (0.34 mmol) of sodium triacetoxyborohydride. After 3 h at rt, the reaction was diluted with 25 mL of CH_2Cl_2 and washed with 25 mL of 1N $NaHCO_3$. After separating phases, the aqueous layer was extracted with 25 mL of CH_2Cl_2. The combined organic layers were washed with 50 mL of sat'd NaCl, dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography using 3:1 v/v hexane/acetone as the eluant to afford 33 mg (32%) of the title compound: R_F: 0.31 (7:3 v/v hexane/acetone); ^{1}H-NMR (500 MHz) δ 0.89 (t, J = 7.0, 3H), 1.27-1.36 (m, 18H), 1.57-1.63 (m, 2H), 1.97 (m, 1H), 2.41-2.54 (m, 2H), 2.59 (t, J = 7.7, 2H), 2.85-2.92 (m, 2H), 3.01 (m, 1H), 3.67 (ABq, J = 13.1, 2H), 4.16-4.23 (m, 4H), 7.12 (d, J = 7.8, 2H), 7.24 (d, J = 7.8, 2H).

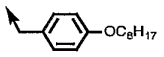
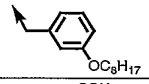
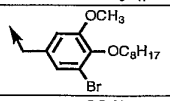
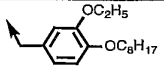
Step F: (R/S)-1-(4-Nonylbenzyl)-3-hydroxypyrrolidin-3-ylphosphonic acid

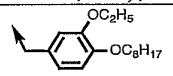
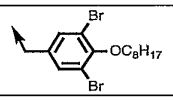
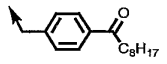
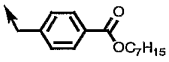
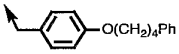
A solution of 33 mg (0.075 mmol) of (R/S)-1-(4-nonylbenzyl)-3-hydroxypyrrolidin-3-ylphosphonic acid, diethyl ester (from Step E) in 1 mL of chloroform was treated with 0.053 mL (0.37 mmol) of iodotrimethylsilane. The reaction was allowed to stir at rt for 1h. The reaction was quenched with MeOH and concentrated several times from MeOH. The residue was purified using LC-2 to afford 4.6 mg (16%) of the title compound: ESI-MS 385 (M+H); LC-1: 3.01 min.

EXAMPLES II-X

EXAMPLES II-X were prepared using procedures analogous to those described in EXAMPLE I substituting the appropriate Aldehyde in Step E. TMS-Br was substituted in Step F with substrates containing TMS-I sensitive functionality (See EXAMPLE 11, Step D). In EXAMPLES V and VI enantiomers were resolved after Step E by preparative chiral HPLC (Chiralpak AD 2 x 25 cm HPLC column, 9:1 v/v hexane/EtOH, flow rate = 9.0 mL/min, λ = 210 nM).



EXAMPLE #	R	HPLC Method	HPLC RT (min)	ESI-MS (M+H)
II		LC-1	2.7	386
III		LC-1	2.7	386
IV		LC-1	3.0	496
V Enantiomer 1		LC-1	2.8	430

^{1}H-NMR (500 MHz, CD_3OD) δ 0.92 (t, J = 7.0, 3H), 1.20-1.54 (m, 9H), 1.79-1.84 (m, 2H), 2.23 (m, 1H), 2.35 (m, 1H), 2.43 (m, 1H), 2.68 (m, 1H), 3.41-3.50 (m, 2H), 3.58 (m, 1H), 3.68 (m, 1H), 3.75-3.79 (m, 2H), 4.04 (t, J = 6.4, 2H), 4.11-4.15 (m, 2H), 4.38 (ABq, J = 12.9, 2H), 7.02-7.09 (m, 2H), 7.17 (s, 1H)				
VI Enantiomer 2		LC-1	2.8	430
VII		LC-1	3.1	544
^{1}H-NMR (500 MHz, CD_3OD) δ 0.93 (t, J = 6.8, 3H), 1.20-1.46 (m, 9H), 1.55-1.61 (m, 2H), 1.86-1.92 (m, 2H), 2.23-2.35 (m, 2H), 2.72 (m, 1H), 3.47-3.79 (br m, 3H), 4.06 (t, J = 6.4, 2H), 4.44-4.50 (m, 2H), 7.86 (s, 2H)				
VIII		LC-1	2.6	398
IX		LC-1	2.5	400
X		LC-1	2.4	406

EXAMPLE XI

(R/S)-1-(4-Nonylphenyl)methyl-pyrrolidin-3-yl phosphonic acid

Step A: (R/S)-1-Benzyl-pyrrolidin-3-yl phosphonic acid, diethyl ester

A solution of 6.0 g (36.6 mmol) of diethyl vinylphosphonate and 11 mL (44 mmol) of N-(methoxymethyl)-N-(trimethylsilylmethyl)benzylamine in 150 mL of CH_2Cl_2 at 0 °C was stirred for 30 min. The reaction mixture was washed with 150 mL of 1N $NaHCO_3$ and 150 mL of sat'd NaCl. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified on a 40L Biotage column using 3:2 and 1:1 v/v hexane/acetone as the gradient to afford 9.44 g (87%) of the title

compound as a pale yellow oil: R_F: 0.24 (3:2 v/v hexane/acetone); ^{1}H-NMR (500 MHz) δ 1.32 (t, J = 7.0, 6H), 2.04-2.12 (m, 2H), 2.39-2.58 (m, 3H), 2.83 (m, 1H), 2.97 (m, 1H), 3.64 (s, 2H), 4.06-4.16 (m, 4H), 7.24-7.34 (m, 5H); ESI-MS 298 (M+H); LC-1: 1.2 min.

Step B: (R/S)-Pyrrolidin-3-ylphosphonic acid, diethyl ester

A mixture of 3 g (10 mmol) of (R/S)-1-benzyl-pyrrolidin-3-ylphosphonic acid, diethyl ester (from Step A), 9.5 g (150 mmol) of ammonium formate and 1.0 g of 10% palladium on charcoal in 60 mL of MeOH was warmed to 40 °C for 1.5 h. The reaction was cooled, filtered through a pad of celite and concentrated. The mixture was partitioned between 75 mL of 1N NaOH and 100 mL of CH_2Cl_2. After separating layers, the aqueous phase was extracted with 3X100 mL of CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified on a 40M Biotage column using 90:10:1 v/v/v CH_2Cl_2/MeOH/NH_4OH as the eluant to afford the title compound as a pale yellow oil: R_F: 0.13 (95:5:0.5 v/v/v CH_2Cl_2/MeOH/NH_4OH); ^{1}H-NMR (500 MHz) δ 1.22 (t, J = 7.1, 6H), 1.81 (m, 1H), 1.95 (m, 1H), 2.25 (m, 1H), 2.73 (m, 1H), 2.89-2.99 (m, 3H), 4.06-4.16 (m, 4H).

Step C: (R/S)-1-(4-Nonylphenyl)methyl-pyrrolidin-3-ylphosphonic acid, diethyl ester

A solution of 41 mg (0.19 mmol) of (R/S)-pyrrolidin-3-yl phosphonic acid, diethyl ester (from Step B) and 43 mg (0.18 mmol) of Aldehyde I in 1 mL of CH_2Cl_2 was treated with 57 mg (0.27 mmol) of sodium triacetoxyborohydride. After stirring at rt overnight, the reaction was diluted with 25 mL of CH_2Cl_2 and washed with 25 mL of 1N $NaHCO_3$. After separating phases, the aqueous layer was extracted with 25 mL of CH_2Cl_2. The combined organic layers were washed with 50 mL of sat'd NaCl, dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography using 49:1 v/v CH_2Cl_2/MeOH as the eluant to afford 67 mg (99%) of the title compound: R_F: 0.39 (19:1 v/v CH_2Cl_2/MeOH); ^{1}H-NMR (500 MHz) δ 0.90 (t, J = 7.0, 3H), 1.20-1.35 (m, 17H), 1.59-1.65 (m, 2H), 2.04-2.13 (m, 3H), 2.41-

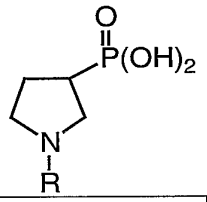
2.62 (m, 5H), 2.85 (m, 1H), 2.99 (m, 1H), 3.62 (s, 2H), 4.08-4.17 (m, 4H), 7.14 (d, J = 8.0, 2H), 7.24 (d, J = 8.0, 2H).

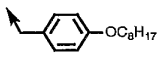
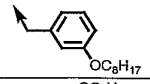
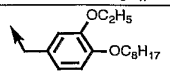
Step D: (R/S)-1-(4-Nonylbenzyl)-pyrrolidin-3-ylphosphonic acid

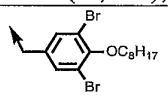
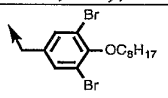
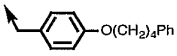
A solution of 67 mg (0.16 mmol) of (R/S)-1-(4-nonylbenzyl)-pyrrolidin-3-ylphosphonic acid, diethyl ester (from Step C) in 1 mL of acetonitrile was treated with 0.094 mL (0.71 mmol) of bromotrimethylsilane. The reaction was allowed to stir at 80 °C for 1h. The reaction was quenched with MeOH and concentrated several times from MeOH. The residue was purified by LC-2 to afford 27 mg (46%) of the title compound: ESI-MS 368 (M+H); LC-1: 3.1 min.

EXAMPLES XII-XVII

EXAMPLES XII-XVII were prepared using procedures analogous to those described in EXAMPLE XI substituting the appropriate Aldehyde in Step C. In EXAMPLES XV and XVI enantiomers were were resolved after Step E by preparative chiral HPLC (Chiralcel OD 2 x 25 cm HPLC column, 19:1 v/v hexane/iPrOH, flow rate = 9.0 mL/min, λ = 210 nM).



EXAMPLE #	R	HPLC Method	HPLC RT (min)	ESI-MS (M+H)
XII		LC-1	2.8	370
XIII		LC-1	2.7	370
XIV		--	--	--

^{1}H-NMR (500 MHz, CD_3OD) δ 0.92 (t, J = 7.0, 3H), 1.34-1.54 (m, 10H), 1.79-1.84 (m, 2H), 2.18 (m ,1H), 2.32-2.45 (m, 2H), 2.69 (m, 1H), 2.88 (m, 1H), 3.22-3.37 (m, 2H), 3.47-3.62 (m, 2H), 3.73 (m, 1H), 4.04 (t, J = 6.4, 2H), 4.13 (q, J = 7.0, 2H), 4.32-4.37 (m, 2H), 7.02-7.08 (m, 2H), 7.16 (s, 1H)				
XV Enantiomer 1		LC-1	3.2	528
^{1}H-NMR (500 MHz, CD_3OD) δ 0.93 (t, J = 6.9, 3H), 1.34-1.46 (m, 8H), 1.55-1.61 (m, 2H), 1.86-1.95 (m, 2H), 2.25-2.47 (m, 2H), 2.72 (m, 1H), 3.28 (m, 1H), 3.63-3.79 (m, 3H), 4.06 (t, J = 6.4, 2H), 4.44 (s, 2H), 7.87 (s, 2H)				
XVI Enantiomer 2		LC-1	3.1	528
XVII		LC-1	2.4	390

EXAMPLE XVIII

(R/S)-1-{4-[(4-Phenyl-5-trifluoromethyl-2-thienyl)methoxy]benzyl}-pyrrolidin-3-yl carboxylic acid

Step A: (R/S)-1-Benzyl-pyrrolidin-3-yl carboxylic acid, benzyl ester

A solution of 10.0 g (61.6 mmol) of benzyl acrylate and 19 mL (74.2 mmol) of N-(methoxymethyl)-N-(trimethylsilylmethyl)benzylamine in 75 mL of CH_2Cl_2 at 0 °C was treated with 0.5 mL (6.5 mmol) of TFA while maintaining the internal temperature at less than 3 °C. The reaction was warmed to rt and stirred for 2.5 h. The reaction mixture was washed with 250 mL of 1N $NaHCO_3$ and 250 mL of sat'd NaCl. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified on a 40L Biotage column using 19:1 v/v hexane/acetone as the eluant to

afford 18 g (99%) of the title compound as a light yellow oil: R_F: 0.28 (9:1 v/v hexane/acetone); ^{1}H-NMR (500 MHz) δ 2.15-2.20 (m, 2H), 2.60 (m, 1H), 2.73-2.77 (m, 2H), 3.02 (m, 1H), 3.13 (m, 1H), 3.66-3.73 (m, 2H), 5.17 (s, 2H), 7.28-7.42 (m, 5H).

Step B: (R/S)-1-Benzyloxycarbonyl-pyrrolidin-3-yl carboxylic acid, benzyl ester

A solution of 18 g (61 mmol) of (R/S)-1-benzyl-pyrrolidin-3-yl carboxylic acid, benzyl ester (from Step A) in 100 mL of CH_2Cl_2 at 0 °C was treated with 21.3 mL (231 mmol) of benzyl chloroformate while maintaining the internal temperature at less than 6 °C. The reaction was allowed to warm to rt overnight. After 24 hours at rt, an additional 10 mL (10.8 mmol) of benzyl chloroformate was added. After 24 hours of stirring at rt, the reaction was concentrated. The residue was purified on a 40L Biotage column using 19:1 v/v hexane/acetone as the eluant to afford 8.42 g (39%) of the title compound as a colorless oil: R_F: 0.14 (9:1 v/v hexane/acetone); ^{1}H-NMR (500 MHz) δ 2.19-2.22 (m, 2H), 3.15 (m,1H), 3.45-3.75 (m, 4H), 5.13-5.20 (m, 4H), 7.33-7.41 (m, 10H).

Step C: (R/S)-Pyrrolidin-3-yl carboxylic acid

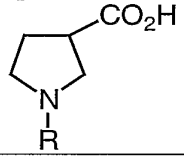
A mixture of 8.4 g (24.7 mmol) of (R/S)-1-benzyloxycarbonyl-pyrrolidin-3-yl carboxylic acid, benzyl ester (from Step B) and 2.86 g of 10% palladium on charcoal in 80 mL of MeOH was hydrogenated at atmospheric pressure using a balloon of hydrogen for 6.5 h. The reaction was filtered through a pad of Celite and concentrated to afford 2.72 g (95%) of the title compound as a white solid: ^{1}H-NMR (500 MHz, CD_3OD) δ 2.17-2.26 (m, 2H), 3.03 (m, 1H), 3.24-3.38 (m, 3H), 3.51 (m, 1H).

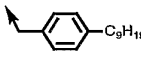
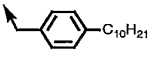
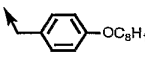
Step D: (R/S)-1-{4-[(4-Phenyl-5-trifluoromethyl-2-thienyl)methoxy]benzyl}-pyrrolidin-3-yl carboxylic acid

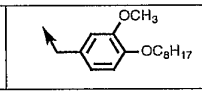
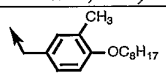
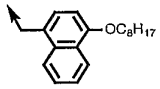
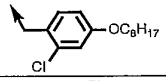
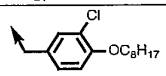
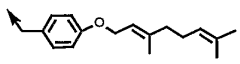
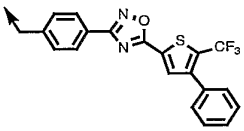
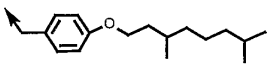
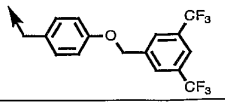
A mixture of 17.5 mg (0.15 mmol) of (R/S)-pyrrolidin-3-yl carboxylic acid (from Step C), 78 mg (0.21 mmol) of Aldehyde XVI and 9 mg (0.14 mmol) of sodium cyanoborohydride in 2 mL of MeOH was stirred at rt overnight. The reaction was concentrated and purified by flash chromatography using 19:1 v/v CH_2Cl_2/MeOH, then 85:15:1.5 v/v/v CH_2Cl_2/MeOH/NH_4OH as the eluant to afford 42 mg (63%) of the title compound as a white foam: R_F: 0.29 (85:15:1.5 v/v/v CH_2Cl_2/MeOH/NH_4OH); ^{1}H-NMR (500 MHz, CD_3OD) δ 2.23-2.35 (m, 2H), 3.09 (m, 1H), 3.26-3.41 (m, 3H), 3.53 (m, 1H), 4.30 (ABq, J = 13.0, 2H), 5.38 (s, 2H), 7.13 (d, J = 8.5, 2H), 7.22 (s, 1H), 7.39-7.45 (m, 5H), 7.48 (d, J = 8.5, 2H); ESI-MS 462 (M+H); LC-1: 2.7 min.

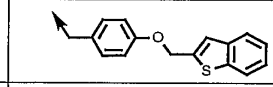
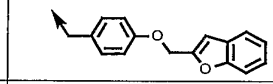
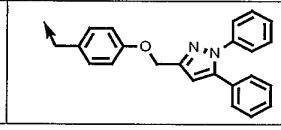
EXAMPLES XIX-XXXIII

EXAMPLES 19-33 were prepared using procedures analogous to those described in EXAMPLE 18 substituting the appropriate Aldehyde in Step D.



EXAMPLE #	R	HPLC Method	HPLC RT (min)	ESI-MS (M+H)
XIX		LC-1	2.8	332
^{1}H-NMR (500 MHz) δ 0.91 (t, J = 6.9, 3H), 1.30-1.34 (m, 12H), 1.60-1.63 (m, 2H), 2.33-2.41 (m, 2H), 2.60-2.63 (m, 2H), 3.09-3.29 (m, 4H), 3.73 (m, 1H), 4.20 (ABq, J = 12.5, 2H), 7.21 (d, J = 7.7, 2H), 7.44 (d, J = 7.7, 2H)				
XX		LC-1	3.0	346
XXI		LC-1	3.0	334
^{1}H-NMR (500 MHz, CD_3OD) δ 0.91 (t, J = 7.0, 3H), 1.31-1.50 (m, 10H), 1.75-1.80 (m, 2H), 2.22-2.33 (m, 2H), 3.08 (m, 1H), 3.25-3.40 (m, 3H), 3.52 (m, 1H), 3.99 (t, J = 6.4, 2H), 4.28 (ABq, J = 13.0, 2H), 6.97 (d, J = 8.6, 2H), 7.41 (d, J = 8.6, 2H)				

XXII		LC-1	2.9	364
^{1}H-NMR (500 MHz, CD_3OD) δ 0.91 (t, J = 6.9, 3H), 1.31-1.51 (m, 10H), 1.76-1.82 (m, 2H), 2.24-2.37 (m, 2H), 3.17 (m, 1H), 3.29-3.43 (m, 3H), 3.56 (m, 1H), 3.87 (s, 3H), 4.01 (t, J = 6.5, 2H), 4.29 (ABq, J = 12.8, 2H), 6.98 (d, J = 8.2, 1H), 7.03 (dd, J = 8.2, 1.7, 1H), 7.12 (d, J = 1.7, 1H)				
XXIII		LC-1	3.3	348
XXIV		LC-1	3.5	384
XXV		LC-1	3.2	368
XXVI		LC-1	3.2	368
XXVII		LC-1	2.9	358
XXVIII		LC-1	3.2	500
^{1}H-NMR (500 MHz, CD_3OD) δ 2.26-2.37 (m, 2H), 3.13 (m, 1H), 3.25-3.43 (m, 3H), 3.52 (m, 1H), 4.37 (ABq, J = 12.9, 2H), 7.49-7.50 (m, 5H), 7.69 (d, J = 8.1, 2H), 8.00 (s, 1H), 8.16 (d, J = 8.1, 2H)				
XXIX		LC-1	3.0	362
EXAMPLE XXIX was prepared by catalytic hydrogenation of EXAMPLE 27 using a procedure analogous to that described in EXAMPLE 18, Step C.				
XXX		LC-1	2.9	448

^{1}H-NMR (500 MHz, CD_3OD) δ 2.23-2.34 (m, 2H), 3.09 (m, 1H), 3.25-3.40 (m, 3H), 3.53 (m, 1H), 4.30 (ABq, J = 13.0, 2H), 5.31 (s, 2H), 7.14 (d, J = 8.6, 2H), 7.48 (d, J = 8.6, 2H), 7.94 (s, 1H), 8.07 (s, 2H)				
XXXI		--	--	368
XXXII		--	--	352
XXXIII		--	--	454

EXAMPLE XXXV

(R/S)-1-(4-Nonylphenyl)methyl-3-fluoro-pyrrolidin-3-yl carboxylic acid

Step A: (R/S)-1-Benzyl-pyrrolidin-3-yl carboxylic acid, methyl ester

The title compound was prepared using a procedure analogous to that described in EXAMPLE XVIII, Step A substituting methyl acrylate for benzyl acrylate: R_F: 0.29 (9:1 v/v hexane/acetone); ^{1}H-NMR (500 MHz) δ 2.10-2.14 (m, 2H), 2.55 (m, 1H), 2.66 (m, 1H), 2.75 (m, 1H), 2.94 (m, 1H), 3.06 (m, 1H), 3.65 (s, 2H), 3.69 (s, 3H), 7.25-7.35 (m, 5H).

Step B: (R/S)-Pyrrolidin-3-yl carboxylic acid, methyl ester hydrochloride salt

A solution of 0.52 g (2.3 mmol) of (R/S)-1-benzyl-pyrrolidin-3-yl carboxylic acid, methyl ester (from Step A) in 5 mL of 1,2-dichloroethane was treated with 0.3 mL (2.7 mmol) of 1-chloroethyl chloroformate (ACE-Cl). The resulting mixture was stirred at rt for 3 h, then at reflux for 30 min. The reaction was cooled

and concentrated. The residue was warmed to reflux in 5 mL of MeOH for 1 h. The reaction was cooled and concentrated. The crude product was used in Step C without further purification.

Step C: (R/S)- 1-(4-Nonylphenyl)methyl-pyrrolidin-3-yl carboxylic acid, methyl ester

The title compound was prepared using an analogous procedure described in EXAMPLE I, Step E substituting (R/S)-pyrrolidin-3-yl carboxylic acid, methyl ester hydrochloride salt (from Step B) for (R/S)-3-hydroxypyrrolidin-3-ylphosphonic acid, diethyl ester and using DIEA to neutralize the hydrochloride salt: R_F: 0.44 (4:1 v/v hexane/acetone); ^{1}H-NMR (500 MHz) δ 0.91 (t, J = 6.9, 3H), 1.30-1.35 (m, 12H), 1.60-1.66 (m, 2H), 2.13-2.17 (m, 2H), 2.54-2.69 (m, 4H), 2.80 (m, 1H), 2.99 (m, 1H), 3.09 (m, 1H), 3.66 (s, 2H), 3.72 (s, 3H), 7.16 (d, J = 8.0, 2H), 7.27 (d, J = 8.0, 2H).

Step D: (R/S)-1-(4-Nonylphenyl)methyl- 3-fluoropyrrolidin-3-yl carboxylic acid, methyl ester

To a solution of 1 mL (0.32 mmol) of 0.32M lithium diisopropylamide in THF at –78 °C was added 90 mg (0.26 mmol) of (R/S)-1-1-(4-nonylphenyl) methylbenzyl)-pyrrolidin-3-yl carboxylic acid, methyl ester (from Step C) in 1.5 mL of THF while maintaining the internal temperature at less –70 °C. After 15 min, 111 mg (0.35 mmol) of fluorobenzenesulfonimide in 0.5 mL THF was added while maintaining the internal temperature at less –68 °C. After stirring for 15 min, the reaction was warmed to 0 °C and quenched with 0.1N HCl. The reaction mixture was poured into 50 mL of Et_2O and washed with 50 mL of 1N $NaHCO_3$ and 50 mL of sat'd NaCl. The organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography using 19:1 v/v hexane/acetone as the eluant to afford 47 mg (50%) of the title compound as a colorless film: R_F: 0.36 (9:1 v/v hexane/acetone); ^{1}H-NMR (500 MHz) δ 0.91 (t, J = 6.8, 3H), 1.30-1.35 (m, 12H), 1.60-1.66 (m, 2H), 2.28 (m, 1H), 2.49 (m, 1H), 2.62 (t, J = 7.8, 2H), 2.69 (m, 1H), 2.95-3.10 (m, 3H), 3.69 (ABq, J = 12.8, 2H), 3.83 (s, 3H), 7.16 (d, J = 7.8, 2H), 7.27 (d, J = 7.8, 2H).

Step E: (R/S)-1-(4-Nonylphenyl)methyl-3-fluoropyrrolidin-3-yl carboxylic acid

A solution of 46 mg (0.12 mmol) of (R/S)-1-(4-nonylphenyl)methyl-3-fluoropyrrolidin-3-yl carboxylic acid, methyl ester (from Step D) in 3 mL of EtOH was treated with 0.16 mL (0.16 mmol) of 1N NaOH and stirred overnight at rt. The reaction was neutralized with 2 mL of pH 7 buffer and concentrated. Toluene was added and the resulting mixture was concentrated. The residue was purified by flash chromatography using 19:1 v/v CH_2Cl_2/MeOH, then 90:10:1 v/v/v CH_2Cl_2/MeOH/NH_4OH as the eluant to afford 38 mg (86%) of the title compound as a white, waxy solid: R_F: 0.21 (85:15:1.5 v/v/v CH_2Cl_2/MeOH/NH_4OH); ^{1}H-NMR (500 MHz) δ 0.79 (t, J = 6.8, 3H), 1.18-1.23 (m, 12H), 1.48-1.52 (m, 2H), 2.30 (m, 1H), 2.47-2.59 (m, 3H), 3.29-3.44 (m, 3H), 3.73 (m, 1H), 3.87 (br m, 1H), 4.17 (ABq, J = 12.9, 2H), 7.12 (d, J = 7.9, 2H), 7.28 (d, J = 7.9, 2H); ESI-MS 350 (M+H); LC-1: 3.3 min.

EXAMPLE XXXVI

(R/S)-1-(4-Nonylphenyl)methyl-3-hydroxypyrrolidin-3-yl carboxylic acid

Step A: (R/S) 1-(4-Nonylphenyl)methyl-3-hydroxypyrrolidin-3-yl carboxylic acid, methyl ester

To a solution of 0.52 mL (0.52 mmol) of 1.0M sodium hexamethylsilazide in THF at –78 °C was added 153 mg (0.44 mmol) of (R/S)- 1-(4-nonylphenyl)methyl-pyrrolidin-3-yl carboxylic acid, methyl ester (from EXAMPLE XXXIV, Step C) in 1 mL of THF while maintaining the internal temperature at less –72 °C. After 20 min, 172 mg (0.65 mmol) of 2-(phenylsulfonyl)-3-phenyloxaziridine (Davis Reagent) in 1 mL of THF was added while maintaining the internal temperature at less –69 °C. After stirring for 1.25 h at –78 °C, the reaction was quenched with 1N $NaHCO_3$ and warmed to rt. After removing volatiles under reduced pressure, the reaction mixture was diluted with 50 mL of 1N $NaHCO_3$ and 50 mL of sat'd NaCl. The aqueous phase was extracted with 3X50 mL of CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography using 4:1 v/v hexane/EtOAc and 4:1 v/v hexane/acetone as the gradient to afford 11 mg (7%) of the title compound as a

colorless film: R_F: 0.39 (4:1 v/v hexane/acetone); ^{1}H-NMR (500 MHz) δ 0.90 (t, J = 6.8, 3H), 1.28-1.33 (m, 12H), 1.59-1.64 (m, 2H), 2.02 (m, 1H), 2.42 (m, 1H), 2.60 (t, J = 7.8, 2H), 2.67 (m, 1H), 2.86 (ABq, J = 10.1, 2H), 2.97 (m, 1H), 3.69 (s, 2H), 3.82 (s, 3H), 7.14 (d, J = 7.9, 2H), 7.26 (d, J = 7.9, 2H).

Step B: (R/S)- 1-(4-Nonylphenyl)methyl-3-hydroxypyrrolidin-3-yl carboxylic acid

The title compound was prepared using an analogous procedure described in EXAMPLE XXXIV, Step E substituting (R/S)-1-(4-nonylphenyl)methyl-3-hydroxypyrrolidin-3-yl carboxylic acid, methyl ester (from Step A) for (R/S)-1-(4-nonylphenyl)methyl-3-fluoropyrrolidin-3-yl carboxylic acid, methyl ester: R_F: 0.15 (90:10:1 v/v/v CH_2Cl_2/MeOH/NH_4OH); ^{1}H-NMR (500 MHz, CD_3OD) δ 0.89 (t, J = 6.9, 3H), 1.28-1.33 (m, 12H), 1.60-1.63 (m, 2H), 2.10 (m, 1H), 2.49 (m, 1H), 2.64 (t, J = 7.7, 2H), 3.25 (m, 1H), 3.49-3.62 (m, 3H), 4.38 (ABq, J = 13.0, 2H), 7.28 (d, J = 7.8, 2H), 7.42 (d, J = 7.8, 2H); ESI-MS 348 (M+H); LC-1: 3.0 min.

EXAMPLE XXXVII

(R/S)-1-(4-Nonylphenyl)methyl-pyrrolidin-3-yl acetic acid

Step A: (R/S)- 1-(4-Nonylphenyl)methyl-pyrrolidin-3-ylacetic acid, tert-butyl ester

The title compound was prepared using an analogous procedure described in EXAMPLE I, Step E substituting (R/S)-pyrrolidin-3-yl acetic acid, tert-butyl ester hydrochloride salt for (R/S)-3-hydroxypyrrolidin-3-ylphosphonic acid, diethyl ester and using DIEA to neutralize the hydrochloride salt: R_F: 0.53 (4:1 v/v hexane/acetone); ^{1}H-NMR (500 MHz) δ 0.90 (t, J = 6.8, 3H), 1.28-1.64 (m, 25H), 2.09 (m, 1H), 2.26-2.37 (m, 3H), 2.58-2.69 (m, 4H), 2.89 (m, 1H), 3.61-3.64 (m, 2H), 7.14 (d, J = 7.4, 2H), 7.26 (d, J = 7.4, 2H).

Step B: (R/S)-1-(4-Nonylphenyl)methyl-pyrrolidin-3-yl acetic acid

A solution of 50.5 mg (0.12 mmol) of (R/S)-1-(4-nonylphenyl)methyl-pyrrolidin-3-yl acetic acid, tert-butyl ester (from Step A) in formic acid at 55 °C was stirred for 2.25 h. Volatiles were removed under reduced pressure. The residue was purified by flash chromatography using 19:1 v/v CH_2Cl_2/MeOH, then 85:15:1.5 v/v/v CH_2Cl_2/MeOH/NH_4OH as the eluant to afford 41 mg (94%) of the title compound as a sticky, waxy film: R_F: 0.31 (85:15:1.5 v/v/v CH_2Cl_2/MeOH/NH_4OH); ^{1}H-NMR (500 MHz, CD_3OD) δ 0.90 (t, J = 6.9, 3H), 1.29-1.33 (m, 12H), 1.61-1.64 (m, 2H), 1.77 (m, 1H), 2.26-2.45 (m, 3H), 2.64 (t, J = 7.7, 2H), 2.71 (m, 1H), 3.08 (m, 1H), 3.23 (m, 1H), 3.38-3.44 (m, 2H), 4.28 (s, 2H), 7.28 (d, J = 8.1, 2H), 7.39 (d, J = 8.1, 2H); ESI-MS 346 (M+H); LC-1: 3.3 min.

EXAMPLE XXXVIII

(R/S)-1-{4-[(4-Phenyl-5-trifluoromethyl-2-thienyl)methoxy]benzyl}-pyrrolidin-3-ylacetic acid

The title compound was prepared using procedures analogous to those described in EXAMPLE XXXVI substituting Aldehyde XVI for Aldehyde I in Step A: R_F: 0.29 (85:15:1.5 v/v/v CH_2Cl_2/MeOH/NH_4OH); ^{1}H-NMR (500 MHz, CD_3OD) δ 1.77 (m, 1H), 2.26-2.46 (m, 3H), 2.71 (m, 1H), 3.07 (m, 1H), 3.23 (m, 1H), 3.37-3.34 (m, 2H), 4.28 (s, 2H), 5.38 (s, 2H), 7.13 (d, J = 8.7, 2H), 7.23 (s, 1H), 7.40-7.47 (m, 7H); ESI-MS 476 (M+H); LC-1: 3.0 min.

EXAMPLE XXXIX

(R/S)-5-[1-(4-Nonylphenyl)methylpyrrolidin-3-yl]-1*H*-tetrazole

Step A: (R/S)-1-Benzyloxycarbonyl-3-cyano pyrrolidine

The title compound was prepared using analogous procedures described in EXAMPLE XVIII (Steps A and B) substituting acrylonitrile for benzyl acrylate in Step A: R_F: 0.19 (4:1 v/v hexane/acetone); ^{1}H-NMR (500 MHz) δ 2.18-2.28 (m, 2H), 3.12 (m, 1H), 3.53 (m, 1H), 3.61-3.78 (m, 3H), 5.16 (d, J = 3.0, 2H), 7.32-7.42 (m, 5H).

Step B: (R/S)-5-[1-Benzyloxycarbonyl-pyrrolidin-3-yl]-1*H*-tetrazole

A mixture of 1.8 g (7.8 mmol) of (R/S)-1-benzyloxycarbonyl-3-cyano pyrrolidine (from Step A), 1.5 g (23 mmol) of sodium azide and 1.25 g (23 mmol) of ammonium chloride in 70 mL of DMF was stirred at 105 °C overnight. After cooling to rt, the reaction was poured into 150 mL of CH_2Cl_2 and washed with 150 mL of 1N HCl and 2X150 mL of H_2O. The organic phase was dried over $MgSO_4$ and concentrated. The residue was purified on a 40M Biotage column using 80:20:1 v/v/v CH_2Cl_2/EtOAc/HOAc as the eluant to afford 670 mg (31%) of the title compound: R_F: 0.23 (80:20:1 v/v/v CH_2Cl_2/EtOAc/HOAc); ^{1}H-NMR (500 MHz) δ 2.29, 2.48 (2m, 2H), 3.54-4.03 (m, 5H), 5.14-5.24 (m, 2H), 7.30-7.37 (m, 5H), 10.43 (br, 1H).

Step C: (R/S)-5-(Pyrrolidin-3-yl)-1*H*-tetrazole

A mixture of 662 mg (2.4 mmol) of (R/S)-5-[1-benzyloxycarbonyl-pyrrolidin-3-yl]-1*H*-tetrazole (from Step B) and 220 mg of 10% palladium on charcoal in 5 mL of MeOH was hydrogenated at atmospheric pressure using a balloon of hydrogen for 3 h. The reaction was filtered through a pad of Celite and concentrated to afford the title compound as a white solid: ^{1}H-NMR (500 MHz, CD_3OD) δ 2.27 (m, 1H), 2.49 (m, 1H), 3.39-3.51 (m, 3H), 3.70 (m, 1H), 3.85 (m, 1H).

Step D: (R/S)-5-[1-(4-Nonylbenzyl)methyl-pyrrolidin-3-yl]-1*H*-tetrazole

The title compound was prepared using an analogous procedure described in EXAMPLE XVIII, Step D substituting (R/S)-5-(pyrrolidin-3-yl)-1*H*-tetrazole (from Step C) for (R/S)-pyrrolidin-3-yl carboxylic acid: ^{1}H-NMR (500 MHz, CD_3OD) δ 0.89 (t, J = 7.0, 3H), 1.28-1.33 (m, 12H), 160.-1.63 (m, 2H), 2.33 (m, 1H), 2.55 (m, 1H), 2.64 (t, J = 7.6, 2H), 3.47-3.55 (m, 3H), 3.76 (m, 1H), 3.92 (m, 1H), 4.40 (s, 2H), 7.29 (d, J = 8.0, 2H), 7.42 (d, J = 8.0, 2H); ESI-MS 356 (M+H); LC-1: 3.3 min.

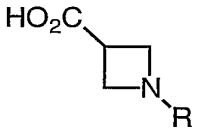
EXAMPLE XL

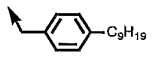
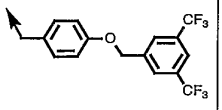
1-{4-[(4-Phenyl-5-trifluoromethyl-2-thienyl)methoxy]benzyl}-3-azetidinecarboxylic acid

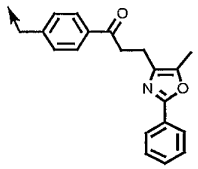
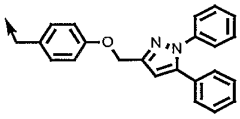
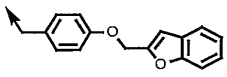
The title compound was prepared by treating a mixture of 0.12 mmol of 3-azetidinecarboxylic acid, 0.1 mmol of Aldehyde XVI, 0.007 mL (0.12 mmol) of acetic acid in 2 mL of MeOH with 10 mg (0.16 mmol) of sodium cyanoborohydride and stirring the resulting mixture at rt for 3 h. The product was purified using LC-2: ^{1}H NMR (500 MHz, CD_3OD) δ 3.34-3.37 (m, 1H), 4.08 (app s, 2H), 4.10 (app s, 2H), 4.22 (s, 2H), 4.86 (s, 2H), 5.35 (s, 2H), 7.10 (app d, J= 8.0, 2H), 7.20 (s, 1H), 7.39-7.43 (5H).

EXAMPLES XLI-XLV

EXAMPLES XLI-XLV were prepared using procedures analogous to that described in EXAMPLE XLI substituting the appropriate Aldehyde for Aldehyde XVI.

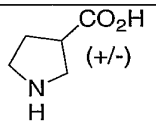
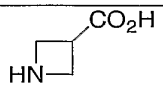
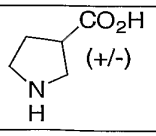


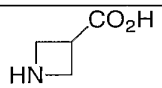
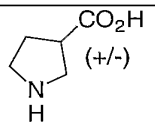
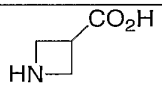
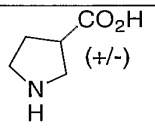
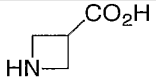
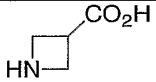
EXAMPLE #	R	HPLC Method	HPLC RT (min)	ESI-MS (M+H)
XLI		LC-1	3.3	318
^{1}H-NMR (500 MHz, CD_3OD) δ 0.89 (t, J = 6.8, 3H), 1.28-1.32 (m, 12H), 1.60-1.62 (m, 2H), 2.63 (t, J = 7.7, 2H), 3.37 (m, 1H), 4.12 (s, 2H), 4.13 (s, 2H), 4.27 (s, 2H), 7.27 (d, J = 8.0, 2H), 7.35 (d, J = 8.0, 2H)				
XLII		LC-1	2.9	434
^{1}H-NMR (500 MHz, CD_3OD) δ 3.35 (m, 1H), 4.14 (s, 2H), 4.16 (s, 2H), 4.28 (s, 2H), 5.31 (s, 2H), 7.14 (d, J = 8.6, 2H), 7.42 (d, J = 8.6, 2H), 7.94 (s, 1H), 8.07 (s, 2H)				

XLIII		LC-1	2.4	405
XLIV		--	--	440
XLV		--	--	338

EXAMPLES XLVI-LIV

The following compounds were prepared by treating a mixture of 0.12 mmol of either azetidine-3-carboxylic acid or (±)-pyrroldine-3-carboxylic acid, 0.1 mmol of Aldehyde, 7 μL (0.12 mmol) of acetic acid in 2 mL of MeOH with 10 mg (0.16 mmol) of sodium cyanoborohydride and stirring the resulting mixture at rt for 1-3 h. The reaction mixtures were purified using LC-2.

EXAMPLE	Amino acid	Aldehyde #	LC-1	MS
XLVI		19	2.9 min	496 (M+H)
XLVII		19	2.9 min	482 (M+H)
XLVIII		18	3.1 min	496 (M+H)

XLIX		18	3.1 min	482 (M+H)
L		21	2.9 min	492 (M+H)
LI		21	2.9 min	478 (M+H)
LII		20	3.1 min	476 (M+H)
LIII		20	3.1 min	462 (M+H)
LIV		15	3.2 min	485 (M+H)

XAMPLE LV

(3S,4R or 3R,4S)-1-(4-Nonylbenzyl)-4-trifluoromethylpyrrolidin-3-yl carboxylic acid

Step A: 4-(Nonyl)benzylamine

4-Nonylbenzoyl chloride (6g, 20mmol) and NH_4OAc (6g,) were suspended in acetone (100mL) and stirred for 1 h at rt. Water (50mL) was added and the mixture filtered. The residue was washed with water and dried . The resulting crude amide (2.47g, ~10mmol) was dissolved in THF (5mL) and borane dimethylsulfide complex (10mL of 2M solution, 20mmol) was added dropwise, while warming to reflux. The mixture was heated for 1h. then cooled in an ice bath.

Methanol (2.5mL) was added dropwise, followed by 1N HCl in ether (11mL). The white precipitate of the HCl salt of the benzyl amine was filtered off and washed with ether. The HCl salt was taken up in 2.5N NaOH and ether and the organic layer was separated and dried over Na_2SO_4. Evaporation afforded 1.3 g of the title compound.

Step B: N-(Methoxymethyl)-N-(trimethylsilylmethyl)-(4-nonyl)benzylamine

A solution of 1.3 g (6 mmol) of 4-(nonyl)benzylamine (from Step A) and 700 mg (6 mmol) of chloromethyltrimethylsilane in 5 mL of DMSO was stirred at 90 °C for 3 h, then at rt for 16 h. The mixture was partitioned between MTBE and 1N NaOH. The organic layer was separated, washed with sat'd NaCl, dried and concentrated. Flash chromatography using 9:1 v/v hexane/EtOAc as the eluant afforded 700 mg of N-(trimethylsilylmethyl)-4-(nonyl)benzylamine.

A mixture of the crude N-(trimethylsilylmethyl)-4-(nonyl)benzylamine, 140 mg of paraformaldehyde and 15 mg of powdered NaOH in 5 mL of MeOH was stirred at 40 °C for 1 h. The mixture was diluted with ether and aged for 16 h. The mixture was concentrated and dried to afford 700 mg of the title compound: ^{1}H NMR (500 MHz, CD_3OD) δ: 7.25 (m, 2H); 7.15 (m, 2H); 4.03 (m, 2H); 3.74 (m, 2H); 3.28 (m, 2H); 2.61 (m, 2H); 2.22 (m, 2H); 1.63 (m, 4H); 1.30 (m, 14H); 0.90 (m, 3H); 0.08 (m, 9H).

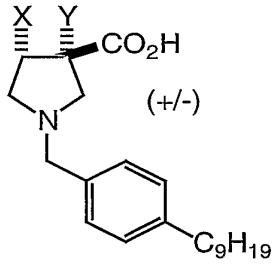
Step C: 1-(4-(Nonyl)phenyl)methyl-3-(R/S)-carboxy-4-(R/S)-trifluoromethyl pyrrolidine

A solution of 50 mg (0.14 mmol) of N-(methoxymethyl)-N-(trimethylsilylmethyl)-(4-nonyl)benzylamine (from Step B) and 20 mg (0.14 mmol) of *trans*-4,4,4-trifluoro-2-butenoic acid (0.137mmol) in 1 mL of CH_2Cl_2 was treated with 1 drop of TFA and the resulting mixture was heated at 35 °C for 1h. The reaction was cooled, concentrated then and then purified using LC-2 to afford the title compound: ^{1}H NMR (500 MHz, CD_3OD) δ 7.25 (d, J = 8, 2H); 7.19 (d, J = 8, 2H);

3.87 (m, 2H); 3.54 (m, 1H); 3.27(m, 4H); 2.93 (m, 1H); 2.61 (m, 2H); 1.62 (m, 2H); 1.30 (m, 14H); 0.90 (t, J = 6.7, 3H); ESI-MS 400.3 (M+H).

EXAMPLES LVI-LVIII

EXAMPLES LVI-LVIII were prepared using procedures analogous to those described in EXAMPLE LV substituting the appropriate α,β-unsaturated acid in Step C.



EXAMPLE #	X	Y	ESI-MS (M+H)
LVI	H	CF_3	400.3
^{1}H NMR (500 MHz, CD_3OD) δ: 7.43 (d, J = 8 Hz, 2H); 7.29 (d, J = 8 Hz 2H); 4.35 (s, 2H); 4.04 (d, J = 12Hz, 1H); 3.46 (m, 1H); 2.65 (m, 3H); 2.42 (m, 1H); 1.62 (m, 2H); 1.30 (m, 14H); 0.90 (t, J = 6.7 3H)			
LVII	CO_2H	H	375.3
^{1}H NMR (500 MHz, CD_3OD) δ: 7.35 (m, , 4H); 4.4 (m, 1H); 4.12 (m, 2H); 3.64 (m, 1H); 2.69 (m, 5H); 1.64 (m, 1H); 1.30 (m, 14H); 0.90 (m, 3H)			
LVIII	H	CH_2CO_2H	390.3

^{1}H NMR (500 MHz, CD_3OD) δ: 7.36 (m, , 4H); 4.43 (m, , 1H); 4.14 (m, 3H); 3.79 (m, 1H); 3.50 (m, 1H); 3.09 (m, 2H); 2.70 (m, 8H); 3.18 (m, 1H); 2.65 (m, 2H); 2.3 (m, 2H); 1.61 (m, 2H); 1.29 (M, 14H); 0.89 (m, 3H)

METHODS FOR PREPARING N-(BENZYL)AMINOALKYLCARBOXYLATES, PHOSPHINATES AND PHOSPONATES

The structures of Examples 1-150 are shown in the following table:

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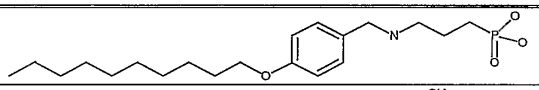
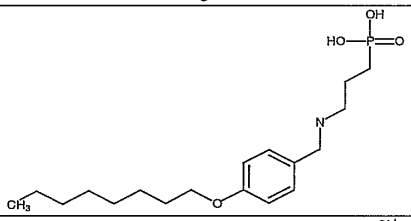
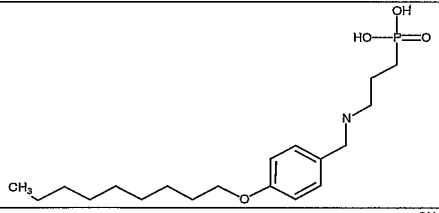
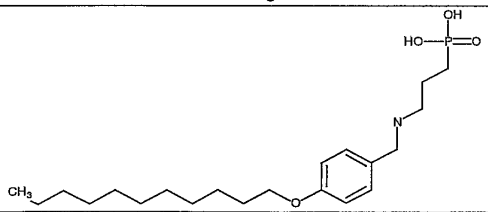
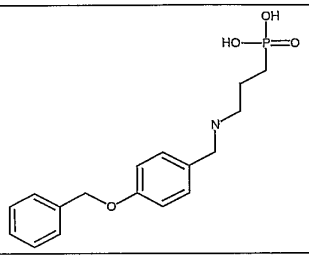
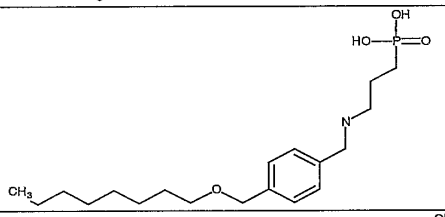
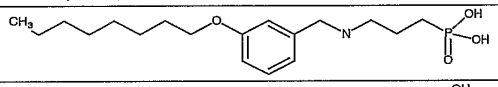
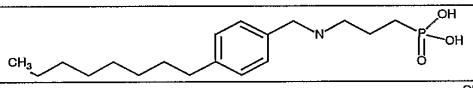
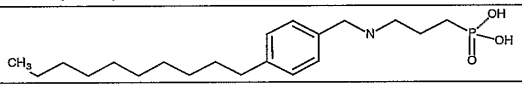
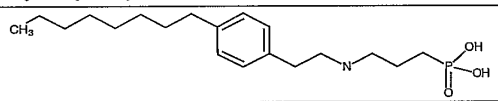
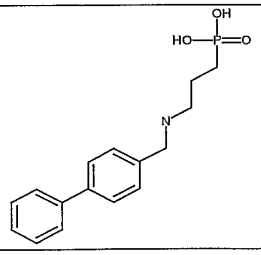
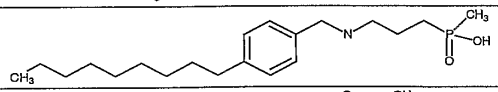
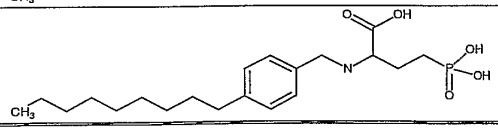
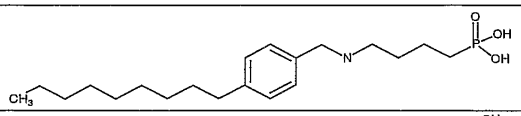
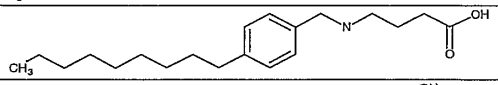
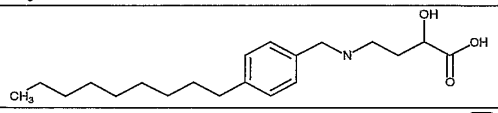
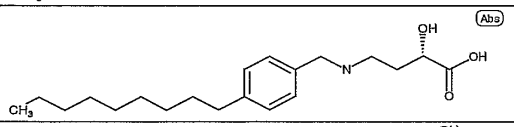
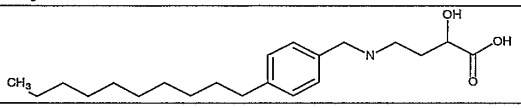
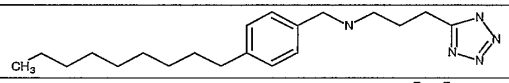
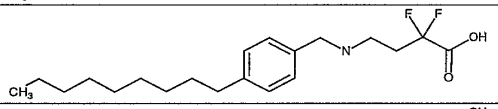
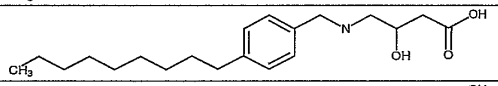
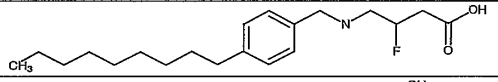
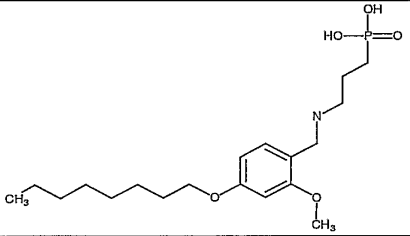
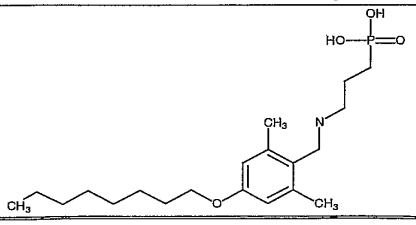
1	
2	
3	
4	

Example Number	Structure
5	
6	
7	
8	
9	
10	
11	
12	
13	

Example Number	Structure
14	
15	
16	
17	
18	
19	
20	
21	
22	
23	
24	

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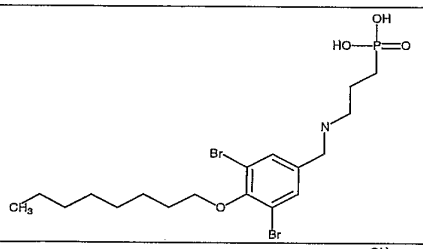
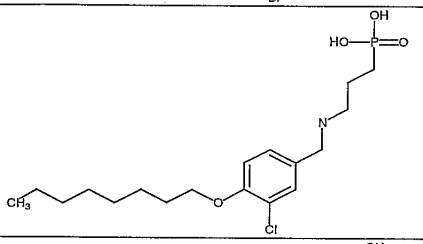
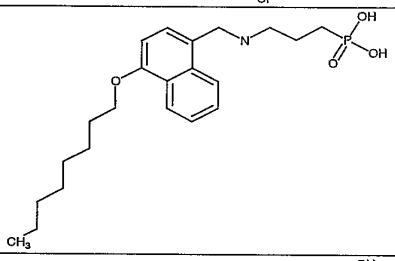
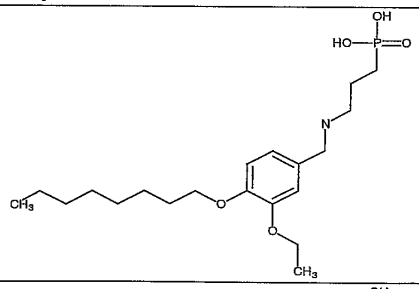
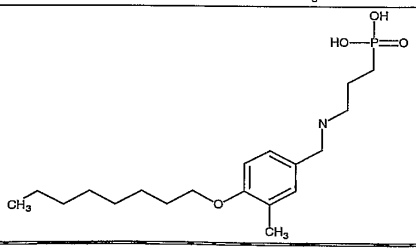
25	
26	
27	
28	
29	

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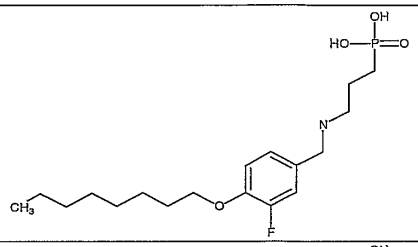
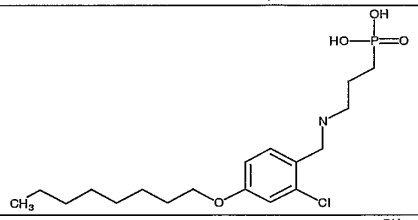
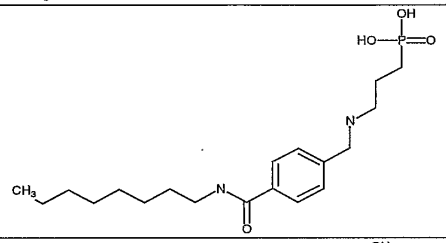
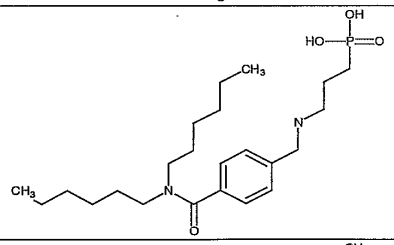
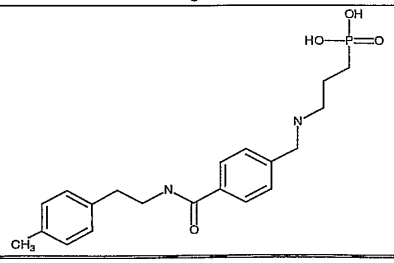
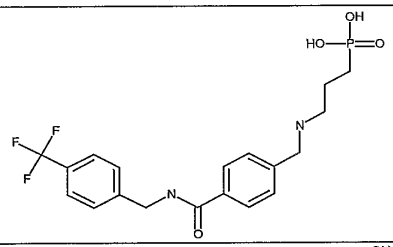
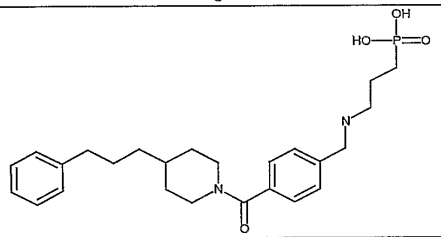
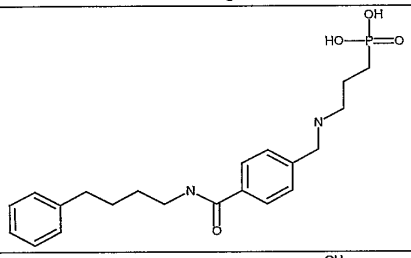
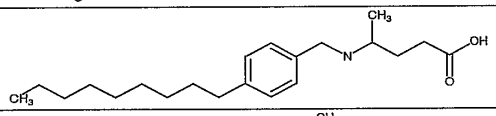
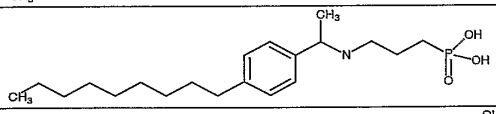
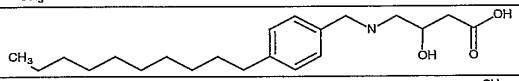
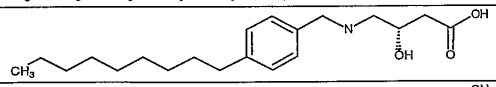
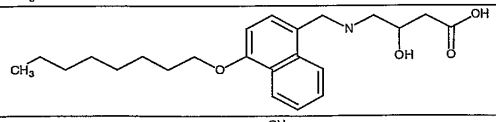
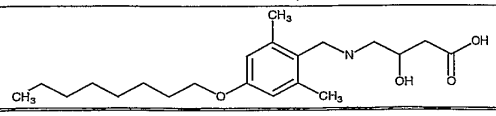
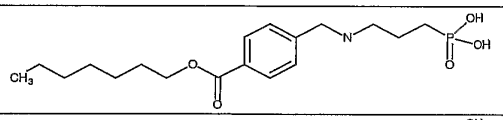
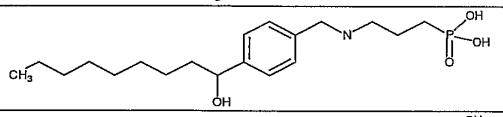
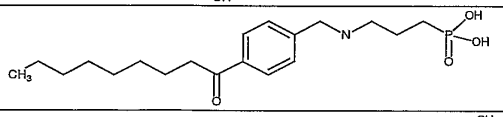
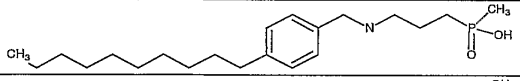
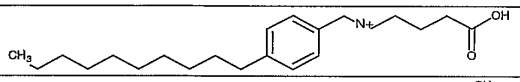
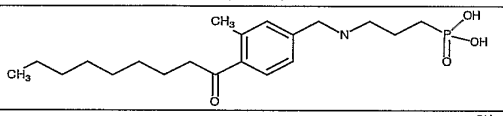
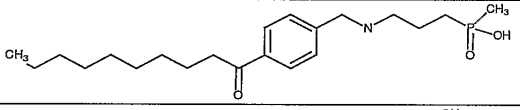
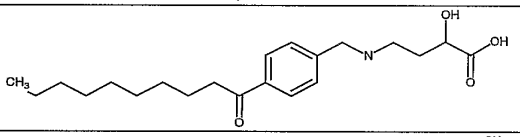
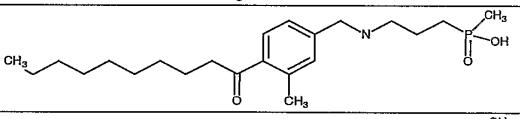
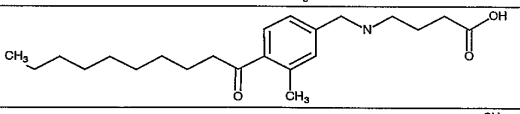
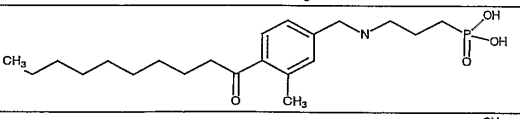
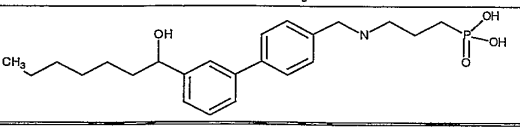
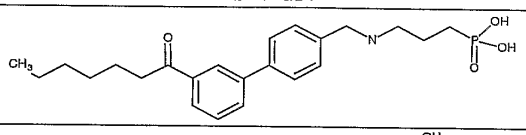
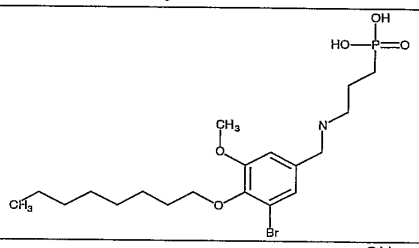
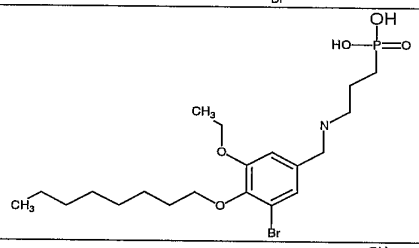
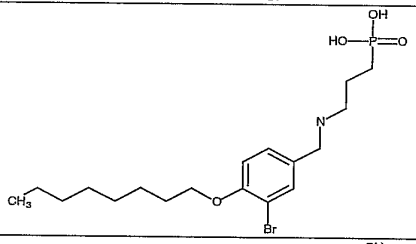
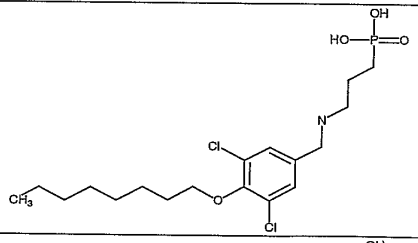
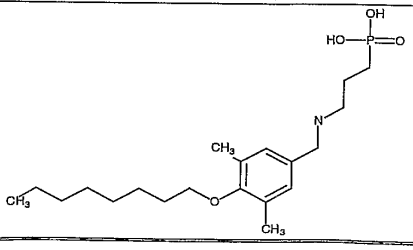
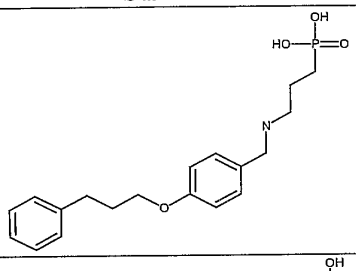
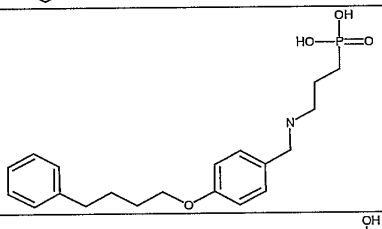
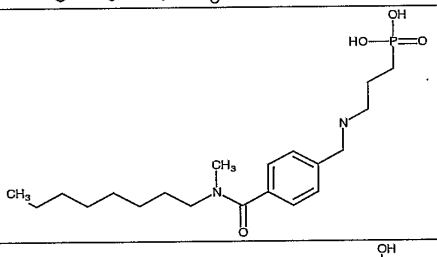
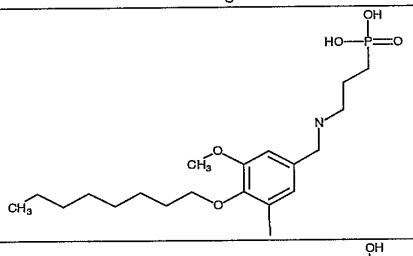
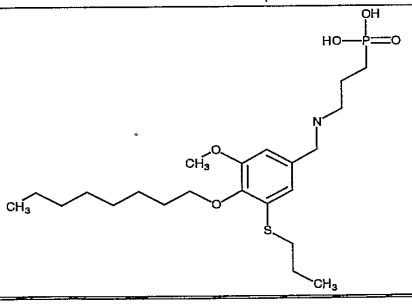
30	
31	
32	
33	
34	

Example Number	Structure
35	
36	
37	
38	
39	
40	
41	
43	
44	

Example Number	Structure
45	
46	
47	
48	
49	
50	
51	
52	
53	
54	
55	
56	

Example Number	Structure
57	
58	
59	
60	
61	
62	

Example Number	Structure
63	
64	
65	
66	
67	

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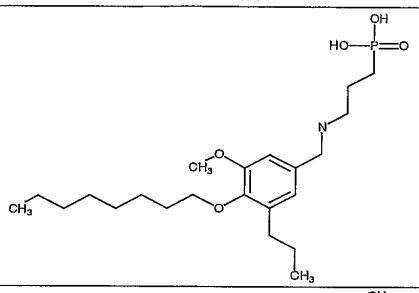
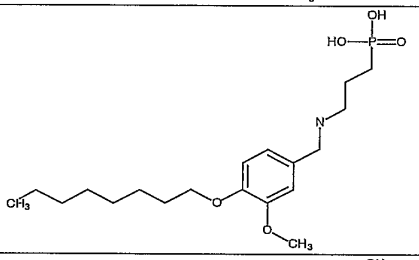
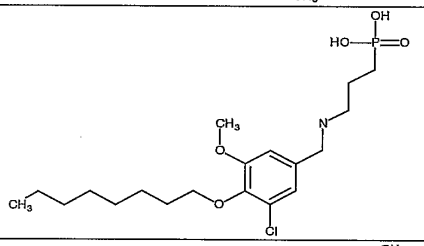
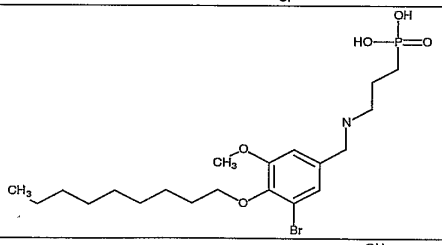
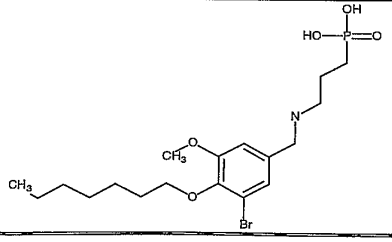
68	
69	
70	
71	
72	

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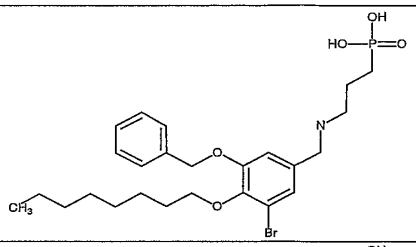
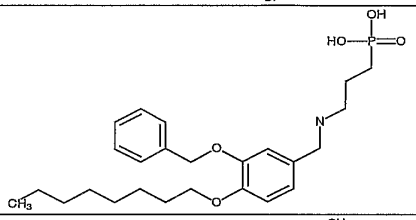
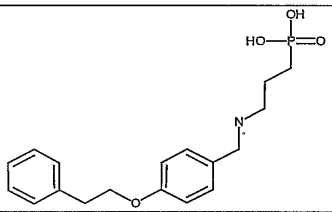
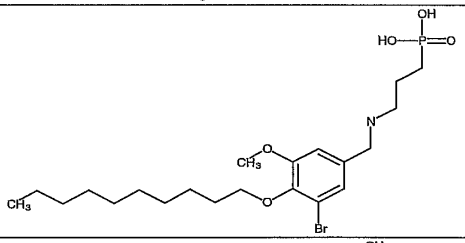
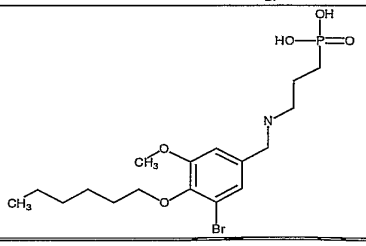
73	
74	
75	
76	
77	

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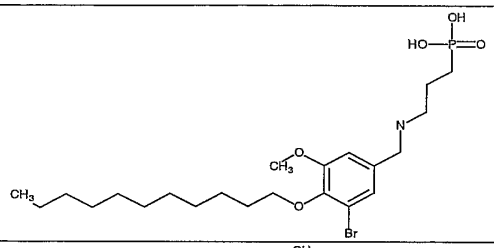
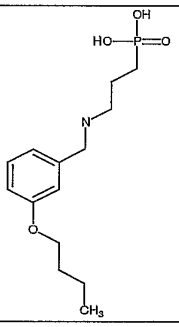
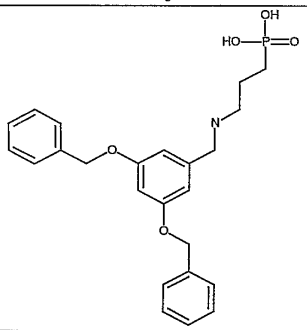
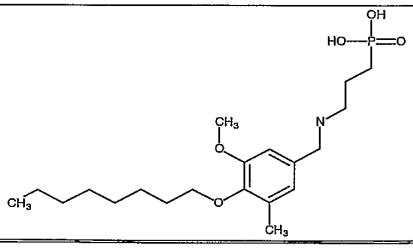
78	
79	
80	
81	

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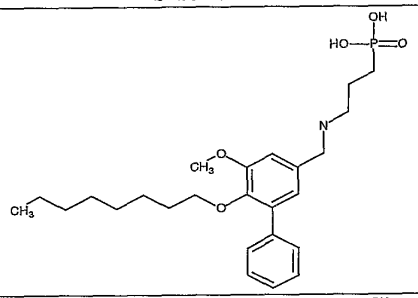
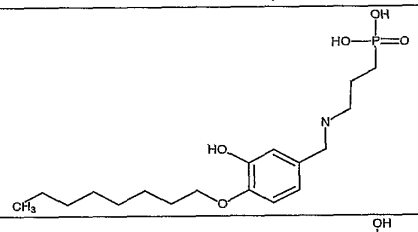
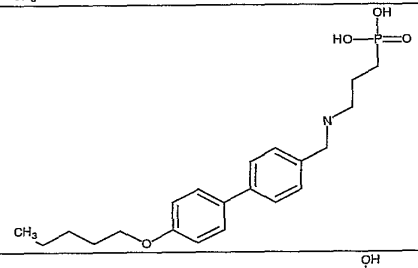
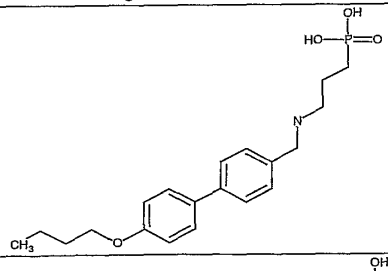
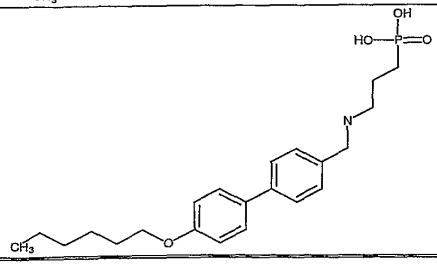
82	
83	
84	
85	
86	

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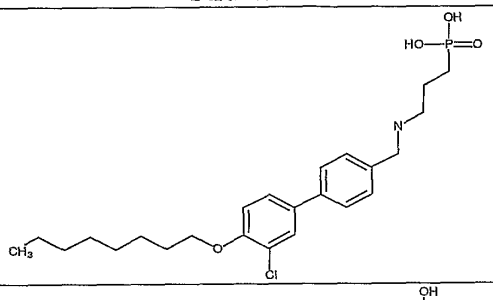
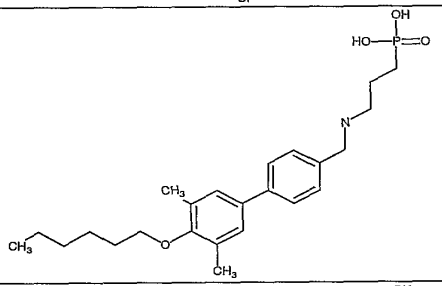
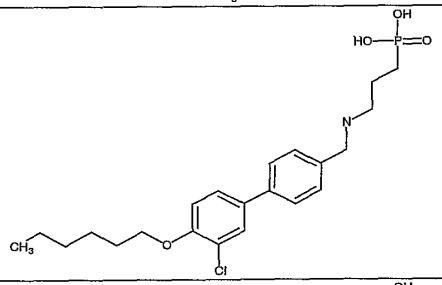
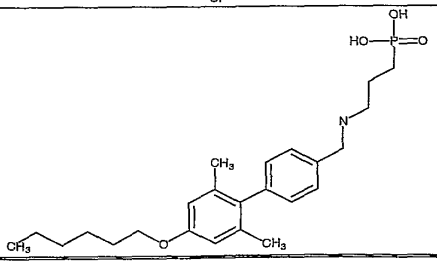
87	
88	
89	
90	

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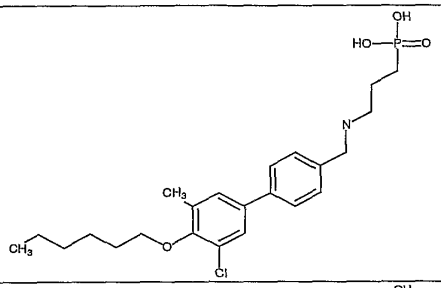
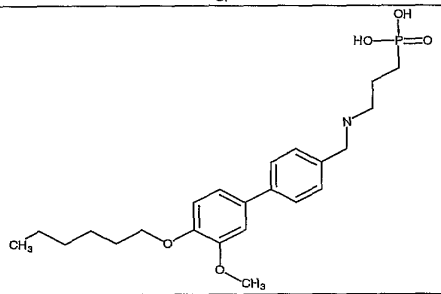
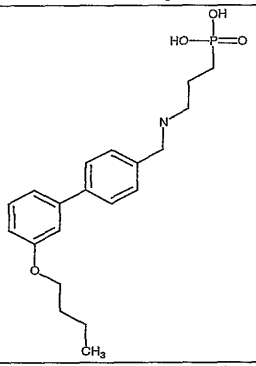
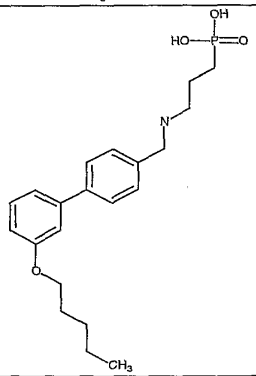
91	
92	
93	
94	

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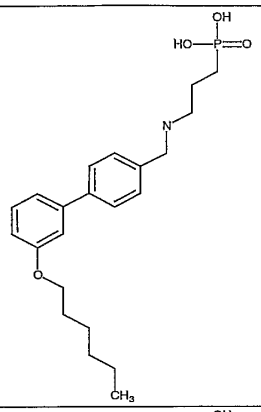
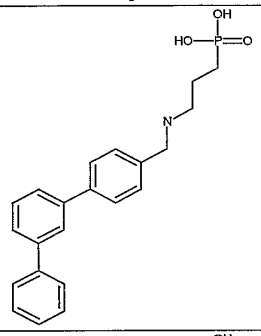
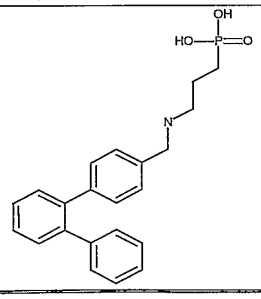
95	
96	
97	

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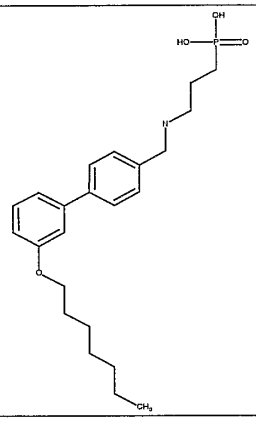
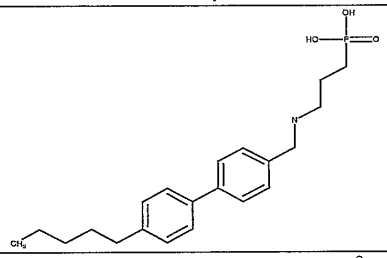
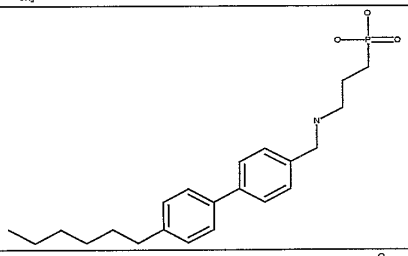
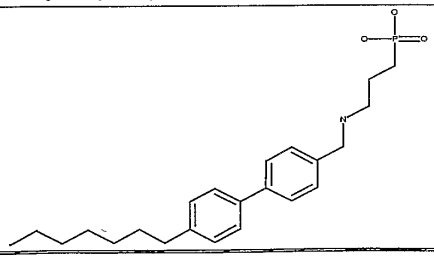
98	
99	
100	
101	

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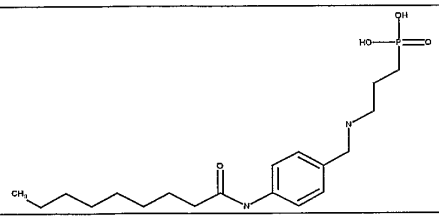
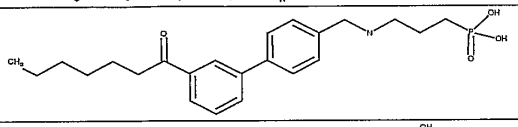
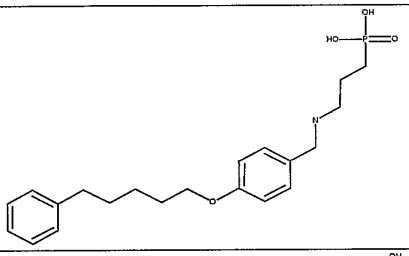
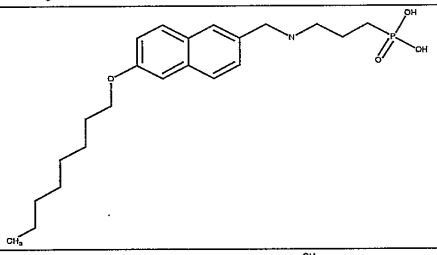
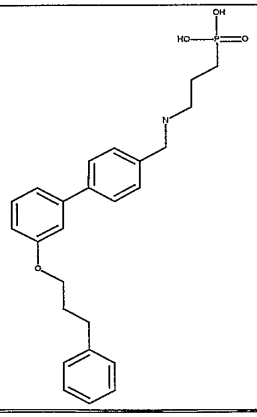
102	
103	
104	
105	
106	

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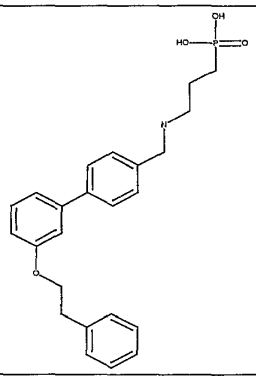
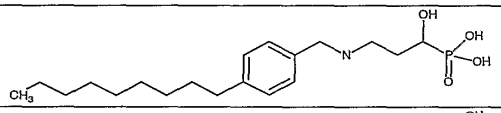
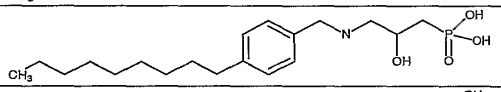
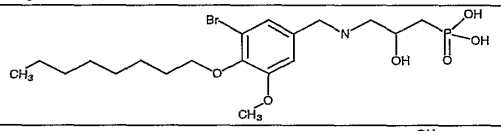
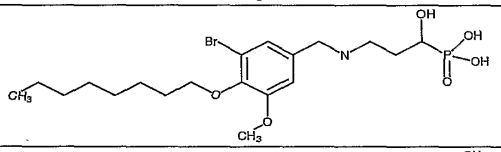
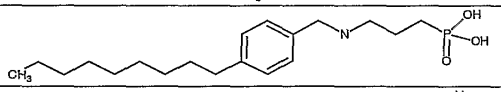
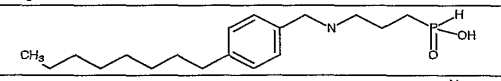
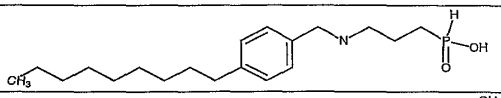
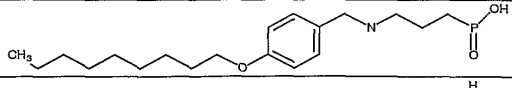
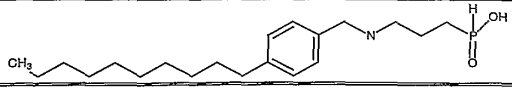
107	
108	
109	
110	
111	
112	
113	
114	
115	
116	

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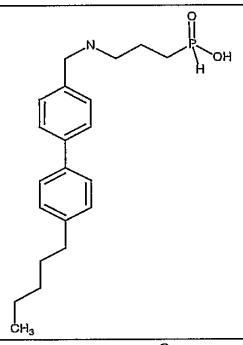
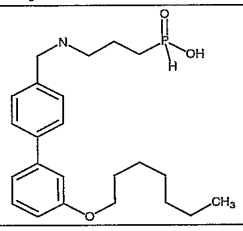
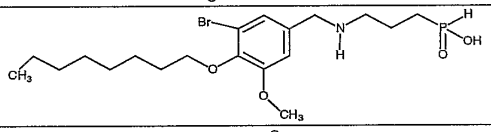
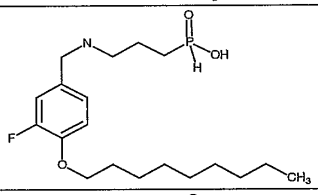
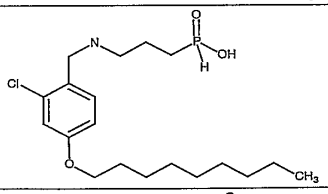
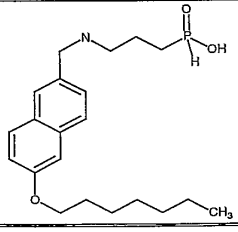
117	
118	
119	
120	
121	
122	

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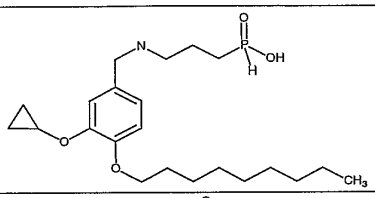
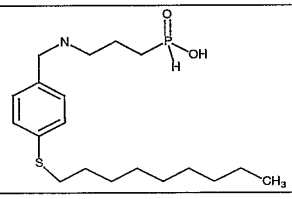
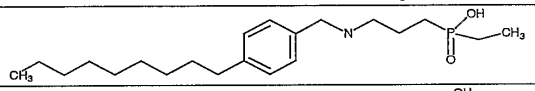
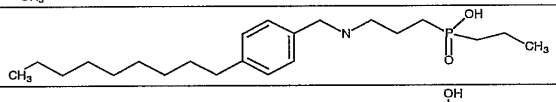
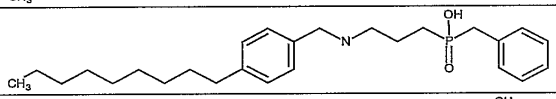
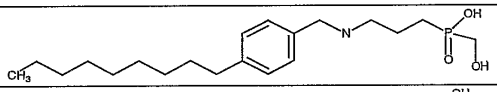
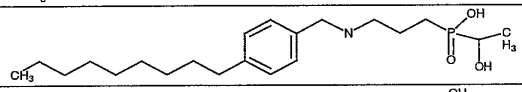
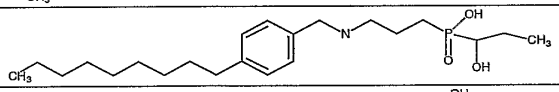
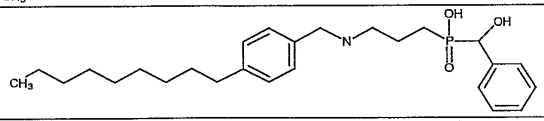
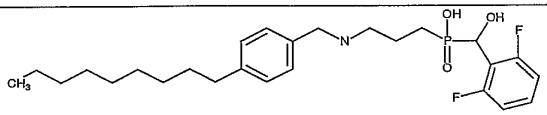
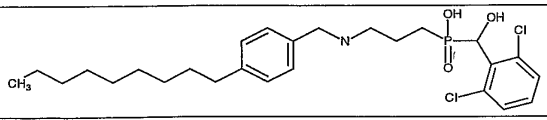
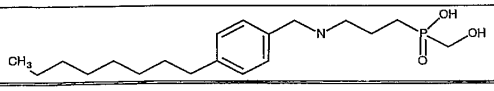
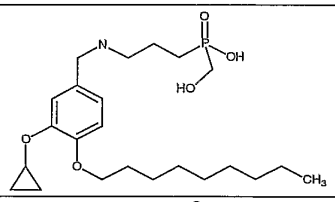
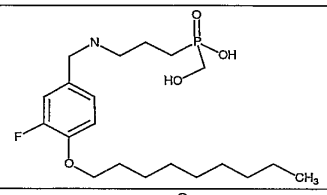
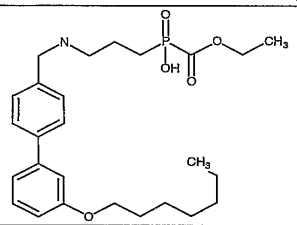
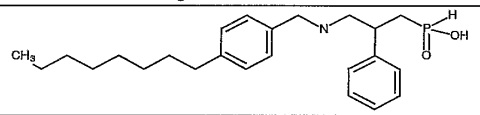
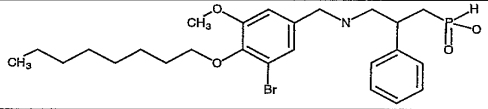
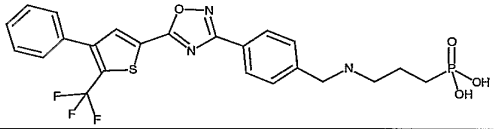
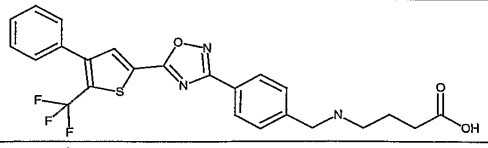
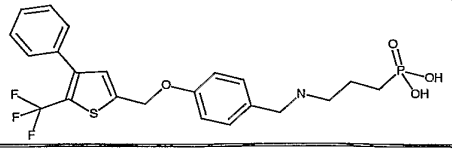
123	
124	
125	
126	
127	
128	
129	
130	
131	
132	
133	
134	

Example Number	Structure
135	
136	
137	
138	
139	
140	
141	
142	

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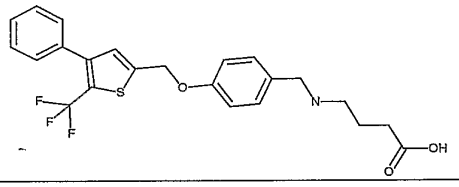
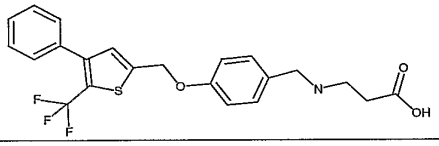
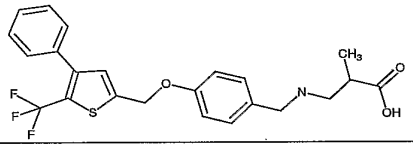
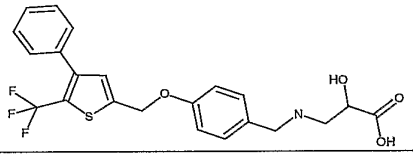
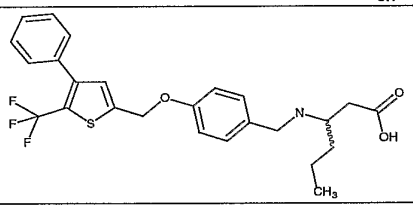
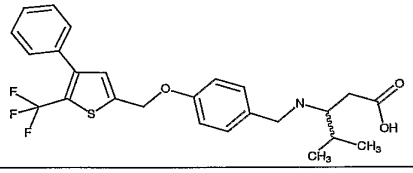
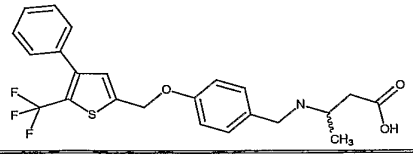
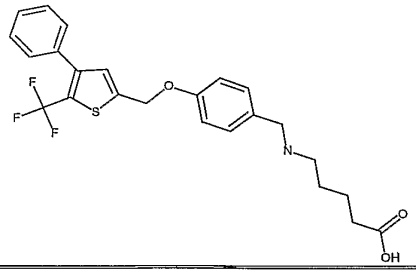
143	
144	
145	
146	
147	
148	
149	

Example Number	Structure
150	

GENERAL METHODS

Concentration of solutions was carried out on a rotary evaporator under reduced pressure. Conventional flash chromatography was carried out on silica gel (230-400 mesh). Flash chromatography was also carried out using a Biotage Flash Chromatography apparatus (Dyax Corp.) on silica gel (32-63 mM, 60 Å pore size) in pre-packed cartridges of the size noted. NMR spectra were obtained in $CDCl_3$ unless otherwise noted. Coupling constants (J) are in hertz (Hz). Abbreviations: diethyl ether (ether), triethylamine (TEA), N,N-diisopropylethylamine (DIEA), tetrahydrofuran (THF), saturated (sat'd), room temperature (rt), hour(s) (h or hr), min(s) (min). For all tables that follow any NMR data follows the compound.

HPLC METHODS

LC-1: Waters Xterra MS C18, 5 μ, 4.6 x 50 mm column, 10:90 to 95:5 v/v CH_3CN/H_2O + 0.05% TFA over 4.5 min, hold 1 min, PDA detection 200-600 nm, flow rate = 2.5 mL/min.

LC-2: Analytical Sales and Service Armor C8 5 μ 20 x 100 mm column, 10:90 to 90:10 v/v CH_3CN/H_2O + 0.05% TFA over 12 min, hold 4 min, UV detection at either 210, 220 or 254 nM, flow rate = 10 mL/min.

LC-3: YMC-Pack Pro C18, 5μ, 20 mm x 150 mm column, gradient 10:90-80:20 v/v $CH_3CN:H_2O$ + 0.1% TFA over 23 min then hold at 100:0 v/v $CH_3CN:H_2O$ + 0.1% TFA for 7 min; 20 mL/min, 254 nm.

PREPARATION OF ALDEHYDE INTERMEDIATES

Aldehyde 1

4-Octyloxybenzaldehyde

4-Hydroxybenzaldehyde (1.00 g, 0.82 mmol), potassium carbonate (1.70 g, 12.28 mmol) and 1-iodooctane (2.16 g, 9.00 mmol) were heated together in acetonitrile at 80°C for 16 h. The reaction was cooled, filtered and concentrated. Silica gel chromatography eluting with hexane/ethyl acetate (20:1) gave a colorless oil (1.63 g): ^{1}H NMR (500 MHz) δ 9.99 (s, 1H), 7.44-7.46 (m, 2H), 7.40 (s, 1H), 7.19 (m, 1H), 4.01 (t, J=6.6 Hz, 2H), 1.80 (m, 2H), 1.42-1.50 (m, 2H), 1.24-1.39 (m, 8H), 0.89 (t, J=6.9 Hz, 3H).

Aldehyde 2

4-Hydroxy-3-propyloxybenzaldehyde

3,4-Dihydroxybenzaldehyde (0.5 g, 3.62 mmol) was dissolved in DMF (10 mL) and sodium hydride (0.087 g, 3.62 mmol) was added. The reaction mixture was stirred at rt for 10 min. Iodopropane (0.35 mL, 0.62 mmol) was added and the reaction was stirred at 80 °C for 2.5 h. The reaction was diluted with ethyl acetate and washed with 2N HCl and water. Silica gel chromatography eluting with 35% ethyl acetate/hexane yielded 0.16 g of desired product: ESI-MS 181 (M+H).

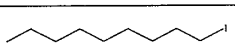
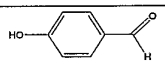
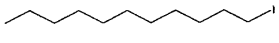
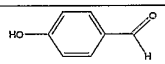
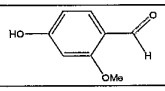
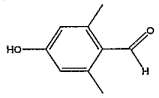
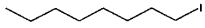
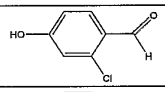
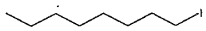
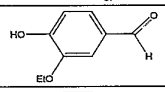
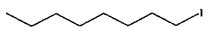
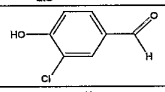
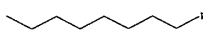
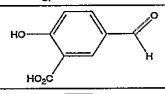
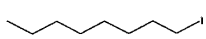
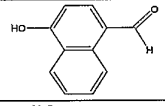
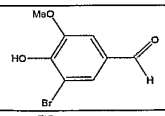
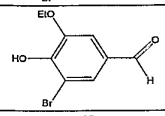
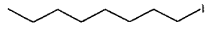
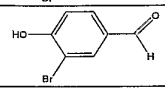
Aldehyde 3

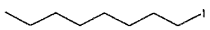
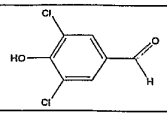
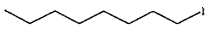
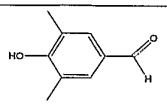
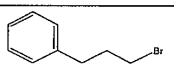
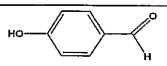
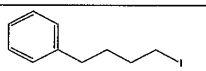
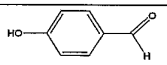
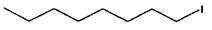
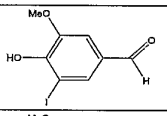
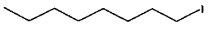
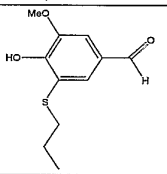
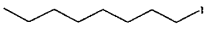
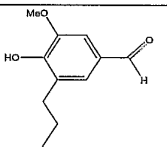
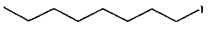
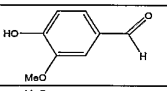
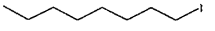
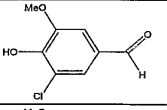
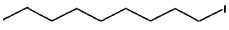
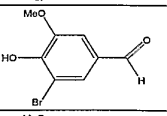
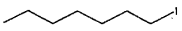
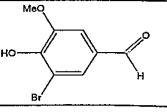
6-Hydroxy-2-naphthaldehyde

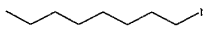
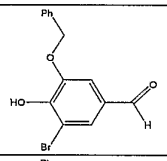
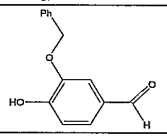
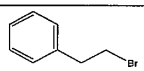
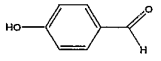
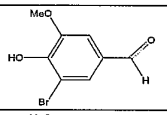
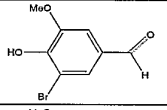
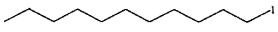
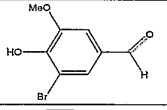
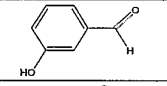
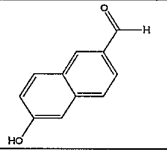
Aluminum trichloride (1.07 g, 8.06 mmol) was added to a solution of 6-methoxy-2-naphthaldehyde (1.0 g, 5.37 mmol) in chlorobenzene (15 mL). The reaction mixture was stirred at 130 °C for 4 h. The reaction was quenched with water (5 mL) and conc. HCl (2 mL). The reaction mixture was dissolved in ethyl acetate and washed with water and brine and dried over anhydrous magnesium sulfate. Silica gel chromatography eluting with 10% ethyl acetate/hexane yielded 0.35 g of desired product: ESI-MS173.0 (M+H).

Aldehydes 4-34

The following Aldehydes (4-34) were prepared using a procedure analogous to that described for Aldehyde 1 substituting A for 1-iodooctane and B for 4-hydroxybenzaldehyde.

Aldehyde	A	B	ESI-MS
4			249.3
5			277.1
6			265.4
7			263.1
8			269.0
9			279.1
10			
11			262.0
12			
13			343.0
14			357.1
15			

16			
^{1}H NMR (500 MHz, CD_3OD) δ 9.88 (s, 1H), 7.94 (s, 1H), 7.47 (s, 1H), 4.26 (t, J=6.3 Hz, 2H), 4.14 (t, J=6.3 Hz, 2H), 4.02 (t, J=6.3 Hz, 2H), 3.25 (t, J=6.8 Hz, 2H), 1.76-1.94 (m, 4H), 1.52-1.62 (m, 2H), 0.88-1.00 (m, 3H)			
17			
18			241.1
19			255.2
20			391.1
21			339.3
22			307.3
23			265.2
24			299.1
25			357.1
26			329.0

27			419.1
28			341.3
29			227.1
30			370.9
31			317.1
32			382.7
33			179.1
34			285.1

Aldehyde 35

3-Methoxy-5-methyl-4-octyloxybenzaldehyde

Aldehyde 20 (0.20 g, 0.51 mmol) and tetramethyl tin (0.2 g, 1.12 mmol) were dissolved in N-methyl pyrrolidinone (1 mL) in a sealed tube. Palladium tetrakis(triphenylphosphine) (0.016 g, 0.014 mmol) and copper iodide (0.01 g, 0.05 mmol) were added to the reaction mixture which was heated at 65° for 16 h. The reaction mixture was diluted with ethyl acetate and washed with 2N HCl, brine and was dried over magnesium sulfate. Silica gel chromatography eluting with 10% ethyl acetate/hexane gave desired product: ESI-MS 279.2 (M+H).

Aldehyde 36

3-Methoxy-5-phenyl-4-octyloxybenzaldehyde

Aldehyde 20 (0.25 g, 0.64 mmol), phenylboronic acid (0.12 g, 0.96 mmol), potassium carbonate (0.27 g, 1.92 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.15 g, 0.016 mmol) and 2-(dicyclohexylphosphino)biphenyl (0.022 g, 0.064 mmol) were dissolved in tetrahydrofuran (1 mL). The reaction mixture was stirred at rt for 3 h then at 50 °C for 16 h. The reaction mixture was filtered through celite. Silica gel chromatography eluting with 10% ethyl acetate/hexane gave desired product: ESI-MS 341.2 (M+H).

Aldehyde 37

3-Hydroxy-4-octyloxybenzaldehyde

Aldehyde 28 (0.25 g, 0.77 mmol) was dissolved in methylene chloride (4 mL) and boron tribromide dimethylsulfide complex (0.6 g, 1.93 mmol) was added dropwise. The reaction mixture was stirred at rt for 1 h. The reaction was quenched with methanol and concentrated *in vacuo*. Silica gel chromatography eluting with 10% ethyl acetate/hexane yielded 0.155 g of desired product: ESI-MS 251.2 (M+H).

Aldehyde 38

4-(Nonoylamido)benzaldehyde

4-Aminobenzaldehyde (0.3 g, 2.5 mmol) was dissolved in methylene chloride (8 mL) and nonanoyl chloride (0.5 mL, 2.7 mmol) was added followed by DIEA (1.14 mL, 6.25 mmol). The reaction was stirred at rt for 3 h. Silica gel chromatography eluting with 25% ethyl acetate/hexane yielded impure product Further purified by HPLC to give 30.0 mg of desired product: ESI-MS 262.0 (M+H).

Aldehyde 39

4-(5-Phenylpentyloxy)benzaldehyde

Diethylazodicarboxylate (0.49 g, 2.8 mmol) in tetrahydrofuran (2 mL) was added to a solution of 4-hydroxybenzaldehyde (0.25 g, 2.05 mmol), 5-phenyl-1-pentanol (0.34 mL, 2.05 mmol) and triphenylphosphine (0.73 g, 2.80 mmol) in tetrahydrofuran (10 mL) at rt. The reaction was stirred for 2h. The reaction mixture

was concentrated *in vacuo*. Silica gel chromatography eluting with 20% ethyl acetate/hexane yielded 0.070 g of desired product: ^{1}H NMR (500 MHz , CD_3OD): δ 9.83 (s, 1H), 7.86 (d, J=8.7 Hz, 2H), 7.25 (t, 2H), 7.14-7.20 (m, 3H), 7.06 (d, J=8.7 Hz, 2H), 4.09 (t, J=6.4 Hz, 2H), 2.65 (t, J=7.7 Hz, 2H), 1.80-1.88 (m, 2H), 1.68-1.75 (m, 2H), 1.49-1.57 (m, 2H).

Aldehyde 40

3'-Chloro-4'-octyloxy-4-biphenylbenzaldehyde

Step A: 1-Bromo-3-chloro-4-octyloxybenzene

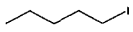
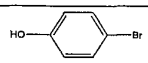
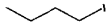
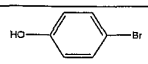
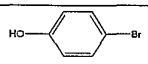
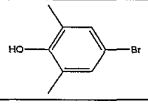
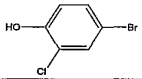
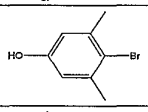
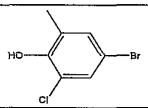
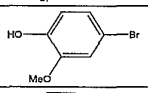
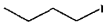
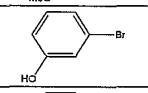
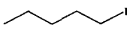
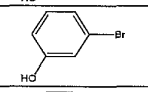
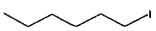
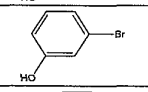
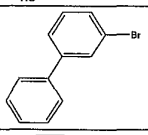
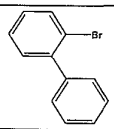
1-Bromo-3-chloro-4-hydroxybenzene (0.50 g, 2.41 mmol) was dissolved in acetonitrile (20 mL) and stirred at rt. Potassium carbonate (0.47 g, 3.37 mmol) and iodooctane (0.57 mL, 3.13 mmol) were added and the reaction was heated to 80 °C for 4 h. The reaction was diluted with ethyl acetate, washed with water and dried over anhydrous magnesium sulfate. Silica gel chromatography eluting with 1% ethyl acetate/hexane yielded 0.6 g of product: ESI-MS 317.0 (M+H).

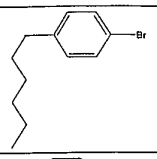
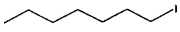
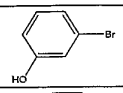
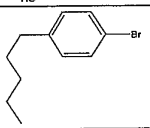
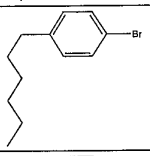
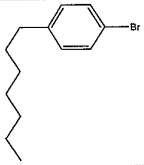
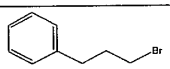
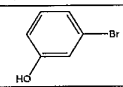
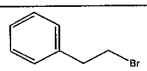
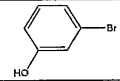
Step B: 3'-Chloro-4'-octyloxy-4-biphenylbenzaldehyde

Palladium acetate (0.005 g, 0.022 mmol) and 2-(dicyclohexylphosphino)biphenyl (0.015 g, 0.044 mmol) were added to a solution of (4-formylphenyl)boronic acid (0.25 g, 1.65 mmol), 1-bromo-3-chloro-4-octoxybenzene (0.35 g, 1.10 mmol, from Step A), and potassium fluoride (0.19 g, 3.30 mmol) in 1,4-dioxane (3 mL). The reaction mixture was heated at 75 °C for 3 h. The reaction was cooled, filtered through celite and concentrated *in vacuo*. Silica gel chromatography eluting with 1% ethyl acetate/hexane yielded 0.17 g of desired product: ^{1}H NMR (500 MHz , CD_3OD): δ 10.01 (s, 1H), 7.97 (d, J=8.0 Hz, 2H), 7.80 (d, J=8.0 Hz, 2H), 7.74 (s, 1H), 7.61 (d, J=7.7 Hz, 1H), 7.16 (d, J=8.7 Hz, 1H) 4.11 (t, J=6.2 Hz, 2H), 1.80-1.89 (m, 2H), 1.50-1.60 (m, 2H), 1.28-1.46 (m, 8H), 0.88-0.97 (m, 3H)

Aldehydes 41-60

The following Aldehydes (41-60) were made using procedures analogous to those described for Aldehyde 40 substituting A for 1-iodooctane and B for 1-bromo-3-chloro-4-hydroxybenzene in Step A

Aldehyde	A	B	ESI-MS
41			269.1
42			255.0
43			283.1
44			311.0
45			
46			311.3
47			331.1
48			313.2
49			255.1
50			269.2
51			
52	N/A		259.0
53	N/A		259.0

54	N/A		267.1
55			297.1
56	N/A		253.2
57	N/A		267.1
58	N/A		
59			
60			

Aldehyde 61

4-(Octyloxymethyl)benzaldehyde

Step A: 4-(Octyloxymethyl)benzyl alcohol

Sodium hydride (0.17 g, 7.20 mmol) was added to a solution of 1,4-benzene dimethanol (1.00 g, 7.20 mmol) in THF at 0 °C. The reaction was stirred for 1 h. 1-iodooctane (1.73 g; 7.20 mmol) was added and the reaction mixture was warmed to rt for 4 h and then heated at 50°C for 2 days. The reaction was cooled and filtered. Silica gel chromatography eluting with 15% ethyl acetate/hexane gave 0.14 g of product: ^{1}H NMR (500 MHz) δ 7.34-7.40 (m, 4H), 4.68-4.72 (m, 2H), 4.51 (s, 2H), 3.46-3.50 (m, 2H), 1.61-1.68 (m, 2H), 1.24-1.40 (m, 10H), 0.88-0.92 (m, 3H).

Step B: 4-(Octyloxymethyl)benzaldehyde

4-(Octyloxymethyl)benzyl alcohol (0.14 g, 0.56 mmol, from Step A) was dissolved in methylene chloride (1.5 mL) and the reaction mixture was cooled to 0 °C. 4-methylmorpholine N-oxide (0.10 g, 0.84 mmol) and molecular sieves (4A) (0.25 g) were added. Tetrapropylammonium perruthenate (0.004 g, 0.011 mmol) was added and the resulting mixture was stirred for 1 h. The reaction mixture was filtered through celite. Silica gel chromatography eluting with 6% ethyl acetate/hexane gave 0.018 g of product: ^{1}H NMR (500 MHz) δ 10.02 (s, 1H), 7.86-7.90 (m, 2H), 7.50-7.55 (m, 2H), 4.58-4.62 (s, 2H), 3.50-3.55 (m, 2H), 1.62-1.70 (m, 2H), 1.24-1.35 (m, 2H), 0.87-0.93 (m, 2H).

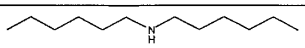
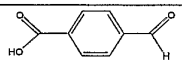
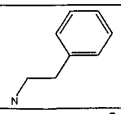
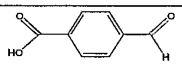
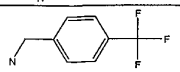
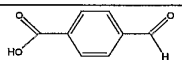
Aldehyde 62

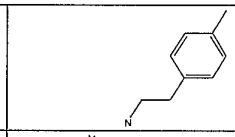
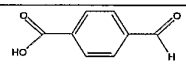
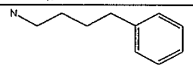
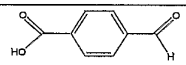
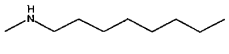
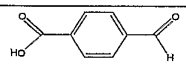
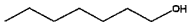
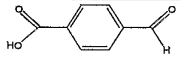
4-(N-Octylcarboxamido)benzaldehyde

DIEA (0.43 mL, 2.33 mmol) was added to a solution of 4-carboxybenzaldehyde (0.23 g, 1.55 mmol), octylamine (0.20 g, 1.55 mmol) and PyBoP (0.89 g, 1.71 mmol) in methylene chloride (2.5 mL). The reaction was stirred at rt for 16 h after which it was concentrated. Silica gel chromatography eluting with 25% ethyl acetate/hexane gave 0.30 g of product: ESI-MS 262.1 (M+H).

Aldehydes 63-73

The following Aldehydes (63-73) were made using a procedure analogous to that described for Aldehyde 62 substituting A for octylamine.

Aldehyde	A	B	ESI-MS
63			318.2
64			253.0
65			

66			282.2
67			282.2
68			
69			
^{1}H NMR (500 MHz): δ 10.10 (s, 1H), 8.20 (d, J=8.2 Hz, 2H), 7.95 (d, J=8.2 Hz, 2H), 4.35 (t, J=6.8 Hz, 2H), 1.75-1.85 (m, 2H), 1.40-1.50 (m, 2H), 1.25-1.40 (m, 6H), 0.89 (t, J=7.0 Hz, 3H).			

Aldehyde 70

4-(1-Hydroxynon-1-yl)benzaldehyde

Terephthaldicarboxaldehyde (2.00 g, 14.91 mmol) was dissolved in tetrahydrofuran (25 mL) and cooled to 0°C. Octylmagnesium chloride (7.5 mL, 2.0M in THF, 15 mmol) was added dropwise. After 15 min, the reaction was quenched with 2N aqueous hydrochloric acid (50 mL) and diluted with ethyl acetate (50 mL). The organic layer was separated, washed with sat'd sodium chloride (50 mL), dried over magnesium sulfate and concentrated *in vacuo*. Silica gel chromatography eluting with 9% ethyl acetate/hexane gave 0.19 g (0.77 mmol, 5.1%) of product: ^{1}H NMR (500 MHz) δ 10.0 (s, 1H), 7.87 (d, J=8.0 Hz, 2H), 7.52 (d, J=8.3 Hz, 2H), 4.75-4.80 (m, 1H), 1.68-1.82 (m, 2H), 1.22-1.45 (m, 12H), 0.91 (t, J=7.0 Hz, 3H).

Aldehyde 71

4-(1-Nonoyl)benzaldehyde

Dess-Martin periodinane (0.268 g, 0.632 mmol) was added to a solution of Aldehyde 70 (0.125 g, 0.505 mmol) in methylene chloride (3.0 mL). After 1 h, the reaction was filtered and concentrated in vacuo. Silica gel chromatography eluting with 5% ethyl acetate/hexane gave 0.107 g (0.446 mmol, 88%) of product: ^{1}H NMR (500 MHz) δ 10.1 (s, 1H), 8.10 (d, J=8.2 Hz, 2H), 7.97 (d, J=8.2 Hz, 2H), 3.00 (t, J= 7.3 Hz, 2H), 1.70-1.8 (m, 2H), 1.22-1.42 (m, 10H), 0.88 (t, J=7.0 Hz, 3H).

Aldehyde 72

4-(1-Decanoyl)benzaldehyde

Tetrakis(triphenylphosphine)palladium(0) (50 mg) was added to a solution of 4-formylphenylboronic acid (0.50 g, 3.33 mmol), nonanoyl chloride (1.7 mL, 8.33 mmol) and cesium carbonate (2.70 g, 8.33 mmol) in toluene (40 mL) and heated to 80 °C. After stirring overnight, the reaction was diluted with ethyl acetate (50 mL) and washed with 2N hydrochloric acid (50 mL), sat'd sodium chloride (50 mL), dried over magnesium sulfate and concentrated *in vacuo*. Silica gel chromatography eluting with 6% ethyl acetate/hexane gave 0.022 g (0.083 mmol, 3%) of product: ^{1}H NMR (500 MHz) δ 10.1 (s, 1H), 8.09 (d, J=8.2 Hz, 2H), 7.98 (d, J=8.2 Hz, 2H), 3.00 (t, J= 7.4 Hz, 2H), 1.70-1.80 (m, 2H), 1.22-1.42 (m, 12H), 0.88 (t, J=6.9 Hz, 3H).

Aldehyde 73

3-Methyl-4-decanoyl benzaldehyde

Step A: 4-Bromo-3-methylbenzyl alcohol

DIBALH (1.0M solution in methylene chloride, 31 mL, 31 mmol) was added dropwise to a solution of methyl 4-bromo-3-methylbenzoate (3.0 g, 14.0 mmol) in methylene chloride (20 mL) at 0 °C. After 1 h, the reaction was quenched with 10% aqueous sodium bisulfite (100 mL). The aqueous layer was separated and extracted with methylene chloride (50 mL). The combined organic layers were combined, dried over magnesium sulfate and concentrated i*n vacuo*. Silica gel chromatography eluting with 17% ethyl acetate/hexane gave 1.90 g (9.50 mmol, 68%)

of product: ^{1}H NMR (500 MHz) δ 7.50 (d, J=8.3 Hz, 1H), 7.24 (s, 1H), 7.04 (d, J=8.0 Hz, 1H), 4.62 (d, J= 5.7 Hz, 2H), 2.40 (s, 3H).

Step B: 4-(1-Hydroxydec-1-yl)-3-methylbenzyl alcohol

n-Butyllithium (2.5 M in hexanes, 8.3 mL, 20.7 mmol) was added dropwise to a solution of 4-bromo-3-methylbenzyl alcohol (1.90 g, 9.44 mmol, from Step A) in tetrahydrofuran (25 mL) at –78 °C. After 1 h, n-decanal (2.95 g, 18.89 mmol) was added and the reaction allowed to warm to 0°C. After 30 min, the reaction was quenched with water (25 mL) and diluted with ethyl acetate (25 mL). The organic layer was washed with sat'd sodium chloride (30 mL), dried over magnesium sulfate and concentrated *in vacuo*. Silica gel chromatography eluting with 25% ethyl acetate/hexane gave 1.69 g (6.07 mmol, 64%) of product: ^{1}H NMR (500 MHz): δ 7.45 (d, J=8.0 Hz, 1H), 7.21 (d, J=7.8 Hz, 1H), 7.14 (s, 1H), 4.88-4.94 (m, 1H), 4.64 (s, 2H), 2.34 (s, 3H), 1.22-1.80 (m, 16H), 0.87 (t, J=7.0 Hz, 3H).

Step C: 3-Methyl-4-decanoyl benzaldehyde

Dess-Martin periodinane (1.00 g, 2.37 mmol) was added to a solution of 4-(1-hydroxydec-1-yl)-3-methylbenzyl alcohol (0.300 g, 1.07 mmol, from Step B) in methylene chloride (5.0 mL). After 20 min, the reaction was filtered and concentrated *in vacuo*. Silica gel chromatography eluting with 5% ethyl acetate/hexane gave 0.24 g (0.89 mmol, 83%) of product: ^{1}H NMR (500 MHz) δ 10.0 (s, 1H), 7.76 (d, J=7.8 Hz, 1H), 7.74 (s, 1H), 7.66 (d, J=7.8 Hz, 1H), 2.87 (t, J=7.5 Hz, 2H), 2.51 (s, 3H), 1.66-1.74 (m, 2H), 1.22-1.38 (m, 12H), 0.87 (t, J=7.0 Hz, 3H).

Aldehyde 74

3-Methyl-4-(4-(nonyl)benzoyl)benzaldehyde

The title compound was prepared using procedures analogous to those used to prepare Aldehyde 73 substituting 4-(nonyl)benzaldehyde for n-decanal in Step B: ^{1}H NMR (500 MHz) δ 10.0 (s, 1H), 7.76 (d, J=7.8 Hz, 1H), 7.74 (s, 1H), 7.66 (d, J=7.8 Hz, 1H), 2.88 (t, J=7.5 Hz, 2H), 2.51 (s, 3H), 1.66-1.74 (m, 2H), 1.22-1.38 (m, 10H), 0.88 (t, J=7.0 Hz, 3H).

Aldehyde 75

3'-(1-Hydroxyhept-1-yl)-4-biphenylcarboxaldehyde

Step A: 1-Bromo-3-(1-hydroxyhept-1-yl)benzene

Hexylmagnesium bromide (2.0M in THF, 3.7 mL, 7.4 mmol) was added to a solution of 3-bromobenzaldehyde (1.50g, 8.11 mmol) in tetrahydrofuran (10 mL) at –78 °C. After 10 min, the reaction was quenched by the addition of 2N hydrochloric acid (30 mL) and the product extracted into ethyl acetate (30 mL). The organic layer was washed with sat'd sodium chloride (25 mL), dried over magnesium sulfate and concentrated *in vacuo*. Silica gel chromatography eluting with 17% ethyl acetate/hexane gave 1.42 g (5.25 mmol, 65%) of product.

Step B: 3'-(1-Hydroxyhept-1-yl)-4-biphenylcarboxaldehyde

To a solution of 1-bromo-3-(1-hydroxyhept-1-yl)benzene (1.00 g, 3.70 mmol, from Step A), 4-formylphenylboronic acid (0.83 g, 5.55 mmol) and potassium fluoride (0.65 g, 11.10 mmol) in tetrahydrofuran (10 mL) was added palladium(II) acetate (0.016 g, 0.071 mmol) and 2-(dicyclohexylphosphino)biphenyl (0.052 g, 0.148 mmol). After stirring for 24 h at rt, the reaction was diluted with ethyl acetate (50 mL), washed with water (50 mL), sat'd sodium chloride (50 mL), dried over magnesium sulfate and concentrated in vacuo. Silica gel chromatography eluting with 25% ethyl acetate/hexanes gave 0.81 g of product as a yellow oil.

Aldehyde 76

3'-(Heptanoyl)-4-biphenylcarboxaldehyde

Step A: 1-Bromo-3-heptanoyl benzene

Dess-Martin periodinane (4.40 g, 15% solution in methylene chloride, 1.56 mmol) was added to a solution of 1-bromo-3-(1-hydroxyhept-1-yl)benzene (0.39 g, 1.42 mmol, from Aldehyde 75, Step A). After 1 h, the reaction was quenched by the addition of 1N sodium hydroxide (20 mL). The aqueous layer was separated, washed with methylene chloride (20 mL) and the organic layers combined, dried over magnesium sulfate and concentrated *in vacuo*. Silica gel chromatography eluting with 5% ethyl acetate/hexane gave 0.30 g (1.11 mmol, 78%) of product: ^{1}H NMR (500 MHz) δ 8.08 (t, J=1.7 Hz, 1H), 7.87 (d, J=7.7 Hz, 1H), 7.68 (d, J=8.0 Hz, 1H), 7.34 (t,

J=7.9 Hz, 1H), 2.93 (t, J=7.4 Hz, 2H), 1.68-1.76 (m, 2H), 1.28-1.40 (m, 6H), 0.89 (t, J=7.0 Hz, 3H).

Step B: 3'-(Heptanoyl)-4-biphenylcarboxaldehyde

To a solution of 1-bromo-3-heptanoyl benzene (0.30 g, 1.11 mmol, from Step A), 4-formylphenylboronic acid (0.25 g, 1.68 mmol) and potassium fluoride (0.20 g, 3.36 mmol) in tetrahydrofuran (2.5 mL) was added palladium(II) acetate (0.006 g, 0.025 mmol) and 2-(dicyclohexylphosphino)biphenyl (0.016 g, 0.050 mmol). After stirring for 3 h at 50°C, the reaction was placed onto silica gel and eluted with 10% ethyl acetate/hexanes to give 0.26 g (0.88 mmol, 80%) of product as a yellow oil: ^{1}H NMR (500 MHz) δ 8.22 (t, J=1.7 Hz, 1H), 7.90-8.10 (m, 3H), 8.30 (d, J=8.0 Hz, 1H), 7.99 (d, J=8.3 Hz, 2H), 7.58 (t, J=7.8 Hz, 1H), 3.02 (t, J=7.4 Hz, 2H), 1.66-1.80 (m, 2H), 1.38-1.44 (m, 2H), 1.30-1.38 (m, 4H), 0.90 (t, J=7.0 Hz, 3H).

Aldehyde 77

3-(Cyclopropyloxy)-4-(nonyloxy)benzaldehyde

To a solution of 1.78 g (10.0 mmol) of 3-(cyclopropyloxy)-4-hydroxybenzaldehyde and 2.54 g(10.0 mmol) of 1-iodononane in 20 mL acetonitrile was added 3.58 g(11.0 mmol) of Cs_2CO_3. The slurry was stirred at rt for 12 h. The reaction was quenched with 30 mL of water and extracted with ethyl acetate (50 mL x 2). The combined extractions were washed with water, dried with sodium sulfate and concentrated to a solid. Flash chromatography on a Biotage 40M cartridge using 10 % ethyl acetate/hexanes afforded 2.9 g (95%) of the title compound as a white solid. ^{1}H NMR (500 Mhz) δ 0.87-0.91 (m, 7H), 1.30-1.90 (m, 14H), 3.85 (m, 1H), 4.10 (t, J = 6.9, 2H), 6.98 (d, J = 8.2, 1H), 7.48 (dd, J = 8.5, 1.8, 1H), 7.77 (d, J = 1.8, 1H), 9.89 (s, 1H); LC-1: 4.6 min; ESI-MS 305 (M+H).

Aldehyde 78

4-(Nonylthio)benzaldehyde

To a solution of 3.15 g (10.0 mmol) of 1-bromo-4-(nonylthio)benzene in 50 mL anhydrous THF was slowly added 9.4 mL of *n*-BuLi (1.6 M in hexanes, 15 mmol) at –50 °C. The mixture was aged at the same temperature for 1 h before the addition of 2.3 mL of anhydrous DMF. The reaction mixture was allowed to warm to 0 °C and

was quenched with 2 N HCl to pH=1. The layers were separated and the aqueous layer was extracted with ethyl acetate (50 mL x 2). The combined organic layer and extractions were washed with water and concentrated to oil. Flash chromatography on a Biotage 40M cartridge using 5 % ethyl acetate/hexanes afforded 2.35 g (89%) of the title compound as light yellow oil: ^{1}H NMR (500 MHz) δ 0.91 (t, J = 7.0, 3H), 1.30-1.76 (m, 14H), 3.03 (t, J = 7.4, 2H), 7.37 (d, J = 8.5, 2H), 7.78 (d, J = 8.5, 2H), 9.95 (s, 1H); LC-1: 4.8 min; ESI-MS 265 (M+H).

Aldehyde 79

3-(4-(Formyl)phenyl)-5-(4-phenyl-5-trifluoromethyl-2-thienyl)-1,2,4-oxadiazole

Step A: (E/Z)-2-Phenyl-3-chloro-4,4,4-trifluoro-2-butanal

Phosphorous oxychloride (7.5 mL, 80 mmol) was added to 15 mL of DMF at 0 °C. The resulting mixture was warmed to rt and stirred for 1 h. A solution of 5.0 g (26.6 mmol) of 1,1,1-trifluoromethyl-3-phenyl-2-propanone in 1 mL of DMF was added and the resulting mixture was stirred at 70 °C for 20 h. The reaction mixture was cooled to rt, poured onto 150 g of ice and stirred at ambient temperature for 1 h. The quenched mixture was extracted with 200 mL of ether. The extract was washed with 200 mL of water, dried and concentrated. Chromatography on a Biotage 40 M cartridge using hexanes (4L) as the eluant afforded 5.1 g (82%) of the title compound.

Step B: Ethyl (4-phenyl-5-trifluoromethyl)thiophene-2-carboxylate

Ethyl mercaptoacetate (2.75 mL, 25.0 mmol) was added to a suspension of 600 mg (25 mmol) of NaH in 45 mL of THF maintaining the internal temperature at 25 °C. A solution of 5.10 g (21.7 mmol) of (E/Z)-2-phenyl-3-chloro-4,4,4-trifluoro-2-butanal (from Step A) was added and the resulting mixture was stirred at rt for 20 h. The reaction was quenched with 50 mL of sat'd NH_4Cl and the resulting mixture was partitioned between 250 mL of ether and 100 mL of water. The organic layer was separated, dried and concentrated. Chromatography on a Biotage 40 M cartridge using hexanes (1L), then 4:1 v/v hexanes/CH_2Cl_2 (1L) as the eluant afforded 5.10 g (78%) of the title compound: ^{1}H NMR (400 Mhz) δ 1.40 (t, J= 7.2, 3H), 4.39 (q, J= 7.2, 2H), 7.42 (app s, 5H), 7.74 (q, J=1.6, 1H).

Step C: (4-Phenyl-5-trifluoromethyl)thiophene-2-carboxylic acid

A solution of 5.10 g (17.0 mmol) of ethyl 4-phenyl-5-trifluoromethyl-thiophene-2-carboxylate (from Step B) in 20 mL of EtOH was treated with 10 mL of 5.0 N NaOH and stirred at rt for 30 min. The EtOH was removed in vacuo. The residual aqueous mixture was acidified to pH 2 with 1 N HCl, then extracted with 300 mL of 1:1 v/v EtOAc/ether. The extract was separated, dried and concentrated. Recrystallization from 200 mL of 20:1 v/v hexanes/ether afforded 4.30 g (93%) of the title compound: ^{1}H NMR (500 Mhz) δ 7.43 (app s, 5H), 7.84 (app s, 1H); ^{13}C NMR ($CDCl_3$, 125 Mhz) δ 121.7 (q, J= 269), 128.5, 128.6, 128.8, 132.5 (q, J= 36), 133.3, 133.8, 137.5, 144.8, 167.0.

Step D: 3-[4-(Carbomethoxy)phenyl]-5-(4-phenyl-5-trifluoromethyl-2-thienyl)-1,2,4-oxadiazole

A solution of 408 mg (1.5 mmol) of 4-phenyl-5-trifluoromethyl-thiophene-2-carboxylic acid and 1 mL of oxalyl chloride in 5 mL of CH_2Cl_2 was treated with 5 drops of DMF. The resulting mixture was stirred at rt for 1 h, then concentrated. The crude acid chloride and 291 mg (1.5 mmol) of 4-(carbomethoxy)benzamidoxime were dissolved in 7 mL of 6:1 v/v xylenes/pyridine. The resulting solution was heated at 140 °C for 1 h, then cooled. The mixture was partitioned between 50 mL of 1:1 EtOAc/ether and 50 mL of 1 N HCl. The organic layer was separated, washed with 3 x 50 mL of 1 N HCl, 50 mL of sat'd $NaHCO_3$, dried and concentrated. Chromatography on a Biotage 40 M cartridge using hexanes (1L), then 20:1 v/v hexanes/EtOAc (1L) as the eluant afforded 423 mg (65%) of the title compound: ^{1}H NMR (500 Mhz) δ 3.97 (s, 3H), 7.48 (app s, 5H), 7.92 (s, 1H), 8.18 (app d, J= 8.5, 2H), 8.23 (app d, J= 8.5, 2H).

Step E: 3-[4-(Hydroxymethyl)phenyl]-5-(4-phenyl-5-trifluoromethyl-2-thienyl)-1,2,4-oxadiazole

A solution of 390 mg (0.91 mmol) of 3-[4-(carbomethoxy)phenyl]-5-(4-phenyl-5-trifluoromethyl-2-thienyl)-1,2,4-oxadiazole (from Step D) in 10 mL of CH_2Cl_2 at –78 °C was treated with 2.7 mL of 1.0 M DIBALH solution in CH_2Cl_2. The resulting solution was stirred cold for 1 h, then quenched with 5 mL of sat'd

Rochelle salt solution. The mixture was partitioned between 100 mL CH_2Cl_2 and 50 mL of 1 N NaOH. The organic layer was separated, dried and concentrated. Chromatography on a Biotage 40 S cartridge using 4:1 v/v hexanes/EtOAc (1L) as the eluant afforded 325 mg (89%) of the title compound: ^{1}H NMR (500 Mhz) δ 1.80 (app s, 1H), 4.80 (d, J= 4.0, 2H), 7.46-7.48 (5H), 7.52 (d, J= 8.0, 2H), 7.91 (q, J= 1.5, 1H), 8.14 (d, J= 8.0, 2H).

Step F: 3-[4-(Formyl)phenyl]-5-(4-phenyl-5-trifluoromethyl-2-thienyl)-1,2,4-oxadiazole

A mixture of 310 mg (0.77 mmol) of 3-[4-(hydroxymethyl)phenyl]-5-(4-phenyl-5-trifluoromethyl-2-thienyl)-1,2,4-oxadiazole (from Step E), 527 mg (1.5 mmol) of 4-methylmorpholine N-oxide and 500 mg of 4 A molecular sieves in 15 mL of CH_3CN was treated with 12 mg (0.034 mmol) of tetrapropylammonium perruthnate and the resulting mixture was stirred ar rt for 2 h. The solids were filtered and the filtrated was concentrated. Chromatography on a Biotage 40 S cartridge using 9:1 v/v hexanes/EtOAc (1L) as the eluant afforded 205 mg (66%) of the title compound: ^{1}H NMR (500 Mhz) δ 7.48 (app s, 5H), 7.93 (app s, 1H), 8.03 (d, J= 8.5, 2H), 8.33 (d, J= 8.5, 2H), 10.1 (s, 1H).

Aldehyde 80

4-[(4-Phenyl-5-trifluoromethyl-2-thienyl)methoxy]benzaldehyde

Step A: 2-Hydroxymethyl-4-phenyl-5-trifluoromethyl-thiophene

A solution of 2.10 g (7.7 mmol) of 4-phenyl-5-trifluoromethyl-thiophene-2-carboxylic acid (from Aldehyde 17, Step C) in 20 mL of THF was treated with 5.0 mL of 2.0 M borane dimethylsulfide complex in THF. The resulting solution was heated at reflux for 3 h, cooled to rt, quenched with 10 mL of MeOH and concentrated. Chromatography on a Biotage 40M cartridge using 9:1 v/v hexanes/EtOAc as the eluant afforded 1.95 g (98%) of the title compound: ^{1}H NMR (500 Mhz) δ 2.05 (app s, 1H), 4.87 (s, 2H), 6.99 (s, 1H), 7.41 (app s, 5H).

Step B: 4-((4-Phenyl-5-trifluoromethyl-2-thienyl)methoxy)benzaldehyde

A solution of 1.95 g (7.5 mmol) of 2-hydroxymethyl-4-phenyl-5-trifluoromethyl-thiophene (from Step A), 925 mg (7.6 mmol) of 4-hydroxybenzaldehyde and 3.0 g (11.4 mmol) of triphenylphosphene in 40 mL of THF at 0 °C was treated with 2.0 g (11.4 mmol) of diethylazodicarboxylate. The resulting mixture was warmed to rt, stirred for 2 h, then concentrated. Chromatography on a Biotage 75S cartridge using 9:1 v/v heptane/EtOAc as the eluant afforded 2.5 g of impure title compound. Chromatography on a Biotage 40M cartridge using 19:1 v/v hexanes/EtOAc (1L), then 4:1 v/v hexanes/EtOAc (1L) as the eluant afforded 1.65 g (60%) of the title compound: ^{1}H NMR (500 Mhz) δ 5.32 (s, 2H), 7.10 (d, J= 8.5, 2H), 7.12 (s, 1H), 7.41-7.43 (5H), 7.85-7.90 (2H), 9.92 (s, 1H).

PREPARATION OF EXAMPLES

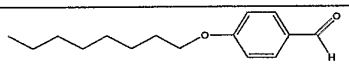
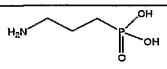
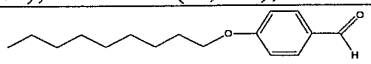
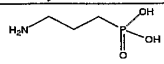
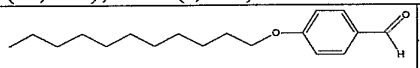
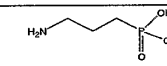
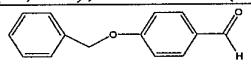
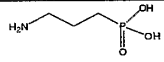
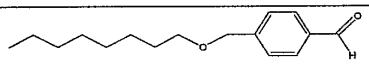
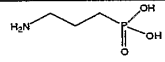
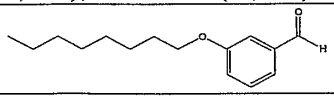
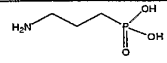
EXAMPLE 1

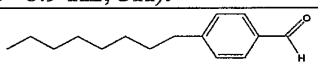
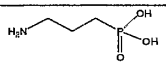
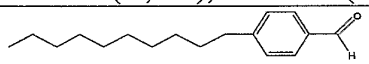
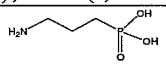
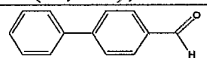
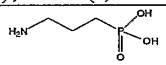
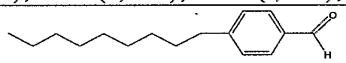
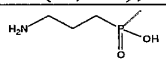
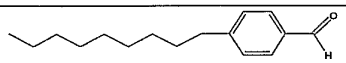
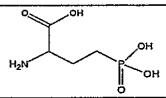
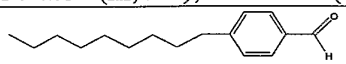
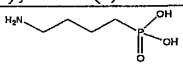
N-((4-Decyloxy)benzyl)-3-aminopropylphosphonic acid

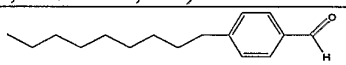
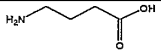
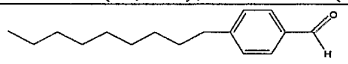
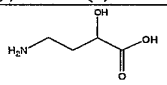
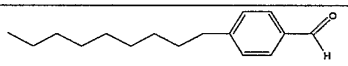
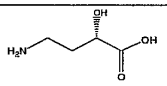
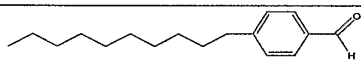
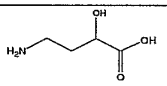
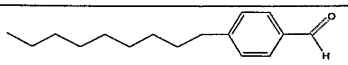
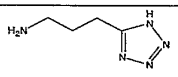
3-Aminopropylphosphonic acid (0.064 g, 0.457 mmol) and tetrabutylammonium hydroxide (1.0M in methanol, 0.46 mL, 0.46 mmol) in methanol (3 mL) were heated at 50 °C for 1 h to dissolve all solids. 4-(Decyloxy)benzaldehyde (0.100g, 0.381 mmol) and sodium cyanoborohydride (0.025 g, 0.40 mmol) were added and stirring was continued for 1 h at 50 °C. The reaction mixture was made acidic (pH~5) by the addition of concentrated HCl then directly purified by LC-3 to give the title compound (0.055 g): ^{1}H NMR (500 MHz , CD_3OD) δ 7.39 (d, J=8.7 Hz, 2H), 6.98 (d, J=8.7 Hz, 2H), 4.12 (s, 2H), 3.99 (t, J=6.4 Hz, 2H), 3.12 (t, J=7.7 Hz, 2H), 2.0 (m, 2H), 1.64-1.84 (m, 4H), 1.47 (m, 2H), 1.24-1.40 (m, 12H), 0.90 (t, J=6.9 Hz, 3H); MS *m/e* 386.4 (M+H).

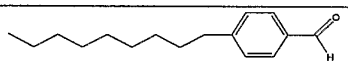
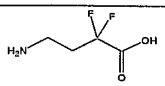
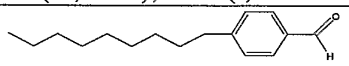
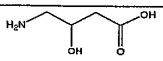
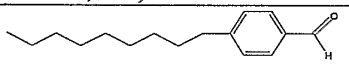
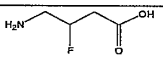
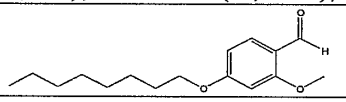
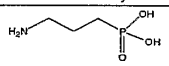
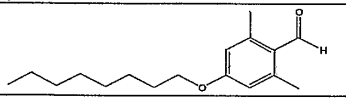
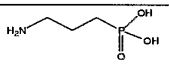
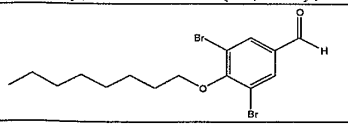
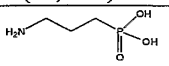
EXAMPLES 2-107

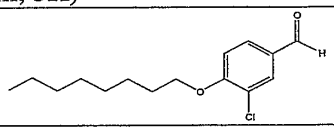
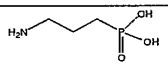
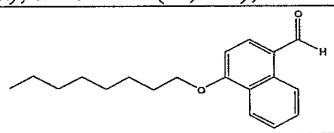
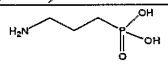
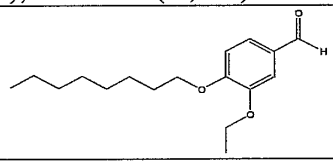
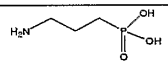
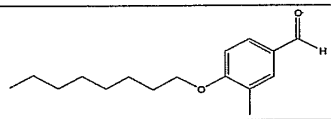
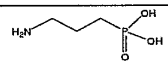
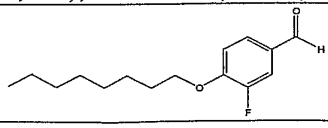
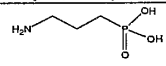
The following Examples (2-112) were prepared using a procedure analogous to that described in EXAMPLE 1 substituting A for 4-(decyloxy)benzaldehyde and B for 3-aminopropylphosphonic acid.

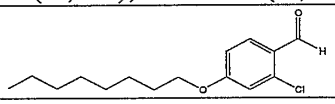
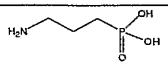
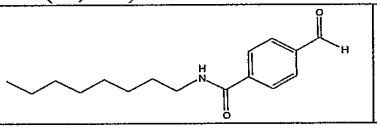
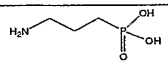
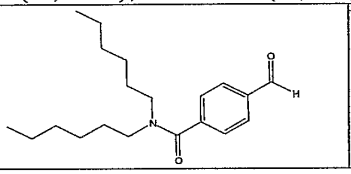
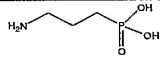
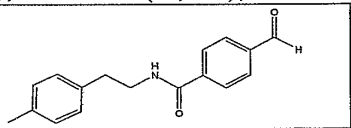
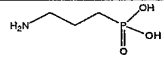
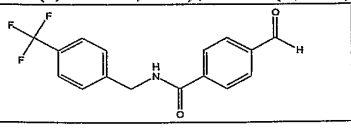
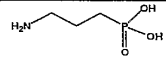
EXAMPLE	A	B	ESI-MS
2			358.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.35-7.41 (m, 2H), 6.94-7.01 (m, 2H), 4.08-4.13 (m, 2H), 3.96-4.02 (m, 2H), 3.08-3.14 (m, 2H), 1.93-2.04 (m, 2H), 1.73-1.82 (m, 4H), 1.43-1.51 (m, 2H), 1.26-1.41 (m, 8H), 0.87-0.94 (m, 3H).			
3			372.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.38 (d, 2H), 6.98 (d, 2H), 4.86 (s, 19H), 4.12 (s, 2H), 3.98 (t, 2H), 3.12 (t, 2H), 1.94-2.04 (m, 2H), 1.72-1.84 (m, 4H), 1.42-1.52 (m, 2H), 1.24-1.41 (m, 8H), 0.90 (t, 3H).			
4			400.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.36-7.40 (m, 2H), 6.95-7.01 (m, 2H), 4.12 (s, 2H), 3.95-4.02 (m, 2H), 3.09-3.15 (m, 2H), 1.94-2.04 (m, 2H), 1.72-1.84 (m, 4H), 1.42-1.52 (m, 2H), 1.24-1.42 (m, 8H), 0.87-0.94 (m, 3H).			
5			336.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.33-7.44 (m, 5H), 7.27-7.33 (m, 2H), 7.03-7.09 (m, 2H), 5.11 (s, 2H), 4.11 (s, 2H), 3.07-3.15 (m, 2H), 1.92-2.04 (m, 2H), 1.73-1.82 (m, 2H).			
6			372.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.42-7.50 (m, 4H), 4.52 (s, 2H), 4.18 (s, 2H), 3.46-3.52 (m, 2H), 3.11-3.18 (m, 2H), 1.95-2.06 (m, 2H), 1.75-1.85 (m, 2H), 1.56-1.64 (m, 2H), 1.25-1.34 (m, 6H), 0.85-0.92 (m, 3H).			
7			358.2

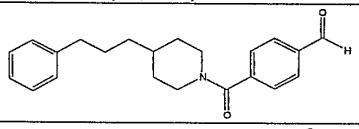
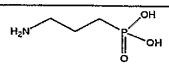
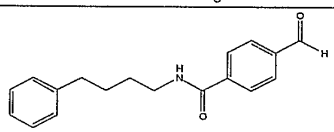
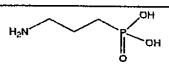
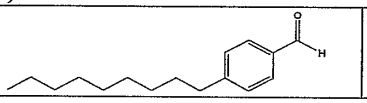
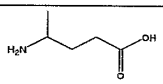
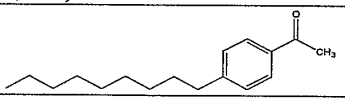
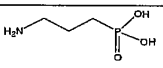
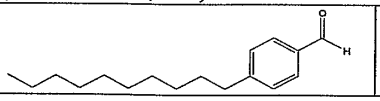
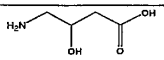
^{1}H NMR (500 MHz , CD_3OD) δ 7.34 (t, J=7.9 Hz, 1H), 7.05 (d, J=2.3 Hz, 1H), 7.03 (d, J=7.8 Hz, 1H), 6.98 (dd, J=2.3, 8.4 Hz), 4.12 (s, 2H), 4.00 (t, J=6.5 Hz, 2H), 3.12 (t, J=6.9 Hz, 2H), 1.94-2.20 (m, 2H), 1.70-1.82 (m, 4H), 1.44-1.52 (m, 2H), 1.26-1.40 (m, 8H), 0.90 (t, J=6.9 Hz, 3H).			
8			342.3
^{1}H NMR (500 MHz , CD_3OD) δ 7.39 (d, J=8.0 Hz, 2H), 7.29 (d, J=8.0 Hz, 2H), 4.15 (s, 2H), 3.14 (t, J=7.7 Hz, 2H), 2.64 (t, J= 7.7 Hz, 2H), 2.00 (m, 2H), 1.81 (td, J= 7.6, 18.5 Hz, 2H), 1.58-1.64 (m, 2H), 1.22-1.36 (m, 10H), 0.89 (t, J=7.0 Hz, 3H).			
9			370.1
^{1}H NMR (500 MHz , CD_3OD) δ 7.38 (d, J=8.0 Hz, 2H), 7.28 (d, J=8.0 Hz, 2H), 4.15 (s, 2H), 3.14 (t, J=7.7 Hz, 2H), 2.64 (t, J= 7.6 Hz, 2H), 2.00 (m, 2H), 1.80 (td, J= 7.6, 18.5 Hz, 2H), 1.56-1.64 (m, 2H), 1.24-1.38 (m, 14H), 0.89 (t, J=7.0 Hz, 3H).			
11			306.1
^{1}H NMR (500 MHz , CD_3OD) δ 7.72 (m, 2H), 7.63 (m, 2H), 7.56 (m, 2H), 7.45 (m, 2H), 7.36 (m, 1H), 4.24 (s, 2H), 3.18 (t, 2H), 1.97-2.08 (m, 2H), 1.76-1.86 (m, 2H).			
12			354.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.38 (d, J=8.3 Hz, 2H), 7.28 (d, J=8.0 Hz, 2H), 4.15 (s, 2H), 3.12 (t, J=7.3 Hz, 2H), 2.64 (t, J= 7.6 Hz, 2H), 1.98 (m, 2H), 1.76-1.84 (m, 2H), 1.58-1.64 (m, 2H), 1.43 (d, J=14 Hz, 3H), 1.24-1.36 (m, 12H), 0.89 (t, J=7.0 Hz, 3H).			
13			400.1
^{1}H NMR (500 MHz , CD_3OD) δ 7.41 (d, J=8.0 Hz, 2H), 7.28 (d, J=8.0 Hz, 2H), 4.14-4.22 (m, 2H), 4.04 (t, J=6.0 Hz, 1H), 2.64 (t, J= 7.6 Hz, 2H), 2.20-2.30 (m, 2H), 1.74-1.98 (m, 2H), 1.58-1.64 (m, 2H), 1.24-1.32 (m, 12H), 0.90 (t, J=7.0 Hz, 3H).			
14			370.3

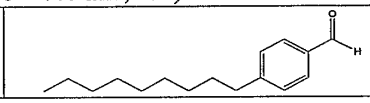
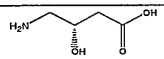
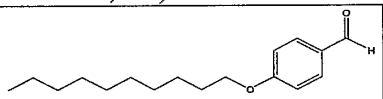
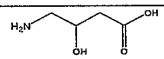
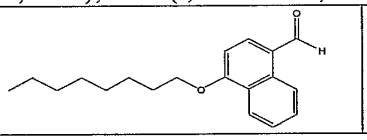
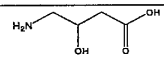
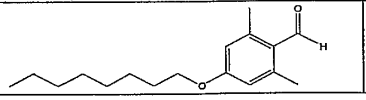
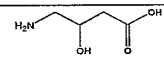
^{1}H NMR (500 MHz , CD_3OD) δ 7.39 (d, J=8.0 Hz, 2H), 7.28 (d, J=8.1 Hz, 2H), 4.15 (s, 2H), 3.05 (t, J=7.8 Hz, 2H), 2.64 (t, J= 7.7 Hz, 2H), 1.58-1.984 (m, 8H), 1.24-1.36 (m, 12H), 0.89 (t, J=7.0 Hz, 3H).			
15			320.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.38 (d, J=8.0 Hz, 2H), 7.29 (d, J=8.0 Hz, 2H), 4.15 (s, 2H), 3.10 (t, J=7.8 Hz, 2H), 2.64 (t, J= 7.7 Hz, 2H), 2.45 (t, J= 7.0 Hz, 2H), 1.93-1.99 (m, 2H), 1.56-1.64 (m, 2H), 1.24-1.34 (m, 12H), 0.89 (t, J=7.0 Hz, 3H).			
16			336.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.38 (d, J=8.1 Hz, 2H), 7.28 (d, J=8.3 Hz, 2H), 4.26 (dd, J=4.1, 7.8 Hz, 1H), 4.17 (s, 2H), 3.16-3.22 (m, 2H), 2.64 (t, J= 7.7 Hz, 2H), 2.16-2.24 (m, 1H), 1.98-2.06 (m, 1H), 1.58-1.64 (m, 2H), 1.24-1.32 (m, 12H), 0.89 (t, J=7.0 Hz, 3H).			
17			336.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.38 (d, J=8.0 Hz, 2H), 7.28 (d, J=8.0 Hz, 2H), 4.26 (dd, J=4.1, 8.0 Hz, 1H), 4.17 (s, 2H), 3.16-3.22 (m, 2H), 2.64 (t, J= 7.7 Hz, 2H), 2.16-2.24 (m, 1H), 1.98-2.06 (m, 1H), 1.58-1.64 (m, 2H), 1.24-1.32 (m, 12H), 0.89 (t, J=7.0 Hz, 3H)			
18			350.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.38 (d, J=8.0 Hz, 2H), 7.28 (d, J=8.0 Hz, 2H), 4.26 (dd, J=4.3, 8.0 Hz, 1H), 4.17 (s, 2H), 3.16-3.22 (m, 2H), 2.64 (t, J= 7.7 Hz, 2H), 2.16-2.24 (m, 1H), 1.98-2.06 (m, 1H), 1.58-1.64 (m, 2H), 1.24-1.32 (m, 14H), 0.89 (t, J=7.0 Hz, 3H)			
19			344.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.38 (d, J=7.0 Hz, 2H), 7.28 (d, J=7.8 Hz, 2H), 4.18 (s, 2H), 3.17 (t, J=7.4 Hz, 2H), 3.06 (t, J=7.4 Hz, 2H), 2.64 (t, J= 7.6 Hz, 2H), 2.20 (m, 2H), 1.56-1.64 (m, 2H), 1.22-1.36 (m, 12H), 0.89 (t, J=7.0 Hz, 3H)			

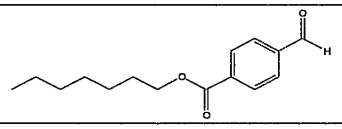
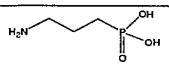
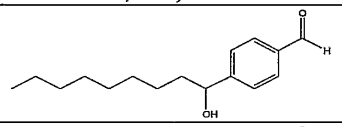
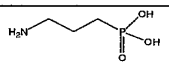
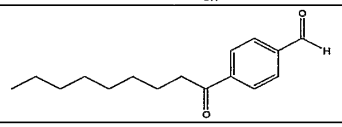
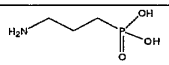
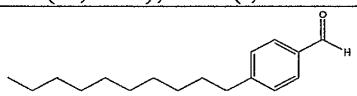
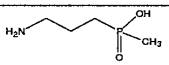
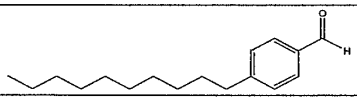
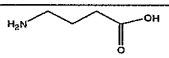
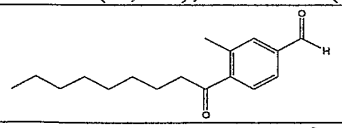
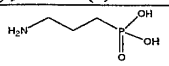
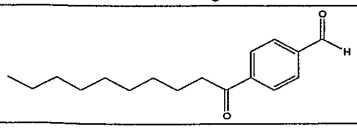
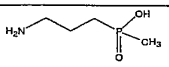
20			356.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.39 (d, J=8.0 Hz, 2H), 7.29 (d, J=8.2 Hz, 2H), 7.03 (d, J=7.8 Hz, 1H), 4.20 (s, 2H), 2.65 (t, J=7.7 Hz, 2H), 2.49-2.60 (m, 2H), 1.58-1.64 (m, 2H), 1.24-1.34 (m, 14H), 0.89 (t, J=7.0 Hz, 3H)			
21			336.3
^{1}H NMR (500 MHz , CD_3OD) δ 7.39 (d, J=8.0 Hz, 2H), 7.28 (d, J=8.3 Hz, 2H), 4.25-4.31 (m, 1H), 4.19 (s, 2H), 3.18 dd, J=2.9, 12.5 Hz, 1H), 2.98 (dd, J= 9.9, 12.6 Hz, 1H), 2.64 (t, J=7.7 Hz, 2H), 2.53 (d, J=6.2 Hz, 2H), 1.56-1.64 (m, 2H), 1.24-1.34 (m, 12H), 0.89 (t, J=7.0 Hz, 3H)			
22			338.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.40 (d, J=8.0 Hz, 2H), 7.30 (d, J=7.7 Hz, 2H), 5.14-5.32 (m, 1H), 4.23 (m, 2H), 3.34-3.42 (m, 2H), 2.74-2.82 (m, 2H), 2.65 (t, J= 7.7Hz, 2H), 1.56-1.63 (m, 2H), 1.24-1.36 (m, 12H), 0.89 (t, J=7.0 Hz, 3H)			
23			388.1
^{1}H NMR (500 MHz , CD_3OD) δ 7.24-7.28 (m, 1H), 6.60-6.63 (m, 1H), 6.53-6.57 (m, 1H), 4.11 (s, 2H), 3.96-4.02 (m, 2H), 3.88-3.92 (m, 3H), 3.28-3.33 (m, 2H), 3.06-3.12 (m, 2H), 1.94-2.05 (m, 2H), 1.72-1.82 (m, 4H), 1.43-1.52 (m, 2H), 1.26-1.41 (m, 8H), 0.87-0.94 (m, 3H)			
24			386.2
^{1}H NMR (500 MHz , CD_3OD) δ 6.68 (s, 2H), 4.20-4.25 (m, 2H), 3.91-3.97 (m, 2H), 3.22-3.27 (m, 2H), 2.41 (s, 6H), 1.99-2.10 (m, 2H), 1.78-1.87 (m, 2H), 1.69-1.78 (m, 2H), 1.41-1.50 (m, 2H), 1.26-1.40 (m, 8H), 0.86-0.94 (m, 3H)			
25			516.1

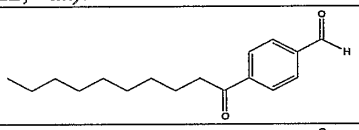
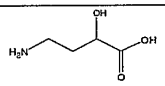
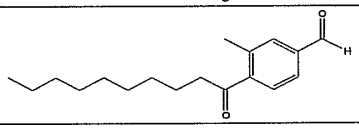
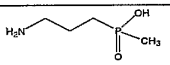
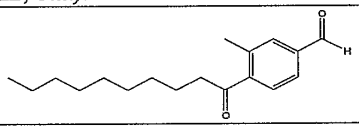
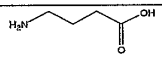
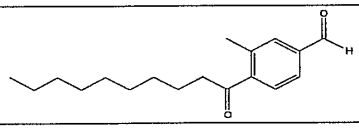
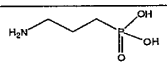
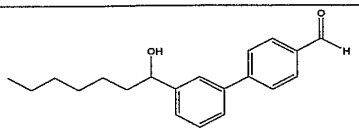
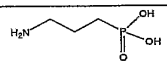
^{1}H NMR (500 MHz , CD_3OD) δ 7.78 (s, 2H), 4.14 (s, 2H), 4.00-4.05 (m, 2H), 3.12-3.18 (m, 2H), 1.94-2.04 (m, 2H), 1.76-1.90 (m, 4H), 1.52-1.59 (m, 2H), 1.29-1.44 (m, 8H), 0.88-0.94 (m, 3H)			
26			392.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.52-7.54 (m, 1H), 7.34-7.38 (m, 1H), 7.08-7.13 (m, 1H), 4.04-4.14 (m, 4H), 3.09-3.16 (m, 2H), 1.93-2.04 (m, 2H), 1.73-1.85 (m, 4H), 1.46-1.55 (m, 2H), 1.26-1.42 (m, 8H), 0.87-0.94 (m, 3H)			
27			408.3
^{1}H NMR (500 MHz , CD_3OD) δ 8.35-8.38 (m, 1H), 8.05-8.09 (m, 1H), 7.64-7.70 (m, 1H), 7.54-7.62 (m, 2H), 6.94-6.98 (m, 1H), 4.61 (s, 2H), 4.18-4.24 (m, 2H), 3.21-3.27 (m, 2H), 1.99-2.08 (m, 2H), 1.91-1.99 (m, 2H), 1.75-1.85 (m, 2H), 1.55-1.64 (m, 2H), 1.27-1.48 (m, 8H), 0.87-0.94 (m, 3H)			
28			402.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.05-7.08 (m, 1H), 6.98-7.01 (m, 2H), 4.06-4.14 (m, 3H), 3.98-4.04 (m, 2H), 3.28-3.32 (m, 2H), 3.08-3.15 (m, 2H), 1.94-2.04 (m, 2H), 1.72-1.84 (m, 4H), 1.45-1.52 (m, 2H), 1.38-1.44 (m, 2H), 1.26-1.38 (m, 8H), 0.86-0.94 (m, 3H)			
29			372.3
^{1}H NMR (500 MHz , CD_3OD) δ 7.22-7.27 (m, 2H), 6.91-6.95 (m, 1H), 4.07 (s, 2H), 3.97-4.03 (m, 2H), 3.07-3.14 (m, 2H), 2.22 (s, 3H), 1.93-2.04 (m, 2H), 1.73-1.84 (m, 4H), 1.46-1.54 (m, 2H), 1.26-1.42 (m, 8H), 0.86-0.93 (m, 3H)			
30			

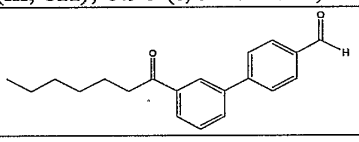
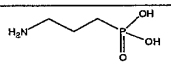
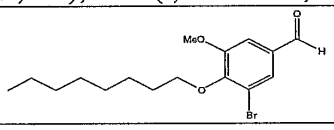
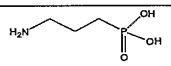
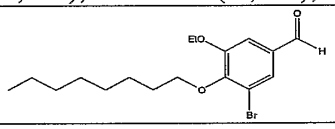
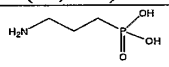
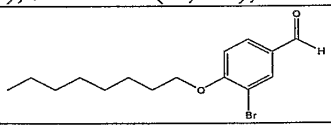
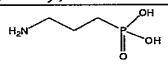
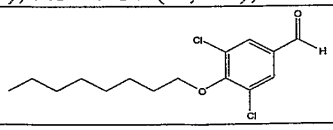
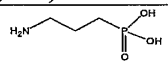
^{1}H NMR (500 MHz , CD_3OD) δ 7.19-7.28 (m, 2H), 7.11-7.16 (m, 1H), 4.11 (s, 2H), 4.03-4.08 (m, 2H), 3.09-3.15 (m, 2H), 1.93-2.04 (m, 2H), 1.72-1.84 (m, 4H), 1.44-1.54 (m, 2H), 1.26-1.42 (m, 8H), 0.86-0.94 (m, 3H)			
31			392.1
^{1}H NMR (500 MHz , CD_3OD) δ 7.48 (d, J=8.5 Hz, 1H), 7.09 (d, J=2.3 Hz, 1H), 6.96 (dd, J=2.6, 8.6, 1H), 4.28 (s, 2H), 4.00 (t, J=6.4 Hz, 2H), 3.29-3.30 (m, 2H), 3.18 (t, J=7.4 Hz, 2H0, 1.97-2.08 (m, 2H), 1.73-1.84 (m, 4H0, 1.42-1.52 (m, 2H), 1.26-1.41 (m, 8H), 0.87-0.94 (m, 3H)			
32			385.4
^{1}H NMR (500 MHz , CD_3OD) δ 7.86-7.91 (m, 2H), 7.56-7.60 (m, 2H), 4.24 (s, 2H), 3.34-3.40 (m, 2H), 3.14-3.19 (m, 2H), 1.95-2.07 (m, 2H), 1.74-1.84 (m, 2H), 1.58-1.67 (m, 2H), 1.25-1.43 (m, 10H), 0.86-0.92 (m, 3H)			
33			441.5
^{1}H NMR (500 MHz , CD_3OD) δ 7.56-7.60 (m, 2H), 7.42-7.46 (m, 2H), 4.23 (s, 2H), 3.46-3.52 (m, 2H), 3.20-3.26 (m, 2H), 3.14-3.20 (m, 2H), 1.94-2.06 (m, 2H), 1.73-1.84 (m, 2H), 1.64-1.72 (m, 2H), 1.45-1.56 (m, 2H), 1.32-1.44 (m, 8H), 1.18-1.27 (m, 2H), 1.04-1.18 (m, 2H), 0.88-0.98 (m, 3H), 0.80-0.88 (m, 3H)			
34			391.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.85 (d, J=8.3 Hz, 2H), 7.57 (d, J=8.2 Hz, 2H), 7.12 (d, J=8.1Hz, 2H), 7.09 (d, J=8.0 Hz, 2H), 4.25 (s, 2H), 3.58 (t, J=7.4 Hz, 2H), 3.17 (t, J=7.6 Hz, 2H), 2.87 (t, J=7.5, 2H), 2.28 (s, 3H), 1.98-2.03 (m, 2H), 1.79-1.84 (m, 2H)			
35			431.1

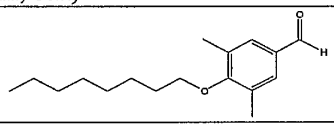
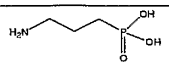
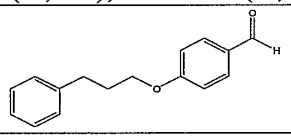
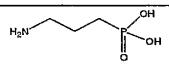
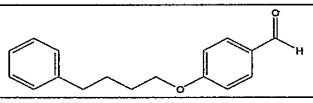
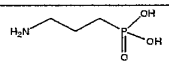
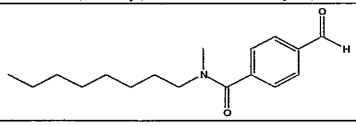
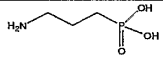
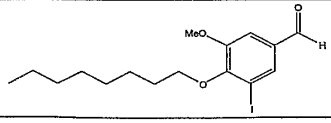
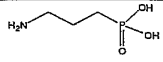
^{1}H NMR (500 MHz , CD_3OD) δ 7.95 (d, J=8.3 Hz, 2H), 7.63 (d, J=8.0, 2H), 7.60 (d, J=8.2, 2H), 7.54 (d, J=8.0 Hz, 2H), 4.65 (s, 2H), 4.26 (s, 2H). 3.17 (t, J=7.3, 2H), 1.98-2.06 (m, 2H), 1.75-1.84 (m, 2H)			
36			459.2
37			405.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.88 (d, J=8.2 Hz, 2H), 7.57 (d, J=8.2 Hz, 2H), 7.23 (t, J=7.5, 2H), 7.18 (d, J=7.1, 2H), 7.13 (t, J=7.2 Hz, 1H), 4.24 (s, 2H), 3.37-3.43 (m, 2H), 3.13-3.20 (m, 2H), 2.62-2.70 (m, 2H), 1.95-2.06 (m, 2H), 1.74-1.84 (m, 2H), 1.60-1.74 (m, 4H)			
38			334.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.39 (d, J=8.2 Hz, 2H), 7.28 (d, J=8.0 Hz, 2H), 4.21 (d, J=13.0 Hz, 1H), 4.18 (d, J=13.0 Hz, 1H), 3.32-3.40 (m, 1H), 2.64 (t, J=7.7 Hz, 2H), 2.52 (ddd, J=16.9, 7.5, 6.2 Hz, 1H), 2.43 (dt, J=17.2, 7.7 Hz, 1H), 2.12-2.20 (m, 1H), 1.76-1.86 (m, 1H), 1.56-1.65 (m, 2H), 1.38 (d, J=6.7 Hz, 3H), 1.22-1.34 (m, 12H), 0.90 (t, J= 6.3 Hz, 3H).			
39			370.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.37 (d, J=8.2 Hz, 2H), 7.30 (d, J=8.2 Hz, 2H), 4.33 (q, J=6.8 Hz, 1H), 3.00-3.08 (m, 1H), 2.82-2.88 (m, 1H), 2.64 (t, J=7.7 Hz, 2H), 1.90-2.00 (m, 2H), 1.70-1.80 (m, 2H), 1.65 (d, J= 6.9 Hz, 3H), 1.58-1.64 (m, 2H), 1.22-1.36 (m, 12H), 0.89 (t, J= 6.9 Hz, 3H).			
40			350.1

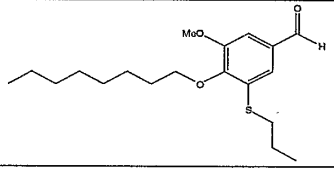
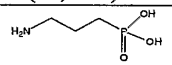
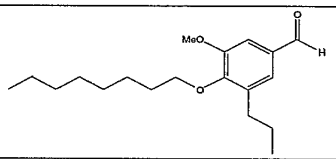
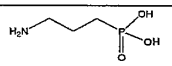
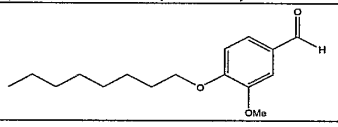
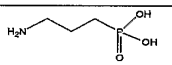
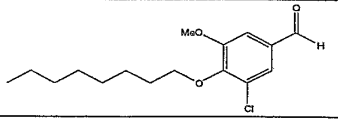
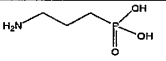
^{1}H NMR (500 MHz , CD_3OD) δ 7.39 (d, J=8.0 Hz, 2H), 7.28 (d, J=8.0 Hz, 2H), 4.24-4.30 (m, 1H), 4.19 (s, 2H), 3.17 (dd, J=12.6, 3.0 Hz, 1H), 2.98 (dd, J=12.9, 9.9 Hz, 1H), 2.64 (t, J=7.7 Hz, 2H), 2.52 (d, J=6.1 Hz, 2H), 1.58-1.65 (m, 2H), 1.24-1.35 (m, 14H), 0.89 (t, J= 7.0 Hz, 3H).			
41			336.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.39 (d, J=8.0 Hz, 2H), 7.28 (d, J=8.0 Hz, 2H), 4.24-4.30 (m, 1H), 4.19 (s, 2H), 3.17 (dd, J=12.6, 3.1 Hz, 1H), 2.98 (dd, J=12.9, 9.8 Hz, 1H), 2.64 (t, J=7.7 Hz, 2H), 2.52 (d, J=6.1 Hz, 2H), 1.58-1.65 (m, 2H), 1.24-1.35 (m, 12H), 0.89 (t, J= 6.9 Hz, 3H).			
42			366.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.39 (d, J=8.7 Hz, 2H), 6.98 (d, J=8.7 Hz, 2H), 4.25-4.30 (m, 1H), 4.16 (s, 2H), 3.99 (t, J=6.5 Hz, 2H), 3.16 (dd, J=12.5, 2.9 Hz, 1H), 2.96 (dd, J=12.8, 9.8 Hz, 1H), 2.52 (d, J=6.2 Hz, 2H), 1.74-1.80 (m, 2H), 1.44-1.51 (m, 2H), 1.22-1.40 (m, 12H), 0.90 (t, J= 7.0 Hz, 3H).			
43			388.1
^{1}H NMR (500 MHz , CD_3OD) δ 8.35 (d, J=8.5 Hz, 1H), 8.09 (d, J=8.5 Hz, 1H), 7.67 (t, J=8.4 Hz, 1H), 7.60 (d, J=8.0 Hz, 1H), 7.57 (t, J=8.0 Hz, 1H), 6.96 (d, J=8.0 Hz, 1H), 4.66 (s, 2H), 4.32-4.38 (m, 1H) 4.21 (t, J=6.4 Hz, 2H), 3.26-3.32 (m, 1H), 3.08 (dd, J=12.8, 9.8 Hz, 1H), 2.55 (d, J=6.2 Hz, 2H), 1.91-1.98 (m, 2H), 1.56-1.62 (m, 2H), 1.28-1.48 (m, 8H), 0.90 (t, J= 6.9 Hz, 3H).			
44			366.2
^{1}H NMR (500 MHz , CD_3OD) δ 6.69 (s, 2H), 4.35-4.40 (m, 1H), 4.33 (d, J=13.8 Hz, 1H), 4.26 (d, J=13.7 Hz, 1H), 3.95 (t, J=6.5 Hz, 2H), 3.30-3.35 (m, 1H), 3.09 (dd, J=12.8, 9.9 Hz, 1H), 2.56 (d, J=6.2 Hz, 2H), 2.42 (s, 6H), 1.71-1.78 (m, 2H), 1.42-1.48 (m, 2H), 1.28-1.38 (m, 8H), 0.90 (t, J= 7.0 Hz, 3H).			

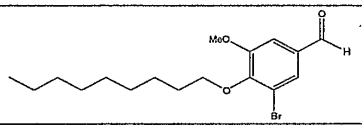
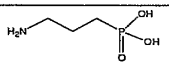
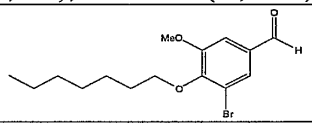
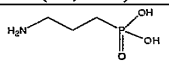
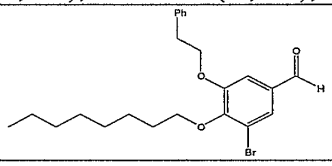
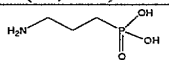
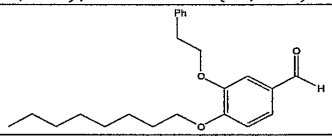
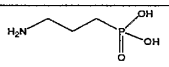
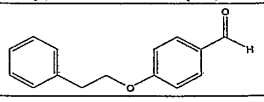
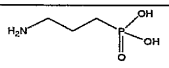
45			372.2
^{1}H NMR (500 MHz , CD_3OD) δ 8.12 (d, J=8.3 Hz, 2H), 7.65 (d, J=8.2 Hz, 2H), 4.36 (t, J=6.6 Hz, 2H), 4.30 (s, 2H), 3.21 (t, J=7.5 Hz, 2H), 2.00-2.10 (m, 4H), 1.32-1.52 (m, 8H), 0.93 (t, J= 7.0 Hz, 3H).			
46			372.2
47			370.2
^{1}H NMR (500 MHz , CD_3OD) δ 8.06 (d, J=8.3 Hz, 2H), 7.65 (d, J=8.3 Hz, 2H), 4.23 (s, 2H), 3.16 (t, J=6.1 Hz, 2H), 3.04 (t, J=7.4 Hz, 2H), 1.96-2.06 (m, 2H), 1.66-1.78 (m, 4H), 1.26-1.44 (m, 10H), 0.91 (t, J= 7.1 Hz, 3H).			
48			368.3
^{1}H NMR (500 MHz , CD_3OD) δ 7.41 (d, J=8.0 Hz, 2H), 7.30 (d, J=8.0 Hz, 2H), 4.18 (s, 2H), 3.16 (t, J=7.4 Hz, 2H), 2.67 (t, J=7.7 Hz, 2H), 1.96-2.06 (m, 2H), 1.82-1.88 (m, 2H), 1.60-1.68 (m, 2H), 1.59 (d, J=14.2 Hz, 3H), 1.26-1.36 (m, 14H), 0.92 (t, J= 7.0 Hz, 3H).			
49			334.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.40 (d, J=8.1 Hz, 2H), 7.31 (d, J=8.0 Hz, 2H), 4.18 (s, 2H), 3.12 (t, J=7.2 Hz, 2H), 2.67 (t, J=7.7 Hz, 2H), 2.48 (t, J=7.0 Hz, 2H), 1.94-2.02 (m, 2H), 1.60-1.68 (m, 2H), 1.26-1.38 (m, 14H), 0.92 (t, J= 7.0 Hz, 3H).			
50			384.2
51			382.2

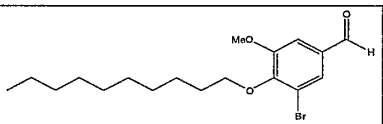
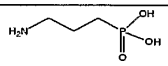
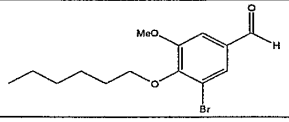
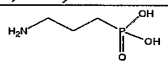
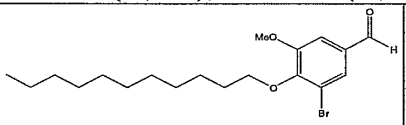
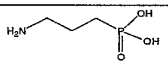
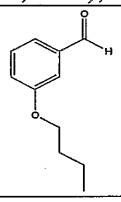
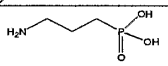
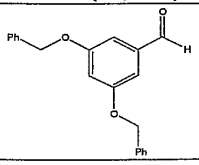
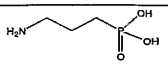
^{1}H NMR (500 MHz , CD_3OD) δ 8.30 (d, J=8.3 Hz, 2H), 7.65 (d, J=8.2 Hz, 2H), 4.25 (s, 2H), 4.30 (s, 2H), 3.20 (t, J=7.3 Hz, 2H), 3.01 (t, J=7.2 Hz, 2H), 2.00-2.08 (m, 2H), 1.82-1.90 (m, 2H), 1.68-1.76 (m, 2H), 1.48 (d, J=14.2 Hz, 3H), 1.26-1.44 (m, 12H), 0.92 (t, J= 7.1 Hz, 3H).			
52			364.1
53			396.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.77 (d, J=7.8 Hz, 1H), 7.42-7.43 (m, 2H), 4.22 (s, 2H), 3.17 (t, J=7.3 Hz, 2H), 2.93 (t, J=7.3 Hz, 2H), 2.48 (s, 3H), 1.96-2.06 (m, 2H), 1.82-1.88 (m, 2H), 1.64-1.70 (m, 2H), 1.47 (d, J=14.0 Hz, 3H), 1.28-1.38 (m, 12H), 0.90 (t, J= 7.0 Hz, 3H).			
54			362.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.76 (d, J=8.4 Hz, 1H), 7.41-7.43 (m, 2H), 4.23 (s, 2H), 3.14 (t, J=7.8 Hz, 2H), 2.93 (t, J=7.3 Hz, 2H), 2.48 (t, J=7.0 Hz, 2H), 2.47 (s, 3H), 1.96-2.04 (m, 2H), 1.64-1.70 (m, 2H), 1.26-1.40 (m, 12H), 0.91 (t, J= 7.0 Hz, 3H).			
55			398.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.76 (d, J=7.8 Hz, 1H), 7.42-7.43 (m, 2H), 4.21 (s, 2H), 3.18 (t, J=7.2 Hz, 2H), 2.93 (t, J=7.3 Hz, 2H), 2.48 (s, 3H), 1.98-2.08 (m, 2H), 1.80 (dt, J=18.1, 7.4 Hz, 2H), 1.64-1.71 (m, 2H), 1.26-1.40 (m, 12H), 0.91 (t, J= 7.0 Hz, 3H).			
56			420.3

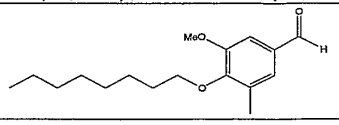
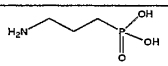
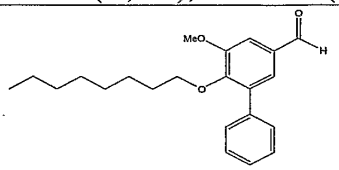
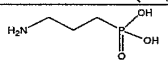
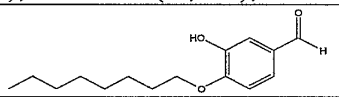
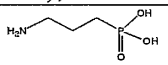
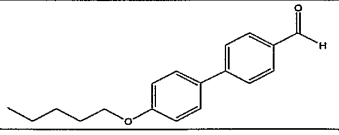
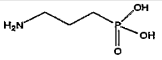
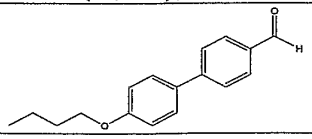
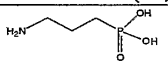
^{1}H NMR (500 MHz , CD_3OD) δ 7.76 (d, J=8.3 Hz, 2H), 7.64 (s, 1H), 7.59 (d, J=8.3 Hz, 2H), 7.55 (d, J=7.7 Hz, 1H), 7.45 (t, J=7.7 Hz, 1H), 7.37 (d, J=7.6 Hz, 1H), 4.70 (t, 6.8 Hz, 1H), 4.27 (s, 2H), 3.21 (t, J=7.6 Hz, 2H), 2.00-2.10 (m, 2H), 1.70-1.88 (m, 4H), 1.26-1.50 (m, 8H), 0.90 (t, J= 7.0 Hz, 3H).			
57			418.3
^{1}H NMR (500 MHz , CD_3OD) δ 8.23 (s, 1H), 8.04 (d, J=7.7 Hz, 1H), 7.91 (d, J=7.8 Hz, 1H), 7.80 (d, J=8.2 Hz, 2H), 7.62-7.66 (m, 3H), 4.28 (s, 2H), 3.22 (t, 7.5 Hz, 2H), 3.11 (t, J=7.2 Hz, 2H), 2.02-2.12 (m, 2H), 1.84 (dt, J=18.3, 7.4 Hz, 2H), 1.72-1.78 (m, 2H), 1.28-1.48 (m, 6H), 0.94 (t, J= 7.0 Hz, 3H).			
58			468.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.29 (s, 1H), 7.16 (s, 1H), 4.01 (s, 2H), 3.98 (t, J=6.4 Hz, 2H), 3.90 (s, 3H), 3.13 (t, J=6.7 Hz, 2H), 1.98-2.01 (m, 2H), 1.73-1.77 (m, 4H), 1.49-1.51 (m, 2H), 1.32-1.34 (m, 8H), 0.89-0.91 (m, 3H)			
59			357.1
^{1}H NMR (500 MHz , CD_3OD) δ 7.28 (s, 1H), 7.13 (s, 1H), 4.12-4.13 (m, 2H), 4.09 (s, 3H), 4.00 (t, J=6.3, 2H), 3.12 (t, J=6.7, 2H), 1.96-2.04 (m, 2H), 1.73-1.78 (m, 4H), 1.48-1.56 (m, 2H), 1.43-1.46 (m, 2H), 1.32-1.37 (m, 8H), 0.88-0.93 (m, 3H)			
60			436.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.7 (s, 1H), 7.41 (d, J=8.5 Hz, 1H), 7.07 (d, J=8.4 Hz, 1H), 4.06-4.10 (m, 4H), 3.12 (t, J=7.2, 2H), 1.95-2.00 (m, 2H), 1.75-1.83 (m, 4H), 1.51-1.54 (m, 2H), 1.32-1.37 (m, 8H), 0.89-0.91 (m, 3H)			
61			426.1

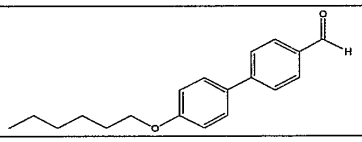
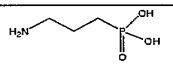
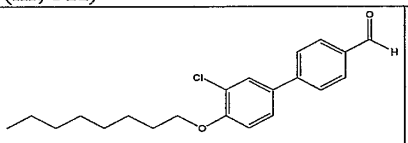
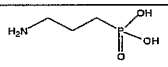
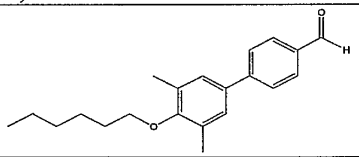
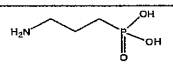
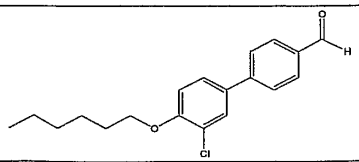
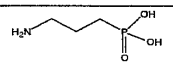
^{1}H NMR (500 MHz , CD_3OD) δ 7.56 (s, 1H), 4.13 (s, 2H), 4.02-4.04 (m, 2H), 3.13-3.12 (m, 2H), 1.98-2.00 (m, 2H), 1.75-1.84 (m, 4H), 1.49-1.58 (m, 2H), 1.26-1.42 (m, 8H), 0.89-0.91 (m, 3H)			
62			386.3
^{1}H NMR (500 MHz , CD_3OD) δ 7.14 (s, 2H), 4.08 (s, 2H), 3.79 (t, J=6.4 Hz, 2H), 3.13 (t, J=7.6 Hz, 2H), 2.30 (s, 6H), 1.95-2.05 (m, 2H), 1.76-1.84 (m, 4H), 1.51-1.58 (m, 2H), 1.31-1.44 (m, 8H), 0.90-0.95 (m, 3H)			
63			364.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.40 (d, J=8.7 Hz, 2H), 7.26 (t, J=7.26 Hz, 2H), 7.17-7.22 (m, 3H), 6.99 (d, J=8.7 Hz, 2H), 4.13 (s, 2H), 3.99 (t, J=6.2 Hz, 2H), 3.13 (t, J=7.6 Hz, 2H), 2.81 (t, J=7.6 Hz, 2H), 2.06-2.12 (m, 2H), 1.95-2.04 (m, 2H), 1.76-1.85 (m, 2H)			
64			255.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.39 (d, J=8.7 Hz, 2H), 7.26 (t, J=7.5 Hz, 2H), 7.20 (d, J=7.1 Hz, 2H), 7.14-7.18 (m, 1H), 6.98 (d, J=8.7 Hz, 2H), 4.12 (s, 2H), 4.02 (s, 2H), 3.12 (t, J=7.4 Hz, 2H), 2.66-2.72 (m, 2H), 1.94-2.04 (m, 2H), 1.76-1.84 (m, 6H)			
65			399.3
^{1}H NMR (500 MHz , CD_3OD) δ 7.60 (d, J=7.8 Hz, 2H), 7.49 (t, J=7.3 Hz, 2H), 4.26 (s, 2H), 3.19 (t, J=7.4 Hz, 3H), 3.09 (s, 2H), 2.96 (s, 2H), 1.98-2.08 (m, 2H), 1.78-1.86 (m, 2H), 1.22-1.32 (m, 4H), 1.00-1.04 (m, 8H)), 0.88-0.94 (m, 3H)			
66			514.0

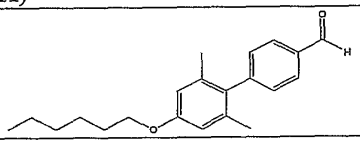
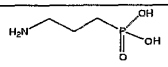
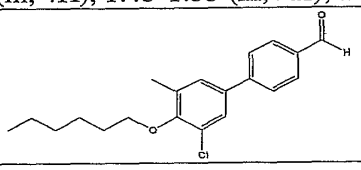
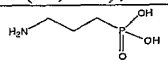
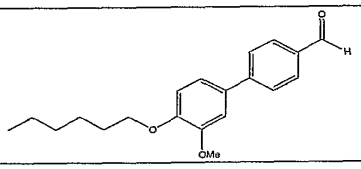
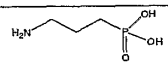
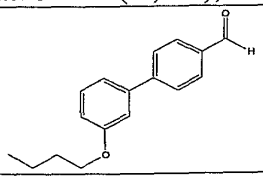
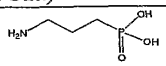
^{1}H NMR (500 MHz , CD_3OD) δ 7.51 (s, 2H), 7.18 (d, 2H), 4.12 (s, 2H), 3.99 (t, J=6.5 Hz, 2H), 3.90 (s, 3H), 3.15 (t, J=7.4 Hz, 2H), 1.96-2.06 (m, 2H), 1.75-1.84 (m, 4H), 1.50-1.56 (m, 2H), 1.29-1.41 (m, 8H), 0.89-0.95 (m, 3H)			
67			462.1
^{1}H NMR (500 MHz , CD_3OD) δ 6.99 (d, 2H), 4.14 (s, 2H), 3.97 (t, J=6.5 Hz, 2H), 3.89 (s, 3H), 3.15 (t, J=7.2 Hz, 2H), 2.93 (t, J=7.2 Hz, 2H), 1.96-2.06 (m, 2H), 1.66-1.84 (m, 6H), 1.48-1.56 (m, 2H), 1.28-1.42 (m, 8H), 1.04-1.10 (m, 3H), 0.90-0.96 (m, 3H)			
68			430.2
^{1}H NMR (500 MHz , CD_3OD) δ 6.99 (s, 1H), 6.91 (s, 1H), 4.12 (s, 2H), 3.95 (t, J=6.4 Hz, 2H), 3.88 (s, 3H), 3.15 (t, J=7.4 Hz, 2H), 2.62 (t, J=7.8 Hz, 2H), 1.96-2.06 (m, 2H), 1.72-1.85 (m, 4H), 1.58-1.68 (m, 2H), 1.48-1.54 (m, 2H), 1.30-1.42 (m, 8H), 0.95-1.00 (m, 3H), 0.90-0.95 (m, 3H)			
69			386.3
^{1}H NMR (500 MHz , CD_3OD) δ 7.10 (s, 1H), 7.00 (s, 2H), 4.12 (s, 2H), 4.02 (s, 2H), 3.89 (s, 3H), 3.10-3.16 (m, 2H), 1.94-2.04 (m, 2H), 1.73-1.83 (m, 4H), 1.62-1.71 (m, 2H), 1.26-1.52 (m, 8H), 0.88-0.96 (m, 3H)			
70			422.1
^{1}H NMR (500 MHz , CD_3OD) δ 7.16 (s, 1H), 7.13 (s, 1H), 4.13 (s, 2H), 4.01 (t, J=6.6 Hz, 2H), 3.92 (s, 3H), 3.15 (t, J=7.2 Hz, 2H), 1.96-2.06 (m, 2H), 1.72-1.84 (m, 4H), 1.48-1.55 (m, 2H), 1.28-1.41 (m, 8H), 0.89-0.95 (m, 3H)			

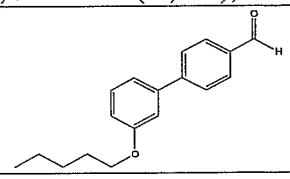
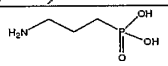
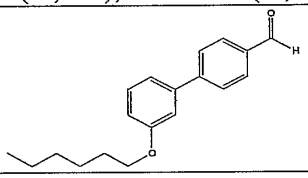
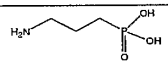
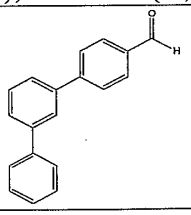
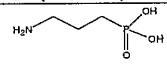
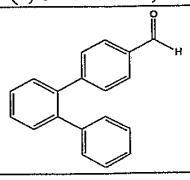
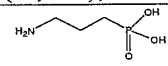
71			482.3
^{1}H NMR (500 MHz , CD_3OD) δ 7.32 (d, 1H), 7.17 (d, 1H), 4.15 (s, 2H), 4.01 (t, J=6.4 Hz, 2H), 3.92 (s, 3H), 3.17 (t, J=7.6 Hz, 2H), 1.98-2.08 (m, 2H), 1.74-1.87 (m, 4H), 1.49-1.59 (m, 2H), 1.28-1.44 (m, 10H), 0.90-0.96 (m, 3H)			
72			454.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.32 (d, 1H), 7.17 (d, 1H), 4.15 (s, 2H), 4.01 (t, J=6.5 Hz, 2H), 3.92 (s, 3H), 3.17 (t, J=7.5 Hz, 2H), 1.98-2.08 (m, 2H), 1.75-1.86 (m, 4H), 1.49-1.56 (m, 2H), 1.32-1.43 (m, 6H), 0.92-0.96 (m, 3H)			
73			544.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.49 (d, J=7.3 Hz, 2H), 7.41 (t, J=7.4 Hz, 2H), 7.37 (d, J=7.3 Hz, 1H), 7.33 (s, 1H), 7.25 (s, 1H), 5.18 (s, 2H), 4.13 (s, 2H), 4.02 (t, J=6.4 Hz, 2H), 3.12 (t, J=7.3 Hz, 2H), 1.96-2.06 (m, 2H), 1.70-1.84 (m, 4H), 1.40-1.48 (m, 2H), 1.22-1.36 (m, 8H), 0.88-0.94 (m, 3H)			
74			464.3
^{1}H NMR (500 MHz , CD_3OD) δ 7.47 (d, J=7.5 Hz, 2H), 7.38 (t, J=7.4 Hz, 2H), 7.33 (d, J=7.4 Hz, 1H), 7.15 (s, 1H), 7.04 (s, 2H), 5.16 (s, 2H), 4.09 (s, 2H), 4.05 (t, J=6.3 Hz, 2H), 3.08 (t, J=7.4 Hz, 2H), 1.93-2.04 (m, 2H), 1.73-1.84 (m, 4H), 1.47-1.55 (m, 8H), 1.26-1.41 (m, 8H), 0.88-0.93 (m, 3H)			
75			350.1
^{1}H NMR (500 MHz , CD_3OD) δ 6.94-6.98 (m, 2H), 6.88-6.92 (m, 1H), 4.05 (s, 4H), 3.32 (s, 2H), 3.11 (t, J=7.2 Hz, 2H), 1.94-2.04 (m, 2H), 1.73-1.86 (m, 4H), 1.27-1.45 (m, 10H), 0.88-0.95 (m, 3H)			

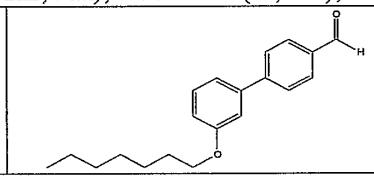
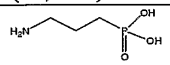
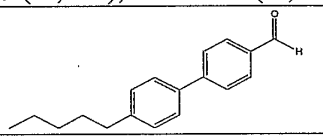
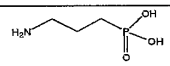
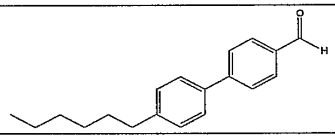
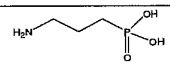
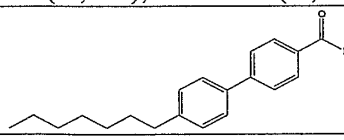
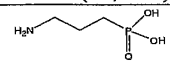
76			496.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.31 (s, 1H), 7.18 (s, 1H), 4.12 (s, 2H), 4.00 (t, J=6.4 Hz, 2H), 3.92 (s, 3H), 3.15 (t, J=7.1 Hz, 2H), 1.96-2.06 (m, 2H), 1.73-1.82 (m, 4H), 1.49-1.56 (m, 2H), 1.27-1.42 (m, 12H), 0.89-0.94 (m, 3H)			
77			438.0
^{1}H NMR (500 MHz , CD_3OD) δ 7.31 (s, 1H), 7.18 (s, 1H), 4.12 (s, 2H), 4.00 (t, J=6.4 Hz, 2H), 3.92 (s, 3H), 3.12-3.17 (t, 2H), 1.96-2.06 (m, 2H), 1.73-1.82 (m, 4H), 1.48-1.57 (m, 2H), 1.34-1.41 (m, 4H), 0.91-0.97 (m, 3H)			
78			510.1
^{1}H NMR (500 MHz , CD_3OD) δ 7.31 (s, 1H), 7.18 (s, 1H), 4.11 (s, 2H), 4.00 (t, J=6.4 Hz, 2H), 3.92 (s, 3H), 3.11-3.17 (t, 2H), 1.95-2.06 (m, 2H), 1.71-1.81 (m, 4H), 1.48-1.56 (m, 2H), 1.27-1.42 (m, 14H), 0.88-0.94 (m, 3H)			
79			302.1
^{1}H NMR (500 MHz , CD_3OD) δ 7.31-7.40 (m, 2H), 7.02-7.08 (m, 2H), 4.12 (s, 2H), 4.03 (t, J=6.4 Hz, 2H), 3.12 (t, J=6.4 Hz, 2H), 1.94-2.04 (m, 2H), 1.66-1.81 (m, 4H), 1.48-1.56 (m, 2H), 0.97-1.02 (m, 3H)			
80			442.2

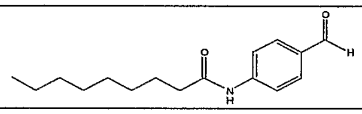
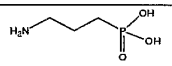
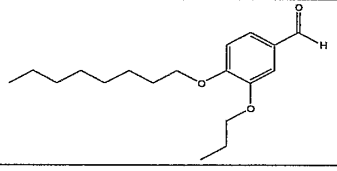
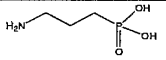
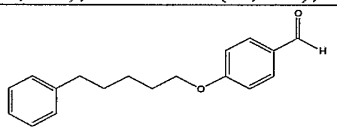
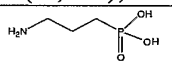
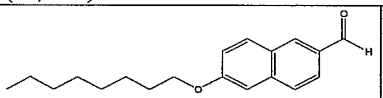
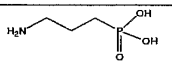
^{1}H NMR (500 MHz , CD_3OD) δ 7.43 (d, J=7.5 Hz, 4H), 7.38 (t, J=7.5 Hz, 4H), 7.33 (d, J=7.1 Hz, 2H), 6.76 (s, 2H), 6.71 (s, 1H), 5.10 (s, 4H), 4.08 (s, 2H), 3.08 (t, J=6.4 Hz, 2H), 1.93-2.04 (m, 2H), 1.68-1.76 (m, 2H)			
81			402.2
^{1}H NMR (500 MHz , CD_3OD) δ 6.98 (s, 1H), 6.90 (s, 1H), 4.10 (s, 2H), 3.94 (t, J=6.6 Hz, 2H), 3.88 (s, 3H), 3.14 (t, J=7.7 Hz, 2H), 2.27 (s, 3H), 1.96-2.06 (m, 2H), 1.71-1.85 (m, 4H), 1.46-1.54 (m, 2H), 1.28-1.42 (m, 8H), 0.90-0.95 (m, 3H)			
82			464.3
^{1}H NMR (500 MHz , CD_3OD) δ 7.52 (d, J=7.4 Hz, 2H), 7.42 (t, J=7.4 Hz, 2H), 7.36 (t, J=7.3 Hz, 1H), 7.17 (s, 1H), 7.08 (s, 1H), 4.20 (s, 2H), 3.95 (s, 3H), 3.71 (t, J=6.3 Hz, 2H), 3.36 (s, 2H), 3.19 (t, J=7.5 Hz, 2H), 1.98-2.09 (m, 2H), 1.78-1.87 (m, 2H), 1.41-1.48 (m, 2H), 1.25-1.34 (m, 2H), 1.08-1.25 (m, 6H), 0.87-0.94 (m, 3H)			
83			374.2
^{1}H NMR (500 MHz , CD_3OD) δ 6.94-6.98 (m, 2H), 6.88-6.92 (m, 1H), 4.05 (s, 4H), 3.32 (s, 2H), 3.11 (t, J=7.2 Hz, 2H), 1.94-2.04 (m, 2H), 1.73-1.86 (m, 4H), 1.27-1.45 (m, 10H), 0.88-0.95 (m, 3H)			
84			392.1
^{1}H NMR (500 MHz , CD_3OD) δ 7.69 (d, J=8.0, 2H), 7.57 (d, J=8.7 Hz, 2H), 7.54 (d, J=8.0 Hz, 2H), 7.01 (d, J=8.5 Hz, 2H), 4.22 (s, 2H), 4.03 (t, 2H), 3.18 (t, 2H), 1.98-2.08 (m, 2H), 1.76-1.86 (m, 4H), 1.40-1.53 (m, 4H), 0.96-1.00 (m, 3H)			
85			378.1

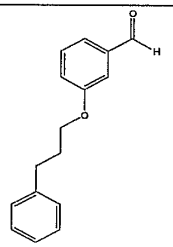
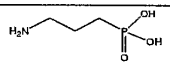
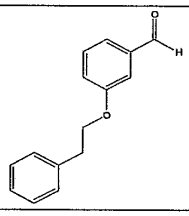
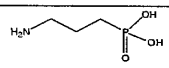
^{1}H NMR (500 MHz , CD_3OD) δ 7.70 (d, J=8.3 Hz, 2H), 7.58 (d, J=8.7 Hz, 2H), 7.55 (d, J=7.55 Hz, 2H), 7.02 (d, J=8.7 Hz, 2H), 4.24 (s, 2H), 4.05 (t, J=6.4 Hz, 2H), 3.20 (t, J=7.6 Hz, 2H), 1.99-2.10 (m, 2H), 1.76-1.88 (m, 4H), 1.51-1.59 (m, 2H), 1.00-1.08 (m, 3H)			
86			406.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.70 (d, J=8.3 Hz, 2H), 7.58 (d, J=8.7 Hz, 2H), 7.55 (d, J=8.3 Hz, 2H), 7.02 (d, J=8.4 Hz, 2H), 4.24 (s, 2H), 4.04 (t, J=6.4 Hz, 2H), 3.16-3.23 (t, 2H), 1.99-2.10 (m, 2H), 1.76-1.88 (m, 4H), 1.48-1.58 (m, 2H), 1.36-1.45 (m, 4H), 0.91-1.00 (m, 3H)			
87			468.3
^{1}H NMR (500 MHz , CD_3OD) δ 7.69 (d, J=8.0 Hz, 2H), 7.67 (s, 1H), 7.56 (d, J=8.2 Hz, 2H), 7.15 (d, J=8.5 Hz, 2H), 4.24 (s, 2H), 4.11 (t, J=6.1 Hz, 2H), 3.19 (t, J=7.2 Hz, 2H), 1.98-2.08 (m, 2H), 1.78-1.88 (m, 4H), 1.51-1.59 (m, 2H), 1.29-1.46 (m, 8H), 0.88-0.96 (m, 3H)			
88			434.1
^{1}H NMR (500 MHz , CD_3OD) δ 7.68 (d, J=8.2 Hz, 2H), 7.54 (d, J=8.2 Hz, 2H), 7.30 (s, 2H), 4.24 (s, 2H), 3.83 (t, J=6.5 Hz, 2H), 3.19 (t, J=7.4 Hz, 2H), 2.34 (s, 6H), 2.00-2.09 (m, 2H), 1.78-1.88 (m, 4H), 1.54-1.62 (m, 2H), 1.38-1.46 (m, 4H), 0.94-1.01 (m, 3H)			
89			440.1

^{1}H NMR (500 MHz , CD_3OD) δ 7.70 (d, J=8.0 Hz, 2H), 7.68 (s, 1H), 7.57 (d, J=8.0 Hz, 3H), 7.16 (d, J=8.5 Hz, 1H), 4.25 (s, 2H), 4.12 (t, J=6.3 Hz, 2H), 3.20 (t, J=7.5 Hz, 2H), 2.00-2.09 (m, 2H), 1.80-1.90 (m, 4H), 1.53-1.61 (m, 2H), 1.38-1.46 (m, 4H), 0.93-0.99 (m, 3H)			
90			
^{1}H NMR (500 MHz , CD_3OD) δ 7.57 (d, J=8.0 Hz, 2H), 7.24 (d, J=7.8 Hz, 2H), 6.67 (s, 2H), 4.25 (s, 2H), 3.94-4.00 (t, 2H), 3.18-3.25 (t, 2H), 2.00-2.05 (m, 2H), 1.99 (s, 6H), 1.78-1.90 (m, 4H), 1.45-1.55 (m, 2H), 1.35-1.40 (m, 4H), 0.95-1.00 (m, 3H)			
91			454.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.68 (d, J=8.0 Hz, 2H), 7.57 (d, J=7.57, 2H), 7.51 (s, 1H), 7.43 (s, 1H), 4.22 (s, 2H), 3.97 (t, J=6.3 Hz, 2H), 3.14-3.22 (t, 2H), 2.38 (s, 3H), 1.98-2.08 (m, 2H), 1.74-1.88 (m, 4H), 1.54-1.62 (m, 2H), 1.36-1.46 (m, 4H), 0.92-1.00 (m, 3H)			
92			436.3
^{1}H NMR (500 MHz , CD_3OD) δ 7.71 (d, J=8.0 Hz, 2H), 7.54 (d, J=8.3 Hz, 2H), 7.20-7.23 (m, 1H), 7.18-7.20 (m, 1H), 7.04 (d, J=8.5 Hz, 1H), 4.24 (s, 2H), 4.05 (t, J=6.5 Hz, 2H), 3.92 (s, 3H), 3.19 (t, J=7.4 Hz, 2H), 2.00-2.08 (m, 2H), 1.78-1.88 (m, 4H), 1.48-1.56 (m, 2H), 1.36-1.43 (m, 4H), 0.92-0.98 (m, 3H)			
93			

^{1}H NMR (500 MHz , CD_3OD) δ 7.71 (d, J=8.1 Hz, 2H), 7.57 (d, J=7.5 Hz, 2H), 7.32-7.39 (m, 1H), 7.10-7.21 (m, 2H), 6.90-6.96 (m, 1H), 4.16-4.25 (m, 2H), 4.00-4.08 (m, 2H), 3.12-3.22 (m, 2H), 1.96-2.06 (m, 2H), 1.72-1.84 (m, 2H), 1.62-1.72 (m, 2H), 1.50-1.60 (m, 2H), 1.38-1.48 (m, 2H), 0.98-1.06 (m, 3H)			
94			302.1
^{1}H NMR (500 MHz , CD_3OD) δ 7.69-7.74 (m, 2H), 7.57 (d, J=7.6 Hz, 2H), 7.32-7.39 (m, 1H), 7.19 (d, J=7.1 Hz, 1H), 7.15 (s, 1H), 6.94 (d, J=8.0 Hz, 1H), 4.25 (s, 2H), 4.03-4.05 (m, 2H), 3.18-3.21 (m, 2H), 1.97-2.09 (m, 2H), 1.76-1.88 (m, 4H), 1.46-1.54 (m, 2H), 1.38-1.46 (m, 2H), 0.94-1.00 (m, 3H)			
95			406.1
^{1}H NMR (500 MHz , CD_3OD) δ 7.73 (d, J=8.3 Hz, 2H), 7.58 (d, J=8.2 Hz, 2H), 7.38 (t, J=7.9 Hz, 1H), 7.21 (d, J=7.8 Hz, 1H), 7.16 (s, 1H), 6.90 (d, J=6.0 Hz, 1H), 4.26 (s, 2H), 4.05 (t, J=6.4 Hz, 2H), 3.21 (t, J=7.5 Hz, 2H), 2.00-2.10 (m, 2H), 1.78-1.88 (m, 4H), 1.50-1.56 (m,, 2H), 1.36-1.44 (m, 4H), 0.92-0.98 (m, 3H)			
96			382.0
^{1}H NMR (500 MHz , CD_3OD) δ 7.87 (s, 1H), 7.82 (d, J=7.7 Hz, 2H), 7.69 (d, J=7.8 Hz, 2H), 7.59-7.67 (m, 4H), 7.54-7.59 (m, 1H), 7.49 (t, J=7.6 Hz, 2H), 7.36-7.42 (m, 1H), 4.29 (s, 2H), 3.22 (t, J=7.6 Hz, 2H), 2.00-2.12 (m, 2H), 1.80-1.90 (m, 2H)			
97			382.0

^{1}H NMR (500 MHz , CD_3OD) δ 7.45-7.48 (m, 2H), 7.40-7.45 (m, 2H), 7.36 (d, J=8.1 Hz, 2H), 7.25 (d, J=8.3 Hz, 2H), 7.18-7.22 (m, 3H), 7.11-7.15 (m, 2H), 4.17 (s, 2H), 3.14 (t, J=7.6 Hz, 2H), 1.99-2.01 (m, 2H), 1.95-1.97 (m, 2H)			
98			420.3
^{1}H NMR (500 MHz , CD_3OD) δ 7.72 (d, J=8.0 Hz, 2H), 7.57 (d, J=8.0 Hz, 2H), 7.34-7.39 (t, 1H), 7.18-7.22 (d, 1H), 7.15 (s, 1H), 6.92-6.96 (d, 1H), 4.25 (s, 2H), 4.04 (t, J=6.4 Hz, 2H), 3.19 (t, J=7.5 Hz, 2H), 1.98-2.08 (m, 2H), 1.76-1.86 (m, 4H), 1.47-1.55 (m, 2H), 1.31-1.45 (m, 6H), 0.90-0.96 (m, 3H)			
99			376.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.72 (d, J=8.3 Hz, 2H), 7.56 (d, J=8.0 Hz, 4H), 7.29 (d, J=8.0 Hz, 2H), 4.24 (s, 2H), 3.19 (t, J=7.6 Hz, 2H), 2.66 (t, J=7.6 Hz, 2H), 2.00-2.09 (m, 2H), 1.79-1.87 (m, 2H), 1.63-1.70 (m, 2H), 1.28-1.41 (m, 4H), 0.89-0.96 (m, 3H)			
100			390.3
^{1}H NMR (500 MHz , CD_3OD) δ 7.72 (d, J=8.0 Hz, 2H), 7.56 (d, J=7.8 Hz, 4H), 7.29 (d, J=8.0 Hz, 2H), 4.25 (s, 2H), 3.19 (t, J=7.5 Ha, 2H), 2.67 (t, J=7.7, 2H), 2.00-2.09 (m, 2H), 1.78-1.87 (m, 2H), 1.61-1.70 (m, 2H), 1.31-1.41 (m, 6H), 0.98-0.94 (m, 3H)			
101			404.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.73 (d, J=8.0 Hz, 2H), 7.57 (d, J=7.6 Hz, 2H), 7.30 (d, J=8.3 Hz, 4H), 4.26 (s, 2H), 3.20 (t, J=7.6 Hz, 2H), 2.68 (t, J=7.7 Hz, 2H), 2.00-2.10 (m, 2H0, 1.80-1.88 (m, 2H), 1.64-1.70 (m, 2H), 1.26-1.40 (m, 8H), 0.90-0.95 (m, 3H)			

102			330.1
^{1}H NMR (500 MHz , CD_3OD) δ 7.37 (t, J=8.0 Hz, 1H), 6.99-7.07 (m, 3H), 4.16 (s, 2H), 4.02 (t, J=6.6 Hz, 2H), 3.15 (t, J=7.6 Hz, 2H), 1.96-2.06 (m, 2H), 1.75-1.84 (m, 4H), 1.46-1.54 (m, 2H), 1.34-1.46 (m, 8H), 0.91-0.97 (m, 3H)			
103			416.3
^{1}H NMR (500 MHz , CD_3OD) δ 7.07 (s, 1H), 6.99 (s, 2H), 4.09 (s, 2H), 4.03 (t, J=6.3 Hz, 2H), 3.97 (t, J=6.3 Hz, 2H), 3.11 (J=7.1 Hz, 2H), 1.93-2.04 (m, 2H), 1.72-1.84 (m, 6H), 1.46-1.54 (m, 2H), 1.26-1.42 (m, 8H), 1.02-1.08 (m, 3H), 0.86-0.94 (m, 3H)			
104			392.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.39 (d, J=8.4 Hz, 2H), 7.25 (t, J=7.5 Hz, 2H), 7.12-7.19 (m, 3H), 6.98 (d, J=8.7 Hz, 2H), 4.12 (s, 2H), 4.00 (t, J=6.4 Hz, 2H), 3.13 (t, J=7.5 Hz, 2H), 2.65 (t, J=7.6 Hz, 2H), 1.94 (m, 2H), 1.74-1.86 (m, 4H), 1.66-1.74 (m, 2H), 1.48-1.56 (m, 2H)			
105			408.4
^{1}H NMR (500 MHz , CD_3OD) δ 7.91 (s, 1H), 7.86 (d, J=8.4 Hz, 1H), 7.82 (d, J=8.9 Hz, 1H), 7.51 (d, J=8.5 Hz, 1H), 7.27 (s, 1H), 7.21 (d, J=8.8 Hz, 1H), 4.32 (s, 2H), 4.11 (t, J=6.3 Hz, 2H), 3.16-3.22 (m, 2H), 1.98-2.08 (m, 2H), 1.76-1.90 (m, 4H), 1.48-1.58 (m, 2H), 1.28-1.46 (m, 8H), 0.90-0.96 (m, 3H)			

106			440.4
107			426.3
^{1}H NMR (500 MHz , CD_3OD) δ 7.71 (d, J=7.8 Hz, 2H), 7.56 (d, J=8.0, 2H), 7.28-7.39 (m, 5H), 7.18-7.25 (m, 2H), 7.14 (s, 1H), 6.95 (d, J=8.0 Hz, 1H), 4.22-4.31 (m, 4H), 3.19 (d, J=7.4 Hz, 2H), 3.11 (d, J=6.6 Hz, 2H), 1.97-2.09 (m, 2H), 1.78-1.88 (m, 2H)			

EXAMPLE 108

(R/S)-3-(N-(4-Nonylbenzyl)amino-1-hydroxypropylphosphonic acid

Step A: (R/S)-Diethyl 3-benzyloxycarbonylamino-1-hydroxypropylphosphonate

To a solution of potassium bis(trimethylsilyl)amide (1.13g, 5.66 mmol) in tetrahydrofuran (10 mL) at 0 °C was added diethyl phosphite (0.73 g, 5.66 mmol). After 10 min, 3-(benzyloxycarbonylamino)propanal (0.78 g, 3.77 mmol) was added as a solution in tetrahydrofuran (5 mL). After 30 min, the reaction was quenched by the addition of 2N hydrochloric acid (25 mL) and extracted with ethyl acetate (50 mL). The organic layer was washed with sat'd sodium chloride (50 mL), dried over magnesium sulfate and concentrated *in vacuo*. Silica gel chromatography eluting with hexane/acetone (1:1) gave a colorless oil (0.36 g): ESI-MS 346.1 (M+H).

Step B: (R/S)-Diethyl 3-amino-1-hydroxypropylphosphonate

(R/S)-Diethyl 3-benzyloxycarbonylamino-1-hydroxypropylphosphonate (0.36 g, 1.04 mmol, from Step A) and palladium on carbon (10%, 0.10 g) were stirred together in methanol (5 mL) under an atmosphere of

hydrogen. After 2 h, the reaction was filtered and concentrated *in vacuo* to give a colorless oil: ^{1}H NMR (500 MHz , CD_3OD) δ 4.10-4.22 (m, 4H), 4.00-4.05 (m, 1H), 2.85-3.00 (m, 2H), 1.85-2.00 (m, 2H), 1.34 (t, J=7.0 Hz, 6H); ESI-MS 211.8 (M+H)

Step: C (R/S)-Diethyl 3-(N-(4-nonylbenzyl)amino-1-hydroxypropylphosphonate

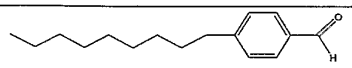
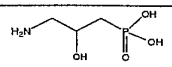
(R/S)-Diethyl 3-amino-1-hydroxypropylphosphonate (0.030 g, 0.142 mmol, from Step C), 4-nonylbenzaldehyde (0.036 g, 0.142 mmol) and sodium cyanoborohydride (0.004 g, 0.071 mmol) in methanol (1.5 mL) were heated at 50°C for 3 h. The reaction was made acidic (pH~5) by the addition of concentrated hydrochloric acid then directly purified by LC-3 to give a colorless oil (0.031 g).

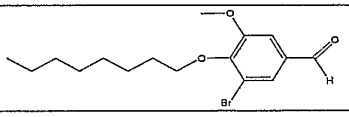
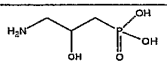
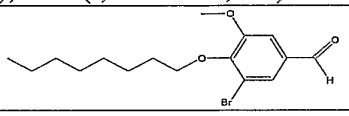
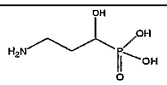
Step D: (R/S)-3-(N-(4-nonylbenzyl)amino-1-hydroxypropylphosphonic acid

(R/S)-Diethyl 3-(N-(4-nonylbenzyl)amino-1-hydroxypropylphosphonate (0.031 g) was dissolved in acetonitrile (1 mL) and treated with bromotrimethylsilane (0.050 mL, 0.362 mmol). After stirring for 1 h at 50°C, the reaction was quenched with methanol (1 mL), stirred for 30 min then concentrated. The residue was purified via HPLC to give desired product (0.011 g): ^{1}H NMR (500 MHz , CD_3OD) δ 7.39 (d, J=8.3 Hz, 2H), 7.28 (d, J=8.3 Hz, 2H), 4.16 (s, 2H), 3.87-3.92 (m, 1H), 3.18-3.34 (m, 2H), 2.64 (t, J=7.7 Hz, 2H), 2.04-2.20 (m, 2H), 1.58-1.64 (m, 2H), 1.24-1.34 (m, 12H), 0.89 (t, J=7.0 Hz, 3H); ESI-MS 372.2 (M+H).

EXAMPLES 109-111

The following EXAMPLES (109-111) were made according to the procedure described for EXAMPLE 108 substituting A for 4-nonylbenzaldehyde and the diethyl ester of B for (R/S)-diethyl 3-amino-1-hydroxyphosphonate in Step C.

EXAMPLE	A	B	ESI-MS
109			372.1
^{1}H NMR (500 MHz , CD_3OD) δ 7.42 (d, J=8.0 Hz, 2H), 7.31 (d, J=8.0 Hz, 2H), 4.24-4.50 (m, 1H), 4.21 (s, 2H), 3.30-3.38 (m, 1H), 3.01 (dd, J=12.8, 9.6 Hz, 1H), 2.67 (t, J=7.7 Hz, 2H), 1.94-2.14 (m, 2H), 1.60-1.68 (m, 2H), 1.26-1.38 (m, 12H), 0.92 (t, J=7.0 Hz, 3H)			

110			482.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.33 (d, J=1.9 Hz, 1H), 7.19 (d, J=1.8 Hz, 1H), 4.22-4.28 (m, 1H), 4.18 (s, 2H), 4.01 (t, J=6.4 Hz, 2H), 3.93 (s, 3H), 3.30-3.35 (m, 1H), 3.03 (dd, J=12.6, 8.7 Hz, 1H), 1.91-2.11 (m, 2H), 1.75-1.82 (m, 2H), 1.50-1.58 (m, 2H), 1.30-1.42 (m, 8H), 0.93 (t, J=7.0 Hz, 3H)			
111			482.1
^{1}H NMR (500 MHz , CD_3OD) δ 7.33 (d, J=2.1 Hz, 1H), 7.19 (d, J=1.8 Hz, 1H), 4.18 (s, 2H), 4.02 (t, J=6.4 Hz, 2H), 3.92-3.96 (m, 1H), 3.93 (s, 3H), 3.23-3.36 (m, 2H), 2.08-2.26 (m, 2H), 1.75-1.82 (m, 2H), 1.50-1.58 (m, 2H), 1.30-1.42 (m, 8H), 0.93 (t, J=7.0 Hz, 3H)			

EXAMPLE 112

N-(4-Nonylbenzyl)-3-aminopropylphosphonic acid

3-Aminopropylphosphonic acid (0.060 g, 0.436 mmol) and tetrabutylammonium hydroxide (1.0M in methanol, 0.44 mL, 0.43 mmol) in methanol (3 mL) were heated at 50°C for 15 min until all of the solids had dissolved. 4-(Nonyl)benzyliodide (0.100 g, 0.291 mmol) and DIEA (0.112 g, 0.872 mmol) were added and stirring was continued for 12 h at 50 °C. The reaction was made acidic (pH~5) by the addition of concentrated hydrochloric acid then directly purified using LC-3 to give the title compound (0.020 g): ^{1}H NMR (500 MHz , CD_3OD) δ 7.39 (d, J=8.0 Hz, 2H), 7.29 (d, J=8.0 Hz, 2H), 4.15 (s, 2H), 3.14 (t, J=7.6 Hz, 2H), 2.64 (t, J=7.7 Hz, 2H), 2.00 (m, 2H), 1.79 (td, J=5.3, 18.5 Hz, 2H), 1.61 (m, 2H), 1.24-1.36 (m, 14H), 0.89 (t, J=7.0 Hz, 3H); ESI-MS 356.2 (M+H).

EXAMPLE 113

3-[(4-Octylbenzyl)amino]propylphosphinic acid

Step A: Ethyl 2-cyanoethyl(diethoxymethyl)phosphinate

To a solution 2.6234 g (13.37 mmol) of ethyldiethoxymethyl phosphinate in 10 mL EtOH was added 0.5670 g (10.70 mmol) acrylonitrile. The resulting mixture was added to a solution of 0.071 g (2.81 mmol) NaH in 10 mL EtOH at 0 °C. The ice bath was removed at the end of the addition, and the reaction mixture was stirred at rt for 16 hr. The mixture was neutralized (pH = 7) with HOAc, and was partitioned between EtOAc and H_2O. The organic layer was separated, dried and concentrated, which provided 2.47 g (93% yield) of the title compound: ^{1}H NMR (500 MHz) δ 1.25 (t, J = 6.9, 6H), 1.34 (t, J = 7.1, 3H), 2.11-2.19 (m, 2H), 2.68-2.74 (m, 2H), 3.62-3.73 (m, 2H), 3.80-3.87 (m, 2H), 4.13-4.25 (m, 2H), 4.70 (d, J = 6.4, 1H); ESI-MS 250 (M+H).

Step B: Ethyl 3-Aminopropyl(diethoxymethyl)phosphinate

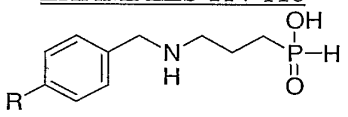
To a solution of 2.47 g (9.91 mmol) of ethyl 2-cyanoethyl (diethoxymethyl)phosphinate (from Step A) in 20 mL 2.0 M ammonia in EtOH was added 250 mg Raney Nickel. The mixture was subjected to hydrogenation conditions (H_2, 40 psi, rt) for 16 hr. The reaction mixture was filtered over Celite and partitioned between CH_2Cl_2 and H_2O. The aqueous phase was extracted twice with CH_2CL_2. The organic layer and extractions were combined, dried, and concentrated to provide 2.13 g (85% yield) of the title compound: ^{1}H NMR (500 MHz) δ 1.23 (dt, J_1 = 7.1, J_2 = 1.6 6H), 1.29 (t, J = 7.1, 3H), 1.42 (s, br, 2H), 1.71-1.82 (m, 4H), 2.72-2.75 (m, 2H), 3.63-3.70 (m, 2H), 3.78-3.86 (m, 2H), 4.08-4.21 (m, 2H), 4.64 (d, J = 6.7, 1H); ESI-MS 254 (M+H).

Step C: 3-[(4-Octylbenzyl)amino]propylphosphinic acid

A mixture of 98.5 mg (0.389 mmol) of ethyl 3-aminopropyl (diethoxymethyl)phosphinate (from Step B) and 84.9 mg (0.389 mmol) of 4-octylbenzaldehyde in 1 mL of MeOH at rt was treated with 12.2 mg (0.194 mmol) $Na(CN)BH_3$. The resulting reaction mixture was stirred at rt for 16 hr. The reaction was quenched with 0.5 mL of 12 N HCl, then heated up to 80 °C for 1 hr. The mixture was cooled and concentrated. HPLC purification (LC-2) afforded 60 mg (47%) of the title compound: ^{1}H NMR (500 MHz, CD_3OD) δ 0.88 (t, J = 7.1, 3H), 1.25-1.33 (m, 10H), 1.59-1.66 (m, 4H), 1.90-1.96 (m, 2H), 2.63 (t, J = 7.7, 2H), 3.09 (t, J = 6.9, 2H),

4.12 (s, 2H), 7.03 (d, J = 505.6, 1H), 7.27 (d, J = 8.0, 2H), 7.38 (d, J = 8.0, 2H); LC-1: 3.02 min; ESI-MS 326 (M+H).

EXAMPLES 114-116



The following compounds were prepared using procedures analogous to those described in EXAMPLE 113 substituting the appropriate Aldehyde for 4-octylbenzaldehyde in Step C.

EXAMPLE	R	LC-1 (min)	ESI-MS (M+H)
114	$CH_3(CH_2)_8$-	3.00	340
115	$CH_3(CH_2)_8O$-	2.93	356
116	$CH_3(CH_2)_9$-	3.23	354

EXAMPLE 117

3-(N-(4-(4'-Pentyl)biphenylmethyl))aminopropylphosphinic acid

The title compound was using a procedure analogous to that described in EXAMPLE 113, substituting Aldehyde 56 for 4-octylbenzaldehyde in Step C: LC-1: 2.86 min; ESI-MS 360 (M+H).

EXAMPLE 118

3-(N-(4-(4'-Heptyloxy)biphenylmethyl))aminopropylphosphinic acid

The title compound was using a procedure analogous to that described in EXAMPLE 113, substituting Aldehyde 51 for 4-octylbenzaldehyde in Step C: LC-1: 3.06 min; ESI-MS 404 (M+H).

EXAMPLE 119

3-N-(3-Bromo-5-methoxy-4-(octyloxy)benzyl)aminopropylphosphinic acid

The title compound was using a procedure analogous to that described in EXAMPLE 113, substituting Aldehyde 13 for 4-octylbenzaldehyde in Step C: LC-1: 2.98 min; ESI-MS 450 (M+H).

EXAMPLE 120

3-N-(3-Fluoro-4-(nonyloxy)benzyl)aminopropylphosphinic acid

The title compound was using a procedure analogous to that described in EXAMPLE 113, substituting 3-fluoro-4-(nonyloxy)benzaldehyde for 4-octylbenzaldehyde in Step C: ^{1}H NMR (500 Mhz) δ 0.91 (t, *J*=7.0, 3H), 1.30-1.40 (m, 10H), 1.48-1.51 (m, 2H), 1.71-1.99 (m, 6H), 3.11 (t, *J*=7.2, 2H), 4.07 (t, *J*=6.4, 2H), 4.12 (s, 2H), 7.06 (d, *J*=519, 1H), 7.13-7.29 (m, 3H); LC-1: 2.96 min; ESI-MS 374 (M+H).

EXAMPLE 121

3-N-(2-Chloro-4-(nonyloxy)benzyl)aminopropylphosphinic acid

The title compound was using a procedure analogous to that described in EXAMPLE 113, substituting 2-chloro-4-(nonyloxy)benzaldehyde for 4-octylbenzaldehyde in Step C: LC-1 : 3.07 min; ESI-MS 390 (M+H).

EXAMPLE 122

3-N-(6-Heptyloxy)napthylmethyl)aminopropylphosphinic acid

The title compound was using a procedure analogous to that described in EXAMPLE 113, substituting 6-heptyloxy-1-napthaldehyde for 4-octylbenzaldehyde in Step C: LC-1: 2.90 min; ESI-MS 378 (M+H).

EXAMPLE 123

3-(N-(3-Cyclopropyloxy-4-(nonyloxy)benzyl)amino)propylphosphinic acid

The title compound was using a procedure analogous to that described in EXAMPLE 113, substituting Aldehyde 77 for 4-octylbenzaldehyde in Step C: LC-1: 3.04 min; ESI-MS 412 (M+H).

EXAMPLE 124

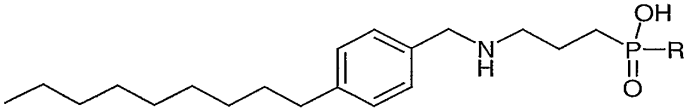
3-(N-(4-(Nonylthio)benzyl)amino)propylphosphinic acid

The title compound was using a procedure analogous to that described in EXAMPLE 113, substituting Aldehyde 78 for 4-octylbenzaldehyde in Step C: ^{1}H NMR (500 Mhz) (CD_3OD) δ 0.90 (t, J = 7.0, 3H), 1.30-1.32 (m, 10H), 1.43-1.46 (m, 2H), 1.63-1.66 (m, 2H), 1.78-1.83 (m, 2H), 1.95-1.99 (m, 2H), 2.98 (t, J = 7.2, 2H), 3.14 (t, J = 7.5, 2H), 4.16 (s, 2H), 7.08 (d, J = 533, 1H), 7.37-7.42 (m, 4H); LC-1: 3.10 min; ESI-MS 372 (M+H).

EXAMPLE 125

Ethyl (3-(4-nonylbenzyl)amino)propylphosphinic acid A solution of 88 mg (0.26 mmol) of 3-((4-nonylbenzyl)amino)propylphosphinic acid (from EXAMPLE 114) in 1 mL N,N-bis(trimethylsilyl)amine was heated to 100 °C for 8 hr. Upon cooling to rt, 81.1 mg (0.52 mmol) of iodoethane was added, followed by the addition of 67.2 mg (0.52 mmol) of DIEA. The resulting mixture was heated to 60 °C overnight. The reaction mixture was cooled and concentrated. HPLC purification (LC-2) afforded 12 mg (13%) of the title compound. ^{1}H NMR (500 MHz) (CD_3OD) δ 0.88 (t, J = 7.1, 3H), 1.09-1.18 (m, 3H), 1.26-1.31 (m, 12H), 1.59-1.75 (m, 6H), 1.94-2.00 (m, 2H), 2.63 (t, J = 7.6, 2H), 3.10 (t, J = 6.9, 2H), 4.13 (s, 2H), 7.27 (d, J = 8.0, 2H), 7.39 (d, J = 8.0 2H); LC-1: 2.92 min; ESI-MS 368 (M+H).

EXAMPLES 126-127



The following compounds were prepared a procedure analogous to that described in EXAMPLE 125 substituting the appropriate alkyl halide for ethyl iodide.

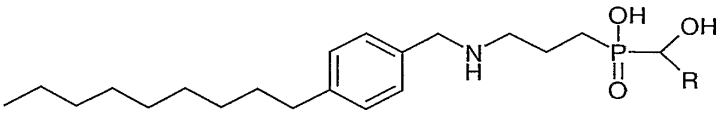
EXAMPLE	R	LC-1 (min)	ESI-MS (M+H)
126	$CH_3CH_2CH_2$-	3.03	382
127	$PhCH_2$-	3.41	430

EXAMPLE 128

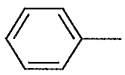
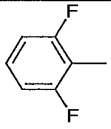
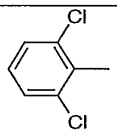
Hydroxymethyl (3-(4-nonylbenzyl)amino)propylphosphinic acid

A solution of 71 mg (0.21 mmol) of 3-(4-nonylbenzyl)aminopropylphosphinic acid (from EXAMPLE 114) in 1 mL of N,N-(trimethylsilyl)amine was heated to 100 °C for 8 hr. Upon cooling to rt, 15.8 mg (0.53 mmol) of paraformaldehyde was added. The resulting mixture was heated at 30 °C for 3 hr, and stirred at rt under nitrogen for 16 hr. The reaction mixture concentrated. HPLC purification (LC-2) afforded 22 mg (28%) of the title compound. ^{1}H NMR (500 MHz) (CD_3OD) δ 0.88 (t, J = 7.1, 3H), 1.27-1.31 (m, 12H), 1.57-1.63 (m, 2H), 1.80-1.85 (m, 2H), 1.97-2.05 (m, 2H), 2.63 (t, J = 7.8, 2H), 3.12 (t, J = 6.9, 2H), 3.70 (d, J = 6.2, 2H), 4.13 (s, 2H), 7.27 (d, J = 8.0, 2H), 7.39 (d, J = 8.2, 2H); LC-1: 2.90 min; ESI-MS 370 (M+H).

EXAMPLES 129-133



The following compounds were prepared using a procedure analogous to that described in EXAMPLE 128 substituting the appropriate aldehyde for paraformaldehyde.

EXAMPLE	R	LC-1 (min)	ESI-MS (M+H)
129	CH_3-	2.89	384
130	CH_3CH_2-	2.95	398
131		3.26	446
132		3.25	482
133		3.45	514

EXAMPLE 134

Hydroxymethyl (3-(4-octylbenzyl)amino)propylphosphinic acid

The title compound was prepared from 3-(4-octylbenzyl)aminopropylphosphinic acid (from EXAMPLE 114) using a procedure analogous to that described in EXAMPLE 128: LC-1: 2.67 min; ESI-MS 356 (M+H).

EXAMPLE 135

Hydroxymethyl 3-(3-(cyclopropyloxy)-4-(nonyloxy)benzyl)aminopropylphosphinic acid

The title compound was prepared from 3-(3-(cyclopropyloxy)-4-(nonyloxy)benzyl)aminopropylphosphinic acid (from EXAMPLE 123) using a procedure analogous to that described in EXAMPLE 128: LC-1: 2.95 min; ESI-MS 442 (M+H).

EXAMPLE 136

Hydroxymethyl 3-(3-fluoro-4-(nonyloxy)benzyl)aminopropylphosphinic acid

The title compound was prepared from 3-(3-fluoro-4-(nonyloxy)benzyl)amino-propylphosphinic acid (from EXAMPLE 125) using a procedure analogous to that described in EXAMPLE 128: LC-1: 2.87 min; ESI-MS 404 (M+H).

EXAMPLE 137

Ethoxycarbonyl 3-(N-(4-(4'-heptyloxy)biphenylmethyl))aminopropylphosphinic acid

To a solution of 32.5 mg (0.081 mmol) of 3-(N-(4-(4'-heptyloxy)biphenylmethyl)) aminopropylphosphinic acid (from EXAMPLE 118) in 2 mL dichloromethane was added 0.1 mL of TMSCl and 0.12 mL of DIEA at 0 °C. The solution was stirred at rt for an additional one hour and 0.1 mL of ethyl chloroformate (0.81 mmol) was added. The reaction was quenched with MeOH and concentrated to oil. The product was isolated and purified by LC-2: ^{1}H NMR (500 Mhz) (CD_3OD) δ 0.94 (t, J = 6.9, 3H), 1.31-1.43 (m, 8H), 1.51-1.53 (m, 2H), 1.80-1.83 (m, 2H), 1.89-1.92 (m, 2H), 2.03-2.06 (m, 2H), 3.18 (t, J = 6.7, 2H), 4.05 (t, J = 6.4, 2H), 4.24 (s, 2H), 4.25 (q, J =7.0, 2H), 6.95-7.72 (m, 8H); LC-1: 3.26 min; ESI-MS 476 (M+H).

EXAMPLE 138

3-(4-Octylbenzyl)amino-2-phenylpropylphosphinic acid

A mixture of 69.2 mg (0.210 mmol) of ethyl 3-amino-2-phenylpropyl(diethoxymethyl)phosphinate (*Tetrahedron*, **1989**, 3787-3808) and 48.2 mg (0.221 mmol) of 4-octylbenzaldehyde in 1 mL of MeOH at rt was treated with 6.7 mg (0.105 mmol) of $Na(CN)BH_3$. The resulting reaction mixture was stirred at rt for 16 hr. The reaction was quenched with 0.3 mL of 12 N HCl, then heated up to 60 °C for 5 hr. The mixture was cooled and concentrated. HPLC purification (LC-2) afforded 22 mg (26%) of the title compound. ^{1}H NMR (500 MHz) (CD_3OD) δ 0.88 (t, J = 7.1, 3H), 1.26-1.30 (m, 10H), 1.58-1.61 (m, 2H), 2.01-2.17 (m, 2H), 2.62 (t, J = 7.8, 2H), 3.20-3.23 (m, 1H),3.35-3.46 (m, 2H), 4.11 (s, 2H), 6.92 (d, J = 525.4, 1H), 7.23-7.37 (m, 9H); LC-1: 3.31 min; ESI-MS 402 (M+H).

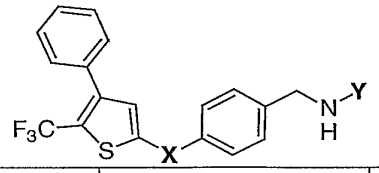
EXAMPLE 139

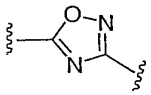
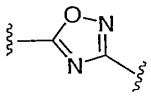
3-(3-Bromo-5-methoxy-4-(octyloxy)benzyl)amino-2-phenylpropylphosphinic acid

The title compound was prepared using a procedure analogous to that described in EXAMPLE 138 substituting Aldehyde 13 for 4-octylbenzaldehyde: LC-1: 3.51 min; ESI-MS 526 (M+H).

EXAMPLES 140-150

The following compounds were prepared using a procedure analogous to that described in EXAMPLE 1 substituting the appropriate aminoalkylcarboxylic acid or aminoalkylphosphonic acid for 3-aminopropylphosphonic acid and either Aldehyde 79 or 80 for 4-(decyloxy)benzaldehyde. The products were purified using LC-2.



EXAMPLE	X	Y	LC-1 (min)	ESI-MS (M+H)
140		-$(CH_2)_3PO_3H_2$	3.01	524
141		-$(CH_2)_3CO_2H$	3.07	448
142	-CH_2O-	-$(CH_2)_3PO_3H_2$	2.77	486
143	-CH_2O-	-$(CH_2)_3CO_2H$	2.79	450
144	-CH_2O-	-$(CH_2)_2CO_2H$	2.72	436
145	-CH_2O-	-$CH_2CH(CH_3)CO_2H$	3.00	450
146	-CH_2O-	-$CH_2CH(OH)CO_2H$		
147	-CH_2O-	-CH(n-Pr)CH_2CO_2H	3.11	478

^{1}H NMR (500 MHz, CD_3OD) δ 0.97 (3H, t, J=7.3); 1.29-1.51 (2H, m); 1.63-1.71 (1H, m); 1.78-1.84 (1H, m); 2.66-2.83 (3H, m); 3.46-3.54 (1H, m); 4.23 (2H, s); 5.38 (2H, s); 7.12 (2H, d, J=8.5); 7.21 (1H, s); 7.41-7.44 (5H, m); 7.47 (2H, d, J=8.5)				
148	$-CH_2O-$	$-CH(i\text{-}Pr)CH_2CO_2H$	3.06	478
^{1}H NMR (500 MHz, CD_3OD) δ 0.97 (3H, d, J=6.8); 1.01 (3H, d, J=6.8); 2.15-2.21 (1H, m); 2.66-2.83 (3H, m); 3.48-3.51 (1H, m); 4.28 (2H, q, J=13 & 28); 5.39 (2H, s); 7.13 (2H, d, J=8.5); 7.21 (1H, s); 7.42-7.47 (5H, m); 7.49 (2H, d, J=8.5)				
149	$-CH_2O-$	$-CH(CH_3)CH_2CO_2H$	2.90	450
^{1}H NMR (500 MHz, CD_3OD) δ 1.42 (3H, d, J=6.6); 2.66-2.79 (2H, m); 2.83 (1H, s); 3.59-3.64 (1H, m); 4.21 (2H, q, J=13 & 28); 5.38 (2H, s); 7.13 (2H, d, J=8.4); 7.21 (1H, s); 7.42-7.45 (5H, m); 7.47 (2H, d, J=8.4)				
150	$-CH_2O-$	$-(CH_2)_4CO_2H$	2.95	464
^{1}H NMR (500 MHz, CD_3OD) δ 1.60-1.80 (4H, m); 2.30-2.50 (2H, m); 3.24 (2H, s); 4.53 (2H, s); 5.31 (2H, s); 7.13 (2H, d, J=8.4); 7.21 (1H, s); 7.42-7.45 (5H, m); 7.47 (2H, d, J=8.4)				

BIOLOGICAL ACTIVITY

The $S1P_1$/Edg1, $S1P_3$,/Edg3, $S1P_2$/Edg5, $S1P_4$/Edg6 or $S1P_5$ /Edg8 activity of the compounds of the present invention can be evaluated using the following assays:

Ligand Binding to Edg/S1P Receptors Assay

^{33}P-sphingosine-1-phosphate was synthesized enzymatically from γ^{33}P-ATP and sphingosine using a crude yeast extract with sphingosine kinase activity in a reaction mix containing 50 mM KH_2PO_4, 1 mM mercaptoethanol, 1 mM Na_3VO_4, 25 mM KF, 2 mM semicarbazide, 1 mM Na_2EDTA, 5 mM $MgCl_2$, 50 mM sphingosine, 0.1% TritonX-114, and 1 mCi γ^{33}P-ATP (NEN; specific activity 3000 Ci/mmol). Reaction products were extracted with butanol and ^{33}P-sphingosine-1-phosphate was purified by HPLC.

Cells expressing EDG/S1P receptors were harvested with enzyme-free dissociation solution (Specialty Media, Lavallette, NJ). They were washed once in cold PBS and suspended in binding assay buffer consisting of 50 mM HEPES-Na, pH 7.5, 5mM $MgCl_2$, 1mM $CaCl_2$, and 0.5% fatty acid-free BSA. ^{33}P-sphingosine-1-phosphate was sonicated with 0.1 nM sphingosine-1-phosphate in binding assay buffer; 100 µl of the ligand mixture was added to 100 µl cells (1 x 10^6 cells/ml) in a 96 well microtiter dish. Binding was performed for 60 min at room temperature with gentle mixing. Cells were then collected onto GF/B filter plates with a Packard Filtermate Universal Harvester. After drying the filter plates for 30 min, 40 µl of Microscint 20 was added to each well and binding was measured on a Wallac Microbeta Scintillation Counter. Non-specific binding was defined as the amount of radioactivity remaining in the presence of 0.5 µM cold sphingosine-1-phosphate.

Alternatively, ligand binding assays were performed on membranes prepared from cells expressing Edg/S1P receptors. Cells were harvested with enzyme-free dissociation solution and washed once in cold PBS. Cells were disrupted by homogenization in ice cold 20 mM HEPES pH 7.4, 10 mM EDTA using a Kinematica polytron (setting 5, for 10 seconds). Homogenates were centrifuged at 48,000 x g for 15 min at 4°C and the pellet was suspended in 20 mM HEPES pH 7.4, 0.1 mM EDTA. Following a second centrifugation, the final pellet was suspended in 20 mM HEPES pH 7.4, 100 mM NaCl, 10 mM $MgCl_2$. Ligand binding assays were performed as described above, using 0.5 to 2 µg of membrane protein.

Agonists and antagonists of Edg/S1P receptors can be identified in the ^{33}P-sphingosine-1-phosphate binding assay. Compounds diluted in DMSO, methanol, or other solvent, were mixed with probe containing ^{33}P-sphingosine-1-phosphate and binding assay buffer in microtiter dishes. Membranes prepared from

cells expressing Edg/S1P receptors were added, and binding to ^{33}P-sphingosine-1-phosphate was performed as described. Determination of the amount of binding in the presence of varying concentrations of compound and analysis of the data by non-linear regression software such as MRLCalc (Merck Research Laboratories) or PRISM (GraphPad Software) was used to measure the affinity of compounds for the receptor. Selectivity of compounds for Edg/S1P receptors was determined by measuring the level of ^{33}P-sphingosine-1-phosphate binding in the presence of the compound using membranes prepared from cells transfected with each respective receptor ($S1P_1$/Edg1, $S1P_3$/Edg3, $S1P_2$/Edg5, $S1P_4$/Edg6, $S1P_5$/Edg8).

^{35}S-GTPγS Binding Assay

Functional coupling of S1P/Edg receptors to G proteins was measured in a ^{35}S-GTPγS binding assay. Membranes prepared as described in the Ligand Binding to Edg/S1P Receptors Assay (1-10 μg of membrane protein) were incubated in a 200 μl volume containing 20 mM HEPES pH 7.4, 100 mM NaCl, 10 mM $MgCl_2$, 5 μM GDP, 0.1% fatty acid-free BSA (Sigma, catalog A8806), various concentrations of sphingosine-1-phosphate, and 125 pM ^{35}S-GTPγS (NEN; specific activity 1250 Ci/mmol) in 96 well microtiter dishes. Binding was performed for 1 hour at room temperature with gentle mixing, and terminated by harvesting the membranes onto GF/B filter plates with a Packard Filtermate Universal Harvester. After drying the filter plates for 30 min, 40 μl of Microscint 20 was added to each well and binding was measured on a Wallac Microbeta Scintillation Counter.

Agonists and antagonists of S1P/Edg receptors can be discriminated in the ^{35}S-GTPγS binding assay. Compounds diluted in DMSO, methanol, or other solvent, were added to microtiter dishes to provide final assay concentrations of 0.01 nM to 10 μM. Membranes prepared from cells expressing S1P/Edg receptors were added, and binding to ^{35}S-GTPγS was performed as described. When assayed in the absence of the natural ligand or other known agonist, compounds that stimulate ^{35}S-GTPγS binding above the endogenous level were considered agonists, while compounds that inhibit the endogenous level of ^{35}S-GTPγS binding were considered inverse agonists. Antagonists were detected in a ^{35}S-GTPγS binding assay in the presence of a sub-maximal level of natural ligand or known S1P/Edg receptor agonist,

where the compounds reduced the level of ^{35}S-GTPγS binding. Determination of the amount of binding in the presence of varying concentrations of compound was used to measure the potency of compounds as agonists, inverse agonists, or antagonists of S1P/Edg receptors. To evaluate agonists, percent stimulation over basal was calculated as binding in the presence of compound divided by binding in the absence of ligand, multiplied by 100. Dose response curves were plotted using a non-linear regression curve fitting program MRLCalc (Merck Research Laboratories), and EC_{50} values were defined to be the concentration of agonist required to give 50% of its own maximal stimulation. Selectivity of compounds for S1P/Edg receptors was determined by measuring the level of ^{35}S-GTPγS binding in the presence of compound using membranes prepared from cells transfected with each respective receptor.

Intracellular Calcium Flux Assay

Functional coupling of S1P/Edg receptors to G protein associated intracellular calcium mobilization was measured using FLIPR (Fluorescence Imaging Plate Reader, Molecular Devices). Cells expressing S1P/Edg receptors were harvested and washed once with assay buffer (Hanks Buffered Saline Solution (BRL) containing 20mM HEPES, 0.1% BSA and 710 μg/ml probenicid (Sigma)). Cells were labeled in the same buffer containing 500 nM of the calcium sensitive dye Fluo-4 (Molecular Probes) for 1 hour at 37°C and 5% CO_2. The cells were washed twice with buffer before plating $1.5x10^5$ per well (90μl) in 96 well polylysine coated black microtiter dishes. A 96-well ligand plate was prepared by diluting sphingosine-1-phosphate or other agonists into 200 μl of assay buffer to give a concentration that was 2-fold the final test concentration. The ligand plate and the cell plate were loaded into the FLIPR instrument for analysis. Plates were equilibrated to 37°C. The assay was initiated by transferring an equal volume of ligand to the cell plate and the calcium flux was recorded over a 3 min interval. Cellular response was quantitated as area (sum) or maximal peak height (max). Agonists were evaluated in the absence of natural ligand by dilution of compounds into the appropriate solvent and transfer to the Fluo-4 labeled cells. Antagonists were evaluated by pretreating Fluo-4 labeled cells with varying concentrations of compounds for 15 min prior to the initiation of calcium flux by addition of the natural ligand or other S1P/Edg receptor agonist.

Preparation of Cells Expressing S1P/Edg Receptors

Any of a variety of procedures may be used to clone $S1P_1$/Edg1, $S1P_3$/Edg3, $S1P_2$/Edg5, $S1P_4$/Edg6 or $S1P_5$/Edg8. These methods include, but are not limited to, (1) a RACE PCR cloning technique (Frohman, et al., 1988, *Proc. Natl. Acad. Sci. USA* 85: 8998-9002). 5′ and/or 3′ RACE may be performed to generate a full-length cDNA sequence; (2) direct functional expression of the Edg/S1P cDNA following the construction of an S1P/Edg-containing cDNA library in an appropriate expression vector system; (3) screening an S1P/Edg-containing cDNA library constructed in a bacteriophage or plasmid shuttle vector with a labeled degenerate oligonucleotide probe designed from the amino acid sequence of the S1P/Edg protein; (4) screening an S1P/Edg-containing cDNA library constructed in a bacteriophage or plasmid shuttle vector with a partial cDNA encoding the S1P/Edg protein. This partial cDNA is obtained by the specific PCR amplification of S1P/Edg DNA fragments through the design of degenerate oligonucleotide primers from the amino acid sequence known for other proteins which are related to the S1P/Edg protein; (5) screening an S1P/Edg-containing cDNA library constructed in a bacteriophage or plasmid shuttle vector with a partial cDNA or oligonucleotide with homology to a mammalian S1P/Edg protein. This strategy may also involve using gene-specific oligonucleotide primers for PCR amplification of S1P/Edg cDNA; or (6) designing 5′ and 3′ gene specific oligonucleotides using the S1P/Edg nucleotide sequence as a template so that either the full-length cDNA may be generated by known RACE techniques, or a portion of the coding region may be generated by these same known RACE techniques to generate and isolate a portion of the coding region to use as a probe to screen one of numerous types of cDNA and/or genomic libraries in order to isolate a full-length version of the nucleotide sequence encoding S1P/Edg.

It is readily apparent to those skilled in the art that other types of libraries, as well as libraries constructed from other cell types-or species types, may be useful for isolating an S1P/Edg-encoding DNA or an S1P/Edg homologue. Other types of libraries include, but are not limited to, cDNA libraries derived from other cells.

It is readily apparent to those skilled in the art that suitable cDNA libraries may be prepared from cells or cell lines which have S1P/Edg activity. The

selection of cells or cell lines for use in preparing a cDNA library to isolate a cDNA encoding S1P/Edg may be done by first measuring cell-associated S1P/Edg activity using any known assay available for such a purpose.

Preparation of cDNA libraries can be performed by standard techniques well known in the art. Well known cDNA library construction techniques can be found for example, in Sambrook et al., 1989, *Molecular Cloning: A Laboratory Manual*; Cold Spring Harbor Laboratory, Cold Spring Harbor, New York. Complementary DNA libraries may also be obtained from numerous commercial sources, including but not limited to Clontech Laboratories, Inc. and Stratagene.

An expression vector containing DNA encoding an S1P/Edg-like protein may be used for expression of S1P/Edg in a recombinant host cell. Such recombinant host cells can be cultured under suitable conditions to produce S1P/Edg or a biologically equivalent form. Expression vectors may include, but are not limited to, cloning vectors, modified cloning vectors, specifically designed plasmids or viruses. Commercially available mammalian expression vectors may be suitable for recombinant S1P/Edg expression.

Recombinant host cells may be prokaryotic or eukaryotic, including but not limited to, bacteria such as *E. coli*, fungal cells such as yeast, mammalian cells including, but not limited to, cell lines of bovine, porcine, monkey and rodent origin; and insect cells including but not limited to *Drosophila* and silkworm derived cell lines.

The nucleotide sequences for the various S1P/Edg receptors are known in the art. See, for example, the following:

S1P$_1$/Edg1 Human

Hla, T. and T. Maciag 1990 An abundant transcript induced in differentiating human endothelial cells encodes a polypeptide with structural similarities to G-protein coupled receptors. J. Biol Chem. 265:9308-9313, hereby incorporated by reference in its entirety.

WO91/15583, published on October 17, 1991, hereby incorporated by reference in its entirety.

WO99/46277, published on September 16, 1999, hereby incorporated by reference in its entirety.

S1P1/Edg1 Mouse

WO0059529, published October 12, 2000, hereby incorporated by reference in its entirety.

U.S. No. 6,323,333, granted November 27, 2001, hereby incorporated by reference in its entirety.

S1P1/Edg1 Rat

Lado, D.C., C. S. Browe, A.A. Gaskin, J. M. Borden, and A. J. MacLennan. 1994 Cloning of the rat edg-1 immediate-early gene: expression pattern suggests diverse functions. Gene 149: 331-336, hereby incorporated by reference in its entirety.

U.S. No. 5,585,476, granted December 17, 1996, hereby incorporated by reference in its entirety.

U.S. No. 5856,443, granted January 5, 1999, hereby incorporated by reference in its entirety.

S1P3/Edg3 Human

An, S., T. Bleu, W. Huang, O.G. Hallmark, S. R. Coughlin, E.J. Goetzl 1997 Identification of cDNAs encoding two G protein-coupled receptors for lysosphingolipids FEBS Lett. 417:279-282, hereby incorporated by reference in its entirety.

WO 99/60019, published November 25, 1999, hereby incorporated by reference in its entirety.

U.S. No. 6,130,067, granted October 10, 2000, hereby incorporated by reference in its entirety.

S1P3/Edg3 Mouse

WO 01/11022, published February 15, 2001, hereby incorporated by reference in its entirety.

S1P3/Edg3 Rat

WO 01/27137, published April 19, 2001, hereby incorporated by reference in its entirety.

S1P2/Edg5 Human

An, S., Y. Zheng, T. Bleu 2000 Sphingosine 1-Phosphate-induced cell proliferation, survival, and related signaling events mediated by G Protein-coupled receptors Edg3 and Edg5. J. Biol. Chem 275: 288-296, hereby incorporated by reference in its entirety.

WO 99/35259, published July 15, 1999, hereby incorporated by reference in its entirety.

WO99/54351, published October 28, 1999, hereby incorporated by reference in its entirety.

WO 00/56135, published September 28, 2000, hereby incorporated by reference in its entirety.

S1P2/Edg5 Mouse

WO 00/60056, published October 12, 2000, hereby incorporated by reference in its entirety.

S1P2/Edg5 Rat

Okazaki, H., N. Ishizaka, T. Sakurai, K. Kurokawa, K. Goto, M. Kumada, Y. Takuwa 1993 Molecular cloning of a novel putative G protein-coupled receptor expressed in the cardiovascular system. Biochem. Biophys. Res. Comm. 190:1104-1109, hereby incorporated by reference in its entirety.

MacLennan, A.J., C. S. Browe, A.A. Gaskin, D.C. Lado, G. Shaw 1994 Cloning and characterization of a putative G-protein coupled receptor potentially involved in development. Mol. Cell. Neurosci. 5: 201-209, hereby incorporated by reference in its entirety.

U.S. No. 5,585,476, granted December 17, 1996, hereby incorporated by reference in its entirety.

U.S. No. 5856,443, granted January 5, 1999, hereby incorporated by reference in its entirety.

S1P4/Edg6 Human

Graler, M.H., G. Bernhardt, M. Lipp 1998 EDG6, a novel G-protein-coupled receptor related to receptors for bioactive lysophospholipids, is specifically expressed in lymphoid tissue. Genomics 53: 164-169, hereby incorporated by reference in its entirety.

WO 98/48016, published October 29, 1998, hereby incorporated by reference in its entirety.

U.S. No. 5,912,144, granted June 15, 1999, hereby incorporated by reference in its entirety.

WO 98/50549, published November 12, 1998, hereby incorporated by reference in its entirety.

U.S. No. 6,060,272, granted May 9, 2000, hereby incorporated by reference in its entirety.

WO 99/35106, published July 15, 1999, hereby incorporated by reference in its entirety.

WO 00/15784, published March 23, 2000, hereby incorporated by reference in its entirety.

WO 00/14233, published March 16, 2000, hereby incorporated by reference in its entirety.

S1P4/Edg6 Mouse

WO 00/15784, published March 23, 2000, hereby incorporated by reference in its entirety.

S1P5/Edg8 Human

Im, D.-S., J. Clemens, T.L. Macdonald, K.R. Lynch 2001 Characterization of the human and mouse sphingosine 1-phosphate receptor, S1P5 (Edg-8): Structure-Activity relationship of sphingosine 1-phosphate receptors. Biochemistry 40:14053-14060, hereby incorporated by reference in its entirety.

WO 00/11166, published March 2, 2000, hereby incorporated by reference in its entirety.

WO 00/31258, published June 2, 2000, hereby incorporated by reference in its entirety.

WO 01/04139, published January 18, 2001, hereby incorporated by reference in its entirety.

EP 1 090 925, published April 11, 2001, hereby incorporated by reference in its entirety.

S1P5/Edg8 Rat

Im, D.-S., C.E. Heise, N. Ancellin, B. F. O'Dowd, G.-J. Shei, R. P. Heavens, M. R. Rigby, T. Hla, S. Mandala, G. McAllister, S.R. George, K.R. Lynch 2000 Characterization of a novel sphingosine 1-phosphate receptor, Edg-8. J. Biol. Chem. 275: 14281-14286, hereby incorporated by reference in its entirety.

WO 01/05829, published January 25, 2001, hereby incorporated by reference in its entirety.

Measurement of cardiovascular effects

The effects of compounds of the present invention on cardiovascular parameters can be evaluated by the following procedure:

Adult male rats (approx. 350 g body weight) were instrumented with femoral arterial and venous catheters for measurement of arterial pressure and intravenous compound administration, respectively. Animals were anesthetized with Nembutal (55 mg/kg, ip). Blood pressure and heart rate were recorded on the Gould Po-Ne-Mah data acquisition system. Heart rate was derived from the arterial pulse wave. Following an acclimation period, a baseline reading was taken (approximately 20 minutes) and the data averaged. Compound was administered intravenously (either bolus injection of approximately 5 seconds or infusion of 15 minutes duration), and data were recorded every 1 minute for 60 minutes post compound administration. Data are calculated as either the peak change in heart rate or mean arterial pressure or are calculated as the area under the curve for changes in heart rate or blood pressure versus time. Data are expressed as mean ± SEM. A one-tailed Student's paired t-test is used for statistical comparison to baseline values and considered significant at $p<0.05$.

The S1P effects on the rat cardiovascular system are described in Sugiyama, A., N.N. Aye, Y. Yatomi, Y. Ozaki, K. Hashimoto 2000 Effects of Sphingosine-1-Phosphate, a naturally occurring biologically active lysophospholipid, on the rat cardiovascular system. Jpn. J. Pharmacol. 82: 338-342, hereby incorporated by reference in its entirety.

Measurement of Mouse Acute Toxicity

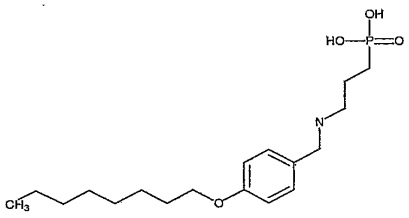
A single mouse is dosed intravenously (tail vein) with 0.1 ml of test compound dissolved in a non-toxic vehicle and is observed for signs of toxicity. Severe signs may include death, seizure, paralysis or unconciousness. Milder signs are also noted and may include ataxia, labored breathing, ruffling or reduced activity relative to normal. Upon noting signs, the dosing solution is diluted in the same vehicle. The diluted dose is administered in the same fashion to a second mouse and is likewise observed for signs. The process is repeated until a dose is reached that produces no signs. This is considered the estimated no-effect level. An additional mouse is dosed at this level to confirm the absence of signs.

Assessment of Lymphopenia

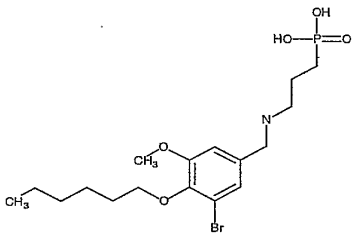
Compounds are administered as described in Measurement of Mouse Acute Toxicity and lymphopenia is assessed in mice at three hours post dose as follows. After rendering a mouse unconscious by CO_2 to effect, the chest is opened, 0.5 ml of blood is withdrawn via direct cardiac puncture, blood is immediately stabilized with EDTA and hematology is evaluated using a clinical hematology autoanalyzer calibrated for performing murine differential counts (H2000, CARESIDE, Culver City CA). Reduction in lymphocytes by test treatment is established by comparison of hematological parameters of three mice versus three vehicle treated mice. The dose used for this evaluation is determined by tolerability using a modification of the dilution method above. For this purpose, no-effect is desirable, mild effects are acceptable and severely toxic doses are serially diluted to levels that produce only mild effects.

Example of Non-selective and Selective S1P1/Edg1 Agonists

To illustrate the utility of selective S1P1/Edg1 agonists, the activity of 2 compounds in GTPgS binding assays using human S1P1/Edg1 and S1P3/Edg3 receptors and mouse acute toxicity and lymphopenia assays conducted as described above are shown. Example 2 is a non-selective potent agonist of S1P1/Edg1 and S1P3/Edg3 that is highly toxic to mice at doses greater than 0.1 mg/kg, and induces immunosuppression as measured by lymphopenia at 0.1 mg/kg. Example 77 is a selective agonist of S1P1/Edg1 that induces lymphopenia at 10 mg/kg without apparent toxicity.



EXAMPLE 2



EXAMPLE 77

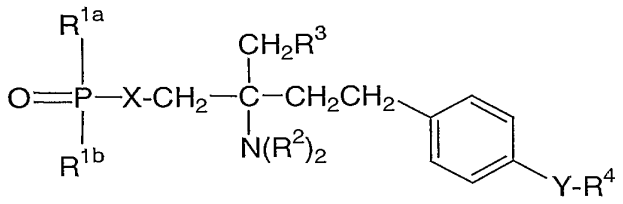
Compound	$S1P_1$ EC_{50} (nM)	$S1P_3$ EC_{50} (nM)	IV dose (mg/kg)	Toxicity	Lymphocytes*
Example 2	1.5	6.0	3	Lethal	NE**
			0.25	severe	NE
			0.1	mild to severe	65
Example 77	8.4	>10000	4	none	38

* % reduction

** NE = not evaluable

A further embodiment of the invention encompasses a method of identifying a candidate compound which is an agonist of the $S1P_1$/Edg1 receptor that is selective over the $S1P_3$/Edg3 receptor, wherein said candidate compound possesses a selectivity for the $S1P_1$/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 20 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay and wherein said candidate compound possesses an EC_{50} for binding to the $S1P_1$/Edg1 receptor of 100 nM or less as evaluated by the ^{35}S-GTPγS binding assay,

with the proviso that the candidate compound does not fall within formula A:



A

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

X is O, S, NR^1 or $(CH_2)_{1-2}$, optionally substituted with 1-4 halo groups;

R^1 is H, C_{1-4}alkyl or haloC_{1-4} alkyl;

R^{1a} is H, OH, C_{1-4}alkyl, or OC_{1-4} alkyl, the alkyl and alkyl portions being optionally substituted with 1-3 halo groups;

R^{1b} represents H, OH, C_{1-4} alkyl or haloC_{1-4} alkyl;

each R^2 is independently selected from the group consisting of: H, C_{1-4} alkyl and haloC_{1-4} alkyl,

R^3 is H, OH, halo, C_{1-4}alkyl, OC_{1-4}alkyl, O-haloC_{1-4}alkyl or hydroxyC_{1-4}alkyl,

Y is selected from the group consisting of: $-CH_2-$, -C(O)-, -CH(OH)-, -C(=NOH)-, O and S, and

R^4 is selected from the group consisting of: C_{4-14}alkyl and C_{4-14}alkenyl,

comprising:

(1) providing a first receptor preparation comprising:
(a) a recombinant cell expressing the $S1P_1$/Edg1 receptor or a functional equivalent of the $S1P_1$/Edg1 receptor capable of binding to sphingosine-1-phosphate ("S1P"); or
(b) a membrane preparation of a recombinant cell in accordance with subsection (1)(a);

(2) providing a second receptor preparation comprising:
(a) a recombinant cell expressing the $S1P_3$/Edg3 receptor or a functional equivalent of the $S1P_3$/Edg3 receptor capable of binding to sphingosine-1-phosphate ("S1P"); or
(b) a membrane preparation of a recombinant cell in accordance with subsection (2)(a);

(3) separately contacting said cells or membrane preparations with the candidate compound; and

(4) determining whether the candidate compound binds to and activates the $S1P_1$/Edg1 and $S1P_3$/Edg3 receptors by measuring the level of a signal generated from the interaction of the candidate compound with each receptor, thereby indicating whether the candidate compound is an agonist of the $S1P_1$/Edg1 receptor that is selective over the $S1P_3$/Edg3 receptor.

For purposes of this Specification, any pathway that is activated by the $S1P_1$/Edg1 and/or $S1P_3$/Edg3 receptors upon contact with an agonist can result in a detectable signal indicating that the receptor has been activated. Activation of the receptor by an agonist, for example, can be identified by an increase in the concentration of a relevant second messenger influenced by the receptor within cells expressing the receptor (an increase that would not be observed in cells not contacted by a receptor agonist). Those of skill in the art can readily identify an assay suitable for detecting an increase in the level of an intracellular second messenger or a

detectable extracellular signal indicative of receptor activation. The signal's primary purpose is to detect (either directly or indirectly) the activation and signaling of the receptor. The signal can be either a component of the pathway or responsive to the presence or functioning of a component of the pathway. In accordance with this description, therefore, the signal can be responsive to an intracellular event which is part of the biochemical cascade initiated by receptor activation or responsive to an extracellular event such as pH changes that occur upon receptor activation. The signal can, thus, be detected by outward characteristics or by a molecule present within or administered to the cells that responds to the signal. One class of molecules that respond to intracellular changes includes those that act on changes in calcium concentration (*e.g.,* aequorin (a jellyfish protein)) which acts on the substrate coelenterazine. Other molecules in that class include calcium chelators with fluorescence capabilities, such as FURA-2, indo-1, Fluo-3, and Fluo-4 The level of cAMP is another signal that is measured. This can be measured, for instance, byradio-immuno or protein binding assays (*e.g.,* using Flashplates or a scintillation proximity assay). The changes in cAMP can also be determining by measuring the activity of the enzyme, adenylyl cyclase. cAMP assays are described in the art, *see, e.g.,* Jakajima *et al.*, 1992 *J. Biol. Chem.* 247:2437-2442; Tigyi *et al.*, 1996 *J. Neurochem.* 66:549-558. Alternative assays disclosed in the art measure changes in inositol 1,4,5-triphosphate levels (*see, e.g.,* Tigyi *et al.,* 1996 *J. Neurochem.* 66:537-548); Cl^- ion efflux (*see, e.g.,* Postma *et al.*, 1996 *EMBO J.* 15:63-72; and Watsky, 1995 *Am. J. Physiol.* 269:C1385-C1393); or, as provided in examples above, changes in intracellular Ca2+ levels (*see also*, Tigyi *et al.*, 1996 *J. Neurochem.* 66:537-548. In the illustrated examples of the instant invention, binding of ^{35}S-GTPγS to G proteins coupled to receptors is detected. This has been described in the art in the following references:

Milligan, 1988, Journal 255:1-13
Stanton and Beer, 1997, Journal 320:267-275

It is appreciated by those skilled in the art that the dose of the candidate compound contacted to said cells or membranes expressing each receptor will affect the signal generated in the assay. A positive and greater signal at the S1P1/Edg1 receptor over the S1P3/Edg3 receptor at an equivalent dose will indicate a compound

that is an agonist of the S1P1/Edg1 receptor that is selective over the S1P3/Edg3 receptor. An "equivalent dose" means a substantially equal amount of the compounds and is well understood by artisans skilled in the art. However, the present invention is meant to include identifying the compounds using any dose as long as one skilled in the art is determining whether the candidate compounds are agonists of the S1P1/Edg1 receptor that is selective over the S1P3/Edg3 receptor.

For purposes of this Specification, the following terms have the indicated meanings:

"S1P" means sphingosine 1-phosphate.

"Functional equivalents" are defined herein as receptors which may not possess the exact amino acid sequence due to alternative splicing, deletions, mutations, or additions, but retain the biological activity of the S1P1/Edg1 or S1P3/Edg3 receptor (*e.g.*, binding of sphingosine 1-phosphate and transduction of signals through Gi, Gq, or $G_{12/13}$ heterotrimeric G proteins). Minor changes in the sequence are known in the art not to change the functionality of the receptors. See for example the following, which are hereby incorporated by reference in their entirety:

Truncation of C-terminus of Edg1:
(Liu et al., 1999, Journal 10:1179-90.)
(Watterson et al., 2002, Journal 277:5767-5777.)

Site Directed Mutagenesis of Edg1
(Parrill et al., 2000, Journal 275:39379-84.)

An embodiment of the invention encompasses the method of the present invention wherein the method further comprises conducting the method in the presence of labeled or unlabeled S1P, di-hydro S1P or a ligand for the S1P1/Edg1 and/or S1P3/Edg3 receptor; provided that if a ligand is utilized that is specific for either the S1P1/Edg1 or S1P3/Edg3 receptor, the receptor ligand utilized in the first receptor preparation is a ligand of the S1P1/Edg1 receptor and the ligand utilized in

the second receptor preparation is a ligand of the S1P3/Edg3 receptor; and provided, further, that the method would additionally comprise measuring the level of a signal generated from the interaction of the S1P, di-hydro S1P or ligand; wherein a compound that effects a reduction of the signal from the interaction of the S1P, di-hydro S1P or ligand, with the receptor and activates the S1P1/Edg1 receptor at a greater level than that obtained at the S1P3/Edg3 receptor is a selective agonist of the S1P1/Edg1 receptor.

Another embodiment of the invention encompasses the method of the present invention wherein the signal indicates extracellular pH changes caused by receptor activation.

Another embodiment of the invention encompasses the method of the present invention wherein the signal indicates levels of cAMP present within the cell.

Another embodiment of the invention encompasses the method of the present invention wherein the signal indicates adenylate cyclase accumulation.

Another embodiment of the invention encompasses the method of the present invention wherein the signal indicates Ca+ flux.

Another embodiment of the invention encompasses the method of the present invention wherein the candidate compound has a selectivity for the $S1P_1$/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 100 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

Another embodiment of the invention encompasses the method of the present invention wherein the candidate compound has a selectivity for the $S1P_1$/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 200 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

Another embodiment of the invention encompasses the method of the present invention wherein the candidate compound has a selectivity for the $S1P_1$/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 500 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

Another embodiment of the invention encompasses the method of the present invention wherein the candidate compound has a selectivity for the

$S1P_1$/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 2000 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

Another embodiment of the invention encompasses the method of the present invention wherein the candidate compound possesses an EC_{50} for binding to the $S1P_1$/Edg1 receptor of 1 nM or less as evaluated by the ^{35}S-GTPγS binding assay.

The invention further encompasses a method of identifying a candidate compound which is an agonist of the $S1P_1$/Edg1 receptor that is selective over the S1P3/Edg3 receptor, wherein said candidate compound possesses a selectivity for the S1P1/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 100 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay and wherein said candidate compound possesses an EC_{50} for binding to the $S1P_1$/Edg1 receptor of 10 nM or less as evaluated by the ^{35}S-GTPγS binding assay, comprising:

(1) providing a first receptor preparation comprising:
  (a) a recombinant cell expressing the S1P1/Edg1 receptor or a functional equivalent of the S1P1/Edg1 receptor capable of binding to sphingosine-1-phosphate ("S1P"); or
  (b) a membrane preparation of a recombinant cell in accordance with subsection (1)(a);

(2) providing a second receptor preparation comprising:
  (a) a recombinant cell expressing the S1P3/Edg3 receptor or a functional equivalent of the S1P3/Edg3 receptor capable of binding to sphingosine-1-phosphate ("S1P"); or
  (b) a membrane preparation of a recombinant cell in accordance with subsection (2)(a);

(3) separately contacting said cells or membrane preparations with the candidate compound; and

(4) determining whether the candidate compound binds to and activates the $S1P_1$/Edg1 and $S1P_3$/Edg3 receptors by measuring the level of a signal generated from the interaction of the candidate compound with each receptor, thereby indicating whether the candidate compound is an agonist of the $S1P_1$/Edg1 receptor that is selective over the $S1P_3$/Edg3 receptor.

Within this embodiment is encompassed the above method wherein the method further comprises conducting the method in the presence of labeled or unlabeled S1P, di-hydro S1P or a ligand for the S1P1/Edg1 and/or S1P3/Edg3 receptor; provided that if a ligand is utilized that is specific for either the S1P1/Edg1 or S1P3/Edg3 receptor, the receptor ligand utilized in the first receptor preparation is a ligand of the S1P1/Edg1 receptor and the ligand utilized in the second receptor preparation is a ligand of the S1P3/Edg 3 receptor; and provided, further, that the method would additionally comprise measuring the level of a signal generated from the interaction of the S1P, di-hydro S1P or ligand; wherein a compound that effects a reduction of the signal from the interaction of the S1P, di-hydro S1P or ligand, with the receptor and activates the SIP1/Edg1 receptor at a greater level than that obtained at the S1P3/Edg3 receptor is a selective agonist of the SIP1/Edg1 receptor.

Also within this embodiment is encompassed the above method wherein the signal indicates extracellular pH changes caused by receptor activation.

Also within this embodiment is encompassed the above method wherein the signal indicates levels of cAMP present within the cell.

Also within this embodiment is encompassed the above method wherein the signal indicates adenylate cyclase accumulation.

Also within this embodiment is encompassed the above method wherein the signal indicates Ca+ flux.

Also within this embodiment is encompassed the above method wherein the candidate compound has a selectivity for the $S1P_1$/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 200 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

Also within this embodiment is encompassed the above method wherein the candidate compound has a selectivity for the $S1P_1$/Edg1 receptor over the

S1P3/Edg3 receptor of at least 500 fold as measured by the ratio of EC_{50} for the S1P1/Edg1 receptor to the EC_{50} for the S1P3/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

Also within this embodiment is encompassed the above method wherein the candidate compound has a selectivity for the S1P1/Edg1 receptor over the S1P3/Edg3 receptor of at least 1000 fold as measured by the ratio of EC_{50} for the S1P1/Edg1 receptor to the EC_{50} for the S1PR3/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

Also within this embodiment is encompassed the above method wherein the candidate compound has a selectivity for the S1P1/Edg1 receptor over the S1P3/Edg3 receptor of at least 2000 fold as measured by the ratio of EC_{50} for the S1P1/Edg1 receptor to the EC_{50} for the S1P3/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

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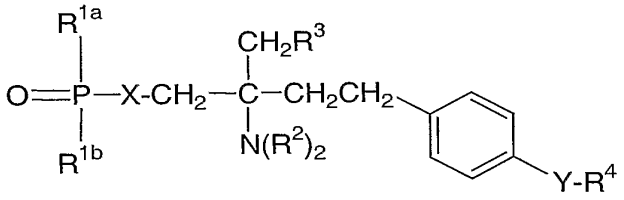
RESPIRATORY DISEASES

An embodiment of the invention encompasses a method of treating a respiratory disease or condition in a mammalian patient in need of such treatment comprising administering to said patient a compound which is an agonist of the $S1P_1$/Edg1 receptor in an amount effective for treating said respiratory disease or condition, wherein said compound possesses a selectivity for the S1P1/Edg1 receptor over the $S1PR_3$/Edg3 receptor of at least 20 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay and wherein said compound possesses an EC_{50} for binding to the $S1P_1$/Edg1 receptor of 100 nM or less as evaluated by the ^{35}S-GTPγS binding assay,

with the proviso that the compound does not fall within formula A:



A

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

X is O, S, NR^1 or $(CH_2)_{1-2}$, optionally substituted with 1-4 halo groups;

R^1 is H, C_{1-4}alkyl or haloC_{1-4} alkyl;

R^{1a} is H, OH, C_{1-4}alkyl, or OC_{1-4} alkyl, the alkyl and alkyl portions being optionally substituted with 1-3 halo groups;

R^{1b} represents H, OH, C_{1-4} alkyl or haloC_{1-4} alkyl;

each R^2 is independently selected from the group consisting of: H, C_{1-4} alkyl and haloC_{1-4} alkyl,

R^3 is H, OH, halo, C_{1-4}alkyl, OC_{1-4}alkyl, O-haloC_{1-4}alkyl or hydroxyC_{1-4}alkyl,

Y is selected from the group consisting of: $-CH_2-$, -C(O)-, -CH(OH)-, -C(=NOH)-, O and S, and

R^4 is selected from the group consisting of: C_{4-14}alkyl and C_{4-14}alkenyl.

Within this embodiment is encompassed the above method wherein the compound has a selectivity for the $S1P_1$/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 100 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

Also within this embodiment is encompassed the above method wherein the compound has a selectivity for the $S1P_1$/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 200 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

Also within this embodiment is encompassed the above method wherein the compound has a selectivity for the $S1P_1$/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 500 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

Also within this embodiment is encompassed the above method wherein the compound has a selectivity for the $S1P_1$/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 2000 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

The invention also encompasses a method of treating a respiratory disease or condition in a mammalian patient in need of such treatment comprising administering to said patient a compound which is an agonist of the $S1P_1$/Edg1 receptor in an amount effective for treating said respiratory disease or condition, wherein said compound possesses a selectivity for the S1P1/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 100 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay and wherein said compound possesses an EC_{50} for binding to the $S1P_1$/Edg1 receptor of 10 nM or less as evaluated by the ^{35}S-GTPγS binding assay.

Within this embodiment is encompassed the above method wherein the compound possesses an EC_{50} for binding to the $S1P_1$/Edg1 receptor of 1 nM or less as evaluated by the ^{35}S-GTPγS binding assay.

Also within this embodiment is encompassed the above method wherein the compound has a selectivity for the $S1P_1$/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 200 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

Also within this embodiment is encompassed the above method wherein the compound has a selectivity for the $S1P_1$/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 500 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

Also within this embodiment is encompassed the above method wherein the compound has a selectivity for the $S1P_1$/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 1000 fold as measured by the ratio of EC_{50} for the

$S1P_1$/Edg1 receptor to the EC_{50} for the S1PR3/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

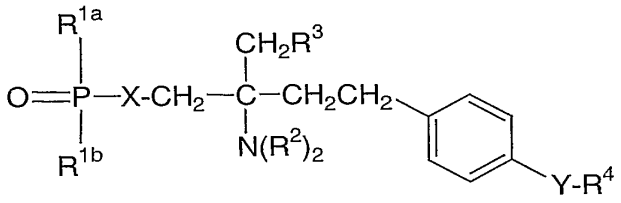
Also within this embodiment is encompassed the above method wherein the compound has a selectivity for the $S1P_1$/Edg1 receptor over the S1PR3/Edg3 receptor of at least 2000 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

The invention also encompasses any of the above embodiments wherein the respiratory disease or condition is selected from the group consisting of: asthma, chronic bronchitis, chronic obstructive pulmonary disease, adult respiratory distress syndrome, infant respiratory distress syndrome, cough, eosinophilic granuloma, respiratory syncytial virus bronchiolitis, bronchiectasis, idiopathic pulmonary fibrosis, acute lung injury and bronchiolitis obliterans organizing pneumonia.

Another embodiment of the invention encompasses any of the above embodiments further comprising concomitantly or sequentially administering one or more agents selected from the group consisting of: a Leukotriene receptor antagonist, a Leukotriene biosynthesis inhibitor, an M2/M3 antagonist, phosphodiesterase 4 inhibitor, calcium activated chloride channel 1 agonist, a corticosteroid, an H1 receptor antagonist, a beta 2 adrenoreceptor agonist and a prostaglandin D2 antagonist. These compounds are well known in the art.

The invention also encompasses a method of modulating airway function in a mammalian patient in need thereof comprising administering to said patient a compound which is an agonist of the $S1P_1$/Edg1 receptor in an amount effective for modulating airway function, wherein said compound possesses a selectivity for the S1P1/Edg1 receptor over the S1PR3/Edg3 receptor of at least 20 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay and wherein said compound possesses an EC_{50} for binding to the $S1P_1$/Edg1 receptor of 100 nM or less as evaluated by the ^{35}S-GTPγS binding assay,

with the proviso that the compound does not fall within formula A:



A

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

X is O, S, NR^1 or $(CH_2)_{1-2}$, optionally substituted with 1-4 halo groups;

R^1 is H, C_{1-4}alkyl or haloC_{1-4} alkyl;

R^{1a} is H, OH, C_{1-4}alkyl, or OC_{1-4} alkyl, the alkyl and alkyl portions being optionally substituted with 1-3 halo groups;

R^{1b} represents H, OH, C_{1-4} alkyl or haloC_{1-4} alkyl;

each R^2 is independently selected from the group consisting of: H, C_{1-4} alkyl and haloC_{1-4} alkyl,

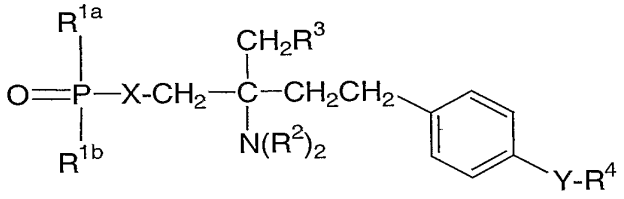
R^3 is H, OH, halo, C_{1-4}alkyl, OC_{1-4}alkyl, O-haloC_{1-4}alkyl or hydroxyC_{1-4}alkyl,

Y is selected from the group consisting of: $-CH_2-$, -C(O)-, -CH(OH)-, -C(=NOH)-, O and S, and

R^4 is selected from the group consisting of: C_{4-14}alkyl and C_{4-14}alkenyl.

The invention also encompasses a method of reducing or preventing the activation of the S1P1/Edg1 receptor in a mammalian patient in need thereof comprising administering to said patient a compound which is an agonist of the $S1P_1$/Edg1 receptor in an amount effective for reducing or preventing the activation of S1P1/EDG1 receptor, wherein said compound possesses a selectivity for the S1P1/Edg1 receptor over the S1PR3/Edg3 receptor of at least 20 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay and wherein said compound possesses an EC_{50} for binding to the $S1P_1$/Edg1 receptor of 100 nM or less as evaluated by the ^{35}S-GTPγS binding assay,

with the proviso that the compound does not fall within formula A:



A

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

X is O, S, NR^1 or $(CH_2)_{1-2}$, optionally substituted with 1-4 halo groups;

R^1 is H, C_{1-4}alkyl or haloC_{1-4} alkyl;

R^{1a} is H, OH, C_{1-4}alkyl, or OC_{1-4} alkyl, the alkyl and alkyl portions being optionally substituted with 1-3 halo groups;

R^{1b} represents H, OH, C_{1-4} alkyl or haloC_{1-4} alkyl;

each R^2 is independently selected from the group consisting of: H, C_{1-4} alkyl and haloC_{1-4} alkyl,

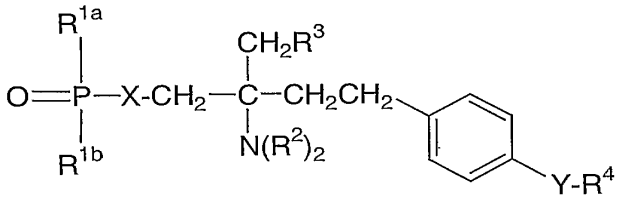
R^3 is H, OH, halo, C_{1-4}alkyl, OC_{1-4}alkyl, O-haloC_{1-4}alkyl or hydroxyC_{1-4}alkyl,

Y is selected from the group consisting of: $-CH_2-$, -C(O)-, -CH(OH)-, -C(=NOH)-, O and S, and

R^4 is selected from the group consisting of: C_{4-14}alkyl and C_{4-14}alkenyl.

The invention also encompasses a method of inhibiting an infiltration of a lymphocyte into a respiratory tissue in a mammalian patient in need thereof by promoting a sequestration of the lymphocyte in a lymph node thereby preventing release of a pro-inflammatory mediator in the respiratory tissue comprising administering to said patient a compound which is an agonist of the $S1P_1$/Edg1 receptor in an amount effective for modulating airway function, wherein said compound possesses a selectivity for the S1P1/Edg1 receptor over the S1PR3/Edg3 receptor of at least 20 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay and wherein said compound possesses an EC_{50} for binding to the $S1P_1$/Edg1 receptor of 100 nM or less as evaluated by the ^{35}S-GTPγS binding assay,

with the proviso that the compound does not fall within formula A:



A

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

X is O, S, NR^1 or $(CH_2)_{1-2}$, optionally substituted with 1-4 halo groups;

R^1 is H, C_{1-4}alkyl or haloC_{1-4} alkyl;

R^{1a} is H, OH, C_{1-4}alkyl, or OC_{1-4} alkyl, the alkyl and alkyl portions being optionally substituted with 1-3 halo groups;

R^{1b} represents H, OH, C_{1-4} alkyl or haloC_{1-4} alkyl;

each R^2 is independently selected from the group consisting of: H, C_{1-4} alkyl and haloC_{1-4} alkyl,

R^3 is H, OH, halo, C_{1-4}alkyl, OC_{1-4}alkyl, O-haloC_{1-4}alkyl or hydroxyC_{1-4}alkyl,

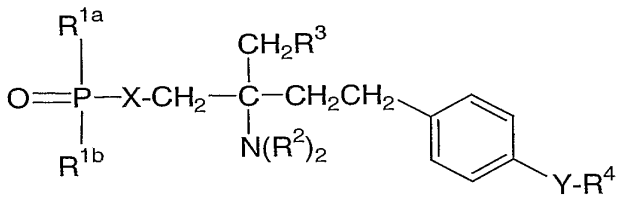
Y is selected from the group consisting of: $-CH_2-$, -C(O)-, -CH(OH)-, -C(=NOH)-, O and S, and

R^4 is selected from the group consisting of: C_{4-14}alkyl and C_{4-14}alkenyl.

WHAT IS CLAIMED IS:

1. A method of treating an immunoregulatory abnormality in a mammalian patient in need of such treatment comprising administering to said patient a compound which is an agonist of the $S1P_1$/Edg1 receptor in an amount effective for treating said immunoregulatory abnormality, wherein said compound possesses a selectivity for the S1P1/Edg1 receptor over the $S1PR_3$/Edg3 receptor of at least 20 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay and wherein said compound possesses an EC_{50} for binding to the $S1P_1$/Edg1 receptor of 100 nM or less as evaluated by the ^{35}S-GTPγS binding assay,

with the proviso that the compound does not fall within formula A:



A

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

X is O, S, NR^1 or $(CH_2)_{1-2}$, optionally substituted with 1-4 halo groups;

R^1 is H, C_{1-4}alkyl or haloC_{1-4} alkyl;

R^{1a} is H, OH, C_{1-4}alkyl, or OC_{1-4} alkyl, the alkyl and alkyl portions being optionally substituted with 1-3 halo groups;

R^{1b} represents H, OH, C_{1-4} alkyl or haloC_{1-4} alkyl;

each R^2 is independently selected from the group consisting of: H, C_{1-4} alkyl and haloC_{1-4} alkyl,

R^3 is H, OH, halo, C_{1-4}alkyl, OC_{1-4}alkyl, O-haloC_{1-4}alkyl or hydroxyC_{1-4}alkyl,

Y is selected from the group consisting of: $-CH_2-$, -C(O)-, -CH(OH)-, -C(=NOH)-, O and S, and

R^4 is selected from the group consisting of: C_{4-14}alkyl and C_{4-14}alkenyl.

2. The method according to Claim 1 wherein the compound has a selectivity for the $S1P_1$/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 100 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

3. The method according to Claim 2 wherein the compound has a selectivity for the $S1P_1$/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 200 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

4. The method according to Claim 3 wherein the compound has a selectivity for the $S1P_1$/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 500 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

5. The method according to Claim 4 wherein the compound has a selectivity for the $S1P_1$/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 2000

fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

6. A method of treating an immunoregulatory abnormality in a mammalian patient in need of such treatment comprising administering to said patient a compound which is an agonist of the $S1P_1$/Edg1 receptor in an amount effective for treating said immunoregulatory abnormality, wherein said compound possesses a selectivity for the S1P1/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 100 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay and wherein said compound possesses an EC_{50} for binding to the $S1P_1$/Edg1 receptor of 10 nM or less as evaluated by the ^{35}S-GTPγS binding assay.

7. The method according to Claim 6 wherein the compound possesses an EC_{50} for binding to the $S1P_1$/Edg1 receptor of 1 nM or less as evaluated by the ^{35}S-GTPγS binding assay.

8. The method according to Claim 6 wherein the compound has a selectivity for the $S1P_1$/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 200 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

9. The method according to Claim 8 wherein the compound has a selectivity for the $S1P_1$/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 500 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

10. The method according to Claim 9 wherein the compound has a selectivity for the $S1P_1$/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 1000 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1PR_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

11. The method according to Claim 10 wherein the compound has a selectivity for the $S1P_1$/Edg1 receptor over the $S1PR_3$/Edg3 receptor of at least 2000 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

12. The method according to Claim 1 wherein the immunoregulatory abnormality is an autoimmune or chronic inflammatory disease selected from the group consisting of: systemic lupus erythematosis, chronic rheumatoid arthritis, type I diabetes mellitus, inflammatory bowel disease, biliary cirrhosis, uveitis, multiple sclerosis, Crohn's disease, ulcerative colitis, bullous pemphigoid, sarcoidosis, psoriasis, autoimmune myositis, Wegener's granulomatosis, ichthyosis, Graves ophthalmopathy and asthma.

13. The method according to Claim 1 wherein the immunoregulatory abnormality is bone marrow or organ transplant rejection or graft-versus-host disease.

14. The method according to Claim 1 wherein the immunoregulatory abnormality is selected from the group consisting of: transplantation of organs or tissue, graft-versus-host diseases brought about by transplantation, autoimmune syndromes including rheumatoid arthritis, systemic lupus erythematosus, Hashimoto's thyroiditis, multiple sclerosis, myasthenia gravis, type I diabetes, uveitis, posterior uveitis, allergic encephalomyelitis, glomerulonephritis, post-infectious autoimmune diseases including rheumatic fever and post-infectious glomerulonephritis, inflammatory and hyperproliferative skin diseases, psoriasis, atopic dermatitis, contact dermatitis, eczematous dermatitis, seborrhoeic dermatitis, lichen planus, pemphigus, bullous pemphigoid, epidermolysis bullosa, urticaria, angioedemas, vasculitis, erythema, cutaneous eosinophilia, lupus erythematosus, acne, alopecia areata, keratoconjunctivitis, vernal conjunctivitis, uveitis associated with Behcet's disease, keratitis, herpetic keratitis, conical cornea, dystrophia epithelialis corneae, corneal leukoma, ocular pemphigus, Mooren's ulcer, scleritis, Graves' opthalmopathy, Vogt-Koyanagi-Harada syndrome, sarcoidosis, pollen allergies,

reversible obstructive airway disease, bronchial asthma, allergic asthma, intrinsic asthma, extrinsic asthma, dust asthma, chronic or inveterate asthma, late asthma and airway hyper-responsiveness, bronchitis, gastric ulcers, vascular damage caused by ischemic diseases and thrombosis, ischemic bowel diseases, inflammatory bowel diseases, necrotizing enterocolitis, intestinal lesions associated with thermal burns, coeliac diseases, proctitis, eosinophilic gastroenteritis, mastocytosis, Crohn's disease, ulcerative colitis, migraine, rhinitis, eczema, interstitial nephritis, Goodpasture's syndrome, hemolytic-uremic syndrome, diabetic nephropathy, multiple myositis, Guillain-Barre syndrome, Meniere's disease, polyneuritis, multiple neuritis, mononeuritis, radiculopathy, hyperthyroidism, Basedow's disease, pure red cell aplasia, aplastic anemia, hypoplastic anemia, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, agranulocytosis, pernicious anemia, megaloblastic anemia, anerythroplasia, osteoporosis, sarcoidosis, fibroid lung, idiopathic interstitial pneumonia, dermatomyositis, leukoderma vulgaris, ichthyosis vulgaris, photoallergic sensitivity, cutaneous T cell lymphoma, chronic lymphocytic leukemia, arteriosclerosis, atherosclerosis, aortitis syndrome, polyarteritis nodosa, myocardosis, scleroderma, Wegener's granuloma, Sjogren's syndrome, adiposis, eosinophilic fascitis, lesions of gingiva, periodontium, alveolar bone, substantia ossea dentis, glomerulonephritis, male pattern alopecia or alopecia senilis by preventing epilation or providing hair germination and/or promoting hair generation and hair growth, muscular dystrophy, pyoderma and Sezary's syndrome, Addison's disease, ischemia-reperfusion injury of organs which occurs upon preservation, transplantation or ischemic disease, endotoxin-shock, pseudomembranous colitis, colitis caused by drug or radiation, ischemic acute renal insufficiency, chronic renal insufficiency, toxinosis caused by lung-oxygen or drugs, lung cancer, pulmonary emphysema, cataracta, siderosis, retinitis pigmentosa, senile macular degeneration, vitreal scarring, corneal alkali burn, dermatitis erythema multiforme, linear IgA ballous dermatitis and cement dermatitis, gingivitis, periodontitis, sepsis, pancreatitis, diseases caused by environmental pollution, aging, carcinogenesis, metastasis of carcinoma and hypobaropathy, disease caused by histamine or leukotriene-C_4 release, Behcet's disease, autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis, partial liver resection, acute liver necrosis, necrosis caused by toxin, viral hepatitis, shock, or anoxia, B-virus hepatitis, non-A/non-B hepatitis, cirrhosis, alcoholic cirrhosis, hepatic

failure, fulminant hepatic failure, late-onset hepatic failure, "acute-on-chronic" liver failure, augmentation of chemotherapeutic effect, cytomegalovirus infection, HCMV infection, AIDS, cancer, senile dementia, trauma, and chronic bacterial infection.

15. The method according to Claim 1 wherein the immunoregulatory abnormality is multiple sclerosis.

16. The method according to Claim 1 wherein the immunoregulatory abnormality is rheumatoid arthritis.

17. The method according to Claim 1 wherein the immunoregulatory abnormality is systemic lupus erythematosus.

18. The method according to Claim 1 wherein the immunoregulatory abnormality is psoriasis.

19. The method according to Claim 1 wherein the immunoregulatory abnormality is rejection of transplanted organ or tissue.

20. The method according to Claim 1 wherein the immunoregulatory abnormality is inflammatory bowel disease.

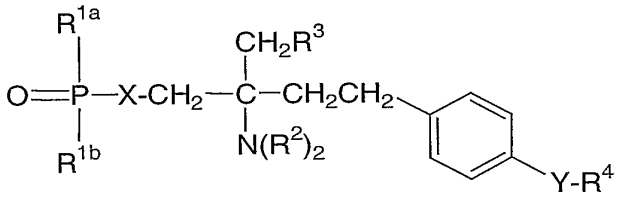
21. The method according to Claim 1 wherein the immunoregulatory abnormality is a malignancy of lymphoid origin.

22. The method according to Claim 21 wherein the immunoregulatory abnormality is acute and chronic lymphocytic leukemias and lymphomas.

23. A pharmaceutical composition comprised of a compound which is an agonist of the $S1P_1$/Edg1 receptor in an amount effective for treating an immunoregulatory abnormality, wherein said compound possesses a selectivity for the S1P1/Edg1 receptor over the $S1PR_3$/Edg3 receptor of at least 20 fold as measured by

the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay and wherein said compound possesses an EC_{50} for binding to the $S1P_1$/Edg1 receptor of 100 nM or less as evaluated by the ^{35}S-GTPγS binding assay,

with the proviso that the compound does not fall within formula A:



A

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

X is O, S, NR^1 or $(CH_2)_{1-2}$, optionally substituted with 1-4 halo groups;

R^1 is H, C_{1-4}alkyl or haloC_{1-4} alkyl;

R^{1a} is H, OH, C_{1-4}alkyl, or OC_{1-4} alkyl, the alkyl and alkyl portions being optionally substituted with 1-3 halo groups;

R^{1b} represents H, OH, C_{1-4} alkyl or haloC_{1-4} alkyl;

each R^2 is independently selected from the group consisting of: H, C_{1-4} alkyl and haloC_{1-4} alkyl,

R^3 is H, OH, halo, C_{1-4}alkyl, OC_{1-4}alkyl, O-haloC_{1-4}alkyl or hydroxyC_{1-4}alkyl,

Y is selected from the group consisting of: -CH_2-, -C(O)-, -CH(OH)-, -C(=NOH)-, O and S, and

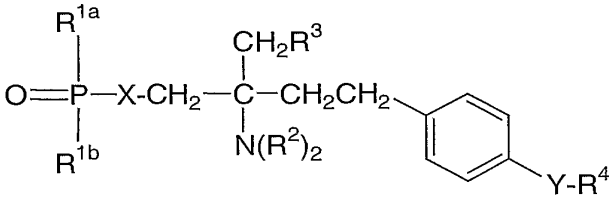
R^4 is selected from the group consisting of: C_{4-14}alkyl and C_{4-14}alkenyl,

in combination with a pharmaceutically acceptable carrier.

24. A pharmaceutical composition comprised of a compound which is an agonist of the $S1P_1$/Edg1 receptor in an amount effective for treating an immunoregulatory abnormality, wherein said compound possesses a selectivity for the S1P1/Edg1 receptor over the S1PR3/Edg3 receptor of at least 100 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay and wherein said compound possesses an EC_{50} for binding to the $S1P_1$/Edg1 receptor of 10 nM or less as evaluated by the ^{35}S-GTPγS binding assay, in combination with a pharmaceutically acceptable carrier.

25. A method of identifying a candidate compound which is an agonist of the $S1P_1$/Edg1 receptor that is selective over the $S1P_3$/Edg3 receptor, wherein said candidate compound possesses a selectivity for the $S1P_1$/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 20 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay and wherein said candidate compound possesses an EC_{50} for binding to the $S1P_1$/Edg1 receptor of 100 nM or less as evaluated by the ^{35}S-GTPγS binding assay,

with the proviso that the candidate compound does not fall within formula A:



A

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

X is O, S, NR^1 or $(CH_2)_{1-2}$, optionally substituted with 1-4 halo groups;

R^1 is H, C_{1-4}alkyl or haloC_{1-4} alkyl;

R^{1a} is H, OH, C_{1-4}alkyl, or OC_{1-4} alkyl, the alkyl and alkyl portions being optionally substituted with 1-3 halo groups;

R^{1b} represents H, OH, C_{1-4} alkyl or haloC_{1-4} alkyl;

each R^2 is independently selected from the group consisting of: H, C_{1-4} alkyl and haloC_{1-4} alkyl,

R^3 is H, OH, halo, C_{1-4}alkyl, OC_{1-4}alkyl, O-haloC_{1-4}alkyl or hydroxyC_{1-4}alkyl,

Y is selected from the group consisting of: $-CH_2-$, -C(O)-, -CH(OH)-, -C(=NOH)-, O and S, and

R^4 is selected from the group consisting of: C_{4-14}alkyl and C_{4-14}alkenyl,

comprising:

(1) providing a first receptor preparation comprising:
(a) a recombinant cell expressing the $S1P_1$/Edg1 receptor or a functional equivalent of the $S1P_1$/Edg1 receptor capable of binding to sphingosine-1-phosphate ("S1P"); or
(b) a membrane preparation of a recombinant cell in accordance with subsection (1)(a);

(2) providing a second receptor preparation comprising:
(a) a recombinant cell expressing the $S1P_3$/Edg3 receptor or a functional equivalent of the $S1P_3$/Edg3 receptor capable of binding to sphingosine-1-phosphate ("S1P"); or
(b) a membrane preparation of a recombinant cell in accordance with subsection (2)(a);

(3) separately contacting said cells or membrane preparations with the candidate compound; and

(4) determining whether the candidate compound binds to and activates the $S1P_1$/Edg1 and $S1P_3$/Ed3 receptors by measuring the level of a signal generated from the interaction of the candidate compound with each receptor, thereby indicating whether the candidate compound is an agonist of the $S1P_1$/Edg1 receptor that is selective over the $S1P_3$/Edg3 receptor.

26. A method in accordance with claim 25 wherein the method further comprises conducting the method in the presence of labeled or unlabeled S1P, di-hydro S1P or a ligand for the S1P1/Edg1 and/or S1P3/Edg3 receptor; provided that if a ligand is utilized that is specific for either the S1P1/Edg1 or S1P3/Edg3 receptor, the receptor ligand utilized in the first receptor preparation is a ligand of the S1P1/Edg1 receptor and the ligand utilized in the second receptor preparation is a ligand of the S1P3/Edg3 receptor; and provided, further, that the method would additionally comprise measuring the level of a signal generated from the interaction of the S1P, di-

hydro S1P or ligand; wherein a compound that effects a reduction of the signal from the interaction of the S1P, di-hydro S1P or ligand, with the receptor and activates the S1P1/Edg1 receptor at a greater level than that obtained at the S1P3/Edg3 receptor is a selective agonist of the S1P1/Edg1 receptor.

27. A method in accordance with claim 25 wherein the signal indicates extracellular pH changes caused by receptor activation.

28. A method in accordance with claim 25 wherein the signal indicates levels of cAMP present within the cell.

29. A method in accordance with claim 25 wherein the signal indicates adenylate cyclase accumulation.

30. A method in accordance with claim 25 wherein the signal indicates Ca+ flux.

31. The method according to Claim 25 wherein the candidate compound has a selectivity for the $S1P_1$/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 100 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

32. The method according to Claim 31 wherein the candidate compound has a selectivity for the $S1P_1$/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 200 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

33. The method according to Claim 32 wherein the candidate compound has a selectivity for the $S1P_1$/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 500 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

34. The method according to Claim 33 wherein the candidate compound has a selectivity for the $S1P_1$/Edg1 receptor over the S1P3/Edg3 receptor of at least 2000 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

35. The method according to Claim 25 wherein the candidate compound possesses an EC_{50} for binding to the $S1P_1$/Edg1 receptor of 1 nM or less as evaluated by the ^{35}S-GTPγS binding assay.

36. A method of identifying a candidate compound which is an agonist of the $S1P_1$/Edg1 receptor that is selective over the S1P3/Edg3 receptor, wherein said candidate compound possesses a selectivity for the S1P1/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 100 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay and wherein said candidate compound possesses an EC_{50} for binding to the $S1P_1$/Edg1 receptor of 10 nM or less as evaluated by the ^{35}S-GTPγS binding assay, comprising:

(1) providing a first receptor preparation comprising:
   (a) a recombinant cell expressing the S1P1/Edg1 receptor or a functional equivalent of the S1P1/Edg1 receptor capable of binding to sphingosine-1-phosphate ("S1P"); or
   (b) a membrane preparation of a recombinant cell in accordance with subsection (1)(a);

(2) providing a second receptor preparation comprising:
   (a) a recombinant cell expressing the S1P3/Edg3 receptor or a functional equivalent of the S1P3/Edg3 receptor capable of binding to sphingosine-1-phosphate ("S1P"); or
   (b) a membrane preparation of a recombinant cell in accordance with subsection (2)(a);

(3) separately contacting said cells or membrane preparations with the candidate compound; and

(4) determining whether the candidate compound binds to and activates the $S1P_1$/Edg1 and $S1P_3$/Ed3 receptors by measuring the level of a signal generated from the interaction of the candidate compound with each receptor, thereby indicating whether the candidate compound is an agonist of the $S1P_1$/Edg1 receptor that is selective over the $S1P_3$/Edg3 receptor.

37. A method in accordance with claim 36 wherein the method further comprises conducting the method in the presence of labeled or unlabeled S1P, di-hydro S1P or a ligand for the S1P1/Edg1 and/or S1P3/Edg3 receptor; provided that if a ligand is utilized that is specific for either the S1P1/Edg1 or S1P3/Edg3 receptor, the receptor ligand utilized in the first receptor preparation is a ligand of the S1P1/Edg1 receptor and the ligand utilized in the second receptor preparation is a ligand of the S1P3/Edg 3 receptor; and provided, further, that the method would additionally comprise measuring the level of a signal generated from the interaction of the S1P, di-hydro S1P or ligand; wherein a compound that effects a reduction of the signal from the interaction of the S1P, di-hydro S1P or ligand, with the receptor and activates the SIP1/Edg1 receptor at a greater level than that obtained at the S1P3/Edg3 receptor is a selective agonist of the SIP1/Edg1 receptor.

38. A method in accordance with claim 36 wherein the signal indicates extracellular pH changes caused by receptor activation.

39. A method in accordance with claim 36 wherein the signal indicates levels of cAMP present within the cell.

40. A method in accordance with claim 36 wherein the signal indicates adenylate cyclase accumulation.

41. A method in accordance with claim 36 wherein the signal indicates Ca+ flux.

42. The method according to Claim 36 wherein the candidate compound has a selectivity for the $S1P_1$/Edg1 receptor over the S1P3/Edg3 receptor of at least 200 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the S1P3/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

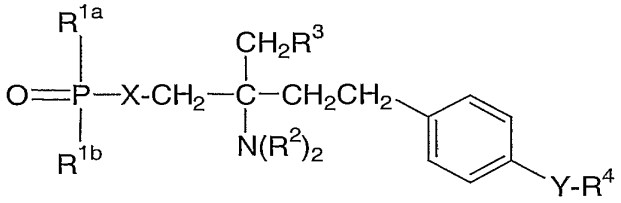
43. The method according to Claim 42 wherein the candidate compound has a selectivity for the $S1P_1$/Edg1 receptor over the S1P3/Edg3 receptor of at least 500 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the S1P3/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

44. The method according to Claim 43 wherein the candidate compound has a selectivity for the $S1P_1$/Edg1 receptor over the S1P3/Edg3 receptor of at least 1000 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the S1PR3/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

45. The method according to Claim 44 wherein the candidate compound has a selectivity for the $S1P_1$/Edg1 receptor over the S1P3/Edg3 receptor of at least 2000 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the S1P3/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

46. A method of treating a respiratory disease or condition in a mammalian patient in need of such treatment comprising administering to said patient a compound which is an agonist of the $S1P_1$/Edg1 receptor in an amount effective for treating said respiratory disease or condition, wherein said compound possesses a selectivity for the S1P1/Edg1 receptor over the S1PR3/Edg3 receptor of at least 20 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the S1P3/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay and wherein said compound possesses an EC_{50} for binding to the $S1P_1$/Edg1 receptor of 100 nM or less as evaluated by the ^{35}S-GTPγS binding assay,

with the proviso that the compound does not fall within formula A:



A

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

X is O, S, NR^1 or $(CH_2)_{1-2}$, optionally substituted with 1-4 halo groups;

R^1 is H, C_{1-4}alkyl or haloC_{1-4} alkyl;

R^{1a} is H, OH, C_{1-4}alkyl, or OC_{1-4} alkyl, the alkyl and alkyl portions being optionally substituted with 1-3 halo groups;

R^{1b} represents H, OH, C_{1-4} alkyl or haloC_{1-4} alkyl;

each R^2 is independently selected from the group consisting of: H, C_{1-4} alkyl and haloC_{1-4} alkyl,

R^3 is H, OH, halo, C_{1-4}alkyl, OC_{1-4}alkyl, O-haloC_{1-4}alkyl or hydroxyC_{1-4}alkyl,

Y is selected from the group consisting of: $-CH_2-$, -C(O)-, -CH(OH)-, -C(=NOH)-, O and S, and

R^4 is selected from the group consisting of: C_{4-14}alkyl and C_{4-14}alkenyl.

47. The method according to Claim 46 wherein the compound has a selectivity for the S1P1/Edg1 receptor over the S1P3/Edg3 receptor of at least 100 fold as measured by the ratio of EC_{50} for the S1P1/Edg1 receptor to the EC_{50} for the S1P3/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

48. The method according to Claim 47 wherein the compound has a selectivity for the S1P1/Edg1 receptor over the S1P3/Edg3 receptor of at least 200 fold as measured by the ratio of EC_{50} for the S1P1/Edg1 receptor to the EC_{50} for the S1P3/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

49. The method according to Claim 48 wherein the compound has a selectivity for the S1P1/Edg1 receptor over the S1P3/Edg3 receptor of at least 500 fold as measured by the ratio of EC_{50} for the S1P1/Edg1 receptor to the EC_{50} for the S1P3/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

50. The method according to Claim 49 wherein the compound has a selectivity for the S1P1/Edg1 receptor over the S1P3/Edg3 receptor of at least 2000 fold as measured by the ratio of EC_{50} for the S1P1/Edg1 receptor to the EC_{50} for the S1P3/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

51. A method of treating a respiratory disease or condition in a mammalian patient in need of such treatment comprising administering to said patient a compound which is an agonist of the S1P1/Edg1 receptor in an amount effective for treating said respiratory disease or condition, wherein said compound possesses a selectivity for the S1P1/Edg1 receptor over the S1P3/Edg3 receptor of at least 100 fold as measured by the ratio of EC_{50} for the S1P1/Edg1 receptor to the EC_{50} for the S1P3/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay and wherein said compound possesses an EC_{50} for binding to the S1P1/Edg1 receptor of 10 nM or less as evaluated by the ^{35}S-GTPγS binding assay.

52. The method according to Claim 51 wherein the compound possesses an EC_{50} for binding to the $S1P_1$/Edg1 receptor of 1 nM or less as evaluated by the ^{35}S-GTPγS binding assay.

53. The method according to Claim 52 wherein the compound has a selectivity for the $S1P_1$/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 200 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

54. The method according to Claim 53 wherein the compound has a selectivity for the $S1P_1$/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 500 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

55. The method according to Claim 54 wherein the compound has a selectivity for the $S1P_1$/Edg1 receptor over the $S1P_3$/Edg3 receptor of at least 1000 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1PR_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

56. The method according to Claim 55 wherein the compound has a selectivity for the $S1P_1$/Edg1 receptor over the $S1PR_3$/Edg3 receptor of at least 2000 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay.

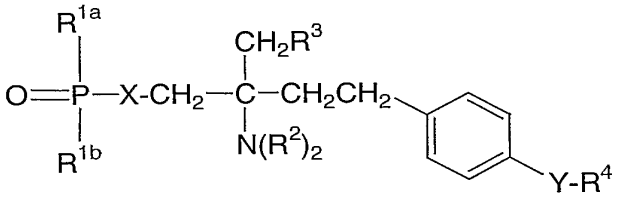
57. The method according to Claim 46 wherein the respiratory disease or condition is selected from the group consisting of: asthma, chronic bronchitis, chronic obstructive pulmonary disease, adult respiratory distress syndrome, infant respiratory distress syndrome, cough, eosinophilic granuloma, respiratory syncytial virus bronchiolitis, bronchiectasis, idiopathic pulmonary fibrosis, acute lung injury and bronchiolitis obliterans organizing pneumonia.

58. The method according to Claim 46 further comprising concomitantly or sequentially administering one or more agents selected from the

group consisting of: a Leukotriene receptor antagonist, a Leukotriene biosynthesis inhibitor, an M2/M3 antagonist, phosphodiesterase 4 inhibitor, calcium activated chloride channel 1 agonist, a corticosteroid, an H1 receptor antagonist, a beta 2 adrenoreceptor agonist and a prostaglandin D2 antagonist.

59. A method of modulating airway function in a mammalian patient in need thereof comprising administering to said patient a compound which is an agonist of the $S1P_1$/Edg1 receptor in an amount effective for modulating airway function, wherein said compound possesses a selectivity for the S1P1/Edg1 receptor over the S1PR3/Edg3 receptor of at least 20 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay and wherein said compound possesses an EC_{50} for binding to the $S1P_1$/Edg1 receptor of 100 nM or less as evaluated by the ^{35}S-GTPγS binding assay,

with the proviso that the compound does not fall within formula A:



A

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

X is O, S, NR^1 or $(CH_2)_{1-2}$, optionally substituted with 1-4 halo groups;

R^1 is H, C_{1-4}alkyl or haloC_{1-4} alkyl;

R^{1a} is H, OH, C_{1-4}alkyl, or OC_{1-4} alkyl, the alkyl and alkyl portions being optionally substituted with 1-3 halo groups;

R^{1b} represents H, OH, C_{1-4} alkyl or haloC_{1-4} alkyl;

each R^2 is independently selected from the group consisting of: H, C_{1-4} alkyl and haloC_{1-4} alkyl,

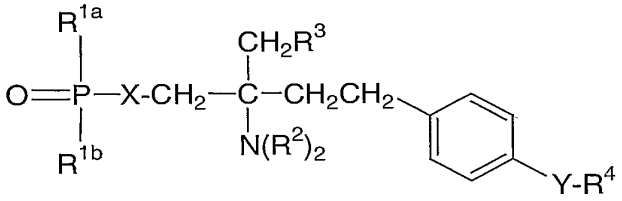
R^3 is H, OH, halo, C_{1-4}alkyl, OC_{1-4}alkyl, O-haloC_{1-4}alkyl or hydroxyC_{1-4}alkyl,

Y is selected from the group consisting of: $-CH_2-$, -C(O)-, -CH(OH)-, -C(=NOH)-, O and S, and

R^4 is selected from the group consisting of: C_{4-14}alkyl and C_{4-14}alkenyl.

60. A method of reducing or preventing the activation of the S1P1/Edg1 receptor in a mammalian patient in need thereof comprising administering to said patient a compound which is an agonist of the $S1P_1$/Edg1 receptor in an amount effective for reducing or preventing the activation of S1P1/Edg1 receptor, wherein said compound possesses a selectivity for the S1P1/Edg1 receptor over the $S1PR_3$/Edg3 receptor of at least 20 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay and wherein said compound possesses an EC_{50} for binding to the $S1P_1$/Edg1 receptor of 100 nM or less as evaluated by the ^{35}S-GTPγS binding assay,

with the proviso that the compound does not fall within formula A:



A

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

X is O, S, NR^1 or $(CH_2)_{1-2}$, optionally substituted with 1-4 halo groups;

R^1 is H, C_{1-4}alkyl or haloC_{1-4} alkyl;

R^{1a} is H, OH, C_{1-4}alkyl, or OC_{1-4} alkyl, the alkyl and alkyl portions being optionally substituted with 1-3 halo groups;

R^{1b} represents H, OH, C_{1-4} alkyl or haloC_{1-4} alkyl;

each R^2 is independently selected from the group consisting of: H, C_{1-4} alkyl and haloC_{1-4} alkyl,

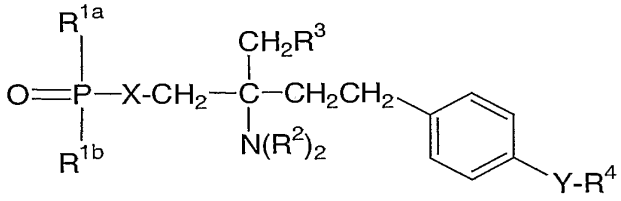
R^3 is H, OH, halo, C_{1-4}alkyl, OC_{1-4}alkyl, O-haloC_{1-4}alkyl or hydroxyC_{1-4}alkyl,

Y is selected from the group consisting of: $-CH_2-$, -C(O)-, -CH(OH)-, -C(=NOH)-, O and S, and

R^4 is selected from the group consisting of: C_{4-14}alkyl and C_{4-14}alkenyl.

61. A method of inhibiting an infiltration of a lymphocyte into a respiratory tissue in a mammalian patient in need thereof by promoting a sequestration of the lymphocyte in a lymph node thereby preventing release of a pro-inflammatory mediator in the respiratory tissue comprising administering to said patient a compound which is an agonist of the $S1P_1$/Edg1 receptor in an amount effective for modulating airway function, wherein said compound possesses a selectivity for the S1P1/Edg1 receptor over the $S1PR_3$/Edg3 receptor of at least 20 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay and wherein said compound possesses an EC_{50} for binding to the $S1P_1$/Edg1 receptor of 100 nM or less as evaluated by the ^{35}S-GTPγS binding assay,

with the proviso that the compound does not fall within formula A:



A

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

X is O, S, NR^1 or $(CH_2)_{1-2}$, optionally substituted with 1-4 halo groups;

R^1 is H, C_{1-4}alkyl or haloC_{1-4} alkyl;

R^{1a} is H, OH, C_{1-4}alkyl, or OC_{1-4} alkyl, the alkyl and alkyl portions being optionally substituted with 1-3 halo groups;

R^{1b} represents H, OH, C_{1-4} alkyl or haloC_{1-4} alkyl;

each R^2 is independently selected from the group consisting of: H, C_{1-4} alkyl and haloC_{1-4} alkyl,

R^3 is H, OH, halo, C_{1-4}alkyl, OC_{1-4}alkyl, O-haloC_{1-4}alkyl or hydroxyC_{1-4}alkyl,

Y is selected from the group consisting of: $-CH_2-$, -C(O)-, -CH(OH)-, -C(=NOH)-, O and S, and

R^4 is selected from the group consisting of: C_{4-14}alkyl and C_{4-14}alkenyl.

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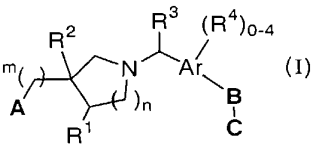
(54) Title: EDG RECEPTOR AGONISTS



(I)

(57) Abstract: The present invention encompasses compounds of Formula I: as well as the pharmaceutically acceptable salts and hydrates thereof. The compounds are useful for treating immune mediated diseases and conditions, such as bone marrow, organ and tissue transplant rejection. Pharmaceutical compositions and methods of use are included.

TITLE OF THE INVENTION

EDG RECEPTOR AGONISTS

BACKGROUND OF THE INVENTION

The present invention is related to compounds that are $S1P_1$/Edg1 receptor agonists and thus have immunosuppressive activities by producing lymphocyte sequestration in secondary lymphoid tissues. The invention is also directed to pharmaceutical compositions containing such compounds and methods of treatment or prevention.

Immunosuppressive agents have been shown to be useful in a wide variety of autoimmune and chronic inflammatory diseases, including systemic lupus erythematosis, chronic rheumatoid arthritis, type I diabetes mellitus, inflammatory bowel disease, biliary cirrhosis, uveitis, multiple sclerosis and other disorders such as Crohn's disease, ulcerative colitis, bullous pemphigoid, sarcoidosis, psoriasis, autoimmune myositis, Wegener's granulomatosis, ichthyosis, Graves ophthalmopathy, atopic dermatitis and asthma. They have also proved useful as part of chemotherapeutic regimens for the treatment of cancers, lymphomas and leukemias.

Although the underlying pathogenesis of each of these conditions may be quite different, they have in common the appearance of a variety of autoantibodies and/or self-reactive lymphocytes. Such self-reactivity may be due, in part, to a loss of the homeostatic controls under which the normal immune system operates. Similarly, following a bone-marrow or an organ transplantation, the host lymphocytes recognize the foreign tissue antigens and begin to produce both cellular and humoral responses including antibodies, cytokines and cytotoxic lymphocytes which lead to graft rejection.

One end result of an autoimmune or a rejection process is tissue destruction caused by inflammatory cells and the mediators they release. Anti-inflammatory agents such as NSAIDs act principally by blocking the effect or secretion of these mediators but do nothing to modify the immunologic basis of the disease. On the other hand, cytotoxic agents, such as cyclophosphamide, act in such a nonspecific fashion that both the normal and autoimmune responses are shut off.

Indeed, patients treated with such nonspecific immunosuppressive agents are as likely to succumb to infection as they are to their autoimmune disease.

Cyclosporin A is a drug used to prevent rejection of transplanted organs. FK-506 is another drug approved for the prevention of transplant organ rejection, and in particular, liver transplantation. Cyclosporin A and FK-506 act by inhibiting the body's immune system from mobilizing its vast arsenal of natural protecting agents to reject the transplant's foreign protein. Cyclosporin A was approved for the treatment of severe psoriasis and has been approved by European regulatory agencies for the treatment of atopic dermatitis.

Though they are effective in delaying or suppressing transplant rejection, Cyclosporin A and FK-506 are known to cause several undesirable side effects including nephrotoxicity, neurotoxicity, and gastrointestinal discomfort. Therefore, an immunosuppressant without these side effects still remains to be developed and would be highly desirable.

The immunosuppressive compound FTY720 is a lymphocyte sequestration agent currently in clinical trials. FTY720 is metabolized in mammals to a compound that is a potent agonist of sphingosine 1-phosphate receptors. Agonism of sphingosine 1-phosphate receptors induces the sequestration of lymphocytes (T-cells and B-cells) in lymph nodes and Peyer's patches without lymphodepletion. Such immunosuppression is desirable to prevent rejection after organ transplantation and in the treatment of autoimmune disorders.

Sphingosine 1-phosphate is a bioactive sphingolipid metabolite that is secreted by hematopoietic cells and stored and released from activated platelets. Yatomi, Y., T. Ohmori, G. Rile, F. Kazama, H. Okamoto, T. Sano, K. Satoh, S. Kume, G. Tigyi, Y. Igarashi, and Y. Ozaki. 2000. *Blood.* 96:3431-8. It acts as an agonist on a family of G protein-coupled receptors to regulate cell proliferation, differentiation, survival, and motility. Fukushima, N., I. Ishii, J.J.A. Contos, J.A. Weiner, and J. Chun. 2001. Lysophospholipid receptors. Annu. Rev. Pharmacol. Toxicol. 41:507-34; Hla, T., M.-J. Lee, N. Ancellin, J.H. Paik, and M.J. Kluk. 2001. Lysophospholipids - Receptor revelations. *Science.* 294:1875-1878; Spiegel, S., and S. Milstien. 2000. Functions of a new family of sphingosine-1-phosphate receptors. *Biochim. Biophys. Acta.* 1484:107-16; Pyne, S., and N. Pyne. 2000. Sphingosine 1-phosphate signalling via the endothelial differentiation gene family of G-protein

coupled receptors. *Pharm. & Therapeutics*. 88:115-131. Five sphingosine 1-phosphate receptors have been identified ($S1P_1$, $S1P_2$, $S1P_3$, S1P4, and $S1P_5$, also known as endothelial differentiation genes Edg1, Edg5, Edg3, Edg6, Edg8), that have widespread cellular and tissue distribution and are well conserved in human and rodent species (see Table). Binding to S1P receptors elicits signal transduction through Gq-, Gi/o, G12-, G13-, and Rho-dependent pathways. Ligand-induced activation of $S1P_1$ and $S1P_3$ has been shown to promote angiogenesis, chemotaxis, and adherens junction assembly through Rac- and Rho-, *see* Lee, M.-J., S. Thangada, K.P. Claffey, N. Ancellin, C.H. Liu, M. Kluk, M. Volpi, R.I. Sha'afi, and T. Hla. 1999. *Cell*. 99:301-12, whereas agonism of $S1P_2$ promotes neurite retraction, *see* Van Brocklyn, J.R., Z. Tu, L.C. Edsall, R.R. Schmidt, and S. Spiegel. 1999. *J. Biol. Chem.* 274:4626-4632, and inhibits chemotaxis by blocking Rac activation, *see* Okamoto, H., N. Takuwa, T. Yokomizo, N. Sugimoto, S. Sakurada, H. Shigematsu, and Y. Takuwa. 2000. *Mol. Cell. Biol.* 20:9247-9261. S1P4 is localized to hematopoietic cells and tissues, *see* Graeler, M.H., G. Bernhardt, and M. Lipp. 1999. *Curr. Top. Microbiol. Immunol.* 246:131-6, whereas $S1P_5$ is primarily a neuronal receptor with some expression in lymphoid tissue, *see* Im, D.S., C.E. Heise, N. Ancellin, B.F. O'Dowd, G.J. Shei, R.P. Heavens, M.R. Rigby, T. Hla, S. Mandala, G. McAllister, S.R. George, and K.R. Lynch. 2000. *J. Biol. Chem.* 275:14281-6. Administration of sphingosine 1-phosphate to animals induces systemic sequestration of peripheral blood lymphocytes into secondary lymphoid organs, stimulates FGF-mediated blood vessel growth and differentiation, *see* Lee, et al., supra, but also has cardiovascular effects that limit the utility of sphingosine 1-phosphate as a therapeutic agent, *see* Sugiyama, A., N.N. Aye, Y. Yatomi, Y. Ozaki, and K. Hashimoto. 2000. *Jpn. J. Pharmacol.* 82:338-342. The reduced heart rate and blood pressure measured with sphingosine 1-phosphate is associated with its non-selective, potent agonist activity on all S1P receptors.

The present invention encompasses compounds which are agonists of the $S1P_1$/Edg1 receptor having selectivity over the $S1P_3$/Edg3 receptor. An $S1P_1$/Edg1 receptor selective agonist has advantages over current therapies and extends the therapeutic window of lymphocytes sequestration agents, allowing better tolerability with higher dosing and thus improving efficacy as monotherapy.

While the main use for immunosuppressants is in treating bone marrow, organ and transplant rejection, other uses for such compounds include the

treatment of arthritis, in particular, rheumatoid arthritis, insulin and non-insulin dependent diabetes, multiple sclerosis, psoriasis, inflammatory bowel disease, Crohn's disease, lupus erythematosis and the like.

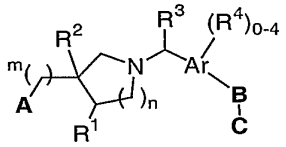
Thus, the present invention is focused on providing immunosuppressant compounds that are safer and more effective than prior compounds. These and other objects will be apparent to those of ordinary skill in the art from the description contained herein.

Summary of S1P receptors

Name	Synonyms	Coupled G proteins	mRNA expression
$S1P_1$	Edg1, LP_{B1}	$G_{i/o}$	Widely distributed, endothelial cells
$S1P_2$	Edg5, LP_{B2}, AGR16, H218	$G_{i/o}$, G_q, $G_{12/13}$	Widely distributed, vascular smooth muscle cells
$S1P_3$	Edg3, LP_{B3}	$G_{i/o}$, G_q, $G_{12/13}$	Widely distributed, endothelial cells
$S1P_4$	Edg6, LP_{C1}	$G_{i/o}$	Lymphoid tissues, lymphocytic cell lines
$S1P_5$	Edg8, LP_{B4}, NRG1	$G_{i/o}$	Brain, spleen

SUMMARY OF THE INVENTION

The present invention encompasses compounds of Formula I:

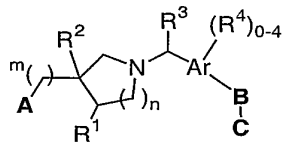


I

as well as the pharmaceutically acceptable salts and hydrates thereof. The compounds are useful for treating immune mediated diseases and conditions, such as bone marrow, organ and tissue transplant rejection. Pharmaceutical compositions and methods of use are included.

DETAILED DESCRIPTION OF THE INVENTION

The present invention encompasses compounds represented by Formula I:



I

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

Ar is phenyl or naphthyl;

m = 0 or 1;

n = 0 or 1;

A is selected from the group consisting of: $-CO_2H$, $-PO_3H_2$, $-PO_2H$, $-SO_3H$, $-PO(C_{1-3}alkyl)OH$ and 1*H*-tetrazol-5-yl;

R^1 and R^2 are each independently selected from the group consisting of: hydrogen, halo, hydroxy, $-CO_2H$ and $C_{1-4}alkyl$, optionally substituted from one up to the maximum number of substitutable positions with halo;

R^3 is selected from the group consisting of: hydrogen and C_{1-4}alkyl, optionally substituted with from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo and hydroxy;

each R^4 is independently selected from the group consisting of: halo, C_{1-4}alkyl and C_{1-3}alkoxy, said C_{1-4}alkyl and C_{1-3}alkoxy optionally substituted from one up to the maximum number of substitutable positions with halo,

C is selected from the group consisting of:

(1) C_{1-8}alkyl, C_{1-8}alkoxy, -(C=O)-C_{1-6}alkyl or –CHOH-C_{1-6}alkyl, said C_{1-8}alkyl, C_{1-8}alkoxy, -(C=O)-C_{1-6}alkyl and –CHOH-C_{1-6}alkyl optionally substituted with phenyl, and

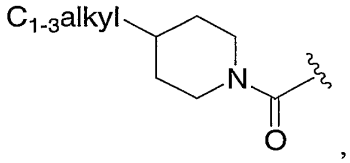
(2) phenyl or HET, each optionally substituted with 1-3 substituents independently selected from the group consisting of: halo, phenyl, C_{1-4}alkyl and C_{1-4}alkoxy, said C_{1-4}alkyl and C_{1-4}alkoxy groups optionally substituted from one up to the maximum number of substitutable positions with a substituent independently selected from halo and hydroxy, and said phenyl optionally substituted with 1 to 5 groups independently selected from the group consisting of : halo and C_{1-4}alkyl, optionally substituted with 1-3 halo groups,

or **C** is not present;

when **C** is not present then **B** is selected from the group consisting of: phenyl, C_{5-16}alkyl, C_{5-16}alkenyl, C_{5-16}alkynyl, -CHOH-C_{4-15}alkyl, -CHOH-C_{4-15}alkenyl, -CHOH-C_{4-15}alkynyl, C_{4-15}alkoxy, -O-C_{4-15}alkenyl, -O-C_{4-15}alkynyl, C_{4-15}alkylthio, -S-C_{4-15}alkenyl, -S-C_{4-15}alkynyl, -CH_2-C_{3-14}alkoxy, -CH_2-O-C_{3-14}alkenyl, -CH_2-O-C_{3-14}alkynyl, -(C=O)-C_{4-15}alkyl, -(C=O)-C_{4-15}alkenyl, -(C=O)-C_{4-15}alkynyl, -(C=O)-O-C_{3-14}alkyl, -(C=O)-O-C_{3-14}alkenyl, -(C=O)-O-C_{3-14}alkynyl, -(C=O)-N(R^6)(R^7)-C_{3-14}alkyl, -(C=O)-N(R^6)(R^7)-C_{3-14}alkenyl, -(C=O)-

$N(R^6)(R^7)$-C_{3-14}alkynyl, -$N(R^6)(R^7)$-(C=O)-C_{3-14}alkyl, -$N(R^6)(R^7)$-(C=O)-C_{3-14}alkenyl and -$N(R^6)(R^7)$-(C=O)-C_{3-14}alkynyl,

when **C** is phenyl or HET then **B** is selected from the group consisting of: C_{1-6}alkyl, C_{1-5}alkoxy, -(C=O)-C_{1-5}alkyl, -(C=O)-O-C_{1-4}alkyl, -(C=O)-$N(R^6)(R^7)$-C_{1-4}alkyl,



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when **C** is C_{1-8}alkyl, C_{1-8}alkoxy, -(C=O)-C_{1-6}alkyl or –CHOH-C_{1-6}alkyl then **B** is phenyl; and

R^6 and R^7 are independently selected from the group consisting of: hydrogen, C_{1-9}alkyl and -$(CH_2)_p$-phenyl, wherein p is 1 to 5 and phenyl is optionally substituted with 1-3 substituents independently selected from the group consisting of: C_{1-3}alkyl and C_{1-3}alkoxy, each optionally substituted with 1-3 halo groups.

An embodiment of the invention encompasses a compound of Formula I wherein:

Ar is phenyl;

the group **–B-C** is attached to the phenyl ring at the 3- or 4-position;

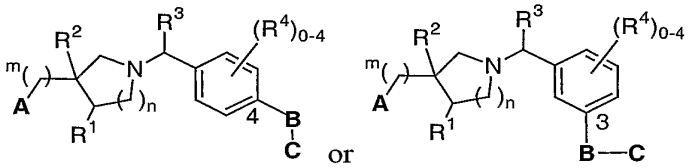
C is phenyl or HET, each optionally substituted with 1-3 substituents independently selected from the group consisting of: halo, phenyl, C_{1-4}alkyl and C_{1-4}alkoxy, said C_{1-4}alkyl and C_{1-4}alkoxy groups optionally substituted from one up to the maximum number of substitutable positions with a substituent independently selected from halo and hydroxy, and said phenyl optionally substituted with 1 to 5 groups independently selected from the group consisting of : halo and C_{1-4}alkyl, optionally substituted with 1-3 halo groups,

or **C** is not present;

when **C** is not present then **B** is selected from the group consisting of: C_{7-12}alkyl, C_{7-12}alkenyl, C_{7-12}alkynyl, C_{6-11}alkoxy, -O-C_{6-11}alkenyl, -O-C_{6-11}alkynyl, -(C=O)-C_{6-11}alkyl, -(C=O)-C_{6-11}alkenyl, -(C=O)-C_{6-11}alkynyl, -(C=O)-O-C_{5-10}alkyl, -(C=O)-O-C_{5-19}alkenyl, and -(C=O)-O-C_{5-10}alkynyl and **C** is not present; and

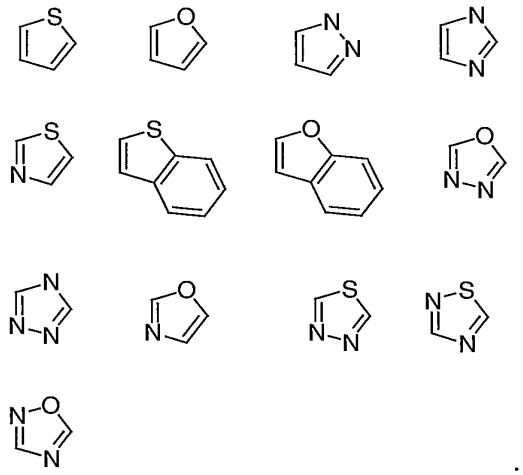
when **C** is phenyl or HET then **B** is selected from the group consisting of C_{1-5}alkyl, C_{1-4}alkoxy, -(C=O)-C_{1-4}alkyl, -(C=O)-O-C_{1-3}alkyl, phenyl and HET.

For purposes of this specification, when the group **–B-C** is attached to the phenyl ring at the 3- or 4-position, it means the positions shown in the following:



For purposes of this specification, **C** may be substituted at any substitutable position on **B**. For example, when **B** is methoxy and **C** is thiophene, thiophene replaces a hydrogen on the methoxy group. Further variations are illustrated in the examples that follow. Also, the point of any attachments shown for **B** is to the Ar group. For example, when **B** is -(C=O)-C_{6-11}alkynyl this means **B** is attached to Ar as follows: Ar-(C=O)-C_{6-11}alkynyl. **C** may then be substituted at any substituable position on **B**.

An embodiment of the invention encompasses the compound of Formula I wherein HET is selected from the group consisting of:



Another embodiment encompasses the compound of Formula I wherein m is 0.

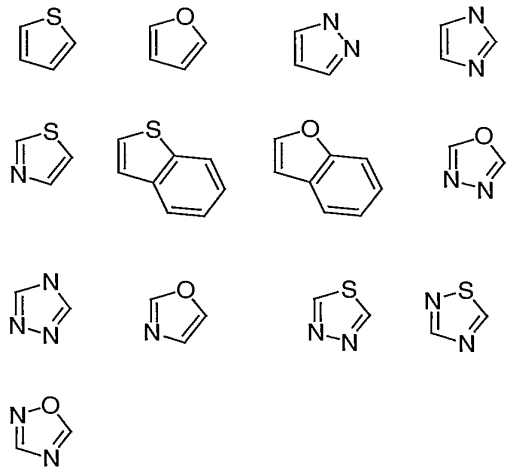
Another embodiment encompasses the compound of Formula I wherein m is 1.

Another embodiment encompasses the compound of Formula I wherein n is 0.

Another embodiment encompasses the compound of Formula I wherein n is 1.

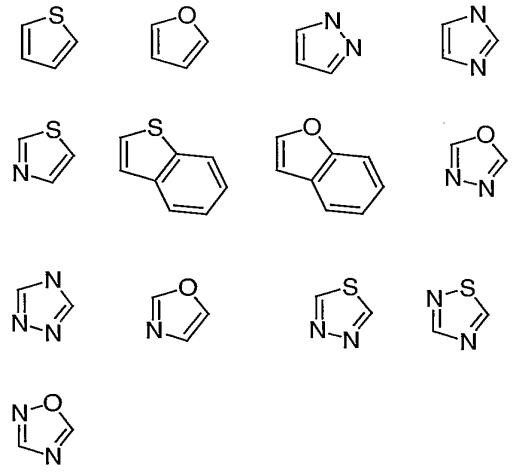
Another embodiment encompasses the compound of Formula I wherein **B** is selected from the group consisting of: C_{7-12}alkyl, C_{7-12}alkenyl, C_{7-12}alkynyl, C_{6-11}alkoxy, -O-C_{6-11}alkenyl, -O-C_{6-11}alkynyl, -(C=O)-C_{6-11}alkyl, -(C=O)-C_{6-11}alkenyl, -(C=O)-C_{6-11}alkynyl, -(C=O)-O-C_{5-10}alkyl, -(C=O)-O-C_{5-19}alkenyl, and -(C=O)-O-C_{5-10}alkynyl and **C** is not present;

Another embodiment of the invention encompasses the compound of Formula I wherein: **B** is methoxy and **C** is HET substituted with phenyl and C_{1-4}alkyl, said C_{1-4}alkyl optionally substituted from one up to the maximum number of substitutable positions with halo, and said phenyl, optionally substituted with 1 to 5 substituents independently selected from the group conisting of: halo and C_{1-4}alkyl, optionally substituted with 1-3 halo groups. Within this embodiment is encompassed the compound of Formula I wherein **C** is selected from the group consisting of:



Also encompassed is a compound of Formula I wherein **C** is thiophene or furan.

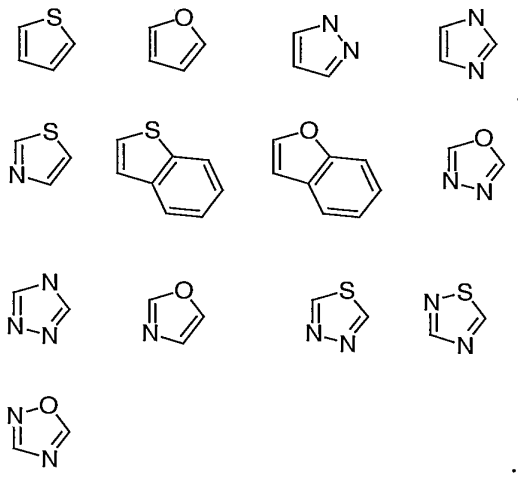
Another embodiment of the invention encompasses the compound of Formula I wherein: **B** is methoxy and **C** is HET. Within this embodiment is encompassed the compound of Formula I wherein **C** is selected from the group consisting of:



Also within this embodiment is encompassed the compound of Formula I wherein **C** is benzothiophene or benzofuran.

Another embodiment of the invention encompasses the compound of Formula I wherein: **B** is methoxy and **C** is phenyl substituted with two C_{1-4}alkyl groups, said C_{1-4}alkyl optionally substituted from one up to the maximum number of substitutable positions with halo.

Another embodiment of the invention encompasses the compound according to Claim 1 wherein: **B** is HET and **C** is HET substituted with phenyl and C_{1-4}alkyl, said C_{1-4}alkyl optionally substituted from one up to the maximum number of substitutable positions with halo, and said phenyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of: halo, C_{1-4}alkyl, optionally substituted with 1-3 halo groups. Within this embodiment is encompassed the compound of Formula I wherein **B** is 1,2,4-oxadiazole. Also within this embodiment is encompassed the compound of Formula I wherein **B** is 1,2,4-oxadiazole **C** is selected from the group consisting of:



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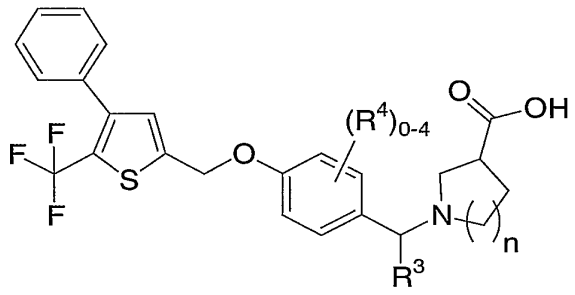
Also within this embodiment is encompassed the compound of Formula I wherein **B** is 1,2,4-oxadiazole and **C** is thiophene or furan.

Another embodiment of the invention encompassed the compound of Formula I wherein m = 0 and **A** is $-CO_2H$. Within this embodiment is encompassed the compound of Formula I wherein R^1, R^2 and R^3 are hydrogen.

Another embodiment of the invention encompassed the compound of Formula I wherein the group **–B-C** is attached to the phenyl ring at the 4-position.

The invention also encompasses a compound represented by Formula II



II

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

n = 0 or 1;

R^3 is selected from the group consisting of: hydrogen and C_{1-4}alkyl, optionally substituted with from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo and hydroxy;

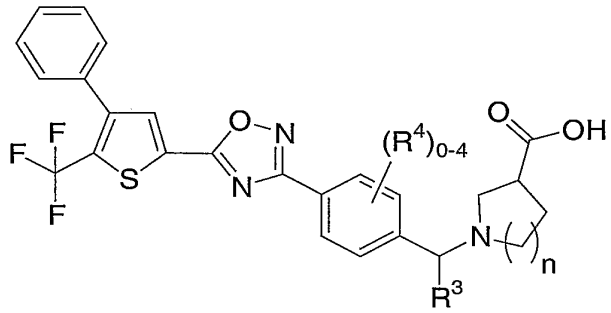
each R^4 is independently selected from the group consisting of: halo, C_1-4alkyl and C_1-3alkoxy, said C_1-4alkyl and C_1-3alkoxy optionally substituted from one up to the maximum number of substitutable positions with halo.

Another embodiment of the invention encompassed a compound of Formula II wherein n is 0.

Another embodiment of the invention encompassed a compound of Formula II wherein n is 1.

Another embodiment of the invention encompassed a compound of Formula II wherein R^3 is hydrogen.

The invention also encompasses a compound represented by Formula III



III

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

n = 0 or 1;

R^3 is selected from the group consisting of: hydrogen and C_{1-4}alkyl, optionally substituted with from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo and hydroxy;

each R^4 is independently selected from the group consisting of: halo, C_1-4alkyl and C_1-3alkoxy, said C_1-4alkyl and C_1-3alkoxy optionally substituted from one up to the maximum number of substitutable positions with halo.

Another embodiment of the invention encompassed a compound of Formula III wherein n is 0.

Another embodiment of the invention encompassed a compound of Formula III wherein n is 1.

Another embodiment of the invention encompassed a compound of Formula II wherein R^3 is hydrogen.

The invention also encompasses a method of treating an immunoregulatory abnormality in a mammalian patient in need of such treatment comprising administering to said patient a compound of Formula I in an amount that is effective for treating said immunoregulatory abnormality.

Within this embodiment is encompassed the above method wherein the immunoregulatory abnormality is an autoimmune or chronic inflammatory disease selected from the group consisting of: systemic lupus erythematosis, chronic rheumatoid arthritis, type I diabetes mellitus, inflammatory bowel disease, biliary cirrhosis, uveitis, multiple sclerosis, Crohn's disease, ulcerative colitis, bullous pemphigoid, sarcoidosis, psoriasis, autoimmune myositis, Wegener's granulomatosis, ichthyosis, Graves ophthalmopathy and asthma.

Also within this embodiment is encompassed the above method wherein the immunoregulatory abnormality is bone marrow or organ transplant rejection or graft-versus-host disease.

Also within this embodiment is encompassed the above method wherein the immunoregulatory abnormality is selected from the group consisting of: transplantation of organs or tissue, graft-versus-host diseases brought about by transplantation, autoimmune syndromes including rheumatoid arthritis, systemic lupus erythematosus, Hashimoto's thyroiditis, multiple sclerosis, myasthenia gravis, type I diabetes, uveitis, posterior uveitis, allergic encephalomyelitis, glomerulonephritis, post-infectious autoimmune diseases including rheumatic fever and post-infectious glomerulonephritis, inflammatory and hyperproliferative skin diseases, psoriasis, atopic dermatitis, contact dermatitis, eczematous dermatitis, seborrhoeic dermatitis, lichen planus, pemphigus, bullous pemphigoid, epidermolysis bullosa, urticaria, angioedemas, vasculitis, erythema, cutaneous eosinophilia, lupus erythematosus, acne, alopecia areata, keratoconjunctivitis, vernal conjunctivitis, uveitis associated with Behcet's disease, keratitis, herpetic keratitis, conical cornea, dystrophia epithelialis corneae, corneal leukoma, ocular pemphigus, Mooren's ulcer, scleritis, Graves' opthalmopathy, Vogt-Koyanagi-Harada syndrome, sarcoidosis, pollen allergies, reversible obstructive airway disease, bronchial asthma, allergic asthma, intrinsic asthma, extrinsic asthma, dust asthma, chronic or inveterate asthma, late asthma and airway hyper-responsiveness, bronchitis, gastric ulcers, vascular damage caused by ischemic diseases and thrombosis, ischemic bowel diseases, inflammatory bowel

diseases, necrotizing enterocolitis, intestinal lesions associated with thermal burns, coeliac diseases, proctitis, eosinophilic gastroenteritis, mastocytosis, Crohn's disease, ulcerative colitis, migraine, rhinitis, eczema, interstitial nephritis, Goodpasture's syndrome, hemolytic-uremic syndrome, diabetic nephropathy, multiple myositis, Guillain-Barre syndrome, Meniere's disease, polyneuritis, multiple neuritis, mononeuritis, radiculopathy, hyperthyroidism, Basedow's disease, pure red cell aplasia, aplastic anemia, hypoplastic anemia, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, agranulocytosis, pernicious anemia, megaloblastic anemia, anerythroplasia, osteoporosis, sarcoidosis, fibroid lung, idiopathic interstitial pneumonia, dermatomyositis, leukoderma vulgaris, ichthyosis vulgaris, photoallergic sensitivity, cutaneous T cell lymphoma, arteriosclerosis, atherosclerosis, aortitis syndrome, polyarteritis nodosa, myocardosis, scleroderma, Wegener's granuloma, Sjogren's syndrome, adiposis, eosinophilic fascitis, lesions of gingiva, periodontium, alveolar bone, substantia ossea dentis, glomerulonephritis, male pattern alopecia or alopecia senilis by preventing epilation or providing hair germination and/or promoting hair generation and hair growth, muscular dystrophy, pyoderma and Sezary's syndrome, Addison's disease, ischemia-reperfusion injury of organs which occurs upon preservation, transplantation or ischemic disease, endotoxin-shock, pseudomembranous colitis, colitis caused by drug or radiation, ischemic acute renal insufficiency, chronic renal insufficiency, toxinosis caused by lung-oxygen or drugs, lung cancer, pulmonary emphysema, cataracta, siderosis, retinitis pigmentosa, senile macular degeneration, vitreal scarring, corneal alkali burn, dermatitis erythema multiforme, linear IgA ballous dermatitis and cement dermatitis, gingivitis, periodontitis, sepsis, pancreatitis, diseases caused by environmental pollution, aging, carcinogenesis, metastasis of carcinoma and hypobaropathy, disease caused by histamine or leukotriene-C_4 release, Behcet's disease, autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis, partial liver resection, acute liver necrosis, necrosis caused by toxin, viral hepatitis, shock, or anoxia, B-virus hepatitis, non-A/non-B hepatitis, cirrhosis, alcoholic cirrhosis, hepatic failure, fulminant hepatic failure, late-onset hepatic failure, "acute-on-chronic" liver failure, augmentation of chemotherapeutic effect, cytomegalovirus infection, HCMV infection, AIDS, cancer, senile dementia, trauma, and chronic bacterial infection

Also within this embodiment is encompassed the above method wherein the immunoregulatory abnormality is multiple sclerosis

Also within this embodiment is encompassed the above method wherein the immunoregulatory abnormality is rheumatoid arthritis

Also within this embodiment is encompassed the above method wherein the immunoregulatory abnormality is systemic lupus erythematosus

Also within this embodiment is encompassed the above method wherein the immunoregulatory abnormality is psoriasis

Also within this embodiment is encompassed the above method wherein the immunoregulatory abnormality is rejection of transplanted organ or tissue

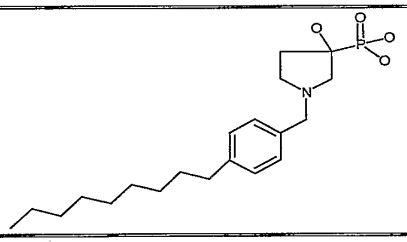
Also within this embodiment is encompassed the above method wherein the immunoregulatory abnormality is inflammatory bowel disease.

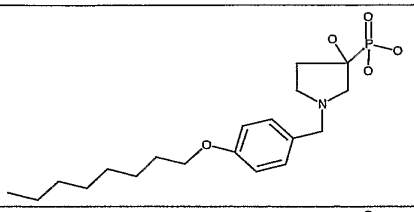
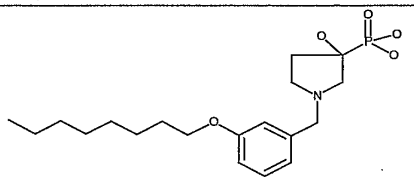
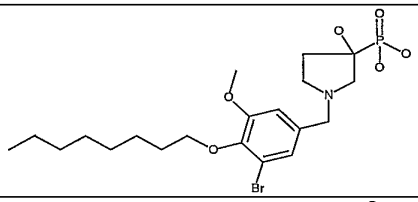
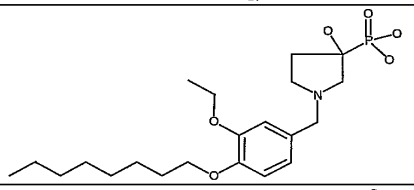
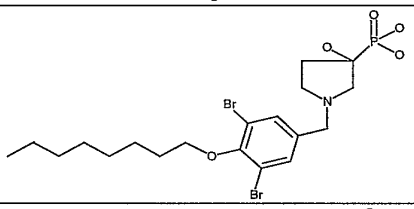
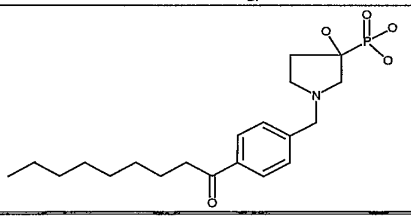
Also within this embodiment is encompassed the above method wherein the immunoregulatory abnormality is a malignancy of lymphoid origin including acute and chronic lymphocytic leukemias and lymphomas.

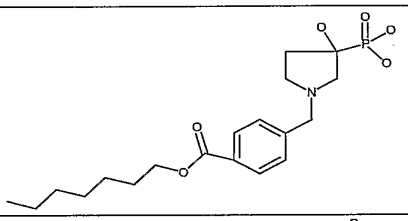
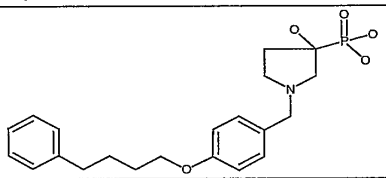
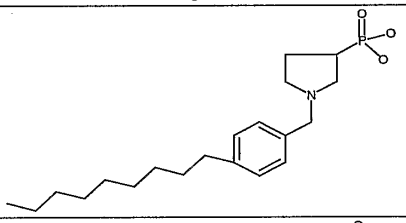
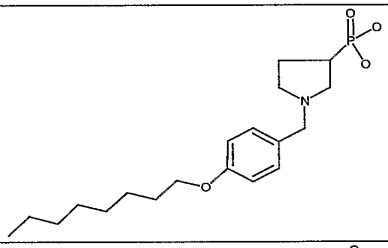
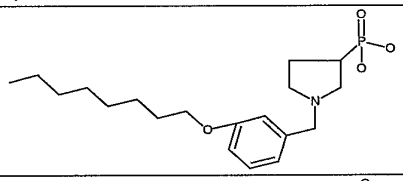
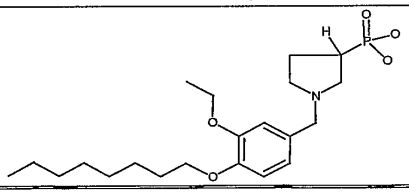
The invention also encompasses a method of suppressing the immune system in a mammalian patient in need of immunosuppression comprising administering to said patient an immunosuppressing effective amount of a compound of Formula I.

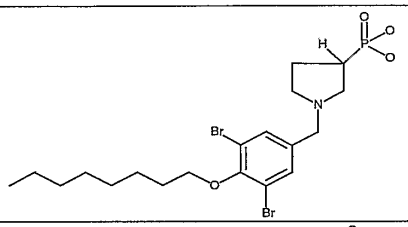
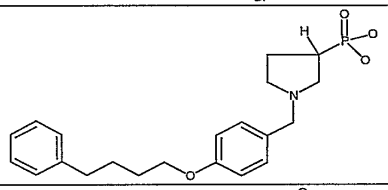
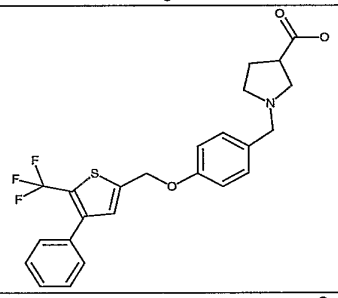
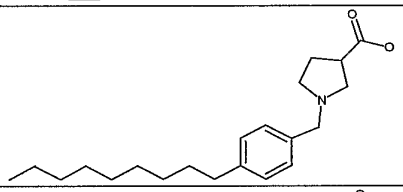
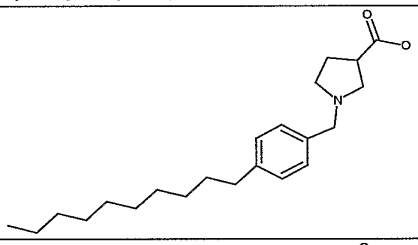
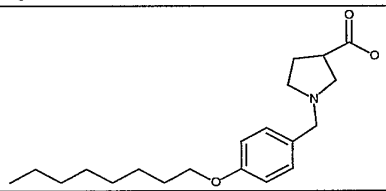
The invention also encompasses a pharmaceutical composition comprised of a compound of Formula I in combination with a pharmaceutically acceptable carrier.

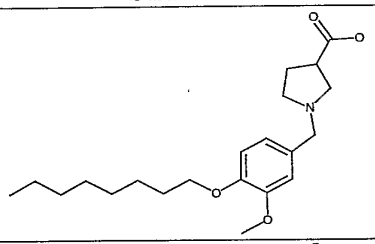
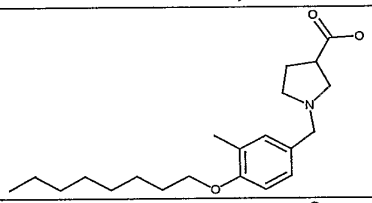
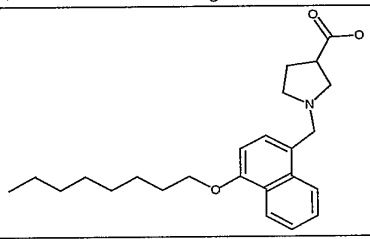
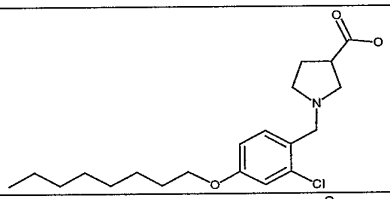
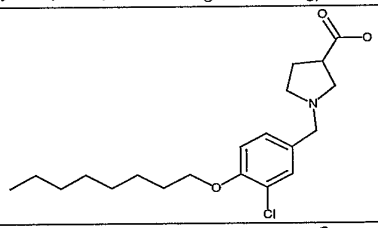
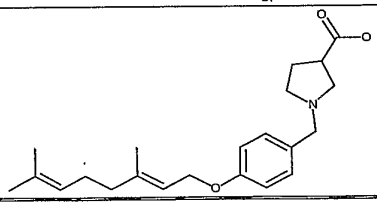
Exemplifying the invention are the following compounds:

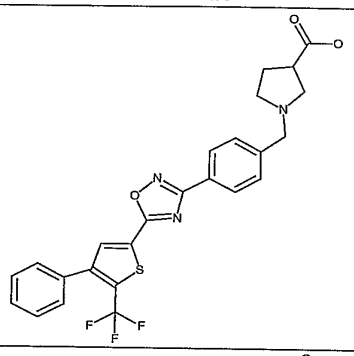
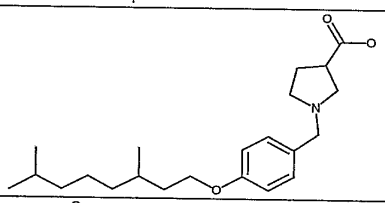
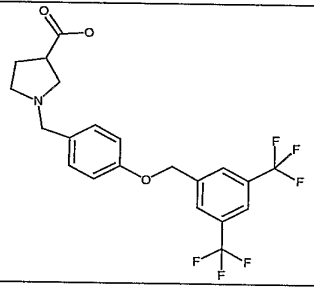
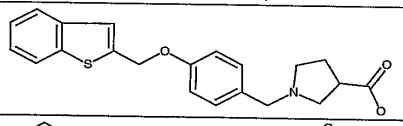
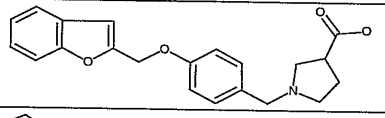
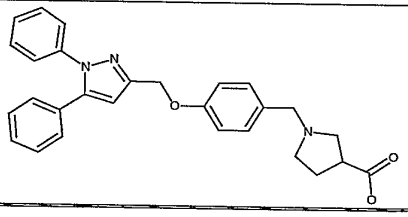
Example No.	Structure
1	

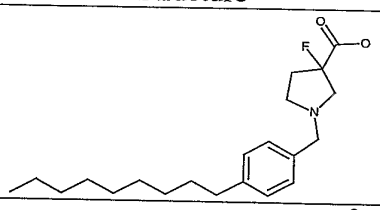
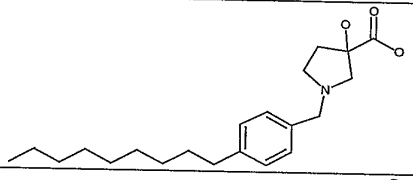
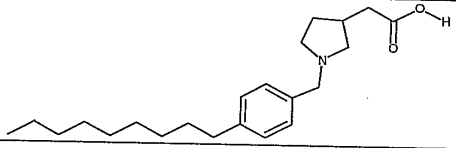
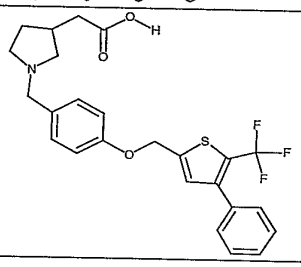
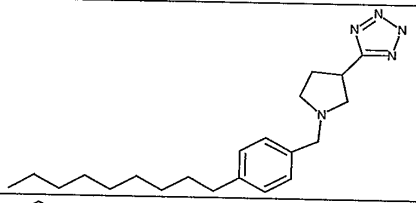
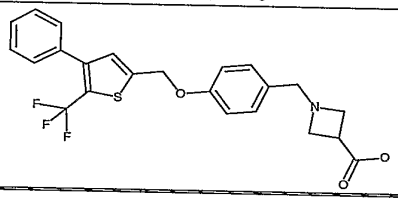
Example No.	Structure
2	
3	
4	
5 + 6	
7	
8	

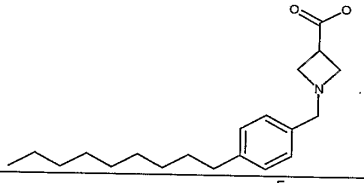
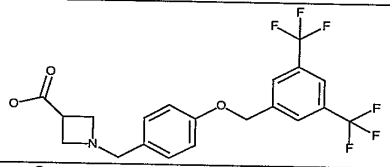
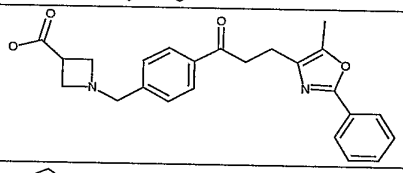
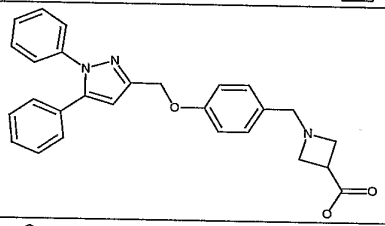
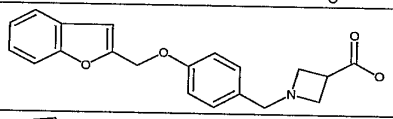
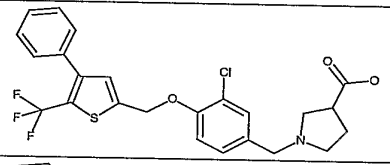
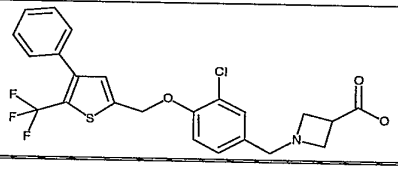
Example No.	Structure
9	
10	
11	
12	
13	
14	

Example No.	Structure
15 + 16	
17	
18	
19	
20	
21	

Example No.	Structure
22	
23	
24	
25	
26	
27	

Example No.	Structure
28	
29	
30	
31	
32	
33	

Example No.	Structure
35	
36	
37	
38	
39	
40	

Example No.	Structure
41	
42	
43	
44	
45	
46	
47	

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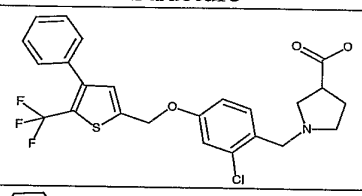
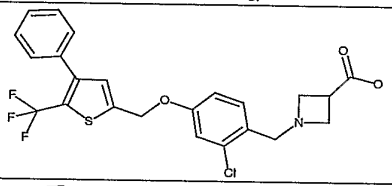
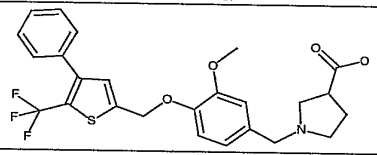
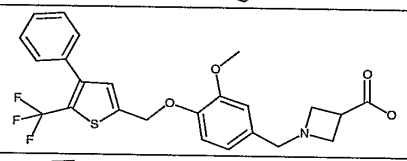
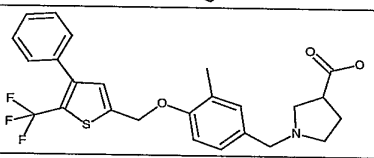
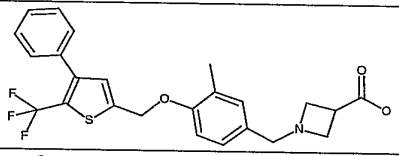
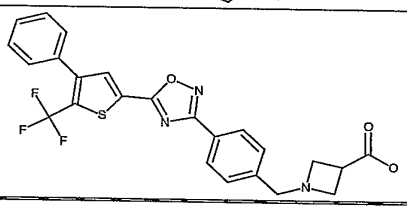
48	
49	
50	
51	
52	
53	
54	

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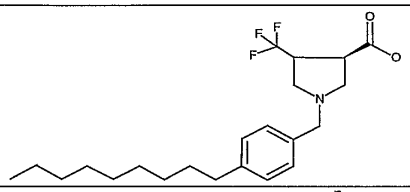
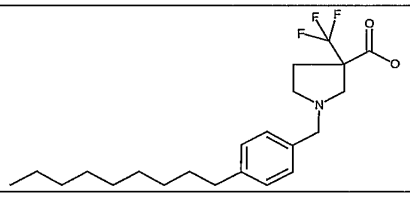
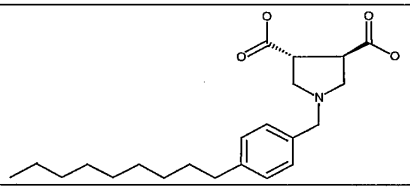
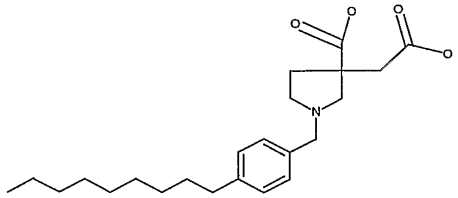
55	
56	
57	
58	

The invention is described using the following definitions unless otherwise indicated.

The term "halogen" or "halo" includes F, Cl, Br, and I.

The term "alkyl" means linear or branched structures and combinations thereof, having the indicated number of carbon atoms. Thus, for example, C_{1-6}alkyl includes methyl, ethyl, propyl, 2-propyl, s- and t-butyl, butyl, pentyl, hexyl, 1,1-dimethylethyl, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term "alkoxy" means alkoxy groups of a straight, branched or cyclic configuration having the indicated number of carbon atoms. C_{1-6}alkoxy, for example, includes methoxy, ethoxy, propoxy, isopropoxy, and the like.

The term "alkylthio" means alkylthio groups having the indicated number of carbon atoms of a straight, branched or cyclic configuration. C_{1-6}alkylthio, for example, includes methylthio, propylthio, isopropylthio, and the like.

The term "alkenyl" means linear or branched structures and combinations thereof, of the indicated number of carbon atoms, having at least one carbon-to-carbon double bond, wherein hydrogen may be replaced by an additional carbon-to-carbon double bond. C_{2-6}alkenyl, for example, includes ethenyl, propenyl, 1-methylethenyl, butenyl and the like.

The term "alkynyl" means linear or branched structures and combinations thereof, of the indicated number of carbon atoms, having at least one carbon-to-carbon triple bond. C_{3-6}alkynyl, for example, includes , propenyl, 1-methylethenyl, butenyl and the like.

The term "cycloalkyl" means mono-, bi- or tri-cyclic structures, optionally combined with linear or branched structures, the indicated number of carbon atoms. Examples of cycloalkyl groups include cyclopropyl, cyclopentyl, cycloheptyl, adamantyl, cyclododecylmethyl, 2-ethyl-1- bicyclo[4.4.0]decyl, and the like.

The term "aryl" is defined as a mono- or bi-cyclic aromatic ring system and includes, for example, phenyl, naphthyl, and the like.

The term "aralkyl" means an alkyl group as defined above of 1 to 6 carbon atoms with an aryl group as defined above substituted for one of the alkyl hydrogen atoms, for example, benzyl and the like.

The term "aryloxy" means an aryl group as defined above attached to a molecule by an oxygen atom (aryl-O) and includes, for example, phenoxy, naphthoxy and the like.

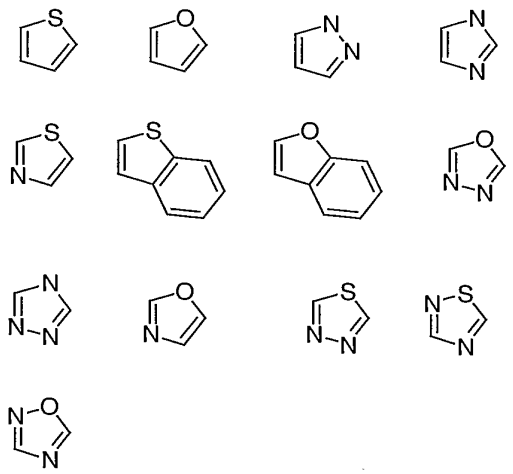
The term "aralkoxy" means an aralkyl group as defined above attached to a molecule by an oxygen atom (aralkyl-O) and includes, for example, benzyloxy, and the like.

The term "arylthio" is defined as an aryl group as defined above attached to a molecule by an sulfur atom (aryl-S) and includes, for example, thiophenyoxy, thionaphthoxy and the like.

The term "aroyl" means an aryl group as defined above attached to a molecule by an carbonyl group (aryl-C(O)-) and includes, for example, benzoyl, naphthoyl and the like.

The term "aroyloxy" means an aroyl group as defined above attached to a molecule by an oxygen atom (aroyl-O) and includes, for example, benzoyloxy or benzoxy, naphthoyloxy and the like.

The term "HET" is defined as a 5- to 10-membered aromatic, partially aromatic or non-aromatic mono- or bicyclic ring, containing 1-5 heteroatoms selected from O, S and N, and optionally substituted with 1-2 oxo groups. Preferably, "HET" is a 5- or 6-membered aromatic or non-aromatic monocyclic ring containing 1-3 heteroatoms selected from O, S and N, for example, pyridine, pyrimidine, pyridazine, furan, thiophene, thiazole, oxazole, isooxazole and the like, or heterocycle is a 9- or 10-membered aromatic or partially aromatic bicyclic ring containing 1-3 heteroatoms selected from O, S, and N, for example, benzofuran, benzothiophene, indole, pyranopyrrole, benzopyran, quionoline, benzocyclohexyl, naphtyridine and the like. "HET" also includes the following: benzimidazolyl, benzofuranyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, indolazinyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthyridinyl, oxadiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridopyridinyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, azetidinyl, 1,4-dioxanyl, hexahydroazepinyl, piperazinyl, piperidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, dihydrobenzimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidinyl, methylenedioxybenzoyl, tetrahydrofuranyl, and tetrahydrothienyl. A preferred group of HET is as follows:



The term "treating" encompasses not only treating a patient to relieve the patient of the signs and symptoms of the disease or condition but also prophylactically treating an asymptomatic patient to prevent the onset or progression of the disease or condition. The term "amount effective for treating" is intended to mean that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, a system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician. The term also encompasses the amount of a pharmaceutical drug that will prevent or reduce the risk of occurrence of the biological or medical event that is sought to be prevented in a tissue, a system, animal or human by a researcher, veterinarian, medical doctor or other clinician.

The invention described herein includes pharmaceutically acceptable salts and hydrates. Pharmaceutically acceptable salts include both the metallic (inorganic) salts and organic salts; a list of which is given in *Remington's Pharmaceutical Sciences*, 17th Edition, pg. 1418 (1985). It is well known to one skilled in the art that an appropriate salt form is chosen based on physical and chemical stability, flowability, hydroscopicity and solubility. As will be understood by those skilled in the art, pharmaceutically acceptable salts include, but are not limited to salts of inorganic acids such as hydrochloride, sulfate, phosphate, diphosphate, hydrobromide, and nitrate or salts of an organic acid such as malate, maleate, fumarate, tartrate, succinate, citrate, acetate, lactate, methanesulfonate, p-toluenesulfonate or pamoate, salicylate and stearate. Similarly pharmaceutically

acceptable cations include, but are not limited to sodium, potassium, calcium, aluminum, lithium and ammonium (especially ammonium salts with secondary amines). Preferred salts of this invention for the reasons cited above include potassium, sodium, calcium and ammonium salts. Also included within the scope of this invention are crystal forms, hydrates and solvates of the compounds of Formula I.

For purposes of this Specification, "pharmaceutically acceptable hydrate" means the compounds of the instant invention crystallized with one or more molecules of water to form a hydrated form.

The invention also includes the compounds falling within formula I in the form of one or more stereoisomers, in substantially pure form or in the form of a mixture of stereoisomers. All such isomers are encompassed within the present invention.

By virtue of their $S1P_1$/Edg1 agonist activity, the compounds of the present invention are immunoregulatory agents useful for treating or preventing automimmune or chronic inflammatory diseases. The compounds of the present invention are useful to suppress the immune system in instances where immunosuppression is in order, such as in bone marrow, organ or transplant rejection, autoimmune and chronic inflammatory diseases, including systemic lupus erythematosis, chronic rheumatoid arthritis, type I diabetes mellitus, inflammatory bowel disease, biliary cirrhosis, uveitis, multiple sclerosis, Crohn's disease, ulcerative colitis, bullous pemphigoid, sarcoidosis, psoriasis, autoimmune myositis, Wegener's granulomatosis, ichthyosis, Graves ophthalmopathy and asthma.

More particularly, the compounds of the present invention are useful to treat or prevent a disease or disorder selected from the group consisting of: transplantation of organs or tissue, graft-versus-host diseases brought about by transplantation, autoimmune syndromes including rheumatoid arthritis, systemic lupus erythematosus, Hashimoto's thyroiditis, multiple sclerosis, myasthenia gravis, type I diabetes, uveitis, posterior uveitis, allergic encephalomyelitis, glomerulonephritis, post-infectious autoimmune diseases including rheumatic fever and post-infectious glomerulonephritis, inflammatory and hyperproliferative skin diseases, psoriasis, atopic dermatitis, contact dermatitis, eczematous dermatitis, seborrhoeic dermatitis, lichen planus, pemphigus, bullous pemphigoid, epidermolysis bullosa, urticaria, angioedemas, vasculitis, erythema, cutaneous eosinophilia, lupus erythematosus, acne,

alopecia areata, keratoconjunctivitis, vernal conjunctivitis, uveitis associated with Behcet's disease, keratitis, herpetic keratitis, conical cornea, dystrophia epithelialis corneae, corneal leukoma, ocular pemphigus, Mooren's ulcer, scleritis, Graves' opthalmopathy, Vogt-Koyanagi-Harada syndrome, sarcoidosis, pollen allergies, reversible obstructive airway disease, bronchial asthma, allergic asthma, intrinsic asthma, extrinsic asthma, dust asthma, chronic or inveterate asthma, late asthma and airway hyper-responsiveness, bronchitis, gastric ulcers, vascular damage caused by ischemic diseases and thrombosis, ischemic bowel diseases, inflammatory bowel diseases, necrotizing enterocolitis, intestinal lesions associated with thermal burns, coeliac diseases, proctitis, eosinophilic gastroenteritis, mastocytosis, Crohn's disease, ulcerative colitis, migraine, rhinitis, eczema, interstitial nephritis, Goodpasture's syndrome, hemolytic-uremic syndrome, diabetic nephropathy, multiple myositis, Guillain-Barre syndrome, Meniere's disease, polyneuritis, multiple neuritis, mononeuritis, radiculopathy, hyperthyroidism, Basedow's disease, pure red cell aplasia, aplastic anemia, hypoplastic anemia, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, agranulocytosis, pernicious anemia, megaloblastic anemia, anerythroplasia, osteoporosis, sarcoidosis, fibroid lung, idiopathic interstitial pneumonia, dermatomyositis, leukoderma vulgaris, ichthyosis vulgaris, photoallergic sensitivity, cutaneous T cell lymphoma, arteriosclerosis, atherosclerosis, aortitis syndrome, polyarteritis nodosa, myocardosis, scleroderma, Wegener's granuloma, Sjogren's syndrome, adiposis, eosinophilic fascitis, lesions of gingiva, periodontium, alveolar bone, substantia ossea dentis, glomerulonephritis, male pattern alopecia or alopecia senilis by preventing epilation or providing hair germination and/or promoting hair generation and hair growth, muscular dystrophy, pyoderma and Sezary's syndrome, Addison's disease, ischemia-reperfusion injury of organs which occurs upon preservation, transplantation or ischemic disease, endotoxin-shock, pseudomembranous colitis, colitis caused by drug or radiation, ischemic acute renal insufficiency, chronic renal insufficiency, toxinosis caused by lung-oxygen or drugs, lung cancer, pulmonary emphysema, cataracta, siderosis, retinitis pigmentosa, senile macular degeneration, vitreal scarring, corneal alkali burn, dermatitis erythema multiforme, linear IgA ballous dermatitis and cement dermatitis, gingivitis, periodontitis, sepsis, pancreatitis, diseases caused by environmental pollution, aging, carcinogenesis, metastasis of carcinoma and hypobaropathy, disease caused by

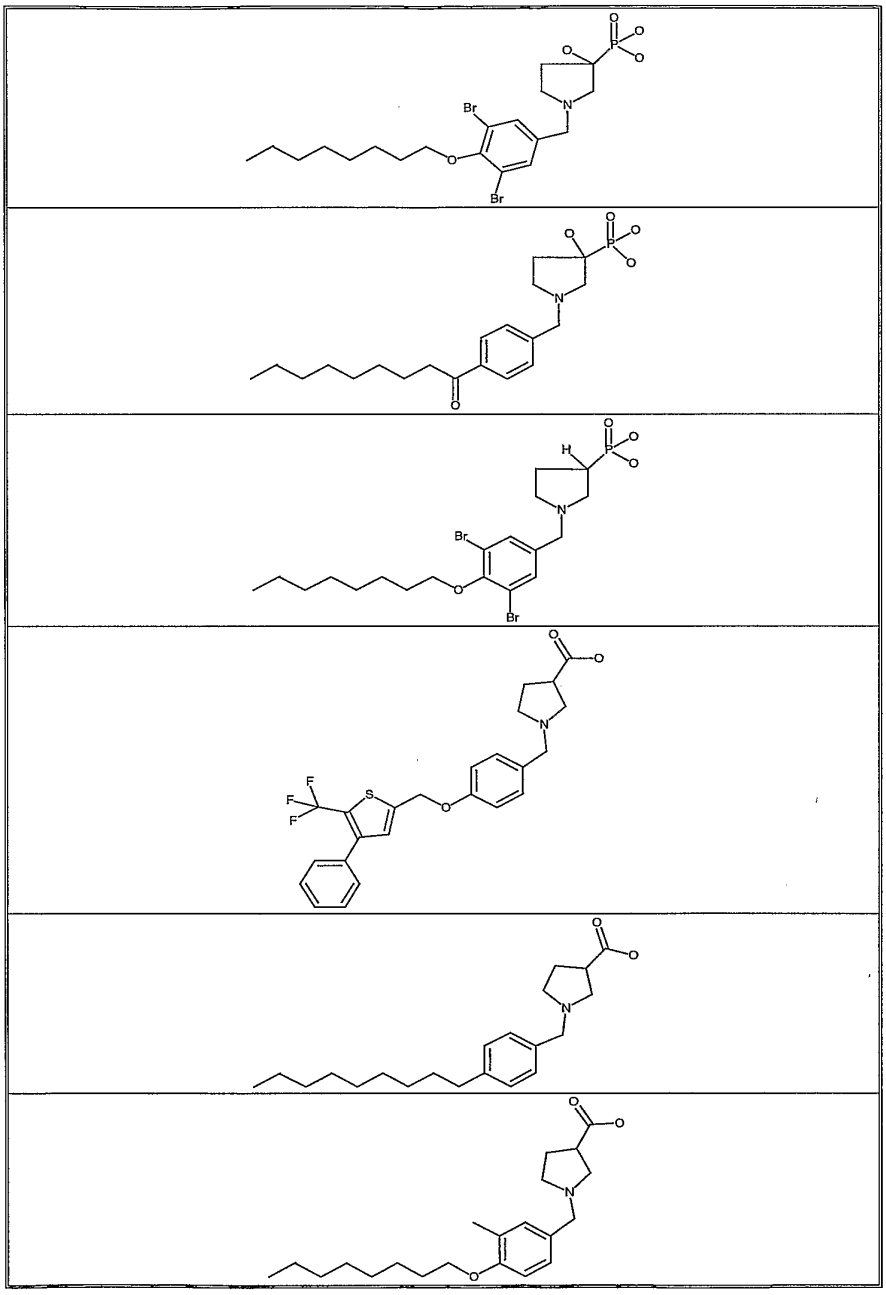
histamine or leukotriene-C4 release, Behcet's disease, autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis, partial liver resection, acute liver necrosis, necrosis caused by toxin, viral hepatitis, shock, or anoxia, B-virus hepatitis, non-A/non-B hepatitis, cirrhosis, alcoholic cirrhosis, hepatic failure, fulminant hepatic failure, late-onset hepatic failure, "acute-on-chronic" liver failure, augmentation of chemotherapeutic effect, cytomegalovirus infection, HCMV infection, AIDS, cancer, senile dementia, trauma, and chronic bacterial infection.

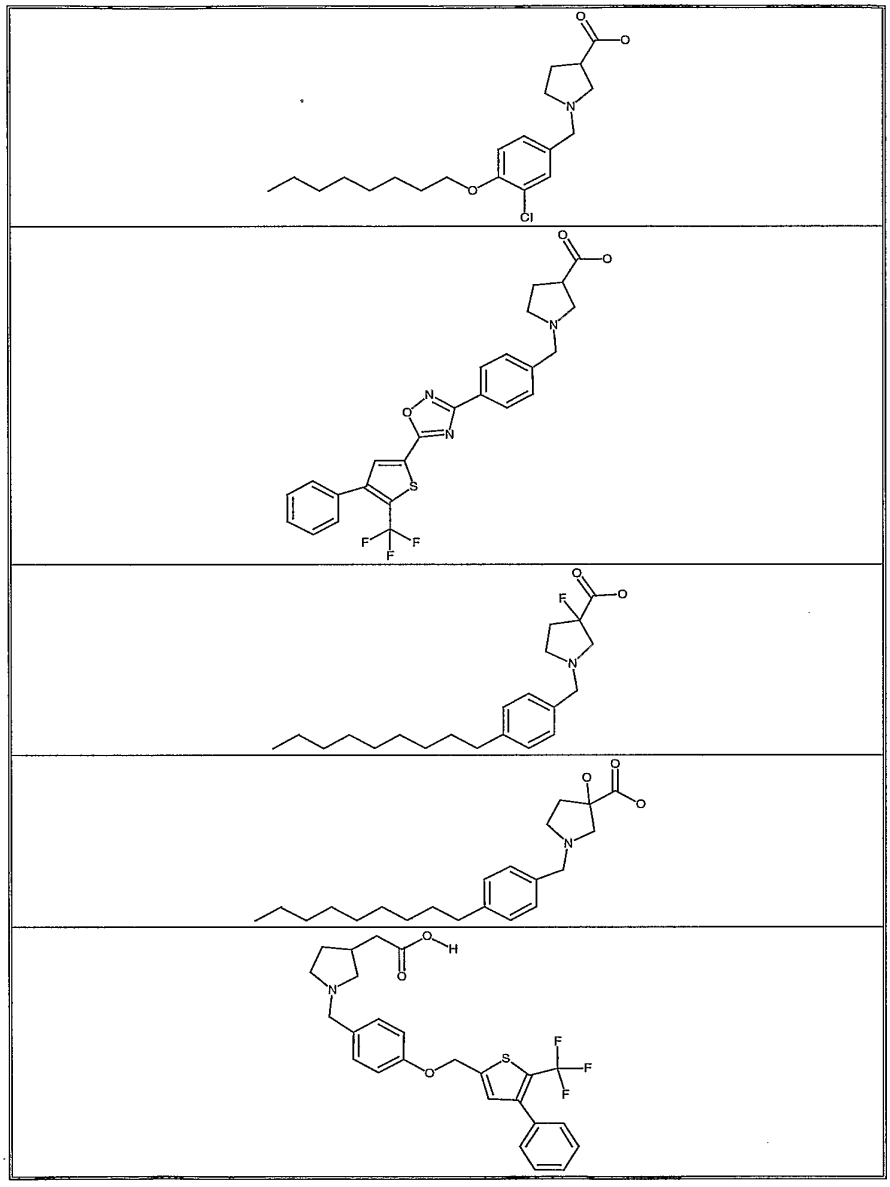
Also embodied within the present invention is a method of preventing or treating resistance to transplantation or transplantation rejection of organs or tissues in a mammalian patient in need thereof, which comprises administering a therapeutically effective amount of the compound of Formula I.

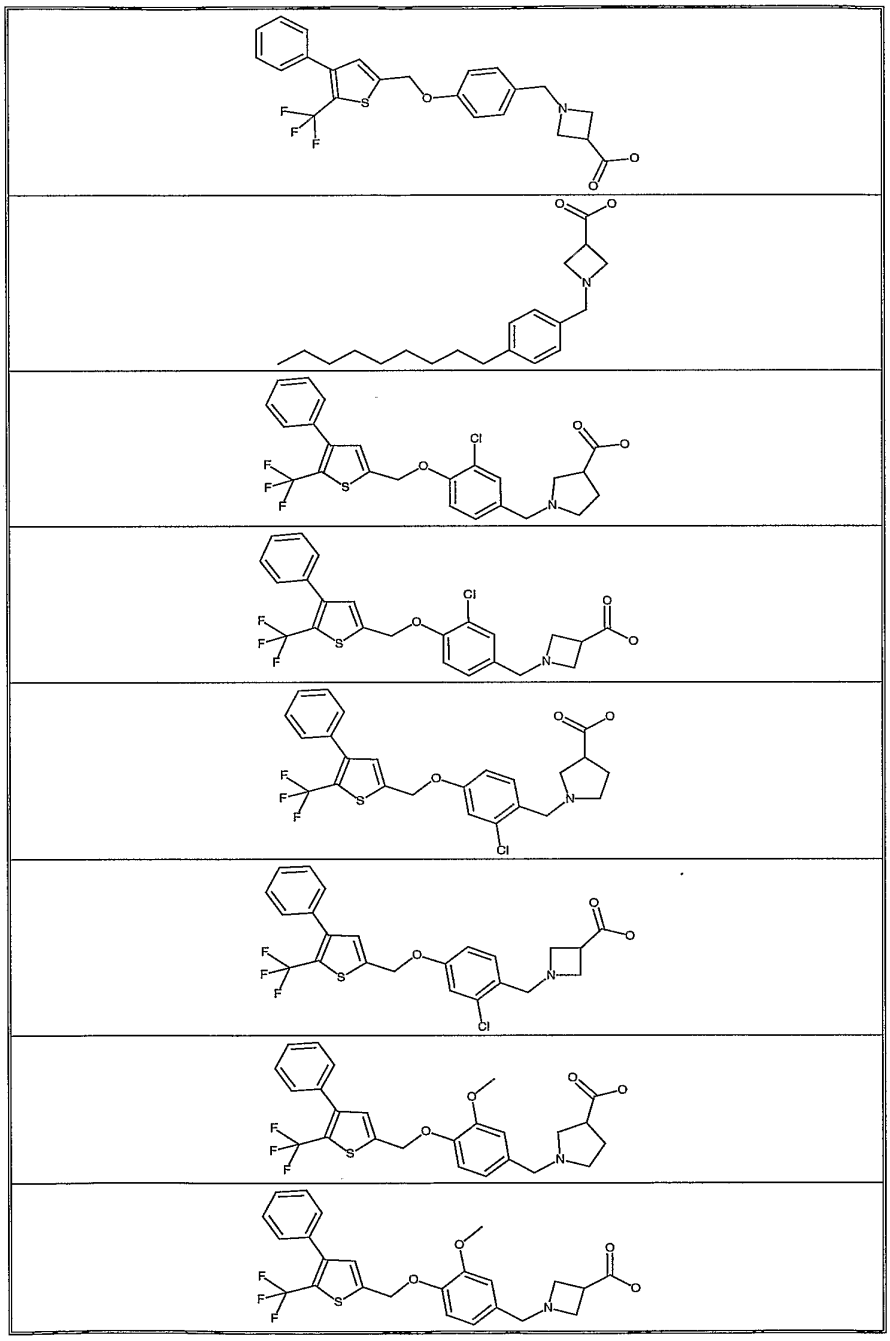
A method of suppressing the immune system in a mammalian patient in need thereof, which comprises administering to the patient an immune system suppressing amount of the compound of Formula I is yet another embodiment.

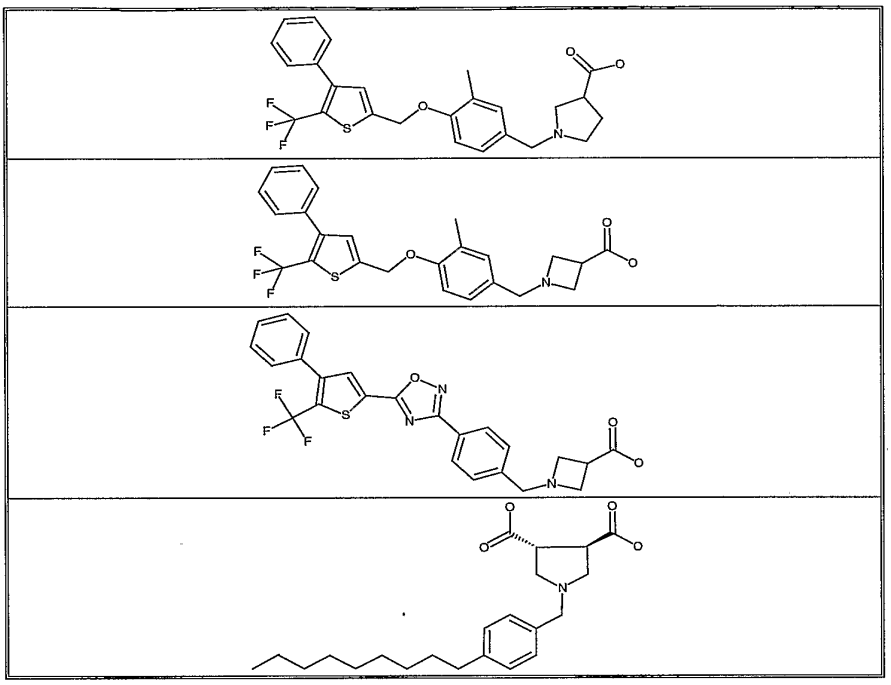
Most particularly, the method described herein encompasses a method of treating or preventing bone marrow or organ transplant rejection which is comprised of admininstering to a mammalian patient in need of such treatment or prevention a compound of formula I, or a pharmaceutically acceptable salt or hydrate thereof, in an amount that is effective for treating or preventing bone marrow or organ transplant rejection.

Furthermore, a preferred group of compounds of the present invention are agonists of the $S1P_1$/Edg1 receptor having selectivity over S1P3/Edg3 receptor. An Edg1 selective agonist has advantages over current therapies and extends the therapeutic window of lymphocytes sequestration agents, allowing better tolerability with higher dosing and thus improving efficacy as monotherapy. The following compounds possesses a selectivity for the $S1P_1$/Edg1 receptor over the S1PR3/Edg3 receptor of at least 20 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the S1P3/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay and possesses an EC_{50} for binding to the $S1P_1$/Edg1 receptor of 100 nM or less as evaluated by the ^{35}S-GTPγS binding assay:









The present invention also includes a pharmaceutical formulation comprising a pharmaceutically acceptable carrier and the compound of Formula I or a pharmaceutically acceptable salt or hydrate thereof. A preferred embodiment of the formulation is one where a second immunosuppressive agent is also included. Examples of such second immunosuppressive agents are, but are not limited to azathioprine, brequinar sodium, deoxyspergualin, mizaribine, mycophenolic acid morpholino ester, cyclosporin, FK-506, rapamycin and FTY720.

The present compounds, including salts and hydrates thereof, are useful in the treatment of autoimmune diseases, including the prevention of rejection of bone marrow transplant, foreign organ transplants and/or related afflictions, diseases and illnesses.

The compounds of this invention can be administered by any means that effects contact of the active ingredient compound with the site of action in the body of a warm-blooded animal. For example, administration, can be oral, topical, including transdermal, ocular, buccal, intranasal, inhalation, intravaginal, rectal,

intracisternal and parenteral. The term "parenteral" as used herein refers to modes of administration which include subcutaneous, intravenous, intramuscular, intraarticular injection or infusion, intrasternal and intraperitoneal.

The compounds can be administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in a combination of therapeutic agents. They can be administered alone, but are generally administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage administered will be dependent on the age, health and weight of the recipient, the extent of disease, kind of concurrent treatment, if any, frequency of treatment and the nature of the effect desired. Usually, a daily dosage of active ingredient compound will be from about 0.1-2000 milligrams per day. Ordinarily, from 1 to 100 milligrams per day in one or more applications is effective to obtain desired results. These dosages are the effective amounts for the treatment of autoimmune diseases, the prevention of rejection of foreign organ transplants and/or related afflictions, diseases and illnesses.

The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets, troches, dragées, granules and powders, or in liquid dosage forms, such as elixirs, syrups, emulsions, dispersions, and suspensions. The active ingredient can also be administered parenterally, in sterile liquid dosage forms, such as dispersions, suspensions or solutions. Other dosages forms that can also be used to administer the active ingredient as an ointment, cream, drops, transdermal patch or powder for topical administration, as an ophthalmic solution or suspension formation, i.e., eye drops, for ocular administration, as an aerosol spray or powder composition for inhalation or intranasal administration, or as a cream, ointment, spray or suppository for rectal or vaginal administration.

Gelatin capsules contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene gycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propylparaben, and chlorobutanol.

Suitable pharmaceutical carriers are described in *Remington's Pharmaceutical Sciences*, A. Osol, a standard reference text in this field.

For administration by inhalation, the compounds of the present invention may be conveniently delivered in the form of an aerosol spray presentation from pressurized packs or nebulisers. The compounds may also be delivered as powders which may be formulated and the powder composition may be inhaled with the aid of an insufflation powder inhaler device. The preferred delivery system for inhalation is a metered dose inhalation (MDI) aerosol, which may be formulated as a suspension or solution of a compound of Formula I in suitable propellants, such as fluorocarbons or hydrocarbons.

For ocular administration, an ophthalmic preparation may be formulated with an appropriate weight percent solution or suspension of the compounds of Formula I in an appropriate ophthalmic vehicle, such that the compound is maintained in contact with the ocular surface for a sufficient time period to allow the compound to penetrate the corneal and internal regions of the eye.

Useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

CAPSULES

A large number of unit capsules are prepared by filling standard two-piece hard gelatin capsules each with 100 milligrams of powdered active ingredient, 150 milligrams of lactose, 50 milligrams of cellulose, and 6 milligrams magnesium stearate.

SOFT GELATIN CAPSULES

A mixture of active ingredient in a digestible oil such as soybean oil, cottonseed oil or olive oil is prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 100 milligrams of the active ingredient. The capsules are washed and dried.

TABLETS

A large number of tablets are prepared by conventional procedures so that the dosage unit is 100 milligrams of active ingredient, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 milligrams of microcrystalline cellulose, 11 milligrams of starch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

INJECTABLE

A parenteral composition suitable for administration by injection is prepared by stirring 1.5% by weight of active ingredient in 10% by volume propylene glycol. The solution is made to volume with water for injection and sterilized.

SUSPENSION

An aqueous suspension is prepared for oral administration so that each 5 milliliters contain 100 milligrams of finely divided active ingredient, 100 milligrams of sodium carboxymethyl cellulose, 5 milligrams of sodium benzoate, 1.0 grams of sorbitol solution, U.S.P., and 0.025 milliliters of vanillin.

The same dosage forms can generally be used when the compounds of this invention are administered stepwise or in conjunction with another therapeutic agent. When drugs are administered in physical combination, the dosage form and administration route should be selected depending on the compatibility of the combined drugs. Thus the term coadministration is understood to include the administration of the two agents concomitantly or sequentially, or alternatively as a fixed dose combination of the two active components.

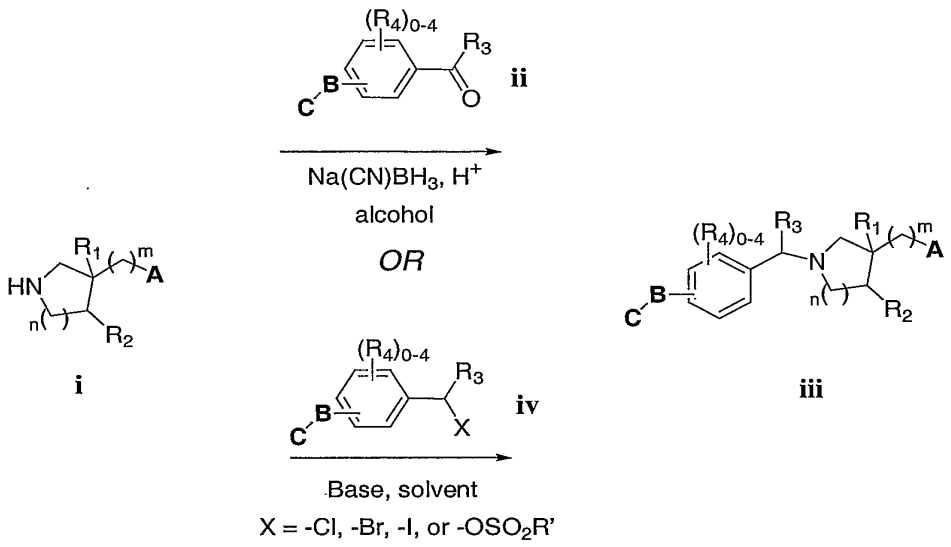
METHODS OF SYNTHESIS

Two general methods that can be employed to prepare compounds in the current invention are depicted in Scheme 1. Intermediates **i** may be available from commercial sources (e.g., azetidine-3-carboxylic acid, where R_1 = H, R_2 = H, m = 0, n

= 0 or pyrrolidine-3-carboxylic acid, where R_1 = H, R_2 = H, m = 0, n = 1) or they can be prepared using methods described below. Combining **i** with an aryl aldehyde **ii** in the presence of an appropriate reducing agent (e.g., sodium cyanoborohydride, sodium triacetoxyborohydride, sodium borohydride) in a compatible solvent (e.g., methanol, ethanol, acetonitrile, methylene chloride) can afford compounds of structure **iii**. Alternatively, intermediates **i** can be combined with a benzyl halide or sulfonate ester **iv** in the presence of an appropriate base (e.g., sodium carbonate, potassium carbonate, triethylamine, N,N-diisopropylethylamine) in a compatible solvent solvent (e.g., methanol, ethanol, acetonitrile) at or above room temperature to give compounds of structure **iii**. In cases where **A** in structure **i** would interfere with the transformation to **iii**, an appropriate protecting group (Greene & Wuts, eds., "Protecting Groups in Organic Synthesis", John Wiley & Sons, Inc.) that would mask **A** and allow for the liberation of **A** after coupling with either **ii** or **iv** can be employed. In cases where **iii** contains asymmetric centers, the individual stereoisomers of **iii** can obtained by methods known to those skilled in the art which include (but are not limited to): stereospecific synthesis, resolution of salts of **iii** or any of the intermediates used in its preparation with enantiopure acids or bases, resolution of **iii** or any of the intermediates used in its preparation by HPLC employing enantiopure stationary phases.

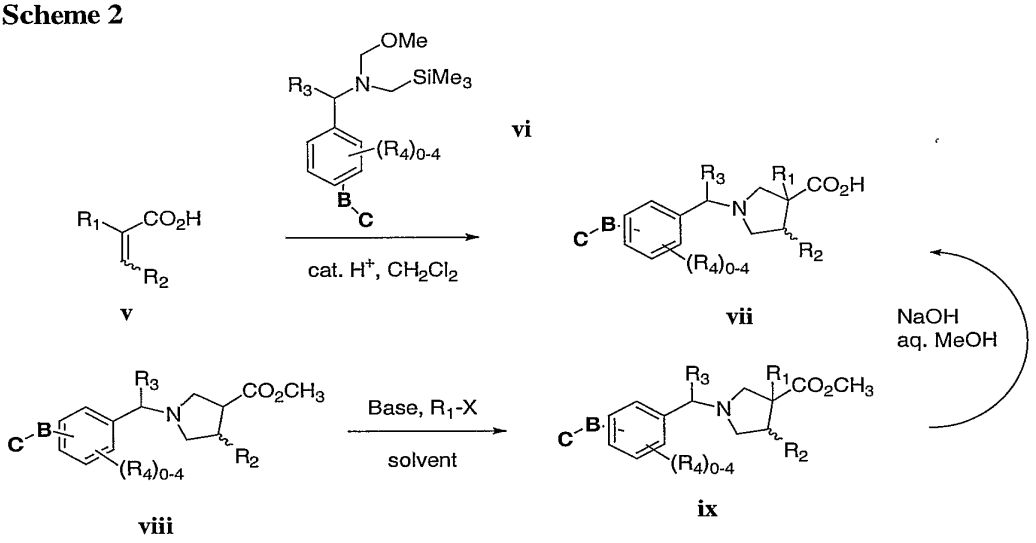
Compounds in the current invention in which m = 0, n = 1 and **A** = $-CO_2H$ can be prepared using methods shown in Scheme 2. An acrylic acid (**v**) substituted with

Scheme 1



functional groups R_1 and/or R_2 (e.g., R_1 and/or R_2 = H, alkyl, trihaloalkyl or carboxy) can be reacted with an azomethine ylide generated from **vi** in the presence of a catalytic amount of an acid (e.g., trifluoroacetic acid, phosphoric acid) in an appropriate solvent (e.g., methylene chloride, acetonitrile) to give compounds of the structure **vii**. Alternatively, **viii** (prepared similarly to **vii**, but employing an acrylate ester as the starting material) can be treated with a strong base (e.g., lithium diisopropylamide, sodium bis(trimethylsilyl)amide, potassium bis(trimethylsilyl)amide) in an ethereal solvent (e.g., THF, 1,2-dimethoxyethane) at or below room temperature followed by an electrophile (e.g., methyl iodide, 2-(phenylsulfonyl)-3-phenyloxaziridine, fluorobenzenesulfonimide) to give **ix**. Saponification of **ix** can then give **vii**. In cases

Scheme 2



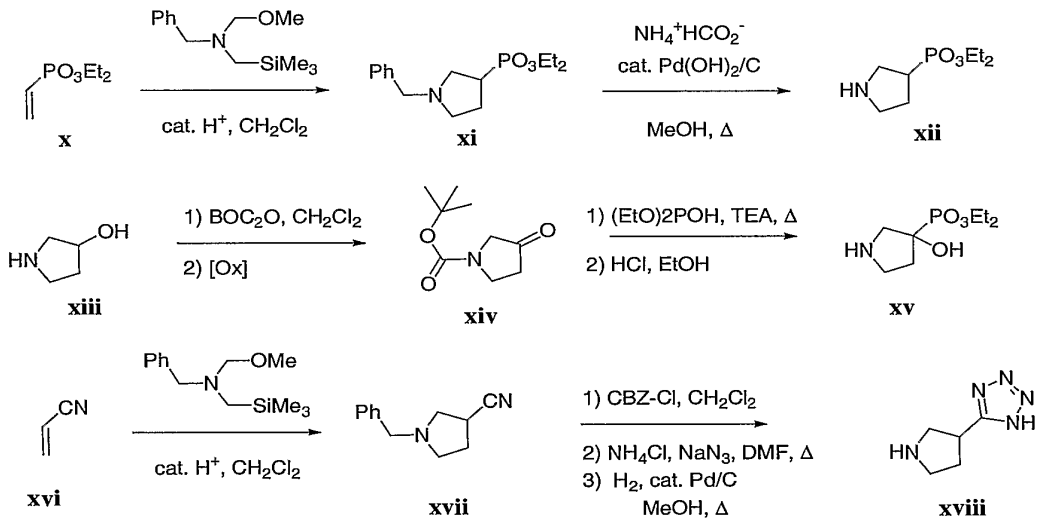
where **vii** contains asymmetric centers, individual stereoisomers can be obtained using methods similar to those described for **iii** in Scheme 1.

Several methods that can be used to prepare compounds that could be employed as intermediate **i** in Scheme 1 above are shown in Scheme 3. For cases where m = 0, n = 1, R_1 = H, R_2 = H and **A** = -PO_3H_2, diethyl vinylphosphonate (**x**) can be reacted with N-methoxymethyl-N-trimethylsilylmethyl benzyl amine in in the presence of a catalytic amount of an acid (e.g., trifluoroacetic acid, phosphoric acid) in an appropriate solvent (e.g., methylene chloride, acetonitrile) to a give compound of the structure **xi**. Cleavage of the N-benzyl group using catalytic hydrogenation (H_2, $Pd(OH)_2/C$, HOAc; ammonium formate, $Pd(OH)_2/C$, MeOH) or chemical methods (1-chloroethyl chloroformate, DCE, reflux, followed by MeOH, reflux) can give **xii**. For cases where m = 0, n = 1, R_1 = OH, R_2 = H and **A** = -PO_3H_2, N-t-butoxycarbonyl protection of 3-hydroxypyrrolidine (**xiii**) followed by mild oxidation (e.g., treatment with oxalyl chloride and DMSO at – 78 °C in dichloromethane followed by a trialkylamine base and warming (Swern oxidation); treatment with 4-methylmorpholine N-oxide and catalytic tetrapropylammonium peruthenate in acetonitrile) can give **xiv**. Treating **xiv** with a dialkylphosphite in the presence of a tertiary amine base (triethylamine, N,N-diisopropylethylamine) at or above room

temperature followed by removal of the t-butylcarbamate under acidic conditions (e.g., HCl in MeOH, neat TFA) can give **xv**. For cases where m = 0, n = 1, R_1 = H, R_2 = H and **A** = 5-tetrazolyl, acrylonitrile (**xvi**) can be reacted with N-methoxymethyl-N-trisilylmethyl benzyl amine in the presence of a catalytic amount of an acid (e.g., trifluoroacetic acid, phosphoric acid) in an appropriate solvent (e.g., methylene chloride, acetonitrile) to a give compound of the structure **xvii**. Converting the N-benzyl group of **xvii** to a benzyl carbamate following by tetrazole formation (e.g., ammonium chloride, sodium azide, DMF at elevated temperature; trimethyltin azide, toluene, reflux) then catalytic hydrogenation can give **xviii**.

Several methods that can be used to prepare compounds that can be employed as intermediate **ii** in Scheme 1 above are shown in Scheme 4. Many aryl carboxylic acids, aryl carboxylic acid halides, aryl carboxylic esters, and aryl N-alkoxyl-N-alkyl carboxamides (**xix**) are commercially available and can be converted to aryl aldehydes (**xx**) using reduction methods known by those skilled in the art (see Larock, "Comprehensive Organic Transformations, A Guide to Functional Group Preparations", VCH Publishers, Inc.). Alternatively, many benzyl alcohols (**xxi**) are commercially

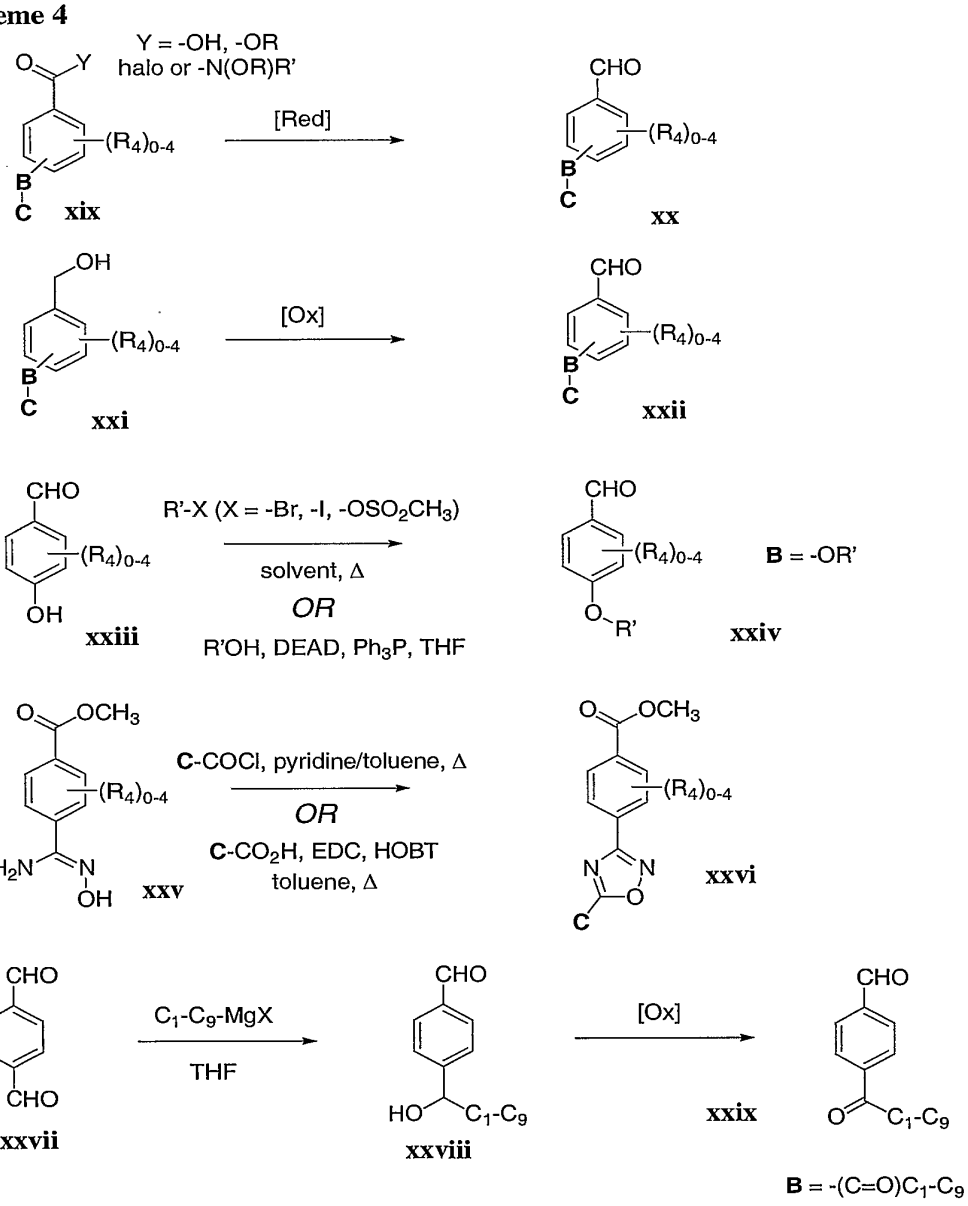
Scheme 3



available and can be converted to aryl aldehydes (**xxii**) using oxidation methods known by those skilled in the art. For cases where **B** = alkoxy, a hydroxy benzaldehyde **xxiii** can be combined with a alkyl halide or sulfonate ester in the presence of an appropriate base (e.g., sodium carbonate, potassium carbonate, triethylamine, N,N-diisopropylethylamine) in a compatible solvent solvent (e.g., methanol, ethanol, acetonitrile) at or above room temperature to give compounds of structure **xxiv**. Alternatively, a hydroxy benzaldehyde **xxiii** can be combined with an alcohol, a dialkyl azodicarboxylate (e.g., diethyl azodicarboxylate, diisopropylazodicarboxylate) and triphenylphosphine in an appropriate solvent (THF, toluene, methylene chloride) to give **xxiv**. For cases where **B** is 1,2,4-oxadiazolyl, N-hydroxyamidine **xxv** can be treated with an acid chloride in an appropriate solvent (xylenes, toluene) in the presence of an amine base (pyridine, DBU) with heating to give an intermediate **xxvi**. Alternatively, **xxv** can be treated with a carboxylic acid, a carbodiimide (e.g., N,N'-dicyclohexylcarbodiimide, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide) and 1-hydroxybenzotriazole in an appropriate solvent (xylenes, toluene) to give **xxvi**. Prepared by either manner, the ester group of **xxvi** can be

converted to aldehyde with methods employed to convert **xix** to **xx**. For cases where **B** is $-(C=O)C_{6-11}$ alkyl and R_4 = H, an aryl 1,4-dialdehyde (**xxvii**) can be treated with a limiting amount of an alkyl organometallic reagent (e.g., alkyl magnesium bromide, alkyl lithium) at or below room temperature in an ethereal solvent (e.g., THF, diethyl ether, 1,2-dimethoxyethane) to afford intermediate **xxviii**. Mild oxidation of **xxviii**(e.g., treatment with oxalyl chloride and DMSO at – 78 °C in dichloromethane followed by a trialkylamine base and warming (Swern oxidation); treatment with 4-methylmorpholine N-oxide and catalytic tetrapropylammonium peruthenate in acetonitrile) can give aldehyde **xix**.

Scheme 4



Methods for preparing the compounds of this invention are further illustrated in the following examples. Alternative routes will be easily discernible to practitioners in the field.

GENERAL

Concentration of solutions was carried out on a rotary evaporator under reduced pressure. Conventional flash chromatography was carried out on silica gel (230-400 mesh). Flash chromatography was also carried out using a Biotage Flash Chromatography apparatus (Dyax Corp.) on silica gel (32-63 mM, 60 Å pore size) in pre-packed cartridges of the size noted. NMR spectra were obtained in $CDCl_3$ solution unless otherwise noted. Coupling constants (J) are in hertz (Hz). Abbreviations: diethyl ether (ether), triethylamine (TEA), N,N-diisopropylethylamine (DIEA), saturated aqueous (sat'd), room temperature (rt), hour(s) (h or hr), minute(s) (min). For the tables that follow any NMR data follows the compounds.

HPLC CONDITIONS

LC-1: Waters Xterra MS C18, 5 μ, 4.6 x 50 mm column, 10:90 to 95:5 v/v CH_3CN/H_2O + 0.05% TFA over 4.5 min, hold 1 min, PDA detection 200-600 nm, flow rate = 2.5 mL/min.

LC-2: Analytical Sales and Service Armor C8 5 μ 20 x 100 mm column, 10:90 to 90:10 v/v CH_3CN/H_2O + 0.05% TFA over 12 min, hold 4 min, UV detection at either 210 or 254 nM, flow rate = 10 mL/min.

PREPARATION OF ALDEHYDE INTERMEDIATES

Aldehyde 1

4-Nonylbenzaldehyde

A solution of 2.0 g (7.5 mmol) of 4-nonylbenzoyl chloride in 75 mL of THF at –78 °C was treated with 7.5 mL (7.5 mmol) of 1M lithium tri-(tert-butoxy) aluminum hydride in THF. After 30 min at –78 °C, the reaction was quenched with

2N HCl and was allowed to warm to rt. The mixture was poured into Et_2O and washed with 2N HCl, sat'd $NaHCO_3$ and sat'd NaCl. The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified on a 40M Biotage column using 100:1 v/v hexane/Et_2O as the eluant to afford 708 mg (41%) of the title compound: ^{1}H-NMR (500 MHz) δ 0.87 (t, J = 7.0, 3H), 1.26-1.31 (m, 12H), 1.60-1.66 (m, 2H), 2.68 (t, J = 7.8, 2H), 7.32 (d, J = 8.0, 2H), 7.79 (d, J = 8.0, 2H), 9.97 (s, 1H).

Aldehyde 2

4-Decylbenzaldehyde

The title compound was prepared using a procedure analogous to Aldehyde 1 substituting 4-decylbenzoyl chloride for 4-nonylbenzoyl chloride: ^{1}H-NMR (500 MHz) δ 0.87 (t, J = 6.9, 3H), 1.25-1.31 (m, 14H), 1.60-1.66 (m, 2H), 2.68 (t, J = 7.7, 2H), 7.33 (d, J = 8.0, 2H), 7.79 (d, J = 8.0, 2H), 9.97 (s, 1H).

Aldehyde 3

3-(Octyloxy)benzaldehyde

A mixture of 1.00 g (0.82 mmol) of 3-hydroxybenzaldehyde, 1.70 g (12.2 mmol) of potassium carbonate and 2.16 g (9.00 mmol) of 1-iodooctane were warmed in acetonitrile at 80 °C for 16 h. The reaction was cooled, filtered and concentrated. The residue was purified using flash chromatography using 20:1 v/v hexane/ethyl acetate to afford 1.63 g of the title compound as a colorless oil: ^{1}H-NMR (500 MHz) δ 0.89 (t, J = 6.9, 3H), 1.24-1.39 (m, 8H), 1.42-1.50 (m, 2H), 1.80 (m, 2H), 4.01 (t, J = 6.6, 2H), 7.19 (m, 1H), 7.40 (s, 1H), 7.44-7.46 (m, 2H), 9.99 (s, 1H).

Aldehyde 4

4-(Octyloxy)benzaldehyde

The title compound was prepared using a procedure analogous to Aldehyde 3 substituting 4-hydroxybenzaldehyde for 3-hydroxybenzaldehyde: ^{1}H NMR (500 MHz) δ 0.91 (t, J = 6.9, 3H), 1.29-1.41 (m, 8H), 1.46-1.52 (m, 2H), 1.71-1.86 (m, 2H), 4.06 (t, J = 6.6, 2H), 7.01 (d, J = 8.7, 2H), 7.85 (d, J = 8.7, 2H), 9.90 (s, 1H).

Aldehyde 5

3-Bromo-5-methoxy-4-octyloxybenzaldehyde

The title compound was prepared using a procedure analogous to Aldehyde 3 substituting 3-bromo-4-hydroxy-5-methoxybenzaldehyde for 3-hydroxybenzaldehyde: ESI-MS: 343 (M+H)

Aldehyde 6

3-Ethoxy-4-(octyloxy)benzaldehyde

The title compound was prepared using a procedure analogous to Aldehyde 3 substituting 3-ethoxy-4-hydroxybenzaldehyde for 3-hydroxybenzaldehyde: ^{1}H-NMR (500 MHz) δ 0.88-0.98 (m, 3H), 1.30-1.41 (m, 8H), 1.46-1.51 (m, 5H), 1.85-1.91 (m, 2H), 4.06-4.18 (m, 4H), 6.97 (d, J = 8.0, 1H), 7.39-7.44 (m, 2H), 9.84 (s, 1H); ESI-MS 279.1 (M+H).

Aldehyde 7

3,5-Dibromo-4-(octyloxy)benzaldehyde

The title compound was prepared using a procedure analogous to Aldehyde 3 substituting 3,5-dibromo-4-hydroxybenzaldehyde for 3-hydroxybenzaldehyde.

Aldehyde 8

3-Methoxy-4-(octyloxy)benzaldehyde

The title compound was prepared using a procedure analogous to Aldehyde 3 substituting 3-methoxy-4-hydroxybenzaldehyde for 3-hydroxybenzaldehyde: ESI-MS 265.2 (M+H)

Aldehyde 9

3-Methyl-4-(octyloxy)benzaldehyde

The title compound was prepared using a procedure analogous to Aldehyde 3 substituting 3-methyl-4-hydroxybenzaldehyde for 3-hydroxybenzaldehyde.

Aldehyde 10

4-(Octyloxy)-1-naphthaldehyde

The title compound was prepared using a procedure analogous to Aldehyde 3 substituting 4-hydroxy-1-naphthaldehyde for 3-hydroxybenzaldehyde.

Aldehyde 11

2-Chloro-4-(octyloxy)benzaldehyde

The title compound was prepared using a procedure analogous to Aldehyde 3 substituting 2-chloro-4-hydroxybenzaldehyde for 3-hydroxybenzaldehyde: ESI-MS 269.0 (M+H)

Aldehyde 12

3-Chloro-4-(octyloxy)benzaldehyde

The title compound was prepared using a procedure analogous to Aldehyde 3 substituting 3-chloro-4-hydroxybenzaldehyde for 3-hydroxybenzaldehyde.

Aldehyde 13

4-(*trans*-3,7-Dimethyl-2,6-octadien-1-yloxy)benzaldehyde

The title compound was prepared using a procedure analogous to Aldehyde 3 using 4-hydroxybenzaldehyde and geranyl bromide: R_F: 0.29 (19:1 v/v hexane/EtOAc); ^{1}H-NMR (500 MHz) δ 1.58-1.83 (m, 9H), 2.00-2.16 (m, 4H), 4.65 (d, J = 6.6, 2H), 5.10 (m, 1H), 5.50 (m, 1H), 7.02 (d, J = 8.7, 2H), 7.85 (d, J = 8.7, 2H), 9.90 (s, 1H).

Aldehyde 14

4-[Bis(3,5-trifluoromethyl)benzyloxy]benzaldehyde

The title compound was prepared using a procedure analogous to Aldehyde 3 using 4-hydroxybenzaldehyde and bis(3,5-trifluoromethyl)benzyl bromide: R_F: 0.28 (9:1 v/v hexane/EtOAc); ^{1}H-NMR (500 MHz) δ 5.28 (s, 2H), 7.14 (d, J = 8.7, 2H), 7.91-7.95 (m, 5H), 9.95 (s, 1H).

Aldehyde 15

3-(4-(Formyl)phenyl)-5-(4-phenyl-5-trifluoromethyl-2-thienyl)-1,2,4-oxadiazole

Step A: (E/Z)-2-Phenyl-3-chloro-4,4,4-trifluoro-2-butanal

Phosphorous oxychloride (7.5 mL, 80 mmol) was added to 15 mL of DMF at 0 °C. The resulting mixture was warmed to rt and stirred for 1 h. A solution of 5.0 g (26.6 mmol) of 1,1,1-trifluoromethyl-3-phenyl-2-propanone in 1 mL of DMF was added and the resulting mixture was stirred at 70 °C for 20 h. The reaction mixture was cooled to rt, poured onto 150 g of ice and stirred at ambient temperature for 1 h. The quenched mixture was extracted with 200 mL of ether. The extract was washed with 200 mL of water, dried and concentrated. Chromatography on a Biotage 40 M cartridge using hexanes (4L) as the eluant afforded 5.1 g (82%) of the title compound.

Step B: Ethyl (4-phenyl-5-trifluoromethyl)thiophene-2-carboxylate

Ethyl mercaptoacetate (2.75 mL, 25.0 mmol) was added to a suspension of 600 mg (25 mmol) of NaH in 45 mL of THF maintaining the internal temperature at 25 °C. A solution of 5.10 g (21.7 mmol) of (E/Z)-2-phenyl-3-chloro-4,4,4-trifluoro-2-butanal (from Step A) was added and the resulting mixture was stirred at rt for 20 h. The reaction was quenched with 50 mL of sat'd NH_4Cl and the resulting mixture was partitioned between 250 mL of ether and 100 mL of water. The organic layer was separated, dried and concentrated. Chromatography on a Biotage 40 M cartridge using hexanes (1L), then 4:1 v/v hexanes/CH_2Cl_2 (1L) as the eluant afforded 5.10 g (78%) of the title compound: ^1H NMR (400 Mhz) δ 1.40 (t, J= 7.2, 3H), 4.39 (q, J= 7.2, 2H), 7.42 (app s, 5H), 7.74 (q, J=1.6, 1H).

Step C: (4-Phenyl-5-trifluoromethyl)thiophene-2-carboxylic acid

A solution of 5.10 g (17.0 mmol) of ethyl 4-phenyl-5-trifluoromethyl-thiophene-2-carboxylate (from Step B) in 20 mL of EtOH was treated with 10 mL of 5.0 N NaOH and stirred at rt for 30 min. The EtOH was removed in vacuo. The residual aqueous mixture was acidified to pH 2 with 1 N HCl, then extracted with 300 mL of 1:1 v/v EtOAc/ether. The extract was separated, dried and concentrated. Recrystallization from 200 mL of 20:1 v/v hexanes/ether afforded 4.30 g (93%) of the title compound: ^1H NMR (500 Mhz) δ 7.43 (app s, 5H), 7.84 (app s, 1H); ^{13}C

NMR ($CDCl_3$, 125 Mhz) δ 121.7 (q, J= 269), 128.5, 128.6, 128.8, 132.5 (q, J= 36), 133.3, 133.8, 137.5, 144.8, 167.0.

Step D: 3-[4-(Carbomethoxy)phenyl]-5-(4-phenyl-5-trifluoromethyl-2-thienyl)-1,2,4-oxadiazole

A solution of 408 mg (1.5 mmol) of 4-phenyl-5-trifluoromethyl-thiophene-2-carboxylic acid and 1 mL of oxalyl chloride in 5 mL of CH_2Cl_2 was treated with 5 drops of DMF. The resulting mixture was stirred at rt for 1 h, then concentrated. The crude acid chloride and 291 mg (1.5 mmol) of 4-(carbomethoxy)benzamidoxime were dissolved in 7 mL of 6:1 v/v xylenes/pyridine. The resulting solution was heated at 140 °C for 1 h, then cooled. The mixture was partitioned between 50 mL of 1:1 EtOAc/ether and 50 mL of 1 N HCl. The organic layer was separated, washed with 3 x 50 mL of 1 N HCl, 50 mL of sat'd $NaHCO_3$, dried and concentrated. Chromatography on a Biotage 40 M cartridge using hexanes (1L), then 20:1 v/v hexanes/EtOAc (1L) as the eluant afforded 423 mg (65%) of the title compound: ^1H NMR (500 Mhz) δ 3.97 (s, 3H), 7.48 (app s, 5H), 7.92 (s, 1H), 8.18 (app d, J= 8.5, 2H), 8.23 (app d, J= 8.5, 2H).

Step E: 3-[4-(Hydroxymethyl)phenyl]-5-(4-phenyl-5-trifluoromethyl-2-thienyl)-1,2,4-oxadiazole

A solution of 390 mg (0.91 mmol) of 3-[4-(carbomethoxy)phenyl]-5-(4-phenyl-5-trifluoromethyl-2-thienyl)-1,2,4-oxadiazole (from Step D) in 10 mL of CH_2Cl_2 at –78 °C was treated with 2.7 mL of 1.0 M DIBALH solution in CH_2Cl_2. The resulting solution was stirred cold for 1 h, then quenched with 5 mL of sat'd Rochelle salt solution. The mixture was partitioned between 100 mL CH_2Cl_2 and 50 mL of 1 N NaOH. The organic layer was separated, dried and concentrated. Chromatography on a Biotage 40 S cartridge using 4:1 v/v hexanes/EtOAc (1L) as the eluant afforded 325 mg (89%) of the title compound: ^1H NMR (500 Mhz) δ 1.80 (app s, 1H), 4.80 (d, J= 4.0, 2H), 7.46-7.48 (5H), 7.52 (d, J= 8.0, 2H), 7.91 (q, J= 1.5, 1H), 8.14 (d, J= 8.0, 2H).

Step F: 3-[4-(Formyl)phenyl]-5-(4-phenyl-5-trifluoromethyl-2-thienyl)-1,2,4-oxadiazole

A mixture of 310 mg (0.77 mmol) of 3-[4-(hydroxymethyl)phenyl]-5-(4-phenyl-5-trifluoromethyl-2-thienyl)-1,2,4-oxadiazole (from Step E), 527 mg (1.5 mmol) of 4-methylmorpholine N-oxide and 500 mg of 4 A molecular sieves in 15 mL of CH_3CN was treated with 12 mg (0.034 mmol) of tetrapropylammonium perruthnate and the resulting mixture was stirred ar rt for 2 h. The solids were filtered and the filtrated was concentrated. Chromatography on a Biotage 40 S cartridge using 9:1 v/v hexanes/EtOAc (1L) as the eluant afforded 205 mg (66%) of the title compound: ^{1}H NMR (500 Mhz) δ 7.48 (app s, 5H), 7.93 (app s, 1H), 8.03 (d, J= 8.5, 2H), 8.33 (d, J= 8.5, 2H), 10.1 (s, 1H).

Aldehyde 16

4-[(4-Phenyl-5-trifluoromethyl-2-thienyl)methoxy]benzaldehyde

Step A: 2-Hydroxymethyl-4-phenyl-5-trifluoromethyl-thiophene

A solution of 2.10 g (7.7 mmol) of 4-phenyl-5-trifluoromethyl-thiophene-2-carboxylic acid (from Aldehyde 15, Step C) in 20 mL of THF was treated with 5.0 mL of 2.0 M borane dimethylsulfide complex in THF. The resulting solution was heated at reflux for 3 h, cooled to rt, quenched with 10 mL of MeOH and concentrated. Chromatography on a Biotage 40M cartridge using 9:1 v/v hexanes/EtOAc as the eluant afforded 1.95 g (98%) of the title compound: ^{1}H NMR (500 Mhz) δ 2.05 (app s, 1H), 4.87 (s, 2H), 6.99 (s, 1H), 7.41 (app s, 5H).

Step B: 4-((4-Phenyl-5-trifluoromethyl-2-thienyl)methoxy)benzaldehyde

A solution of 1.95 g (7.5 mmol) of 2-hydroxymethyl-4-phenyl-5-trifluoromethyl-thiophene (from Step A), 925 mg (7.6 mmol) of 4-hydroxybenzaldehyde and 3.0 g (11.4 mmol) of triphenylphosphene in 40 mL of THF at 0 °C was treated with 2.0 g (11.4 mmol) of diethylazodicarboxylate. The resulting mixture was warmed to rt, stirred for 2 h, then concentrated. Chromatography on a Biotage 75S cartridge using 9:1 v/v heptane/EtOAc as the eluant afforded 2.5 g of impure title compound. Chromatography on a Biotage 40M cartridge using 19:1 v/v

hexanes/EtOAc (1L), then 4:1 v/v hexanes/EtOAc (1L) as the eluant afforded 1.65 g (60%) of the title compound: ^{1}H NMR (500 Mhz) δ 5.32 (s, 2H), 7.10 (d, J= 8.5, 2H), 7.12 (s, 1H), 7.41-7.43 (5H), 7.85-7.90 (2H), 9.92 (s, 1H).

Aldehydes 17-21 were prepared using procedures analogous to those described in Aldehyde 16 substituting the appropriately substituted benzaldehyde for 4-(hydroxy)benzaldehyde in Step B:

Aldehyde 17

3-((4-Phenyl-5-trifluoromethyl-2-thienyl)methoxy)benzaldehyde

Aldehyde 18

2-Chloro-4-((4-phenyl-5-trifluoromethyl-2-thienyl)methoxy)benzaldehyde

Aldehyde 19

3-Chloro-4-((4-phenyl-5-trifluoromethyl-2-thienyl)methoxy)benzaldehyde

Aldehyde 20

3-Methyl-4-((4-phenyl-5-trifluoromethyl-2-thienyl)methoxy)benzaldehyde

Aldehyde 21

3-Methoxy-4-((4-phenyl-5-trifluoromethyl-2-thienyl)methoxy)benzaldehyde

Aldehyde 22

4-(4-Phenylbutoxy)benzaldehyde

The title compound was prepared using a procedure analogous to Aldehyde 4 substituting 4-(iodobutyl)benzene for 1-iodooctane: ESI-MS 255.2 (M+H)

Aldehyde 23

4-(Non-1-oyl)benzaldehyde

Step A: 4-(1-Hydroxynon-1-yl)benzaldehyde

Terephthaldicarboxaldehyde (2.00 g, 14.91 mmol) was dissolved in tetrahydrofuran (25 ml) and cooled to 0°C. Octylmagnesium chloride (7.5 ml, 2.0M in THF, 15 mmol) was added dropwise. After 15 minutes, the reaction was quenched with 2N aqueous hydrochloric acid (50 ml) and diluted with ethyl acetate (50 ml). The organic layer was separated, washed with sat'd NaCl (50 ml), dried over magnesium sulfate and concentrated . Silica gel chromatography eluting with 91:9 v/v hexane/EtOAc gave 0.19 g (0.77 mmol, 5.1%) of the title compound: ^{1}H NMR (500 MHz) δ 10.0 (s, 1H), 7.87 (d, J = 8.0, 2H), 7.52 (d, J = 8.3, 2H), 4.75-4.80 (m, 1H), 1.68-1.82 (m, 2H), 1.22-1.45 (m, 12H), 0.91 (t, J = 7.0, 3H).

Step B: 4-(Non-1-oyl)benzaldehyde

Dess-Martin periodinane (0.268 g, 0.632 mmol) was added to a solution of 4-(1-hydroxynon-1-yl)benzaldehyde (0.125 g, 0.505 mmol) from Step A in CH_2Cl_2 (3.0 ml). After 1 h, the reaction was filtered and concentrated. Silica gel chromatography eluting with 19:1 v/v hexane/EtOAc gave 0.107 g (0.446 mmol, 88%) of the title compound: ^{1}H NMR (500 MHz) δ 10.1 (s, 1H), 8.10 (d, J = 8.2, 2H), 7.97 (d, J = 8.2, 2H), 3.00 (t, J = 7.3, 2H), 1.70-1.8 (m, 2H), 1.22-1.42 (m, 10H), 0.88 (t, J = 7.0, 3H).

Aldehyde 24

Heptyl 4-(formyl)benzoate

The title compound was prepared through a condensation between 1-heptanol and 4-formylbenzoic acid. ^{1}H NMR (500 MHz , $CDCl_3$): δ 10.10 (s, 1H), 8.20 (d, J = 8.2, 2H), 7.95 (d, J = 8.2, 2H), 4.35 (t, J = 6.8, 2H), 1.75-1.85 (m, 2H), 1.40-1.50 (m, 2H), 1.25-1.40 (m, 6H), 0.89 (t, J = 7.0, 3H).

Aldehydes 25 and 26 were prepared using procedures analogous to those described in Aldehyde 16 substituting the appropriately substituted alcohol for 2-hydroxymethyl-4-phenyl-5-trifluoromethyl-thiophene in Step B:

Aldehyde 25

4-[(Benzothien-2-yl)methoxy]benzaldehyde

^{1}H NMR (500 MHz) δ 5.34 (s, 2H), 7.04 (d, J = 8.7, 2H), 7.18 (s, 1H), 7.25-7.30 (m, 4H), 7.76 (d, J = 8.7, 2H), 9.82 (s, 1H).

Aldehyde 26

4-[(2,3-Diphenyl-2H-pyrazol-5-yl)methoxy]benzaldehyde

^{1}H NMR (500 MHz) δ 5.21 (s, 2H), 6.55 (s, 1H), 7.10 (d, J = 8.7, 2H), 7.14-7.17 (m, 5H), 7.21-7.30 (m, 5H), 7.79 (d, J = 8.7, 2H), 9.82 (s, 1H).

PREPARATION OF EXAMPLES

EXAMPLE 1

(R/S)-1-(4-(Nonyl)phenyl)methyl-3-hydroxy-pyrrolidin-3-yl)phosphonic acid

Step A: (R/S)-1-tert-Butoxycarbonyl-3-hydroxypyrrolidine

A solution of 2.5 g (28.7 mmol) of (R/S)-3-hydroxypyrrolidine in 10 mL of CH_2Cl_2 at 0 °C was treated with 6.89 g (31.6 mmol) of di-tert-butyl-dicarbonate in 2 mL CH_2Cl_2 and 0.35 g (2.8 mmol) of 4-(N,N-dimethylamino) pyridine. After stirring for 10 min, the reaction was warmed to rt and stirred overnight. The reaction was diluted with 100 mL of CH_2Cl_2 and washed with 100 mL of 1N HCl and 100 mL of 1N $NaHCO_3$. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified on a 40M Biotage column using 7:3 v/v hexane/acetone as the eluant to afford 5.3 g (99%) of the title compound: R_F: 0.26 (7:3 v/v hexane/acetone); ^{1}H-NMR (500 MHz) δ 1.45 (s, 9H), 1.88-2.00 (m, 2H), 2.52 (br s, 1H), 3.29-3.50 (m, 4H), 4.42 (m, 1H).

Step B: 1-tert-Butoxycarbonyl-3-oxo-pyrrolidine

A solution of 2.3 mL (26 mmol) of oxalyl chloride in 80 mL of CH_2Cl_2 at -78 °C was treated with 3.8 mL (53 mmol) of DMSO in 5 mL of CH_2Cl_2. The resulting mixture was stirred cold for 5 min. A solution of 2.0 g (10.7 mmol) of (R/S)-1-tert-butoxycarbonyl-3-hydroxypyrrolidine (from Step A) in 10 mL of CH_2Cl_2 was added. The resulting mixture was stirred for 30 min, treated with 18.7 mL (107 mmol) of DIEA and warmed to 0 °C. After stirring for 45 min, the reaction was quenched with H_2O and poured into 100 mL of 1N HCl. After separating the layers, the organic layer was washed with 100 mL sat'd NaCl, dried over Na_2SO_4 and concentrated. The residue was purified on a 40M Biotage column using 4:1 v/v hexane/acetone as the eluant to afford 1.9 g (96%) of the title compound: R_F: 0.49 (7:3 v/v hexane/acetone); ^{1}H-NMR (500 MHz) δ 1.48 (s, 9H), 2.58 (t, J = 7.9, 2H), 3.71-3.78 (m, 4H).

Step C: (R/S)-1-tert-Butoxycarbonyl-3-hydroxy-pyrrolidin-3-yl phosphonic acid, diethyl ester

A mixture of 1.9 g (10.3 mmol) of 1-tert-butoxycarbonyl-3-oxopyrrolidine (from Step B), 1.3 mL (10.3 mmol) of diethyl phosphite and 1.4 mL (10.3 mmol) of TEA was stirred at 100 °C for 1.5 h. Volatiles were removed under reduced pressure. The residue was purified on a 40M Biotage column using 13:7 v/v hexane/acetone as the eluant to afford 1.78 g (53%) of the title compound as a yellow oil: R_F: 0.16 (7:3 v/v hexane/acetone); ^{1}H-NMR (500 MHz) δ 1.33 (t, J = 7.0, 6H), 1.45 (s, 9H), 2.08 (m, 1H), 2.18 (m, 1H), 3.47-3.64 (m, 4H), 4.13-4.22 (m, 4H).

Step D: (R/S)-3-Hydroxy-pyrrolidin-3-yl phosphonic acid, diethyl ester

A solution of 1.78 g (5.5 mmol) of (R/S)-1-tert-butoxycarbonyl-3-hydroxy-pyrrolidin-3-yl phosphonic acid, diethyl ester (from Step C) in 2N HCl in EtOH was stirred at rt for 5.5 h. The reaction was concentrated from CH_2Cl_2 several times. The crude product was partitioned between aqueous NH_4OH and $CHCl_3$/isopropanol (3:1 v/v). After separating phases, the aqueous layer was extracted with 3X $CHCl_3$/isopropanol (3:1 v/v). The combined organics were dried over Na_2SO_4 and concentrated. The residue was purified on a 40S Biotage column using 90:10:1 v/v/v CH_2Cl_2/MeOH/NH_4OH as the eluant to afford the title

compound as a light brown oil: ^{1}H-NMR (500 MHz) δ 1.35 (t, J = 7.0, 6H), 1.92 (m, 1H), 2.20 (m, 1H), 2.78-2.99 (m, 3H), 3.06 (dd, J = 12.7, 3.7, 1H), 3.13 (dd, J = 12.7, 6.2, 1H), 3.20 (m, 1H), 4.16-4.23 (m, 4H).

Step E: (R/S)-1-(4-(Nonylphenyl)methyl-3-hydroxy-pyrrolidin-3-yl phosphonic acid, diethyl ester

A solution of 60 mg (0.23 mmol) of (R/S)-3-hydroxypyrrolidin-3-ylphosphonic acid, diethyl ester (from Step D) and 54 mg (0.23 mmol) of Aldehyde 1 in 1.5 mL of CH_2Cl_2 was treated with 73 mg (0.34 mmol) of sodium triacetoxyborohydride. After 3 h at rt, the reaction was diluted with 25 mL of CH_2Cl_2 and washed with 25 mL of 1N $NaHCO_3$. After separating phases, the aqueous layer was extracted with 25 mL of CH_2Cl_2. The combined organic layers were washed with 50 mL of sat'd NaCl, dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography using 3:1 v/v hexane/acetone as the eluant to afford 33 mg (32%) of the title compound: R_F: 0.31 (7:3 v/v hexane/acetone); ^{1}H-NMR (500 MHz) δ 0.89 (t, J = 7.0, 3H), 1.27-1.36 (m, 18H), 1.57-1.63 (m, 2H), 1.97 (m, 1H), 2.41-2.54 (m, 2H), 2.59 (t, J = 7.7, 2H), 2.85-2.92 (m, 2H), 3.01 (m, 1H), 3.67 (ABq, J = 13.1, 2H), 4.16-4.23 (m, 4H), 7.12 (d, J = 7.8, 2H), 7.24 (d, J = 7.8, 2H).

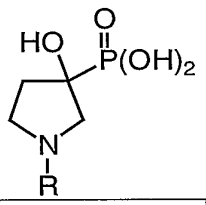
Step F: (R/S)-1-(4-Nonylbenzyl)-3-hydroxypyrrolidin-3-ylphosphonic acid

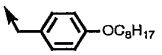
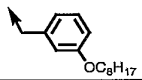
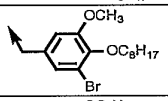
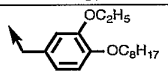
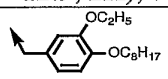
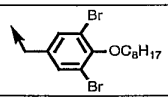
A solution of 33 mg (0.075 mmol) of (R/S)-1-(4-nonylbenzyl)-3-hydroxypyrrolidin-3-ylphosphonic acid, diethyl ester (from Step E) in 1 mL of chloroform was treated with 0.053 mL (0.37 mmol) of iodotrimethylsilane. The reaction was allowed to stir at rt for 1h. The reaction was quenched with MeOH and concentrated several times from MeOH. The residue was purified using LC-2 to afford 4.6 mg (16%) of the title compound: ESI-MS 385 (M+H); LC-1: 3.01 min.

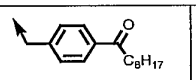
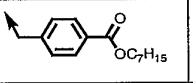
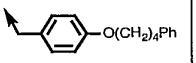
EXAMPLES 2-10

EXAMPLES 2-10 were prepared using procedures analogous to those described in EXAMPLE 1 substituting the appropriate Aldehyde in Step E. TMS-Br was substituted in Step F with substrates containing TMS-I sensitive functionality (See

EXAMPLE 11, Step D). In EXAMPLES 5 and 6 enantiomers were resolved after Step E by preparative chiral HPLC (Chiralpak AD 2 x 25 cm HPLC column, 9:1 v/v hexane/EtOH, flow rate = 9.0 mL/min, λ = 210 nM).



EXAMPLE #	R	HPLC Method	HPLC RT (min)	ESI-MS (M+H)
2		LC-1	2.7	386
3		LC-1	2.7	386
4		LC-1	3.0	496
5 Enantiomer 1		LC-1	2.8	430
^{1}H-NMR (500 MHz, CD_3OD) δ 0.92 (t, J = 7.0, 3H), 1.20-1.54 (m, 9H), 1.79-1.84 (m, 2H), 2.23 (m, 1H), 2.35 (m, 1H), 2.43 (m, 1H), 2.68 (m, 1H), 3.41-3.50 (m, 2H), 3.58 (m, 1H), 3.68 (m, 1H), 3.75-3.79 (m, 2H), 4.04 (t, J = 6.4, 2H), 4.11-4.15 (m, 2H), 4.38 (ABq, J = 12.9, 2H), 7.02-7.09 (m, 2H), 7.17 (s, 1H)				
6 Enantiomer 2		LC-1	2.8	430
7		LC-1	3.1	544
^{1}H-NMR (500 MHz, CD_3OD) δ 0.93 (t, J = 6.8, 3H), 1.20-1.46 (m, 9H), 1.55-1.61 (m, 2H), 1.86-1.92 (m, 2H), 2.23-2.35 (m, 2H), 2.72 (m, 1H), 3.47-3.79 (br m, 3H), 4.06 (t, J = 6.4, 2H), 4.44-4.50 (m, 2H), 7.86 (s, 2H)				

8		LC-1	2.6	398
9		LC-1	2.5	400
10		LC-1	2.4	406

EXAMPLE 11

(R/S)-1-(4-Nonylphenyl)methyl-pyrrolidin-3-yl phosphonic acid

Step A: (R/S)-1-Benzyl-pyrrolidin-3-yl phosphonic acid, diethyl ester

A solution of 6.0 g (36.6 mmol) of diethyl vinylphosphonate and 11 mL (44 mmol) of N-(methoxymethyl)-N-(trimethylsilylmethyl)benzylamine in 150 mL of CH_2Cl_2 at 0 °C was stirred for 30 min. The reaction mixture was washed with 150 mL of 1N $NaHCO_3$ and 150 mL of sat'd NaCl. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified on a 40L Biotage column using 3:2 and 1:1 v/v hexane/acetone as the gradient to afford 9.44 g (87%) of the title compound as a pale yellow oil: R_F: 0.24 (3:2 v/v hexane/acetone); ^{1}H-NMR (500 MHz) δ 1.32 (t, J = 7.0, 6H), 2.04-2.12 (m, 2H), 2.39-2.58 (m, 3H), 2.83 (m, 1H), 2.97 (m, 1H), 3.64 (s, 2H), 4.06-4.16 (m, 4H), 7.24-7.34 (m, 5H); ESI-MS 298 (M+H); LC-1: 1.2 min.

Step B: (R/S)-Pyrrolidin-3-ylphosphonic acid, diethyl ester

A mixture of 3 g (10 mmol) of (R/S)-1-benzyl-pyrrolidin-3-ylphosphonic acid, diethyl ester (from Step A), 9.5 g (150 mmol) of ammonium formate and 1.0 g of 10% palladium on charcoal in 60 mL of MeOH was warmed to 40 °C for 1.5 h. The reaction was cooled, filtered through a pad of celite and concentrated. The mixture was partitioned between 75 mL of 1N NaOH and 100 mL of CH_2Cl_2. After separating layers, the aqueous phase was extracted with 3X100 mL of CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified on a 40M Biotage column using 90:10:1 v/v/v

CH_2Cl_2/MeOH/NH_4OH as the eluant to afford the title compound as a pale yellow oil: R_F: 0.13 (95:5:0.5 v/v/v CH_2Cl_2/MeOH/NH_4OH); ^{1}H-NMR (500 MHz) δ 1.22 (t, J = 7.1, 6H), 1.81 (m, 1H), 1.95 (m, 1H), 2.25 (m, 1H), 2.73 (m, 1H), 2.89-2.99 (m, 3H), 4.06-4.16 (m, 4H).

Step C: (R/S)-1-(4-Nonylphenyl)methyl-pyrrolidin-3-ylphosphonic acid, diethyl ester

A solution of 41 mg (0.19 mmol) of (R/S)-pyrrolidin-3-yl phosphonic acid, diethyl ester (from Step B) and 43 mg (0.18 mmol) of Aldehyde 1 in 1 mL of CH_2Cl_2 was treated with 57 mg (0.27 mmol) of sodium triacetoxyborohydride. After stirring at rt overnight, the reaction was diluted with 25 mL of CH_2Cl_2 and washed with 25 mL of 1N $NaHCO_3$. After separating phases, the aqueous layer was extracted with 25 mL of CH_2Cl_2. The combined organic layers were washed with 50 mL of sat'd NaCl, dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography using 49:1 v/v CH_2Cl_2/MeOH as the eluant to afford 67 mg (99%) of the title compound: R_F: 0.39 (19:1 v/v CH_2Cl_2/MeOH); ^{1}H-NMR (500 MHz) δ 0.90 (t, J = 7.0, 3H), 1.20-1.35 (m, 17H), 1.59-1.65 (m, 2H), 2.04-2.13 (m, 3H), 2.41-2.62 (m, 5H), 2.85 (m, 1H), 2.99 (m, 1H), 3.62 (s, 2H), 4.08-4.17 (m, 4H), 7.14 (d, J = 8.0, 2H), 7.24 (d, J = 8.0, 2H).

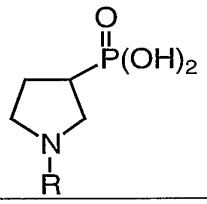
Step D: (R/S)-1-(4-Nonylbenzyl)-pyrrolidin-3-ylphosphonic acid

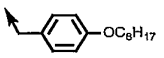
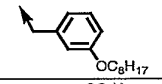
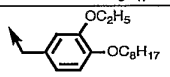
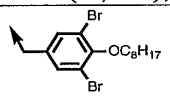
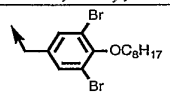
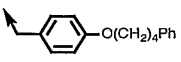
A solution of 67 mg (0.16 mmol) of (R/S)-1-(4-nonylbenzyl)-pyrrolidin-3-ylphosphonic acid, diethyl ester (from Step C) in 1 mL of acetonitrile was treated with 0.094 mL (0.71 mmol) of bromotrimethylsilane. The reaction was allowed to stir at 80 °C for 1h. The reaction was quenched with MeOH and concentrated several times from MeOH. The residue was purified by LC-2 to afford 27 mg (46%) of the title compound: ESI-MS 368 (M+H); LC-1: 3.1 min.

EXAMPLES 12-17

EXAMPLES 12-17 were prepared using procedures analogous to those described in EXAMPLE 11 substituting the appropriate Aldehyde in Step C. In EXAMPLES 15 and 16 enantiomers were were resolved after Step E by preparative chiral HPLC

(Chiralcel OD 2 x 25 cm HPLC column, 19:1 v/v hexane/iPrOH, flow rate = 9.0 mL/min, λ = 210 nM).



EXAMPLE #	R	HPLC Method	HPLC RT (min)	ESI-MS (M+H)
12		LC-1	2.8	370
13		LC-1	2.7	370
14		--	--	--
^{1}H-NMR (500 MHz, CD_3OD) δ 0.92 (t, J = 7.0, 3H), 1.34-1.54 (m, 10H), 1.79-1.84 (m, 2H), 2.18 (m ,1H), 2.32-2.45 (m, 2H), 2.69 (m, 1H), 2.88 (m, 1H), 3.22-3.37 (m, 2H), 3.47-3.62 (m, 2H), 3.73 (m, 1H), 4.04 (t, J = 6.4, 2H), 4.13 (q, J = 7.0, 2H), 4.32-4.37 (m, 2H), 7.02-7.08 (m, 2H), 7.16 (s, 1H)				
15 Enantiomer 1		LC-1	3.2	528
^{1}H-NMR (500 MHz, CD_3OD) δ 0.93 (t, J = 6.9, 3H), 1.34-1.46 (m, 8H), 1.55-1.61 (m, 2H), 1.86-1.95 (m, 2H), 2.25-2.47 (m, 2H), 2.72 (m, 1H), 3.28 (m, 1H), 3.63-3.79 (m, 3H), 4.06 (t, J = 6.4, 2H), 4.44 (s, 2H), 7.87 (s, 2H)				
16 Enantiomer 2		LC-1	3.1	528
17		LC-1	2.4	390

EXAMPLE 18

(R/S)-1-{4-[(4-Phenyl-5-trifluoromethyl-2-thienyl)methoxy]benzyl}-pyrrolidin-3-yl carboxylic acid

Step A: (R/S)-1-Benzyl-pyrrolidin-3-yl carboxylic acid, benzyl ester

A solution of 10.0 g (61.6 mmol) of benzyl acrylate and 19 mL (74.2 mmol) of N-(methoxymethyl)-N-(trimethylsilylmethyl)benzylamine in 75 mL of CH_2Cl_2 at 0 °C was treated with 0.5 mL (6.5 mmol) of TFA while maintaining the internal temperature at less than 3 °C. The reaction was warmed to rt and stirred for 2.5 h. The reaction mixture was washed with 250 mL of 1N $NaHCO_3$ and 250 mL of sat'd NaCl. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified on a 40L Biotage column using 19:1 v/v hexane/acetone as the eluant to afford 18 g (99%) of the title compound as a light yellow oil: R_F: 0.28 (9:1 v/v hexane/acetone); ^{1}H-NMR (500 MHz) δ 2.15-2.20 (m, 2H), 2.60 (m, 1H), 2.73-2.77 (m, 2H), 3.02 (m, 1H), 3.13 (m, 1H), 3.66-3.73 (m, 2H), 5.17 (s, 2H), 7.28-7.42 (m, 5H).

Step B: (R/S)-1-Benzyloxycarbonyl-pyrrolidin-3-yl carboxylic acid, benzyl ester

A solution of 18 g (61 mmol) of (R/S)-1-benzyl-pyrrolidin-3-yl carboxylic acid, benzyl ester (from Step A) in 100 mL of CH_2Cl_2 at 0 °C was treated with 21.3 mL (231 mmol) of benzyl chloroformate while maintaining the internal temperature at less than 6 °C. The reaction was allowed to warm to rt overnight. After 24 hours at rt, an additional 10 mL (10.8 mmol) of benzyl chloroformate was added. After 24 hours of stirring at rt, the reaction was concentrated. The residue was purified on a 40L Biotage column using 19:1 v/v hexane/acetone as the eluant to afford 8.42 g (39%) of the title compound as a colorless oil: R_F: 0.14 (9:1 v/v hexane/acetone); ^{1}H-NMR (500 MHz) δ 2.19-2.22 (m, 2H), 3.15 (m,1H), 3.45-3.75 (m, 4H), 5.13-5.20 (m, 4H), 7.33-7.41 (m, 10H).

Step C: (R/S)-Pyrrolidin-3-yl carboxylic acid

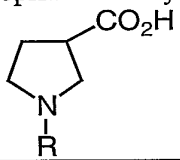
A mixture of 8.4 g (24.7 mmol) of (R/S)-1-benzyloxycarbonyl-pyrrolidin-3-yl carboxylic acid, benzyl ester (from Step B) and 2.86 g of 10% palladium on charcoal in 80 mL of MeOH was hydrogenated at atmospheric pressure using a balloon of hydrogen for 6.5 h. The reaction was filtered through a pad of Celite and concentrated to afford 2.72 g (95%) of the title compound as a white solid: ^{1}H-NMR (500 MHz, CD_3OD) δ 2.17-2.26 (m, 2H), 3.03 (m, 1H), 3.24-3.38 (m, 3H), 3.51 (m, 1H).

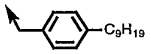
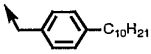
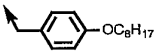
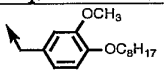
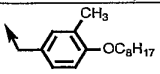
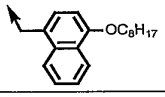
Step D: (R/S)-1-{4-[(4-Phenyl-5-trifluoromethyl-2-thienyl)methoxy]benzyl}-pyrrolidin-3-yl carboxylic acid

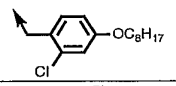
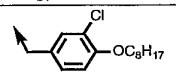
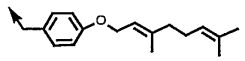
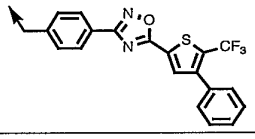
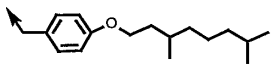
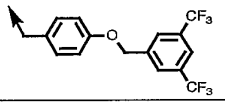
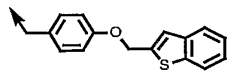
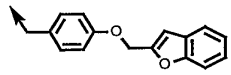
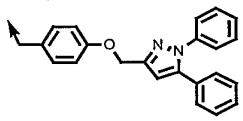
A mixture of 17.5 mg (0.15 mmol) of (R/S)-pyrrolidin-3-yl carboxylic acid (from Step C), 78 mg (0.21 mmol) of Aldehyde 16 and 9 mg (0.14 mmol) of sodium cyanoborohydride in 2 mL of MeOH was stirred at rt overnight. The reaction was concentrated and purified by flash chromatography using 19:1 v/v CH_2Cl_2/MeOH, then 85:15:1.5 v/v/v CH_2Cl_2/MeOH/NH_4OH as the eluant to afford 42 mg (63%) of the title compound as a white foam: R_F: 0.29 (85:15:1.5 v/v/v CH_2Cl_2/MeOH/NH_4OH); ^{1}H-NMR (500 MHz, CD_3OD) δ 2.23-2.35 (m, 2H), 3.09 (m, 1H), 3.26-3.41 (m, 3H), 3.53 (m, 1H), 4.30 (ABq, J = 13.0, 2H), 5.38 (s, 2H), 7.13 (d, J = 8.5, 2H), 7.22 (s, 1H), 7.39-7.45 (m, 5H), 7.48 (d, J = 8.5, 2H); ESI-MS 462 (M+H); LC-1: 2.7 min.

EXAMPLES 19-33

EXAMPLES 19-33 were prepared using procedures analogous to those described in EXAMPLE 18 substituting the appropriate Aldehyde in Step D.



EXAMPLE #	R	HPLC Method	HPLC RT (min)	ESI-MS (M+H)
19		LC-1	2.8	332
^{1}H-NMR (500 MHz) δ 0.91 (t, J = 6.9, 3H), 1.30-1.34 (m, 12H), 1.60-1.63 (m, 2H), 2.33-2.41 (m, 2H), 2.60-2.63 (m, 2H), 3.09-3.29 (m, 4H), 3.73 (m, 1H), 4.20 (ABq, J = 12.5, 2H), 7.21 (d, J = 7.7, 2H), 7.44 (d, J = 7.7, 2H)				
20		LC-1	3.0	346
21		LC-1	3.0	334
^{1}H-NMR (500 MHz, CD_3OD) δ 0.91 (t, J = 7.0, 3H), 1.31-1.50 (m, 10H), 1.75-1.80 (m, 2H), 2.22-2.33 (m, 2H), 3.08 (m, 1H), 3.25-3.40 (m, 3H), 3.52 (m, 1H), 3.99 (t, J = 6.4, 2H), 4.28 (ABq, J = 13.0, 2H), 6.97 (d, J = 8.6, 2H), 7.41 (d, J = 8.6, 2H)				
22		LC-1	2.9	364
^{1}H-NMR (500 MHz, CD_3OD) δ 0.91 (t, J = 6.9, 3H), 1.31-1.51 (m, 10H), 1.76-1.82 (m, 2H), 2.24-2.37 (m, 2H), 3.17 (m, 1H), 3.29-3.43 (m, 3H), 3.56 (m, 1H), 3.87 (s, 3H), 4.01 (t, J = 6.5, 2H), 4.29 (ABq, J = 12.8, 2H), 6.98 (d, J = 8.2, 1H), 7.03 (dd, J = 8.2, 1.7, 1H), 7.12 (d, J = 1.7, 1H)				
23		LC-1	3.3	348
24		LC-1	3.5	384

25		LC-1	3.2	368
26		LC-1	3.2	368
27		LC-1	2.9	358
28		LC-1	3.2	500
^{1}H-NMR (500 MHz, CD_3OD) δ 2.26-2.37 (m, 2H), 3.13 (m, 1H), 3.25-3.43 (m, 3H), 3.52 (m, 1H), 4.37 (ABq, J = 12.9, 2H), 7.49-7.50 (m, 5H), 7.69 (d, J = 8.1, 2H), 8.00 (s, 1H), 8.16 (d, J = 8.1, 2H)				
29		LC-1	3.0	362
EXAMPLE 29 was prepared by catalytic hydrogenation of EXAMPLE 27 using a procedure analogous to that described in EXAMPLE 18, Step C.				
30		LC-1	2.9	448
^{1}H-NMR (500 MHz, CD_3OD) δ 2.23-2.34 (m, 2H), 3.09 (m, 1H), 3.25-3.40 (m, 3H), 3.53 (m, 1H), 4.30 (ABq, J = 13.0, 2H), 5.31 (s, 2H), 7.14 (d, J = 8.6, 2H), 7.48 (d, J = 8.6, 2H), 7.94 (s, 1H), 8.07 (s, 2H)				
31		--	--	368
32		--	--	352
33		--	--	454

EXAMPLE 35

(R/S)-1-(4-Nonylphenyl)methyl-3-fluoro-pyrrolidin-3-yl carboxylic acid

Step A: (R/S)-1-Benzyl-pyrrolidin-3-yl carboxylic acid, methyl ester

The title compound was prepared using a procedure analogous to that described in EXAMPLE 18, Step A substituting methyl acrylate for benzyl acrylate: R_F: 0.29 (9:1 v/v hexane/acetone); ^{1}H-NMR (500 MHz) δ 2.10-2.14 (m, 2H), 2.55 (m, 1H), 2.66 (m, 1H), 2.75 (m, 1H), 2.94 (m, 1H), 3.06 (m, 1H), 3.65 (s, 2H), 3.69 (s, 3H), 7.25-7.35 (m, 5H).

Step B: (R/S)-Pyrrolidin-3-yl carboxylic acid, methyl ester hydrochloride salt

A solution of 0.52 g (2.3 mmol) of (R/S)-1-benzyl-pyrrolidin-3-yl carboxylic acid, methyl ester (from Step A) in 5 mL of 1,2-dichloroethane was treated with 0.3 mL (2.7 mmol) of 1-chloroethyl chloroformate (ACE-Cl). The resulting mixture was stirred at rt for 3 h, then at reflux for 30 min. The reaction was cooled and concentrated. The residue was warmed to reflux in 5 mL of MeOH for 1 h. The reaction was cooled and concentrated. The crude product was used in Step C without further purification.

Step C: (R/S)- 1-(4-Nonylphenyl)methyl-pyrrolidin-3-yl carboxylic acid, methyl ester

The title compound was prepared using an analogous procedure described in EXAMPLE 1, Step E substituting (R/S)-pyrrolidin-3-yl carboxylic acid, methyl ester hydrochloride salt (from Step B) for (R/S)-3-hydroxypyrrolidin-3-ylphosphonic acid, diethyl ester and using DIEA to neutralize the hydrochloride salt: R_F: 0.44 (4:1 v/v hexane/acetone); ^{1}H-NMR (500 MHz) δ 0.91 (t, J = 6.9, 3H), 1.30-1.35 (m, 12H), 1.60-1.66 (m, 2H), 2.13-2.17 (m, 2H), 2.54-2.69 (m, 4H), 2.80 (m, 1H), 2.99 (m, 1H), 3.09 (m, 1H), 3.66 (s, 2H), 3.72 (s, 3H), 7.16 (d, J = 8.0, 2H), 7.27 (d, J = 8.0, 2H).

Step D: (R/S)-1-(4-Nonylphenyl)methyl- 3-fluoropyrrolidin-3-yl carboxylic acid, methyl ester

To a solution of 1 mL (0.32 mmol) of 0.32M lithium diisopropylamide in THF at –78 °C was added 90 mg (0.26 mmol) of (R/S)-1-1-(4-nonylphenyl) methylbenzyl)-pyrrolidin-3-yl carboxylic acid, methyl ester (from Step C) in 1.5 mL of THF while maintaining the internal temperature at less –70 °C. After 15 min, 111 mg (0.35 mmol) of fluorobenzenesulfonimide in 0.5 mL THF was added while maintaining the internal temperature at less –68 °C. After stirring for 15 min, the reaction was warmed to 0 °C and quenched with 0.1N HCl. The reaction mixture was poured into 50 mL of Et_2O and washed with 50 mL of 1N $NaHCO_3$ and 50 mL of sat'd NaCl. The organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography using 19:1 v/v hexane/acetone as the eluant to afford 47 mg (50%) of the title compound as a colorless film: R_F: 0.36 (9:1 v/v hexane/acetone); ^{1}H-NMR (500 MHz) δ 0.91 (t, J = 6.8, 3H), 1.30-1.35 (m, 12H), 1.60-1.66 (m, 2H), 2.28 (m, 1H), 2.49 (m, 1H), 2.62 (t, J = 7.8, 2H), 2.69 (m, 1H), 2.95-3.10 (m, 3H), 3.69 (ABq, J = 12.8, 2H), 3.83 (s, 3H), 7.16 (d, J = 7.8, 2H), 7.27 (d, J = 7.8, 2H).

Step E: <u>(R/S)-1-(4-Nonylphenyl)methyl-3-fluoropyrrolidin-3-yl carboxylic acid</u>

A solution of 46 mg (0.12 mmol) of (R/S)-1-(4-nonylphenyl)methyl-3-fluoropyrrolidin-3-yl carboxylic acid, methyl ester (from Step D) in 3 mL of EtOH was treated with 0.16 mL (0.16 mmol) of 1N NaOH and stirred overnight at rt. The reaction was neutralized with 2 mL of pH 7 buffer and concentrated. Toluene was added and the resulting mixture was concentrated. The residue was purified by flash chromatography using 19:1 v/v CH_2Cl_2/MeOH, then 90:10:1 v/v/v CH_2Cl_2/MeOH/NH_4OH as the eluant to afford 38 mg (86%) of the title compound as a white, waxy solid: R_F: 0.21 (85:15:1.5 v/v/v CH_2Cl_2/MeOH/NH_4OH); ^{1}H-NMR (500 MHz) δ 0.79 (t, J = 6.8, 3H), 1.18-1.23 (m, 12H), 1.48-1.52 (m, 2H), 2.30 (m, 1H), 2.47-2.59 (m, 3H), 3.29-3.44 (m, 3H), 3.73 (m, 1H), 3.87 (br m, 1H), 4.17 (ABq, J = 12.9, 2H), 7.12 (d, J = 7.9, 2H), 7.28 (d, J = 7.9, 2H); ESI-MS 350 (M+H); LC-1: 3.3 min.

EXAMPLE 36

(R/S)-1-(4-Nonylphenyl)methyl-3-hydroxypyrrolidin-3-yl carboxylic acid

Step A: (R/S) 1-(4-Nonylphenyl)methyl-3-hydroxypyrrolidin-3-yl carboxylic acid, methyl ester

To a solution of 0.52 mL (0.52 mmol) of 1.0M sodium hexamethylsilazide in THF at –78 °C was added 153 mg (0.44 mmol) of (R/S)- 1-(4-nonylphenyl)methyl-pyrrolidin-3-yl carboxylic acid, methyl ester (from EXAMPLE 34, Step C) in 1 mL of THF while maintaining the internal temperature at less –72 °C. After 20 min, 172 mg (0.65 mmol) of 2-(phenylsulfonyl)-3-phenyloxaziridine (Davis Reagent) in 1 mL of THF was added while maintaining the internal temperature at less –69 °C. After stirring for 1.25 h at –78 °C, the reaction was quenched with 1N $NaHCO_3$ and warmed to rt. After removing volatiles under reduced pressure, the reaction mixture was diluted with 50 mL of 1N $NaHCO_3$ and 50 mL of sat'd NaCl. The aqueous phase was extracted with 3X50 mL of CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography using 4:1 v/v hexane/EtOAc and 4:1 v/v hexane/acetone as the gradient to afford 11 mg (7%) of the title compound as a colorless film: R_F: 0.39 (4:1 v/v hexane/acetone); ^{1}H-NMR (500 MHz) δ 0.90 (t, J = 6.8, 3H), 1.28-1.33 (m, 12H), 1.59-1.64 (m, 2H), 2.02 (m, 1H), 2.42 (m, 1H), 2.60 (t, J = 7.8, 2H), 2.67 (m, 1H), 2.86 (ABq, J = 10.1, 2H), 2.97 (m, 1H), 3.69 (s, 2H), 3.82 (s, 3H), 7.14 (d, J = 7.9, 2H), 7.26 (d, J = 7.9, 2H).

Step B: (R/S)- 1-(4-Nonylphenyl)methyl-3-hydroxypyrrolidin-3-yl carboxylic acid

The title compound was prepared using an analogous procedure described in EXAMPLE 34, Step E substituting (R/S)-1-(4-nonylphenyl)methyl-3-hydroxypyrrolidin-3-yl carboxylic acid, methyl ester (from Step A) for (R/S)-1-(4-nonylphenyl)methyl-3-fluoropyrrolidin-3-yl carboxylic acid, methyl ester: R_F: 0.15 (90:10:1 v/v/v CH_2Cl_2/MeOH/NH_4OH); ^{1}H-NMR (500 MHz, CD_3OD) δ 0.89 (t, J = 6.9, 3H), 1.28-1.33 (m, 12H), 1.60-1.63 (m, 2H), 2.10 (m, 1H), 2.49 (m, 1H), 2.64 (t, J

= 7.7, 2H), 3.25 (m, 1H), 3.49-3.62 (m, 3H), 4.38 (ABq, J = 13.0, 2H), 7.28 (d, J = 7.8, 2H), 7.42 (d, J = 7.8, 2H); ESI-MS 348 (M+H); LC-1: 3.0 min.

EXAMPLE 37

(R/S)-1-(4-Nonylphenyl)methyl-pyrrolidin-3-yl acetic acid

Step A: (R/S)- 1-(4-Nonylphenyl)methyl-pyrrolidin-3-ylacetic acid, tert-butyl ester

The title compound was prepared using an analogous procedure described in EXAMPLE 1, Step E substituting (R/S)-pyrrolidin-3-yl acetic acid, tert-butyl ester hydrochloride salt for (R/S)-3-hydroxypyrrolidin-3-ylphosphonic acid, diethyl ester and using DIEA to neutralize the hydrochloride salt: R_F: 0.53 (4:1 v/v hexane/acetone); ^{1}H-NMR (500 MHz) δ 0.90 (t, J = 6.8, 3H), 1.28-1.64 (m, 25H), 2.09 (m, 1H), 2.26-2.37 (m, 3H), 2.58-2.69 (m, 4H), 2.89 (m, 1H), 3.61-3.64 (m, 2H), 7.14 (d, J = 7.4, 2H), 7.26 (d, J = 7.4, 2H).

Step B: (R/S)-1-(4-Nonylphenyl)methyl-pyrrolidin-3-yl acetic acid

A solution of 50.5 mg (0.12 mmol) of (R/S)-1-(4-nonylphenyl)methyl-pyrrolidin-3-yl acetic acid, tert-butyl ester (from Step A) in formic acid at 55 °C was stirred for 2.25 h. Volatiles were removed under reduced pressure. The residue was purified by flash chromatography using 19:1 v/v CH_2Cl_2/MeOH, then 85:15:1.5 v/v/v CH_2Cl_2/MeOH/NH_4OH as the eluant to afford 41 mg (94%) of the title compound as a sticky, waxy film: R_F: 0.31 (85:15:1.5 v/v/v CH_2Cl_2/MeOH/NH_4OH); ^{1}H-NMR (500 MHz, CD_3OD) δ 0.90 (t, J = 6.9, 3H), 1.29-1.33 (m, 12H), 1.61-1.64 (m, 2H), 1.77 (m, 1H), 2.26-2.45 (m, 3H), 2.64 (t, J = 7.7, 2H), 2.71 (m, 1H), 3.08 (m, 1H), 3.23 (m, 1H), 3.38-3.44 (m, 2H), 4.28 (s, 2H), 7.28 (d, J = 8.1, 2H), 7.39 (d, J = 8.1, 2H); ESI-MS 346 (M+H); LC-1: 3.3 min.

EXAMPLE 38

(R/S)-1-{4-[(4-Phenyl-5-trifluoromethyl-2-thienyl)methoxy]benzyl}-pyrrolidin-3-ylacetic acid

The title compound was prepared using procedures analogous to those described in EXAMPLE 36 substituting Aldehyde 16 for Aldehyde 1 in Step A: R_F: 0.29 (85:15:1.5 v/v/v CH_2Cl_2/MeOH/NH_4OH); ^{1}H-NMR (500 MHz, CD_3OD) δ 1.77 (m, 1H), 2.26-2.46 (m, 3H), 2.71 (m, 1H), 3.07 (m, 1H), 3.23 (m, 1H), 3.37-3.34 (m, 2H), 4.28 (s, 2H), 5.38 (s, 2H), 7.13 (d, J = 8.7, 2H), 7.23 (s, 1H), 7.40-7.47 (m, 7H); ESI-MS 476 (M+H); LC-1: 3.0 min.

EXAMPLE 39

(R/S)-5-[1-(4-Nonylphenyl)methylpyrrolidin-3-yl]-1*H*-tetrazole

Step A: (R/S)-1-Benzyloxycarbonyl-3-cyano pyrrolidine

The title compound was prepared using analogous procedures described in EXAMPLE 18 (Steps A and B) substituting acrylonitrile for benzyl acrylate in Step A: R_F: 0.19 (4:1 v/v hexane/acetone); ^{1}H-NMR (500 MHz) δ 2.18-2.28 (m, 2H), 3.12 (m, 1H), 3.53 (m, 1H), 3.61-3.78 (m, 3H), 5.16 (d, J = 3.0, 2H), 7.32-7.42 (m, 5H).

Step B: (R/S)-5-[1-Benzyloxycarbonyl-pyrrolidin-3-yl]-1*H*-tetrazole

A mixture of 1.8 g (7.8 mmol) of (R/S)-1-benzyloxycarbonyl-3-cyano pyrrolidine (from Step A), 1.5 g (23 mmol) of sodium azide and 1.25 g (23 mmol) of ammonium chloride in 70 mL of DMF was stirred at 105 °C overnight. After cooling to rt, the reaction was poured into 150 mL of CH_2Cl_2 and washed with 150 mL of 1N HCl and 2X150 mL of H_2O. The organic phase was dried over $MgSO_4$ and concentrated. The residue was purified on a 40M Biotage column using 80:20:1 v/v/v CH_2Cl_2/EtOAc/HOAc as the eluant to afford 670 mg (31%) of the title compound: R_F: 0.23 (80:20:1 v/v/v CH_2Cl_2/EtOAc/HOAc); ^{1}H-NMR (500 MHz) δ 2.29, 2.48 (2m, 2H), 3.54-4.03 (m, 5H), 5.14-5.24 (m, 2H), 7.30-7.37 (m, 5H), 10.43 (br, 1H).

Step C: (R/S)-5-(Pyrrolidin-3-yl)-1*H*-tetrazole

A mixture of 662 mg (2.4 mmol) of (R/S)-5-[1-benzyloxycarbonyl-pyrrolidin-3-yl]-1*H*-tetrazole (from Step B) and 220 mg of 10% palladium on charcoal in 5 mL of MeOH was hydrogenated at atmospheric pressure using a balloon of hydrogen for 3 h. The reaction was filtered through a pad of Celite and concentrated to afford the title compound as a white solid: ^{1}H-NMR (500 MHz, CD_3OD) δ 2.27 (m, 1H), 2.49 (m, 1H), 3.39-3.51 (m, 3H), 3.70 (m, 1H), 3.85 (m, 1H).

Step D: (R/S)-5-[1-(4-Nonylbenzyl)methyl-pyrrolidin-3-yl]-1*H*-tetrazole

The title compound was prepared using an analogous procedure described in EXAMPLE 18, Step D substituting (R/S)-5-(pyrrolidin-3-yl)-1*H*-tetrazole (from Step C) for (R/S)-pyrrolidin-3-yl carboxylic acid: ^{1}H-NMR (500 MHz, CD_3OD) δ 0.89 (t, J = 7.0, 3H), 1.28-1.33 (m, 12H), 160.-1.63 (m, 2H), 2.33 (m, 1H), 2.55 (m, 1H), 2.64 (t, J = 7.6, 2H), 3.47-3.55 (m, 3H), 3.76 (m, 1H), 3.92 (m, 1H), 4.40 (s, 2H), 7.29 (d, J = 8.0, 2H), 7.42 (d, J = 8.0, 2H); ESI-MS 356 (M+H); LC-1: 3.3 min.

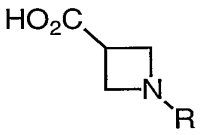
EXAMPLE 40

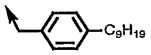
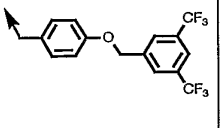
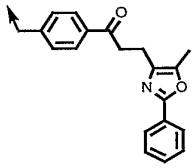
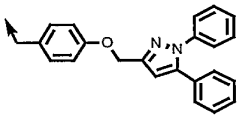
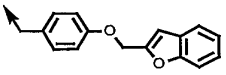
1-{4-[(4-Phenyl-5-trifluoromethyl-2-thienyl)methoxy]benzyl}-3-azetidinecarboxylic acid

The title compound was prepared by treating a mixture of 0.12 mmol of 3-azetidinecarboxylic acid, 0.1 mmol of Aldehyde 16, 0.007 mL (0.12 mmol) of acetic acid in 2 mL of MeOH with 10 mg (0.16 mmol) of sodium cyanoborohydride and stirring the resulting mixture at rt for 3 h. The product was purified using LC-2: ^{1}H NMR (500 MHz, CD_3OD) δ 3.34-3.37 (m, 1H), 4.08 (app s, 2H), 4.10 (app s, 2H), 4.22 (s, 2H), 4.86 (s, 2H), 5.35 (s, 2H), 7.10 (app d, J= 8.0, 2H), 7.20 (s, 1H), 7.39-7.43 (5H).

EXAMPLES 41-45

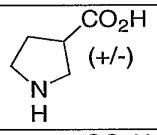
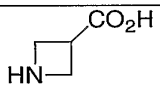
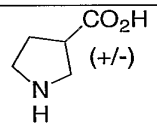
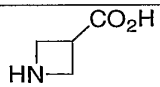
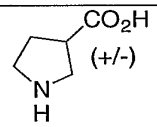
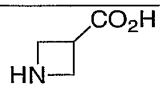
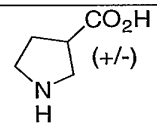
EXAMPLES 41-45 were prepared using procedures analogous to that described in EXAMPLE 41 substituting the appropriate Aldehyde for Aldehyde 16.

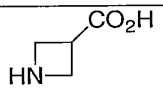
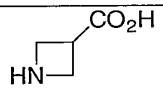


EXAMPLE #	R	HPLC Method	HPLC RT (min)	ESI-MS (M+H)
41		LC-1	3.3	318
^{1}H-NMR (500 MHz, CD_3OD) δ 0.89 (t, J = 6.8, 3H), 1.28-1.32 (m, 12H), 1.60-1.62 (m, 2H), 2.63 (t, J = 7.7, 2H), 3.37 (m, 1H), 4.12 (s, 2H), 4.13 (s, 2H), 4.27 (s, 2H), 7.27 (d, J = 8.0, 2H), 7.35 (d, J = 8.0, 2H)				
42		LC-1	2.9	434
^{1}H-NMR (500 MHz, CD_3OD) δ 3.35 (m, 1H), 4.14 (s, 2H), 4.16 (s, 2H), 4.28 (s, 2H), 5.31 (s, 2H), 7.14 (d, J = 8.6, 2H), 7.42 (d, J = 8.6, 2H), 7.94 (s, 1H), 8.07 (s, 2H)				
43		LC-1	2.4	405
44		--	--	440
45		--	--	338

EXAMPLES 46-53

The following compounds were prepared by treating a mixture of 0.12 mmol of either azetidine-3-carboxylic acid or (±)-pyrroldine-3-carboxylic acid, 0.1 mmol of Aldehyde, 7 μL (0.12 mmol) of acetic acid in 2 mL of MeOH with 10 mg (0.16 mmol) of sodium cyanoborohydride and stirring the resulting mixture at rt for 1-3 h. The reaction mixtures were purified using LC-2.

EXAMPLE	Amino acid	Aldehyde #	LC-1	MS
46		19	2.9 min	496 (M+H)
47		19	2.9 min	482 (M+H)
48		18	3.1 min	496 (M+H)
49		18	3.1 min	482 (M+H)
50		21	2.9 min	492 (M+H)
51		21	2.9 min	478 (M+H)
52		20	3.1 min	476 (M+H)

53		20	3.1 min	462 (M+H)
54		15	3.2 min	485 (M+H)

EXAMPLE 55

(3S,4R or 3R,4S)-1-(4-Nonylbenzyl)-4-trifluoromethylpyrrolidin-3-yl carboxylic acid

Step A: 4-(Nonyl)benzylamine

4-Nonylbenzoyl chloride (6g, 20mmol) and NH_4OAc (6g,) were suspended in acetone (100mL) and stirred for 1 h at rt. Water (50mL) was added and the mixture filtered. The residue was washed with water and dried . The resulting crude amide (2.47g, ~10mmol) was dissolved in THF (5mL) and borane dimethylsulfide complex (10mL of 2M solution, 20mmol) was added dropwise, while warming to reflux. The mixture was heated for 1h. then cooled in an ice bath. Methanol (2.5mL) was added dropwise, followed by 1N HCl in ether (11mL). The white precipitate of the HCl salt of the benzyl amine was filtered off and washed with ether. The HCl salt was taken up in 2.5N NaOH and ether and the organic layer was separated and dried over Na_2SO_4. Evaporation afforded 1.3 g of the title compound.

Step B: N-(Methoxymethyl)-N-(trimethylsilylmethyl)-(4-nonyl)benzylamine

A solution of 1.3 g (6 mmol) of 4-(nonyl)benzylamine (from Step A) and 700 mg (6 mmol) of chloromethyltrimethylsilane in 5 mL of DMSO was stirred at 90 °C for 3 h, then at rt for 16 h. The mixture was partitioned between MTBE and 1N NaOH. The organic layer was separated, washed with sat'd NaCl, dried and

concentrated. Flash chromatography using 9:1 v/v hexane/EtOAc as the eluant afforded 700 mg of N-(trimethylsilylmethyl)-4-(nonyl)benzylamine.

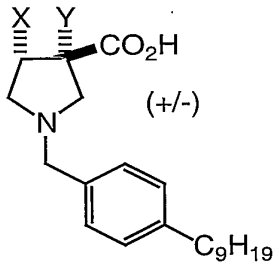
A mixture of the crude N-(trimethylsilylmethyl)-4-(nonyl)benzylamine, 140 mg of paraformaldehyde and 15 mg of powdered NaOH in 5 mL of MeOH was stirred at 40 °C for 1 h. The mixture was diluted with ether and aged for 16 h. The mixture was concentrated and dried to afford 700 mg of the title compound: ^{1}H NMR (500 MHz, CD_3OD) δ: 7.25 (m, 2H); 7.15 (m, 2H); 4.03 (m, 2H); 3.74 (m, 2H); 3.28 (m, 2H); 2.61 (m, 2H); 2.22 (m, 2H); 1.63 (m, 4H); 1.30 (m, 14H); 0.90 (m, 3H); 0.08 (m, 9H).

Step C: 1-(4-(Nonyl)phenyl)methyl-3-(R/S)-carboxy-4-(R/S)-trifluoromethyl pyrrolidine

A solution of 50 mg (0.14 mmol) of N-(methoxymethyl)-N-(trimethylsilylmethyl)-(4-nonyl)benzylamine (from Step B) and 20 mg (0.14 mmol) of *trans*-4,4,4-trifluoro-2-butenoic acid (0.137mmol) in 1 mL of CH_2Cl_2 was treated with 1 drop of TFA and the resulting mixture was heated at 35 °C for 1h. The reaction was cooled, concentrated then and then purified using LC-2 to afford the title compound: ^{1}H NMR (500 MHz, CD_3OD) δ 7.25 (d, J = 8, 2H); 7.19 (d, J = 8, 2H); 3.87 (m, 2H); 3.54 (m, 1H); 3.27(m, 4H); 2.93 (m, 1H); 2.61 (m, 2H); 1.62 (m, 2H); 1.30 (m, 14H); 0.90 (t, J = 6.7, 3H); ESI-MS 400.3 (M+H).

EXAMPLES 56-59

EXAMPLES 56-58 were prepared using procedures analogous to those described in EXAMPLE 55 substituting the appropriate α,β-unsaturated acid in Step C.



EXAMPLE #	X	Y	ESI-MS (M+H)
56	H	CF_3	400.3
^1H NMR (500 MHz, CD_3OD) δ: 7.43 (d, J = 8 Hz, 2H); 7.29 (d, J = 8 Hz 2H); 4.35 (s, 2H); 4.04 (d, J = 12Hz, 1H); 3.46 (m, 1H); 2.65 (m, 3H); 2.42 (m, 1H); 1.62 (m, 2H); 1.30 (m, 14H); 0.90 (t, J = 6.7 3H)			
57	CO_2H	H	375.3
^1H NMR (500 MHz, CD_3OD) δ: 7.35 (m, , 4H); 4.4 (m, 1H); 4.12 (m, 2H); 3.64 (m, 1H); 2.69 (m, 5H); 1.64 (m, 1H); 1.30 (m, 14H); 0.90 (m, 3H)			
58	H	CH_2CO_2H	390.3
^1H NMR (500 MHz, CD_3OD) δ: 7.36 (m, , 4H); 4.43 (m, , 1H); 4.14 (m, 3H); 3.79 (m, 1H); 3.50 (m, 1H); 3.09 (m, 2H); 2.70 (m, 8H); 3.18 (m, 1H); 2.65 (m, 2H); 2.3 (m, 2H); 1.61 (m, 2H); 1.29 (M, 14H); 0.89 (m, 3H)			

BIOLOGICAL ACTIVITY

The $S1P_1$/Edg1, $S1P_3$,/Edg3, $S1P_2$/Edg5, $S1P_4$/Edg6 or $S1P_5$ /Edg8 activity of the compounds of the present invention can be evaluated using the following assays:

Ligand Binding to Edg/S1P Receptors Assay

^{33}P-sphingosine-1-phosphate was synthesized enzymatically from γ^{33}P-ATP and sphingosine using a crude yeast extract with sphingosine kinase activity in a reaction mix containing 50 mM KH_2PO_4, 1 mM mercaptoethanol, 1 mM Na_3VO_4, 25 mM KF, 2 mM semicarbazide, 1 mM Na_2EDTA, 5 mM $MgCl_2$, 50 mM sphingosine, 0.1% TritonX-114, and 1 mCi γ^{33}P-ATP (NEN; specific activity 3000 Ci/mmol). Reaction products were extracted with butanol and ^{33}P-sphingosine-1-phosphate was purified by HPLC.

Cells expressing EDG/S1P receptors were harvested with enzyme-free dissociation solution (Specialty Media, Lavallette, NJ). They were washed once in cold PBS and suspended in binding assay buffer consisting of 50 mM HEPES-Na, pH 7.5, 5mM $MgCl_2$, 1mM $CaCl_2$, and 0.5% fatty acid-free BSA. ^{33}P-sphingosine-1-phosphate was sonicated with 0.1 nM sphingosine-1-phosphate in binding assay buffer; 100 µl of the ligand mixture was added to 100 µl cells (1 x 10^6 cells/ml) in a 96 well microtiter dish. Binding was performed for 60 min at room temperature with gentle mixing. Cells were then collected onto GF/B filter plates with a Packard Filtermate Universal Harvester. After drying the filter plates for 30 min, 40 µl of Microscint 20 was added to each well and binding was measured on a Wallac Microbeta Scintillation Counter. Non-specific binding was defined as the amount of radioactivity remaining in the presence of 0.5 µM cold sphingosine-1-phosphate.

Alternatively, ligand binding assays were performed on membranes prepared from cells expressing Edg/S1P receptors. Cells were harvested with enzyme-free dissociation solution and washed once in cold PBS. Cells were disrupted by homogenization in ice cold 20 mM HEPES pH 7.4, 10 mM EDTA using a Kinematica polytron (setting 5, for 10 seconds). Homogenates were centrifuged at 48,000 x g for 15 min at 4°C and the pellet was suspended in 20 mM HEPES pH 7.4, 0.1 mM EDTA. Following a second centrifugation, the final pellet was suspended in

20 mM HEPES pH 7.4, 100 mM NaCl, 10 mM $MgCl_2$. Ligand binding assays were performed as described above, using 0.5 to 2 μg of membrane protein.

Agonists and antagonists of Edg/S1P receptors can be identified in the ^{33}P-sphingosine-1-phosphate binding assay. Compounds diluted in DMSO, methanol, or other solvent, were mixed with probe containing ^{33}P-sphingosine-1-phosphate and binding assay buffer in microtiter dishes. Membranes prepared from cells expressing Edg/S1P receptors were added, and binding to ^{33}P-sphingosine-1-phosphate was performed as described. Determination of the amount of binding in the presence of varying concentrations of compound and analysis of the data by non-linear regression software such as MRLCalc (Merck Research Laboratories) or PRISM (GraphPad Software) was used to measure the affinity of compounds for the receptor. Selectivity of compounds for Edg/S1P receptors was determined by measuring the level of ^{33}P-sphingosine-1-phosphate binding in the presence of the compound using membranes prepared from cells transfected with each respective receptor ($S1P_1$/Edg1, $S1P_3$/Edg3, $S1P_2$/Edg5, $S1P_4$/Edg6, $S1P_5$/Edg8).

^{35}S-GTPγS Binding Assay

Functional coupling of S1P/Edg receptors to G proteins was measured in a ^{35}S-GTPγS binding assay. Membranes prepared as described in the Ligand Binding to Edg/S1P Receptors Assay (1-10 μg of membrane protein) were incubated in a 200 μl volume containing 20 mM HEPES pH 7.4, 100 mM NaCl, 10 mM $MgCl_2$, 5 μM GDP, 0.1% fatty acid-free BSA (Sigma, catalog A8806), various concentrations of sphingosine-1-phosphate, and 125 pM ^{35}S-GTPγS (NEN; specific activity 1250 Ci/mmol) in 96 well microtiter dishes. Binding was performed for 1 hour at room temperature with gentle mixing, and terminated by harvesting the membranes onto GF/B filter plates with a Packard Filtermate Universal Harvester. After drying the filter plates for 30 min, 40 μl of Microscint 20 was added to each well and binding was measured on a Wallac Microbeta Scintillation Counter.

Agonists and antagonists of S1P/Edg receptors can be discriminated in the ^{35}S-GTPγS binding assay. Compounds diluted in DMSO, methanol, or other solvent, were added to microtiter dishes to provide final assay concentrations of 0.01 nM to 10 μM. Membranes prepared from cells expressing S1P/Edg receptors were

added, and binding to ^{35}S-GTPγS was performed as described. When assayed in the absence of the natural ligand or other known agonist, compounds that stimulate ^{35}S-GTPγS binding above the endogenous level were considered agonists, while compounds that inhibit the endogenous level of ^{35}S-GTPγS binding were considered inverse agonists. Antagonists were detected in a ^{35}S-GTPγS binding assay in the presence of a sub-maximal level of natural ligand or known S1P/Edg receptor agonist, where the compounds reduced the level of ^{35}S-GTPγS binding. Determination of the amount of binding in the presence of varying concentrations of compound was used to measure the potency of compounds as agonists, inverse agonists, or antagonists of S1P/Edg receptors. To evaluate agonists, percent stimulation over basal was calculated as binding in the presence of compound divided by binding in the absence of ligand, multiplied by 100. Dose response curves were plotted using a non-linear regression curve fitting program MRLCalc (Merck Research Laboratories), and EC_{50} values were defined to be the concentration of agonist required to give 50% of its own maximal stimulation. Selectivity of compounds for S1P/Edg receptors was determined by measuring the level of ^{35}S-GTPγS binding in the presence of compound using membranes prepared from cells transfected with each respective receptor.

Intracellular Calcium Flux Assay

Functional coupling of S1P/Edg receptors to G protein associated intracellular calcium mobilization was measured using FLIPR (Fluorescence Imaging Plate Reader, Molecular Devices). Cells expressing S1P/Edg receptors were harvested and washed once with assay buffer (Hanks Buffered Saline Solution (BRL) containing 20mM HEPES, 0.1% BSA and 710 μg/ml probenicid (Sigma)). Cells were labeled in the same buffer containing 500 nM of the calcium sensitive dye Fluo-4 (Molecular Probes) for 1 hour at 37°C and 5% CO_2. The cells were washed twice with buffer before plating $1.5x10^5$ per well (90μl) in 96 well polylysine coated black microtiter dishes. A 96-well ligand plate was prepared by diluting sphingosine-1-phosphate or other agonists into 200 μl of assay buffer to give a concentration that was 2-fold the final test concentration. The ligand plate and the cell plate were loaded into the FLIPR instrument for analysis. Plates were equilibrated to 37°C. The assay was initiated by transferring an equal volume of ligand to the cell plate and the

calcium flux was recorded over a 3 min interval. Cellular response was quantitated as area (sum) or maximal peak height (max). Agonists were evaluated in the absence of natural ligand by dilution of compounds into the appropriate solvent and transfer to the Fluo-4 labeled cells. Antagonists were evaluated by pretreating Fluo-4 labeled cells with varying concentrations of compounds for 15 min prior to the initiation of calcium flux by addition of the natural ligand or other S1P/Edg receptor agonist.

Preparation of Cells Expressing S1P/Edg Receptors

Any of a variety of procedures may be used to clone $S1P_1$/Edg1, $S1P_3$/Edg3, $S1P_2$/Edg5, $S1P_4$/Edg6 or $S1P_5$/Edg8. These methods include, but are not limited to, (1) a RACE PCR cloning technique (Frohman, et al., 1988, *Proc. Natl. Acad. Sci. USA* 85: 8998-9002). 5′ and/or 3′ RACE may be performed to generate a full-length cDNA sequence; (2) direct functional expression of the Edg/S1P cDNA following the construction of an S1P/Edg-containing cDNA library in an appropriate expression vector system; (3) screening an S1P/Edg-containing cDNA library constructed in a bacteriophage or plasmid shuttle vector with a labeled degenerate oligonucleotide probe designed from the amino acid sequence of the S1P/Edg protein; (4) screening an S1P/Edg-containing cDNA library constructed in a bacteriophage or plasmid shuttle vector with a partial cDNA encoding the S1P/Edg protein. This partial cDNA is obtained by the specific PCR amplification of S1P/Edg DNA fragments through the design of degenerate oligonucleotide primers from the amino acid sequence known for other proteins which are related to the S1P/Edg protein; (5) screening an S1P/Edg-containing cDNA library constructed in a bacteriophage or plasmid shuttle vector with a partial cDNA or oligonucleotide with homology to a mammalian S1P/Edg protein. This strategy may also involve using gene-specific oligonucleotide primers for PCR amplification of S1P/Edg cDNA; or (6) designing 5′ and 3′ gene specific oligonucleotides using the S1P/Edg nucleotide sequence as a template so that either the full-length cDNA may be generated by known RACE techniques, or a portion of the coding region may be generated by these same known RACE techniques to generate and isolate a portion of the coding region to use as a probe to screen one of numerous types of cDNA and/or genomic libraries in order to isolate a full-length version of the nucleotide sequence encoding S1P/Edg.

It is readily apparent to those skilled in the art that other types of libraries, as well as libraries constructed from other cell types-or species types, may be useful for isolating an S1P/Edg-encoding DNA or an S1P/Edg homologue. Other types of libraries include, but are not limited to, cDNA libraries derived from other cells.

It is readily apparent to those skilled in the art that suitable cDNA libraries may be prepared from cells or cell lines which have S1P/Edg activity. The selection of cells or cell lines for use in preparing a cDNA library to isolate a cDNA encoding S1P/Edg may be done by first measuring cell-associated S1P/Edg activity using any known assay available for such a purpose.

Preparation of cDNA libraries can be performed by standard techniques well known in the art. Well known cDNA library construction techniques can be found for example, in Sambrook et al., 1989, *Molecular Cloning: A Laboratory Manual*; Cold Spring Harbor Laboratory, Cold Spring Harbor, New York. Complementary DNA libraries may also be obtained from numerous commercial sources, including but not limited to Clontech Laboratories, Inc. and Stratagene.

An expression vector containing DNA encoding an S1P/Edg-like protein may be used for expression of S1P/Edg in a recombinant host cell. Such recombinant host cells can be cultured under suitable conditions to produce S1P/Edg or a biologically equivalent form. Expression vectors may include, but are not limited to, cloning vectors, modified cloning vectors, specifically designed plasmids or viruses. Commercially available mammalian expression vectors may be suitable for recombinant S1P/Edg expression.

Recombinant host cells may be prokaryotic or eukaryotic, including but not limited to, bacteria such as *E. coli*, fungal cells such as yeast, mammalian cells including, but not limited to, cell lines of bovine, porcine, monkey and rodent origin; and insect cells including but not limited to *Drosophila* and silkworm derived cell lines.

The nucleotide sequences for the various S1P/Edg receptors are known in the art. See, for example, the following:

S1P$_1$/Edg1 Human

Hla, T. and T. Maciag 1990 An abundant transcript induced in differentiating human endothelial cells encodes a polypeptide with structural

similarities to G-protein coupled receptors. J. Biol Chem. 265:9308-9313, hereby incorporated by reference in its entirety.

WO91/15583, published on October 17, 1991, hereby incorporated by reference in its entirety.

WO99/46277, published on September 16, 1999, hereby incorporated by reference in its entirety.

S1P1/Edg1 Mouse

WO0059529, published October 12, 2000, hereby incorporated by reference in its entirety.

U.S. No. 6,323,333, granted November 27, 2001, hereby incorporated by reference in its entirety.

S1P1/Edg1 Rat

Lado, D.C., C. S. Browe, A.A. Gaskin, J. M. Borden, and A. J. MacLennan. 1994 Cloning of the rat edg-1 immediate-early gene: expression pattern suggests diverse functions. Gene 149: 331-336, hereby incorporated by reference in its entirety.

U.S. No. 5,585,476, granted December 17, 1996, hereby incorporated by reference in its entirety.

U.S. No. 5856,443, granted January 5, 1999, hereby incorporated by reference in its entirety.

S1P3/Edg3 Human

An, S., T. Bleu, W. Huang, O.G. Hallmark, S. R. Coughlin, E.J. Goetzl 1997 Identification of cDNAs encoding two G protein-coupled receptors for lysosphingolipids FEBS Lett. 417:279-282, hereby incorporated by reference in its entirety.

WO 99/60019, published November 25, 1999, hereby incorporated by reference in its entirety.

U.S. No. 6,130,067, granted October 10, 2000, hereby incorporated by reference in its entirety.

S1P3/Edg3 Mouse

WO 01/11022, published February 15, 2001, hereby incorporated by reference in its entirety.

S1P3/Edg3 Rat

WO 01/27137, published April 19, 2001, hereby incorporated by reference in its entirety.

S1P2/Edg5 Human

An, S., Y. Zheng, T. Bleu 2000 Sphingosine 1-Phosphate-induced cell proliferation, survival, and related signaling events mediated by G Protein-coupled receptors Edg3 and Edg5. J. Biol. Chem 275: 288-296, hereby incorporated by reference in its entirety.

WO 99/35259, published July 15, 1999, hereby incorporated by reference in its entirety.

WO99/54351, published October 28, 1999, hereby incorporated by reference in its entirety.

WO 00/56135, published September 28, 2000, hereby incorporated by reference in its entirety.

S1P2/Edg5 Mouse

WO 00/60056, published October 12, 2000, hereby incorporated by reference in its entirety.

S1P2/Edg5 Rat

Okazaki, H., N. Ishizaka, T. Sakurai, K. Kurokawa, K. Goto, M. Kumada, Y. Takuwa 1993 Molecular cloning of a novel putative G protein-coupled receptor expressed in the cardiovascular system. Biochem. Biophys. Res. Comm. 190:1104-1109, hereby incorporated by reference in its entirety.

MacLennan, A.J., C. S. Browe, A.A. Gaskin, D.C. Lado, G. Shaw 1994 Cloning and characterization of a putative G-protein coupled receptor potentially

involved in development. Mol. Cell. Neurosci. 5: 201-209, hereby incorporated by reference in its entirety.

U.S. No. 5,585,476, granted December 17, 1996, hereby incorporated by reference in its entirety.

U.S. No. 5856,443, granted January 5, 1999, hereby incorporated by reference in its entirety.

S1P4/Edg6 Human

Graler, M.H., G. Bernhardt, M. Lipp 1998 EDG6, a novel G-protein-coupled receptor related to receptors for bioactive lysophospholipids, is specifically expressed in lymphoid tissue. Genomics 53: 164-169, hereby incorporated by reference in its entirety.

WO 98/48016, published October 29, 1998, hereby incorporated by reference in its entirety.

U.S. No. 5,912,144, granted June 15, 1999, hereby incorporated by reference in its entirety.

WO 98/50549, published November 12, 1998, hereby incorporated by reference in its entirety.

U.S. No. 6,060,272, granted May 9, 2000, hereby incorporated by reference in its entirety.

WO 99/35106, published July 15, 1999, hereby incorporated by reference in its entirety.

WO 00/15784, published March 23, 2000, hereby incorporated by reference in its entirety.

WO 00/14233, published March 16, 2000, hereby incorporated by reference in its entirety.

S1P4/Edg6 Mouse

WO 00/15784, published March 23, 2000, hereby incorporated by reference in its entirety.

S1P5/Edg8 Human

Im, D.-S., J. Clemens, T.L. Macdonald, K.R. Lynch 2001 Characterization of the human and mouse sphingosine 1-phosphate receptor, S1P5 (Edg-8): Structure-Activity relationship of sphingosine 1-phosphate receptors. Biochemistry 40:14053-14060, hereby incorporated by reference in its entirety.

WO 00/11166, published March 2, 2000, hereby incorporated by reference in its entirety.

WO 00/31258, published June 2, 2000, hereby incorporated by reference in its entirety.

WO 01/04139, published January 18, 2001, hereby incorporated by reference in its entirety.

EP 1 090 925, published April 11, 2001, hereby incorporated by reference in its entirety.

S1P5/Edg8 Rat

Im, D.-S., C.E. Heise, N. Ancellin, B. F. O'Dowd, G.-J. Shei, R. P. Heavens, M. R. Rigby, T. Hla, S. Mandala, G. McAllister, S.R. George, K.R. Lynch 2000 Characterization of a novel sphingosine 1-phosphate receptor, Edg-8. J. Biol. Chem. 275: 14281-14286, hereby incorporated by reference in its entirety.

WO 01/05829, published January 25, 2001, hereby incorporated by reference in its entirety.

Measurement of cardiovascular effects

The effects of compounds of the present invention on cardiovascular parameters can be evaluated by the following procedure:

Adult male rats (approx. 350 g body weight) were instrumented with femoral arterial and venous catheters for measurement of arterial pressure and intravenous compound administration, respectively. Animals were anesthetized with Nembutal (55 mg/kg, ip). Blood pressure and heart rate were recorded on the Gould Po-Ne-Mah data acquisition system. Heart rate was derived from the arterial pulse wave. Following an acclimation period, a baseline reading was taken (approximately 20 minutes) and the data averaged. Compound was administered intravenously (either

bolus injection of approximately 5 seconds or infusion of 15 minutes duration), and data were recorded every 1 minute for 60 minutes post compound administration. Data are calculated as either the peak change in heart rate or mean arterial pressure or are calculated as the area under the curve for changes in heart rate or blood pressure versus time. Data are expressed as mean ± SEM. A one-tailed Student's paired t-test is used for statistical comparison to baseline values and considered significant at $p<0.05$.

The S1P effects on the rat cardiovascular system are described in Sugiyama, A., N.N. Aye, Y. Yatomi, Y. Ozaki, K. Hashimoto 2000 Effects of Sphingosine-1-Phosphate, a naturally occurring biologically active lysophospholipid, on the rat cardiovascular system. Jpn. J. Pharmacol. 82: 338-342, hereby incorporated by reference in its entirety.

Measurement of Mouse Acute Toxicity

A single mouse is dosed intravenously (tail vein) with 0.1 ml of test compound dissolved in a non-toxic vehicle and is observed for signs of toxicity. Severe signs may include death, seizure, paralysis or unconciousness. Milder signs are also noted and may include ataxia, labored breathing, ruffling or reduced activity relative to normal. Upon noting signs, the dosing solution is diluted in the same vehicle. The diluted dose is administered in the same fashion to a second mouse and is likewise observed for signs. The process is repeated until a dose is reached that produces no signs. This is considered the estimated no-effect level. An additional mouse is dosed at this level to confirm the absence of signs.

Assessment of Lymphopenia

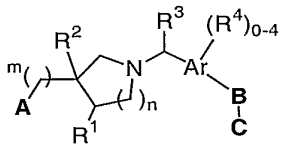
Compounds are administered as described in Measurement of Mouse Acute Toxicity and lymphopenia is assessed in mice at three hours post dose as follows. After rendering a mouse unconscious by CO_2 to effect, the chest is opened, 0.5 ml of blood is withdrawn via direct cardiac puncture, blood is immediately stabilized with EDTA and hematology is evaluated using a clinical hematology autoanalyzer calibrated for performing murine differential counts (H2000, CARESIDE, Culver City CA). Reduction in lymphocytes by test treatment is established by comparison of hematological parameters of three mice versus three

vehicle treated mice. The dose used for this evaluation is determined by tolerability using a modification of the dilution method above. For this purpose, no-effect is desirable, mild effects are acceptable and severely toxic doses are serially diluted to levels that produce only mild effects.

5

WHAT IS CLAIMED IS:

1. A compound represented by Formula I:



I

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

Ar is phenyl or naphthyl;

m = 0 or 1;

n = 0 or 1;

A is selected from the group consisting of: $-CO_2H$, $-PO_3H_2$, $-PO_2H$, $-SO_3H$, $-PO(C_{1-3}alkyl)OH$ and 1*H*-tetrazol-5-yl;

R^1 and R^2 are each independently selected from the group consisting of: hydrogen, halo, hydroxy, $-CO_2H$ and $C_{1-4}alkyl$, optionally substituted from one up to the maximum number of substitutable positions with halo;

R^3 is selected from the group consisting of: hydrogen and $C_{1-4}alkyl$, optionally substituted with from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo and hydroxy;

each R^4 is independently selected from the group consisting of: halo, $C_{1-4}alkyl$ and $C_{1-3}alkoxy$, said $C_{1-4}alkyl$ and $C_{1-3}alkoxy$ optionally substituted from one up to the maximum number of substitutable positions with halo,

C is selected from the group consisting of:

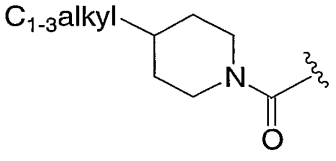
(1) C_{1-8}alkyl, C_{1-8}alkoxy, -(C=O)-C_{1-6}alkyl or –CHOH-C_{1-6}alkyl, said C_{1-8}alkyl, C_{1-8}alkoxy, -(C=O)-C_{1-6}alkyl and –CHOH-C_{1-6}alkyl optionally substituted with phenyl, and

(2) phenyl or HET, each optionally substituted with 1-3 substituents independently selected from the group consisting of: halo, phenyl, C_{1-4}alkyl and C_{1-4}alkoxy, said C_{1-4}alkyl and C_{1-4}alkoxy groups optionally substituted from one up to the maximum number of substitutable positions with a substituent independently selected from halo and hydroxy, and said phenyl optionally substituted with 1 to 5 groups independently selected from the group consisting of : halo and C_{1-4}alkyl, optionally substituted with 1-3 halo groups,

or **C** is not present;

when **C** is not present then **B** is selected from the group consisting of: phenyl, C_{5-16}alkyl, C_{5-16}alkenyl, C_{5-16}alkynyl, -CHOH-C_{4-15}alkyl, -CHOH-C_{4-15}alkenyl, -CHOH-C_{4-15}alkynyl, C_{4-15}alkoxy, -O-C_{4-15}alkenyl, -O-C_{4-15}alkynyl, C_{4-15}alkylthio, -S-C_{4-15}alkenyl, -S-C_{4-15}alkynyl, -CH_2-C_{3-14}alkoxy, -CH_2-O-C_{3-14}alkenyl, -CH_2-O-C_{3-14}alkynyl, -(C=O)-C_{4-15}alkyl, -(C=O)-C_{4-15}alkenyl, -(C=O)-C_{4-15}alkynyl, -(C=O)-O-C_{3-14}alkyl, -(C=O)-O-C_{3-14}alkenyl, -(C=O)-O-C_{3-14}alkynyl, -(C=O)-N(R^6)(R^7)-C_{3-14}alkyl, -(C=O)-N(R^6)(R^7)-C_{3-14}alkenyl, -(C=O)-N(R^6)(R^7)-C_{3-14}alkynyl, -N(R^6)(R^7)-(C=O)-C_{3-14}alkyl, -N(R^6)(R^7)-(C=O)-C_{3-14}alkenyl and -N(R^6)(R^7)-(C=O)-C_{3-14}alkynyl,

when **C** is phenyl or HET then **B** is selected from the group consisting of: C_{1-6}alkyl, C_{1-5}alkoxy, -(C=O)-C_{1-5}alkyl, -(C=O)-O-C_{1-4}alkyl, -(C=O)-N(R^6)(R^7)-C_{1-4}alkyl,



, phenyl and HET, and

when **C** is C_{1-8}alkyl, C_{1-8}alkoxy, -(C=O)-C_{1-6}alkyl or –CHOH-C_{1-6}alkyl then **B** is phenyl; and

R^6 and R^7 are independently selected from the group consisting of: hydrogen, C_{1-9}alkyl and -$(CH_2)_p$-phenyl, wherein p is 1 to 5 and phenyl is optionally substituted with 1-3 substituents independently selected from the group consisting of: C_{1-3}alkyl and C_{1-3}alkoxy, each optionally substituted with 1-3 halo groups.

2. The compound according to Claim 1 wherein:

Ar is phenyl;

the group **–B-C** is attached to the phenyl ring at the 3- or 4-position;

C is phenyl or HET, each optionally substituted with 1-3 substituents independently selected from the group consisting of: halo, phenyl, C_{1-4}alkyl and C_{1-4}alkoxy, said C_{1-4}alkyl and C_{1-4}alkoxy groups optionally substituted from one up to the maximum number of substitutable positions with a substituent independently selected from halo and hydroxy, and said phenyl optionally substituted with 1 to 5 groups independently selected from the group consisting of : halo and C_{1-4}alkyl, optionally substituted with 1-3 halo groups,

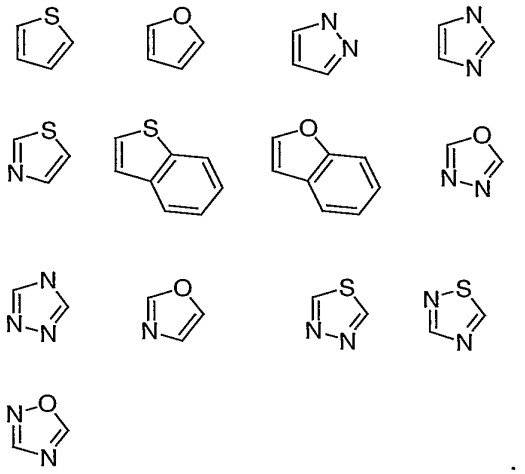
or **C** is not present;

when **C** is not present then **B** is selected from the group consisting of: C_{7-12}alkyl, C_{7-12}alkenyl, C_{7-12}alkynyl, C_{6-11}alkoxy, -O-C_{6-11}alkenyl, -O-C_{6-11}alkynyl, -(C=O)-C_{6-11}alkyl, -(C=O)-C_{6-11}alkenyl, -(C=O)-C_{6-11}alkynyl, -(C=O)-O-C_{5-10}alkyl, -(C=O)-O-C_{5-19}alkenyl, and -(C=O)-O-C_{5-10}alkynyl and **C** is not present;

and

when **C** is phenyl or HET then **B** is selected from the group consisting of C_{1-5}alkyl, C_{1-4}alkoxy, -(C=O)-C_{1-4}alkyl, -(C=O)-O-C_{1-3}alkyl, phenyl and HET.

3. The compound according to Claim 1 wherein HET is selected from the group consisting of:



4. The compound according to Claim 1 wherein m is 0.

5. The compound according to Claim 1 wherein m is 1.

6. The compound according to Claim 1 wherein n is 0.

7. The compound according to Claim 1 wherein n is 1.

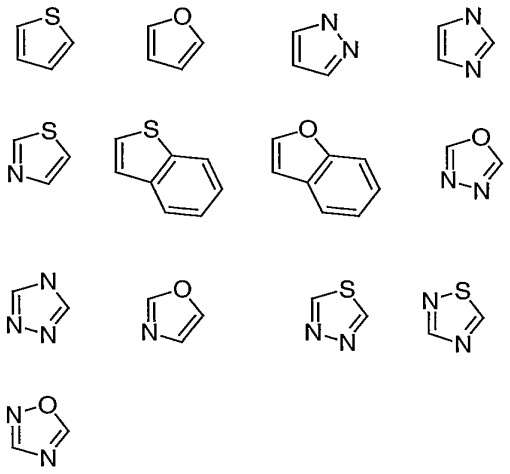
8. The compound according to Claim 1 wherein **B** is selected from the group consisting of: C_{7-12}alkyl, C_{7-12}alkenyl, C_{7-12}alkynyl, C_{6-11}alkoxy, -O-C_{6-11}alkenyl, -O-C_{6-11}alkynyl, -(C=O)-C_{6-11}alkyl, -(C=O)-C_{6-11}alkenyl, -(C=O)-

C_{6-11}alkynyl, -(C=O)-O-C_{5-10}alkyl, -(C=O)-O-C_{5-19}alkenyl, and -(C=O)-O-C_{5-10}alkynyl and **C** is not present.

9. The compound according to Claim 1 wherein:

B is methoxy and **C** is HET substituted with phenyl and C_{1-4}alkyl, said C_{1-4}alkyl optionally substituted from one up to the maximum number of substitutable positions with halo, and said phenyl, optionally substituted with 1 to 5 substituents independently selected from the group conisting of: halo and C_{1-4}alkyl, optionally substituted with 1-3 halo groups.

10. The compound according to Claim 8 wherein **C** is selected from the group consisting of:

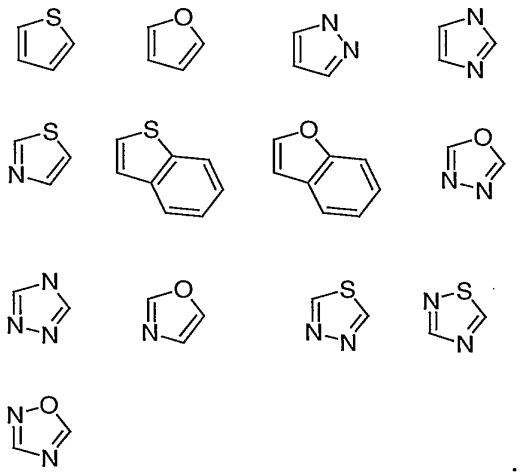


11. The compound according to Claim 9 wherein **C** is thiophene or furan.

12. The compound according to Claim 1 wherein:

B is methoxy and **C** is HET.

13. The compound according to Claim 12 wherein **C** is selected from the group consisting of:



14. The compound according to Claim 13 wherein **C** is benzothiophene or benzofuran.

15. The compound according to Claim 1 wherein:

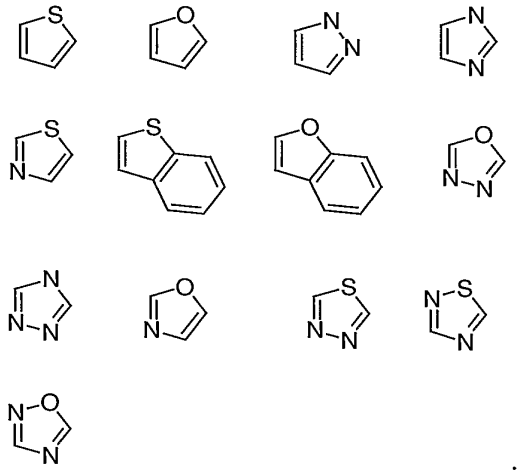
B is methoxy and **C** is phenyl substituted with two C_{1-4}alkyl groups, said C_{1-4}alkyl optionally substituted from one up to the maximum number of substitutable positions with halo.

16. The compound according to Claim 1 wherein:

B is HET and **C** is HET substituted with phenyl and C_{1-4}alkyl, said C_{1-4}alkyl optionally substituted from one up to the maximum number of substitutable positions with halo, and said phenyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of: halo, C_{1-4}alkyl, optionally substituted with 1-3 halo groups.

17. The compound according to Claim 16 wherein **B** is 1,2,4-oxadiazole.

18. The compound according to Claim 17 wherein **C** is selected from the group consisting of:



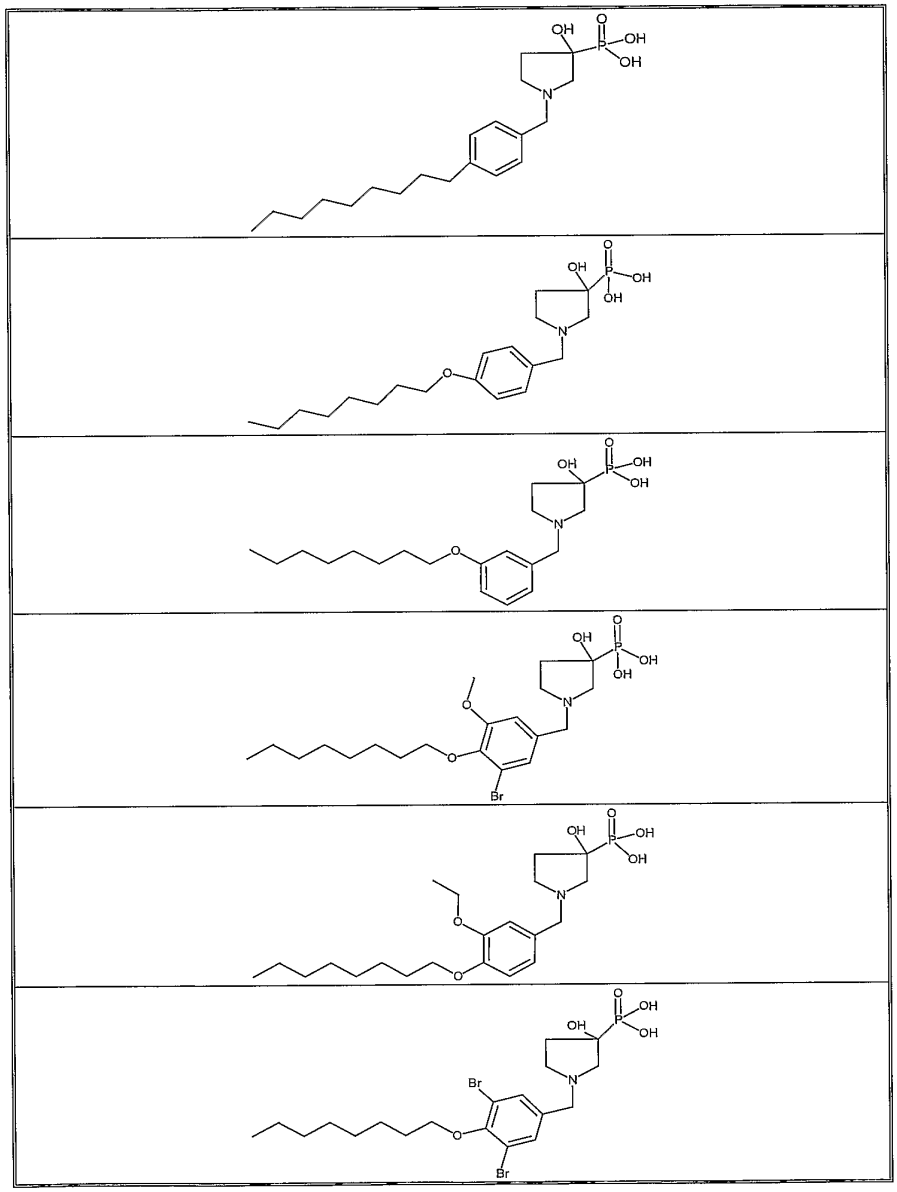
19. The compound according to Claim 18 wherein **C** is thiophene or furan.

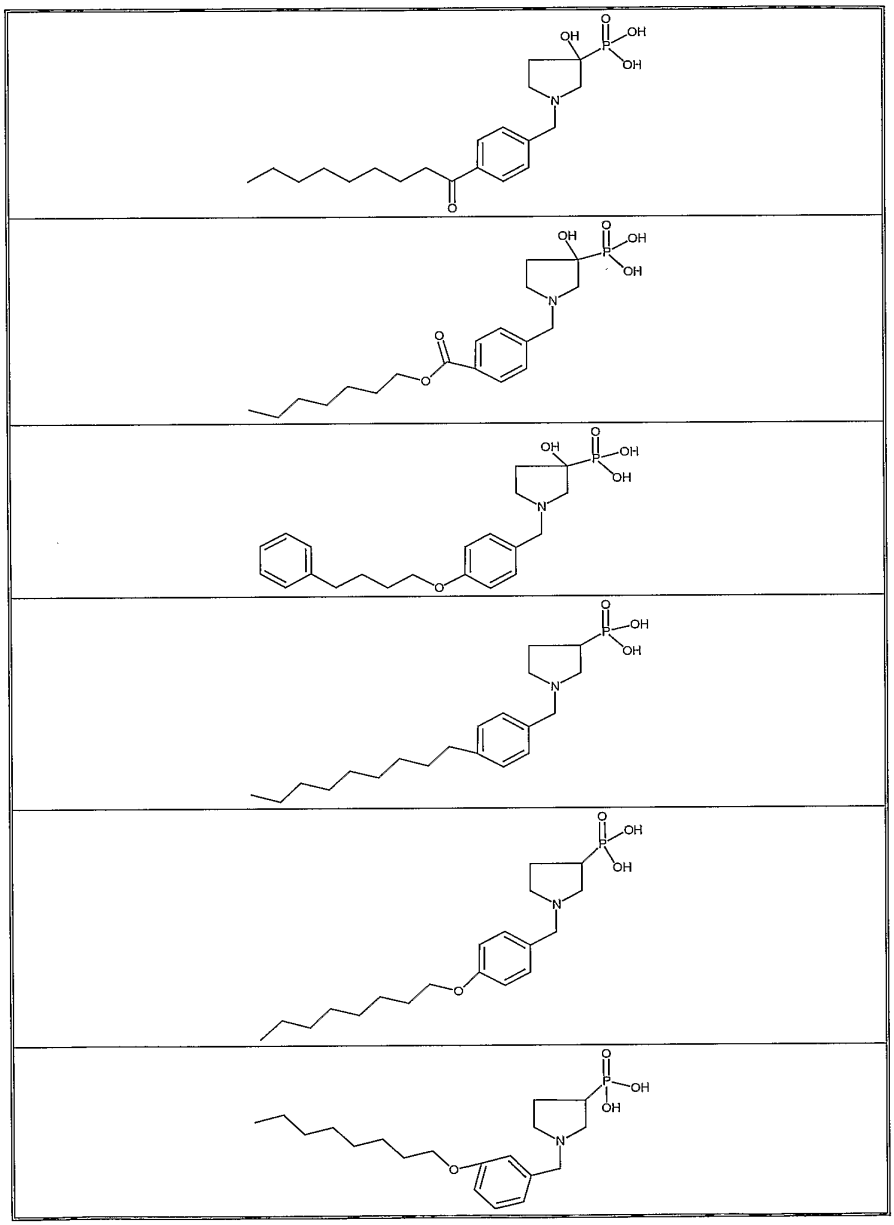
20. The compound according to Claim 1 wherein m = 0 and **A** is $-CO_2H$.

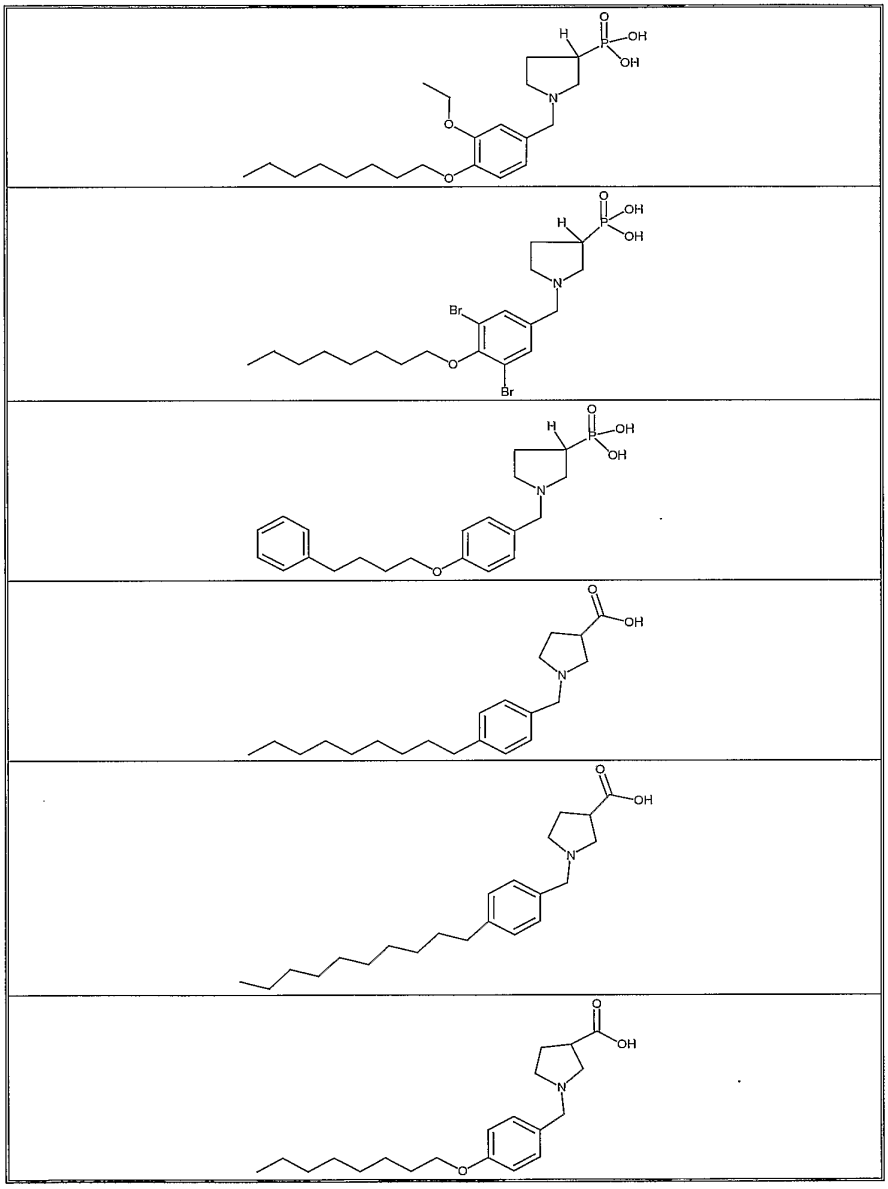
21. The compound according to Claim 20 wherein R^1, R^2 and R^3 are hydrogen.

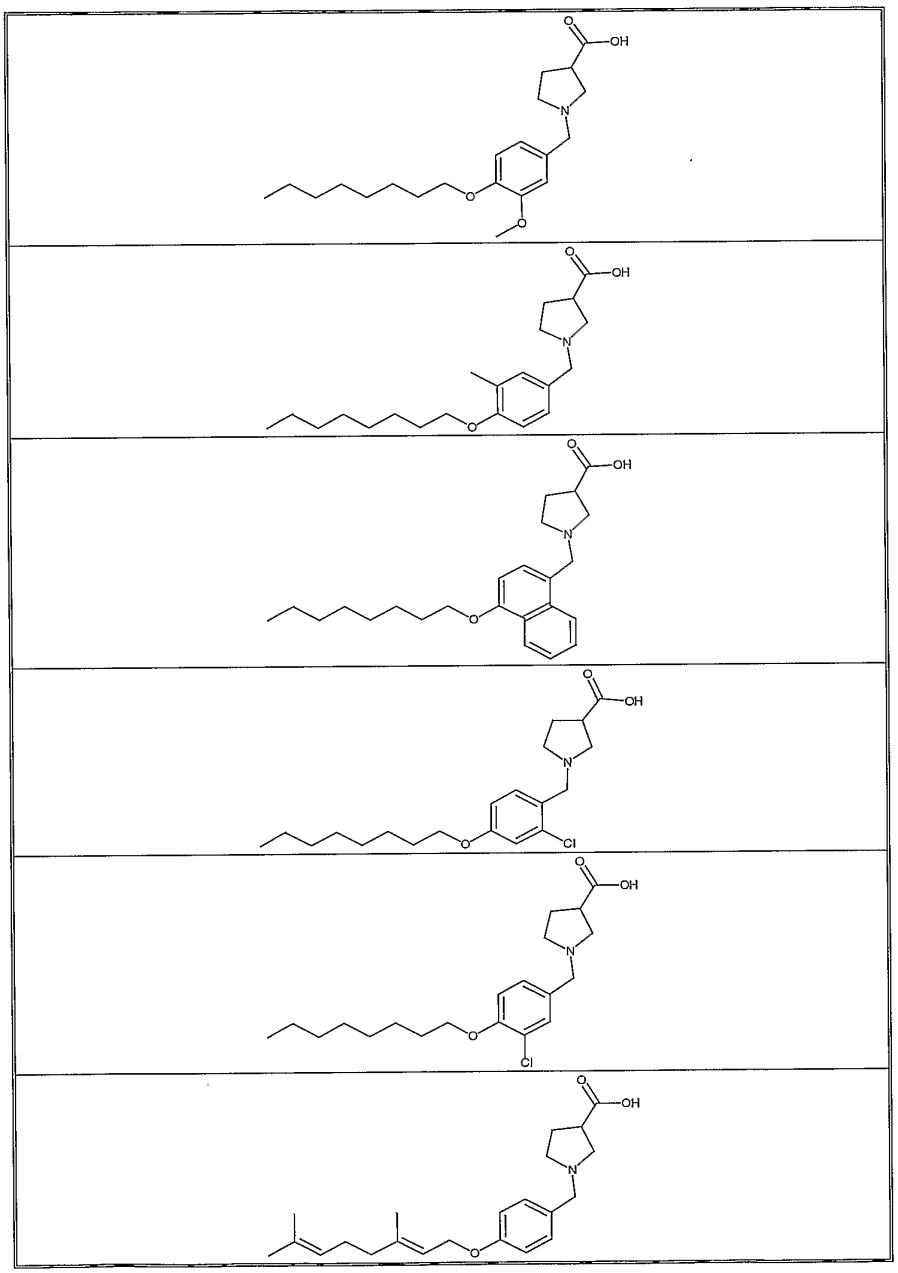
22. The compound according to Claim 2 wherein the group **–B-C** is attached to the phenyl ring at the 4-position.

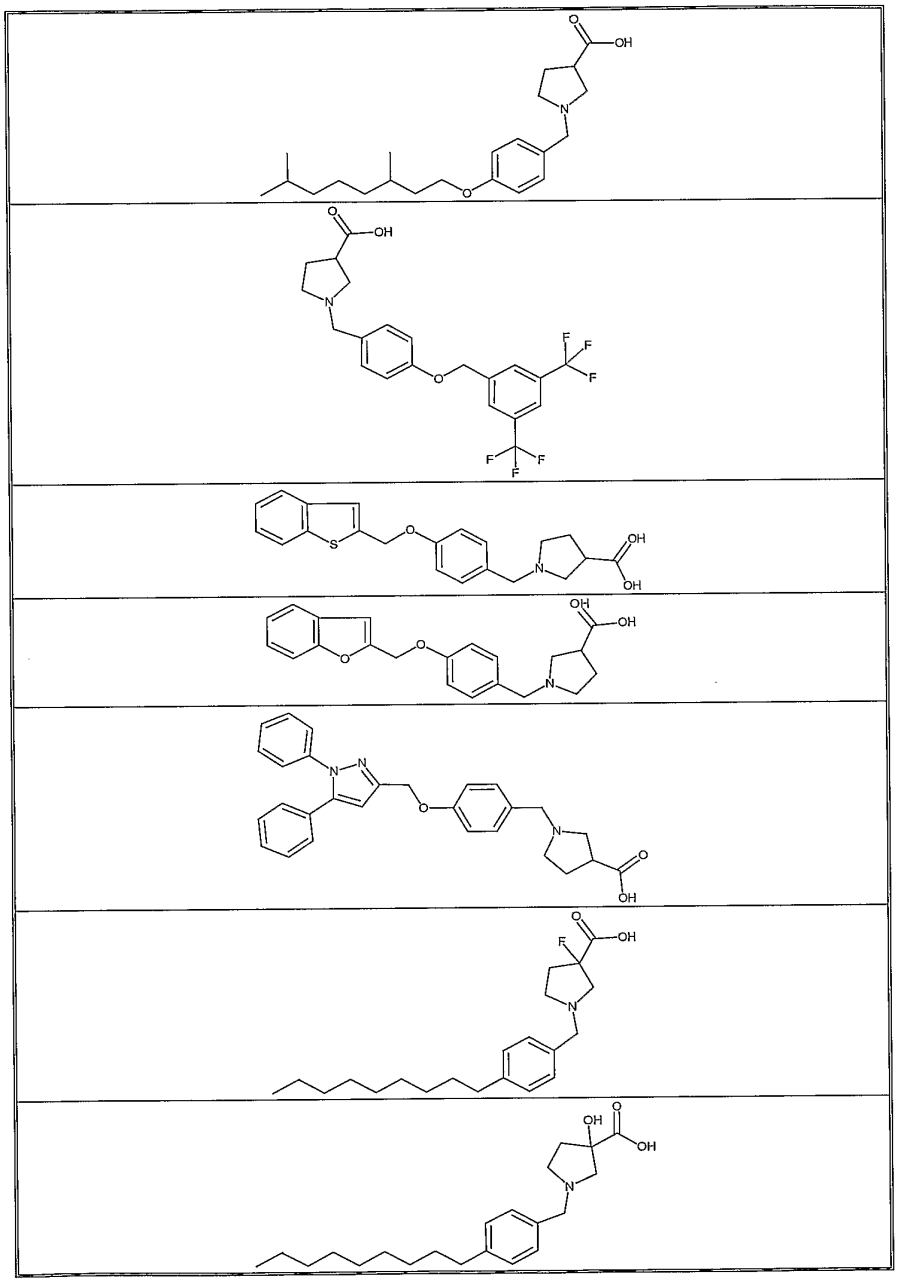
23. The compound according to Claim 1 selected from the following table:

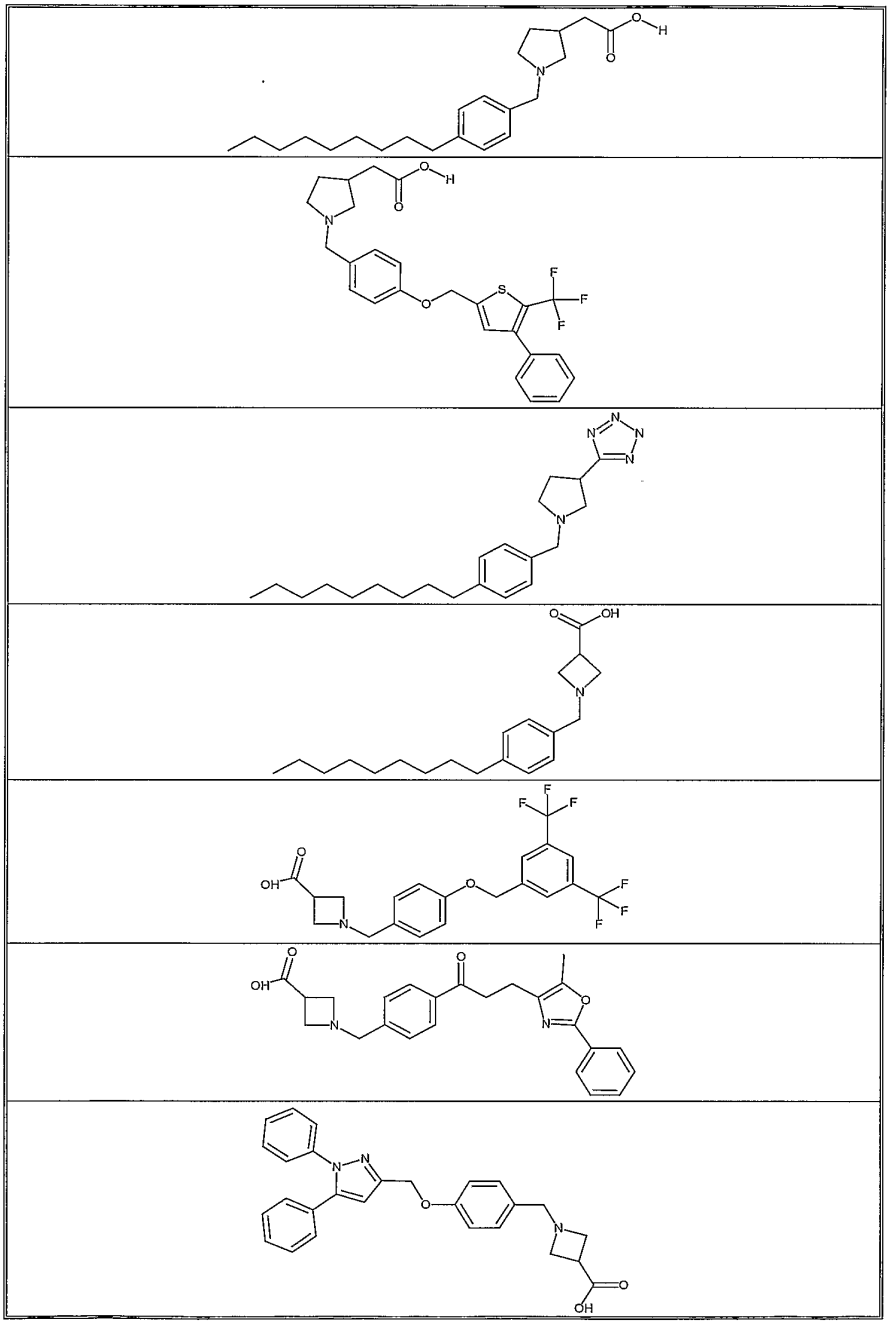


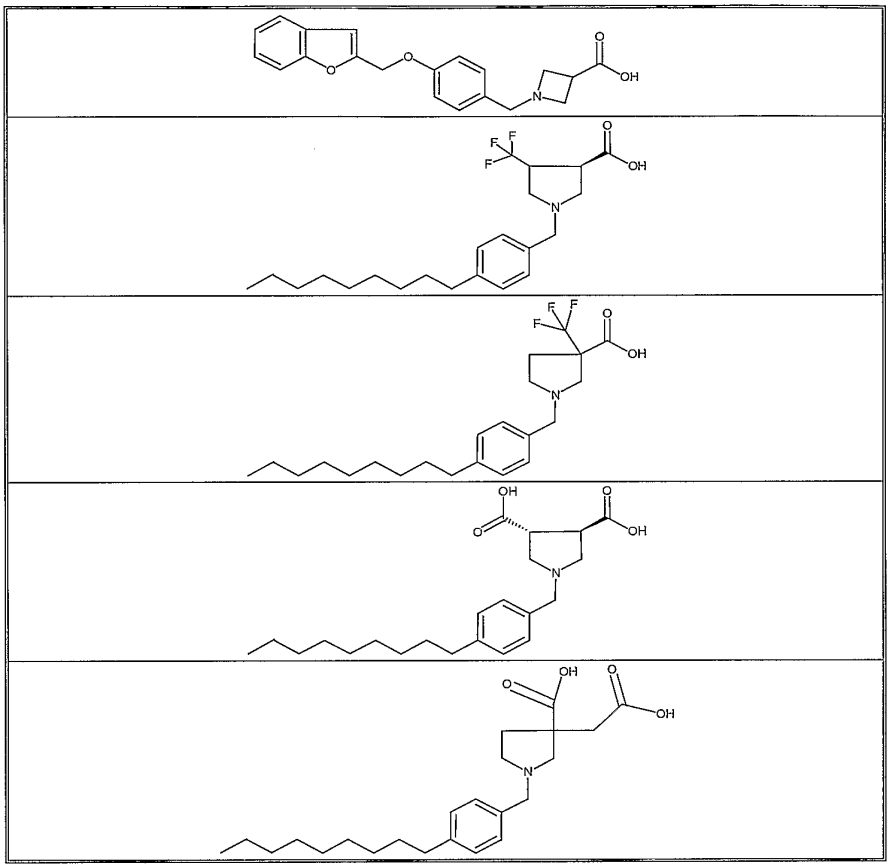




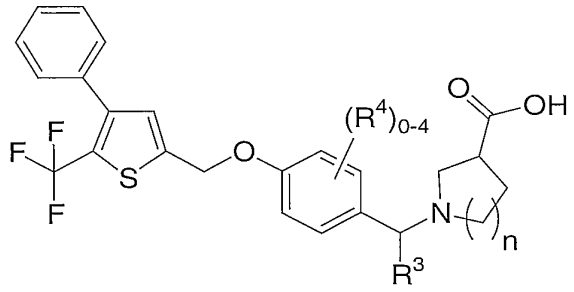








24. A compound represented by Formula II



II

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

n = 0 or 1;

R^3 is selected from the group consisting of: hydrogen and C_{1-4}alkyl, optionally substituted with from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo and hydroxy;

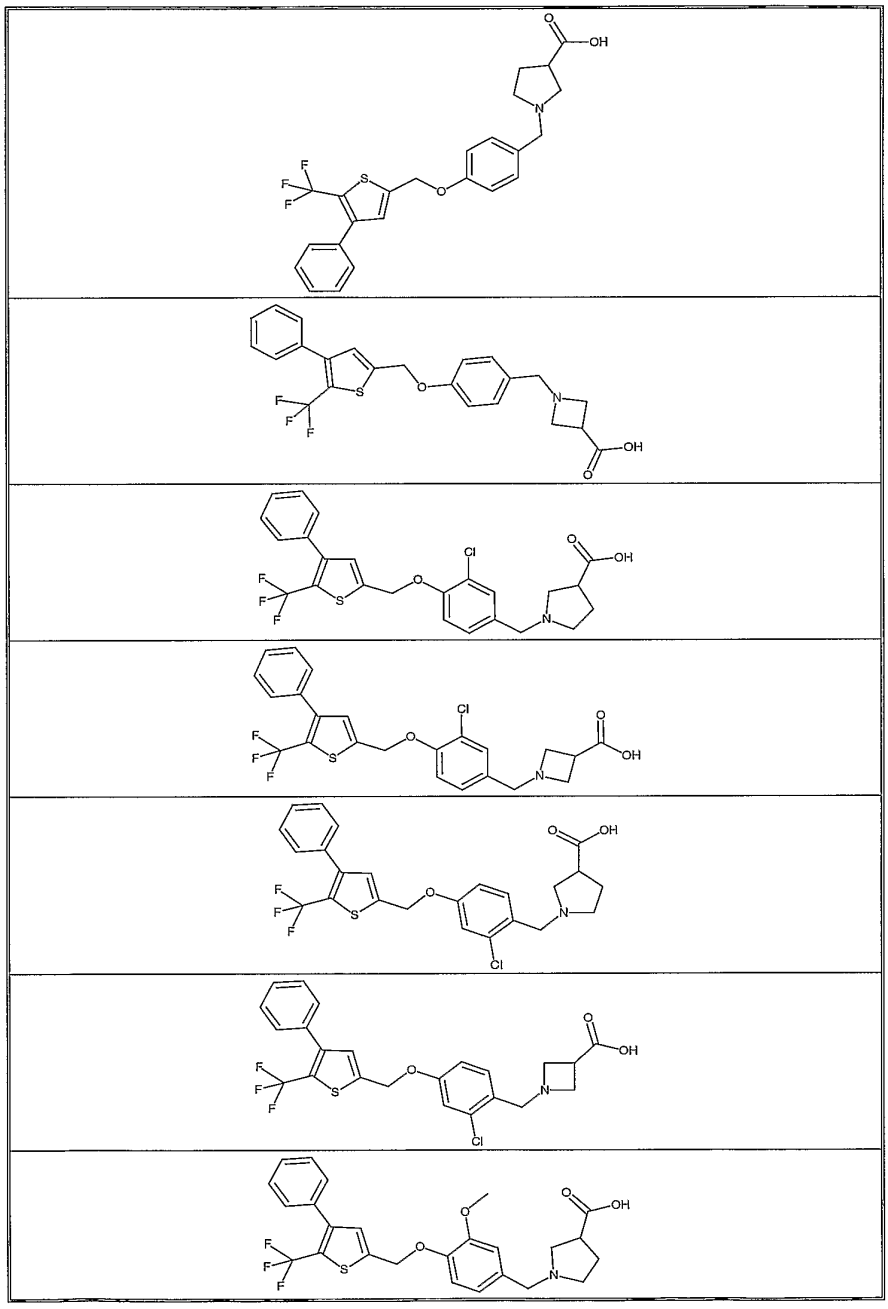
each R^4 is independently selected from the group consisting of: halo, C_1-4alkyl and C_1-3alkoxy, said C_1-4alkyl and C_1-3alkoxy optionally substituted from one up to the maximum number of substitutable positions with halo.

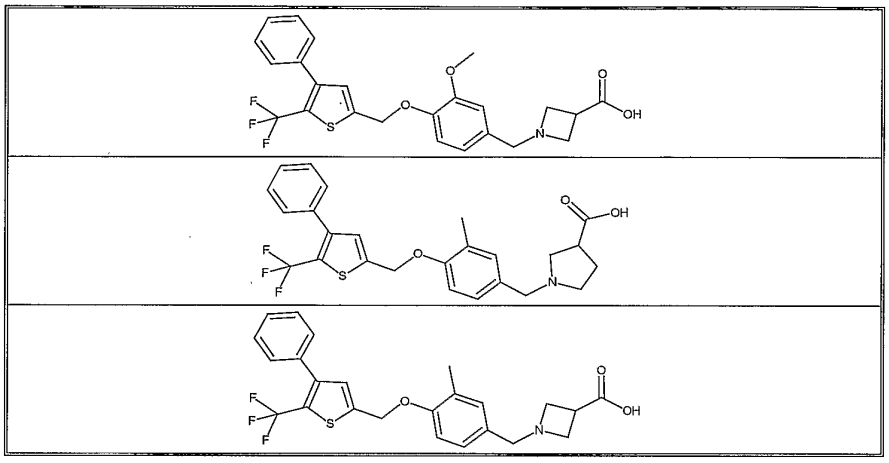
25. The compound according to Claim 24 wherein n is 0.

26. The compound according to Claim 24 wherein n is 1.

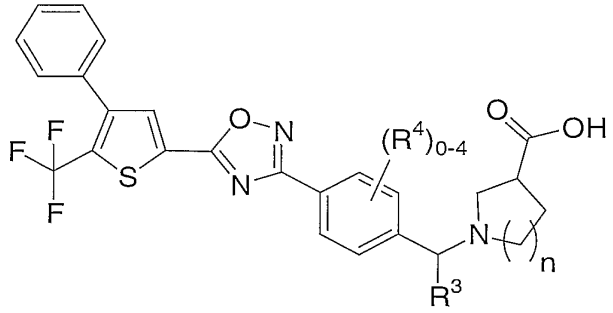
27. The compound according to Claim 24 wherein R^3 is hydrogen.

28. The compound according to Claim 24 selected from the following table:





29. A compound represented by Formula III



III

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

n = 0 or 1;

R^3 is selected from the group consisting of: hydrogen and C_{1-4}alkyl, optionally substituted with from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo and hydroxy;

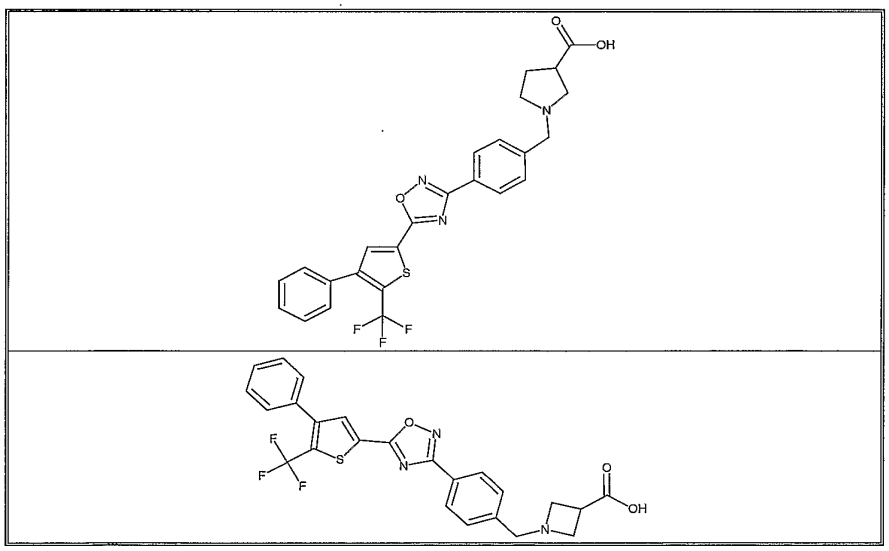
each R^4 is independently selected from the group consisting of: halo, C_{1-4}alkyl and C_{1-3}alkoxy, said C_{1-4}alkyl and C_{1-3}alkoxy optionally substituted from one up to the maximum number of substitutable positions with halo.

30. The compound according to Claim 29 wherein n is 0.

31. The compound according to Claim 29 wherein n is 1.

32. The compound according to Claim 29 wherein R^3 is hydrogen.

33. The compound according to Claim 29 selected from the following table:



34. A method of treating an immunoregulatory abnormality in a mammalian patient in need of such treatment comprising administering to said patient

a compound in accordance with Claim 1 in an amount that is effective for treating said immunoregulatory abnormality.

35. The method according to Claim 34 wherein the immunoregulatory abnormality is an autoimmune or chronic inflammatory disease selected from the group consisting of: systemic lupus erythematosis, chronic rheumatoid arthritis, type I diabetes mellitus, inflammatory bowel disease, biliary cirrhosis, uveitis, multiple sclerosis, Crohn's disease, ulcerative colitis, bullous pemphigoid, sarcoidosis, psoriasis, autoimmune myositis, Wegener's granulomatosis, ichthyosis, Graves ophthalmopathy and asthma.

36. The method according to Claim 34 wherein the immunoregulatory abnormality is bone marrow or organ transplant rejection or graft-versus-host disease.

37. The method according to Claim 34 wherein the immunoregulatory abnormality is selected from the group consisting of: transplantation of organs or tissue, graft-versus-host diseases brought about by transplantation, autoimmune syndromes including rheumatoid arthritis, systemic lupus erythematosus, Hashimoto's thyroiditis, multiple sclerosis, myasthenia gravis, type I diabetes, uveitis, posterior uveitis, allergic encephalomyelitis, glomerulonephritis, post-infectious autoimmune diseases including rheumatic fever and post-infectious glomerulonephritis, inflammatory and hyperproliferative skin diseases, psoriasis, atopic dermatitis, contact dermatitis, eczematous dermatitis, seborrhoeic dermatitis, lichen planus, pemphigus, bullous pemphigoid, epidermolysis bullosa, urticaria, angioedemas, vasculitis, erythema, cutaneous eosinophilia, lupus erythematosus, acne, alopecia areata, keratoconjunctivitis, vernal conjunctivitis, uveitis associated with Behcet's disease, keratitis, herpetic keratitis, conical cornea, dystrophia epithelialis corneae, corneal leukoma, ocular pemphigus, Mooren's ulcer, scleritis, Graves' opthalmopathy, Vogt-Koyanagi-Harada syndrome, sarcoidosis, pollen allergies, reversible obstructive airway disease, bronchial asthma, allergic asthma, intrinsic asthma, extrinsic asthma, dust asthma, chronic or inveterate asthma, late asthma and airway hyper-responsiveness, bronchitis, gastric ulcers, vascular damage caused by

ischemic diseases and thrombosis, ischemic bowel diseases, inflammatory bowel diseases, necrotizing enterocolitis, intestinal lesions associated with thermal burns, coeliac diseases, proctitis, eosinophilic gastroenteritis, mastocytosis, Crohn's disease, ulcerative colitis, migraine, rhinitis, eczema, interstitial nephritis, Goodpasture's syndrome, hemolytic-uremic syndrome, diabetic nephropathy, multiple myositis, Guillain-Barre syndrome, Meniere's disease, polyneuritis, multiple neuritis, mononeuritis, radiculopathy, hyperthyroidism, Basedow's disease, pure red cell aplasia, aplastic anemia, hypoplastic anemia, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, agranulocytosis, pernicious anemia, megaloblastic anemia, anerythroplasia, osteoporosis, sarcoidosis, fibroid lung, idiopathic interstitial pneumonia, dermatomyositis, leukoderma vulgaris, ichthyosis vulgaris, photoallergic sensitivity, cutaneous T cell lymphoma, arteriosclerosis, atherosclerosis, aortitis syndrome, polyarteritis nodosa, myocardosis, scleroderma, Wegener's granuloma, Sjogren's syndrome, adiposis, eosinophilic fascitis, lesions of gingiva, periodontium, alveolar bone, substantia ossea dentis, glomerulonephritis, male pattern alopecia or alopecia senilis by preventing epilation or providing hair germination and/or promoting hair generation and hair growth, muscular dystrophy, pyoderma and Sezary's syndrome, Addison's disease, ischemia-reperfusion injury of organs which occurs upon preservation, transplantation or ischemic disease, endotoxin-shock, pseudomembranous colitis, colitis caused by drug or radiation, ischemic acute renal insufficiency, chronic renal insufficiency, toxinosis caused by lung-oxygen or drugs, lung cancer, pulmonary emphysema, cataracta, siderosis, retinitis pigmentosa, senile macular degeneration, vitreal scarring, corneal alkali burn, dermatitis erythema multiforme, linear IgA ballous dermatitis and cement dermatitis, gingivitis, periodontitis, sepsis, pancreatitis, diseases caused by environmental pollution, aging, carcinogenesis, metastasis of carcinoma and hypobaropathy, disease caused by histamine or leukotriene-C4 release, Behcet's disease, autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis, partial liver resection, acute liver necrosis, necrosis caused by toxin, viral hepatitis, shock, or anoxia, B-virus hepatitis, non-A/non-B hepatitis, cirrhosis, alcoholic cirrhosis, hepatic failure, fulminant hepatic failure, late-onset hepatic failure, "acute-on-chronic" liver failure, augmentation of chemotherapeutic effect, cytomegalovirus infection, HCMV infection, AIDS, cancer, senile dementia, trauma, and chronic bacterial infection.

38. The method according to Claim 34 wherein the immunoregulatory abnormality is multiple sclerosis.

39. The method according to Claim 34 wherein the immunoregulatory abnormality is rheumatoid arthritis.

40. The method according to Claim 34 wherein the immunoregulatory abnormality is systemic lupus erythematosus.

41. The method according to Claim 34 wherein the immunoregulatory abnormality is psoriasis.

42. The method according to Claim 34 wherein the immunoregulatory abnormality is rejection of transplanted organ or tissue.

43. The method according to Claim 34 wherein the immunoregulatory abnormality is inflammatory bowel disease.

44. The method according to Claim 33 wherein the immunoregulatory abnormality is a malignancy of lymphoid origin.

45. The method according to Claim 44 wherein the immunoregulatory abnormality is acute and chronic lymphocytic leukemias and lymphomas.

46. A method of suppressing the immune system in a mammalian patient in need of immunosuppression comprising administering to said patient an immunosuppressing effective amount of a compound of Claim 1.

47. A pharmaceutical composition comprised of a compound in accordance with Claim 1 in combination with a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/01196

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07F 9/38

US CL : 548/570, 574

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 548/570, 574

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A, P	US 2002/0042443 A1 (DAY et al.) 11 April 2002 (11.04.2002), page 7.	23

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

04 April 2003 (04.04.2003)

Date of mailing of the international search report

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Name and mailing address of the ISA/US

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Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/01196

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claim Nos.: 1-22 and 24-47
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Please See Continuation Sheet

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest
☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

Continuation of Item 4 of the first sheet:
The title is not short and precise, PCT Rule 4.3, suggested new title follows: "EDG Receptor Agonists".

Continuation of Box I Reason 2:
In these claims, the numerous variables (e.g. Ar, m, n, A, R1, R2, R3, R4, C, HET, B, R6, R7, etc.) and their voluminous complex meanings and their seemingly endless permutations and combinations make it virtually impossible to determine the full scope and complete meaning of the claimed subject matter. As presented, the claimed subject matter cannot be regarded as being a clear and concise description for which protection is sought and as such the listed claims do not comply with the requirements of PCT article 6. Thus it is impossible to carry out a meaningful search on same. A search will be made on the first discernable invention, which is the first 15 compounds of claim 23.

Continuation of B. FIELDS SEARCHED Item 3:
CAS ONLINE
STN structure search

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(74) Agent: **GROS, Florent**; Novartis AG, Corporate Intellectual Property, Patent & Trademark Department, CH-4002 Basel (CH).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LT, LU, LV, MA, MD, MK, MN, MX, NO, NZ, OM, PH, PL, PT, RO, RU, SE, SG, SI, SK, TJ, TM, TN, TR, TT, UA, US, UZ, VN, YU, ZA, ZW.

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Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: TREATMENT OR PROPHYLAXIS OF INSULIN-PRODUCING CELL GRAFT REJECTION

(57) Abstract: A pharmaceutical combination comprising an accelerated lymphocyte homing agent in free form or in pharmaceutically acceptable salt form, and one or more compounds selected from the group consisting of an antibody to the IL-2 receptor, an immunosuppressive macrocylic lactone and a soluble human complement inhibitor is used to treat or prevent insulin-producing cell graft rejection.

WO 02/100148 A2

Treatment or Prophylaxis

of Insulin-Producing Cell Graft Rejection

The present invention relates to a method of treatment or prophylaxis of insulin-producing cell graft rejection, particularly pancreatic islet graft rejection.

Type 1 diabetes is caused by a progressive, autoimmune destruction of the insulin-producing β-cells within the islets of the pancreas. At present, multiple daily insulin injections, or insulin pump therapy, remain the treatments of choice for the majority of diabetic patients. Intensive insulin therapy can decrease the incidence of secondary complications, but the effect is not absolute and patients are at increased risk for serious episodes of hypoglycemia.

Islet transplantation is a significantly safer method for replacing the diseased glandular tissue in diabetics than pancreatic organ transplantation, and has been investigated for more than 10 years as a treatment for type 1 diabetes mellitus in patients with inadequate glucose control despite intensive insulin therapy.

The majority of islet transplant procedures have been performed in kidney graft recipients already receiving an immunosuppressive regimen consisting of antibody induction with antilymphocyte globulin and life-long treatment with ciclosporine, azathioprine and glucocorticoids, see Brendel et al., International Islet Transplant Registry report., Giessen, Germany, 1999, pp. 1-20.

However, islet engraftment has been difficult to achieve with such an immunosuppressive regimen due to rejection, recurrent autoimmunity, primary nonfunction (PNF), and the diabetogenicity of conventional immunosuppressive drugs. In particular, proinflammatory mediators, produced by activated intrahepatic macrophages and endothelial cells subsequent to islet infusion, are detrimental to islet function and may lead to early islet loss or primary nonfunction of the graft.

Thus it has been estimated that over 10,000 islet equivalents (IEQ) per kg of recipient body weight are required in order to reproducibly achieve insulin independence in non-human primates (baboons, rhesus and cynomolgus monkeys), see Kenyon et al, Diabetes, 48, pp. 8132-8137, 1999 and humans, see Shapiro et al, The New England J. of Med., 343 (4), pp. 230-238, 2000.

Yamasaki and co-workers have reported achieving prolonged islet allograft survival of up to 20 days in male rats rendered hyperglycemic with streptozotocin by pre-administration of FTY720 the day before and the day of grafting, Cell Transplantation, Vol. 7, No. 4, pp. 403-406 (1998).

Kenyon and co-workers demonstrated that islet transplantation can result in the reversal of hyperglycemia and in long-term insulin independence in humans and in several animal models of diabetes, including rodents, dogs, cynomolgus monkeys, rhesus monkeys, and baboons (Kenyon et al., Diabetes, 48, pp. 8132-8137, 1999), using an immunosuppresive regimen consisting of anti-CD154.

Shapiro and co-workers recently reported achieving favorable results in patients with type 1 diabetes and a history of severe hypoglycemia and metabolic instability who underwent islet transplantation in conjunction with a glucocorticoid-free immuno- suppressive regimen consisting of rapamycin (i.e. sirolimus), tacrolimus and daclizumab (i.e. a humanized antibody to the IL-2 receptor). Seven out of seven patients who received islet allografts became insulin independent. The longest reported patient follow up was 17 months posttransplantation, see Shapiro et al., NEJM 343:230-238 (2000).

However, there is still a need for an improved therapy to achieve improved insulin-producing cell engraftment, e.g. pancreatic islet engraftment with an improved quality of life.

It has now been found that co-administration of an accelerated lymphocyte homing ("ALH") agent with one or more immunosuppressive agents acting via a different mechanism than the ALH agent, to an islet graft recipient, provides an effective treatment or prophylaxis of pancreatic islet cell transplant rejection, and in particular enables type I diabetic transplant patients to achieve extended insulin independence.

In a particular embodiment the present invention comprises a method for the treatment or prophylaxis of insulin-producing cell graft rejection in an insulin-producing cell graft recipient comprising co-administering to the recipient an effective amount of an accelerated lymphocyte homing (ALH) agent and one or more compounds selected from the group consisting of an antibody to the IL-2 receptor, an immunosuppressive macrocyclic lactone, and a soluble human complement inhibitor. Preferably the co-administration therapy of the invention is glucocorticoid-free.

Preferably, the invention comprises combined administration of an ALH agent, an antibody to the IL-2 receptor and an immunosuppressive macrocyclic lactone. Optionally, such a treatment may additionally include administration of a soluble human complement inhibitor.

The combination therapy of the invention facilitates engraftment, sustained insulin independence, and long-term survival of insulin-producing cell allo- or xenografts. A particular advantage of the present therapy is in facilitating single-donor transplants, which are less clinically challenging than multiple donor grafts, by effectively reducing the numbers of transplanted cells needed to provide functional insulin-producing cell mass in the patient. For example, the present therapy can reduce the required number of islet equivalents (IEQ) to 5,000 mg/kg per recipient, or less.

By "insulin independence" is meant endogenous insulin production as determined after intravenous glucose tolerance test to the extent that the subject has normal glucose tolerance.

By "insulin-producing cell" are meant islets of Langerhans (of allo or xeno origin) and other cells such as suitable insulin-secreting cells or cell lines, e.g. stem cell derived or cloned insulin-secreting cells.

As alternative to the above, the present invention also provides:

1. Use of an ALH agent in free form or in pharmaceutically acceptable salt form in combination with one or more compounds selected from the group consisting of an antibody to the IL-2 receptor, an immunosuppressive macrocyclic lactone and a soluble human complement inhibitor,
   to treat or prevent insulin-producing cell graft rejection.

2. A pharmaceutical combination comprising a) an ALH agent in free form or in pharmaceutically acceptable salt form, and b) one or more compounds selected from the group consisting of an antibody to the IL-2 receptor, an immunosuppressive macrocyclic lactone and a soluble human complement inhibitor.

   The term "pharmaceutical combination" as used herein preferably includes a non-fixed combination, e.g. the active components are administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific limits, wherein such administration provides therapeutically effective levels of the components in the body of the patient. Each active component may be administered in the form of a

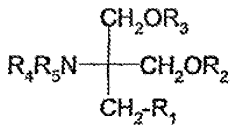
pharmaceutical composition, e.g. the active component is associated with one or more pharmaceutically acceptable diluents or carriers therefor.

3. Use of a pharmaceutical combination as described above in a method as disclosed above.

4. Use of an ALH agent in free form or in pharmaceutically acceptable salt form, in the manufacture of a medicament for use in treating or preventing insulin-producing cell graft rejection in an insulin-producing cell graft recipient, in combination with one or more compounds selected from the group consisting of an antibody to the IL-2 receptor, an immunosuppressive macrocyclic lactone and a soluble human complement inhibitor.

Preferably the ALH agent is administered in combination with an immunosuppressive macrocyclic lactone, optionally together with a soluble human complement inhibitor; alternatively, the ALH agent may be administered in combination with an immunosuppressive macrocyclic lactone and an antibody to the IL-2 receptor, optionally together with a soluble human complement inhibitor.

The ALH agents of the invention are compounds which may be phosphorylated by sphingosine kinase and are in the phosphorylated form potent agonists at S1P receptors, thereby modulating lymphocyte trafficking, e.g. synthetic analogs of myriocin or ISP-1, a natural metabolite of the ascomycete *Isaria sinclairii*. Examples of an ALH agent include e.g. 2-aminopropane1-3-diol compounds, e.g. a compound of formula I

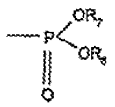


I

wherein

R_1 is an optionally substituted straight- or branched carbon chain having 12 to 22 carbon atoms which may be optionally interrupted by an optionally substituted phenylene,

R_2 is H or a residue of formula



wherein R_6 is H or C_{1-4}alkyl optionally substituted by 1, 2 or 3 halogen atoms, and R_7 is H or C_{1-4}alkyl optionally substituted by halogen,

R_3 is H or C_{1-4}alkyl, and

each of R_4 and R_5, independently, is H; C_{1-4}alkyl optionally substituted by halogen; or acyl, in free form or in pharmaceutically acceptable salt form.

When the carbon chain as R_1 is substituted, it is preferably substituted by halogen, nitro, amino, hydroxy or carboxy. When the carbon chain is interrupted by an optionally substituted phenylene, the carbon chain is preferably unsubstituted. When the phenylene moiety is substituted, it is preferably substituted by halogen, nitro, amino, methoxy, hydroxy or carboxy. Acyl may be a residue R-CO- wherein R is C_{1-6}alkyl, C_{3-6}cycloalkyl, phenyl or phenyl-C_{1-4}alkyl.

Preferred compounds of formula I are those wherein R_1 is a straight or branched, preferably straight, chain alkyl having 13 to 20 carbon atoms, optionally substituted by nitro, halogen, amino, hydroxy or carboxy, and, more preferably those wherein R_1 is phenylalkyl substituted by a straight or branched C_{6-14}-alkyl chain optionally substituted by halogen and the alkyl moiety is a C_{1-6}alkyl optionally substituted by hydroxy. More preferably, R_1 is phenyl-C_{1-6}alkyl substituted on the phenyl by a straight or branched, preferably straight, C_{6-14}alkyl chain. The C_{6-14}alkyl chain may be in ortho, meta or para, preferably in para.

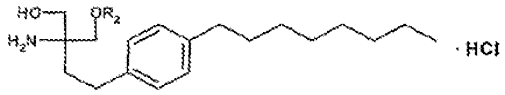
Preferably each of R_2 to R_5 is H.

When the compounds of formula I have one or more asymmetric centers in the molecule, the present invention is to be understood as embracing the various optical isomers, as well as racemates, diastereoisomers and mixtures thereof are embraced.

Examples of pharmaceutically acceptable salts of the compounds of the formula (I) include salts with inorganic acids, such as hydrochloride, hydrobromide and sulfate, salts with organic acids, such as acetate, fumarate, maleate, benzoate, citrate, malate, methanesulfonate and benzenesulfonate salts, or, when appropriate, salts with metals such as sodium, potassium, calcium and aluminium, salts with amines, such as triethylamine and salts with dibasic amino acids, such as lysine. The compounds and salts of the methods of the present invention encompass hydrate and solvate forms.

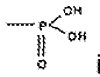
A preferred compound of formula I is 2-amino-2-tetradecyl-1,3-propanediol. A particularly preferred ALH compound for use in the invention is FTY720, i.e. 2-amino-2-[2-(4-

octylphenyl) ethyl]propane-1,3-diol in free form or in a pharmaceutically salt form, e.g.the hydrochloride, as shown:



wherein R_2 is H,

or its corresponding phosphate, wherein R_2 is

 in free form or in a pharmaceutically acceptable salt form.

A disclosure of compounds, substituent groups, and variations included in the ALH-compounds of this invention and methods of preparing said compounds can be found in U.S. Patent Nos. 5,604229 and 6,004,565, in EP-A-1,002,792 and in WO 02/18395A, incorporated herein by reference in their entirety.

FTY720, a novel immunomodulator, increases the responsiveness of lymphocytes to homing chemokines. Naïve cells are sequestered; CD4 and CD8 T-cells and B-cells from the blood are stimulated to migrate into lymph nodes (LN) and Peyer's patches (PP), and infiltration of cells into transplanted organs is inhibited. However, FTY720 does not impair lymphocyte activation, expansion and memory within the lymphoid system, and therefore does not suppress immunity to systemic infection.

The anti-IL-2 receptor antibody of the invention is preferably an antibody to the high affinity receptor for IL-2, i.e. CD25. Suitable antibodies comprise native or recombinant antibodies, and include recombinant chimeric or humanized antibodies, as well as recombinant single chain polypeptides consisting of a native antibody binding (i.e. Fv) domain, e.g. basiliximab (Simulect™), which is a chimeric antibody comprising the variable region of murine monoclonal antibody CHI-621 and a human IgG1 region, see EP 449,769, incorporated herein by reference, or daclizumab (Zenapax®), see WO 90/07,861 incorporated herein by reference. A particularly preferred antibody is basiliximab.

By "immunosuppressive macrocyclic lactone" is meant rapamycin, i.e. sirolimus, and immunosuppressant derivatives thereof. Of particular interest are rapamycin derivatives which are substituted in position 40 (or 42 or 43 depending on the nomenclature used), e.g. 40-O-substituted rapamycin derivatives as described in U.S. Patent No., 5,258,389 and WO 94/09010, especially 40-O-alkylated rapamycin derivatives, e.g. wherein the 40-O-

substituent is hydroxyalkylated, e.g. 40-O-(2-hydroxyethyl) rapamycin, i.e. everolimus, or derivatives substituted in position 40 and/or in other positions of the molecule, e.g. in position 28 and/or 16, including epimers thereof, and optionally further hydrogenated, e.g. as disclosed in WO 95/14023 and 99/15530, e.g. ABT578, or rapalogs as disclosed e.g. in WO 98/02441 and WO01/14387, e.g. AP23573. 40-O-(2-hydroxyethyl) rapamycin is particularly preferred.

Suitable soluble complement inhibitor includes e.g. a C3/C5 inhibitor, e.g. a soluble complement receptor type I (CR1), TP-10, which is a recombinant protein that is a potent systemic inhibitor of the complement system, since it blocks both C3 and C5 activation by all three activation pathways (classical, alternative, and lectin); and it is subsequent to C3 activation that the majority of complement-dependent effector mechanisms are recruited. Specifically, TP-10 binds C3b and C4b, activation fragments of the complement system, blocking their interaction with other proteins in the complement cascade and subsequently the formation of multi-molecular enzyme complexes which generate the biologically active protein fragments of complement. TP-10 also acts as a co-factor in the enzymatic degradation of C3b and C4b to their inactive forms.

TP-10 is a modified CR1 molecule lacking the transmembrane and cytoplasmic domains, e.g. as disclosed in WO 89/09220, incorporated herein by reference. TP-10 is expressed by Chinese hamster ovary (CHO) cells in serum-free media and purified on anti-CR1 affinity columns and by HPLC. Administration of TP10 to islet transplant recipients was reported by Bennett, et. al., Diabetes 2000.

Other embodiments of a soluble complement receptor inhibitor suitable for use in the invention comprise TP-20, a combined complement and selectin inhibitor that integrates sCR1 (soluble complement receptor-1) with the sLex (sialyl Lewis x) carbohydrate in a single molecule; and TP-18, an sCR1 derivative inserted into a selectin-(receptor)-blocking carbohydrate.

Daily dosages of the therapeutic agents required in practicing the method of the present invention will vary, depending upon for example the ALH agent employed, the host, the mode of administration, the severity of the condition to be treated, and the further selected therapeutic agents used in combined administration.

The terms "co-administration" or "combined administration" or the like as utilized herein are meant to encompass administration of the selected therapeutic agents to a single transplant

recipient, and are intended to include treatment regimens in which the agents are not necessarily administered by the same route of administration or at the same time.

It is preferred that administration of the ALH agent, e.g., FTY720, be commenced preoperatively. In general, the compound may be administered starting from just prior to the day the transplant operation is carried out (i.e. "Day 0"), for example starting on Day –1, and continuing indefinitely thereafter. The compound may be administered e.g. orally or by injection.

A preferred daily dosage range for the ALH agent, e.g. a compound of formula I (e.g, FTY720) is about from 0.03 to 2.5 mg/kg per day, particularly 0.1 to 2.5 mg/kg per day, e.g. 0.5 to 2.5 mg/kg per day as a single dose or in divided doses. Suitable daily dosages for patients are in the order of from e.g. 0.25 to 100 mg p.o. Suitable unit dosage forms for oral administration of a compound of formula I comprise from ca. 0.125 to 10 mg together with one or more pharmaceutically acceptable diluents or carriers therefor. As an alternative, the compound of formula I in free form or in pharmaceutically acceptable salt form may also be administered twice or three times a week, e.g. at a dosage as indicated above. The ALH agent, e.g. the compounds of formula I, may be administered by any conventional route, in particular enterally, e.g. orally, for example in the form of solutions for drinking, tablets or capsules or parenterally, for example in the form of injectable solutions or suspensions. Pharmaceutical compositions comprising the compounds of formula I may be manufactured in conventional manner, e.g. as described in U.S. Patent No. 5,604,229.

The anti-IL2 receptor antibody, e.g., basiliximab, is preferably administered in a two-dose regimen, the first dose being administered on Day 0 (i.e. day of transplant) and a second on about Day 4. Additionally doses following about Day 4 may optionally be administered, e.g. once weekly for 2 to 4 weeks. For primates, including humans, each dose is generally about 1 to 50 mg, and preferably about 5 to 20 mg.

The immunosuppressive macrocyclic lactone, e.g., 40-O-2-(hydroxyethyl)-rapamycin, is preferably administered on a daily basis, commencing on or just prior to the day of transplant (e.g., Day –1) and continuing on an indefinite basis following the transplant. For primates, including humans and non-human primates, suitable doses are in the range of 0.25 - 7 mg /day, and more particularly 0.5 - 5 mg /day. The compound may be administered orally or alternatively by subcutaneous injection.

The soluble complement receptor, e.g., TP-10, can be administered in single dosages of about 5 to 15 mg/kg, preferably about 10 mg/kg, as an intravenous infusion over about 30 minutes.

Most preferably, the invention is directed to a glucocorticoid-free combination therapy for use in connection with insulin-producing cell transplantation, e.g. pancreatic islet cell transplantation, comprising co-administration of an ALH agent, such as in particular a compound of formula I, e.g. 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol in free form or in a pharmaceutically acceptable salt form, preferably the hydrochloride salt thereof; in combination with one or more of basiliximab, 40-O-(2-hydroxyethyl)-rapamycin and the soluble recombinant human complement inhibitor, sCR1 ("TP10").

The therapeutic methods of the invention may optionally include co-administration of still other immunomodulating drugs or anti-inflammatory agents, examples of which may comprise a calcineurin inhibitor, e.g. cyclosporins or ascomycins, and their immunosuppressive analogs, e.g. cyclosporin A, FK-506; cyclophosphamide; azathioprene; methotrexate; brequinar; leflunomide; mizoribine; mycophenolic acid; mycophenolate mofetil; 15-deoxyspergualine or analogues; immunosuppressive monoclonal antibodies, e.g., monoclonal antibodies to leukocyte receptors, e.g., to MHC, CD2, CD3, CD4, CD7, CD25, CD28, B7, CD40, CD45, or CD58 or to their ligands; or other immunomodulatory compounds, e.g. CTLA4-Ig or a homolog or mutant thereof, e.g. LEA29Y, or a LFA-1 inhibitor.

The methods of the invention may be employed as a prophylaxis or treatment of insulin-producing cell allograft or xenograft rejection.

Example: Transplantation of allogeneic islets into cynomolgus monkeys suppressed with FTY 720, Everolimus, Basiliximab and TP10.

Therapeutic agents:

FTY720: The compound is prepared for administration by emptying the contents of a capsule (1 mg/capsule) in a 60 mL clear glass mortar. 30 mL of sterile water are added and mixed with the capsule content until the powder is in a uniform suspension. The FTY720 is administered orally using a syringe and a nasogastric tube.

Basiliximab: The material is obtained as a package containing 20 mg of powder in a vial and a second vial containing 5 mL of diluent. Each vial is formulated according to the manufacturer's instructions and administered i.v. accordingly.

Everolimus: The compound is obtained as a concentrate of 20 mg/ml in a sealed ampoule. 1 ml of the concentrate is mixed with 8.5 ml vehicle (50% Cremophor and 50% ethanol) to give a final concentration of 2.1 mg/ml (pH 6.0) and the mixture is used within 2 hours.

TP10: the material is obtained as 50 mg multi-dose vials (no formulation required).

(a) Pancreatectomy of donor animals Donor animals are adult cynomolgus monkeys over 4 kg, of either sex. Prior to pancreatectomy, fasting serum glucose analysis and aginine stimulation are performed to assure normal endocrine pancreatic function. For arginine stimulation, 0.07 mg/kg arginine are injected intravenously, and blood collected at -5, -1, 2, 3, 4, and 5 minutes after arginine injection. Plasma is collected and stored frozen at -80°C. Plasma insulin and C-peptide levels are confirmed to be within normal range.

Pancreatectomy is performed under general anaesthesia with 0.5 to 2% isofluorane, and the pancreas is harvested. Lymph nodes and spleen are also harvested for donor lymphocyte isolation and cryopreservation. Following organ and tissue harvest the donor is euthanized with 150 mg/Kg of Na pentobarbital i.v., and cardiac arrest confirmed by visual inspection.

(b) Islet isolation Islet isolation is performed using modifications of the automated method for human islet isolation, as described by Ricordi et al., Diabetes, 38, (Suppl.1): 140-142, 1989; Kenyon et al., Diabetes, 48, pp. 8132-8137, 1999; and Ranuncoli et al., Cell Transplantation 2000.

Islet quality assessment is performed according to international standards {Ricordi, Gray, et al. 1990 13 /id}, including determination of islet yield, purity, and viability. The number of islets obtained is reported as islet equivalents (IEQ), which is the number of islets that would be present if the particles were all 150 µm in diameter. For this purpose, the number of dithizone (DTZ) positive islets in different size categories (50-100 µm, 100-150 µm, 150-200 µm, etc.) is counted and the data will be entered into a computer program that translates the information into IEQ. Purity is estimated based on the percentage of DTZ positive particles present in the preparation, and viability is estimated based on FDA/PI staining. In vitro functional capacity is determined via assessment of glucose stimulated insulin release in static cultures (see Ranuncoli et. al., Cell Transplantation, 2000).

(b) Transplant of islet allografts into recipient animals Recipient animals are juvenile cynomolgus monkeys of > 1.5 kg, of either sex. Recipient animals are rendered diabetic by infusion of streptozotocin (STZ), 150 mg/kg i.v., followed by intravenous hydration (20 ml/kg of 0.9% NaCl over 30 minutes) to prevent nephrotoxic side effects, as described by Theriault

Thistlethwaite et al., 1999, 16 /id. Blood glucose level is monitored frequently during the first 48 hours after streptozotocin application to avoid severe hypoglycemia or hyperglycemia with eventual ketoacidosis. Thereafter, blood sugar levels are monitored 2-3 times daily and corrected with Regular, NPH, Lente, Ultralente, or Humalog insulin via subcutaneous injection or intravenous insulin-drip, as needed. Induction of diabetes is confirmed by daily blood glucose measurements, assessment of insulin requirements and by a negative C-peptide value subsequent to arginine stimulation. To confirm that diabetes has been induced, an arginine stimulation test is performed prior to initiation of immunosuppression. For arginine stimulation, 0.07 mg/kg arginine is injected intravenously, and blood collected – 5, -1, 2, 3, 4, 5 min. after arginine injection. Plasma is collected and stored frozen at -80°C. Plasma glucose is measured using a Cobas Mira glucose analyzer (Roche Diagnostic Systems, Montclair, NJ). A double antibody method (Diagnostic Products, Corp., Los Angeles, CA) is utilized to assess plasma insulin and C-peptide levels. The lower limit of detection for C-peptide is 0.20 ng/ml and for insulin is 5 uU/ml. Standard curves, as well as positive and negative control samples are incorporated into the assays.

Sedated and anaesthetized recipient animals are placed supine on the operating table and the abdomen is prepped and draped. Special attention is paid to avoid hypothermia and a heat lamp and heating pads are used. A small central midline incision is made and a minimum of 10,000 freshly isolated islet equivalents/kg body weight are resuspended in 20 ml of transplant media and infused into a mesenteric tributary of the portal vein through a 24-gauge intravenous catheter. To provide hemostasis, the vessel is either ligated or digital pressure is applied. The abdominal wall is closed in a routine fashion. Blood glucose is monitored twice each day and arginine stimulation tests are performed to document reversal of the diabetic state.

Three groups of 4 recipients each are administered different immunosuppressive regimens and islet doses, as follows:

Group 1: FTY720 + everolimus + basiliximab, 10,000 IEQ/kg body weight.

Group 2: FTY720 + everolimus + basiliximab, 5,000 IEQ/kg body weight.

Group 3: FTY720 + everolimus + basiliximab + TP10, 5,000 IEQ/kg body weight.

Recipient animals in the indicated groups receive the following treatments prior to and following the day of transplant (Day "0") as detailed below:

FTY720 is administered p.o at 0.3 mg/kg, day –1 through day +30.
Basiliximab is administered by intravenous injection at 10 mg on day 0 and day 4.
Everolimus administered by subcutaneous injection once daily from day –1 through day +30, targeting trough levels of 15-30 ng/ml. The recommended dose is in the range of 0.075 mg/kg/day.
TP10 is administered by intravenous injection at a dosage level of 40 mg/kg on day –1, 20 mg/kg on days 0 and 1, and 17 mg/kg from days 2 to 7.
Drug monitoring is as follows:
FTY720 - weekly. Everolimus - twice weekly. SC5b-9 is monitored for proof of TP10 efficacy.
The recipient animals are dosed at approximately the same time each morning and in the afternoon when applicable. Blood glucose levels are determined frequently over the first 4-5 hours post-transplant to prevent hypoglycemic episodes. Such episodes are treated with dextrose 5-10% intravenously as needed. The presence of rejection is suspected if three consecutive fasting blood glucose levels rise above 150 mg/dl or three post-prandial blood glucose levels of more than 200 mg/dl are recorded. Rejection is assumed if these levels are present 3 days in a row. Thereafter, fasting and post-prandial blood glucose (fasting blood glucose, post-prandial glucose) levels are monitored 2-3 times a day via heel stick. Daily blood glucose measurements plus periodic arginine stimulation tests (human insulin and C-peptide) at 14 and 30 days posttransplant are used to document glucose control. Exogenous insulin requirement after transplantation is also monitored. For the first 14 days after transplantation, blood glucose levels are corrected with Regular, NPH, Lente, or Ultralente Humalog insulin via subcutaneous injection according to an individualized sliding scheme. An arginine stimulation test is performed at 14 days and 1 month posttransplant and at additional time points thereafter.

(c) Pre-terminal blood and tissue sampling The transplant recipients are sedated by ketamine (5-10 mg/kg), intubated and pre-terminal blood sampling is performed under general anaesthesia with 0.5 to 2% Isofluorane. The monkey is put in a supine position and the groin and abdomen are prepped and draped in a sterile fashion. The femoral vein, superior vena cava, or aorta is isolated, a catheter is placed, and 80-160 ml of blood are drawn. Samples of liver and spleen are harvested and frozen in liquid Nitrogen for RNA analysis. After completion of sterile sampling, the animal is euthanized by i.v. injection of sodium pentobarbital at a dose of 150 mg/Kg. Necropsy samples are taken and fixed

according to known procedures. Besides graft and organ samples, a sample of the pancreas is snap-frozen for insulin extraction.

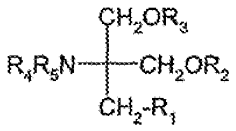
The pathology of the graft organ is evaluated. Routine H&E stained sections are evaluated histologically. In this model, the combined treatment with FTY720, everolimus and basiliximab prevents islet allograft rejection.

CLAIMS

1. A pharmaceutical combination comprising a) an accelerated lymphocyte homing (ALH) agent in free form or in pharmaceutically acceptable salt form, and b) one or more compounds selected from the group consisting of an antibody to the IL-2 receptor, an immunosuppressive macrocyclic lactone and a soluble human complement inhibitor.

2. A pharmaceutical combination according to claim 1 comprising a) an ALH agent in free form or in pharmaceutically acceptable salt form, and b) an antibody to the IL-2 receptor and an immunosuppressive macrocyclic lactone, and optionally a soluble human complement inhibitor.

3. A pharmaceutical combination according to claim 1 or 2 wherein the ALH agent is a compound of formula I

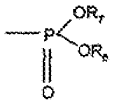


I

wherein

R_1 is an optionally substituted straight- or branched carbon chain having 12 to 22 carbon atoms which may be optionally interrupted by an optionally substituted phenylene,

R_2 is H or a residue of formula



wherein R_6 is H or C_{1-4}alkyl optionally substituted by 1, 2 or 3 halogen atoms, and R_7 is H or C_{1-4}alkyl optionally substituted by halogen,

R_3 is H or C_{1-4}alkyl, and

each of R_4 and R_5, independently, is H; C_{1-4}alkyl optionally substituted by halogen; or acyl,

in free form or in pharmaceutically acceptable salt form.

4. A combination according to claim 1 or 2 wherein the ALH agent is 2-amino-2-[2-(4-octylphenyl) ethyl]propane-1,3-diol in free form or in a pharmaceutically salt form.

5. A combination according to claim 1 or 2 wherein the antibody to the IL-2 receptor is a recombinant chimeric or humanized antibody.

6. A combination according to claim 1 or 2 wherein the immunosuppressive macrocyclic lactone is rapamycin or a rapamycin derivative substituted in position 40 and/or 28 and/or 16, including epimers thereof., and optionally hydrogenated.

7. A combination according to claim 1 or 2 wherein the immunosuppressive macrocyclic lactone is 40-O-(2-hydroxyethyl)-rapamycin.

8. A combination according to claim 1 or 2 wherein the soluble human complement inhibitor is a C3/C5 inhibitor.

9. A combination according to claim 1 or 2 for use in the treatment or prophylaxis of insulin-producing cell graft rejection.

10. Use of an ALH agent in free form or in pharmaceutically acceptable salt form in combination with one or more compounds selected from the group consisting of an antibody to the IL-2 receptor, an immunosuppressive macrocyclic lactone and a soluble human complement inhibitor, to treat or prevent insulin-producing cell graft rejection.

11. A method for the treatment or prophylaxis of insulin-producing cell graft rejection in an insulin-producing cell graft recipient comprising co-administering to the recipient an effective amount of an ALH agent and one or more compounds selected from the group consisting of an antibody to the IL-2 receptor, an immunosuppressive macrocyclic lactone, and a soluble human complement inhibitor.

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
11/720,205	05/25/2007	

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☐		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	03/15/2011	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 16	Minus	** 20	= 0	X $ =		OR	X $52=	0
	Independent (37 CFR 1.16(h))	* 6	Minus	***8	= 0	X $ =		OR	X $220=	0
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)	OR	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/KIMBERLY PANNELL/

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/720,205	05/25/2007	John M. Kovarik	34053-US-PCT	5868

1095 7590 09/15/2010

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EXAMINER	
BLAKELY III, NELSON CLARENCE	
ART UNIT	**PAPER NUMBER**
1614	

MAIL DATE	DELIVERY MODE
09/15/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	11/720,205	KOVARIK ET AL.	
	Examiner	Art Unit	
	NELSON C. BLAKELY III	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 July 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5 and 7-16* is/are pending in the application.

4a) Of the above claim(s) *9-11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7,8 and 12-16* is/are rejected.

7)☒ Claim(s) *2,3,7,13 and 15* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *05/25/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application Status

Claims 1-5 and 7-16 of the instant application are pending. Claims 9-11 are withdrawn pursuant to Applicant's Response, filed 07/30/2010. Accordingly, instant claims 1-5, 7, 8 and 12-16 are presented for examination on their merits.

Election/Restrictions

Applicant's election of Group II, claims 1-5, 7, 8 and 11-16, drawn to a method for inhibiting graft rejection or treating an inflammatory or autoimmune disease or disorder in a subject in need thereof, comprising administering to the subject a S1P receptor modulator or agonist in a pharmaceutically effective amount, in the reply filed on 07/30/2010, is acknowledged. Because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election ***without*** ***traverse*** (MPEP § 818.03(a)).

Applicant's election ***with*** ***traverse*** of an inflammatory or autoimmune disease or disorder, in the reply filed on 07/30/2010, is acknowledged. The traversal is on the ground(s) that all the diseases and disorders embraced with in the genus of "inflammatory or autoimmune diseases or disorders" share a technical feature that defines a contribution that each of the claimed inventions of the Group II claims makes over the prior art.

This is not found persuasive. The search for each of the broadly claimed inflammatory or autoimmune disease or disorder of, at least, claim 1 is not co-extensive

particularly with regard to the literature search. Burden consists not only of specific searching of classes and subclasses, but also of searching multiple databases for foreign references and literature searches. Burden also resides in the examination of independent claim set for clarity, enablement and double patenting issues. Further, a reference that would anticipate the invention of one group would not necessarily anticipate, or even make obvious, another group. Finally, the consideration for patentability is different in each case.

Thus, it would be an undue burden to examine all of the above inventions in one application and the restriction for examination purposes, as indicated above, is still deemed proper, and is therefore made **FINAL**.

It is acknowledged that Applicant elected wherein: a) the disclosed S1P receptor modulator or agonist is 2-amino-2-[2-(4-octylphenyl)ethyl]propaine-1,3-diol (or FTY720), and b) the single disclosed inflammatory or autoimmune disease or disorder is multiple sclerosis.

Claims 9-11 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected subject matter, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 07/30/2010.

Priority

Receipt is acknowledged of the certified copy of US 60/631,483, filed 11/29/2004, submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Information Disclosure Statement

The Information Disclosure Statement, filed 05/25/2007, is acknowledged and considered.

The Information Disclosure Statement, filed 05/25/2007, fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609. Foreign patent documents WO 03/061567, WO 03/062252 and WO 02/100148, wherein at least the Abstract is in English, have not been received. The Skerjanec *et al*. reference (NPL document) has not been received. However, the Examiner has supplied the aforementioned reference. The IDS has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this Information Disclosure Statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

Applicant's Amendment

Applicant's Preliminary Amendment, filed 05/25/2007, wherein the specification and claims 3, 4 and 11 are amended, is acknowledged. Applicant's Preliminary Amendment, filed 10/08/2007, wherein claims 1-5 and 7-12 are amended, claim 6 is canceled, and claims 13-16 are added, is acknowledged. Applicant's Amendment, filed 07/29/2010, wherein claims 3-5 and 7 are amended, and claim 6 is canceled, is acknowledged.

Specification

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and ***generally limited to a single paragraph on a separate sheet*** within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

It is noted that in the Preliminary Amendment, filed 05/25/2007, Applicant supplied an Abstract that was limited to a single paragraph on a separate sheet. However, confusingly, on 07/20/2009, Applicant filed an Abstract that did not meet this requirement. Appropriate correction is required.

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Objections

Claims 2, 3, 7, 13 and 15 are objected to for the following informalities:

With regard to instant claims 2 and 15, Applicant is required to insert a ". (period)" at the end of the claims.

With regard to instant claim 3, Applicant is required to remove the space between the terms "S1" and "P", in line 4.

It is noted that claim 7 is amended to inset the term "such" in line 4. Therefore, the instant claim should have the status identifier "(Currently Amended)" instead of "(Previously Amended)".

With regard to instant claim 13, Applicant is encouraged to insert a ", (comma)" and space after the recitation "2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol", in lines 2 and 3.

With regard to instant claim 15, Applicant is encouraged to insert a space between the term "0.5" and the term "mg" in line 2.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Instant claims 12 and 13 recite the term "prodrugs," which are commonly known in the art as drugs which are administered in an inactive (or less active) form, and then metabolized *in vivo* into an active metabolite. As disclosed in Stella (Expert Opinion on Therapeutic Patents, *Prodrugs as therapeutics*, Vol. 14, No. 3, pages 277-280; 2004), "'prodrugs' are bioreversible derivatives of drug molecules used to overcome some barriers to the utility of the parent drug molecule. These barriers include, but are not limited to, solubility, permeability, stability, presystemic metabolism, and targeting limitations". Wolff (Burger's Medicinal Chemistry, 5th Ed., Vol. 1, pages 975-977; 1994) summarizes the state of the "prodrug" art, the lengthy research involved in successfully identifying a "prodrug," and difficulties extrapolating between species. With the limited direction and exemplification the specification offers, it is highly unpredictable that effective prodrugs will formed. Testa (Biochemical Pharmacology, *Prodrug Research: futile or fertile?*, Vol. 68, pages 2097-2106; 2004), discloses, on page 2098, the various challenges in "prodrug" research, concluding that all of these challenges may render "prodrug" optimization difficult to predict and achieve. Finally, Ettmayer *et al*. (Medicinal

Chemistry, *Lessons Learned from Marketed and Investigational Prodrugs*, Vol. 47, No. 10, pages 2394-2404; 2004), discloses, on page 2401, that "the 'prodrug' strategy should only be considered as a last resort to improve the oral bioavailability of important therapeutic agents" and "At the beginning of each 'prodrug' program, there should be a clear definition of the problem to solve and defect to improve. The 'prodrug' approach should not be misunderstood as a universal solution to all barriers to a drug's usefulness," and on page 2402, "The majority of all 'prodrug' approaches face the challenge of identifying the optimal 'prodrug' plus its activation system to enhance or prolong the concentration of the active principle at the site of action. Because of the complex situation of 'prodrug' transport and processing, we recommend, especially for novel 'prodrug' principles, that the first step should be to design and investigate different 'prodrug' prototypes of high diversity (different attachment sites, linkers, promoieties, hydrolytic, oxidative, reductive activation, chemical vs. enzymatic activation)." Ettmayer *et al*. conclude that "the focus on victorious 'prodrugs' should not be misunderstood as neglecting the inherent difficulties and additional layers of complexity a drug strategy might face." The evidence supports the conclusion that the method of making claimed "prodrugs" is a subject for further study and experimentation.

Regarding the requirement for adequate written description of chemical entities, Applicant's attention is directed to the MPEP § 2163. In particular, *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997), cert. denied, 523 U.S. 1089, 118 S. Ct. 1548 (1998), holds that an adequate written description requires a precise definition, such as by structure, formula, chemical name,

or physical properties, "not a mere wish or plan for obtaining the claimed chemical invention." *Eli Lilly*, 119 F.3d at 1566. The Federal Circuit has adopted the standard set forth in the Patent and Trademark Office ("PTO") Guidelines for Examination of Patent Applications under the 35 U.S.C. 112.1 "Written Description" Requirement ("Guidelines"), 66 Fed. Reg. 1099 (Jan. 5, 2001), which state that the written description requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics, "including, *inter alia*, "functional characteristics when coupled with a known or disclosed correlation between function and structure…" *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 316, 1324-25 (Fed. Cir. 2002) (quoting Guidelines, 66 Fed. Reg. at 1106 (emphasis added)). Moreover, although Eli Lily and Enzo were decided within the factual context of DNA sequences, this does not preclude extending the reasoning of those cases to chemical structures in general. *Univ. of Rochester v. G.D. Searle & Co.*, 249 Supp. 2d 216, 225 (W.D.N.Y. 2003).

In the instant case, Applicants have not described the genus of "prodrugs" in a manner that would allow one skilled in the art to immediately envisage the compounds contemplated for use. As such, the claims lack adequate written description for the claimed "prodrugs."

With regard to instant claim 14, a review of the specification fails to disclose the recitation "0.1-20 mg." See *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981) and MPEP §2163.06. It is acknowledged that Applicant recites, on page 15, lines 1-5 of the specification, wherein FTY720 may be administered, for example, in ranges

from 2-5, 5-10, 10-15 and 15-20 mg, and further, 0.1-0.5 mg. It is also acknowledged that Applicant recites on page 19, on Days 1 and 2-4, of Treatment 2, wherein 1.25 mg of FTY720 was administered. However, a recitation disclosing the range of 0.1-20 mg is not seen in the instant disclosure. As such, the claims lack adequate written description for the aforementioned claimed limitations.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 4, 8 and 12-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lake *et al*. (U.S. Patent Application Publication No. 2003/0003099A1; cited by Applicant), in view of Skerjanec *et al*. (Am J Transplant, Vol. 2, Suppl. 3, Abstract 964; 2002; cited by Applicant; provided by the Examiner).

With regard to instant claims 1, 2, 4, 8 and 12-15, Lake *et al*. disclose, in reference claims 15 and 17, a method for the treatment or prophylaxis of insulin-producing cell graft rejection in an insulin-producing cell graft recipient comprising co-administering to the recipient an effective amount of an ALH (accelerated lymphocyte homing) agent and one or more compounds of reference claim 15, wherein the ALH agent is 2-amino-2-[2-(4-octylphenyl)ethyl]propaine-1,3-diol (or FTY720) in free form, or in a pharmaceutically acceptable salt form. Lake *et al*. disclose, in paragraph **[0052]**, page 4, wherein a preferred daily dosage range for the ALH agent is about from 0.03-2.5 mg/kg/day, as a single dose or in divided doses. See instant claims 14 and 15.

Lake *et al*. fail to disclose specifically wherein an effective amount of the S1P receptor modulator or agonist is administered such that a steady-state of the aforementioned modulator or agonist blood levels is attained in less than a week, and thereafter the treatment is continued at a dosage lower than the standard daily dosage (instant claim 2). However, Lake *et al*. disclose, in paragraph **[0049]**, page 3, wherein daily dosages of the therapeutic agents required in practicing the method of the

reference invention will vary depending upon, for example, the ALH agent employed, the host, the mode of administration, the severity of the condition to be treated. Further, Skerjanec *et al*. disclose, in the Abstract, FTY720 as an EDG receptor agonist with the potential to protect organ grafts without inducing general immunosuppression. In the instant excerpt, Skerjanec *et al*. further disclose wherein adult *de novo* renal transplant patients were randomized within 24 hours of transplantation to FTY720 with a loading dose of 1, 2 or 4 mg followed by a once daily maintenance dose of 0.25, 0.5, 1 or 2.5 mg. See also the referenced Table.

Therefore, a skilled artisan would have envisaged the instantly claimed method for inhibiting graft rejection in a subject comprising administering to the subject a S1P receptor modulator or agonist, e.g., FTY720, as disclosed by Lake *et al*., modified to include a loading dose and a maintenance dose, as disclosed by Skerjanec *et al*. One of ordinary skill in the art would have been motivated to combine the teachings of the aforementioned references when seeking a method of inhibiting graft rejection in a dose-dependent manner, which provides for sustained treatment, as well as decreased instances of graft rejection. It would have been obvious to one of ordinary skill in the art, at the time of the invention, because the combined teachings of the prior art are suggestive of the claimed invention.

Accordingly, the instant invention, as claimed in claims 1, 2, 4, 8 and 12-15, is *prima facie* obvious over the combination of the aforementioned teachings.

Claims 3, 5 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lake *et al*. (U.S. Patent Application Publication No. 2003/0003099A1; cited by Applicant), in view of Skerjanec *et al*. (Am. J. Transplant., Vol. 2, Suppl. 3, Abstract 964; 2002; cited by Applicant; provided by the Examiner), as applied to claims 1, 2, 4, 8 and 12-15 above, and further in view of Galinsky *et al*. ["Basic Pharmacokinetics and Pharmacodynamics." in: *Remington: The Science and Practice of Pharmacy* (Baltimore, Lippincott Williams & Wilkins, 2006), p. 1171].

With regard to instant claims 3, 5 and 7, the teachings of Lake *et al*. and Skerjanec *et al*. are set forth *supra*.

Lake *et al*. fail to disclose specifically wherein a steady-state of the S1P receptor modulator or agonist blood levels is attained in the subject in a period of from 3 to 6 days, and wherein the dosage of said S1P receptor or agonist during the initial 3 to 6 days of treatment is increased stepwise up to the 3- to 21-fold standard daily dosage of said S1P receptor agonist (instant claim 3), wherein during the initial 3 to 6 days of treatment the dosage is raised so that in total the R-fold standard dosage is administered, and thereafter the treatment is continued with the standard daily dosage or with a daily dosage lower than the standard daily dosage (instant claim 5), or wherein during the initial 3 to 6 days of treatment the dosage is raised so that in total the R-fold standard dosage is administered (instant claim 7). However, it is not inventive to discover the optimum ranges or regimens by routine experimentation when general conditions of a claim are disclosed in the prior art. See *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) and MPEP §2144.05(II). In addition, Galinsky *et al*.

recite in the left column of page 1171, lines 12-27 of text, that it is recognized that drug therapy may be optimized by designing regimens that account for the concentration of a drug, for example, to achieve a desired pharmacological response. Therefore, the determination of the optimum characterization of the composition and dosage amounts would have been a matter well within the purview of one of ordinary skill in the art, at the time of the invention, through no more than routine experimentation.

Therefore, a skilled artisan would have envisaged the instantly claimed method for inhibiting graft rejection in a subject comprising administering to the subject a S1P receptor modulator or agonist, e.g., FTY720, as disclosed by Lake *et al.*, wherein the dosage amounts and regimen are modified to achieve a desired pharmacological response, as disclosed by Skerjanec *et al*. and Galinsky *et al*. One of ordinary skill in the art would have been motivated to combine the teachings of the aforementioned references when seeking a method of inhibiting graft rejection in a dose-dependent manner, which provides for sustained treatment, as well as decreased instances of graft rejection. It would have been obvious to one of ordinary skill in the art, at the time of the invention, because the combined teachings of the prior art are suggestive of the claimed invention.

Accordingly, the instant invention, as claimed in claims 3, 5 and 7, is *prima facie* obvious over the combination of the aforementioned teachings.

Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lake *et al*. (U.S. Patent Application Publication No. 2003/0003099A1; cited by Applicant), in

view of Skerjanec *et al*. (Am J Transplant, Vol. 2, Suppl. 3, Abstract 964; 2002; cited by Applicant; provided by the Examiner), as applied to claims 1, 2, 4, 8 and 12-15 above, and further in view of Chiba *et al*. (U.S. Patent Application Publication No. 2002/0102279A1).

With regard to instant claim 16, the teachings of Lake *et al*. and Skerjanec *et al*. are set forth *supra*.

Lake *et al*. fail to disclose specifically wherein the autoimmune disease is multiple sclerosis (instant claim 16). However, Chiba *et al*. disclose, in reference claims 1-6, 8 and 9, page 14, a method of suppressing the immune response in a mammal comprising accelerating lymphocyte homing (ALH) to any of the mesenteric or peripheral lymph tissues, for example, by administering an ALH-immunosuppressive compound or composition, wherein the compound or composition comprises 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol hydrochloride (FTY720). In the instant excerpt, Chiba *et al*. disclose wherein the therapeutic treatment comprising suppressing the rejection of an organ, cell or bone marrow transplantation, or wherein the treatment comprises the treatment of an autoimmune disease, e.g., multiple sclerosis.

Therefore, a skilled artisan would have envisaged the instantly claimed method for inhibiting graft rejection or treating an inflammatory or autoimmune disease or disorder in a subject comprising administering to the subject a S1P receptor modulator or agonist, e.g., FTY720, as disclosed by Lake *et al*. and Chiba *et al*., modified to include a loading dose and a maintenance dose, as disclosed by Skerjanec *et al*. One of ordinary skill in the art would have been motivated to combine the teachings of the

aforementioned references when seeking a method of inhibiting graft rejection or treating an inflammatory or autoimmune disease or disorder, such as multiple sclerosis, in a dose-dependent manner, which provides for sustained treatment, as well as decreased instances of graft rejection and therapeutic treatment of the inflammatory or autoimmune disease or disorder. It would have been obvious to one of ordinary skill in the art, at the time of the invention, because the combined teachings of the prior art are suggestive of the claimed invention.

Accordingly, the instant invention, as claimed in claim 16, is *prima facie* obvious over the combination of the aforementioned teachings.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to NELSON C. BLAKELY III whose telephone number is (571) 270-3290. The Examiner can normally be reached on Mon - Thurs, 7:00 am - 5:30 pm (EST).

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ardin H. Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Phyllis G. Spivack/
Primary Examiner, Art Unit 1614
September 12, 2010

/N. C. B. III/

Examiner, Art Unit 1614

Notice of References Cited	Application/Control No. 11/720,205	Applicant(s)/Patent Under Reexamination KOVARIK ET AL.	
	Examiner NELSON C. BLAKELY III	Art Unit 1614	Page 1 of 2

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-2002/0102279 A1	08-2002	CHIBA et al.	424/278.1
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Skerjanec et al. (Am J Transplant, Vol. 2, Suppl. 3, Abstract 964; 2002).
	V	Galinsky et al. ["Basic Pharmacokinetics and Pharmacodynamics." in: Remington: The Science and Practice of Pharmacy (Baltimore, Lippincott Williams & Wilkins, 2006), p. 1171].
	W	Stella (Expert Opinion on Therapeutic Patents, Prodrugs as therapeutics, Vol. 14, No. 3, pages 277-280; 2004).
	X	Wolff (Burger's Medicinal Chemistry, 5th Ed., Vol. 1, pages 975-977; 1994).

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Notice of References Cited	Application/Control No. 11/720,205	Applicant(s)/Patent Under Reexamination KOVARIK ET AL.	
	Examiner NELSON C. BLAKELY III	Art Unit 1614	Page 2 of 2

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
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	K	US-			
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*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Testa (Biochemical Pharmacology, Prodrug Research: futile or fertile?, Vol. 68, pages 2097-2106; 2004).
	V	Ettmayer et al. (Medicinal Chemistry, Lessons Learned from Marketed and Investigational Prodrugs, Vol. 47, No. 10, pages 2394-2404; 2004).
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11720205	KOVARIK ET AL.
	Examiner	Art Unit
	NELSON C BLAKELY III	1614

SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
EAST Database Search	09/10/2010	NCB III
NPL	09/10/2010	NCB III
PALM Inventor Search	09/10/2010	NCB III
STN Database Search	09/10/2010	NCB III

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

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CONFIRMATION NO. 5868

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
11/720,205	05/25/2007 RULE	514	1614	34053-US-PCT

APPLICANTS

John M. Kovarik, Basel, SWITZERLAND;
Silke Appel-Dingemanse, Allschwil, SWITZERLAND;

**** CONTINUING DATA ***************************

This application is a 371 of PCT/US05/43044 11/28/2005
which claims benefit of 60/631,483 11/29/2004

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****

07/24/2009

Foreign Priority claimed	35 USC 119(a-d) conditions met	Verified and Acknowledged	Met after Allowance	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
☐ Yes ☑ No	☐ Yes ☑ No	/NELSON CLARENCE BLAKELY III/ Examiner's Signature	☐ Initials	SWITZERLAND	0	12	8

ADDRESS

NOVARTIS
CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 101/2
EAST HANOVER, NJ 07936-1080
UNITED STATES

TITLE

DOSAGE REGIMEN OF AN S1P RECEPTOR AGONIST

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1900	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S1	0	("2003003099").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2010/01/20 16:07
S2	1	("20030003099").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2010/01/20 16:07
S3	1	("20050070506").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2010/09/10 13:56
S4	702	fty720	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2010/09/10 14:52
S5	437	S4 AND "multiple sclerosis"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2010/09/10 14:52
S6	0	S4 AND "multiple sclerosis"".CLM"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2010/09/10 14:52
S7	120	S4 AND "multiple sclerosis".CLM.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2010/09/10 14:53
S8	23	S7 AND FTY720.CLM.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2010/09/10 14:53
S9	5	((JOHN) NEAR2 (KOVARIK)).INV.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2010/09/10 15:04

S10	3	((SILKE) NEAR2 (APPEL)).INV.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2010/09/10 15:04
S11	3	((SILKE) NEAR2 (DINGEMANSE)).INV.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2010/09/10 15:05
S12	0	S10 NOT S9	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2010/09/10 15:05

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Receipt date: 05/25/2007

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Sheet 1 of 1

FORM PTO-1449 (REV. 7-85) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

INFORMATION DISCLOSURE CITATION

(Use several sheets if necessary)

ATTY. DOCKET NO. 34053-US-PCT

APPLICATION NO.

APPLICANT KOVARIK ET AL.

FILING DATE

Group 1614

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE
	AA	2003/003099	1/2/03	Lake et al.	424	145.1	6/7/02
	AB						
	AC						
	AD						
	AE						
	AF						
	AG						
	AH						
	AI						
	AJ						
	AK						
	AL						

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	OFFICE	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
	~~AM~~	~~03/061567~~	~~7/31/03~~	~~WO~~			☐	☐
	~~AN~~	~~03/062252~~	~~7/31/03~~	~~WO~~			☐	☐
	~~AO~~	~~02/100148~~	~~12/19/02~~	~~WO~~			☐	☐
	AP						☐	☐
	AQ						☐	☐

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent pages, Etc.)

	~~AR~~	~~Skorjanec A, et al., "Systemic exposure and preliminary efficacy of FTY720 in de novo renal transplant recipients", Am J Transplant (Suppl. 3): ABST 364, Vol. 2, (2002).~~
	AS	
	AT	

EXAMINER	/Nelson Blakely III/	DATE CONSIDERED	09/10/2010

*EXAMINER: Initial of reference considered, whether or not citation is in conformance with MPEP 609: Draw a line through citation if not in conformance and not considered. Include a copy of this form with the next communication to applicant.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /N.B./

0829

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE PCT NATIONAL STAGE APPLICATION OF Art Unit: 1614
Kovarik, John M. et al. Examiner: BLAKELY III, NELSON CLARENCE
INTERNATIONAL APPLICATION NO: PCT/US2005/43044
FILED: November 28, 2005
U.S. APPLICATION NO: 11/720205
35 USC §371 DATE: May 25, 2007
FOR: Dosage Regimen of an S1P Receptor Agonist

MS: Amendment
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

SUPPLEMENTAL RESPONSE TO RESTRICTION REQUIREMENT

Sir:

This *Supplemental Response to Restriction Requirement* is being submitted to supplement the *Amendment and Response to Restriction Requirement* that Applicants submitted on July 29, 2010 in response to the Office Action in the above application that was mailed to Applicants' attorney on February 16, 2010.

No amendments are being made to the specification or claims in this paper.

Remarks begin on page 2 of this paper.

Remarks

This *Supplemental Response to Restriction Requirement* is being submitted to supplement the *Amendment and Response to Restriction Requirement* that Applicants submitted on July 29, 2010 in response to the Office Action in the above application that was mailed to Applicants' attorney on February 16, 2010.

In the above mentioned Office Action, the Examiner required that Applicants elect one of two specified groups of inventions, referred to as Group I and Group II, to prosecute in the present application, and further required that, with respect to both Group I and Group II, Applicants make a species election of a single disclosed S1P receptor modulator. The Examiner further required, with respect to the Group II claims, that Applicants elect a species of an inflammatory or autoimmune disease/disorder. In the *Amendment and Response to Restriction Requirement* that Applicants submitted on July 29, 2010, Applicants elected to prosecute the Group II claims in the present application, and, in response to the Examiner's election of species requirement, Applicants elected the S1P receptor agonist 2-amino-2-[2-(4-octylphenyl) ethyl]propane-1,3-diol, in free form or in a pharmaceutically acceptable salt form.

Applicants did not, however, in the *Amendment and Response to Restriction Requirement* submitted on July 29, 2010, elect a single species of inflammatory or autoimmune disease/disorder. Applicants' undersign attorney apologizes for this inadvertent omission on her part and for any resulting inconvenience to the Examiner. In response to the Examiner's requirement of an election of a single species of inflammatory or autoimmune disease/disorder, Applicants elect, with traverse, the species of multiple sclerosis. All of the claims in the elected Group II relate to methods of treating a genus of diseases or disorders that embraces this elected species.

Applicants respectfully traverse the Examiner's restriction and election of species requirement solely with respect to the requirement that Applicants elect a single species of inflammatory or autoimmune disease or disorder. All the diseases and disorders embraced within the genus of "inflammatory or autoimmune diseases or disorders" share a technical feature that defines a contribution that each of the claimed inventions of the Group II claims makes over the prior art. This feature is the attainment, in subjects in need of treatment of any of these diseases or disorders, of a steady-state blood level of an S1P modulator or agonist in less than one week, resulting from the treatment regimens claimed in the Group II claims. The novel and nonobvious treatment regimens of the Group II claims distinguishes these claims over the prior art and is common to all the species embraced within the above genus of disorders and diseases. In view of this, Applicants respectfully request that the Examiner reconsider his

requirement of a species election and limit that requirement to the election of a single S1P receptor modulator or agonist.

Respectfully submitted,

Karen DeBenedictis
Attorney for Applicant
Reg. No. 32,977

Novartis Pharmaceuticals Corporation
One Health Plaza, Bldg. 101
East Hanover, NJ 07936
(862) 778-3785

Date: 7/30/10

Electronic Acknowledgement Receipt

EFS ID:	8125526
Application Number:	11720205
International Application Number:	
Confirmation Number:	5868
Title of Invention:	DOSAGE REGIMEN OF AN S1P RECEPTOR AGONIST
First Named Inventor/Applicant Name:	John M. Kovarik
Customer Number:	01095
Filer:	Karen DeBenedictis/Andrea Jacquin
Filer Authorized By:	Karen DeBenedictis
Attorney Docket Number:	34053-US-PCT
Receipt Date:	30-JUL-2010
Filing Date:	25-MAY-2007
Time Stamp:	14:04:19
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		34053_US_PCT_Supplemental_Resp_to_OA_7_30_10.pdf	414389 d4537e7c446ecfb9459914d54ed38ddbb5961b9f	yes	3

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Supplemental Response or Supplemental Amendment	1	1
	Applicant Arguments/Remarks Made in an Amendment	2	3
Warnings:			
Information:			
	Total Files Size (in bytes):	414389	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE PCT NATIONAL STAGE APPLICATION OF Art Unit: 1614
Kovarik, John M. et al. Examiner: BLAKELY III, NELSON CLARENCE
INTERNATIONAL APPLICATION NO: PCT/US2005/43044
FILED: November 28, 2005
U.S. APPLICATION NO: 11/720205
35 USC §371 DATE: May 25, 2007
FOR: Dosage Regimen of an S1P Receptor Agonist

MS: Amendment
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

AMENDMENT AND RESPONSE TO RESTRICTION REQUIREMENT

Sir:

This *Amendment and Response to Restriction Requirement* is being submitted in response to the Office Action in the above application that was mailed to Applicants' attorney on February 16, 2010. A Petition for Extension of Time, requesting that the allowable period for responding to such Office Action be extended by five months, so that it does not expire until August 16, 2010, is being submitted concurrently with this paper.

Amendments to the Claims are reflected in the listing of the claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 5 of this paper.

Remarks/Arguments

There are 15 claims pending in this application. There are claims 1 – 5 and 7 – 16. By the present Amendment, Applicants have cancelled claims 9 and 10 as relating to nonelected subject matter, and have amended claims 3, 4 and 5 to increase their clarity. Applicants reserve the right to prosecute the subject matter of the cancelled claims 9 and 10 in a divisional application. The above amendments add no new matter to this application. Support for these amendments can be found in the specification on pages 13 and 14 (referring to the published application WO2006/058316).

In the Office Action, the Examiner required that Applicants elect one of two specified groups of inventions, referred to as Group I and Group II, to prosecute in the present application, and further required that Applicants make a species election of a single disclosed S1P receptor modulator.

Applicants elect to prosecute in the present application the subject matter of Group II, which includes claims 1 – 5, 7, 8 and 11 – 16 and relates to a method for inhibiting graft rejection or treating an inflammatory or autoimmune disease in a subject in need thereof comprising administering to the subject a S1P receptor modulator or agonist.

In response to the Examiner's election of species requirement, Applicants elect the compound 2-amino-2-[2-(4-octylphenyl) ethyl]propane-1,3-diol, in free form or in a pharmaceutically acceptable salt form. This compound can be found in paragraph 2 on page 13 of the specification (referring to the published application WO2006/058316), and in claim 12. This compound is a compound of the formula I wherein R_1 is a 4-octylphenylethyl and each of R_2, R_3, R_4 and R_5 is hydrogen. All of the Group II claims, 1 – 5, 7, 8 and 11 – 16, relate to methods comprising the administration of a genus of compounds that embraces the above elected species. Claim 12 relates to a method comprising the administration of a compound selected from a group consisting of four compounds, one of which is the above elected species.

Applicants submit that claims 1 – 5 and 7 – 16, as amended, are patentable and they respectfully request that these claims be allowed to issue.

Respectfully submitted,

Karen DeBenedictis
Attorney for Applicant
Reg. No. 32,977

Novartis Pharmaceuticals Corporation
One Health Plaza, Bldg. 101
East Hanover, NJ 07936
(862) 778-3785

Date: 7/29/10

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE PCT NATIONAL STAGE APPLICATION OF
Kovarik, John M. et al.
INTERNATIONAL APPLICATION NO: PCT/US2005/43044
FILED: November 28, 2005
U.S. APPLICATION NO: 11/720205
35 USC §371 DATE: May 25, 2007
FOR: Dosage Regimen of an S1P Receptor Agonist

Art Unit: 1614
Examiner: BLAKELY III, NELSON CLARENCE

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

PETITION FOR EXTENSION OF TIME

Sir:

The Office Action of February 16, 2010 has a shortened statutory time set to expire on March 16, 2010. A five-month extension is hereby requested pursuant to 37 CFR §1.136(a).

Please charge Deposit Account No. 19-0134 in the name of Novartis in the amount of $2350 for payment of the extension fee. The Commissioner is hereby authorized to charge any additional fees under 37 CFR §1.17 which may be required, or credit any overpayment, to Account No. 19-0134 in the name of Novartis.

Respectfully submitted,

Karen DeBenedictis
Attorney for Applicant
Reg. No. 32,977

Novartis Pharmaceuticals Corporation
One Health Plaza, Bldg. 101
East Hanover, NJ 07936
(862) 778-3785

Date: 7/29/10

Electronic Patent Application Fee Transmittal

Application Number:	11720205
Filing Date:	25-May-2007
Title of Invention:	DOSAGE REGIMEN OF AN S1P RECEPTOR AGONIST
First Named Inventor/Applicant Name:	John M. Kovarik
Filer:	Karen DeBenedictis/Andrea Jacquin
Attorney Docket Number:	34053-US-PCT

Filed as Large Entity

U.S. National Stage under 35 USC 371 Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 5 months with $0 paid	1255	1	2350	2350

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
		Total in USD ($)		**2350**

Electronic Acknowledgement Receipt	
EFS ID:	8119579
Application Number:	11720205
International Application Number:	
Confirmation Number:	5868
Title of Invention:	DOSAGE REGIMEN OF AN S1P RECEPTOR AGONIST
First Named Inventor/Applicant Name:	John M. Kovarik
Customer Number:	01095
Filer:	Karen DeBenedictis/Andrea Jacquin
Filer Authorized By:	Karen DeBenedictis
Attorney Docket Number:	34053-US-PCT
Receipt Date:	29-JUL-2010
Filing Date:	25-MAY-2007
Time Stamp:	17:09:47
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$2350
RAM confirmation Number	3738
Deposit Account	190134
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		34053_US_PCT_Resp_to_OA_7_29_10.pdf	980689 25e2226155fc214b25f4b214dbf043b1780bca86	yes	6

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Response to Election / Restriction Filed	1	1
Claims	2	4
Applicant Arguments/Remarks Made in an Amendment	5	5
Extension of Time	6	6

Warnings:

Information:

2	Fee Worksheet (PTO-875)	fee-info.pdf	30520 75a1f507361cc977ca48c8e120cfe12310695198	no	2

Warnings:

Information:

Total Files Size (in bytes):	1011209

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
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New International Application Filed with the USPTO as a Receiving Office
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Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

Claim 1. (Previously presented) A method for inhibiting graft rejection or treating an inflammatory or autoimmune disease or disorder in a subject in need thereof, comprising administering to the subject a S1P receptor modulator or agonist in such a pharmaceutically effective amount that a steady-state of the S1P receptor modulator or agonist blood levels is attained in the subject in less than a week.

Claim 2. (Previously presented) A method for inhibiting graft rejection or treating an inflammatory or autoimmune disease or disorder in a subject in need thereof, comprising administering to the subject an S1P receptor modulator or agonist in such a pharmaceutically effective amount that a steady-state of the S1P receptor modulator or agonist blood levels is attained in less than a week, and thereafter the treatment is continued at a dosage lower than the standard daily dosage

Claim 3. (Currently amended) The method of claim 1, wherein the S1P receptor modulator or agonist is administered in a pharmaceutically effective amount such that a steady-state of the S1P receptor modulator or agonist blood levels is attained in the subject in a period of from 3 to 6 days, and wherein ~~whereby~~ the dosage of said S1 P receptor modulator or agonist during the initial 3 to 6 days of treatment is increased stepwise up to the 3- to 21-fold standard daily dosage of said S1P receptor agonist.

Claim 4. (Currently amended) The method of claim 1, wherein the S1P receptor modulator or agonist is administered in a pharmaceutically effective amount such that a steady-state of the S1P receptor modulator or agonist blood levels is attained in the subject in a period of from 4 to 5 days ~~whereby the initial period is 4 or 5 days~~.

Claim 5. (Currently amended) A method for inhibiting graft rejection or treating an inflammatory or autoimmune disease or disorder in a subject in need thereof, comprising administering to the subject an S1P receptor modulator or agonist in such a pharmaceutically effective amount such that during the initial 3 to 6 days of treatment the dosage is raised so that in total the R-fold standard daily dosage is administered and thereafter the treatment is continued with the standard daily dosage or with a daily dosage lower than the standard daily dosage.

Claim 6. (Canceled)

Claim 7. (Previously amended) A method for inhibiting graft rejection or treating an inflammatory or autoimmune disease or disorder in a subject in need thereof, comprising administering to the subject an S1P receptor modulator or agonist in such a pharmaceutically effective amount such that during the initial 3 to 6 days of treatment the dosage is raised so that in total the R-fold standard daily dosage is administered.

Claim 8. (Previously presented) A method for inhibiting graft rejection or treating an inflammatory or autoimmune disease in a subject in need thereof, comprising administering to the subject, after a loading regimen, a S1P receptor modulator or agonist at a daily dosage which is lower than the standard daily dosage.

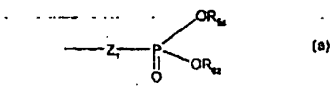
Claim 9. (Previously presented) A kit containing daily units of medication of an S1P receptor modulator or agonist of varying daily dosage, whereby the daily dosage of said S1P receptor modulator or agonist for the initial 3 to 6 days of treatment is incrementally increased so that the total amount present in the daily units corresponds to the R-fold standard daily dosage of said S1P receptor modulator or agonist for this initial time period.

Claim 10. (Previously presented) A kit containing daily units of medication of an S1P receptor modulator or agonist of varying daily dosage, whereby the daily dosage of S1P receptor modulator or agonist for the initial 4 days of treatment is ¼; ½; and ¾ of the highest installment dose of the S1P receptor modulator or agonist; and 4x the maintenance dose of the S1P receptor modulator or agonist, respectively.

Claim 11. (Previously presented) The method of claim 1, wherein the S1P receptor modulator or agonist comprises a group of formula X

(X)

wherein Z is H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, phenyl, phenyl substituted by OH, C_{1-6} alkyl substituted by 1 to 3 substituents selected from the group consisting of halogen, C_{3-8} cycloalkyl, phenyl and phenyl substituted by OH, or CH_2-R_{4Z} wherein R_{4Z} is OH, acyloxy or a residue of formula (a)



(a)

wherein Z_1 is a direct bond or O, preferably O; each of R_{5Z} and R_{6Z}, independently, is H, or C_{1-4}alkyl optionally substituted by 1, 2 or 3 halogen atoms;

R_{1Z} is OH, acyloxy or a residue of formula (a); and each of R_{2Z} and R_{3Z} independently, is H, C_{1-4}alkyl or acyl; in free form or the isomers, phosphates, prodrugs or pharmaceutically acceptable salts thereof.

Claim 12. (Previously presented) The method of claim 1, [[13]] wherein the S1P receptor modulator or agonist is 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol, 2-amino-2-[4-(3-benzyloxyphenoxy)-2-chlorophenyl]ethyl-1,3-propane-diol, 2-amino-2-[4-(benzyloxyphenylthio)-2-chlorophenyl]ethyl-1,3-propane-diol or 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, in free form or the isomers, phosphates, prodrugs or pharmaceutically acceptable salts thereof.

Claim 13. (Previously presented) The method of claim 1 wherein the S1P receptor modulator or agonist is 2-amino-2-tetradecyl-1,3-propanediol, 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol2-amino-2-{2-[4-(1-oxo-5-phenylpentyl)phenyl]ethyl}propane-1,3-diol, 2-amino-4-(4-heptyloxyphenyl)-2-methyl-butanol, phosphoric acid mono-[(R)-2~amino-2-methyl-4-(4-pentyloxy-phenyl)-butyl]ester, (2R)~2-amino-4-[3-(4-cyclohexyloxybutyl)- benzo[b]thien-6-yl]-2-methylbutan-1-ol, 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl- benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, in free form or the isomers, phosphates, prodrugs or pharmaceutically acceptable salts thereof.

Claim 14. (Previously presented) The method of claim 1, wherein the dosage is from 0.1 – 20 mg.

Claim 15. (Previously presented) The method of claim 1, wherein the dosage is from 0.1 – 0.5mg

Claim 16. (Previously presented) The method of claim 1, wherein the autoimmune disease is selected from the group consisting of multiple sclerosis, lupus nephritis, rheumatoid arthritis, inflammatory bowel diseases and psoriasis.

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
11/720,205	05/25/2007	

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☐		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	44 minus 20 =	* 24	X $ =		OR	X $50 =	1200
INDEPENDENT CLAIMS (37 CFR 1.16(h))	3 minus 3 =	* 0	X $ =			X $200 =	0
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	1200

APPLICATION AS AMENDED – PART II

		(Column 1)		(Column 2)	(Column 3)	SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
AMENDMENT	07/29/2010	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 62	Minus	** 44	= 18	X $ =		OR	X $52=	936
	Independent (37 CFR 1.16(h))	* 3	Minus	***3	= 0	X $ =		OR	X $220=	0
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	936

		(Column 1)		(Column 2)	(Column 3)					
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/DAVID HAUGHTON/

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
11/720,205	05/25/2007	

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☐		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	12 minus 20 =	* 0	X $ =		OR	X $50 =	0
INDEPENDENT CLAIMS (37 CFR 1.16(h))	8 minus 3 =	* 5	X $ =			X $200 =	1000
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	1000

APPLICATION AS AMENDED – PART II

		(Column 1)		(Column 2)	(Column 3)	SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
	07/29/2010	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
AMENDMENT	Total (37 CFR 1.16(i))	* 15	Minus	** 12	= 3	X $ =		OR	X $52=	156
	Independent (37 CFR 1.16(h))	* 7	Minus	***8	= 0	X $ =		OR	X $220=	0
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	156

		(Column 1)		(Column 2)	(Column 3)					
		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
AMENDMENT	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/DAVID HAUGHTON/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/720,205	05/25/2007	John M. Kovarik	34053-US-PCT	5868

1095 7590 02/16/2010

NOVARTIS
CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
EAST HANOVER, NJ 07936-1080

EXAMINER	
BLAKELY III, NELSON CLARENCE	
ART UNIT	**PAPER NUMBER**
1614	

MAIL DATE	DELIVERY MODE
02/16/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	11/720,205	KOVARIK ET AL.	
	Examiner	Art Unit	
	NELSON C. BLAKELY III	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5 and 7-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-5 and 7-16* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application Status

Claims 1-5 and 7-16 of the instant application are pending.

Election/Restrictions

Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claim(s) 9 and 10, drawn to a kit containing daily units of medication of a S1P receptor modulator or agonist of varying daily dosage.

Group II, claim(s) 1-5, 7, 8 and 11-16, drawn to a method for inhibiting graft rejection or treating an inflammatory or autoimmune disease or disorder in a subject in need thereof, comprising administering to the subject a S1P receptor modulator or agonist in such a pharmaceutically effective amount.

The inventions listed as Groups I and II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

An international application should relate to only one invention, or if there is more than one invention, the inclusion of those inventions in one international application is only permitted if all inventions are so linked as to form a single general inventive concept (PCT Rule 13.1). With respect to a group of inventions claimed in an

international application, unity of invention exists only when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding special technical features.

The expression "special technical features" is defined in PCT Rule 13.2 as meaning those technical features that define a contribution which each of the inventions, considered as a whole, makes over the prior art. The determination is made on the contents of the claims as interpreted in light of the description and drawings (if any). Whether or not any particular technical feature makes a "contribution" over the prior art, and therefore constitutes a "special technical feature", should be considered with respect to novelty and inventive step.

The common technical feature in all groups is a S1P receptor modulator or agonist. This composition cannot be a special technical feature under PCT Rule 13.2 because the composition is shown in the prior art.

Lake *et al*. (U.S. Patent Application Publication No. 2003/0003099A1; cited by Applicant) disclose, in at least reference claims 15 and 17, a method for the treatment or prophylaxis of insulin-producing cell graft refection in an insulin-producing cell graft recipient comprising administering, at least, an ALH agent, e.g., 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol. See instant claims 1, 12 and 13. Further, Lake *et al*. disclose, in paragraph **[0024]**, wherein the ALH agents of the reference invention are compounds which may be phosphorylated by sphingosine kinase and are in the phosphorylated form potent agonists at S1P receptors. Thus, there is no "special technical feature", which renders this restriction requirement proper.

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

The species are as follows: an inflammatory or autoimmune disease/disorder and a S1P receptor modulator or agonist.

With regard to Groups I and II, Applicant is required to elect a disclosed S1P receptor modulator or agonist. In order for this election to be considered fully responsive to this specie requirement the election **must include:**

a) the name and structure of one species of the instantly claimed compound;

b) the location of the species (a) within the claims or (b) within the specification;

c) the claims that read on the elected species; and

d) a definition of the exact substitutions, e.g. R^1 is hydrogen, etc…

With regard to Group II, Applicant is required to elect a single disclosed inflammatory or autoimmune disease/disorder.

Applicant is required, in reply to this action, to elect a single species to which the claims shall be restricted if no generic claim is finally held to be allowable. The reply must also identify the claims readable on the elected species, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered non-responsive unless accompanied by an election.

Upon the allowance of a generic claim, Applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims

are added after the election, Applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

The claims are deemed to correspond to the species listed above in the following manner:

(a) an inflammatory or autoimmune disease/disorder – Instant claims 1-5, 7, 8 and 11-16, and
(b) a S1P receptor modulator or agonist – Instant claims 1-5 and 7-16.

The following claim(s) are generic: 1-5 and 7-16.

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons:

An international application should relate to only one invention or, if there is more than one invention, the inclusion of those inventions in one international application is only permitted if all inventions are so linked as to form a single general inventive concept (PCT Rule 13.1). With respect to the species, unity of invention exists only when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding special technical features. The expression "special technical features" shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art.

The claims herein lack unity of invention under PCT Rule 13.1 and 13.2 because the instant invention does not set forth a technical relationship among the claimed inventions. For instance, the instant invention lacks unity in that the Z substituents, as set forth in instant claim 11 (e.g. H; phenyl substituted by OH), do not share a technical relationship, such as a common core structure or biological, physical, or chemical properties. Therefore, with compositions comprising components of varying structural

moieties, such as those claimed in instant claim 11, there is not a technical relationship among the claimed inventions.

Applicant is advised that to be complete, the reply to this requirement must include (i) an election of a species or invention to be examined even though the requirement may be traversed (37 CFR 1.143) and (ii) identification of the claims encompassing the elected invention.

The election of an invention or species may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

The Examiner has required restriction between product and process claims. Where Applicant elects claims directed to the product, and the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder. All claims directed to a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product claim will not be rejoined. See MPEP § 821.04(b). Additionally, in order to retain the right to rejoinder in accordance with the above policy, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder**. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Conclusion

Claims 1-5 and 7-16 are subject to a restriction/election of species requirement.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to NELSON C. BLAKELY III whose telephone number is (571) 270-3290. The Examiner can normally be reached on Mon - Thurs, 7:00 am - 5:30 pm (EST).

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ardin H. Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/N. C. B. III/
Examiner, Art Unit 1614

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
11/720,205	05/25/2007	John M. Kovarik	34053-US-PCT

CONFIRMATION NO. 5868

1095
NOVARTIS
CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
EAST HANOVER, NJ 07936-1080

PUBLICATION NOTICE

OC000000038629114

Title:DOSAGE REGIMEN OF AN S1P RECEPTOR AGONIST

Publication No.US-2009-0275553-A1
Publication Date:11/05/2009

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Office of Public Records. The Office of Public Records can be reached by telephone at (703) 308-9726 or (800) 972-6382, by facsimile at (703) 305-8759, by mail addressed to the United States Patent and Trademark Office, Office of Public Records, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently http://pair.uspto.gov/. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
11/720,205	05/25/2007	1614	1900	34053-US-PCT	12	8

CONFIRMATION NO. 5868

CORRECTED FILING RECEIPT

1095
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ONE HEALTH PLAZA 104/3
EAST HANOVER, NJ 07936-1080

OC000000037302318

Date Mailed: 08/11/2009

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Applicant(s)

John M. Kovarik, Basel, SWITZERLAND;
Silke Appel-Dingemanse, Allschwil, SWITZERLAND;

Power of Attorney: The patent practitioners associated with Customer Number 1095

Domestic Priority data as claimed by applicant

This application is a 371 of PCT/US05/43044 11/28/2005
which claims benefit of 60/631,483 11/29/2004

Foreign Applications

If Required, Foreign Filing License Granted: 07/24/2009

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 11/720,205**

Projected Publication Date: 11/05/2009

Non-Publication Request: No

Early Publication Request: No

Title

DOSAGE REGIMEN OF AN S1P RECEPTOR AGONIST

Preliminary Class

514

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

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Title 37, Code of Federal Regulations, 5.11 & 5.15

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set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

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NOT GRANTED

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CASE PAT034053-US-PCT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE PCT NATIONAL STAGE APPLICATION OF
Kovarik, John M. et al.
INTERNATIONAL APPLICATION NO: PCT/US2005/43044
FILED: November 28, 2005
U.S. APPLICATION NO: 11/720205
35 USC §371 DATE: May 25, 2007
FOR: Dosage Regimen of an S1P Receptor Agonist

Art Unit: 1614
Examiner: MARSCHEL, ARDIN H

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

LETTER CORRECTING OFFICIAL FILING RECEIPT

Sir:

The official filing receipt received in the above-identified application erroneously omits Inventor Two. Please issue a corrected filing receipt listing the second inventor as follows:

--Silke Appel-Dingemanse, Allschwil, Switzerland--

A copy of the filing receipt with the correction noted is enclosed.

No fee is believed to be required by this request for a corrected filing receipt.

Respectfully submitted,

Cozette McAvoy
Attorney for Applicant
Reg. No. 60,457

Novartis Pharmaceuticals Corporation
One Health Plaza, Bldg. 101
East Hanover, NJ 07936
(862) 778-9273

Date: 10th August 2009

CRL

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
11/720,205	05/25/2007	1614	1900	34053-US-PCT	12	8

CONFIRMATION NO. 5868

1095
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CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
EAST HANOVER, NJ 07936-1080

FILING RECEIPT

OC000000037077073

Pharma Intellectual Property
JUL 31 2009
F/F | Inv | RF | LE | PA

Date Mailed: 07/29/2009

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Applicant(s)

John M. Kovarik, Basel, SWITZERLAND; Silke Appel-Dingemanse, Allschwil, Switzerland

Power of Attorney: The patent practitioners associated with Customer Number 1095

Domestic Priority data as claimed by applicant

This application is a 371 of PCT/US05/43044 11/28/2005
which claims benefit of 60/631,483 11/29/2004

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If Required, Foreign Filing License Granted: 07/24/2009

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 11/720,205**

Projected Publication Date: 11/05/2009

Non-Publication Request: No

Early Publication Request: No

Title

DOSAGE REGIMEN OF AN S1P RECEPTOR AGONIST

Preliminary Class

514

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For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as

set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

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Electronic Acknowledgement Receipt

EFS ID:	5857977
Application Number:	11720205
International Application Number:	
Confirmation Number:	5868
Title of Invention:	DOSAGE REGIMEN OF AN S1P RECEPTOR AGONIST
First Named Inventor/Applicant Name:	John M. Kovarik
Customer Number:	01095
Filer:	Cozette Marie McAvoy/Barbara Brower-Anglim
Filer Authorized By:	Cozette Marie McAvoy
Attorney Docket Number:	34053-US-PCT
Receipt Date:	10-AUG-2009
Filing Date:	25-MAY-2007
Time Stamp:	15:09:10
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		Corr_Filing_Receipt_Aug_2009.pdf	551535 ba571f4a5caaf6e38cbff450e43ba3023de44745	yes	4

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Request for Corrected Filing Receipt	1	1
	Miscellaneous Incoming Letter	2	4
Warnings:			
Information:			
	Total Files Size (in bytes):	551535	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

DO/EO WORKSHEET

Francine Young

Patent Application Specialist/ National Stage Division

U.S. Appl. No. **11/720205** International Appl. No. **PCT/ US05/043044**

Application filed by : ☐ 20 months ☑ 30 months

WIPO PUBLICATION INFORMATION :

Publication No.: WO2006/058316 Publication Language : English (IA used as specification)

Publication Date : 1 JUNE 2006 Not Published : ☐ U.S. only designated ☐ EP request Published : ☐ EP Request

INTERNATIONAL APPLICATION PAPERS IN THE APPLICATION FILE :

- ☑ International Application
- ☐ Article 19 Amendments
- ☐ PCT/IPEA/409 IPER :
- ☐ Annexes to 409
- ☑ PCT/ISA/237 : EP
- ☑ IB 373
- ☐ PCT/IB/306
- ☐ Request form PCT/RO/101
- ☑ PCT/ISA/210 - Search Report : EP
- ☑ Priority Document (s) : 1
  - ☐ N/A
  - ☐ Priority Document was NOT AVAILABLE at the time of paralegal review

RECEIPTS FROM THE APPLICANT *(filed with the application unless noted otherwise) :* 29 MAY 07

- ☑ Basic National Fee (*or authorization to charge*)
- ☑ Description ☑ Claims ☑ Abstract
- ☐ Drawing Figure(s) - (# of drwgs. ☐)
- ☐ Translation of Article 19 Amendments
  - ☐ entered ☐ not entered :
    - ☐ not a page for page substitution
    - ☐ replaced by Article 34 Amendment
- ☐ Annexes to 409
  - ☐ entered ☐ not entered :
    - ☐ not a page for page substitution
    - ☐ no translation ☐ other : ☐
- ☑ Application Data Sheet 25-May-07
- ☐ Power of Attorney
- ☐ Change of Address
- ☑ Preliminary Amendment(s) Filed on :
  1. ☑ same as 371 request date 2. 8 OCT 07 3. ☐
- ☑ Information Disclosure Statement(s) Filed on :
  1. ☑ same as 371 request date 2. ☐ 3. ☐
- ☐ Express Request to Begin National Examination Procedures
- ☐ Assignee Statement Under 37 CFR 3.73(b)
- ☐ Assignee PG Publication Notice
- ☐ Substitute Specification Filed on :
  1. ☐ same as 371 request date 2. ☐ 3. ☐
- ☐ Verified Small Status Statement
- ☑ Executed Oath or Declaration 25 MAY 2007
- ☐ Defective Oath or Declaration
- ☐ Sequence Listing
- ☐ DNA Diskette
- ☐ Other Doc(s):

NOTES :

35 U.S.C. 371 - Receipt of Request (PTO-1390)	25 MAY 2007
Date Acceptable Oath/ Declaration Received	☐ Same as 371 Req. Date ☐ Other
Date of Completion of requirements under 35 U.S.C. 371	☐ Same as 371 Req. Date ☐ Same as OATH Date
Date of Completion of DO/ EO 903 - Notification of Acceptance	23 JUL 09
Date of Completion of DO/ EO 905 - Notification of Missing Requirements	
Date of Completion of DO/ EO 922 - Notification to Comply w/ Requirements for Patent Applications Containing Nucleotide and/or Amino Acid Sequence Disclosures	

PATENT APPLICATION FEE DETERMINATION RECORD
Effective December 8, 2004

Application or Docket Number: **11/720205**

CLAIMS AS FILED - PART I

	(Column 1)	(Column 2)	SMALL ENTITY RATE	SMALL ENTITY FEE	OR	LARGE ENTITY RATE	LARGE ENTITY FEE
U.S. NATIONAL STAGE FEES							
BASIC FEE			BASIC FEE		OR	BASIC FEE	$300
EXAMINATION FEE			EXAM. FEE			EXAM. FEE	$200
SEARCH FEE			SEARCH FEE			SEARCH FEE	$400
FEE FOR EXTRA SPEC. PGS.	minus 100 =	/ 50 =	X $ 125 =			X $ 250 =	
TOTAL CHARGEABLE CLAIMS	12 minus 20 =		X $ 25 =		OR	X $ 50 =	
INDEPENDENT CLAIMS	8 minus 3 =	5	X $ 100 =		OR	X $ 200 =	$1,000
MULTIPLE DEPENDENT CLAIM PRESENT		☐	+ $ 180 =		OR	+ $ 360 =	
* If the difference in column 1 is less than zero, enter "0" in column 2			TOTAL		OR	TOTAL	$1,900

CLAIMS AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE	SMALL ENTITY ADDITIONAL FEE	OR	OTHER THAN SMALL ENTITY RATE	OTHER THAN SMALL ENTITY ADDITIONAL FEE
AMENDMENT A	Total		Minus	**		X $ 25 =		OR	X $ 50 =	
	Independent		Minus	***		X $ 100 =		OR	X $ 200 =	
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐	+ $ 180 =		OR	+ $ 360 =	
						TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE	ADDITIONAL FEE	OR	RATE	ADDITIONAL FEE
AMENDMENT B	Total		Minus	**		X $ 25 =		OR	X $ 50 =	
	Independent		Minus	***		X $ 100 =		OR	X $ 200 =	
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐	+ $ 180 =		OR	+ $ 360 =	
						TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than '20', enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than '3', enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

MULTIPLE DEPENDENT CLAIM FEE CALCULATION SHEET (FOR USE WITH FORM PTO-875)	SERIAL NO. 11/720205	FILING DATE
	APPLICANT(S)	

CLAIMS

	AS FILED		AFTER 1st AMENDMENT		AFTER 2nd AMENDMENT	
	IND.	DEP.	IND.	DEP.	IND.	DEP.
1	1		1			
2		1	1			
3		2		1		
4		Φ		1		
5	1		1			
6	1		1			
7	1		1			
8	1		1			
9	1		1			
10	1		1			
11		Φ		1		
12		Φ		Φ		
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TOTAL IND.	7	↓	8	↓	0	↓
TOTAL DEP.	6	←	4	←	0	←
TOTAL CLAIMS	13		12		0	

	AS FILED		AFTER 1st AMENDMENT		AFTER 2nd AMENDMENT	
	IND.	DEP.	IND.	DEP.	IND.	DEP.
51						
52						
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100						
TOTAL IND.	0	↓	0	↓	0	↓
TOTAL DEP.	0	←	0	←	0	←
TOTAL CLAIMS	0		0		0	

PTO - 1360 (REV. 04/2009)

U.S. DEPARTMENT of COMMERCE
Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

U.S. APPLICATION NUMBER NO.	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
11/720,205	John M. Kovarik	34053-US-PCT

1095
NOVARTIS
CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
EAST HANOVER, NJ 07936-1080

INTERNATIONAL APPLICATION NO.	
PCT/US05/43044	
I.A. FILING DATE	PRIORITY DATE
11/28/2005	11/29/2004

CONFIRMATION NO. 5868
371 ACCEPTANCE LETTER

OC000000037077074

Date Mailed: 07/29/2009

NOTICE OF ACCEPTANCE OF APPLICATION UNDER 35 U.S.C 371 AND 37 CFR 1.495

The applicant is hereby advised that the United States Patent and Trademark Office in its capacity as a Designated / Elected Office (37 CFR 1.495), has determined that the above identified international application has met the requirements of 35 U.S.C. 371, and is ACCEPTED for national patentability examination in the United States Patent and Trademark Office.

The United States Application Number assigned to the application is shown above and the relevant dates are:

05/25/2007	05/29/2007
DATE OF RECEIPT OF 35 U.S.C. 371(c)(1), (c)(2) and (c)(4) REQUIREMENTS	DATE OF COMPLETION OF ALL 35 U.S.C. 371 REQUIREMENTS

A Filing Receipt (PTO-103X) will be issued for the present application in due course. **THE DATE APPEARING ON THE FILING RECEIPT AS THE " FILING DATE" IS THE DATE ON WHICH THE LAST OF THE 35 U.S.C. 371 (c)(1), (c)(2) and (c)(4) REQUIREMENTS HAS BEEN RECEIVED IN THE OFFICE. THIS DATE IS SHOWN ABOVE.** *The filing date of the above identified application is the international filing date of the international application (Article 11(3) and 35 U.S.C. 363).* Once the Filing Receipt has been received, send all correspondence to the Group Art Unit designated thereon.

The following items have been received:

- Copy of the International Application filed on 05/25/2007
- Copy of the International Search Report filed on 05/25/2007
- Preliminary Amendments filed on 05/25/2007
- Information Disclosure Statements filed on 05/25/2007
- Oath or Declaration filed on 05/25/2007
- U.S. Basic National Fees filed on 05/25/2007
- Priority Documents filed on 05/25/2007

Applicant is reminded that any communications to the United States Patent and Trademark Office must be mailed to the address given in the heading and include the U.S. application no. shown above (37 CFR 1.5)

FRANCINE YOUNG

Telephone: (703) 756-1462

FORM PCT/DO/EO/903 (371 Acceptance Notice)

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
11/720,205	05/25/2007	1614	1900	34053-US-PCT	12	8

CONFIRMATION NO. 5868

1095
NOVARTIS
CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
EAST HANOVER, NJ 07936-1080

FILING RECEIPT

OC000000037077073

Date Mailed: 07/29/2009

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Applicant(s)

John M. Kovarik, Basel, SWITZERLAND;

Power of Attorney: The patent practitioners associated with Customer Number 1095

Domestic Priority data as claimed by applicant

This application is a 371 of PCT/US05/43044 11/28/2005
which claims benefit of 60/631,483 11/29/2004

Foreign Applications

If Required, Foreign Filing License Granted: 07/24/2009

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 11/720,205**

Projected Publication Date: 11/05/2009

Non-Publication Request: No

Early Publication Request: No

Title

DOSAGE REGIMEN OF AN S1P RECEPTOR AGONIST

Preliminary Class

514

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

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For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/US2005/043044

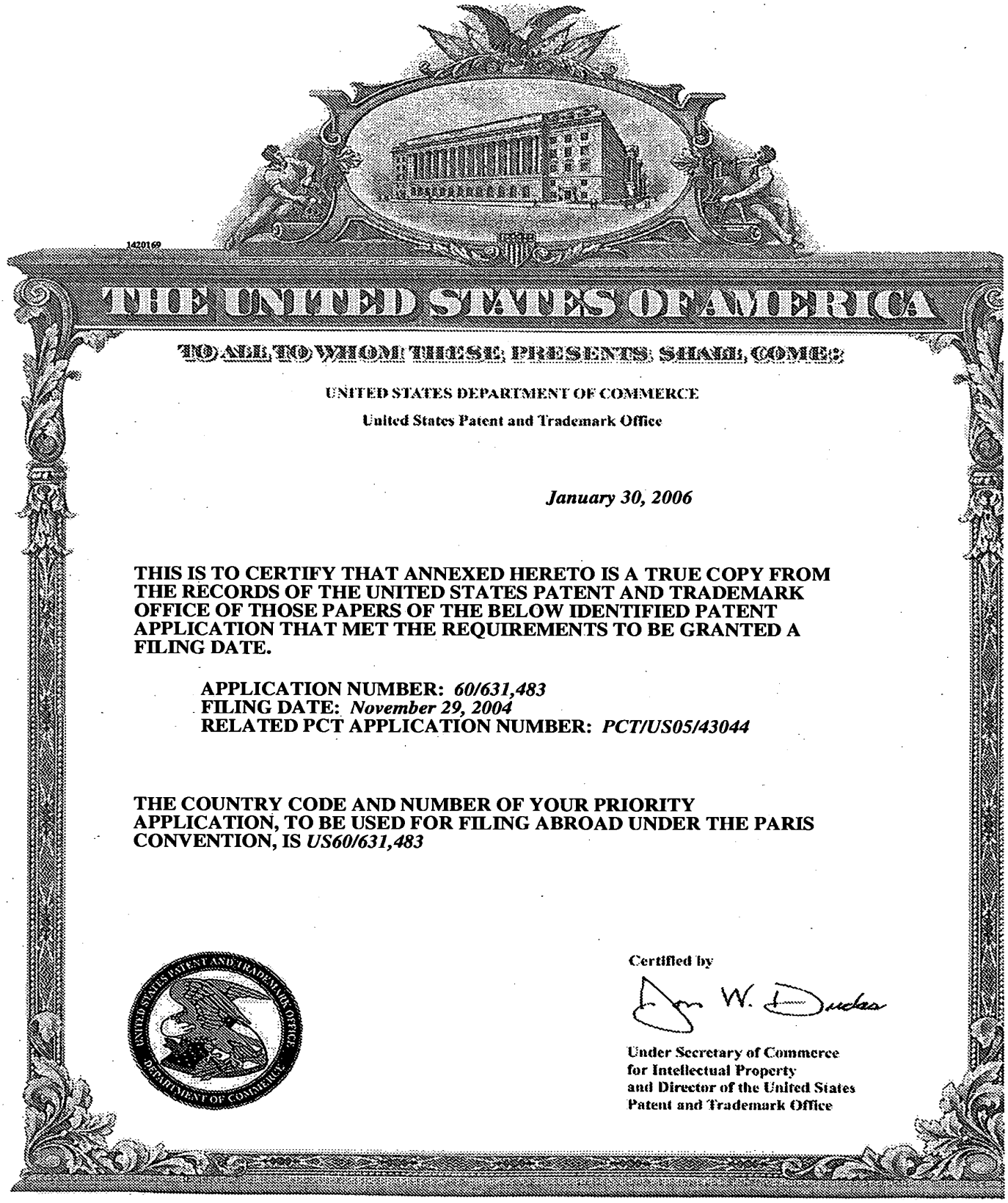
International filing date: 28 November 2005 (28.11.2005)

Document type: Certified copy of priority document

Document details: Country/Office: US
Number: 60/631,483
Filing date: 29 November 2004 (29.11.2004)

Date of receipt at the International Bureau: 02 February 2006 (02.02.2006)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)



3420169

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

January 30, 2006

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE.

APPLICATION NUMBER: *60/631,483*
FILING DATE: *November 29, 2004*
RELATED PCT APPLICATION NUMBER: *PCT/US05/43044*

THE COUNTRY CODE AND NUMBER OF YOUR PRIORITY APPLICATION, TO BE USED FOR FILING ABROAD UNDER THE PARIS CONVENTION, IS *US60/631,483*

Certified by

Under Secretary of Commerce
for Intellectual Property
and Director of the United States
Patent and Trademark Office

20427 U.S. PTO
112904

Docket Number	TX/4-34053P1

FILING BY "EXPRESS MAIL" UNDER 37 CFR 1.10

EV483667524US	November 29, 2004
Express Mail Label Number	Date of Deposit

00746 U.S. PTO
60/631483
112904

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

PATENT COVER SHEET FOR PROVISIONAL APPLICATION

Transmitted herewith for filing under 37 CFR §1.53(c) is the PROVISIONAL APPLICATION for patent of

INVENTOR(S)		
Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
John M	Kovarik	Basel, Switzerland

TITLE OF THE INVENTION (280 characters max)

ORGANIC COMPOUNDS

CORRESPONDENCE ADDRESS

Direct all correspondence to the address associated with Customer No. 001095, which is currently:

Novartis
Corporate Intellectual Property
One Health Plaza, Building 104
East Hanover, NJ 07936-1080

ENCLOSED APPLICATION PARTS *(check all that apply)*

- ☒ Specification (Including Any Claims and Abstract) - 20 pages
- ☐ Drawings - sheets
- ☒ Other (specify): Application Data Sheet

METHOD OF PAYMENT

The Commissioner is hereby authorized to charge filing fee and any additional fees required to Deposit Account Number: 19-0134 in the name of Novartis.	PROVISIONAL FILING FEE AMOUNT: $ 160

☐ U.S. Government agency and contract number: (if the invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.)

Respectfully submitted,

Thomas R. Savitsky

Thomas R. Savitsky
Attorney for Applicant
Reg. No. 31,661
Tel. No. (862) 778-7909

Date: November 29, 2004

Organic Compounds

The present invention relates to a dosage regimen of an S1P receptor agonist particularly in the course of the treatment of transplant patients.

S1P receptor agonists are compounds which signal as agonists at one or more sphingosine-1 phosphate receptors, e.g. S1P1 to S1P8. Agonist binding to a S1P receptor may e.g. result in dissociation of intracellular heterotrimeric G-proteins into Gα-GTP and Gβγ-GTP, and/or increased phosphorylation of the agonist-occupied receptor and activation of downstream signaling pathways/kinases.

S1P receptor agonists are valuable compounds for the manufacture of medication for the treatment of various conditions in mammals, especially in human beings. For example, S1P receptor agonists have successfully been used in the treatment of transplant patients, particularly prolonging allograft survival with great potency and efficacy and demonstrating excellent synergy with several immunosuppressants. This has been documented in rats (skin, heart, liver, small bowel), dogs (kidney), and monkeys (kidney). Combination experiments with cyclosporin A showed synergy in skin and heart transplantation models in rats and in monkey renal transplantation. S1P receptor agonists combined with everolimus prolong survival of cardiac (rat) and renal (monkey) allografts. Due to their immune-modulating potency, S1P receptor agonists are also useful for the treatment of inflammatory and autoimmune diseases. Further characteristics of S1P receptor agonists can be found in the following publications:

Brinkmann V, Chen S, Feng L, et al (2001) FTY720 alters lymphocyte homing and protects allografts without inducing general immunosuppression. Transplant Proc; 33:530-531.

Brinkmann V, Pinschewer D, Feng L, et al (2001) FTY720: altered lymphocyte traffic results in allograft protection (review). Transplantation; 72:764-769.

Pinschewer DD, Ochsenbein AF, Odermatt B, et al (2000) FTY720 immunosuppression impairs effector T-cell peripheral homing without affecting induction, expansion, and memory. J Immunol; 164:5761.

Yanagawa Y, Sugahara K, Kataoka H, et al (1998) FTY720, a novel immunosuppressant, induces sequestration of circulating mature lymphocytes by acceleration of lymphocyte homing in rats. II. FTY720 prolongs skin allograft survival by decreasing T cell infiltration into grafts but not cytokine production in vivo. J Immunol.; 160(11):5493-9.

It has now surprisingly been found that a specific dosage regimen, e.g. a loading dose, will provide further unexpected benefits. In particular, the otherwise observed moderate and

transient decrease in heart rate associated with the up-take of S1P receptor agonists by the body is suppressed or no longer observed after at most one week of treatment. Also the specific dosage regimen allows for re-initiation of the treatment after a hiatus avoiding said decrease in heart rate.

Accordingly it is provided the use of an S1P receptor agonist in the manufacture of a medication, whereby said medication is administered in such a way that during the initial 3 to 6 days, preferably 4 or 5 days, most preferred 4 days, of treatment the dosage of said S1P receptor agonist is raised so that in total the R-fold (R being the accumulation factor) standard daily dosage of said S1P receptor agonist is administered and thereafter the treatment is continued with the standard daily dosage of said S1P receptor agonist.

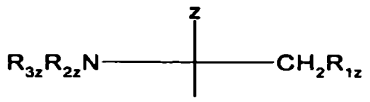
Preferred medications comprise medication for transplant patients providing prolonged survival rates, in particular prolonged allograft survival rates especially for renal or liver transplants, or for patients suffering from autoimmune diseases, e.g. multiple sclerosis.

In view of the normally prolonged taking of the medication, the standard daily dosage refers to the dosage of an S1P receptor agonist necessary for a steady-state trough blood level of the medication or its active metabolite(s) providing effective treatment. Said dosage is dependent on the accumulation factor (R). Steady-state trough blood levels may be assessed, for example, by averaging data collected at months 2, 3, and 6 of a treatment with a constant daily dosage, thereby allowing calculation of R. Preferably R is approximately from 3 to 12, preferably about 10.

Preferably, the dosage of said S1P receptor agonist during the initial 3 to 6 days of treatment is increased stepwise. A particularly preferred dosage of the preferred S1P receptor agonist FTY720 is 5, 10, 15 and 20 mg, respectively, during the initial period of 4 days. Thereafter the treatment is continued with the maintenance therapy, e.g. a daily dosage of 5 mg.

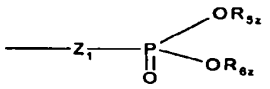
Preferably, the dosage of said S1P receptor agonist during the initial 3 to 6 days, preferably 4 or 5 days, most preferred 4 days, of treatment is increased incrementally up to 3- to 6-fold, particularly preferred up to 4-fold, the standard daily dosage of said S1P receptor agonist.

S1 P receptor agonists are typically sphingosine analogues, such as 2-substituted 2-amino-propane-1,3-diol or 2-amino-propanol derivatives, e. g. a compound comprising a group of formula X



(X)

wherein Z is H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, phenyl, phenyl substituted by OH, C_{1-6}alkyl substituted by 1 to 3 substituents selected from the group consisting of halogen, C_{3-8}cycloalkyl, phenyl and phenyl substituted by OH, or CH_2-R_{4z} wherein R_{4z} is OH, acyloxy or a residue of formula (a)



(a)

wherein Z_1 is a direct bond or O, preferably O;

each of R_{5z} and R_{6z}, independently, is H, or C_{1-4}alkyl optionally substituted by 1, 2 or 3 halogen atoms;

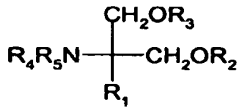
R_{1z} is OH, acyloxy or a residue of formula (a); and each of R_{2z} and R_{3z} independently, is H, C_{1-4}alkyl or acyl.

Group of formula X is a functional group attached as a terminal group to a moiety which may be hydrophilic or lipophilic and comprise one or more aliphatic, alicyclic, aromatic and/or heterocyclic residues, to the extent that the resulting molecule wherein at least one of Z and R_{1z} is or comprises a residue of formula (a), signals as an agonist at one of more sphingosine-1-phosphate receptor.

Preferred S1P receptor agonists are e.g. compounds which in addition to their S1P binding properties also have accelerating lymphocyte homing properties, e.g. compounds which elicit a lymphopenia resulting from a re-distribution, preferably reversible, of lymphocytes from circulation to secondary lymphatic tissue, without evoking a generalized immunosuppression. Naïve cells are sequestered; CD4 and CD8 T-cells and B-cells from the blood are stimulated to migrate into lymph nodes (LN) and Peyer's patches (PP).

Examples of appropriate S1P receptor agonists are, for example:

- Compounds as disclosed in EP627406A1, e.g. a compound of formula I



I

wherein R_1 is a straight- or branched (C_{12-22})chain

- which may have in the chain a bond or a hetero atom selected from a double bond, a triple bond, O, S, NR_6, wherein R_6 is H, alkyl, aralkyl, acyl or alkoxycarbonyl, and carbonyl, and/or
  - which may have as a substituent alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, acyl, alkylamino, alkylthio, acylamino, alkoxycarbonyl, alkoxycarbonylamino, acyloxy, alkylcarbamoyl, nitro, halogen, amino, hydroxyimino, hydroxy or carboxy; or

R_1 is

- a phenylalkyl wherein alkyl is a straight- or branched (C_{6-20})carbon chain; or
- a phenylalkyl wherein alkyl is a straight- or branched (C_{1-30})carbon chain wherein said phenylalkyl is substituted by
- a straight- or branched (C_{6-20})carbon chain optionally substituted by halogen,
- a straight- or branched (C_{6-20})alkoxy chain optionally substitued by halogen,
- a straight- or branched (C_{6-20})alkenyloxy,
- phenylalkoxy, halophenylalkoxy, phenylalkoxyalkyl, phenoxyalkoxy or phenoxyalkyl,
- cycloalkylalkyl substituted by C_{6-20}alkyl,
- heteroarylalkyl substituted by C_{6-20}alkyl,
- heterocyclic C_{6-20}alkyl, or
- heterocyclic alkyl substituted by C_{2-20}alkyl,

and wherein

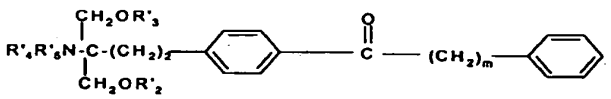
the alkyl moiety may have

- in the carbon chain, a bond or a heteroatom selected from a double bond, a triple bond, O, S, sulfinyl, sulfonyl, or NR_6, wherein R_6 is as defined above, and
- as a substituent alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, acyl, alkylamino, alkylthio, acylamino, alkoxycarbonyl, alkoxycarbonylamino, acyloxy, alkylcarbamoyl, nitro, halogen, amino, hydroxy or carboxy, and

each of R_2, R_3, R_4 and R_5, independently, is H, C_{1-4} alkyl or acyl

or a pharmaceutically acceptable salt thereof;

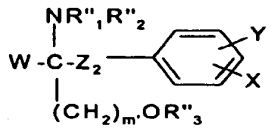
- Compounds as disclosed in EP 1002792A1, e.g. a compound of formula II



II

wherein m is 1 to 9 and each of R'$_2$, R'$_3$, R'$_4$ and R'$_5$, independently, is H, alkyl or acyl, or a pharmaceutically acceptable salt thereof;

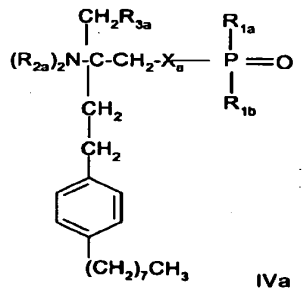
- Compounds as disclosed in EP0778263 A1, e.g. a compound of formula III



III

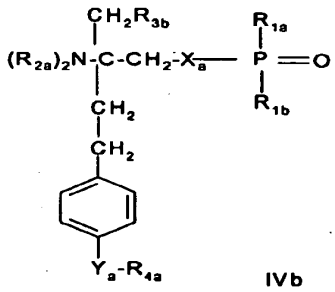
wherein W is H; C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl; unsubstituted or by OH substituted phenyl; R"$_4$O(CH$_2$)$_n$; or C_{1-6}alkyl substituted by 1 to 3 substituents selected from the group consisting of halogen, C_{3-6}cycloalkyl, phenyl and phenyl substituted by OH;
X is H or unsubstituted or substituted straight chain alkyl having a number p of carbon atoms or unsubstituted or substituted straight chain alkoxy having a number (p-1) of carbon atoms, e.g. substituted by 1 to 3 substitutents selected from the group consisting of C_{1-6} alkyl, OH, C_{1-6}alkoxy, acyloxy, amino, C_{1-6}alkylamino, acylamino, oxo, haloC_{1-6}alkyl, halogen, unsubstituted phenyl and phenyl substituted by 1 to 3 substituents selected from the group consisting of C_{1-6}alkyl, OH, C_{1-6}alkoxy, acyl, acyloxy, amino, C_{1-6}alkylamino, acylamino, haloC_{1-6}alkyl and halogen; Y is H, C_{1-6}alkyl, OH, C_{1-6}alkoxy, acyl, acyloxy, amino, C_{1-6}alkylamino, acylamino, haloC_{1-6}alkyl or halogen, Z_2 is a single bond or a straight chain alkylene having a number or carbon atoms of q,
each of p and q, independently, is an integer of 1 to 20, with the proviso of $6 \leq p+q \leq 23$, m' is 1, 2 or 3, n is 2 or 3,
each of R"$_1$, R"$_2$, R"$_3$ and R"$_4$, independently, is H, C_{1-4}alkyl or acyl,
or a pharmaceutically acceptable salt thereof,

- Compounds as disclosed in WO02/18395, e.g. a compound of formula IVa or IVb



IVa

or

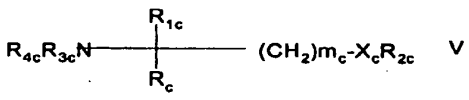


IVb

wherein X_a is O, S, NR_{1a} or a group $-(CH_2)_{na}-$, which group is unsubstituted or substituted by 1 to 4 halogen; n_a is 1 or 2, R_{1a} is H or (C_{1-4})alkyl, which alkyl is unsubstituted or substituted by halogen; R_{1a} is H, OH, (C_{1-4})alkyl or $O(C_{1-4})$alkyl wherein alkyl is unsubstituted or substituted by 1 to 3 halogen; R_{1b} is H, OH or (C_{1-4})alkyl, wherein alkyl is unsubstituted or substituted by halogen; each R_{2a} is independently selected from H or (C_{1-4})alkyl, which alkyl is unsubstituted or substitued by halogen; R_{3a} is H, OH, halogen or $O(C_{1-4})$alkyl wherein alkyl is unsubstituted or substituted by halogen; and R_{3b} is H, OH, halogen, (C_{1-4})alkyl wherein alkyl is unsubstituted or substituted by hydroxy, or $O(C_{1-4})$alkyl wherein alkyl is unsubstituted or substituted by halogen; Y_a is $-CH_2-$, -C(O)-, -CH(OH)-, -C(=NOH)-, O or S, and R_{4a} is (C_{4-14})alkyl or (C_{4-14})alkenyl;

or a pharmaceutically acceptable salt or hydrate thereof;

- Compounds as disclosed in WO 02/076995, e.g. a compound of formula V



V

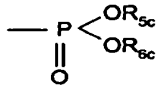
wherein

m_c is 1, 2 or 3;

X_c is O or a direct bond;

R_{1c} is H; C_{1-8} alkyl optionally substituted by OH, acyl, halogen, C_{3-10}cycloalkyl, phenyl or hydroxy-phenylene; C_{2-6}alkenyl; C_{2-6}alkynyl; or phenyl optionally substituted by OH;

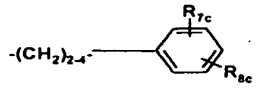
R_{2c} is



wherein R_{5c} is H or C_{1-4}alkyl optionally substituted by 1, 2 or 3 halogen atoms, and R_{6c} is H or C_{1-4}alkyl optionally substituted by halogen;

each of R_{3c} and R_{4c}, independently, is H, C_{1-4}alkyl optionally substituted by halogen, or acyl, and

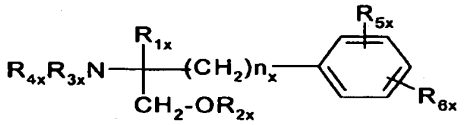
R_c is C_{13-20}alkyl which may optionally have in the chain an oxygen atom and which may optionally be substituted by nitro, halogen, amino, hydroxy or carboxy; or a residue of formula (a)


(a)

wherein R_{7c} is H, C_{1-4}alkyl or C_{1-4}alkoxy, and R_{8c} is substituted C_{1-20}alkanoyl, phenylC_{1-14}alkyl wherein the C_{1-14}alkyl is optionally substituted by halogen or OH, cycloalkylC_{1-14}alkoxy or phenylC_{1-14}alkoxy wherein the cycloalkyl or phenyl ring is optionally substituted by halogen, C_{1-4}alkyl and/or C_{1-4}alkoxy, phenylC_{1-14}alkoxy-C_{1-14}alkyl, phenoxyC_{1-14}alkoxy or phenoxyC_{1-14}alkyl,

R_c being also a residue of formula (a) wherein R_{8c} is C_{1-14}alkoxy when R_{1c} is C_{1-4}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl,

or a compound of formula VI


VI

wherein

n_x is 2, 3 or 4

R_{1x} is H; C_{1-6}alkyl optionally substituted by OH; acyl, halogen, cycloalkyl, phenyl or hydroxy-phenylene; C_{2-6}alkenyl; C_{2-6}alkynyl; or phenyl optionally substituted by OH;

R_{2x} is H, C_{1-4} alkyl or acyl

each of R_{3x} and R_{4x}, independently is H, C_{1-4}alkyl optionally substituted by halogen or acyl,

R_{5x} is H, C_{1-4}alkyl or C_{1-4}alkoxy, and

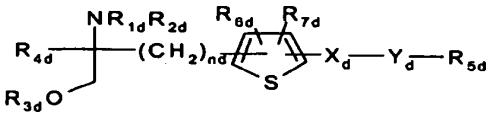
R_{6x} is C_{1-20} alkanoyl substituted by cycloalkyl; cyloalkylC_{1-14}alkoxy wherein the cycloalkyl ring is optionally substituted by halogen, C_{1-4}alkyl and/or C_{1-4}alkoxy; phenylC_{1-14}alkoxy wherein the phenyl ring is optionally substituted by halogen, C_{1-4}alkyl and/or C_{1-4}alkoxy,

R_{6x} being also C_{4-14}alkoxy when R_{1x} is C_{2-4}alkyl substituted by OH, or pentyloxy or hexyloxy when R_{1x} is C_{1-4}akyl,

provided that R_{6x} is other than phenyl-butylenoxy when either R_{5x} is H or R_{1x} is methyl,

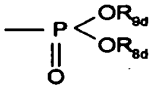
or a pharmaceutically acceptable salt thereof;

- Compounds as disclosed in WO02/06268Al, e.g. a compound of formula VII



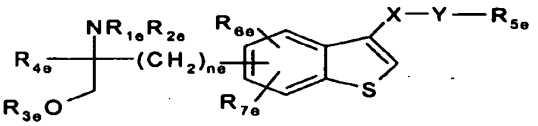
VII

wherein each of R_{1d} and R_{2d}, independently, is H or an amino-protecting group;
R_{3d} is hydrogen, a hydroxy-protecting group or a residue of formula



R_{4d} is lower alkyl;
n_d is an integer of 1 to 6;
X_d is ethylene, vinylene, ethynylene, a group having a formula – D-CH_2- (wherein D is carbonyl, – CH(OH)-, O, S or N), aryl or aryl substituted by up to three substitutents selected from group a as defined hereinafter;
Y_d is single bond, C_{1-10}alkylene, C_{1-10}alkylene which is substituted by up to three substitutents selected from groups a and b, C_{1-10}alkylene having O or S in the middle or end of the carbon chain, or C_{1-10}alkylene having O or S in the middle or end of the carbon chain which is substituted by up to three substituents selected from groups a and b;
R_{5d} is hydrogen, cycloalkyl, aryl, heterocycle, cycloalkyl substituted by up to three substituents selected from groups a and b, aryl substituted by up to three substituents selected from groups a and b, or heterocycle substituted by up to three substituents selected from groups a and b;
each of R_{6d} and R_{7d}, independently, is H or a substituent selected from group a;
each of R_{8d} and R_{9d}, independently, is H or C_{1-4}alkyl optionally substituted by halogen;
<group a > is halogen, lower alkyl, halogeno lower alkyl, lower alkoxy, lower alkylthio, carboxyl, lower alkoxycarbonyl, hydroxy, lower aliphatic acyl, amino, mono-lower alkylamino, di-lower alkylamino, lower aliphatic acylamino, cyano or nitro; and
<group b > is cycloalkyl, aryl, heterocycle, each being optionally substituted by up to three substituents selected from group a;
with the proviso that when R_{5d} is hydrogen, Y_d is a either a single bond or linear C_{1-10} alkylene, or a pharmacologically acceptable salt or ester thereof;

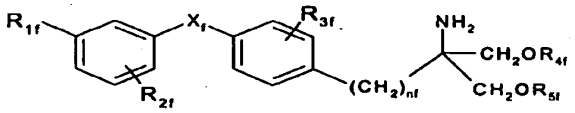
-Compounds as disclosed in JP-14316985 (JP2002316985), e.g. a compound of formula VIII



VIII

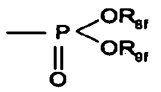
wherein R_{1e},R_{2e},R_{3e},R_{4e},R_{5e},R_{6e},R_{7e}, n_e, X_e and Y_e are as disclosed in JP-14316985;
or a pharmacologically acceptable salt or ester thereof;

-Compounds as disclosed in WO 03/29184 and WO 03/29205, e.g. compounds of formula IX



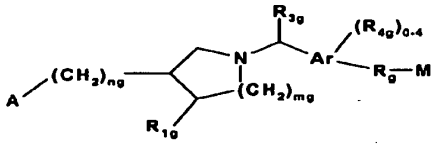
IX

wherein X_f is O or S, and R_{1f}, R_{2f}, R_{3f} and n_f are as disclosed in WO 03/29184 and WO 03/29205, each of R_{4f} and R_{5f}, independently is H or a residue of formula



wherein each of R_{8f} and R_{9f}, independently, is H or C_{1-4}alkyl optionally substituted by halogen; e.g. 2-amino-2-[4-(3-benzyloxyphenoxy)-2-chlorophenyl]propyl-1,3-propane-diol or 2-amino-2-[4-(benzyloxyphenylthio)-2- chlorophenyl]propyl-1,3-propane-diol, or a pharmacological salt thereof;

-Compounds as disclosed in WO03/062252A1, e.g. a compound of formula X

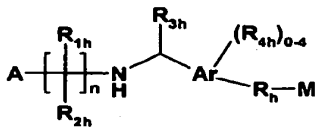


X

wherein

Ar is phenyl or naphthyl; each of m_g and n_g independently is 0 or 1; A is selected from COOH, PO_3H_2, PO_2H, SO_3H, $PO(C_{1-3}alkyl)OH$ and 1*H*-tetrazol-5-yl; each of R_{1g} and R_{2g} independently is H, halogen, OH, COOH or C_{1-4}alkyl optionally substituted by halogen; R_{3g} is H or C_{1-4}alkyl optionally substituted by halogen or OH; each R_{4g} independently is halogen, or optionally halogen substituted C_{1-4}alkyl or C_{1-3}alkoxy; and each of R_g and M has one of the significances as indicated for B and C, respectively, in WO03/062252A1;

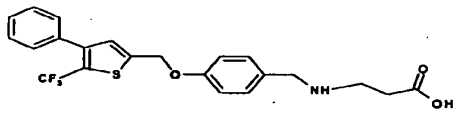
-Compounds as disclosed in WO 03/062248A2, e.g. a compound of formula XI



XI

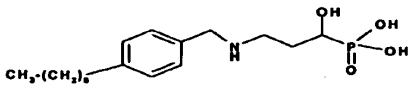
wherein Ar is phenyl or naphthyl; n is 2,3 or 4; A is COOH, 1*H*-tetrazol-5-yl, PO_3H_2, PO_2H_2, $-SO_3H$ or $PO(R_{5h})OH$ wherein R_{5h} is selected from C_{1-4}alkyl, hydroxyC_{1-4}alkyl, phenyl, -CO-C_{1-3}alkoxy and –CH(OH)-phenyl wherein said phenyl or phenyl moiety is opitonally substituted; each of R_{1h} and R_{2h} independently is H, halogen, OH, COOH, or optionally halogeno substituted C_{1-6}alkyl or phenyl; R_{3h} is H or C_{1-4}alkyl optionally substituted by halogen and/ OH; each R_{4h} independently is halogeno, OH, COOH, C_{1-4}alkyl, $S(O)_{0,1 \text{ or } 2}C_{1-3}$alkyl, C_{1-3}alkoxy, C_{3-6}cycloalkoxy, aryl or aralkoxy, wherein the alkyl portions may optionally be substituted by 1-3 halogens; and each of R_9 and M has one of the significances as indicated for B and C, respectively, in WO03/062248A2.

According to a further embodiment of the invention, a S1P receptor agonist for use in the invention may also be a selective S1P1 receptor, e.g. a compound which possesses a selectivity for the S1P1 receptor over the S1P3 receptor of at least 20 fold, e.g. 100, 500, 1000 or 2000 fold, as measured by the ratio of EC_{50} for the S1P1 receptor to the EC_{50} for the S1P3 receptor as evaluated in a ^{35}S-GTPγS binding assay, said compound having an EC_{50} for binding to the S1P1 receptor of 100 nM or less as evaluated by the ^{35}S-GTPγS binding assay. Representative S1P1 receptor agonists are e.g. the compounds listed in WO 03/061567, the contents of which being incorporated herein by reference, for instance a compound of formula



XII

or



XIII

When the compounds of formulae I to XIII have one or more asymmetric centers in the molecule, the present invention is to be understood as embracing the various optical isomers, as well as racemates, diastereoisomers and mixtures thereof are embraced. Compounds of formula III or IVb, when the carbon atom bearing the amino group is asymmetric, have preferably the R-configuration at this carbon atom.

The compounds of formulae I to XIII may exist in free or salt form. Examples of pharmaceutically acceptable salts of the compounds of the formulae I to XIII include salts with inorganic acids, such as hydrochloride, hydrobromide and sulfate, salts with organic acids, such as acetate, fumarate, maleate, benzoate, citrate, malate, methanesulfonate and benzenesulfonate salts, or, when appropriate, salts with metals such as sodium, potassium, calcium and aluminium, salts with amines, such as triethylamine and salts with dibasic amino acids, such as lysine. The compounds and salts of the combination of the present invention encompass hydrate and solvate forms.

Acyl as indicated above may be a residue R_y-CO- wherein R_y is C_{1-6}alkyl, C_{3-6}cycloalkyl, phenyl or phenyl-C_{1-4}alkyl. Unless otherwise stated, alkyl, alkoxy, alkenyl or alkynyl may be straight or branched.

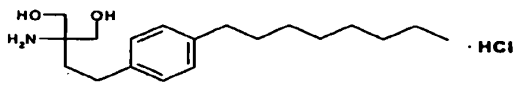
When in the compounds of formula I the carbon chain as R_1 is substituted, it is preferably substituted by halogen, nitro, amino, hydroxy or carboxy. When the carbon chain is interrupted by an optionally substituted phenylene, the carbon chain is preferably unsubstituted. When the phenylene moiety is substituted, it is preferably substituted by halogen, nitro, amino, methoxy, hydroxy or carboxy.

Preferred compounds of formula I are those wherein R_1 is C_{13-20}alkyl, optionally substituted by nitro, halogen, amino, hydroxy or carboxy, and, more preferably those wherein R_1 is phenylalkyl substituted by C_{8-14}-alkyl chain optionally substituted by halogen and the alkyl moiety is a C_{1-6}alkyl optionally substituted by hydroxy. More preferably, R_1 is phenyl-C_{1-6}alkyl substituted on the phenyl by a straight or branched, preferably straight, C_{8-14}alkyl chain. The C_{8-14}alkyl chain may be in ortho, meta or para, preferably in para.

Preferably each of R_2 to R_5 is H.

Preferred S1P receptor agonists are those having a half-life of approximately 5 to 10, preferably 7 to 10 days.

A preferred compound of formula I is 2-amino-2-tetradecyl-1,3-propanediol. A particularly preferred S1P receptor agonist of formula I is FTY720, i.e. 2-amino-2-[2-(4-octylphenyl) ethyl]propane-1,3-diol in free form or in a pharmaceutically acceptable salt form (referred to hereinafter as Compound A), e.g. the hydrochloride, as shown:



A preferred compound of formula II is the one wherein each of R'_2 to R'_5 is H and m is 4, i.e. 2-amino-2-{2-[4-(1-oxo-5-phenylpentyl)phenyl]ethyl}propane-1,3-diol, in free form or in pharmaceutically acceptable salt form (referred to hereinafter as Compound B), e.g. the hydrochloride.

A preferred compound of formula III is the one wherein W is CH_3, each of R''_1 to R''_3 is H, Z_2 is ethylene, X is heptyloxy and Y is H, i.e. 2-amino-4-(4-heptyloxyphenyl)-2-methyl-butanol, in free form or in pharmaceutically acceptable salt form (referred to hereinafter as Compound C), e.g. the hydrochloride. The R-enantiomer is particularly preferred.

A preferred compound of formula IVa is the FTY720-phosphate (R_{2a} is H, R_{3a} is OH, X_a is O, R_{1a} and R_{1b} are OH). A preferred compound of formula IVb is the Compound C-phosphate (R_{2a} is H, R_{3b} is OH, X_a is O, R_{1a} and R_{1b} are OH, Y_a is O and R_{4a} is heptyl). A preferred compound of formula V is Compound B-phosphate.

A preferred compound of formula V is phosphoric acid mono-[(R)-2-amino-2-methyl-4-(4-pentyloxy-phenyl)-butyl]ester.

A preferred compound of formula VIII is (2R)-2-amino-4-[3-(4-cyclohexyloxybutyl)-benzo[b]thien-6-yl]-2-methylbutan-1-ol.

Binding affinity of S1P receptor agonists to individual human S1P receptors may be determined in following assays:

Transient transfection of human S1P receptors into HEK293 cells

EDG receptors and G_i proteins are cloned, and equal amounts of 4 cDNAs for the EDG receptor, G_i-α, G_i-β and G_i-γ are mixed and used to transfect monolayers of HEK293 cells using the calcium phosphate precipitate method (M. Wigler et al., Cell. 1977;11;223 and DS. Im et al., Mol. Pharmacol. 2000;57;753). Briefly, a DNA mixture containing 25 µg of DNA and 0.25 M CaCl is added to HEPES-buffered 2 mM Na_2HPO_4. Subconfluent monolayers of HEK293 cells are poisoned with 25 mM chloroquine, and the DNA precipitate is then applied to the cells. After 4 h, the monolayers are washed with phosphate-buffered saline and refed media (90% 1:1 Dulbecco's modified essential media (DMEM):F-12 + 10% fetal bovine serum). The cells are harvested 48-72 h after addition of the DNA by scraping in HME buffer (in mM: 20 HEPES, 5 $MgCl_2$, 1 EDTA, pH 7.4) containing 10% sucrose on ice, and disrupted using a Dounce homogenizer. After centrifugation at 800×g, the supernatant is diluted with HME without sucrose and centrifuged at 100,000×g for 1h. The resulting pellet is

rehomogenized and centrifuged a second hour at 100,000×g. This crude membrane pellet is resuspended in HME with sucrose, aliquoted, and snap-frozen by immersion in liquid nitrogen. The membranes are stored at 70°C. Protein concentration is determined spectroscopically by Bradford protein assay.

GTPγS binding assay using S1P receptor/HEK293 membrane preparations

GTPγS binding experiments are performed as described by DS. Im et al., Mol. Pharmacol. 2000; 57:753. Ligand-mediated GTPγS binding to G-proteins is measured in GTP binding buffer (in mM: 50 HEPES, 100 NaCl, 10 $MgCl_2$, pH 7.5) using 25 µg of a membrane preparation from transiently transfected HEK293 cells. Ligand is added to membranes in the presence of 10 µM GDP and 0.1 nM [^{35}S]GTPγS (1200 Ci/mmol) and incubated at 30°C for 30 min. Bound GTPγS is separated from unbound using the Brandel harvester (Gaithersburg, MD) and counted with a liquid scintillation counter.

In a series of further specific or alternative embodiments, the present invention also provides:

1.1 The use of a S1P receptor agonist, e.g. FTY720, in the manufacture of a medication, whereby said medication is administered in such a way to a subject that a steady-state of the S1P receptor agonist blood levels is attained in less than a week.

The steady-state attained is such that the subject is sufficiently immunosuppressed, e.g. it shows no signs or symptoms of acute graft rejection or relapse or rebound of the autoimmune disease. During the initial 3 to 6 days, preferably 4 or 5 days, most preferred 4 days, of treatment the daily dosage of the S1P receptor agonist is raised stepwise up to 3- to 6-fold the standard daily dosage of said S1P receptor agonist and thereafter the treatment is continued with the standard daily dosage of said S1P receptor agonist. The S1P receptor agonist is preferably a compound having a half-life of from 5 to 10 days.

1.2. The use of FTY720 in the manufacture of a medication, whereby said medication is administered in such a way that during the initial 4 days of treatment the dosage of FTY720 is 5, 10, 15 and 20 mg, respectively, and thereafter the treatment is continued with the standard daily dosage of FTY720, e.g. 5 mg.

1.3. The use of an S1P receptor agonist, e.g. FTY720, in the manufacture of a medication, whereby said medication is administered in such a way that during the initial 3 to 6 days, preferably 4 or 5 days, most preferred 4 days, of treatment the dosage of said S1P receptor agonist is raised so that in total the R-fold standard daily

dosage of said S1P receptor agonist is administered and thereafter the treatment is continued with the standard daily dosage of said S1P receptor agonist.

2. A method for inhibiting graft rejection or treating an autoimmune disease in a subject in need thereof, comprising administering to the subject a S1 P receptor agonist, e.g. FTY720, in such a pharmaceutically effective amount that a steady-state of the S1P receptor agonist blood levels is attained in the subject in less than a week. Thereafter the treatment is continued with the standard daily dosage of said S1P receptor agonist. Preferably the S1P receptor agonist is a compound having a half-life of from 5 to 10 days.

2.1 A method for producing a steady-state of S1P receptor agonist blood levels in a subject in less than a week comprising administering during the initial 3 to 6 days, preferably 4 or 5 days, most preferred 4 days, an incremental daily dosage of up 3- to 6-fold the standard daily dosage of said S1P receptor agonist. Preferably the S1P receptor agonist is a compound having a half-life of from 5 to 10 days.

2.2 In a treatment method with a S1P receptor agonist, e.g. FTY720, the improvement being that the S1P receptor agonist is administered in such a way that during the initial 3 to 6 days, preferably 4 or 5 days, most preferred 4 days, of treatment the dosage is raised so that in total the R-fold standard daily dosage is administered. Thereafter the treatment is continued with the standard effective daily dosage.

2.3 A method for providing prolonged transplant survival rates in a subject, whereby an S1P receptor agonist, e.g. FTY720, is administered in such a way that during the initial 3 to 6 days, preferably 4 or 5 days, most preferred 4 days, of treatment the dosage is raised stepwise so that in total the R-fold standard daily dosage is administered and thereafter the treatment is continued with the standard daily dosage.

3. A kit containing daily units of medication of an S1P receptor agonist, e.g. FTY720, of varying daily dosage, whereby the daily dosage of said S1P receptor agonist for the initial 3 to 6 days, preferably 4 or 5 days, most preferred 4 days, of treatment is incrementally increased so that the total amount present in the daily units corresponds to the R-fold standard daily dosage of said S1P receptor agonist for this initial time period.

3.1. A kit containing daily units of medication of FTY720, of varying daily dosage, whereby the daily dosage of FTY720 for the initial 4 days of treatment is 5, 10, 15 and 20 mg,

respectively. The kit may further comprise units for the standard daily dosage of FTY720, e.g. 5 mg. The kit may also contain instructions for use.

The loading regimen of S1P receptor agonist which is administered to the subject according to the invention may be given either during the initial 3-6 days post-transplantation or may start even prior to the transplantation surgery, or at the beginning of an autoimmune disease therapy, e.g multiple sclerosis, or after an interruption of S1P receptor agonist therapy.

Utility of an S1P receptor agonist dosage regimen in treating diseases and conditions as hereinabove specified may be demonstrated in standard animal or clinical tests, e.g. in accordance with the methods described hereinafter.

2-Phase Multiple/Single-dose-study:

Initial baseline (Day -2): on Day –2, subjects enter the study center at least 12-hours prior to dosing for verification of inclusion/exclusion criteria and baseline assessments.

Placebo run-in (Day -1): On Day –1, subjects receive a single, placebo dose of FTY720. A 24-hour, 2-lead Holter monitoring commences from at least 1 hour prior to the time of the placebo drug administration.

FTY720 treatment (Days 1-7): All subjects receive FTY720 once daily for 7 consecutive days as follows,

Day 1: Subjects receive a single 5 mg FTY720 oral dose at the exact time the Day –1 dose was administered. The 24-hour Holter monitoring started on Day –1 continues from 1 hour predose on Day 1 for an additional 24 hours postdose.

Days 2-4: Subject receive a single 10 mg FTY720 oral dose on Day 2, a single 15 mg FTY720 oral dose on Day 3, and a single 20 mg FTY720 oral dose on Day 4, in order to achieve the FTY720 steady-state concentration typically measured in patients on chronic dosing of FTY720 5 mg qd.

Day 5-7: Subjects receive single 5 mg FTY720 oral doses once daily.

Pharmacokinetic, pharmacodynamic and safety assessments are performed at specified times during the multiple-dose study. Subjects are released from the study center approximately 24 hours after the last drug administration on Day 7, after the safety evaluations have been completed (i.e., Day 8).

The multiple-dose phase is followed by a 1-month (28 days) intertreatment interval.

Second baseline (Day 33): On Day 33, subjects enter the study center at least 12-hours prior to dosing for verification of inclusion/exclusion criteria and baseline assessments.

Placebo run-in (Day 34): On Day 34, subjects receive a single, placebo dose of FTY720. A 24-hour, 2-lead Holter monitoring commences from at least 1 hour prior to the time of the placebo drug administration.

FTY720 treatment (Day 35):. Subjects receive a single 5 mg FTY720 oral dose at the exact time the Day 34 dose was administered. The 24-hour Holter monitoring started on Day 34 continues from 1 hour predose on Day 35 for an additional 24 hours postdose

Pharmacokinetic, pharmacodynamic and safety assessments are performed at specified times during the multiple-dose study. Subjects are released from the study center approximately 24 hours after the drug administration on Day 35, after the safety evaluations have been completed (i.e., Day 36).

- Analytes, media and methods:

FTY720 is measured in whole blood using LC/MS/MS (LLOQ = 0.080 ng/mL)

- PK evaluations: Noncompartmental analysis to derive tmax, Cmax, AUC(0-24) on day 1. Peak and trough concentrations are summarized from days 2 through 7 to estimate drug accumulation and attainment of steady state.

Pharmacodynamic assessments

- Telemetry: Phase 1, Days 2 to 4: continuous heart rate monitoring from 0 to 6h post-FTY720 dose.

Telemetry

6-hour continuous telemetry monitoring of heart rate is performed on from 0 to 6 hours post-FTY720 dose on Day 2, Day 3, and Day 4.

Holter monitoring

Holter monitor(s) and recording media are provided by eResearch Technology, Inc.

On the placebo run-in day and the first FTY720 dosing day, 24-hour, continuous, ECG data is captured via a digital Holter monitor.

All Holter monitors are connected and started approximately 30 minutes prior to dosing.

The heart rate and rhythm from the Holter monitors are reported on a continuum over each 24-hour period including the mean hourly heart rate. In addition, standard assessments of the Holter data is made (e.g., frequency and duration of sinus pauses, frequency and duration of atrio-ventricular blocks, etc).

The dosage regimen of Phase 1 allowed to reach FTY720 steady-state levels which are otherwise typically achieved in renal transplant patients after 5 weeks of daily dosing.

Lymphocyte assessment

Blood samples for absolute lymphocyte counts is collected at screening, at initial baseline (Day -2), Day 1 (6h postdose), Day 3 (predose), Day 5 (predose) and Day 7 (predose).

The samples are analyzed for safety.

CLAIMS

1. Use of a S1P receptor agonist in the manufacture of a medication, whereby said medication is administered in such a way to a subject that a steady-state of the S1P receptor agonist blood levels is attained in less than a week.

2. Use of an S1P receptor agonist in the manufacture of a medication, whereby said medication is administered in such a way that during the initial 3 to 6 days of treatment the dosage of said S1P receptor agonist is raised so that in total the R-fold standard daily dosage of said S1P receptor agonist is administered and thereafter the treatment is continued with the standard daily dosage of said S1P receptor agonist.

3. Use according to claim 1 or 2, whereby the dosage of said S1P receptor agonist during the initial 3 to 6 days of treatment is increased stepwise up to the 3- to 6-fold standard daily dosage of said S1P receptor agonist.

4. Use according to claim 1, 2 or 3, whereby the initial period is 4 or 5 days.

5. A method for providing an S1P receptor agonist treatment, whereby said S1P receptor agonist is administered in such a way that during the initial 3 to 6 days of treatment the dosage is raised so that in total the R-fold standard daily dosage is administered and thereafter the treatment is continued with the standard daily dosage.

6. A method for inhibiting graft rejection or treating an autoimmune disease in a subject in need thereof, comprising administering to the subject a S1 P receptor agonist in such a pharmaceutically effective amount that a steady-state of the S1P receptor agonist blood levels is attained in the subject in less than a week.

7. A method for producing a steady-state of S1P receptor agonist blood levels in a subject in less than a week comprising administering during the initial 3 to 6 days an incremental daily dosage of up 3- to 6-fold the standard daily dosage of said S1P receptor agonist.

8. In a treatment method with a S1P receptor agonist, the improvement being that the S1P receptor agonist is administered in such a way that during the initial 3 to 6 days of treatment the dosage is raised so that in total the R-fold standard daily dosage is administered.

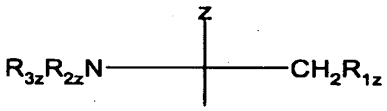
9. A method for providing prolonged transplant survival rates in a subject, whereby an S1P receptor agonist is administered in such a way that during the initial 3 to 6 days of treatment the dosage is raised stepwise so that in total the R-fold standard daily dosage is administered and thereafter the treatment is continued with the standard daily dosage.

10. A kit containing daily units of medication of an S1P receptor agonist of varying daily dosage, whereby the daily dosage of said S1P receptor agonist for the initial 3 to 6 days of treatment is incrementally increased so that the total amount present in the daily units corresponds to the R-fold standard daily dosage of said S1P receptor agonist for this initial time period.

11. Use, method or kit according to any of claims 1 to 10 providing prolonged transplant survival rates.

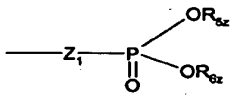
12. Use, method or kit according to any of claims 1 to 10 wherein the S1P receptor agonist has a half-life of approximately 5-10 days.

13. Use, method or kit according to any of claims 1 to 10 wherein the S1P receptor agonist comprises a group of formula X



(X)

wherein Z is H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, phenyl, phenyl substituted by OH, C_{1-6}alkyl substituted by 1 to 3 substituents selected from the group consisting of halogen, C_{3-8}cycloalkyl, phenyl and phenyl substituted by OH, or CH_2-R_{4z} wherein R_{4z} is OH, acyloxy or a residue of formula (a)



(a)

wherein Z_1 is a direct bond or O, preferably O;

each of R_{5z} and R_{8z}, independently, is H, or C_{1-4}alkyl optionally substituted by 1, 2 or 3 halogen atoms;

R_{1z} is OH, acyloxy or a residue of formula (a); and each of R_{2z} and R_{3z} independently, is H, C_{1-4}alkyl or acyl.

14. Use, method or kit according to claim 13 wherein the S1P receptor agonist is 2-amino-2-[2-(4-octylphenyl) ethyl]propane-1,3-diol in free form or in a pharmaceutically acceptable salt form.

15. A use, a method or a kit according to claim 14 wherein the dosage is 5, 10, 15 and 20 mg, respectively, during the initial period of 4 days.

ABSTRACT

S1P receptor agonists are administered following a dosage regimen whereby during the initial 3 to 6 days of treatment the daily dosage is raised so that in total the R-fold (R being the accumulation factor) standard daily dosage is administered and thereafter continued at the standard daily dosage.

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PCT

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Applicant NOVARTIS AG et al	

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(54) Title (EN): DOSAGE REGIMEN OF AN S1P RECEPTOR AGONIST

(54) Title (FR): POSOLOGIE D'UN AGONISTE DU RECEPTEUR S1P

(57) Abstract:

(EN): S1P receptor modulators or agonists are administered following a dosage regimen whereby during the initial 3 to 6 days of treatment the daily dosage is raised so that in total the R-fold (R being the accumulation factor) standard daily dosage is administered and thereafter continued at the standard daily dosage or at a daily dosage lower than the standard daily dosage.

(FR): Selon l'invention, des modulateurs ou agonistes du récepteur S1P sont administrés conformément à une posologie selon laquelle, au cours des 3 à 6 jours initiaux de traitement, la dose quotidienne est augmentée si bien qu'au total, la dose quotidienne normale multipliée par R (R étant le facteur d'accumulation) est administrée, et le traitement poursuivi ensuite à ladite dose quotidienne normale ou à une dose quotidienne inférieure à la dose quotidienne normale.

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(54) Title: DOSAGE REGIMEN OF AN S1P RECEPTOR AGONIST

(57) Abstract: S1P receptor modulators or agonists are administered following a dosage regimen whereby during the initial 3 to 6 days of treatment the daily dosage is raised so that in total the R-fold (R being the accumulation factor) standard daily dosage is administered and thereafter continued at the standard daily dosage or at a daily dosage lower than the standard daily dosage.

WO 2006/058316 A1

Dosage Regimen of an S1P Receptor Agonist

The present invention relates to a dosage regimen of an S1P receptor modulator or agonist particularly in the course of the treatment of transplant patients or patients suffering from autoimmune diseases or disorders.

S1P receptor modulators or agonists are compounds which signal as agonists at one or more sphingosine-1 phosphate receptors, e.g. S1P1 to S1P8. Agonist binding to a S1P receptor may e.g. result in dissociation of intracellular heterotrimeric G-proteins into Gα-GTP and Gβγ-GTP, and/or increased phosphorylation of the agonist-occupied receptor and activation of downstream signaling pathways/kinases.

S1P receptor modulators or agonists are valuable compounds for the manufacture of medication for the treatment of various conditions in mammals, especially in human beings. For example, efficacy in transplantation has been demonstrated in rats (skin, heart, liver, small bowel), dogs (kidney), and monkeys (kidney) models. Combination experiments with cyclosporin A showed synergy in skin and heart transplantation models in rats and in monkey renal transplantation. S1P receptor agonists or modulators combined with everolimus prolong survival of cardiac (rat) and renal (monkey) allografts. Due to their immune-modulating potency, S1P receptor modulators or agonists are also useful for the treatment of inflammatory and autoimmune diseases. Further characteristics of S1P receptor agonists can be found in the following publications:

Brinkmann V, Chen S, Feng L, et al (2001) FTY720 alters lymphocyte homing and protects allografts without inducing general immunosuppression. Transplant Proc; 33:530-531.

Brinkmann V, Pinschewer D, Feng L, et al (2001) FTY720: altered lymphocyte traffic results in allograft protection (review). Transplantation; 72:764-769.

Pinschewer DD, Ochsenbein AF, Odermatt B, et al (2000) FTY720 immunosuppression impairs effector T-cell peripheral homing without affecting induction, expansion, and memory. J Immunol; 164:5761.

Yanagawa Y, Sugahara K, Kataoka H, et al (1998) FTY720, a novel immunosuppressant, induces sequestration of circulating mature lymphocytes by acceleration of lymphocyte homing in rats. II. FTY720 prolongs skin allograft survival by decreasing T cell infiltration into grafts but not cytokine production in vivo. J Immunol.; 160(11):5493-9.

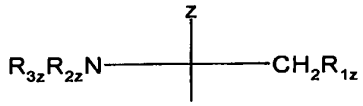
It has now surprisingly been found that a specific dosage regimen, e.g. a loading dose, will provide further unexpected benefits.

The binding affinity of S1P receptor agonists or modulators to individual human S1P receptors may be determined in following assay:
S1P receptor agonist or modulator activities of compounds are tested on the human S1P receptors $S1P_1$, $S1P_2$, $S1P_3$, $S1P_4$ and $S1P_5$. Functional receptor activation is assessed by quantifying compound induced GTP [γ-^{35}S] binding to membrane protein prepared from transfected CHO or RH7777 cells stably expressing the appropriate human S1P receptor. The assay technology used is SPA (scintillation proximity based assay). Briefly, DMSO dissolved compounds are serially diluted and added to SPA- bead (Amersham-Pharmacia) immobilised S1P receptor expressing membrane protein (10-20µg/well) in the presence of 50 mM Hepes, 100 mM NaCl, 10 mM $MgCl_2$, 10 µM GDP, 0.1% fat free BSA and 0.2 nM GTP [γ-^{35}S] (1200 Ci/mmol). After incubation in 96 well microtiterplates at RT for 120 min, unbound GTP [γ-^{35}S] is separated by a centrifugation step. Luminescence of SPA beads triggered by membrane bound GTP [γ-^{35}S] is quantified with a TOPcount plate reader (Packard). EC_{50}s are calculated using standard curve fitting software. In this assay, the S1P receptor modulators or agonists preferably have a binding affinity to S1P receptor <50 nM.

Preferred S1P receptor agonists or modulators are e.g. compounds which in addition to their S1P binding properties also have accelerating lymphocyte homing properties, e.g. compounds which elicit a lymphopenia resulting from a re-distribution, preferably reversible, of lymphocytes from circulation to secondary lymphatic tissue, without evoking a generalized immunosuppression. Naïve cells are sequestered; CD4 and CD8 T-cells and B-cells from the blood are stimulated to migrate into lymph nodes (LN) and Peyer's patches (PP).

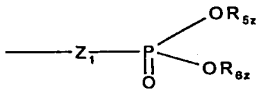
The lymphocyte homing property may be measured in following Blood Lymphocyte Depletion assay:
A S1P receptor agonist or modulator or the vehicle is administered orally by gavage to rats. Tail blood for hematological monitoring is obtained on day –1 to give the baseline individual values, and at 2, 6, 24, 48 and 72 hours after application. In this assay, the S1P receptor agonist or modulator depletes peripheral blood lymphocytes, e.g. by 50%, when administered at a dose of e.g. < 20 mg/kg.

S1 P receptor modulators or agonists are typically sphingosine analogues, such as 2-substituted 2-amino- propane-1,3-diol or 2-amino-propanol derivatives, e. g. a compound comprising a group of formula X



(X)

wherein Z is H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, phenyl, phenyl substituted by OH, C_{1-6}alkyl substituted by 1 to 3 substituents selected from the group consisting of halogen, C_{3-8}cycloalkyl, phenyl and phenyl substituted by OH, or CH_2-R_{4z} wherein R_{4z} is OH, acyloxy or a residue of formula (a)



(a)

wherein Z_1 is a direct bond or O, preferably O;

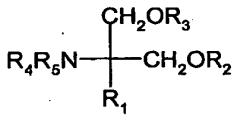
each of R_{5z} and R_{6z}, independently, is H, or C_{1-4}alkyl optionally substituted by 1, 2 or 3 halogen atoms;

R_{1z} is OH, acyloxy or a residue of formula (a); and each of R_{2z} and R_{3z} independently, is H, C_{1-4}alkyl or acyl.

Group of formula X is a functional group attached as a terminal group to a moiety which may be hydrophilic or lipophilic and comprise one or more aliphatic, alicyclic, aromatic and/or heterocyclic residues, to the extent that the resulting molecule wherein at least one of Z and R_{1z} is or comprises a residue of formula (a), signals as an agonist at one of more sphingosine-1-phosphate receptor.

Examples of appropriate S1P receptor agonists or modulators are, for example:

- Compounds as disclosed in EP627406A1, e.g. a compound of formula I



I

wherein R_1 is a straight- or branched (C_{12-22})chain

- which may have in the chain a bond or a hetero atom selected from a double bond, a triple bond, O, S, NR_6, wherein R_6 is H, C_{1-4}alkyl, aryl-C_{1-4}alkyl, acyl or (C_{1-4}alkoxy)carbonyl, and carbonyl, and/or
  - which may have as a substituent C_{1-4}alkoxy, C_{2-4}alkenyloxy, C_{2-4}alkynyloxy, arylC_{1-4}alkyl-oxy, acyl, C_{1-4}alkylamino, C_{1-4}alkylthio, acylamino, (C_{1-4}alkoxy)carbonyl, (C_{1-4}alkoxy)-

carbonylamino, acyloxy, (C_{1-4}alkyl)carbamoyl, nitro, halogen, amino, hydroxyimino, hydroxy or carboxy; or

R_1 is

- a phenylalkyl wherein alkyl is a straight- or branched (C_{6-20})carbon chain; or
- a phenylalkyl wherein alkyl is a straight- or branched (C_{1-30})carbon chain wherein said phenylalkyl is substituted by
- a straight- or branched (C_{6-20})carbon chain optionally substituted by halogen,
- a straight- or branched (C_{6-20})alkoxy chain optionally substitued by halogen,
- a straight- or branched (C_{6-20})alkenyloxy,
- phenyl-C_{1-14}alkoxy, halophenyl-C_{1-4}alkoxy, phenyl-C_{1-14}alkoxy-C_{1-14}alkyl, phenoxy-C_{1-4}alkoxy or phenoxy-C_{1-4}alkyl,
- cycloalkylalkyl substituted by C_{6-20}alkyl,
- heteroarylalkyl substituted by C_{6-20}alkyl,
- heterocyclic C_{6-20}alkyl or
- heterocyclic alkyl substituted by C_{2-20}alkyl,

and wherein

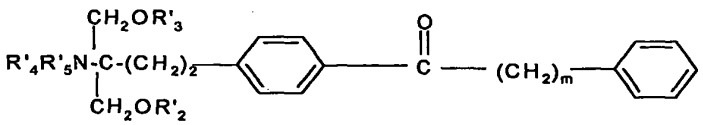
the alkyl moiety may have

- in the carbon chain, a bond or a heteroatom selected from a double bond, a triple bond, O, S, sulfinyl, sulfonyl, or NR_6, wherein R_6 is as defined above, and
- as a substituent C_{1-4}alkoxy, C_{2-4}alkenyloxy, C_{2-4}alkynyloxy, arylC_{1-4}alkyloxy, acyl, C_{1-4}alkyl-amino, C_{1-4}alkylthio, acylamino, (C_{1-4}alkoxy)carbonyl, (C_{1-4}alkoxy)carbonylamino, acyloxy, (C_{1-4}alkyl)carbamoyl, nitro, halogen, amino, hydroxy or carboxy, and

each of R_2, R_3, R_4 and R_5, independently, is H, C_{1-4} alkyl or acyl

or a pharmaceutically acceptable salt or hydrate thereof;

- Compounds as disclosed in EP 1002792A1, e.g. a compound of formula II

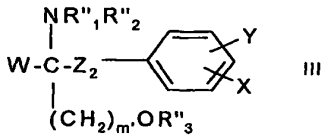


II

wherein m is 1 to 9 and each of R'_2, R'_3, R'_4 and R'_5, independently, is H, C_{1-6}alkyl or acyl,

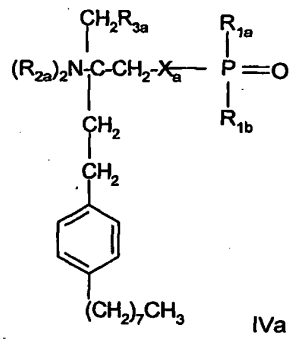
or a pharmaceutically acceptable salt or hydrate thereof;

- Compounds as disclosed in EP0778263 A1, e.g. a compound of formula III



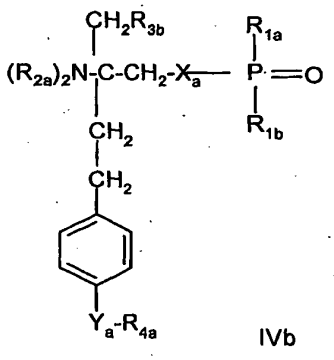
III

wherein W is H; C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl; unsubstituted or by OH substituted phenyl; $R''_4O(CH_2)_n$; or C_{1-6}alkyl substituted by 1 to 3 substituents selected from the group consisting of halogen, C_{3-8}cycloalkyl, phenyl and phenyl substituted by OH;
X is H or unsubstituted or substituted straight chain alkyl having a number p of carbon atoms or unsubstituted or substituted straight chain alkoxy having a number (p-1) of carbon atoms, e.g. substituted by 1 to 3 substitutents selected from the group consisting of C_{1-6}alkyl, OH, C_{1-6}alkoxy, acyloxy, amino, C_{1-6}alkylamino, acylamino, oxo, haloC_{1-6}alkyl, halogen, unsubstituted phenyl and phenyl substituted by 1 to 3 substituents selected from the group consisting of C_{1-6}alkyl, OH, C_{1-6}alkoxy, acyl, acyloxy, amino, C_{1-6}alkylamino, acylamino, haloC_{1-6}alkyl and halogen; Y is H, C_{1-6}alkyl, OH, C_{1-6}alkoxy, acyl, acyloxy, amino, C_{1-6}alkylamino, acylamino, haloC_{1-6}alkyl or halogen, Z_2 is a single bond or a straight chain alkylene having a number or carbon atoms of q,
each of p and q, independently, is an integer of 1 to 20, with the proviso of $6 \leq p+q \leq 23$, m' is 1, 2 or 3, n is 2 or 3,
each of R''_1, R''_2, R''_3 and R''_4, independently, is H, C_{1-4}alkyl or acyl,
or a pharmaceutically acceptable salt or hydrate thereof,
- Compounds as disclosed in WO02/18395, e.g. a compound of formula IVa or IVb



IVa

or



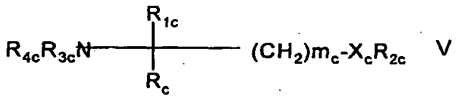
IVb

wherein X_a is O, S, NR_{1s} or a group $-(CH_2)_{na}-$, which group is unsubstituted or substituted by 1 to 4 halogen; n_a is 1 or 2, R_{1s} is H or (C_{1-4})alkyl, which alkyl is unsubstituted or substituted

by halogen; R_{1a} is H, OH, (C_{1-4})alkyl or $O(C_{1-4})$alkyl wherein alkyl is unsubstituted or substituted by 1 to 3 halogen; R_{1b} is H, OH or (C_{1-4})alkyl, wherein alkyl is unsubstituted or substituted by halogen; each R_{2a} is independently selected from H or (C_{1-4})alkyl, which alkyl is unsubstituted or substitued by halogen; R_{3a} is H, OH, halogen or $O(C_{1-4})$alkyl wherein alkyl is unsubstituted or substituted by halogen; and R_{3b} is H, OH, halogen, (C_{1-4})alkyl wherein alkyl is unsubstituted or substituted by hydroxy, or $O(C_{1-4})$alkyl wherein alkyl is unsubstituted or substituted by halogen; Y_a is $-CH_2-$, -C(O)-, -CH(OH)-, -C(=NOH)-, O or S, and R_{4a} is (C_{4-14})alkyl or (C_{4-14})alkenyl;

or a pharmaceutically acceptable salt or hydrate thereof;

- Compounds as disclosed in WO 02/076995, e.g. a compound of formula V



V

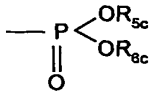
wherein

m_c is 1, 2 or 3;

X_c is O or a direct bond;

R_{1c} is H; C_{1-6} alkyl optionally substituted by OH, acyl, halogen, C_{3-10}cycloalkyl, phenyl or hydroxy-phenylene; C_{2-6}alkenyl; C_{2-6}alkynyl; or phenyl optionally substituted by OH;

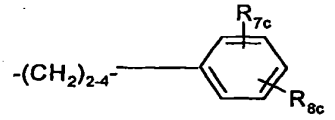
R_{2c} is



wherein R_{5c} is H or C_{1-4}alkyl optionally substituted by 1, 2 or 3 halogen atoms, and R_{6c} is H or C_{1-4}alkyl optionally substituted by halogen;

each of R_{3c} and R_{4c}, independently, is H, C_{1-4}alkyl optionally substituted by halogen, or acyl, and

R_c is C_{13-20}alkyl which may optionally have in the chain an oxygen atom and which may optionally be substituted by nitro, halogen, amino, hydroxy or carboxy; or a residue of formula (a)

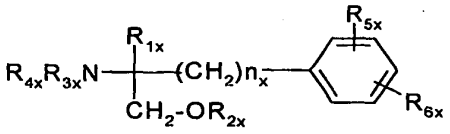


(a)

wherein R_{7c} is H, C_{1-4}alkyl or C_{1-4}alkoxy, and R_{8c} is substituted C_{1-20}alkanoyl, phenylC_{1-14}alkyl wherein the C_{1-14}alkyl is optionally substituted by halogen or OH, cycloalkylC_{1-14}alkoxy or phenylC_{1-14}alkoxy wherein the cycloalkyl or phenyl ring is optionally substituted by halogen, C_{1-4}alkyl and/or C_{1-4}alkoxy, phenylC_{1-14}alkoxy-C_{1-14}alkyl, phenoxyC_{1-14}alkoxy or phenoxyC_{1-14}alkyl,

R_c being also a residue of formula (a) wherein R_{8c} is C_{1-14}alkoxy when R_{1c} is C_{1-4}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl,

or a compound of formula VI



VI

wherein

n_x is 2, 3 or 4

R_{1x} is H; C_{1-6}alkyl optionally substituted by OH, acyl, halogen, cycloalkyl, phenyl or hydroxy-phenylene; C_{2-6}alkenyl; C_{2-6}alkynyl; or phenyl optionally substituted by OH;

R_{2x} is H, C_{1-4} alkyl or acyl

each of R_{3x} and R_{4x}, independently is H, C_{1-4}alkyl optionally substituted by halogen or acyl,

R_{5x} is H, C_{1-4}alkyl or C_{1-4}alkoxy, and

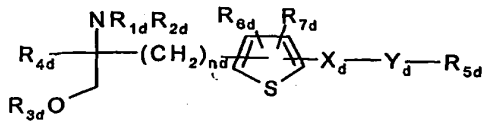
R_{6x} is C_{1-20} alkanoyl substituted by cycloalkyl; cyloalkylC_{1-14}alkoxy wherein the cycloalkyl ring is optionally substituted by halogen, C_{1-4}alkyl and/or C_{1-4}alkoxy; phenylC_{1-14}alkoxy wherein the phenyl ring is optionally substituted by halogen, C_{1-4}alkyl and/or C_{1-4}alkoxy,

R_{6x} being also C_{4-14}alkoxy when R_{1x} is C_{2-4}alkyl substituted by OH, or pentyloxy or hexyloxy when R_{1x} is C_{1-4}akyl,

provided that R_{6x} is other than phenyl-butylenoxy when either R_{5x} is H or R_{1x} is methyl,

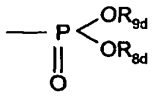
or a pharmaceutically acceptable salt or hydrate thereof;

- Compounds as disclosed in WO02/06268Al, e.g. a compound of formula VII



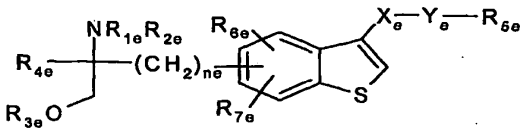
VII

wherein each of R_{1d} and R_{2d}, independently, is H or an amino-protecting group;
R_{3d} is hydrogen, a hydroxy-protecting group or a residue of formula



R_{4d} is C_{1-4}alkyl;
n_d is an integer of 1 to 6;
X_d is ethylene, vinylene, ethynylene, a group having a formula – D-CH_2- (wherein D is carbonyl, – CH(OH)-, O, S or N), aryl or aryl substituted by up to three substitutents selected from group a as defined hereinafter;
Y_d is single bond, C_{1-10}alkylene, C_{1-10}alkylene which is substituted by up to three substitutents selected from groups a and b, C_{1-10}alkylene having O or S in the middle or end of the carbon chain, or C_{1-10}alkylene having O or S in the middle or end of the carbon chain which is substituted by up to three substituents selected from groups a and b;
R_{5d} is hydrogen, C_{3-6}cycloalkyl, aryl, heterocyclic group, C_{3-6}cycloalkyl substituted by up to three substituents selected from groups a and b, aryl substituted by up to three substituents selected from groups a and b, or heterocyclic group substituted by up to three substituents selected from groups a and b;
each of R_{6d} and R_{7d}, independently, is H or a substituent selected from group a;
each of R_{8d} and R_{9d}, independently, is H or C_{1-4}alkyl optionally substituted by halogen;
<group a > is halogen, lower alkyl, halogeno lower alkyl, lower alkoxy, lower alkylthio, carboxyl, lower alkoxycarbonyl, hydroxy, lower aliphatic acyl, amino, mono-lower alkylamino, di-C_{1-4}alkylamino, acylamino, cyano or nitro; and
<group b > is C_{3-6}cycloalkyl, aryl or heterocyclic group, each being optionally substituted by up to three substituents selected from group a;
with the proviso that when R_{5d} is hydrogen, Y_d is a either a single bond or linear C_{1-10} alkylene, or a pharmacologically acceptable salt, ester or hydrate thereof;

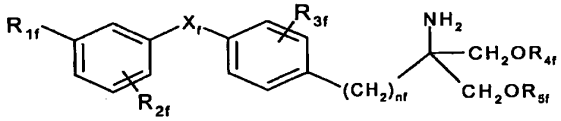
-Compounds as disclosed in JP-14316985 (JP2002316985), e.g. a compound of formula VIII



VIII

wherein R_{1e},R_{2e},R_{3e},R_{4e},R_{5e},R_{6e},R_{7e}, n_e, X_e and Y_e are as disclosed in JP-14316985;
or a pharmacologically acceptable salt, ester or hydrate thereof;

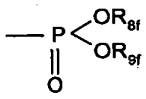
-Compounds as disclosed in WO 03/29184 and WO 03/29205, e.g. compounds of formula IX



IX

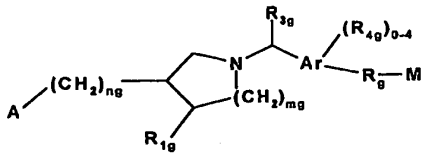
wherein X_f is O, S, SO or SO_2

R_{1f} is halogen, trihalomethyl, OH, C_{1-7}alkyl, C_{1-4}alkoxy, trifluoromethoxy, phenoxy, cyclohexylmethyloxy, pyridylmethoxy, cinnamyloxy, naphthylmethoxy, phenoxymethyl, CH_2-OH, CH_2-CH_2-OH, C_{1-4}alkylthio, C_{1-4}alkylsulfinyl, C_{1-4}alkylsulfonyl, benzylthio, acetyl, nitro or cyano, or phenyl, phenylC_{1-4}alkyl or phenyl-C_{1-4}alkoxy each phenyl group thereof being optionally substituted by halogen, CF_3, C_{1-4}alkyl or C_{1-4}alkoxy;
R_{2f} is H, halogen, trihalomethyl, C_{1-4}alkoxy, C_{1-7}alkyl, phenethyl or benzyloxy;
R_{3f} H, halogen, CF_3, OH, C_{1-7}alkyl, C_{1-4}alkoxy, benzyloxy or C_{1-4}alkoxymethyl;
each of R_{4f} and R_{5f}, independently is H or a residue of formula



wherein each of R_{8f} and R_{9f}, independently, is H or C_{1-4}alkyl optionally substituted by halogen;and
n_f is an integer from 1 to 4;
e.g. 2-amino-2-[4-(3-benzyloxyphenoxy)-2-chlorophenyl]ethyl-1,3-propane-diol, 2-amino-2-[4-(benzyloxyphenylthio)-2- chlorophenyl]ethyl-1,3-propane-diol, 2-amino-2-[4-(3-benzyloxyphenoxy)-2-chlorophenyl]propyl-1,3-propane-diol or 2-amino-2-[4-(benzyloxyphenylthio)-2- chlorophenyl]propyl-1,3-propane-diol,
or a pharmacological salt, solvate or hydrate thereof;

-Compounds as disclosed in WO03/062252A1, e.g. a compound of formula X

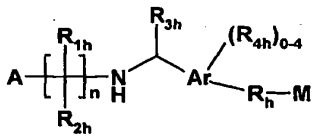


X

wherein

Ar is phenyl or naphthyl; each of m_g and n_g independently is 0 or 1; A is selected from COOH, PO_3H_2, PO_2H, SO_3H, $PO(C_{1-3}alkyl)OH$ and 1*H*-tetrazol-5-yl; each of R_{1g} and R_{2g} independently is H, halogen, OH, COOH or C_{1-4}alkyl optionally substituted by halogen; R_{3g} is H or C_{1-4}alkyl optionally substituted by halogen or OH; each R_{4g} independently is halogen, or optionally halogen substituted C_{1-4}alkyl or C_{1-3}alkoxy; and each of R_g and M has one of the significances as indicated for B and C, respectively, in WO03/062252A1;
or a pharmacologically acceptable salt, solvate or hydrate thereof;

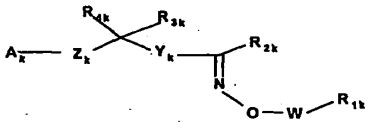
-Compounds as disclosed in WO 03/062248A2, e.g. a compound of formula XI



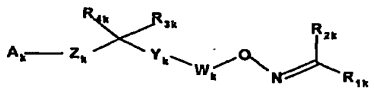
XI

wherein Ar is phenyl or naphthyl; n is 2,3 or 4; A is COOH, 1*H*-tetrazol-5-yl, PO_3H_2, PO_2H_2, SO_3H or $PO(R_{5h})OH$ wherein R_{5h} is selected from C_{1-4}alkyl, hydroxyC_{1-4}alkyl, phenyl, -CO-C_{1-3}alkoxy and –CH(OH)-phenyl wherein said phenyl or phenyl moiety is opitonally substituted; each of R_{1h} and R_{2h} independently is H, halogen, OH, COOH, or optionally halogeno substituted C_{1-6}alkyl or phenyl; R_{3h} is H or C_{1-4}alkyl optionally substituted by halogen and/ OH; each R_{4h} independently is halogeno, OH, COOH, C_{1-4}alkyl, $S(O)_{0,1 or 2}C_{1-3}$alkyl, C_{1-3}alkoxy, C_{3-6}cycloalkoxy, aryl or aralkoxy, wherein the alkyl portions may optionally be substituted by 1-3 halogens; and each of R_h and M has one of the significances as indicated for B and C, respectively, in WO03/062248A2;
or a pharmacologically acceptable salt, solvate or hydrate thereof;

- Compounds as disclosed in WO 04/103306A, WO 05/000833, WO 05/103309 or WO 05/113330, e.g. compounds of formula XIIa or XIIb



XIIa

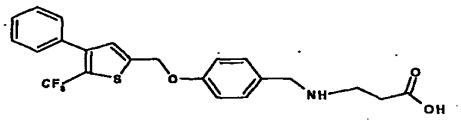


XIIb

wherein
A_k is $COOR_{5k}$, $OPO(OR_{5k})_2$, $PO(OR_{5k})_2$, SO_2OR_{5k}, $POR_{5k}OR_{5k}$ or 1*H*-tetrazol-5-yl, R_{5k} being H or C_{1-6}alkyl;
W_k is a bond, C_{1-3}alkylene or C_{2-3}alkenylene;

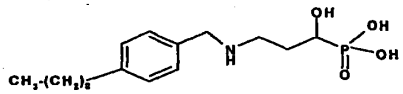
Y_k is C_{6-10}aryl or C_{3-9}heteroaryl, optionally substituted by 1 to 3 radicals selected from halogene, OH, NO_2, C_{1-6}alkyl, C_{1-6}alkoxy; halo-substituted C_{1-6}alkyl and halo-substituted C_{1-6}alkoxy;
Z_k is a heterocyclic group as indicated in WO 04/103306A, e.g. azetidine;
R_{1k} is C_{6-10}aryl or C_{3-9}heteroaryl, optionally substituted by C_{1-6}alkyl, C_{6-10}aryl, C_{6-10}arylC_{1-4}alkyl, C_{3-9}heteroaryl, C_{3-9}heteroarylC_{1-4}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-4}alkyl, C_{3-6}heterocycloalkyl or C_{3-6}heterocycloalkylC_{1-4}alkyl; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl of R_{1k} may be substituted by 1 to 5 groups selected from halogen, C_{1-6}alkyl, C_{1-6}alkoxy and halo substituted-C_{1-6}alkyl or -C_{1-6}alkoxy;
R_{2k} is H, C_{1-6}alkyl, halo substituted C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl: and
each of R_{3k} or R_{4k}, independently, is H, halogen, OH, C_{1-6}alkyl, C_{1-6}alkoxy or halo substituted C_{1-6}alkyl or C_{1-6}alkoxy;
and the N-oxide derivatives thereof or prodrugs thereof,
or a pharmacologically acceptable salt, solvate or hydrate thereof.

According to a further embodiment of the invention, a S1P receptor agonist or modulator for use in a combination of the invention may also be a selective S1P1 receptor, e.g. a compound which possesses a selectivity for the S1P1 receptor over the S1P3 receptor of at least 20 fold, e.g. 100, 500, 1000 or 2000 fold, as measured by the ratio of EC_{50} for the S1P1 receptor to the EC_{50} for the S1P3 receptor as evaluated in a ^{35}S-GTPγS binding assay, said compound having an EC_{50} for binding to the S1P1 receptor of 100 nM or less as evaluated by the ^{35}S-GTPγS binding assay. Representative S1P1 receptor agonists or modulators are e.g. the compounds listed in WO 03/061567, the contents of which being incorporated herein by reference, for instance a compound of formula XIII or XIV



XIII

or



XIV

When the compounds of formulae I to XIV have one or more asymmetric centers in the molecule, the present invention is to be understood as embracing the various optical isomers, as well as racemates, diastereoisomers and mixtures thereof are embraced. Compounds of formula III or IVb, when the carbon atom bearing the amino group is asymmetric, have preferably the R-configuration at this carbon atom.

The compounds of formulae I to XIV may exist in free or salt form. Examples of pharmaceutically acceptable salts of the compounds of the formulae I to XIV include salts with inorganic acids, such as hydrochloride, hydrobromide and sulfate, salts with organic acids, such as acetate, fumarate, maleate, benzoate, citrate, malate, methanesulfonate and benzenesulfonate salts, or, when appropriate, salts with metals such as sodium, potassium, calcium and aluminium, salts with amines, such as triethylamine and salts with dibasic amino acids, such as lysine. The compounds and salts of the combination of the present invention encompass hydrate and solvate forms.

Acyl as indicated above may be a residue R_y-CO- wherein R_y is C_{1-6}alkyl, C_{3-6}cycloalkyl, phenyl or phenyl-C_{1-4}alkyl. Unless otherwise stated, alkyl, alkoxy, alkenyl or alkynyl may be straight or branched.

Aryl may be phenyl or naphthyl, preferably phenyl.

When in the compounds of formula I the carbon chain as R_1 is substituted, it is preferably substituted by halogen, nitro, amino, hydroxy or carboxy. When the carbon chain is interrupted by an optionally substituted phenylene, the carbon chain is preferably unsubstituted. When the phenylene moiety is substituted, it is preferably substituted by halogen, nitro, amino, methoxy, hydroxy or carboxy.

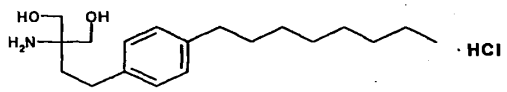
Preferred compounds of formula I are those wherein R_1 is C_{13-20}alkyl, optionally substituted by nitro, halogen, amino, hydroxy or carboxy, and, more preferably those wherein R_1 is phenylalkyl substituted by C_{6-14}-alkyl chain optionally substituted by halogen and the alkyl moiety is a C_{1-6}alkyl optionally substituted by hydroxy. More preferably, R_1 is phenyl-C_{1-6}alkyl substituted on the phenyl by a straight or branched, preferably straight, C_{6-14}alkyl chain. The C_{6-14}alkyl chain may be in ortho, meta or para, preferably in para.

Preferably each of R_2 to R_5 is H.

In the above formula of VII "heterocyclic group" represents a 5- to 7 membered heterocyclic group having 1 to 3 heteroatoms selected from S, O and N. Examples of such heterocyclic groups include the heteroaryl groups indicated above, and heterocyclic compounds corresponding to partially or completely hydrogenated heteroaryl groups, e.g. furyl, thienyl, pyrrolyl, azepinyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, 1,2,3-oxadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyranyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, pyrrolidinyl, pyrrolyl, imidazolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl or pyrazolidinyl.

Preferred heterocyclic groups are 5-or 6-membered heteroaryl groups and the most preferred heteocyclic group is a morpholinyl, thiomorpholinyl or piperidinyl group.

A preferred compound of formula I is 2-amino-2-tetradecyl-1,3-propanediol. A particularly preferred S1P receptor agonist of formula I is FTY720, i.e. 2-amino-2-[2-(4-octylphenyl) ethyl]propane-1,3-diol in free form or in a pharmaceutically acceptable salt form (referred to hereinafter as Compound A), e.g. the hydrochloride, as shown:



A preferred compound of formula II is the one wherein each of R'_2 to R'_5 is H and m is 4, i.e. 2-amino-2-{2-[4-(1-oxo-5-phenylpentyl)phenyl]ethyl}propane-1,3-diol, in free form or in pharmaceutically acceptable salt form (referred to hereinafter as Compound B), e.g the hydrochloride.

A preferred compound of formula III is the one wherein W is CH_3, each of R''_1 to R''_3 is H, Z_2 is ethylene, X is heptyloxy and Y is H, i.e. 2-amino-4-(4-heptyloxyphenyl)-2-methyl-butanol, in free form or in pharmaceutically acceptable salt form (referred to hereinafter as Compound C), e.g. the hydrochloride. The R-enantiomer is particularly preferred.

A preferred compound of formula IVa is the FTY720-phosphate (R_{2a} is H, R_{3a} is OH, X_a is O, R_{1a} and R_{1b} are OH). A preferred compound of formula IVb is the Compound C-phosphate (R_{2a} is H, R_{3b} is OH, X_a is O, R_{1a} and R_{1b} are OH, Y_a is O and R_{4a} is heptyl). A preferred compound of formula V is Compound B-phosphate.

A preferred compound of formula V is phosphoric acid mono-[(R)-2-amino-2-methyl-4-(4-pentyloxy-phenyl)-butyl]ester.

A preferred compound of formula VIII is (2R)-2-amino-4-[3-(4-cyclohexyloxybutyl)-benzo[b]thien-6-yl]-2-methylbutan-1-ol.

A preferred compound of formula XIIa is e.g. 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, or a prodrug thereof.

According to the invention, it provides the use of an S1P receptor modulator or agonist in the manufacture of a medication, whereby said medication is administered in such a way that during the initial 3 to 6 days, preferably 4 or 5 days, most preferred 4 days, of treatment the

dosage of said S1P receptor modulator or agonist is raised so that in total the R-fold (R being the accumulation factor) standard daily dosage of said S1P receptor modulator or agonist is administered and thereafter the treatment is continued with the standard or a lower daily dosage of said S1P receptor modulator or agonist.

Preferred medications comprise medication for transplant patients providing prolonged survival rates, in particular prolonged allograft survival rates especially for renal, heart, lung or liver transplants, or for patients suffering from autoimmune diseases, e.g. multiple sclerosis, lupus nephritis, rheumatoid arthritis, inflammatory bowel diseases or psoriasis.

In view of the normally prolonged taking of the medication, the standard daily dosage (also called maintenance dose) refers to the dosage of an S1P receptor modulator or agonist necessary for a steady-state trough blood level of the medication or its active metabolite(s) providing effective treatment. Said dosage is dependent on the accumulation factor (R). By blood level is meant the concentration of a drug in blood at any time. Trough blood level corresponds to a pre-dose blood level. Steady-state means whether the trough or blood level is stable over time. Steady-state trough blood levels may be assessed, for example, by obtaining a pre-dose blood sample anytime after month 3. The accumulation factor (R) is calculated on the ratio of the steady-state trough to the trough just before the second dose.

Preferably, the dosage of the S1P receptor modulator or agonist during the initial 3 to 6 days, of treatment is increased stepwise. Thereafter the treatment is continued with the maintenance therapy with the standard daily dosage or with a lower daily dosage. When the treatment is continued at a lower daily dosage, it may be e.g. about 1/50 to ½, preferably 1/50 to 1/10, of the standard daily dosage of the S1P receptor modulator or agonist.

Preferably, the total dosage of said S1P receptor modulator or agonist during the initial 3 to 6 days, preferably 4 or 5 days, most preferred 4 days, of treatment is increased incrementally from 3- to 21-fold, more preferred from 4 to 12-fold, particularly about 10-fold, the standard daily dosage of said S1P receptor modulator or agonist. For example, the loading dose may be 1; 1.5-2; 2-3; and 3-4 fold the standard daily dosage, on day 1, 2, 3 and 4, respectively.

According to a preferred embodiment of the invention, the highest loading regimen dose instalment on the last day of the loading regimen, e.g. on day 4, is 4x the maintenance dose of the S1P receptor modulator or agonist. The instalment doses on days 1, 2 and 3 of the loading regimen may be e.g. about ¼; ½; and ¾ of the highest instalment dose of the S1P receptor modulator or agonist.

A particularly preferred dosage of the S1P receptor modulator or agonist, e.g. the preferred S1P receptor modulator FTY720, is e.g. 2-5, 5-10, 10-15 and 15-20 mg, e.g. a regimen of 2.5mg/5mg/7.5mg/10mg or 5mg/10mg/15mg/20mg, respectively, during the initial period of 4 days. Thereafter the treatment is continued with the maintenance therapy, e.g. a daily dosage of 2.5 mg or 5 mg, or at a lower daily dosage, e.g. 0.1 to 0,5 mg.

In a further embodiment of the invention, a preferred loading regimen of a S1P receptor agonist or modulator, e.g. the preferred S1P receptor modulator FTY720, may also be e.g. 0.5mg/1mg/1.5mg/2mg during the initial period of 4 days. Thereafter the treatment is continued with the maintenance therapy, e.g. a daily dosage of 0,5 mg.

In a series of further specific or alternative embodiments, the present invention also provides:

1.1 The use of a S1P receptor modulator or agonist, e.g. FTY720, in the manufacture of a medication, whereby said medication is administered in such a way to a subject that a steady-state of the S1P receptor modulator or agonist blood levels is attained in less than a week.

The steady-state attained is such that the subject is sufficiently immunosuppressed, e.g. it shows no signs or symptoms of acute graft rejection or relapse or rebound of the autoimmune disease. During the initial 3 to 6 days, preferably 4 or 5 days, most preferred 4 days, of treatment the daily dosage of the S1P receptor modulator or agonist is raised stepwise up to 3- to 21-fold the standard daily dosage of said S1P receptor modulator or agonist and thereafter the treatment is continued with the standard daily dosage of said S1P receptor modulator or agonist.

1.2 The use of a S1P receptor modulator or agonist, e.g. FTY720, in the manufacture of a medication, whereby said medication is administered in such a way to a subject that a steady-state of the S1P receptor modulator or agonist blood levels is attained in less than a week, and thereafter the treatment is continued at a dosage lower than the standard daily dosage.

1.3. The use of a S1P receptor modulator or agonist, e.g. FTY720, in the manufacture of a medication, whereby said medication is administered in such a way that during the initial 4 days of treatment the dosage of the S1P receptor modulator or agonist is 1; 1.5-2; 2-3; and 3-4 fold the standard daily dosage, respectively, and thereafter the treatment is continued with the standard daily dosage of the S1P receptor modulator or agonist, or at a lower daily dosage.

1.4 The use of a S1P receptor modulator or agonist, e.g. FTY720, in the manufacture of a medication, whereby said medication is administered in such a way that during the initial 4 days of treatment the dosage of the S1P receptor modulator or agonist is ¼; ½; and ¾ of the highest instalment dose of the S1P receptor modulator or agonist; and 4x the maintenance dose of the S1P receptor modulator or agonist, respectively, and thereafter the treatment is continued with the maintenance dose or optionally with a lower daily dosage of the S1P receptor modulator or agonist.

1.5 The use of an S1P receptor modulator or agonist, e.g. FTY720, in the manufacture of a medication, whereby said medication is administered in such a way that during the initial 3 to 6 days, preferably 4 or 5 days, most preferred 4 days, of treatment the dosage of said S1P receptor modulator or agonist is raised so that in total the R-fold standard daily dosage of said S1P receptor modulator or agonist is administered and thereafter the treatment is continued with the standard daily dosage of said S1P receptor agonist or at a lower daily dosage.

1.6 The use of an S1P receptor modulator or agonist, e.g. FTY720, in the manufacture of a medication, whereby said medication is administered, after a loading regimen, at a daily dosage which is lower than the standard daily dosage.

1.7 The use of FTY720 in the manufacture of a medication, whereby said medication is administered, after a loading regimen, at a daily dosage of 0.1 to 0.5 mg.

2. A method for inhibiting graft rejection or treating an autoimmune disease in a subject in need thereof, comprising administering to the subject a S1 P receptor modulator or agonist, e.g. FTY720, in such a pharmaceutically effective amount that a steady-state of the S1P receptor modulator or agonist blood levels is attained in the subject in less than a week. Thereafter the treatment is continued with the standard daily dosage of said S1P receptor modulator or agonist or at a lower daily dosage

2.1 A method for producing a steady-state of S1P receptor modulator or agonist blood levels in a subject in less than a week comprising administering during the initial 3 to 6 days, preferably 4 or 5 days, most preferred 4 days, an incremental daily dosage of up 3- to 21-fold the standard daily dosage of said S1P receptor modulator or agonist.

2.2 In a treatment method with a S1P receptor modulator or agonist, e.g. FTY720, the improvement being that the S1P receptor modulator or agonist is administered in such a way that during the initial 3 to 6 days, preferably 4 or 5 days, most preferred 4

days, of treatment the dosage is raised so that in total the R-fold standard daily dosage is administered. Thereafter the treatment is continued with the standard effective daily dosage or at a lower daily dosage.

2.3 A method for providing prolonged transplant survival rates in a subject, whereby an S1P receptor modulator or agonist is administered in such a way that during the initial 3 to 6 days, preferably 4 or 5 days, most preferred 4 days, of treatment the dosage is raised stepwise so that in total the R-fold standard daily dosage is administered and thereafter the treatment is continued with the standard daily dosage or at a lower daily dosage.

2.4 A method for inhibiting graft rejection or treating an autoimmune disease in a subject in need thereof, comprising administering to the subject, after a loading regimen, a S1 P receptor modulator or agonist, e.g. FTY720, at a daily dosage which is lower than the standard daily dosage.

2.5 A method for treating an autoimmune disease in a subject in need thereof, comprising administering to the subject, after a loading regimen, a daily dosage of FTY720 of about 0.1 to 0.5mg.

3. A kit containing daily units of medication of an S1P receptor modulator or agonist, e.g. FTY720, of varying daily dosage, whereby the daily dosage of said S1P receptor modulator or agonist for the initial 3 to 6 days, preferably 4 or 5 days, most preferred 4 days, of treatment is incrementally increased so that the total amount present in the daily units corresponds to the R-fold standard daily dosage of said S1P receptor modulator or agonist for this initial time period.

3.1. A kit containing daily units of medication of an S1P receptor modulator or agonist, e.g. FTY720, of varying daily dosage, whereby the daily dosage of S1P receptor modulator or agonist for the initial 4 days of treatment is 1; 1.5-2; 2-3; and 3-4 fold the standard daily dosage, respectively. The kit may further comprise units for the standard daily dosage of the S1P receptor modulator or agonist, e.g. FTY720, or for the subsequent treatment with a lower daily dosage. The kit may also contain instructions for use.

3.2 A kit containing daily units of medication of an S1P receptor modulator or agonist, e.g. FTY720, of varying daily dosage, whereby the daily dosage of S1P receptor modulator or agonist for the initial 4 days of treatment is ¼; ½; and ¾ of the highest

instalment dose of the S1P receptor modulator or agonist; and 4x the maintenance dose of the S1P receptor modulator or agonist, respectively. The kit may further comprise units for the standard daily dosage of the S1P receptor modulator or agonist, e.g. FTY720, or for the subsequent treatment with a lower daily dosage. The kit may also contain instructions for use.

The loading regimen of S1P receptor modulator or agonist which is administered to the subject according to the invention may be given either during the initial 3-6 days post-transplantation or may start even prior to the transplantation surgery, or at the beginning of an autoimmune disease therapy, or after an interruption of S1P receptor modulator or agonist therapy.

Utility of an S1P receptor modulator or agonist dosage regimen in treating diseases and conditions as hereinabove specified may be demonstrated in standard animal or clinical tests, e.g. in accordance with the methods described hereinafter.

2-Phase Loading Regimen-Study:

Initial baseline (Day -2): on Day –2, subjects enter the study center at least 12-hours prior to dosing for verification of inclusion/exclusion criteria and baseline assessments.

Placebo run-in (Day -1): On Day –1, subjects receive a single, placebo dose of FTY720

FTY720 treatment (Days 1-7): All subjects receive FTY720 once daily for 7 consecutive days as follows,

Day 1: Subjects receive a single 5 mg FTY720 oral dose at the exact time the Day –1 dose was administered.

Days 2-4: Subject receive a single 10 mg FTY720 oral dose on Day 2, a single 15 mg FTY720 oral dose on Day 3, and a single 20 mg FTY720 oral dose on Day 4, in order to achieve the FTY720 steady-state concentration typically measured in patients on chronic dosing of FTY720 5 mg qd.

Day 5-7: Subjects receive single 5 mg FTY720 oral doses once daily.

Pharmacokinetic, pharmacodynamic and safety assessments are performed at specified times during the multiple-dose study. Subjects are released from the study center approximately 24 hours after the last drug administration on Day 7, after the safety evaluations have been completed (i.e., Day 8).

- Analytes, media and methods:

FTY720 is measured in whole blood using LC/MS/MS (LLOQ = 0.080 ng/mL)

- PK evaluations: Noncompartmental analysis to derive tmax, Cmax, AUC(0-24) on day 1. Peak and trough concentrations are summarized from days 2 through 7 to estimate drug accumulation and attainment of steady state.

Lymphocyte assessment

Blood samples for absolute lymphocyte counts is collected at screening, at initial baseline (Day -2), Day 1 (6h postdose), Day 3 (predose), Day 5 (predose) and Day 7 (predose).

The samples are analyzed for pharmacodynamics.

Above procedure may be repeated and the patients are then treated Day 5 and followings with a daily maintenance dose of 0.5mg/kg. The patients have lower steady-state blood levels.

Above procedure may be repeated with following loading treatments:

1. Day 1: Subjects receive a single 2.5 mg FTY720 oral dose at the exact time the Day –1 dose was administered.

   Days 2-4: Subject receive a single 5 mg FTY720 oral dose on Day 2, a single 7.5 mg FTY720 oral dose on Day 3, and a single 10 mg FTY720 oral dose on Day 4, in order to achieve the FTY720 steady-state concentration typically measured in patients on chronic dosing of FTY720 2.5 mg qd.

   Day 5-7 and following: Subjects receive single 2.5 mg FTY720 oral doses once daily.

2. Day 1: Subjects receive a single 1.25 mg FTY720 oral dose at the exact time the Day –1 dose was administered.

   Days 2-4: Subject receive a single 2.5 mg FTY720 oral dose on Day 2, a single 3.75 mg FTY720 oral dose on Day 3, and a single 5 mg FTY720 oral dose on Day 4, in order to achieve the FTY720 steady-state concentration typically measured in patients on chronic dosing of FTY720 1.25 mg qd.

   Day 5-7 and following: Subjects receive single 1.25 mg FTY720 oral doses once daily.

CLAIMS

1. Use of a S1P receptor modulator or agonist in the manufacture of a medication, whereby said medication is administered in such a way to a subject that a steady-state of the S1P receptor modulator or agonist blood levels is attained in less than a week.

2. Use of a S1P receptor modulator or agonist in the manufacture of a medication, whereby said medication is administered in such a way to a subject that a steady-state of the S1P receptor modulator or agonist blood levels is attained in less than a week, and thereafter the treatment is continued at a dosage lower than the standard daily dosage

3. Use according to claim 1 or 2, whereby the dosage of said S1P receptor modulator or agonist during the initial 3 to 6 days of treatment is increased stepwise up to the 3- to 21-fold standard daily dosage of said S1P receptor agonist.

4. Use according to claim 1, 2 or 3, whereby the initial period is 4 or 5 days.

5. A method for providing an S1P receptor agonist treatment, whereby said S1P receptor agonist is administered in such a way that during the initial 3 to 6 days of treatment the dosage is raised so that in total the R-fold standard daily dosage is administered and thereafter the treatment is continued with the standard daily dosage or with a daily dosage lower than the standard daily dosage.

6. A method for inhibiting graft rejection or treating an autoimmune disease or disorder in a subject in need thereof, comprising administering to the subject a S1 P receptor modulator or agonist in such a pharmaceutically effective amount that a steady-state of the S1P receptor agonist blood levels is attained in the subject in less than a week.

7. In a treatment method with a S1P receptor modulator or agonist, the improvement being that the S1P receptor modulator or agonist is administered in such a way that during the initial 3 to 6 days of treatment the dosage is raised so that in total the R-fold standard daily dosage is administered.

8. A method for inhibiting graft rejection or treating an autoimmune disease in a subject in need thereof, comprising administering to the subject, after a loading regimen, a S1 P receptor modulator or agonist at a daily dosage which is lower than the standard daily dosage.

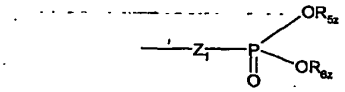
9. A kit containing daily units of medication of an S1P receptor agonist of varying daily dosage, whereby the daily dosage of said S1P receptor agonist for the initial 3 to 6 days of treatment is incrementally increased so that the total amount present in the daily units corresponds to the R-fold standard daily dosage of said S1P receptor agonist for this initial time period.

10. A kit containing daily units of medication of an S1P receptor modulator or agonist of varying daily dosage, whereby the daily dosage of S1P receptor modulator or agonist is ¼; ½; and ¾ of the highest instalment dose of the S1P receptor modulator or agonist; and 4x the maintenance dose of the S1P receptor modulator or agonist, respectively, and units for for the standard daily dosage of the S1P receptor modulator or agonist, or for the subsequent treatment with a daily dosage lower than the standard daily dosage.

11. Use, method or kit according to any of claims 1 to 11 wherein the S1P receptor modulator or agonist comprises a group of formula X

(X)

wherein Z is H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, phenyl, phenyl substituted by OH, C_{1-6}alkyl substituted by 1 to 3 substituents selected from the group consisting of halogen, C_{3-8}cycloalkyl, phenyl and phenyl substituted by OH, or CH_2-R_{4z} wherein R_{4z} is OH, acyloxy or a residue of formula (a)



(a)

wherein Z_1 is a direct bond or O, preferably O;
each of R_{5z} and R_{6z}, independently, is H, or C_{1-4}alkyl optionally substituted by 1, 2 or 3 halogen atoms;
R_{1z} is OH, acyloxy or a residue of formula (a); and each of R_{2z} and R_{3z} independently, is H, C_{1-4}alkyl or acyl.

12. Use, method or kit according to claim 13 wherein the S1P receptor modulator or agonist is 2-amino-2-[2-(4-octylphenyl) ethyl]propane-1,3-diol, 2-amino-2-[4-(3-benzyloxyphenoxy)-2-chlorophenyl]ethyl-1,3-propane-diol, 2-amino-2-[4-(benzyloxyphenylthio)-2-

chlorophenyl]ethyl-1,3-propane-diol or 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, in free form or in a pharmaceutically acceptable salt form.

INTERNATIONAL SEARCH REPORT

PCT/US2005/043044

A. CLASSIFICATION OF SUBJECT MATTER
A61K31/135 A61K31/397 A61P37/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SKERJANEC, A. ET AL: "Systemic exposure and preliminary efficacy of FTY720 in de novo renal transplant recipients" AM J TRANSPLANT (SUPPL. 3): ABST 964, vol. 2, 2002, XP002375195 USA the whole document	1-12
X	WO 03/061567 A (MERCK & CO., INC; DOHERTY, GEORGE, A; FORREST, MICHAEL, J; HAJDU, RICH) 31 July 2003 (2003-07-31) page 33, last paragraph; claims 1,13,14	1-12
X	US 2003/003099 A1 (LAKE PHILIP ET AL) 2 January 2003 (2003-01-02) paragraph [0051]	1-12

-/--

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 March 2006	13/04/2006

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Ansaldo, M

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

PCT/US2005/043044

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/062252 A (MERCK & CO., INC; BUGIANESI, ROBERT, L; DOHERTY, GEORGE, A; GENTRY, AM) 31 July 2003 (2003-07-31) cited in the application page 36, paragraph 3; claims 1,35,37	1-12
X	WO 02/100148 A (NOVARTIS AG; NOVARTIS-ERFINDUNGEN VERWALTUNGSGESELLSCHAFT M.B.H; LAKE,) 19 December 2002 (2002-12-19) page 8, paragraph 3	1-12

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

PCT/US2005/043044

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 5-8 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

PCT/US2005/043044

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 03061567	A	31-07-2003	CA	2472680 A1	31-07-2003
			EP	1469863 A2	27-10-2004
US 2003003099	A1	02-01-2003	NONE		
WO 03062252	A	31-07-2003	CA	2472715 A1	31-07-2003
			EP	1470137 A1	27-10-2004
			JP	2005515259 T	26-05-2005
WO 02100148	A	19-12-2002	BR	0209319 A	20-07-2004
			CA	2445605 A1	19-12-2002
			CN	1524002 A	25-08-2004
			EP	1429845 A2	23-06-2004
			JP	2004534788 T	18-11-2004
			PL	364359 A1	13-12-2004
			ZA	200307893 A	06-09-2004

VIII-3-1	**Declaration: Entitlement to claim priority** Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application specified below, where the applicant is not the applicant who filed the earlier application or where the applicant's name has changed since the filing of the earlier application (Rules 4.17(iii) and 51bis.1(a)(iii)) Name	in relation to this international application NOVARTIS AG is entitled to claim priority of earlier application No. 60/631,483 by virtue of the following:
VIII-3-1(iv)		an assignment from KOVARIK, John M. to NOVARTIS AG, dated 21 January 2005 (21.01.2005)
VIII-3-1(ix)	This declaration is made for the purposes of:	all designations

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference TX/4-34053A	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/US2005/043044	International filing date *(day/month/year)* 28 November 2005 (28.11.2005)	Priority date *(day/month/year)* 29 November 2004 (29.11.2004)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant NOVARTIS AG		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 30 May 2007 (30.05.2007)
The International Bureau of WIPO 34, chemin des Colombettes 121 I Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Yoshiko Kuwahara e-mail: pt07.pct@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

1/6

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below
International application No. PCT/US2005/043044	International filing date *(day/month/year)* 28.11.2005
Priority date *(day/month/year)* 29.11.2004	
International Patent Classification (IPC) or both national classification and IPC INV. A61K31/135 A61K31/397 A61P37/06	
Applicant NOVARTIS AG	

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Ansaldo, M Telephone No. +49 89 2399-7876

Form (PCT/ISA/237) (Cover Sheet) (January 2004)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2005/043044

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 5-8

because:

☒ the said international application, or the said claims Nos. 5-8 with respect to i.a. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-12
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-12
Industrial applicability (IA)	Yes:	Claims	1-4,9-12
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Claims 5-8 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

The documents cited in the International Search Report (ISR) are numbered D1-D5 in the order of their listing. Unless otherwise specified, reference is made to the passages cited in the search report.

1. Claims 1-12 do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claims attempt to define the subject-matter in terms of the result to be achieved ("is administered in such a way that a steady state of the S1P receptor modulator is attained in less than a week"), which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result.

2. Furthermore the above-mentioned lack of clarity notwithstanding, the subject-matter of claims 1-12 lacks novelty (Art. 33 (2) PCT) over D1.

   D1 discloses the use of a S1P receptor agonist, such as FTY720, for treating graft rejection, which is administered at a loading dose of 1,2,4 mg followed by 0.25, 0.5, 1 or 2.5 mg once daily maintenance dose.
   This corresponds to the dosage regimen described in the examples on pages 18-19 of the present application.

3. Even by overcoming the above-mentioned novelty objection (Art. 33 (1) PCT) for claims 1-12 with the introduction of new embodiments, no inventiveness (Art. 33 (3) PCT) will be acknowledged for the following reasons:

   The problem to be solved by the present application is not identified in the description. The description in fact only refers to the provision of "further unexpected benefits".

This cannot be considered a technical problem to be solved by the skilled person.

Furthermore the application does not provide any clinical data showing that the selected dosage regimen solves a problem or provides any advantages over FTY720 compositions already used and known in the art for inhibiting graft rejection (see documents D1-D5).

4. For the assessment of the present claims 5-8 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

1/6

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2005/043044	28.11.2005	29.11.2004

International Patent Classification (IPC) or both national classification and IPC
INV. A61K31/135 A61K31/397 A61P37/06

Applicant
NOVARTIS AG

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Ansaldo, M Telephone No. +49 89 2399-7876

Form (PCT/ISA/237) (Cover Sheet) (January 2004)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2005/043044

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ in written format

      ☐ in computer readable form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in computer readable form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 5-8

because:

☒ the said international application, or the said claims Nos. 5-8 with respect to i.a. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-12
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-12
Industrial applicability (IA)	Yes:	Claims	1-4,9-12
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Claims 5-8 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

The documents cited in the International Search Report (ISR) are numbered D1-D5 in the order of their listing. Unless otherwise specified, reference is made to the passages cited in the search report.

1. Claims 1-12 do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claims attempt to define the subject-matter in terms of the result to be achieved ("is administered in such a way that a steady state of the S1P receptor modulator is attained in less than a week"), which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result.

2. Furthermore the above-mentioned lack of clarity notwithstanding, the subject-matter of claims 1-12 lacks novelty (Art. 33 (2) PCT) over D1.

   D1 discloses the use of a S1P receptor agonist, such as FTY720, for treating graft rejection, which is administered at a loading dose of 1,2,4 mg followed by 0.25, 0.5, 1 or 2.5 mg once daily maintenance dose.
   This corresponds to the dosage regimen described in the examples on pages 18-19 of the present application.

3. Even by overcoming the above-mentioned novelty objection (Art. 33 (1) PCT) for claims 1-12 with the introduction of new embodiments, no inventiveness (Art. 33 (3) PCT) will be acknowledged for the following reasons:

   The problem to be solved by the present application is not identified in the description. The description in fact only refers to the provision of "further unexpected benefits".

This cannot be considered a technical problem to be solved by the skilled person.

Furthermore the application does not provide any clinical data showing that the selected dosage regimen solves a problem or provides any advantages over FTY720 compositions already used and known in the art for inhibiting graft rejection (see documents D1-D5).

4. For the assessment of the present claims 5-8 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

CASE 34053-US-PCT

FILING BY "EXPRESS MAIL" UNDER 37 CFR 1.10	
Express Mail Label Number	Date of Deposit

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE PCT NATIONAL STAGE APPLICATION OF
KOVARIK ET AL.
INTERNATIONAL APPLICATION NO: PCT/US2005/043044
FILED: 28 NOVEMBER 2005
U.S. APPLICATION NO: 11/720,205
35 USC §371 DATE: 25 MAY 2007
FOR: DOSAGE REGIMEN OF AN S1P RECEPTOR AGONIST

Art Unit: NYA
Examiner: NYA

MS: Amendment
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

SECOND PRELIMINARY AMENDMENT

Sir:

Prior to the examination of the above-referenced patent application, please enter the following preliminary amendments.

Amendments to the Claims are reflected in the listing of the claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 6 of this paper.

Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

Claim 1. (Currently amended) ~~Use of a S1 P receptor modulator or agonist in the manufacture of a medication, whereby said medication is administered in such a way to a subject~~ A method for inhibiting graft rejection or treating an inflammatory or autoimmune disease or disorder in a subject in need thereof, comprising administering to the subject a S1P receptor modulator or agonist in such a pharmaceutically effective amount that a steady-state of the S1P receptor modulator or agonist blood levels is attained in the subject in less than a week.

Claim 2. (Currently amended) ~~Use of a S1P receptor modulator or agonist in the manufacture of a medication, whereby said medication is administered in such a way to a subject~~ A method for inhibiting graft rejection or treating an inflammatory or autoimmune disease or disorder in a subject in need thereof, comprising administering to the subject an S1P receptor modulator or agonist in such a pharmaceutically effective amount that a steady-state of the S1P receptor modulator or agonist blood levels is attained in less than a week, and thereafter the treatment is continued at a dosage lower than the standard daily dosage

Claim 3. (Currently amended) The method of claim 1 ~~Use according to claim 1~~, whereby the dosage of said S1 P receptor modulator or agonist during the initial 3 to 6 days of treatment is increased stepwise up to the 3- to 21-fold standard daily dosage of said S1P receptor agonist

Claim 4. (Currently amended) The method of claim 1 ~~Use according to claim 1~~, whereby the initial period is 4 or 5 days.

Claim 5. (Currently amended) ~~A method for providing an S1P receptor agonist treatment, whereby said S1P receptor agonist is administered in such a way~~ A method for inhibiting graft rejection or treating an inflammatory or autoimmune disease or disorder in a subject in need thereof, comprising administering to the subject an S1P receptor modulator or agonist in such a pharmaceutically effective amount that during the initial 3 to 6 days of treatment the dosage is raised so that in total the R-fold standard daily dosage is administered and

thereafter the treatment is continued with the standard daily dosage or with a daily dosage lower than the standard daily dosage.

Claim 6. (Canceled)

Claim 7. (Currently amended) ~~In a treatment method with a S1P receptor modulator or agonist, the improvement being that the S1P receptor modulator or agonist is administered in such a way~~ A method for inhibiting graft rejection or treating an inflammatory or autoimmune disease or disorder in a subject in need thereof, comprising administering to the subject an S1P receptor modulator or agonist in such a pharmaceutically effective amount that during the initial 3 to 6 days of treatment the dosage is raised so that in total the R-fold standard daily dosage is administered.

Claim 8. (Currently amended) A method for inhibiting graft rejection or treating an inflammatory or autoimmune disease in a subject in need thereof, comprising administering to the subject, after a loading regimen, a S1P receptor modulator or agonist at a daily dosage which is lower than the standard daily dosage.

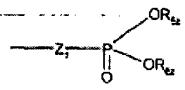
Claim 9. (Currently amended) A kit containing daily units of medication of an S1P receptor modulator or agonist of varying daily dosage, whereby the daily dosage of said S1P receptor modulator or agonist for the initial 3 to 6 days of treatment is incrementally increased so that the total amount present in the daily units corresponds to the R-fold standard daily dosage of said S1P receptor modulator or agonist for this initial time period.

Claim 10. (Currently amended) A kit containing daily units of medication of an S1P receptor modulator or agonist of varying daily dosage, whereby the daily dosage of S1P receptor modulator or agonist for the initial 4 days of treatment is ¼; ½; and ¾ of the highest installment ~~instalment~~ dose of the S1P receptor modulator or agonist; and 4x the maintenance dose of the S1P receptor modulator or agonist, respectively~~, and units for for the standard daily dosage of the S1P receptor modulator or agonist, or for the subsequent treatment with a daily dosage lower than the standard daily dosage~~.

Claim 11. (Currently amended) ~~Use,~~ The method ~~or kit according to~~ of claim 1, wherein the S1P receptor modulator or agonist comprises a group of formula X

(X)

wherein Z is H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, phenyl, phenyl substituted by OH, C_{1-6} alkyl substituted by 1 to 3 substituents selected from the group consisting of halogen, C_{3-8} cycloalkyl, phenyl and phenyl substituted by OH, or CH_2-R_{4Z} wherein R_{4Z} is OH, acyloxy or a residue of formula (a)



(a)

wherein Z_1 is a direct bond or O, preferably O; each of R_{5Z} and R_{6Z}, independently, is H, or C_{1-4}alkyl optionally substituted by 1, 2 or 3 halogen atoms;
R_{1Z} is OH, acyloxy or a residue of formula (a); and each of R_{2Z} and R_{3Z} independently, is H, C_{1-4}alkyl or acyl; in free form or the isomers, phosphates, prodrugs or pharmaceutically acceptable salts thereof.

Claim 12. (Currently amended) ~~Use,~~ The method ~~or kit according to~~ of claim 1, [[13]] wherein the S1P receptor modulator or agonist is 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol, 2-amino-2-[4-(3-benzyloxyphenoxy)-2-chlorophenyl]ethyl-1,3-propane-diol, 2-amino-2-[4-(benzyloxyphenylthio)-2-chlorophenyl]ethyl-1,3-propane-diol or 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, in free form or the isomers, phosphates, prodrugs or pharmaceutically acceptable salts thereof ~~in a pharmaceutically acceptable salt form~~.

Claim 13. (New) The method of claim 1 wherein the S1P receptor modulator or agonist is 2-amino-2-tetradecyl-1,3-propanediol, 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol2-amino-2-{2-[4-(1-oxo-5-phenylpentyl)phenyl]ethyl}propane-1,3-diol, 2-amino-4-(4-heptyloxyphenyl)-2-methyl-butanol, phosphoric acid mono-[(R)-2~amino-2-methyl-4-(4-pentyloxy-phenyl)-butyl]ester, (2R)~2-amino-4-[3-(4-cyclohexyloxybutyl)- benzo[b]thien-6-yl]-2-methylbutan-1-ol, 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl- benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, in free form or the isomers, phosphates, prodrugs or pharmaceutically acceptable salts thereof.

Claim 14. (New) The method of claim 1, wherein the dosage is from 0.1 – 20 mg.

Claim 15. (New) The method of claim 1, wherein the dosage is from 0.1 – 0.5mg

Claim 16. (New) The method of claim 1, wherein the autoimmune disease is selected from the group consisting of multiple sclerosis, lupus nephritis, rheumatoid arthritis, inflammatory bowel diseases and psoriasis.

REMARKS/ARGUMENTS

Upon entry of the foregoing claim amendments, claims 1 to 5 and 7 to 16 will be pending. Claims 1 to 5, 7 to 12 are amended, without prejudice, to place the claims in better form. Claim 6 has been canceled, without prejudice. New claims 13 to 16 have been added, and are supported in the specification as filed, in particular on pages 13 to 15. No new matter has been added. Should the Examiner have any questions, please contact the undersigned attorney.

Respectfully submitted,

Novartis
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East Hanover, NJ 07936-1080
(862) 778-9273

Cozette M. McAvoy
Attorney for Applicants
Reg. No. 60,457

Date: 9th October 2007

Electronic Acknowledgement Receipt

EFS ID:	2289694
Application Number:	11720205
International Application Number:	
Confirmation Number:	5868
Title of Invention:	DOSAGE REGIMEN OF AN S1P RECEPTOR AGONIST
First Named Inventor/Applicant Name:	John M Kovarik
Customer Number:	1095
Filer:	Cozette Marie McAvoy/Cindy Klepacky
Filer Authorized By:	Cozette Marie McAvoy
Attorney Docket Number:	34053-US-PCT
Receipt Date:	08-OCT-2007
Filing Date:	
Time Stamp:	12:54:37
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes) /Message Digest	Multi Part /.zip	Pages (if appl.)
1		34053.pdf	192511 d662ed1b69c028717f2635792 4f83b2275634902	yes	6

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Preliminary Amendment	1	1
	Claims	2	5
	Applicant Arguments/Remarks Made in an Amendment	6	6
Warnings:			
Information:			
	Total Files Size (in bytes):	192511	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 11/720,205	Filing Date 05/25/2007	☐ To be Mailed

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☐		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

		(Column 1)		(Column 2)	(Column 3)	SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
	05/25/2007	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
AMENDMENT	Total (37 CFR 1.16(i))	* 12	Minus	** 20	= 0	X $ =		OR	X $50=	0
	Independent (37 CFR 1.16(h))	* 8	Minus	***8	= 0	X $ =		OR	X $200=	0
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	**0**

		(Column 1)		(Column 2)	(Column 3)					
	10/08/2007	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
AMENDMENT	Total (37 CFR 1.16(i))	* 16	Minus	** 20	= 0	X $ =		OR	X $50 =	0
	Independent (37 CFR 1.16(h))	* 7	Minus	*** 8	= 0	X $ =		OR	X $210 =	0
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	**0**

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/ADRIENE D. SELLMAN/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

FILING BY "EXPRESS MAIL" UNDER 37 CFR 1.10	
Express Mail Label Number	Date of Deposit

Form PTO-1390-MOD (REV 10-96) U. S. Department of Commerce Patent and Trademark Office		ATTORNEY'S DOCKET NUMBER 34053-US-PCT
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		U.S. APPLICATION NO. (If known, see 37 CFR 1.5)
INTERNATIONAL APPLICATION NO. PCT/US2005/043044	INTERNATIONAL FILING DATE 28 November 2005 (28.11.05)	PRIORITY DATE CLAIMED 29 November 2004 (29.11.04)
TITLE OF INVENTION DOSAGE REGIMEN OF AN S1P RECEPTOR AGONIST		
APPLICANT(S) FOR DO/EO/US KOVARIK ET AL.		

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☐ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau. (See Form PCT/IB/308)
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C.371(c)(3)).
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. ☒ An executed Declaration and Power of Attorney (original or copy) (35 U.S.C. 371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included.

11. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.

12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

13. ☒ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.

14. ☒ An Application Data Sheet under 37 CFR 1.76.

15. ☐ A substitute specification.

16. ☐ A change of power of attorney and/or address letter.

17. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13*ter*.2 and 37 CFR 1.821-1.825.

18. ☐ A second copy of the published International Application under 35 U.S.C. 154(d)(4).

19. ☐ A second copy of the English language translation of the International application under 35 U.S.C. 154(d)(4).

20. ☐ Other items or information:

U.S. APPLICATION NO. (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
	PCT/US2005/043044	34053-US-PCT

The following fees are submitted:

CALCULATIONS PTO USE ONLY

21. ☒ Basic national fee. $300

22. Examination Fee
- ☐ If International preliminary examination report was prepared by USPTO and all claims satisfy provisions of PCT Article 33(1)-(4) . . . . . $
- ☒ All other situations. $200

23. Search fee
- ☐ If Search fee (37 CFR 1.445(a)(2)) has been paid on the international application to the USPTO as an International Searching Authority. . . . . $
- ☒ If International Search Report was prepared and provided to the Office. . . $400
- ☐ All other situations. . . . . $

TOTAL OF 21, 22 AND 23 = $ 900

Additional fee for specification and drawings filed in paper over 100 sheets (excluding sequence listing or computer program listing filed in an electronic medium). The fee is **$250** for each additional 50 sheets of paper or fraction thereof.

Total Sheets	Extra sheets		Number of each additional 50 or fraction thereof (round **up** to a whole number)	RATE	
22 - 100 =		/50 =	0	X $ 250	$

Surcharge of **$130** for furnishing the oath of declaration later than ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)). $

CLAIMS	NUMBER FILED		NUMBER EXTRA	RATE	
Total claims	12	- 20 =	0	X $ 50	$
Independent claims	8	- 3 =	5	X $ 200	$ 1,000
MULTIPLE DEPENDENT CLAIM(S) (if applicable)				+ $ 360	$
			TOTAL OF ABOVE CALCULATIONS =		$ **1,900**

Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28). $

SUBTOTAL = $ **1,900**

Processing fee of **$130** for furnishing the English translation later than ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)). + $

TOTAL NATIONAL FEE = $ **1,900**

Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40** per property + $

TOTAL FEES ENCLOSED = $ **1,900**

Amount to be: refunded $

charged $

a. ☐ A check in the amount of $_____ to cover the above fees is enclosed.

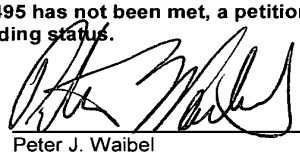
b. ☒ Please charge Deposit Account No. 19-0134 in the name of Novartis in the amount of $1,900 to cover the above fees. A duplicate copy of this form is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 19-0134 in the name of Novartis.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

Send all correspondence to the address associated with Customer No. 001095, which is currently:

Novartis
Corporate Intellectual Property
One Health Plaza, Building 104
East Hanover, NJ 07936-1080



Peter J. Waibel
Attorney for Applicants
Reg. No. 43,228
(862) 778-7951

US Case **TX/4-34053A**

DECLARATION AND POWER OF ATTORNEY FOR UNITED STATES PATENT APPLICATION

☐ Original ☐ Supplemental ☐ Substitute

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name, and

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if more than one name is listed below) of the subject matter which is claimed and for which a United States patent is sought on the invention entitled

DOSAGE REGIMEN OF AN S1P RECEPTOR AGONIST

the specification of which:

☐ is attached hereto.

☐ was filed on _____ (day/month/year) as Application No. _____

and, if this box (☐) contains an *

☐ was amended on _____ (day/month/year)

☒ was filed as Patent Cooperation Treaty international Application No.

PCT/US 2005/043044 on **28 November 2005** (day/month/year)

and, if this box (☐) contains an *

☐ entered the national stage in the United States and was accorded Application No.

_____

and, if this box (☐) contains an *

☐ was amended, subsequent to entry into the national stage, on _____ (day/month/year)

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment(s) specifically referred to above and, if this application was filed as a Patent Cooperation Treaty international application, by any amendments made during the international stage (including any made under Patent Cooperation Treaty Rule 91, Article 19 and Article 34).

I acknowledge my duty to disclose information which is material to patentability as defined in 37 C.F.R. 1.56, including, for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or Patent Cooperation Treaty international filing date of the continuation-in-part application.

I hereby claim the benefit under 35 U.S.C. 119(a)-(d) or (f) or 365(b) of any foreign application(s) for patent, inventor's certificate or plant breeder's right certificate listed below and under 35 U.S.C. 365(a) of any Patent Cooperation Treaty international application(s) designating at least one country other than the United States listed below and have also listed below any foreign application(s) for patent, inventor's certificate or plant breeder's right certificate and Patent Cooperation Treaty international application(s) designating at least one country other than the United States for the same subject matter and having a filing date before that of the application the priority of which is claimed for that subject matter:

COUNTRY/REGION (OR P.C.T.)	APPLICATION No.	FILING DATE (day/month/year)	PRIORITY CLAIMED
			☐ Yes ☐ No
			☐ Yes ☐ No
			☐ Yes ☐ No
			☐ Yes ☐ No
			☐ Yes ☐ No

I hereby claim the benefit under 35 U.S.C. 119(e) of any United States provisional application(s) listed below:

APPLICATION NO.	FILING DATE (day/month/year)
60/631,483	**29 November 2004**

I hereby claim the benefit under 35 U.S.C. 120 of any United States application(s) listed below and under 35 U.S.C. 365(c) of any Patent Cooperation Treaty international application(s) designating the United States listed below:

United States Application No.	United States Filing Date (day/month/year)	Status (Pending, Abandoned or U.S. Patent No.)	International Application No. and Filing Date (day/month/year)

US Case **TX/4-34053A**

I hereby appoint all of the registered practitioners associated with Customer No. 001095, respectively and individually, as my attorneys and agents, with full power of substitution and revocation, to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith.

If this box (☐) contains an x ☒, I hereby authorize the registered practitioners associated with Customer No. 001095 and any others acting on my behalf to take any action relating to this application based on communications from Corporate Intellectual Property of Novartis International AG, Basle, Switzerland, or an affiliate thereof or a successor thereto, without direct communication from me.

Please send all correspondence relating to this application to the address associated with Customer No. 001095.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Full name of sole or first joint inventor: **John M. KOVARIK**

Inventor's signature: John M. K... Date: 25 Aug 2006 (day/month/year)

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Inventor's signature: S Appel-Dingemanse Date: 25-Aug-06 (day/month/year)

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IMPORTANT: Before this declaration is signed, the patent application (the specification, the claims and this declaration) must be read and understood by each person signing it, and no changes may be made in the application after this declaration has been signed.

CASE 34053-US-PCT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE PCT NATIONAL STAGE APPLICATION OF
KOVARIK ET AL.
INTERNATIONAL APPLICATION NO: PCT/US2005/043044
FILED: 28 NOVEMBER 2005
U.S. APPLICATION NO: NOT YET KNOWN
35 USC §371 DATE:
FOR: DOSAGE REGIMEN OF AN S1P RECEPTOR AGONIST

MS: Amendment
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT

Sir:

This paper is being filed within three months of the date of entry of the national stage as set forth in 37 C.F.R. §1.491 of the international application. Therefore, no fees are required. If a fee is deemed to be required, the Commissioner is hereby authorized to charge such fee to Deposit Account No. 19-0134.

In accordance with 37 C.F.R. §1.56, applicants wish to call the Examiner's attention to the references cited on the attached form(s) PTO-1449.

The listed references were cited in the international stage search report. Since these references are of record in the instant PCT application PCT/US2005/043044, copies are not enclosed herewith.

The Examiner is requested to consider the foregoing information in relation to this application and indicate that each reference was considered by returning a copy of the initialed PTO 1449 form(s).

Respectfully submitted,

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Peter J. Waibel
Attorney for Applicants
Reg. No. 43,228

Date: 5/25/07

FORM PTO-1449 (REV. 7-85) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

INFORMATION DISCLOSURE CITATION

(Use several sheets if necessary)

ATTY. DOCKET NO. 34053-US-PCT
APPLICATION NO.

APPLICANT KOVARIK ET AL.
FILING DATE Group

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE
	AA	2003/003099	1/2/03	Lake et al.	424	145.1	6/7/02
	AB						
	AC						
	AD						
	AE						
	AF						
	AG						
	AH						
	AI						
	AJ						
	AK						
	AL						

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	OFFICE	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
	AM	03/061567	7/31/03	WO			☐	☐
	AN	03/062252	7/31/03	WO			☐	☐
	AO	02/100148	12/19/02	WO			☐	☐
	AP						☐	☐
	AQ						☐	☐

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent pages, Etc.)

	AR	Skerjanec A. et al., "Systemic exposure and preliminary efficacy of FTY720 in de novo renal transplant recipients", Am J Transplant (Suppl. 3): ABST 964, Vol. 2, (2002).
	AS	
	AT	

EXAMINER	DATE CONSIDERED

*EXAMINER: Initial of reference considered, whether or not citation is in conformance with MPEP 609: Draw a line through citation if not in conformance and not considered. Include a copy of this form with the next communication to applicant.

CASE 34053-US-PCT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE PCT NATIONAL STAGE APPLICATION OF
KOVARIK ET AL.
INTERNATIONAL APPLICATION NO: PCT/US2005/043044
FILED: 28 NOVEMBER 2005
U.S. APPLICATION NO: Not Yet Known
35 USC §371 DATE: Herewith
FOR: DOSAGE REGIMEN OF AN S1P RECEPTOR AGONIST

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

PRELIMINARY AMENDMENT

Sir:

Prior to the examination of the above-referenced patent application, please enter the following preliminary amendments.

Amendments to the Specification begin on page 2 of this paper.

Amendments to the Claims are reflected in the listing of the claims which begins on page 4 of this paper.

Remarks/Arguments begin on page 6 of this paper.

Amendments to the Specification:

Please insert the following as the first paragraph beneath the title on page 1:

--This application claims benefit of U.S. Provisional Application No. 60/631,483, filed November 29, 2004, which in its entirety is herein incorporated by reference.--

A copy of the abstract is herein provided on the following separate sheet.

Abstract

S1P receptor modulators or agonists are administered following a dosage regimen whereby during the initial 3 to 6 days of treatment the daily dosage is raised so that in total the R-fold (R being the accumulation factor) standard daily dosage is administered and thereafter continued at the standard daily dosage or at a daily dosage lower than the standard daily dosage.

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

Claim 1. (Original): Use of a S1P receptor modulator or agonist in the manufacture of a medication, whereby said medication is administered in such a way to a subject that a steady-state of the S1P receptor modulator or agonist blood levels is attained in less than a week.

Claim 2. (Original): Use of a S1P receptor modulator or agonist in the manufacture of a medication, whereby said medication is administered in such a way to a subject that a steady-state of the S1P receptor modulator or agonist blood levels is attained in less than a week, and thereafter the treatment is continued at a dosage lower than the standard daily dosage

Claim 3. (Currently amended): Use according to claim 1 ~~or 2~~, whereby the dosage of said S1P receptor modulator or agonist during the initial 3 to 6 days of treatment is increased stepwise up to the 3- to 21-fold standard daily dosage of said S1P receptor agonist.

Claim 4. (Currently amended): Use according to claim 1, ~~2 or 3,~~ whereby the initial period is 4 or 5 days.

Claim 5. (Original): A method for providing an S1P receptor agonist treatment, whereby said S1P receptor agonist is administered in such a way that during the initial 3 to 6 days of treatment the dosage is raised so that in total the R-fold standard daily dosage is administered and thereafter the treatment is continued with the standard daily dosage or with a daily dosage lower than the standard daily dosage.

Claim 6. (Original): A method for inhibiting graft rejection or treating an autoimmune disease or disorder in a subject in need thereof, comprising administering to the subject a S1 P receptor modulator or agonist in such a pharmaceutically effective amount that a steady-state of the S1P receptor agonist blood levels is attained in the subject in less than a week.

Claim 7. (Original): In a treatment method with a S1P receptor modulator or agonist, the improvement being that the S1P receptor modulator or agonist is administered in such a way that during the initial 3 to 6 days of treatment the dosage is raised so that in total the R-fold standard daily dosage is administered.

Claim 8. (Original): A method for inhibiting graft rejection or treating an autoimmune disease in a subject in need thereof, comprising administering to the subject, after a loading regimen, a S1 P receptor modulator or agonist at a daily dosage which is lower than the standard daily dosage.

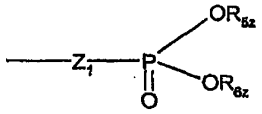
Claim 9. (Original): A kit containing daily units of medication of an S1P receptor agonist of varying daily dosage, whereby the daily dosage of said S1P receptor agonist for the initial 3 to 6 days of treatment is incrementally increased so that the total amount present in the daily units corresponds to the R-fold standard daily dosage of said S1P receptor agonist for this initial time period.

Claim 10. (Original): A kit containing daily units of medication of an S1P receptor modulator or agonist of varying daily dosage, whereby the daily dosage of S1P receptor modulator or agonist is ¼; ½; and ¾ of the highest instalment dose of the S1P receptor modulator or agonist; and 4x the maintenance dose of the SI P receptor modulator or agonist, respectively, and units for for the standard daily dosage of the S1P receptor modulator or agonist, or for the subsequent treatment with a daily dosage lower than the standard daily dosage.

Claim 11. (Currently amended): Use, method or kit according to claim 1 ~~any of claims 1 to 11~~ wherein the S1P receptor modulator or agonist comprises a group of formula X

(X)

wherein Z is H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, phenyl, phenyl substituted by OH, C_{1-6}alkyl substituted by 1 to 3 substituents selected from the group consisting of halogen, C_{3-8}cycloalkyl, phenyl and phenyl substituted by OH, or CH_2-R_{4Z} wherein R_{4Z} is OH, acyloxy or a residue of formula (a)



(a)

wherein Z_1 is a direct bond or O, preferably O;
each of R_{5Z} and R_{6Z}, independently, is H, or C_{1-4}alkyl optionally substituted by 1, 2 or 3 halogen atoms; R_{1Z} is OH, acyloxy or a residue of formula (a); and each of R_{2Z} and R_{3Z} independently, is H, C_{1-4}alkyl or acyl.

Claim 12. (Original): Use, method or kit according to claim 13 wherein the S1P receptor modulator or agonist is 2-amino-2-[2-(4-octylphenyl) ethyl]propane-1,3-diol, 2-amino-2-[4-(3-benzyloxyphenoxy)-2-chlorophenyl]ethyl-1,3-propane-diol, 2-amino-2-[4-(benzyloxyphenylthio)-2-chlorophenyl]ethyl-1,3-propane-diol or 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, in free form or in a pharmaceutically acceptable salt form.

REMARKS/ARGUMENTS

The foregoing amendments to the specification are to place the Abstract on a separate sheet. The amendments to the claims are to place the claims in better form and remove multiple dependencies. No new matter has been added. Should the Examiner have any questions, please contact the undersigned attorney.

Respectfully submitted,

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Date: 5/25/07

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CORRESPONDENCE INFORMATION

Correspondence Customer Number:: 0010905
Fax One:: 973-781-8064

APPLICATION INFORMATION

Title Line One:: DOSAGE REGIMEN OF AN S1P RECEPTOR AGONIS
Title Line Two:: T
Total Drawing Sheets:: 0
Formal Drawings?:: No
Application Type:: Utility
Docket Number:: 34053-US-PCT
Secrecy Order in Parent Appl.?:: No

REPRESENTATIVE INFORMATION

Representative Customer Number:: 1095

CONTINUITY INFORMATION

This application is a:: 371 OF
> Application One:: PCT/US05/043044
Filing Date:: 11-28-2005

Which is a:: claims benefit of
>> Application Two:: 60/631,483
Filing Date:: 11-29-2004

Source:: PrintEFS Version 2.0

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	DOSAGE REGIMEN OF AN S1P RECEPTOR AGONIST
First Named Inventor/Applicant Name:	John M Kovarik
Filer:	Peter J. Waibel/Cindy Klepacky
Attorney Docket Number:	34053-US-PCT

Filed as Large Entity

U.S. National Stage under 35 USC 371 Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
National Stage Fee	1631	1	300	300
Natl Stage Search Fee - Report provided	1642	1	400	400
National Stage Exam - all other cases	1633	1	200	200
Pages:				
Claims:				
Independent claims in excess of 3	1614	5	200	1000
Miscellaneous-Filing:				
Petition:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**1900**

Electronic Acknowledgement Receipt

EFS ID:	1810877
Application Number:	11720205
International Application Number:	PCT/EP05/43044
Confirmation Number:	5868
Title of Invention:	DOSAGE REGIMEN OF AN S1P RECEPTOR AGONIST
First Named Inventor/Applicant Name:	John M Kovarik
Customer Number:	01095
Filer:	Peter J. Waibel/Cindy Klepacky
Filer Authorized By:	Peter J. Waibel
Attorney Docket Number:	34053-US-PCT
Receipt Date:	25-MAY-2007
Filing Date:	
Time Stamp:	09:56:24
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment was successfully received in RAM	$1900
RAM confirmation Number	3564
Deposit Account	190134
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.16 and 1.17	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)	Multi Part /.zip	Pages (if appl.)
1		34053-US-PCT.pdf	519344	yes	16

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Transmittal of New Application	1	2
	Oath or Declaration filed	3	5
	Information Disclosure Statement (IDS) Filed	6	8
	Preliminary Amendment	9	10
	Abstract	11	11
	Claims	12	13
	Applicant Arguments/Remarks Made in an Amendment	14	14
	Application Data Sheet	15	16

Warnings:					
Information:					
2	Fee Worksheet (PTO-06)	fee-info.pdf	8540	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	527884		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.