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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/303,765	12/08/2008	Peter C. Hiestand	50279-US-PCT	9401

1095 7590 06/14/2011

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

EXAMINER	
SPIVACK, PHYLLIS G	
ART UNIT	**PAPER NUMBER**
1629	

MAIL DATE	DELIVERY MODE
06/14/2011	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.

Notice of Abandonment	Application No.	Applicant(s)	
	12/303,765	HIESTAND ET AL.	
	Examiner	Art Unit	
	PHYLLIS SPIVACK	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 *29 November 2010*.
   (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:

On May 31, 2011 Applicants' representative, Karen DeBenedictis, filed a request for a continuation of application S.N. 12/303,765.

/Phyllis G. Spivack/
Primary 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 PAT050279-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 — Art Unit: 1614

Hiestand, Peter C. et al. — Examiner: Spivack, Phyllis G

INTERNATIONAL APPLICATION NO: PCT/EP07/005597

FILED: June 25, 2007

U.S. APPLICATION NO: 12/303765

35 USC §371 DATE: December 08, 2008

FOR: S1P Receptor Modulators for Treating Multiple Sclerosis

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

PETITION FOR EXTENSION OF TIME

Sir:

The Office Action of November 29, 2010 has a shortened statutory time set to expire on February 28, 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 $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,

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: 5/31/11

Electronic Patent Application Fee Transmittal

Application Number:	12303765
Filing Date:	08-Dec-2008
Title of Invention:	S1P RECEPTOR MODULATORS FOR TREATING MULTIPLE SCLEROSIS
First Named Inventor/Applicant Name:	Peter C. Hiestand
Filer:	Karen DeBenedictis/Denise Cooper
Attorney Docket Number:	50279-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	004 1253	1	1110	1110

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
		Total in USD ($)		**1110**

Electronic Acknowledgement Receipt	
EFS ID:	10198772
Application Number:	12303765
International Application Number:	
Confirmation Number:	9401
Title of Invention:	S1P RECEPTOR MODULATORS FOR TREATING MULTIPLE SCLEROSIS
First Named Inventor/Applicant Name:	Peter C. Hiestand
Customer Number:	01095
Filer:	Karen DeBenedictis/Denise Cooper
Filer Authorized By:	Karen DeBenedictis
Attorney Docket Number:	50279-US-PCT
Receipt Date:	31-MAY-2011
Filing Date:	08-DEC-2008
Time Stamp:	16:55:22
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	$1110
RAM confirmation Number	4054
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. 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)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

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	50279_Ext.pdf	33432 0cbeb0db6dc632a778e30d2db6fde0e5c1d0e7df	no	1
Warnings:					
Information:					
2	Fee Worksheet (PTO-875)	fee-info.pdf	30465 54afa82a8c17aedd0a9c1310a78a56cd1a528165	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	63897		

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.

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12/303,765	12/08/2008	Peter C. Hiestand	50279-US-PCT	9401

1095 7590 11/29/2010

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EXAMINER	
SPIVACK, PHYLLIS G	
ART UNIT	**PAPER NUMBER**
1614	

MAIL DATE	DELIVERY MODE
11/29/2010	PAPER

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

Office Action Summary	Application No.	Applicant(s)	
	12/303,765	HIESTAND ET AL.	
	Examiner	Art Unit	
	Phyllis G. Spivack	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 *14 September 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) *4-14* is/are pending in the application.

4a) Of the above claim(s) *10,11,13 and 14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-9 and 12* is/are rejected.

7)☐ Claim(s) _____ 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 *12/8/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Applicants' Preliminary Amendment filed December 8, 2008 is acknowledged. Updated priority information and a new Abstract are noted. New claims 12-14 are presented. Claims 1-3 are canceled. Accordingly, claims 4-14 are pending.

An Information Disclosure Statement filed December 8, 2008 is further acknowledged and has been considered.

In response to a Species Requirement, Applicants elected the compound 2-amino-2-[2-(4-octylphenyl)ethyl]propane-l,3-diol (also referred to as "FTY720"), in free form or in a pharmaceutically acceptable salt or hydrate form, as the species of S1P receptor modulator. Applicants further elected multiple sclerosis (MS) as the species of demyelinating disease. Because Applicants 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)).

Thus the subject matter initially under consideration is drawn to methods for preventing, inhibiting or treating neo-angiogenesis associated with a demyelinating disease in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of an S1P receptor modulator, wherein the demyelinating disease is multiple sclerosis, and, 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, and a pharmaceutical combination comprising a) a first agent which is a SIP receptor modulator, i.e., FTY 720, in free form or in pharmaceutically acceptable salt form, and b) a VEGF-receptor antagonist, claims 4-9 and 12. Those methods drawn to treating neo-angiogenesis

associated with demyelinating diseases in a subject in need thereof other than multiple sclerosis and S1P receptor modulators or agonists other than FTY720, as well as claims 10, 11, 13 and 14, are presently withdrawn from consideration by the Examiner, 37 CFR 1.142(b), as drawn to non-elected inventions. Re-affirmation of the elections is requested when Applicants respond to this Office Action.

The abstract of the disclosure is objected to because the subject matter under consideration excludes methods of prevention. Correction is required. See MPEP § 608.01(b).

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 4 and 5 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 Applicants regard as the invention.

Claim 4 recites the limitation "medicament." There is insufficient antecedent basis for this limitation in independent claim 7 from which claim 4 depends.

Claim 5, drawn to a pharmaceutical composition, does not properly further limit the subject matter of claim 7 which is drawn to a method of treatment.

Correction is required.

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 4-9 and 12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention. The claims are directed to treating, preventing or inhibiting neo-angiogenesis associated with the demyelinating disease multiple sclerosis. On page 13 of the specification, the administration of Compound A, a S1P receptor modulator, is described as blocking disease-associated neo-angiogenesis, as well as inhibiting the relapse phases of multiple sclerosis in an animal assay. The present specification does not reasonably provide enablement for methods of prevention, within the full scope of the claims.

To be enabling, the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir., 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman*, 230 USPQ 546 (Bd. Apls. 1986) at 547,

the court recited eight factors to consider when assessing whether or not a disclosure would require undue experimentation. These factors are:

1) the quantity of experimentation necessary

2) the amount of direction or guidance provided

3) the presence or absence of working examples

4) the nature of the invention

5) the state of the art

6) the relative skill of those in the art

7) the predictability of the art and

8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

The nature of the invention, state of the prior art, relative skill of those in the art and the predictability of the art

The invention encompasses prevention of multiple sclerosis. The relative skill of those in the art is high, generally that of an M.D. or Ph.D. with expertise in the area of neurology. However, that factor is outweighed by the unpredictable nature of MS, as indicated by Miller et al., Current Neurolog. Neurosci. Reports.

According to Miller, which is cited for evidentiary purposes only, multiple sclerosis is a complex demyelinating disease with an unpredictable course. See the Abstract and Introduction. As such, one skilled in the art would not readily accept an assertion that multiple sclerosis would be prevented following administration of FTY720.

In cases involving unpredictable factors, such as the instant claims drawn to physiological activity, the scope of enablement varies inversely with the degree of unpredictability of the factors involved. One skilled in the chemical or biological arts cannot always reasonably predict how different chemical compounds might behave under varying circumstances. See *Ex parte Sudilovsky* 21 USPQ2d 1701.

The amount of direction or guidance provided and the presence or absence of working examples

A clinical trial is described on page 13 wherein 20 patients with relapsing-remitting MS receive Compound A in a scheduled regimen. No therapeutic outcome is noted. There are no working examples drawn to a prevention modality in which a claimed compound is shown to be clinically effective. Such an assertion is beyond the scope of the instantly claimed invention.

The quantity of experimentation necessary

Absent reasonable *a priori* expectations of success for preventing multiple sclerosis, one skilled in the neurology art would have had to test extensively numerous laboratory models of MS using various dosages and dosing regimens to discover which is effective. Since each prospective embodiment, as well as future embodiments as the

art progresses, would have to be empirically tested, undue experimentation would be required to practice the invention as it is claimed in its current scope. The specification provides inadequate guidance to do otherwise.

Due to the known unpredictability of the art, and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that administering one of the claimed compounds, e.g., FTY720, would result in the prevention of multiple sclerosis. The instant claims do not comply with the enablement requirements of 35 U.S.C. 112, first paragraph, since to practice the claimed invention would require a person of ordinary skill in the art to engage in undue experimentation with no assurance of success.

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.

Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over HLA, T., FASEB Journal.

Hla teaches FTY 720 to be an S1P agonist and a potent inhibitor of VEGF-induced vascular permeability *in vivo*. In the control of vascular permeability, S1P receptor agonism may be useful. Since the S1P receptor is strongly induced in tumor vessels, suppression of its expression by local injection of siRNA *in vivo* resulted in

decreased microvessel density, decreased vascular stabilization and attenuated tumor growth. Hla suggests modulation of S1P signaling in the vascular system may provide a way of regulating angiogenesis and vascular formation.

A kit is no more than a conventional type of packaging.

One skilled in the art would have been motivated to combine FTY 720 and a VEGF-receptor antagonist together in a pharmaceutical formulation. Such would have been obvious in the absence of evidence to the contrary because FTY 720 is an inhibitor of VEGF-induced vascular permeability. Thus the combination of FTY 720 with another antagonist of VEGF would have reasonably provided an additive effect when seeking a means of regulating angiogenesis and vascular formation.

Claims 4, 5, 7-9 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kovarik et al., WO 2006/058316, in view of HLA, T., FASEB Journal.

Kovarik teaches the administration of the compound 2-amino-2-[2-(4-octylphenyl)ethyl]propane-l,3-diol, FTY720, to treat autoimmune diseases of which multiple sclerosis is specifically recited. See page 14, lines 7-8. All types of multiple sclerosis are reasonably encompassed in Kovarik's teaching. The elected specie, 2-amino-2-[2-(4-octylphenyl)ethyl]propane-l,3-diol, FTY 720, is described as a preferred embodiment on page 13, lines 3-7.

With respect to an intermittent dosing regimen (claim 9), it is not inventive to discover an optimum dosing regimen 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). The medical arts recognize

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. Factors such as weight, age, gender, renal and hepatic status, *inter alia*, are always considered. Therefore, the determination of the optimum characterization of the composition, dosing regimen 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.

Kovarik does not disclose combination therapy. However, the teachings of Hla, as set forth *supra*, suggest beneficial combination therapy in order to achieve an additive effect when seeking a means of regulating angiogenesis and vascular formation.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phyllis G. Spivack whose telephone number is 571-272-0585. The Examiner can normally be reached on 10:30 AM-7 PM.

If attempts to reach the Examiner by telephone are unsuccessful after one business day, the Examiner's supervisor, Ardin Marschel, can be reached on 591-272-0718. 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.

November 20, 2010

/Phyllis G. Spivack/
Primary Examiner, Art Unit 1614

Notice of References Cited	Application/Control No. 12/303,765	Applicant(s)/Patent Under Reexamination HIESTAND ET AL.	
	Examiner Phyllis G. Spivack	Art Unit 1614	Page 1 of 1

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-			
	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	Miller et al., Neurol. & Neurosci. Reports, (September, 2010), 10(5), pp. 397-406.
	V	Hla, T., FASEB Journal, (March 6, 2006), 20(4), Part 1, A20.
	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
	12/303,765	HIESTAND ET AL.
	Examiner	Art Unit
	Phyllis G. Spivack	1614

SEARCHED			
Class	Subclass	Date	Examiner

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR
PALM inventors search	11/20/2010	PS
STN & inventors search	11/15/2010	PS

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BIB DATA SHEET

CONFIRMATION NO. 9401

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
12/303,765	12/08/2008 RULE	514	1614	50279-US-PCT

APPLICANTS

Peter C. Hiestand, Allschwil, SWITZERLAND;
Christian Schnell, Hesingue, FRANCE;

**** CONTINUING DATA ***************************

This application is a 371 of PCT/EP07/05597 06/25/2007

**** FOREIGN APPLICATIONS ***************************

UNITED KINGDOM 0612721.1 06/27/2006

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****

03/19/2010

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	/PHYLLIS G SPIVACK/ Examiner's Signature	☐ Initials	SWITZERLAND	0	11	2

ADDRESS

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

TITLE

S1P RECEPTOR MODULATORS FOR TREATING MULTIPLE SCLEROSIS

FILING FEE RECEIVED	FEES: Authority has been given in Paper	
980	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

Receipt date: 12/08/2008

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. 50279-US-PCT
APPLICATION NO.

APPLICANT HIESTAND ET AL.
FILING DATE Group

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE
	AA						
	AB						
	AC						
	AD						
	AE						
	AF						
	AG						
	AH						
	AI						
	AJ						
	AK						
	AL						

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	OFFICE	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
/P.S./	AM	2006/058316	6/1/06	WO			☐	☐
/P.S./	AN	2004/113330	12/29/04	WO			☐	☐
	AO						☐	☐
	AP						☐	☐
	AQ						☐	☐

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent pages, Etc.)

/P.S./	AR	Brinkmann, Volker et al., "The Immune Modulator FTY720 Targets Sphingosine 1-Phosphate Receptors", The Journal of Biological Chemistry, Vol. 277, No. 24, Issue of June 14, pp. 21453-21457, (2002).
	AS	
	AT	

EXAMINER /Phyllis Spivack/ **DATE CONSIDERED** 11/18/2010

*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.

```
CROSS REFERENCE:      2004-329817
TITLE:                Use of sphingosine-1-phosphate receptor agonist in
                      preparing medicaments for treating, alleviating or
                      delaying progression of demyelinating disorders such as
                      optic neuritis
DERWENT CLASS:        B04
INVENTOR:             FOSTER C A; GLUE P W; HIESTAND P C
PATENT ASSIGNEE:      (NOVS-C) NOVARTIS AG
COUNTRY COUNT:        1

PATENT INFO ABBR.:

      PATENT NO      KIND DATE     WEEK     LA  PG          MAIN IPC
      ---------------------------------------------------------------
      NZ 564626       A  20090828 (200974)* EN  1[0]

APPLICATION DETAILS:

      PATENT NO      KIND                  APPLICATION    DATE
      ---------------------------------------------------------------
      NZ 564626 A                          NZ 2003-564626 20030923
      NZ 564626 A Div Ex                   NZ 2003-230903 20030923

FILING DETAILS:

      PATENT NO       KIND                  PATENT NO
      ------------------------------------------------
      NZ 564626 A           Div Ex          NZ 538961 A

PRIORITY APPLN. INFO: US 2003-485132       20030707
                      US 2002-413172       20020924
AN   2009-Q30586 [200974]   WPIX
CR   2004-329817
AB    NZ 564626 A   UPAB: 20091118
       NOVELTY - Use of sphingosine-1-phosphate receptor agonist in preparing
      medicaments for treating, alleviating or delaying progression of demyelinating
      disorders, preferably optic neuritis.
             ACTIVITY - Neuroprotective; Ophthalmological; Antiinflammatory.
             MECHANISM OF ACTION - Sphingosine-1-phosphate receptor agonist.
             USE - The sphingosine-1-phosphate receptor agonist is useful in
      preparing medicaments for treating, alleviating or delaying progression of
      demyelinating disorders, preferably optic neuritis.



=> d his ful

     (FILE 'HOME' ENTERED AT 16:30:16 ON 15 NOV 2010)

     FILE 'REGISTRY' ENTERED AT 16:30:22 ON 15 NOV 2010
L1              STR
L2           50 SEA SSS SAM L1
L3              STR L1
L4           50 SEA SSS SAM L3
L5         1421 SEA SSS FUL L3

     FILE 'CAPLUS' ENTERED AT 16:33:08 ON 15 NOV 2010
                E US2008-303765/APPS
L6            1 SEA SPE=ON  ABB=ON  PLU=ON  US2008-303765/AP
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                D SCA
                SEL RN

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L7             4 SEA SPE=ON  ABB=ON  PLU=ON  (162359-55-9/BI OR 507468-43-1/BI
                  OR 800379-64-0/BI OR 162359-56-0/BI)
                  D SCA
L8             4 SEA SPE=ON  ABB=ON  PLU=ON  L7 AND L5

     FILE 'CAPLUS' ENTERED AT 16:35:06 ON 15 NOV 2010
L9           807 SEA SPE=ON  ABB=ON  PLU=ON  L8

     FILE 'REGISTRY' ENTERED AT 16:35:10 ON 15 NOV 2010
                  SEL RN L8
L10           13 SEA SPE=ON  ABB=ON  PLU=ON  (162359-55-9/CRN OR 162359-56-0/CRN
                   OR 507468-43-1/CRN OR 800379-64-0/CRN)
L11           16 SEA SPE=ON  ABB=ON  PLU=ON  L10 OR L8

     FILE 'CAPLUS' ENTERED AT 16:35:36 ON 15 NOV 2010
L12          807 SEA SPE=ON  ABB=ON  PLU=ON  L11
                  E DEMYELIN/CT
                  E E6+ALL
                  E E2+ALL

     FILE 'HCAPLUS' ENTERED AT 16:36:25 ON 15 NOV 2010
L13         3571 SEA SPE=ON  ABB=ON  PLU=ON  DEMYELINATION+PFT,NT/CT
                  E MULTIPLE SCLEROSIS+ALL/CT
L14        21385 SEA SPE=ON  ABB=ON  PLU=ON  MULTIPLE SCLEROSIS+PFT,NT/CT
                  E PP-MS/CT
                  E PPMS/CT
                  E PRIMARY PROGRESSIVE MULTIPLE/CT
                  E VEGF/CT
                  E E9+ALL
                  E E2+ALL
L15       142795 SEA SPE=ON  ABB=ON  PLU=ON  VASCULAR ENDOTHEL? OR VEGF OR PPMS
                  OR PP-MS OR PP MS OR PRIMARY PROGRESSIVE(S)(MS OR MULTIPLE
                  SCLEROS?) OR ?MYELIN? OR ?CANAVAN? OR ?ADRENOLEUK? OR ALEXANDER
                  ?
L16        75629 SEA SPE=ON  ABB=ON  PLU=ON  PPMS OR PP-MS OR PP MS OR PRIMARY
                  PROGRESSIVE(S)(MS OR MULTIPLE SCLEROS?) OR ?MYELIN? OR
                  ?CANAVAN? OR ?ADRENOLEUK? OR ALEXANDER? OR MULTIPLE SCLEROS?
L17        75653 SEA SPE=ON  ABB=ON  PLU=ON  L16 OR L13 OR L14
L18          164 SEA SPE=ON  ABB=ON  PLU=ON  L17 AND L12
L19            5 SEA SPE=ON  ABB=ON  PLU=ON  L18 AND (VASCULAR ENDOTHEL? OR
                  VEGF)
L20           29 SEA SPE=ON  ABB=ON  PLU=ON  L18 AND DEMYELIN?
L21          717 SEA SPE=ON  ABB=ON  PLU=ON  L11(L)(BAC OR DMA OR PAC OR PKT OR
                  THU)/RL
L22          150 SEA SPE=ON  ABB=ON  PLU=ON  L21 AND L16
L23           38 SEA SPE=ON  ABB=ON  PLU=ON  L22 AND ?MYELIN?
L24           24 SEA SPE=ON  ABB=ON  PLU=ON  L22 AND DEMYELIN?
L25           29 SEA SPE=ON  ABB=ON  PLU=ON  L20 OR L24
L26           32 SEA SPE=ON  ABB=ON  PLU=ON  L25 OR L19

     FILE 'MEDLINE, EMBASE, BIOSIS' ENTERED AT 16:44:16 ON 15 NOV 2010
L27         2939 SEA SPE=ON  ABB=ON  PLU=ON  L11
L28           98 SEA SPE=ON  ABB=ON  PLU=ON  L27 AND DEMYELIN?
L29           82 SEA SPE=ON  ABB=ON  PLU=ON  L28 AND (MS OR MULTIPL?(2A)
                  ?SCLEROS?)
L30           81 SEA SPE=ON  ABB=ON  PLU=ON  L29 AND (?TREAT? OR ?PHARM? OR
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                ?DRUG? OR ?THERAP?)
L31           0 SEA SPE=ON  ABB=ON  PLU=ON  L30 AND (VEGF OR VASCULAR ENDOTHEL?
                )

     FILE 'REGISTRY' ENTERED AT 16:47:02 ON 15 NOV 2010
L32           1 SEA SPE=ON  ABB=ON  PLU=ON  FUMARIC ACID/CN
                D SCA
L33           1 SEA SPE=ON  ABB=ON  PLU=ON  FINGOLIMOD/CN
                D SCA

     FILE 'HCAPLUS' ENTERED AT 16:47:53 ON 15 NOV 2010
                D QUE L26

     FILE 'MEDLINE, EMBASE, BIOSIS' ENTERED AT 16:48:06 ON 15 NOV 2010
                D QUE L30

     FILE 'HCAPLUS, MEDLINE, EMBASE, BIOSIS' ENTERED AT 16:48:30 ON 15 NOV 2010
L34          87 DUP REM L26 L30 (26 DUPLICATES REMOVED)
                      ANSWERS '1-32' FROM FILE HCAPLUS
                      ANSWER '33' FROM FILE MEDLINE
                      ANSWERS '34-83' FROM FILE EMBASE
                      ANSWERS '84-87' FROM FILE BIOSIS
                D L34 IBIB ABS HITIND HITSTR 1-32
                D L34 IBIB ABS HITIND 33-87

     FILE 'HCAPLUS' ENTERED AT 16:51:18 ON 15 NOV 2010
L35          11 SEA SPE=ON  ABB=ON  PLU=ON  L26 AND (PY<2007 OR AY<2007 OR
                PRY<2007)
L36          43 SEA SPE=ON  ABB=ON  PLU=ON  L22 AND (PY<2007 OR AY<2007 OR
                PRY<2007)
L37          13 SEA SPE=ON  ABB=ON  PLU=ON  L36 AND ?MYELIN?
L38          43 SEA SPE=ON  ABB=ON  PLU=ON  L36 AND (?MYELIN? OR MULTIPLE
                SCLER?)

     FILE 'MEDLINE, EMBASE, BIOSIS' ENTERED AT 16:53:23 ON 15 NOV 2010
L39         600 SEA SPE=ON  ABB=ON  PLU=ON  L27 AND (DEMYELIN? OR MULTIPLE
                SCLEROS?)
L40          97 SEA SPE=ON  ABB=ON  PLU=ON  L39 AND PY<2007
L41          18 SEA SPE=ON  ABB=ON  PLU=ON  L40 AND DEMYELIN?
L42          26 SEA SPE=ON  ABB=ON  PLU=ON  L40 AND ?MYELIN?
L43          23 SEA SPE=ON  ABB=ON  PLU=ON  L42 AND MULTIPL?

     FILE 'CAPLUS, MEDLINE, EMBASE, BIOSIS, DISSABS, CONFSCI, WPIX' ENTERED AT
     16:55:18 ON 15 NOV 2010
L44         346 SEA SPE=ON  ABB=ON  PLU=ON  HIESTAND P?/AU
L45         403 SEA SPE=ON  ABB=ON  PLU=ON  SCHNELL C?/AU
L46           4 SEA SPE=ON  ABB=ON  PLU=ON  L44 AND L45
L47          19 SEA SPE=ON  ABB=ON  PLU=ON  (L44 OR L45) AND DEMYELIN?
L48          20 SEA SPE=ON  ABB=ON  PLU=ON  L46 OR L47

     FILE 'HCAPLUS' ENTERED AT 16:56:06 ON 15 NOV 2010
                D QUE L38

     FILE 'MEDLINE, EMBASE, BIOSIS' ENTERED AT 16:56:13 ON 15 NOV 2010
                D QUE L43

     FILE 'HCAPLUS, MEDLINE, EMBASE, BIOSIS' ENTERED AT 16:56:21 ON 15 NOV 2010
L49          62 DUP REM L38 L43 (4 DUPLICATES REMOVED)
                      ANSWERS '1-43' FROM FILE HCAPLUS
                      ANSWER '44' FROM FILE MEDLINE
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                    ANSWERS '45-61' FROM FILE EMBASE
                    ANSWER '62' FROM FILE BIOSIS
               D L49 IBIB ABS HITIND HITSTR 1-43
               D L49 IBIB ABS HITIND 44-62

     FILE 'CAPLUS, MEDLINE, EMBASE, BIOSIS, DISSABS, CONFSCI, WPIX' ENTERED AT
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               D QUE L48
L50          9 DUP REM L48 (11 DUPLICATES REMOVED)
                    ANSWERS '1-6' FROM FILE CAPLUS
                    ANSWERS '7-8' FROM FILE MEDLINE
                    ANSWER '9' FROM FILE WPIX
               D L50 IBIB ABS TOT


     FILE HOME

     FILE REGISTRY
     Property values tagged with IC are from the ZIC/VINITI data file
     provided by InfoChem.

     STRUCTURE FILE UPDATES:   14 NOV 2010  HIGHEST RN 1252988-50-3
     DICTIONARY FILE UPDATES:  14 NOV 2010  HIGHEST RN 1252988-50-3

     New CAS Information Use Policies, enter HELP USAGETERMS for details.

     TSCA INFORMATION NOW CURRENT THROUGH June 26, 2010.

       Please note that search-term pricing does apply when
       conducting SmartSELECT searches.

     REGISTRY includes numerically searchable data for experimental and
     predicted properties as well as tags indicating availability of
     experimental property data in the original document.  For information
     on property searching in REGISTRY, refer to:

     http://www.cas.org/support/stngen/stndoc/properties.html

     FILE CAPLUS

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     FILE COVERS 1907 - 15 Nov 2010  VOL 153 ISS 21
     FILE LAST UPDATED: 14 Nov 2010  (20101114/ED)
     REVISED CLASS FIELDS (/NCL) LAST RELOADED:  Aug 2010
     USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE:  Aug 2010

     CAplus now includes complete International Patent Classification (IPC)
     reclassification data for the third quarter of 2010.

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```

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE PCT NATIONAL STAGE APPLICATION OF Art Unit: 1614
Hiestand, P. C. *et al.* Examiner: Spivack, Phyllis G
INTERNATIONAL APPLICATION NO: PCT/EP07/005597
FILED: June 25, 2007
U.S. APPLICATION NO: 12/303765
35 USC §371 DATE: December 08, 2008
FOR: S1P Receptor Modulators for Treating Multiple Sclerosis

MS: Amendment
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

RESPONSE TO ELECTION OF SPECIES REQUIREMENT

Sir:

This *Response to Election of Species Requirement* is being submitted in response to the Office Action in the above application that was mailed to Applicants' attorney on August 25, 2010.

No amendments to the specification or claims of the above application are being made in this paper.

The Listing of Claims begins on page 2 of this paper.

Remarks begin on page 4 of this paper.

Remarks/Arguments

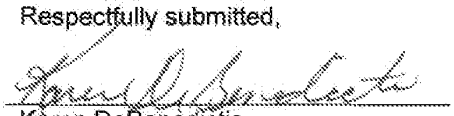
There are 11 claims pending in this application. These are claims 4 – 14. No amendments to the claims or specification of the present application are being made via this paper.

In the above mentioned Office Action, the Examiner required that Applicants make a species election of a single species of demyelinating disease and a single species of S1P receptor modulator. 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 (also referred to as "FTY720"), in free form or in a pharmaceutically acceptable salt or hydrate form, as the species of S1P receptor modulator. FTY720 is referred to as a preferred S1P receptor modulator on page 9 of the specification. Applicants further elect multiple sclerosis as the species of demyelinating disease. Multiple sclerosis is referred to as a demyelinating disease on pages 1 and 10 of the specification.

Each of the 11 pending claims, claims 4 – 14, embraces both FTY720 as an S1P receptor modulator and multiple sclerosis as a demyelinating disease.

Applicants submit that all pending claims 4 – 14 are patentable and in patentable form, 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: September 14, 2010

Electronic Acknowledgement Receipt

EFS ID:	8413590
Application Number:	12303765
International Application Number:	
Confirmation Number:	9401
Title of Invention:	S1P RECEPTOR MODULATORS FOR TREATING MULTIPLE SCLEROSIS
First Named Inventor/Applicant Name:	Peter C. Hiestand
Customer Number:	01095
Filer:	Karen DeBenedictis/Andrea Jacquin
Filer Authorized By:	Karen DeBenedictis
Attorney Docket Number:	50279-US-PCT
Receipt Date:	14-SEP-2010
Filing Date:	08-DEC-2008
Time Stamp:	13:54:50
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		50279_US_PCT_ResptoRR14Sep2010.pdf	541447 cf1b28fd0d698bb4ca9ad396e5f59f053bd4ae3d	yes	4

TEVA EX. 1009
Page 29

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Response to Election / Restriction Filed	1	1
	Claims	2	3
	Applicant Arguments/Remarks Made in an Amendment	4	4
Warnings:			
Information:			
	Total Files Size (in bytes):	541447	

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 12/303,765	Filing Date 12/08/2008	☐ 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

AMENDMENT	09/14/2010	(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))	* 11	Minus	** 20	= 0	X $ =		OR	X $52=	0
	Independent (37 CFR 1.16(h))	* 2	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	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) 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:
/TIA A. BENTLEY/

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.

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

Claims 1-3. (Cancelled)

Claim 4. (Previously presented): A method according to claim 7, wherein the medicament is co-administered, e.g. concomitantly or in sequence, with a VEGF-receptor antagonist.

Claim 5. (Previously presented): A pharmaceutical composition for use in the method according to claim 7, comprising an S1P receptor modulator together with one or more pharmaceutically acceptable diluents or carriers therefore.

Claim 6. (Previously presented): A pharmaceutical combination, e.g. a kit, comprising a) a first agent which is a S1P receptor modulator, in free form or in pharmaceutically acceptable salt form, and b) a VEGF-receptor antagonist.

Claim 7. (Previously presented): A method for preventing, inhibiting or treating neo-angiogenesis associated with a demyelinating disease in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of an S1P receptor modulator.

Claim 8. (Previously presented): A method according to claim 7, wherein the demyelinating disease is multiple sclerosis.

Claim 9. (Original): A method according to claim 8, wherein the S1P receptor modulator is administered intermittently.

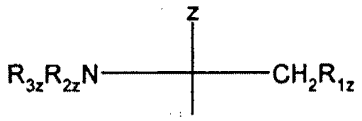
Claim 10. (Previously presented): A method according to claim 14, wherein the S1P receptor modulator or agonist is 2-amino-2-[2-(4-octylphenyl) ethyl]propane-1,3-diol, 2-amino-2-[4-(3-benzyloxyphenoxy)-2- chlorophenyl]ethyl-1,3-propane-diol, or 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl- benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, in free form or in a pharmaceutically acceptable salt form.

Claim 11. (Previously presented): A method according to claim 10, wherein the S1P receptor modulator is 2-amino-2-[2-(4-octylphenyl) ethyl]propane-1,3-diol in free form or in a pharmaceutically acceptable salt form.

Claim 12. (Previously presented): A method according to claim 7, wherein the demyelinating disease is primary progressive multiple sclerosis (PP-MS).

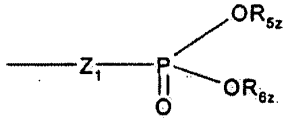
Claim 13. (Previously presented): A method according to claim 7, wherein the S1P receptor modulator comprises a group of formulae I to IXb.

Claim 14. (Previously presented): A method according to claim 7, wherein the S1P receptor modulator 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.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/303,765	12/08/2008	Peter C. Hiestand	50279-US-PCT	9401

1095 7590 08/25/2010

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

EXAMINER	
SPIVACK, PHYLLIS G	
ART UNIT	**PAPER NUMBER**
1614	

MAIL DATE	DELIVERY MODE
08/25/2010	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)	
	12/303,765	HIESTAND ET AL.	
	Examiner	Art Unit	
	Phyllis G. Spivack	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) 4-14 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) 4-14 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: _____.

ELECTION REQUIREMENT

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:

1) demyelinating diseases; and

2) S1P receptor modulators.

Applicants are required, in reply to this Action, to elect single disclosed species as set forth *supra*, and as disclosed throughout the present specification, 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 elections.

If claims are added after the election, Applicants 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:

methods for the treatment or prevention of neo-angiogenesis associated with a demyelinating disease comprising administering a S1P receptor modulator.

The following claims are generic: 4-14.

Should Applicants traverse on the ground that the species are not patentably distinct, Applicants should submit evidence or identify such evidence now of record

showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the Examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

The election of an invention or species may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out the supposed errors in the restriction requirement, the election shall be treated as an election without traverse.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Phyllis G. Spivack whose telephone number is 571-272-0585. The Examiner can normally be reached from 10:30 to 7 PM.

If attempts to reach the Examiner by telephone are unsuccessful after one business day, the Examiner's supervisor, Ardin Marschel, can be reached 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).

August 20, 2010

/Phyllis G. Spivack/
Primary Examiner, Art Unit 1614

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Page 38

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
12/303,765	12/08/2008	Peter C. Hiestand	50279-US-PCT

CONFIRMATION NO. 9401

1095
NOVARTIS
CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 101/2
EAST HANOVER, NJ 07936-1080

PUBLICATION NOTICE

OC000000042379942

Title:S1P RECEPTOR MODULATORS FOR TREATING MULTIPLE SCLEROSIS

Publication No.US-2010-0168078-A1
Publication Date:07/01/2010

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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Page 39

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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
12/303,765	12/08/2008	1614	980	50279-US-PCT	11	2

CONFIRMATION NO. 9401

CORRECTED FILING RECEIPT

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CORPORATE INTELLECTUAL PROPERTY
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EAST HANOVER, NJ 07936-1080

OC000000041210123

Date Mailed: 04/22/2010

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)

Peter C. Hiestand, Allschwil, SWITZERLAND;
Christian Schnell, Hesingue, FRANCE;

Power of Attorney: The patent practitioners associated with Customer Number 001095

Domestic Priority data as claimed by applicant

This application is a 371 of PCT/EP07/05597 06/25/2007

Foreign Applications

UNITED KINGDOM 0612721.1 06/27/2006

If Required, Foreign Filing License Granted: 03/19/2010

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 12/303,765**

Projected Publication Date: 07/01/2010

Non-Publication Request: No

Early Publication Request: No

Title

S1P RECEPTOR MODULATORS FOR TREATING MULTIPLE SCLEROSIS

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).

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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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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CASE PAT050279-US-PCT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE PCT NATIONAL STAGE APPLICATION OF
Hiestand, Peter C. et al.
INTERNATIONAL APPLICATION NO: PCT/EP07/005597
FILED: June 25, 2007
U.S. APPLICATION NO: 12/303765
35 USC §371 DATE: December 08, 2008
FOR: S1P Receptor Modulators for Treating Multiple Sclerosis

Art Unit:
Examiner:

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 omited an Applicant. Please issue a corrected filing receipt listing the additional Applicant as follows:

--Christian Schnell, Hesingue, France --

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,

Jennifer C. Chapman
Attorney for Applicant
Reg. No. 47,487

Novartis Pharmaceuticals Corporation
One Health Plaza, Bldg. 101
East Hanover, NJ 07936
(862) 778-1202

Date: April 30, 2010

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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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
12/303,765	12/08/2008		980	50279-US-PCT	11	2

CONFIRMATION NO. 9401

1095
NOVARTIS
CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
EAST HANOVER, NJ 07936-1080

FILING RECEIPT

OC000000040735741

Pharma Intellectual Property
MAR 2 6 2010
F/F KMD Inv RF LE PA

Date Mailed: 03/24/2010

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)

Peter C. Hiestand, Allschwil, SWITZERLAND;

Power of Attorney: The patent practitioners associated with Customer Number 001095

Domestic Priority data as claimed by applicant

This application is a 371 of PCT/EP07/05597 06/25/2007

Foreign Applications

UNITED KINGDOM 0612721.1 06/27/2006

If Required, Foreign Filing License Granted: 03/19/2010

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 12/303,765**

Projected Publication Date: 07/01/2010

Non-Publication Request: No

Early Publication Request: No

TEVA EX. 1009
Page 44

Title

S1P RECEPTOR MODULATORS FOR TREATING MULTIPLE SCLEROSIS

Preliminary Class

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.

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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

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).

Electronic Acknowledgement Receipt

EFS ID:	7448327
Application Number:	12303765
International Application Number:	
Confirmation Number:	9401
Title of Invention:	S1P RECEPTOR MODULATORS FOR TREATING MULTIPLE SCLEROSIS
First Named Inventor/Applicant Name:	Peter C. Hiestand
Customer Number:	01095
Filer:	Jennifer Chin Chapman/Barbara Brower-Anglim
Filer Authorized By:	Jennifer Chin Chapman
Attorney Docket Number:	50279-US-PCT
Receipt Date:	20-APR-2010
Filing Date:	08-DEC-2008
Time Stamp:	13:34:22
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		50279_ltr_corr_recpt.pdf	818224 e3cbb5a694be94ad5e86fc587b2d742d1f8fe243	yes	4

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Page 47

	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):	818224	

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.

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U.S. APPLICATION NUMBER NO.	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
12/303,765	Peter C. Hiestand	50279-US-PCT

1095
NOVARTIS
CORPORATE INTELLECTUAL PROPERTY
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EAST HANOVER, NJ 07936-1080

INTERNATIONAL APPLICATION NO.	
PCT/EP07/05597	
I.A. FILING DATE	PRIORITY DATE
06/25/2007	06/27/2006

CONFIRMATION NO. 9401
371 ACCEPTANCE LETTER

OC000000040735742

Date Mailed: 03/24/2010

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:

12/08/2008	12/27/2008
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 12/08/2008
- Copy of the International Search Report filed on 12/08/2008
- Preliminary Amendments filed on 12/08/2008
- Information Disclosure Statements filed on 12/08/2008
- Oath or Declaration filed on 12/08/2008
- U.S. Basic National Fees filed on 12/08/2008
- Priority Documents filed on 12/08/2008

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)

NADINE V CLARK

Telephone: (703) 756-1411

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
12/303,765	12/08/2008		980	50279-US-PCT	11	2

CONFIRMATION NO. 9401

1095
NOVARTIS
CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
EAST HANOVER, NJ 07936-1080

FILING RECEIPT

OC000000040735741

Date Mailed: 03/24/2010

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)

Peter C. Hiestand, Allschwil, SWITZERLAND;

Power of Attorney: The patent practitioners associated with Customer Number 001095

Domestic Priority data as claimed by applicant

This application is a 371 of PCT/EP07/05597 06/25/2007

Foreign Applications

UNITED KINGDOM 0612721.1 06/27/2006

If Required, Foreign Filing License Granted: 03/19/2010

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 12/303,765**

Projected Publication Date: 07/01/2010

Non-Publication Request: No

Early Publication Request: No

TEVA EX. 1009
Page 50

Title

S1P RECEPTOR MODULATORS FOR TREATING MULTIPLE SCLEROSIS

Preliminary Class

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).

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

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).

MULTIPLE DEPENDENT CLAIM FEE CALCULATION SHEET (FOR USE WITH FORM PTO-875)	SERIAL NO. 12/303,765	FILING DATE
	APPLICANT(S)	

CLAIMS

	AS FILED		AFTER 1st AMENDMENT		AFTER 2nd AMENDMENT	
	IND.	DEP.	IND.	DEP.	IND.	DEP.
1	1					
2	1					
3		2				
4		8		8		
5		8		8		
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TOTAL IND.		⬇	2	⬇		⬇
TOTAL DEP		⬅	9	⬅		⬅
TOTAL CLAIMS			11			

	AS FILED		AFTER 1st AMENDMENT		AFTER 2nd AMENDMENT	
	IND.	DEP.	IND.	DEP.	IND.	DEP.
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TOTAL IND.		⬇		⬇		⬇
TOTAL DEP		⬅		⬅		⬅
TOTAL CLAIMS						

PATENT APPLICATION FEE DETERMINATION RECORD

Effective October 2, 2008

Application or Docket Number: 12/303,765

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	$330/ $165		BASIC FEE		OR	BASIC FEE	330
EXAMINATION FEE	$220/ $110		EXAM. FEE			EXAM. FEE	220
SEARCH FEE	$430/ $215		SEARCH FEE			SEARCH FEE	430
FEE FOR EXTRA SPEC. PGS.	minus 100 =	/ 50 =	X $ 135 =			X $ 270 =	
TOTAL CHARGEABLE CLAIMS	11 minus 20 =		X $ 26 =		OR	X $ 52 =	
INDEPENDENT CLAIMS	2 minus 3 =		X $ 110 =		OR	X $ 220 =	
MULTIPLE DEPENDENT CLAIM PRESENT		☐	+ $ 195 =		OR	+ $ 390 =	
* If the difference in column 1 is less than zero, enter "0" in column 2			TOTAL		OR	TOTAL	980

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 $ 26 =		OR	X $ 52 =	
	Independent		Minus	***		X $ 110 =		OR	X $ 220 =	
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐	+ $ 195 =		OR	+ $ 390 =	
						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 $ 26 =		OR	X $ 52 =	
	Independent		Minus	***		X $ 110 =		OR	X $ 220 =	
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐	+ $ 195 =		OR	+ $ 390 =	
						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.

FORM PTO-875 (Rev. 02/2009) Patent and Trademark Office - U.S. DEPARTMENT OF COMMERCE

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 50279-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/EP2007/005597	INTERNATIONAL FILING DATE 25 June 2007 (25.06.07)	PRIORITY DATE CLAIMED 27 June 2006 (27.06.06)
TITLE OF INVENTION S1P RECEPTOR MODULATORS FOR TREATING MULTIPLE SCLEROSIS		
APPLICANT(S) FOR DO/EO/US HIESTAND 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/EP2007/005597	50279-US-PCT

The following fees are submitted:	CALCULATIONS PTO USE ONLY
21. ☒ Basic national fee. $330	
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. $220	
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. . . $430 ☐ All other situations. . . . . $	
TOTAL OF 21, 22 AND 23 =	$ 980

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 **$270** 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	
17 - 100 =	/50 =	0	X $ 270	$

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	11 - 20 =	0	X $ 52	$
Independent claims	2 - 3 =	0	X $ 220	$
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ $ 390	$
		TOTAL OF ABOVE CALCULATIONS =		$ **980**

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 =	$ **980**
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 =	$ **980**
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 =	$ **980**
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 $980 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 Pharmaceuticals Corp.
Patents Pharma
One Health Plaza, Building 101
East Hanover, NJ 07936-1080

Cozette McAvoy
Attorney for Applicants
Reg. No. 60,457
(862) 778-9273

US Case **50279-WO-PCT**

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

ORGANIC COMPOUNDS

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/EP2007/005597 on **25/June/2007** (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.

US Case **50279-WO-PCT**

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
Great Britain	**0612721.1**	**27/June/2006**	☒ 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)

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:

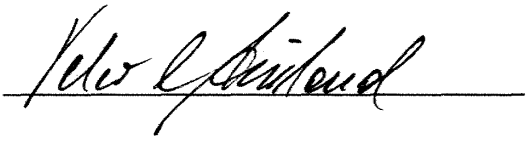
United States Application No.	United States Filing Date (day/month/year)	Status (Pending, Abandoned or U.S. Patent No.)	International Application No.	International and Filing Date (day/month/year)

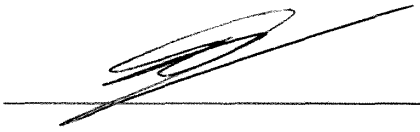
I hereby appoint all of the registered practitioners associated with Customer No. 001095, respectively and individually, as my attorneys and agents, with full power of substitution and revocation, to prosecute this application and to transact all business in the Patent and Trademark Office connected 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	**Peter C. HIESTAND**
Inventor's signature	 Date 2/07/2007 (day/month/year)
Residence	**4123 Allschwil, CH**
Citizenship	**Austria**
Post Office Address	**Schönenbuchstrasse 13a, 4123 Allschwil, CH**

Full name of second joint inventor, if any	**Christian SCHNELL**
Inventor's signature	 Date 16/7/2007 (day/month/year)
Residence	**68220 Hésingue, FR**
Citizenship	**France**
Post Office Address	**Rue de Buschwiller 9, 68220 Hésingue, FR**

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 50279-US-PCT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE PCT NATIONAL STAGE APPLICATION OF

HIESTAND ET AL.

INTERNATIONAL APPLICATION NO: PCT/EP2007/005597

FILED: 25 JUNE 2007

U.S. APPLICATION NO: NOT YET KNOWN

35 USC §371 DATE: HEREWITH

FOR: S1P RECEPTOR MODULATORS FOR TREATING MULTIPLE SCLEROSIS

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. These references are of record in the instant PCT application PCT/EP2007/005597, copies 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 1449 form(s).

Respectfully submitted,

Novartis Pharmaceuticals Corp.
Patents Pharma
One Health Plaza, Building 101
East Hanover, NJ 07936-1080
(862) 778-9273

Cozette M. McAvoy
Attorney for Applicants
Reg. No. 60,457

Date: 8th Dec 2008

TEVA EX. 1009
Page 61

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. 50279-US-PCT
APPLICATION NO.

APPLICANT HIESTAND ET AL.
FILING DATE Group

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE
	AA						
	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	2006/058316	6/1/06	WO			☐	☐
	AN	2004/113330	12/29/04	WO			☐	☐
	AO						☐	☐
	AP						☐	☐
	AQ						☐	☐

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent pages, Etc.)

	AR	Brinkmann, Volker et al., "The Immune Modulator FTY720 Targets Sphingosine 1-Phosphate Receptors", The Journal of Biological Chemistry, Vol. 277, No. 24, Issue of June 14, pp. 21453-21457, (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 50279-US-PCT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE PCT NATIONAL STAGE APPLICATION OF

HIESTAND ET AL.

INTERNATIONAL APPLICATION NO: PCT/EP2007/005597

FILED: 25 JUNE 2007

U.S. APPLICATION NO: NOT YET KNOWN

35 USC §371 DATE: HEREWITH

FOR: S1P RECEPTOR MODULATORS FOR TREATING MULTIPLE SCLEROSIS

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:

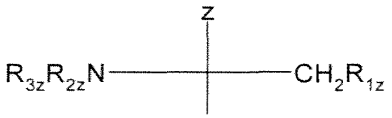
Please insert the following as the first paragraph beneath the title on page 1:

This application is a 371 of PCT/EP2007/005597 filed on June 25, 2007, which claims benefit of Great Britain Application No. 0612721.1 filed on June 27, 2006, which in their entirety are herein incorporated by reference.—

A copy of the abstract is herein provided on the following separate sheet.

Abstract

The present invention relates uses of an S1P receptor modulator 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)

for the treatment or prevention of neo-angiogenesis associated with a demyelinating disease, e.g. multiple sclerosis.

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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:

Claims 1-3. (Cancelled)

Claim 4. (Currently amended): A method according to claim 7, ~~Use of any preceding claim,~~ wherein the medicament is co-administered, e.g. concomitantly or in sequence, with a VEGF-receptor antagonist~~, e.g. as defined hereinabove~~.

Claim 5. (Currently amended): A pharmaceutical composition for use in the method according to claim 7 ~~of any preceding claim~~, comprising an S1P receptor modulator~~, e.g. a compound of formulae I to IXb as defined hereinabove,~~ together with one or more pharmaceutically acceptable diluents or carriers therefor.

Claim 6. (Currently amended): A pharmaceutical combination, e.g. a kit, comprising a) a first agent which is a S1P receptor modulator ~~e.g. a compound of formulae I to XIb as defined herein above~~, in free form or in pharmaceutically acceptable salt form, and b) a VEGF-receptor antagonist~~, e.g. as defined hereinabove~~.

Claim 7. (Currently amended): A method for preventing, inhibiting or treating neo-angiogenesis associated with a demyelinating disease~~, e.g. multiple sclerosis,~~ in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of an S1P receptor modulator~~, e.g. a compound of formulae I to IXb as defined hereinabove~~.

Claim 8. (Currently amended): A method according to claim 7, wherein the demyelinating disease is multiple sclerosis. ~~A method of preventing, inhibiting or treating PP-MS in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of an S1P receptor modulator, e.g. a compound of formulae I to IXb as defined hereinabove~~.

Claim 9. (Original): A method according to claim 8, wherein the S1P receptor modulator is administered intermittently.

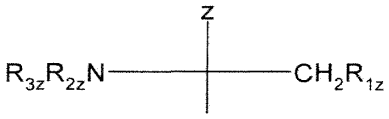
Claim 10. (Currently amended): A method according to claim 14, ~~A method, use, pharmaceutical composition or pharmaceutical combination of any preceding claim,~~ wherein the S1P receptor modulator or agonist is 2-amino-2-[2-(4-octylphenyl) ethyl]propane-1,3-diol, 2-amino-2-[4-(3-benzyloxyphenoxy)-2- chlorophenyl]ethyl-1,3-propane-diol, 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.

Claim 11. (Currently amended): A method according to claim 10, ~~A method, use, pharmaceutical composition or pharmaceutical combination according to any one of the preceding claims,~~ wherein the S1P receptor modulator is 2-amino-2-[2-(4-octylphenyl) ethyl]propane-1,3-diol in free form or in a pharmaceutically acceptable salt form.

Claim 12. (New): A method according to claim 7, wherein the demyelinating disease is primary progressive multiple sclerosis (PP-MS).

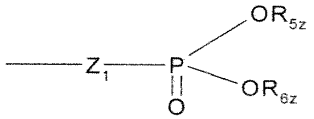
Claim 13. (New): A method according to claim 7, wherein the S1P receptor modulator comprises a group of formulae I to IXb.

Claim 14. (New): A method according to claim 7, wherein the S1P receptor modulator 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.

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REMARKS/ARGUMENTS

The foregoing amendments to the specification are to insert the lineage beneath the title in the specification and 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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CORRESPONDENCE INFORMATION

Correspondence Customer Number:: 001095
Fax One:: 973-781-8064

APPLICATION INFORMATION

Title Line One:: S1P RECEPTOR MODULATORS FOR TREATING MUL
Title Line Two:: TIPLE SCLEROSIS
Total Drawing Sheets:: 0
Formal Drawings?:: No
Application Type:: Utility
Docket Number:: 50279-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/EP07/005597
 Filing Date:: 06-25-2007

PRIOR FOREIGN APPLICATIONS

Foreign Application One:: 0612721.1
Filing Date:: 06-27-2006
Country:: GREAT BRITAIN
Priority Claimed:: Yes

Source:: PrintEFS Version 2.0

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
1 June 2006 (01.06.2006)

PCT

(10) International Publication Number
WO 2006/058316 A1

(51) International Patent Classification:
A61K 31/135 (2006.01) *A61P 37/06* (2006.01)

(21) International Application Number:
PCT/US2005/043044

(22) International Filing Date:
28 November 2005 (28.11.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/631,483 29 November 2004 (29.11.2004) US

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(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, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, 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, IS, IT, LT, LU, LV, 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).

Declaration under Rule 4.17:
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

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: 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

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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.

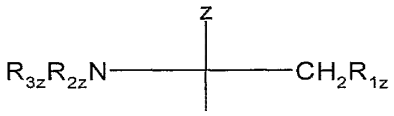
It has now surprisingly been found that a specific dosage regimen, e.g. a loading dose, will provide further unexpected benefits.

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).

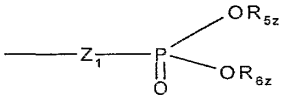
The lymphocyte homing property may be measured in following Blood Lymphocyte Depletion assay:
A S1P receptor agonist or modulator or the vehicle is administered orally by gavage to rats. Tail blood for hematological monitoring is obtained on day –1 to give the baseline individual values, and at 2, 6, 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;

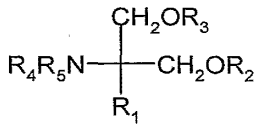
each of R_{5z} and R_{6z}, independently, is H, or C_{1-4}alkyl optionally substituted by 1, 2 or 3 halogen atoms;

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

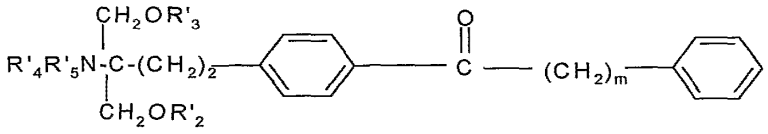
the alkyl moiety may have

- 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

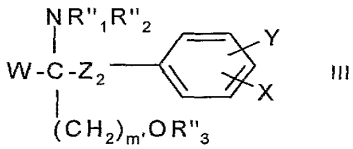


II

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,

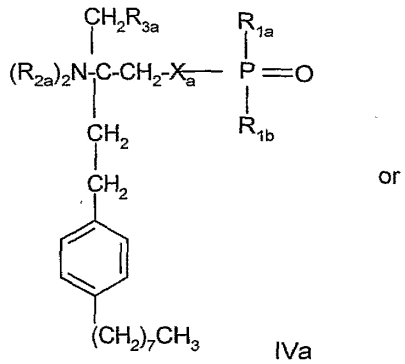
or a pharmaceutically acceptable salt or hydrate thereof;

- Compounds as disclosed in EP0778263 A1, e.g. a compound of formula III



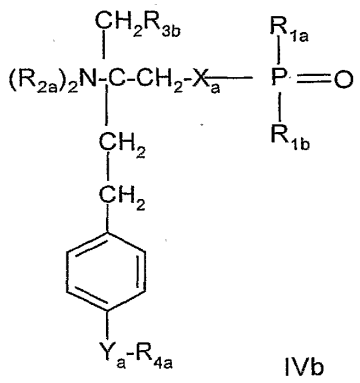
III

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



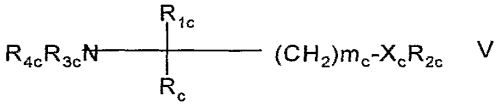
IVb

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

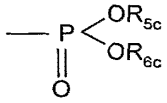
wherein

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;

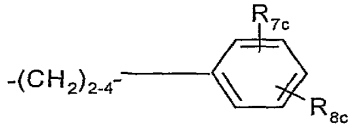
R_{2c} is



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)

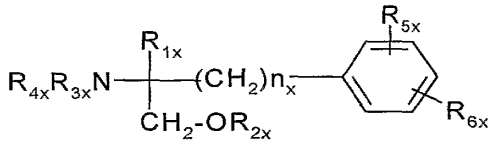


(a)

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

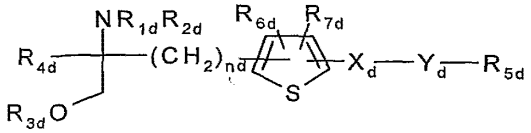
R_{6x} is C_{1-20} alkanoyl substituted by cycloalkyl; cyloalkylC_{1-14}alkoxy wherein the cycloalkyl ring is optionally substituted by halogen, C_{1-4}alkyl and/or C_{1-4}alkoxy; phenylC_{1-14}alkoxy wherein the phenyl ring is optionally substituted by halogen, C_{1-4}alkyl and/or C_{1-4}alkoxy,

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,

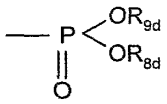
or a pharmaceutically acceptable salt or hydrate thereof;

- Compounds as disclosed in WO02/06268Al, e.g. a compound of formula VII



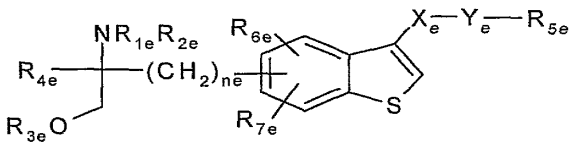
VII

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;

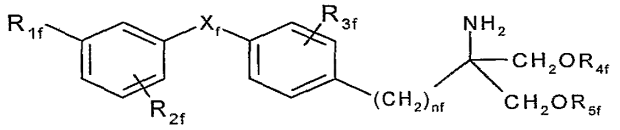
-Compounds as disclosed in JP-14316985 (JP2002316985), e.g. a compound of formula VIII



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;

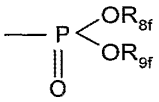
-Compounds as disclosed in WO 03/29184 and WO 03/29205, e.g. compounds of formula IX



IX

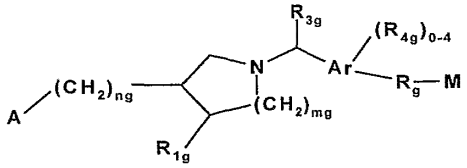
wherein X_f is O, S, SO or SO_2

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

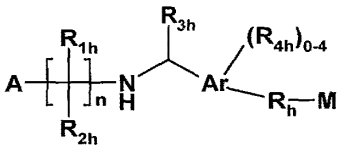


X

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;

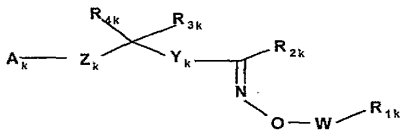
-Compounds as disclosed in WO 03/062248A2, e.g. a compound of formula XI



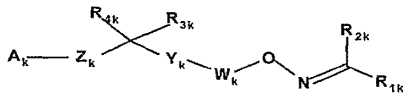
XI

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

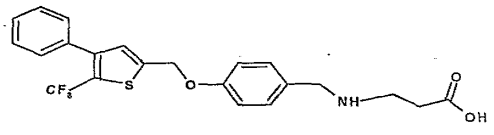


XIIb

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;

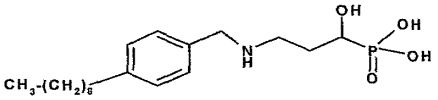
Y_k is C_{6-10}aryl or C_{3-9}heteroaryl, optionally substituted by 1 to 3 radicals selected from halogene, OH, NO_2, C_{1-6}alkyl, C_{1-6}alkoxy; halo-substituted C_{1-6}alkyl and halo-substituted C_{1-6}alkoxy;
Z_k is a heterocyclic group as indicated in WO 04/103306A, e.g. azetidine;
R_{1k} is C_{6-10}aryl 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_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-4}alkyl, C_{3-8}heterocycloalkyl or C_{3-8}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.

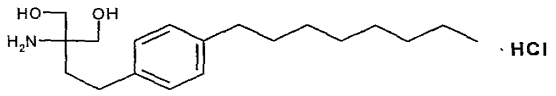
Preferred compounds of formula I are those wherein R_1 is C_{13-20}alkyl, optionally substituted by nitro, halogen, amino, hydroxy or carboxy, and, more preferably those wherein R_1 is phenylalkyl substituted by C_{6-14}-alkyl chain optionally substituted by halogen and the alkyl moiety is a C_{1-6}alkyl 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.

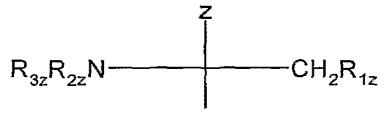
7. In a treatment method with a S1P receptor modulator or agonist, the improvement being that the S1P receptor modulator or agonist is administered in such a way that during the initial 3 to 6 days of treatment the dosage is raised so that in total the R-fold standard daily dosage is administered.

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.

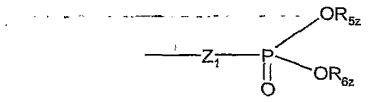
10. A kit containing daily units of medication of an S1P receptor modulator or agonist of varying daily dosage, whereby the daily dosage of S1P receptor modulator or agonist is ¼; ½; and ¾ of the highest instalment dose of the S1P receptor modulator or agonist; and 4x the maintenance dose of the S1P 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-

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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)

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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

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.

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
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		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

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
29 December 2004 (29.12.2004)

PCT

(10) International Publication Number
WO 2004/113330 A1

(51) International Patent Classification[7]: C07D 413/10, A61K 31/4725

(21) International Application Number: PCT/US2004/015699

(22) International Filing Date: 19 May 2004 (19.05.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/471,931 19 May 2003 (19.05.2003) US
60/471,931 14 April 2004 (14.04.2004) US

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(72) Inventors; and
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(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).

Declarations under Rule 4.17:
— *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:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

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.

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PNSDOCID: <WO 2004113330A1 | >

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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 60/562,182 (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

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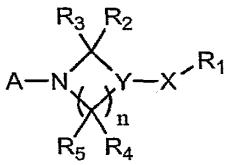
symptomology of these diseases. Accordingly, molecules that themselves alter the activity of EDG receptors are useful as therapeutic agents in the treatment of such diseases.

SUMMARY OF THE INVENTION

This application relates to compounds of Formula I:



in which:

n is 1, 2 or 3;

A is chosen from $-X_1C(O)OR_6$, $-X_1OP(O)(OR_6)_2$, $-X_1P(O)(OR_6)_2$, $-X_1S(O)_2OR_6$, $-X_1P(O)(R_6)OR_6$ and 1*H*-tetrazol-5-yl; wherein X_1 is chosen from a bond and C_{1-3}alkylene; and each R_6 is independently chosen from hydrogen and C_{1-6}alkyl;

X is a bond or is chosen from C_{1-4}alkyelene, $-X_1OX_2-$, $-X_1NR_7X_2-$, $-X_1C(O)NR_7X_2-$, $-X_1NR_7C(O)X_2-$, $-X_1S(O)X_2-$, $-X_1S(O)_2X_2-$, $-X_1SX_2-$ and C_{2-9}heteroarylene; wherein X_1 and X_2 are independently chosen from a bond and C_{1-3}alkylene; R_7 is chosen from hydrogen and C_{1-6}alkyl; and any heteroarylene of X is optionally substituted by a member of the group chosen from halo and C_{1-6}alkyl;

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, cyano, nitro, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted C_{1-6}alkyl and halo-substituted C_{1-6}alkoxy;

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)–, $–S(O)_2–$, $–NR_7–$ and –O–; wherein R_7 is chosen from hydrogen or C_{1-6}alkyl;

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R_2, R_3, R_4 and R_5 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 I 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 I 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 I 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 I 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

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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$_2$heteroaryl includes oxadiazole, triazole, and the like. C$_9$heteroaryl 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

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partially saturated, for example, 2,3-dihydro-1H-isoindole, 1,2,3,4-tetrahydro-quinoline, and the like.

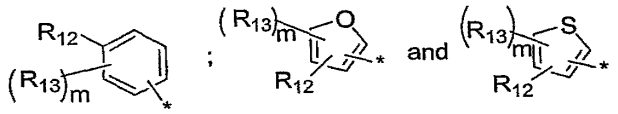
As used in the present invention, an EDG-1 selective compound (agent or modulator) has a specificity that is selective for EDG-1 over EDG-3 and over one or more of EDG-5, EDG-6, and EDG-8. As used herein, selectivity for one EDG receptor (a "selective receptor") over another EDG receptor (a "non-selective 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 I, R_1 is phenyl, naphthyl, furanyl 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_7– and –O–; wherein R_7 is hydrogen or $C_{1-6}alkyl$.

In another embodiment, Y is chosen from phenyl and benzooxazolyl; and X is a bond or is chosen from –X_1OX_2– and $C_{4-6}heteroarylene$; wherein X_1 and X_2 are independently chosen from a bond and $C_{1-3}alkylene$; wherein any heteroarylene of X is optionally substituted by a member of the group chosen from halo and $C_{1-6}alkyl$.

In another embodiment, R_1 is chosen from:

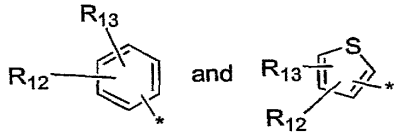


wherein the asterisk is the point of attachment of R_1 with X; m is chosen from 1 and 2; R_{12} is selected from hydrogen, $C_{6-10}arylC_{0-4}alkyl$, $C_{2-9}heteroarylC_{0-4}alkyl$, $C_{3-8}cycloalkylC_{0-4}alkyl$, $C_{3-8}heterocycloalkylC_{0-4}alkyl$ or $C_{1-6}alkyl$; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl group of R_{12} 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_{12} can optionally have a methylene replaced by an atom or group chosen from –S–, –S(O)–, –S(O)$_2$–, –NR$_{10}$– and –O–; wherein R_{10} is hydrogen or $C_{1-6}alkyl$; and R_{13} 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 –(CH$_2$)$_2$C(O)OH; and R_2, R_3, R_4 and R_5 are hydrogen.

In another embodiment, n is 1 or 2; Y is selected from phenyl and benzooxazolyl; and X is a bond or selected from [1,2,4]oxadiazole, -CH$_2$O-, -OCH$_2$-, isoxazoles and [1,3,4]oxadiazole.

In another embodiment, R_1 is selected from:



wherein R_{12} is selected from hydrogen, phenyl and cyclohexyl; wherein any phenyl or cyclohexyl of R_{12} is optionally substituted with methyl; and R_{13} is selected from trifluoromethyl, methyl and ethyl.

Preferred compounds of the invention are selected from 3-{6-[3-(2-trifluoromethyl-biphenyl-4-yl)-[1,2,4]oxadiazol-5-yl]-3,4-dihydro-1H-isoquinolin-2-yl}-propionic acid, 3-[6-(2-trifluoromethyl-biphenyl-4-yloxymethyl)-3,4-dihydro-1H-isoquinolin-2-yl]-propionic acid, 3-{5-[5-(2-trifluoromethyl-biphenyl-4-yl)-isoxazol-3-yl]-1,3-dihydro-isoindol-2-yl}-propionic acid, 3-{5-[5-(2-trifluoromethyl-biphenyl-4-yl)-[1,2,4]oxadiazol-3-yl]-1,3-dihydro-isoindol-2-yl}-propionic acid, 3-{5-[5-(2-trifluoromethyl-biphenyl-4-yl)-

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[1,3,4]oxadiazol-2-yl]-1,3-dihydro-isoindol-2-yl}-propionic acid, 3-[2-(2-trifluoromethyl-biphenyl-4-yl)-5,7-dihydro-oxazolo[4,5-f]isoindol-6-yl]-propionic acid, 3-{7-[5-(2-trifluoromethyl-biphenyl-4-yl)-[1,2,4]oxadiazol-3-yl]-3,4-dihydro-1H-isoquinolin-2-yl}-propionic acid, 3-{6-[5-(2-trifluoromethyl-biphenyl-4-yl)-[1,2,4]oxadiazol-3-yl]-3,4-dihydro-1H-isoquinolin-2-yl}-propionic acid, 3-{6-[5-(2-trifluoromethyl-biphenyl-4-yl)-[1,3,4]oxadiazol-2-yl]-3,4-dihydro-1H-isoquinolin-2-yl}-propionic acid, 3-[6-(3-trifluoromethyl-benzyloxy)-3,4-dihydro-1H-isoquinolin-2-yl]-propionic acid, 3-[6-(4-cyclohexyl-3-trifluoromethyl-benzyloxy)-3,4-dihydro-1H-isoquinolin-2-yl]-propionic acid, 3-[6-(2-trifluoromethyl-biphenyl-4-ylmethoxy)-3,4-dihydro-1H-isoquinolin-2-yl]-propionic acid, 3-[7-(4-cyclohexyl-3-trifluoromethyl-benzyloxy)-3,4-dihydro-1H-isoquinolin-2-yl]-propionic acid, 3-[6-(4-cyclohexyl-3-methyl-phenoxymethyl)-3,4-dihydro-1H-isoquinolin-2-yl]-propionic acid, 3-[6-(4-cyclohexyl-3-ethyl-phenoxymethyl)-3,4-dihydro-1H-isoquinolin-2-yl]-propionic acid, 3-[6-(2-ethyl-biphenyl-4-yloxymethyl)-3,4-dihydro-1H-isoquinolin-2-yl]-propionic acid and 3-[6-(2-ethyl-3'-methyl-biphenyl-4-yloxymethyl)-3,4-dihydro-1H-isoquinolin-2-yl]-propionic 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 I 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 I and their salts in hydrate or solvate form are also part of the invention.

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When the compounds of Formula I 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 I 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 I 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 3 and are therefore indicated for therapy. Compounds of Formula I 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 1×10^{-1011} to 1×10^{-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 I 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,

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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 I 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 I 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

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the form of lotions, gels, ointments or creams, or in a nasal or a suppository form. Pharmaceutical compositions comprising a compound of Formula I 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 I 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 I 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 I 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 I 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 I or a pharmaceutically acceptable salt thereof.

2. A compound of formula I, 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.

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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 I in free form or pharmaceutically acceptable salt form in association with a pharmaceutically acceptable diluent or carrier therefor.

4. A compound of formula I 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 I 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 I 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,

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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 that 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.

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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

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(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

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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^{R}), 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-Abl 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.

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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 I 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 I and

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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 I 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 I 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 I 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.

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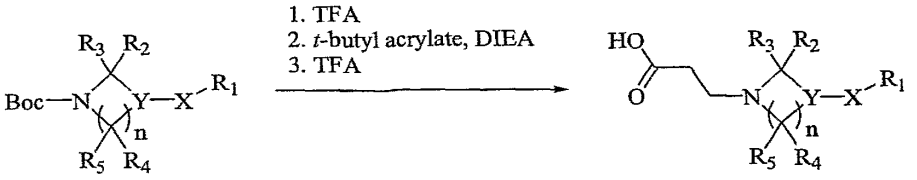
Compounds of Formula I can be prepared by proceeding as in the following reaction scheme:



(2) (I)

in which n, X, R_1, R_2, R_3, R_4 and R_5 are as defined for Formula I above. Compounds of Formula I can be prepared sequentially by treating a compound of formula 2 with a suitable acid (e.g. TFA, and the like), reacting with *t*-butyl acrylate in the presence of a suitable amine (e.g. DIEA, and the like) and removing the *t*-butyl protecting group with a suitable acid (e.g. TFA, and the like). The reaction proceeds at a temperature of about 0 to about 120°C and can take up to about 24 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.).

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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 I can be made by a process, which involves:

(a) the above reaction scheme; 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.

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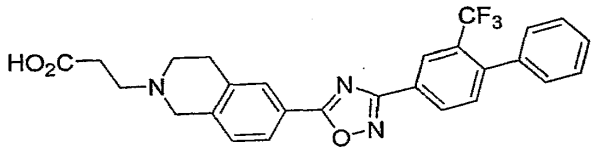
EXAMPLES

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

Synthesis of 3-{6-[3-(2-Trifluoromethyl-biphenyl-4-yl)-[1,2,4]oxadiazol-5-yl]-3,4-dihydro-1H-isoquinolin-2-yl}-propionic acid



To a suspension of 3,4-dihydro-1H-isoquinoline-2,6-dicarboxylic acid 2-tert-butyl ester (96 mg, 0.348 mmol) in toluene (4 mL) is added $SOCl_2$ (254 μL, 10 eq.). The mixture is heated to reflux for 3 hours. All the solvent is removed under reduced pressure. The residue is redissolved in toluene and evaporated to dryness twice to remove excess HCl and is dried under high vacuum for 2 hours to give crude 6-chlorocarbonyl-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester .

In a separate flask is charged with N-hydroxy-2-trifluoromethyl-biphenyl-4-carboxamidine (82 mg, 0.29 mmol) and DIEA (242 μL, 4 eq.) and CH_2Cl_2 (5 mL). The mixture is cooled to 0°C using an ice-salt bath. The chloride from the previous step is dissolved in CH_2Cl_2 (2 mL) and added slowly. After addition, the resulting mixture is warmed to room temperature and is stirred for 2 hours. All the solvent is evaporated and the mixture is purified by column chromatography (silica gel, EtOAc/Hexane, gradient) to 120 mg of the desired product. The product is dissolved in THF (2 mL) and mixed with TBAF (444 μL, 2 eq.) in a microwave vial. The mixture is heated to 100°C for 15 minutes using microwave irradiation. All the solvent is evaporated and the residue is purified by column chromatography (silica gel, EtOAc/Hexane, gradient) to give 70 mg of 6-[3-(2-trifluoromethyl-biphenyl-4-yl)-[1,2,4]oxadiazol-5-yl]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester.

To a solution of 6-[3-(2-trifluoromethyl-biphenyl-4-yl)-[1,2,4]oxadiazol-5-yl]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester (68 mg, 0.13 mmol) in CH_2Cl_2 (1

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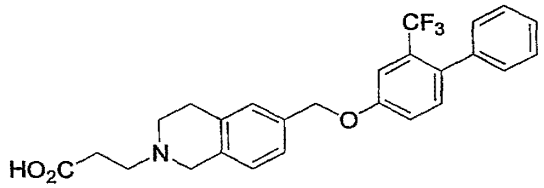
mL) is added TFA(2 mL). The mixture is stirred at room temperature for 30 minutes. All the solvents are removed under reduced pressure. The mixture is dissolved in CH_3OH (1.5 mL). Then DIEA (119 μL, 10 eq.) and acrylic acid tert-butyl ester (38 μL, 2 eq.) are added. The mixture is heated to 90°C for 20 minutes using microwave irradiation. All the solvent is evaporated and the crude product of 3-{6-[3-(2-trifluoromethyl-biphenyl-4-yl)-[1,2,4]oxadiazol-5-yl]-3,4-dihydro-1H-isoquinolin-2-yl}-propionic acid tert-butyl ester is used in the next step without further purification.

To a solution of crude 3-{6-[3-(2-trifluoromethyl-biphenyl-4-yl)-[1,2,4]oxadiazol-5-yl]-3,4-dihydro-1H-isoquinolin-2-yl}-propionic acid tert-butyl ester in CH_2Cl_2 (1 mL) is added TFA(1 mL). The mixture is stirred at room temperature for an hour. All the solvents are evaporated. The mixture is purified by reverse phase preparative LC/MS to give 3-{6-[3-(2-Trifluoromethyl-biphenyl-4-yl)-[1,2,4]oxadiazol-5-yl]-3,4-dihydro-1H-isoquinolin-2-yl}-propionic acid: ^{1}H NMR (DMSO, 400 MHz) δ 8.52 (s, 1H), 8.38 (d, 1H), 8.15 (s, 1H), 8.10 (d, 1H), 7.68 (d, 1H), 7.50 (m, 4H), 7.38 (m, 2H), 3.20-3.50 (m, 8H), 2.92 (t, 2H), MS (ES^+): $(494.10, M+1)^+$.

Example 2

Synthesis of 3-[6-(2-Trifluoromethyl-biphenyl-4-yloxymethyl)-3,4-dihydro-1H-isoquinolin-2-yl]-propionic acid



To a solution of 6-hydroxymethyl-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester (85 mg, 0.323 mmol) in CH_2Cl_2 (1.5 mL) is added a solution of 4-chloro-3-trifluoromethyl-phenol (76 mg, 1.23 eq.) in CH_2Cl_2 (0.5 mL), PPh_3 (127 mg, 1.5 eq.), and 1,1'-(azodicarbonyl)-dipiperidine (122 mg, 1.5 eq.). The mixture is stirred at room temperature overnight. All the solvent is removed under reduced pressure and the mixture is purified by column chromatography (silica gel, EtOAc/Hexane, gradient) to give 70 mg of 6-

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(4-chloro-3-trifluoromethyl-phenoxymethyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester

To a solution of 6-(4-chloro-3-trifluoromethyl-phenoxymethyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester (70 mg, 0.158 mmol) in CH_2Cl_2 (1 mL) is added TFA(1 mL). The mixture is stirred at room temperature for 30 minutes. All the solvents are removed under reduced pressure. The mixture is dissolved in CH_3OH (1.5 mL). Then DIEA (269 μL, 10 eq.) and acrylic acid tert-butyl ester (46 μL, 2 eq.) are added. The mixture is heated to 90°C for 20 minutes using microwave irradiation. All the solvent is evaporated and the mixture is purified by column chromatography (silica gel, EtOAc/Hexane, gradient) to give 56 mg of 3-[6-(4-chloro-3-trifluoromethyl-phenoxymethyl)-3,4-dihydro-1H-isoquinolin-2-yl]-propionic acid tert-butyl ester.

A microwave vial is charged with 3-[6-(4-chloro-3-trifluoromethyl-phenoxymethyl)-3,4-dihydro-1H-isoquinolin-2-yl]-propionic acid tert-butyl ester (56 mg, 0.119 mmol), phenylboronic acid (17 mg, 1.2 eq.), $Pd(OAc)_2$ (1.3 mg, 5 mol%), (dicyclohexylphosphino)biphenyl (4.2mg, 10 mol%), KF (21mg, 3 eq.), and THF (0.25 mL). The resulting mixture is heated to 120°C using microwave irradiation for 20 minutes. The mixture is filtered through celite. The celite is washed with EtOAc several times. The filtrate is then concentrated to give a dark oil. The mixture is purified by column chromatography (silica gel, EtOAc/Hexane, gradient) to give 3-[6-(2-trifluoromethyl-biphenyl-4-yloxymethyl)-3,4-dihydro-1H-isoquinolin-2-yl]-propionic acid tert-butyl ester.

To a solution of 3-[6-(2-trifluoromethyl-biphenyl-4-yloxymethyl)-3,4-dihydro-1H-isoquinolin-2-yl]-propionic acid tert-butyl ester (35 mg, 0.068 mmol) in CH_2Cl_2 (1 mL) is added TFA (1 mL). The mixture is stirred at room temperature for an hour. All the solvents are evaporated. The mixture is purified by reverse phase preparative LC/MS to give 3-[6-(2-trifluoromethyl-biphenyl-4-yloxymethyl)-3,4-dihydro-1H-isoquinolin-2-yl]-propionic acid: ^1H NMR (CD_3OD, 400 MHz) δ 7.45 (m, 2H), 7.38-7.41 (m, 3H), 7.35 (s, 1H), 7.16-7.23 (m, 5H), 4.85 (s, 2H), 4.54 (s, 2H), 3.68 (m, 2H), 3.60 (t, 2H), 3.27 (t, 2H), 2.96 (t, 2H), MS (ES^+): $(456.20, M+1)^+$.

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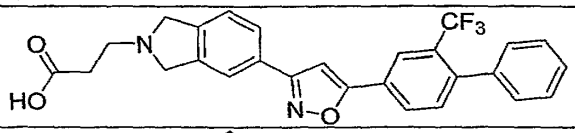
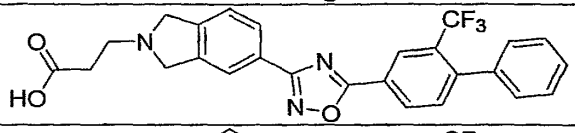
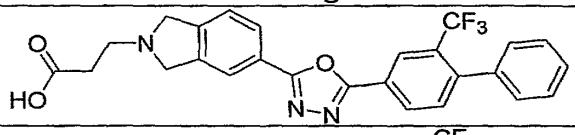
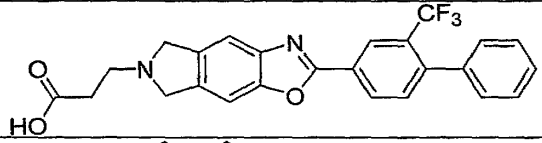
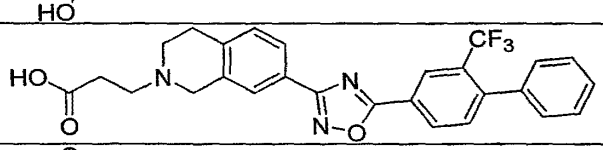
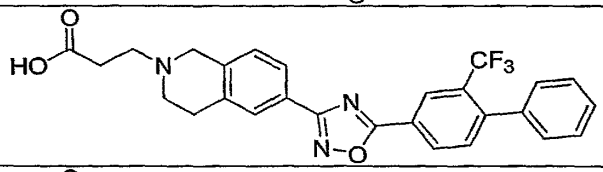
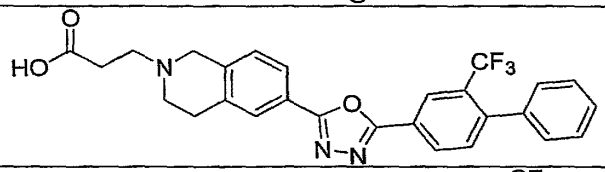
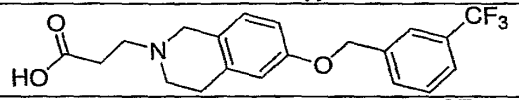
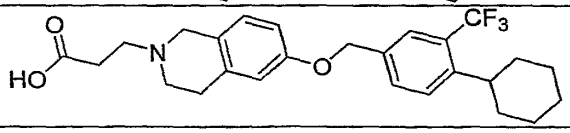
By repeating the procedure described in the above examples, using appropriate starting materials, the following compounds of Formula I are obtained as identified in Table 1.

TABLE 1

Compound	Structure	Physical Data MS ES (M+1)
1		479.2
2		480.2
3		480.2
4		453.1
5		494.2
6		494.2
7		494.2
8		380.1
9		462.2

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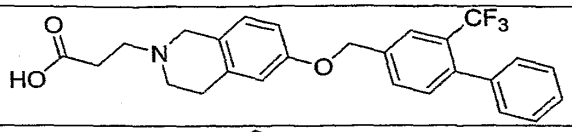
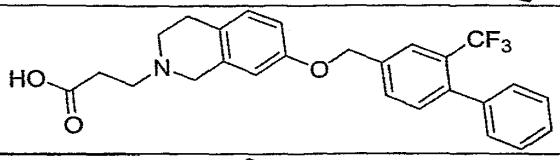
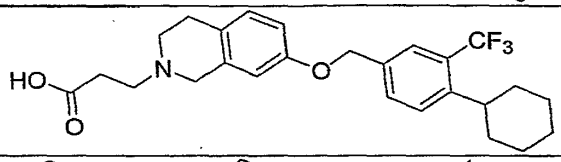
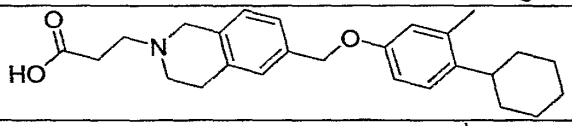
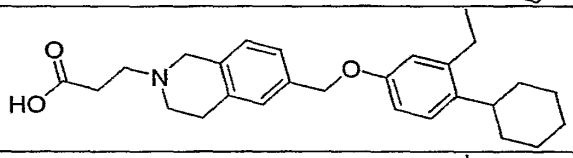
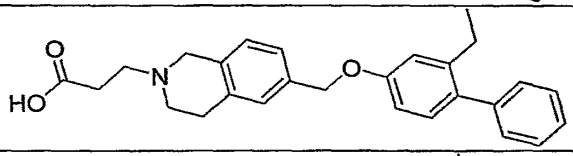
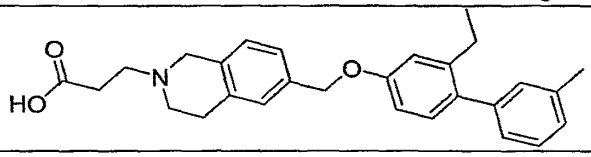
Compound	Structure	Physical Data MS ES (M+1)
10		456.2
11		456.2
12		462.3
13		
14		
15		
16		

Example 3

Compounds of Formula I Exhibit Biological Activity

5

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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).

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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-[6-(4-cyclohexyl-3-trifluoromethyl-benzyloxy)-3,4-dihydro-1H-isoquinolin-2-yl]-propionic acid (compound 9) 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,

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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-[6-(4-cyclohexyl-3-trifluoromethyl-benzyloxy)-3,4-dihydro-1H-isoquinolin-2-yl]-propionic acid (compound 9) exhibits an ED50 of 0.2 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 I 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

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content of the vascularized tissues around the chamber is determined. Animals treated with a compound of formula I show reduced weight and/or blood content of the vascularized tissues compared to animals treated with vehicle alone. Compounds of Formula I are anti-angiogenic when administered at a dose of about 0.3 to about 3mg/kg.

E: <u>In vitro: Antitumor Activity</u>

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 I 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 250□g/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 I 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.

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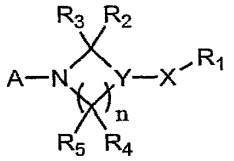
WE CLAIM

1. A compound of Formula I:



in which:

n is 1, 2 or 3;

A is chosen from $-X_1C(O)OR_6$, $-X_1OP(O)(OR_6)_2$, $-X_1P(O)(OR_6)_2$, $-X_1S(O)_2OR_6$, $-X_1P(O)(R_6)OR_6$ and 1*H*-tetrazol-5-yl; wherein X_1 is chosen from a bond and C_{1-3}alkylene; and each R_6 is independently chosen from hydrogen and C_{1-6}alkyl;

X is a bond or is chosen from C_{1-4}alkyelene, $-X_1OX_2-$, $-X_1NR_7X_2-$, $-X_1C(O)NR_7X_2-$, $-X_1NR_7C(O)X_2-$, $-X_1S(O)X_2-$, $-X_1S(O)_2X_2-$, $-X_1SX_2-$ and C_{2-9}heteroarylene; wherein X_1 and X_2 are independently chosen from a bond and C_{1-3}alkylene; R_7 is chosen from hydrogen and C_{1-6}alkyl; and any heteroarylene of X is optionally substituted by a member of the group chosen from halo and C_{1-6}alkyl;

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, cyano, nitro, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted C_{1-6}alkyl and halo-substituted C_{1-6}alkoxy;

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)–, $–S(O)_2–$, $–NR_7–$ and –O–; wherein R_7 is chosen from hydrogen or C_{1-6}alkyl;

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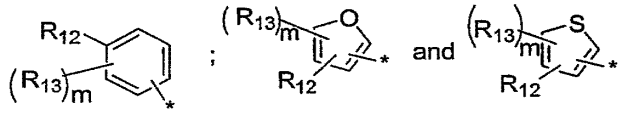
R_2, R_3, R_4 and R_5 are independently chosen from hydrogen, C_{1-6}alkyl, halo, hydroxy, C_{1-6}alkoxy, halo-substituted C_{1-6}alkyl and halo-substituted C_{1-6}alkoxy; and the pharmaceutically acceptable salts, hydrates, solvates, isomers and prodrugs thereof.

2. The compound of claim 1 in which R_1 is phenyl, naphthyl, furanyl 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$_7$– and –O–; wherein R_7 is hydrogen or C_{1-6}alkyl.

3. The compound of claim 1 in which Y is chosen from phenyl and benzooxazolyl; and X is a bond or is chosen from –X_1OX_2– and C_{4-6}heteroarylene; wherein X_1 and X_2 are independently chosen from a bond and C_{1-3}alkylene; wherein any heteroarylene of X is optionally substituted by a member of the group chosen from halo and C_{1-6}alkyl.

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 X; m is chosen from 1 and 2; R_{12} is selected from hydrogen, 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_{12} 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_{12} can optionally have a methylene replaced by an atom or group chosen from –S–, –S(O)–, –S(O)$_2$–, –NR$_{10}$– and –O–; wherein R_{10} is

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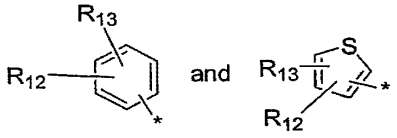
hydrogen or C_{1-6}alkyl; and R_{13} is chosen from halo, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl and halo-substituted-C_{1-6}alkoxy.

5. The compound of claim 1 in which A is $-(CH_2)_2C(O)OH$; and R_2, R_3, R_4 and R_5 are hydrogen.

6. The compound of claim 5 in which n is 1 or 2; Y is selected from phenyl and benzooxazolyl; and X is a bond or selected from [1,2,4]oxadiazole, $-CH_2O-$, $-OCH_2-$, isoxazoles and [1,3,4]oxadiazole.

7. The compound of claim 6 in which R_1 is selected from:



wherein R_{12} is selected from hydrogen, phenyl and cyclohexyl; wherein any phenyl or cyclohexyl of R_{12} is optionally substituted with methyl; and R_{13} is selected from trifluoromethyl, methyl and ethyl.

8. The compound of claim 7 selected from 3-{6-[3-(2-trifluoromethyl-biphenyl-4-yl)-[1,2,4]oxadiazol-5-yl]-3,4-dihydro-1H-isoquinolin-2-yl}-propionic acid, 3-[6-(2-trifluoromethyl-biphenyl-4-yloxymethyl)-3,4-dihydro-1H-isoquinolin-2-yl]-propionic acid, 3-{5-[5-(2-trifluoromethyl-biphenyl-4-yl)-isoxazol-3-yl]-1,3-dihydro-isoindol-2-yl}-propionic acid, 3-{5-[5-(2-trifluoromethyl-biphenyl-4-yl)-[1,2,4]oxadiazol-3-yl]-1,3-dihydro-isoindol-2-yl}-propionic acid, 3-{5-[5-(2-trifluoromethyl-biphenyl-4-yl)-[1,3,4]oxadiazol-2-yl]-1,3-dihydro-isoindol-2-yl}-propionic acid, 3-[2-(2-trifluoromethyl-biphenyl-4-yl)-5,7-dihydro-oxazolo[4,5-f]isoindol-6-yl]-propionic acid, 3-{7-[5-(2-trifluoromethyl-biphenyl-4-yl)-[1,2,4]oxadiazol-3-yl]-3,4-dihydro-1H-isoquinolin-2-yl}-propionic acid, 3-{6-[5-(2-trifluoromethyl-biphenyl-4-yl)-[1,2,4]oxadiazol-3-yl]-3,4-dihydro-1H-isoquinolin-2-yl}-propionic acid, 3-{6-[5-(2-trifluoromethyl-biphenyl-4-yl)-

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[1,3,4]oxadiazol-2-yl]-3,4-dihydro-1H-isoquinolin-2-yl}-propionic acid, 3-[6-(3-trifluoromethyl-benzyloxy)-3,4-dihydro-1H-isoquinolin-2-yl]-propionic acid, 3-[6-(4-cyclohexyl-3-trifluoromethyl-benzyloxy)-3,4-dihydro-1H-isoquinolin-2-yl]-propionic acid, 3-[6-(2-trifluoromethyl-biphenyl-4-ylmethoxy)-3,4-dihydro-1H-isoquinolin-2-yl]-propionic acid, 3-[7-(4-cyclohexyl-3-trifluoromethyl-benzyloxy)-3,4-dihydro-1H-isoquinolin-2-yl]-propionic acid, 3-[6-(4-cyclohexyl-3-methyl-phenoxymethyl)-3,4-dihydro-1H-isoquinolin-2-yl]-propionic acid, 3-[6-(4-cyclohexyl-3-ethyl-phenoxymethyl)-3,4-dihydro-1H-isoquinolin-2-yl]-propionic acid, 3-[6-(2-ethyl-biphenyl-4-yloxymethyl)-3,4-dihydro-1H-isoquinolin-2-yl]-propionic acid and 3-[6-(2-ethyl-3'-methyl-biphenyl-4-yloxymethyl)-3,4-dihydro-1H-isoquinolin-2-yl]-propionic 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.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/15699

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : C07D 413/10; A61K 31/4725
US CL : 546/167; 514/307
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. : 546/167; 514/307

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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SMITH, C.D. et al. Electrospray mass spectrometry of stable iminyl nitroxide and nitronyl nitroxide free radicals. Journal of Mass Spectrometry. 2002, Vol. 37 No. 9, pages 897-902.	8

☐ 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
01 October 2004 (01.10.2004)

Date of mailing of the international search report
20 OCT 2004

Name and mailing address of the ISA/US
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Authorized officer
Janet L Coppins

Telephone No. 571-272-1600

Form PCT/ISA/210 (second sheet) (January 2004)

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Continuation of Box II Reason 2:
In these claims, the numerous variables (e.g. R1-R13, A, X, X1, X2n, etc), their voluminous complex meanings, 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 in the claims, which is the first named compound of claim 8.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/15699

Box No. 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. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-7 and 9-12
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. ☐ 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 No. 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.

Form PCT/ISA/210 (continuation of first sheet(2)) (January 2004)

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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

CORRECTED VERSION

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
29 December 2004 (29.12.2004)

PCT

(10) International Publication Number
WO 2004/113330 A1

(51) International Patent Classification[7]: C07D 413/10, A61K 31/4725

(21) International Application Number: PCT/US2004/015699

(22) International Filing Date: 19 May 2004 (19.05.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/471,931 19 May 2003 (19.05.2003) US
60/562,182 14 April 2004 (14.04.2004) US

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(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).

Declarations under Rule 4.17:

— *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:

— *with international search report*

(48) Date of publication of this corrected version: 30 March 2006

(15) Information about Correction: see PCT Gazette No. 13/2006 of 30 March 2006

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.

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\SDOCID: <WO_____2004113330A1_IA>

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Electronic Patent Application Fee Transmittal	
Application Number:	
Filing Date:	
Title of Invention:	S1P RECEPTOR MODULATORS FOR TREATING MULTIPLE SCLEROSIS
First Named Inventor/Applicant Name:	Peter C Hiestand
Filer:	Cozette Marie McAvoy/Cindy Klepacky
Attorney Docket Number:	50279-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	330	330
Natl Stage Search Fee - Report provided	1642	1	430	430
National Stage Exam - all other cases	1633	1	220	220
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**980**

Electronic Acknowledgement Receipt

EFS ID:	4409272
Application Number:	12303765
International Application Number:	PCT/EP07/05597
Confirmation Number:	9401
Title of Invention:	S1P RECEPTOR MODULATORS FOR TREATING MULTIPLE SCLEROSIS
First Named Inventor/Applicant Name:	Peter C Hiestand
Customer Number:	01095
Filer:	Cozette Marie McAvoy/Cindy Klepacky
Filer Authorized By:	Cozette Marie McAvoy
Attorney Docket Number:	50279-US-PCT
Receipt Date:	08-DEC-2008
Filing Date:	
Time Stamp:	10:44:52
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	$980
RAM confirmation Number	5443
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. 1.492 (National application filing, search, and examination fees)

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		50279-US-PCT.pdf	1034286 5eb03b2f60fca3485f6e0ba9a9e88cc9b20c3e16	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 Letter	6	7
Information Disclosure Statement (IDS) Filed (SB/08)	8	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	Foreign Reference	2006058316.pdf	1240659 7c85688a11198515f30d25aea6ec910b5d45343a	no	27

Warnings:

Information:

3	Foreign Reference	2004113330.pdf	2078119 d3210278a8fed9c0a7db3300220893f05776f7aa	no	40

Warnings:

Information:

4	NPL Documents	Brinkmann.pdf	636115 b2127af9bb628a9fe1e0ca39711ec21db2cefe8d	no	6

Warnings:

Information:

5	Fee Worksheet (PTO-06)	fee-info.pdf	33205 9c4abf4c6c0216383ec9ebf1df52b4d96e1dcf43	no	2
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			Total Files Size (in bytes):	5022384	

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International Application Number:	PCT/EP07/05597
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File Listing:

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1		50279-US-PCT.pdf	1034286 5eb03b2f60fca3485f6e0ba9a9e88cc9b20c3e16	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 Letter	6	7
Information Disclosure Statement (IDS) Filed (SB/08)	8	8
Preliminary Amendment	9	10
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2	Foreign Reference	2006058316.pdf	1240659 7c85688a11198515f30d25aea6ec910b5d45343a	no	27

Warnings:

Information:

3	Foreign Reference	2004113330.pdf	2078119 d3210278a8fed9c0a7db3300220893f05776f7aa	no	40

Warnings:

Information:

4	NPL Documents	Brinkmann.pdf	636115 b2127af9bb628a9fe1e0ca39711ec21db2cefe8d	no	6

Warnings:

Information:

5	Fee Worksheet (PTO-06)	fee-info.pdf	33205 9c4abf4c6c0216383ec9ebf1df52b4d96e1dcf43	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	5022384	

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New International Application Filed with the USPTO as a Receiving Office
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Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/EP2007/005597

International filing date: 25 June 2007 (25.06.2007)

Document type: Certified copy of priority document

Document details: Country/Office: GB
Number: 0612721.1
Filing date: 27 June 2006 (27.06.2006)

Date of receipt at the International Bureau: 16 July 2007 (16.07.2007)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)

World Intellectual Property Organization (WIPO) - Geneva, Switzerland
Organisation Mondiale de la Propriété Intellectuelle (OMPI) - Genève, Suisse

UK Intellectual Property Office

For Creativity and Innovation

EP2007/005597

25.06.07

Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with patent application GB0612721.1 filed on 27 June 2006.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

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Signed Andrew Gerry

Dated 17 April 2007

UK Intellectual Property Office is an operating name of the Patent Office

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28JUN06 30.00 ACCOUNT 0612721.1

Patents Form 1/77

Patents Act 1977
(Rule 16)

1/77

Request for grant of a patent

(An explanatory leaflet on how to fill in this form is available from the Patent Office)

The Patent Office

Cardiff Road
Newport
South Wales
NP10 8QQ

Application number GB

0612721.1

1. Your reference: *(optional)* 50279P1

2. Full name, address and postcode of the applicant or of each applicant *(underline all surnames)*:

Novartis AG
Lichtstrasse 35
CH - 4056 Basel
Switzerland

Patents ADP number *(if you know it)*: 7125487605

If the applicant is a corporate body, give the country/state of its incorporation: Switzerland

3. Title of the invention: Organic Compounds

4. Name of your agent *(if you have one)*:

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*:

Novartis Pharmaceuticals UK Limited
Patents and Trademarks
Wimblehurst Road
Horsham, West Sussex
RH12 5AB

Patents ADP number *(if you know it)*: 07181522002

	Country	Application number *(if you know it)*	Date of filing *(day / month / year)*
5. Priority declaration: Are you claiming priority from one or more earlier-filed patent applications? If so, please give details of the application(s):			

	Number of earlier UK application	Date of filing *(day / month / year)*
6. Divisionals etc: Is this application a divisional application, or being made following resolution of an entitlement dispute about an earlier application? If so, please give the application number and filing date of the earlier application:		

7. Inventorship: (Inventors must be individuals not companies) (Please tick the appropriate boxes)

Are all the applicants named above also inventors?	YES ☐	NO ☑
If yes, are there any other inventors?	YES ☐	NO ☐

8. Are you paying the application fee with this form? YES ☑ NO ☐

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9. Accompanying documents: not counting duplicates, please enter the number of pages of each item accompanying this form:

Continuation sheets of this form:	
Description:	16
Claim(s):	1
Abstract:	
Drawing(s):	

If you are not filing a description, please give details of the previous application you are going to rely upon:

Country	Application number	Date of filing (day / month / year)

10. If you are also filing any of the following, state how many against each item.

Priority documents:	
Statement of inventorship and right to grant of a patent (Patents Form 7/77):	
Request for search (Patents Form 9A/77):	1
Request for substantive examination (Patents Form 10/77):	
Any other documents: (please specify)	

11. I/We request the grant of a patent on the basis of this application.

Signature(s): Date: 27/06/2006

12. Name, e-mail address, telephone, Fax and/or mobile number, if any, of a contact point for the applicant: Mrs S Schnerr phone: 01403 323 069 fax : 01403 323 823

Warning

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Notes

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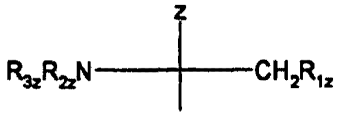
Organic Compounds

The present invention relates to the use of an S1P receptor modulator in the treatment or prevention of neo-angiogenesis associated with a demyelinating disease, e.g. multiple sclerosis.

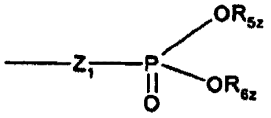
S1 P receptor modulators are typically sphingosine analogues, such as 2-substituted 2-amino- propane-1,3-diol or 2-amino-propanol derivatives, e. g. a compound comprising a group of formula X

Sphingosine-1 phosphate (hereinafter "S1P") is a natural serum lipid. Presently there are eight known S1P receptors, namely S1P1 to S1P8. S1 P receptor modulators 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

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of Z and R_{12} is or comprises a residue of formula (a), signals as an agonist at one of more sphingosine-1-phosphate receptor.

S1P receptor modulators 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.

The binding affinity of S1P receptor modulators to individual human S1P receptors may be determined in following assay:
S1P receptor 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 preferably have a binding affinity to S1P receptor <50 nM.

Preferred S1P receptor 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:

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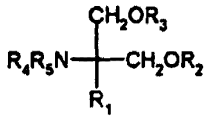
A S1P receptor modulator or the vehicle is administered orally by gavage to rats. Tail blood for hematological monitoring is obtained on day –1 to give the baseline individual values, and at 2, 6, 24, 48 and 72 hours after application. In this assay, the S1P receptor agonist or modulator depletes peripheral blood lymphocytes, e.g. by 50%, when administered at a dose of e.g. < 20 mg/kg.

Examples of appropriate S1P receptor 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

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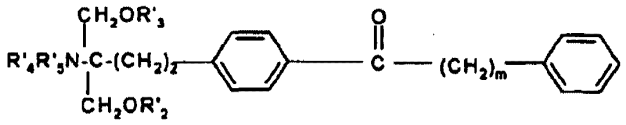
the alkyl moiety may have

- 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}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, 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;

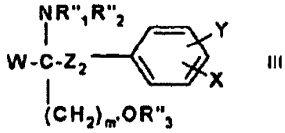
- Compounds as disclosed in EP 1002792A1, e.g. a compound of formula II



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_{3-6}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,

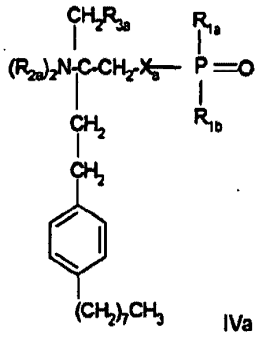
C_{1-6}alkylamino, acylamino, haloC_{1-6}alkyl or halogen, Z_2 is a single bond or a straight chain alkylene having a number or carbon atoms of q,

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,

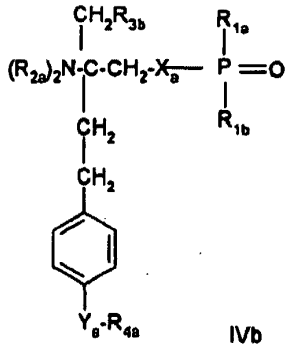
or a pharmaceutically acceptable salt or hydrate thereof,

- 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_{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 WO02/06268Al, e.g. a compound of formula V

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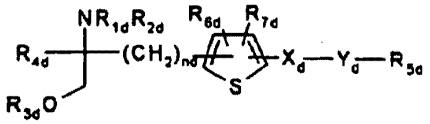
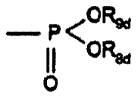


V

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;

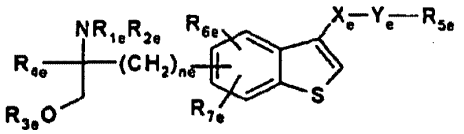
each of R_{8d} and R_{9d}, independently, is H or C_{1-4}alkyl optionally substituted by halogen;

<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;

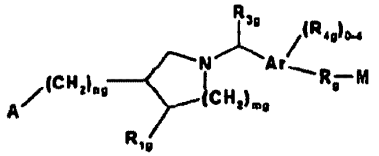
-Compounds as disclosed in JP-14316985 (JP2002316985), e.g. a compound of formula VI



VI

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 WO03/062252A1, e.g. a compound of formula VII

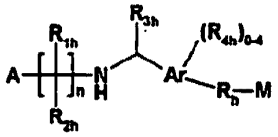


VII

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 VIII



VIII

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 optionally 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

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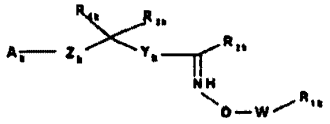
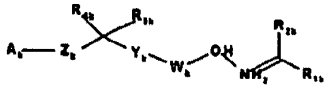
substituted by 1-3 halogens; and each of R_h and M has one of the significances as indicated for B and C, respectively, in WO03/062248A2

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 IXa or IXb



IXa



IXb

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.

The compounds of formulae I to IXb may exist in free or salt form. Examples of pharmaceutically acceptable salts of the compounds of the formulae I to VI 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,

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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 V "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)

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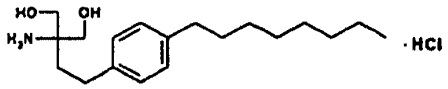
ethyl]propane-1,3-diol in free form or in a pharmaceutically acceptable salt form (referred to hereinafter as Compound A), e.g. the hydrochloride, as shown:



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 VI is (2R)-2-amino-4-[3-(4-cyclohexyloxybutyl)-benzo[b]thien-6-yl]-2-methylbutan-1-ol.

A preferred compound of formula IXa is e.g. 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, or a prodrug thereof.

S1P receptor agonists or modulators are known as having immunosuppressive properties or anti-angiogenic properties in the treatment of tumors, e.g. as disclosed in EP627406A1, WO 04/103306, WO 05/000833, WO 05/103309, WO 05/113330 or WO 03/097028.

Multiple sclerosis (MS) is an immune-mediated disease of the central nervous system with chronic inflammatory demyelination leading to progressive decline of motor and sensory functions and permanent disability. The therapy of multiple sclerosis is only partially effective, and in most cases only offers a short delay in disease progression despite anti-inflammatory and immunosuppressive treatment. Accordingly, there is a need for agents which are effective in the inhibition or treatment of demyelinating diseases, e.g. multiple

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sclerosis or Guillain-Barré syndrome, including reduction of, alleviation of, stabilization of or relief from the symptoms which affect the organism.

Characteristic pathological features of demyelinating diseases include inflammation, demyelination and axonal and oligodendrocyte loss. In addition lesions can also have a significant vascular component. A firm link has recently been established between chronic inflammation and angiogenesis and neovascularization seems to have a significant role in the progression of disease.

It has now been found that S1P receptor modulators have an inhibitory effect on neo-angiogenesis associated with demyelinating diseases, e.g. MS.

In a series of further specific or alternative embodiments, the present invention provides:

1.1 A method for preventing, inhibiting or treating neo-angiogenesis associated with a demyelinating disease, e.g. MS, in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of an S1P receptor modulator, e.g. a compound of formulae I to IXb.

1.2 A method for alleviating or delaying progression of the symptoms of a demyelinating disease, e.g. multiple sclerosis or Guillain-Barré syndrome, in a subject in need thereof, in which method neo-angiogenesis associated with said disease is prevented or inhibited, comprising administering to said subject a therapeutically effective amount of an S1P receptor modulator, e.g. a compound of formulae I to IXb.

1.3 A method for reducing or preventing or alleviating relapses in a demyelinating disease, e.g. multiple sclerosis or Guillain-Barré syndrome, in a subject in need thereof, in which method neo-angiogenesis associated with said disease is prevented or inhibited, comprising administering to said subject a therapeutically effective amount of an S1P receptor modulator, e.g. a compound of formulae I to IXb.

1.4 A method for slowing progression of a demyelinating disease, e.g. multiple sclerosis or Guillain-Barré syndrome, in a subject being in a relapsing-remitting phase of the disease, in which method neo-angiogenesis associated with said disease is prevented or inhibited, comprising administering to said subject a therapeutically effective amount of an S1P receptor modulator, e.g. a compound of formulae I to XIb.

1.5 A method as indicated above, wherein the S1P receptor modulator is administered intermittently.

For example, the S1P receptor modulator may be administered to the subject every 2nd or 3rd day or once a week.

2. A pharmaceutical composition for use in any one of the methods 1.1 to 1.5, comprising an S1P receptor modulator, e.g. a compound of formulae I to IXb as defined hereinabove, together with one or more pharmaceutically acceptable diluents or carriers therefor.

3. An S1P receptor modulator, e.g a compound of formula I to IXb as defined herein above, for use in any one of the methods 1.1 to 1.5.

4 An S1P receptor modulator, e.g. a compound of formulae I to IXb as defined herein above, for use in the preparation of a medicament for use in any one of the methods 1.1 to 1.5.

Clinicians usually categorize patients having MS into four types of disease patterns:

- *Relapsing-remitting* (RR-MS): Discrete motor, sensory, cerebellar or visual attacks that occur over 1-2 weeks and often resolve over 1-2 months. Some patients accrue disability with each episode, yet remain clinically stable between relapses. About 85% of patients initially experience the RR form of MS, but within 10 years about half will develop the secondary progressive form.
- *Secondary-progressive* (SP-MS): Initially RR followed by gradually increasing disability, with or without relapses. Major irreversible disabilities appear most often during SP.
- *Primary-progressive* (PP-MS): Progression disease course from onset without any relapses or remissions, affecting about 15% of MS patients.
- *Progressive-relapsing* (PR-MS): Progressive disease from onset with clear acute relapses; periods between relapses characterized by continuing progression.

Utility of the S1P receptor modulators, e.g. the S1P receptor modulators comprising a group of formula X, in preventing or treating neo-angiogenesis associated with a demyelinating disease as hereinabove specified, may be demonstrated in animal test methods as well as in clinic, for example in accordance with the methods hereinafter described.

<u>In vivo: Relapsing Experimental Autoimmune Encephalomyelitis</u> (EAE)

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Disease is induced in female Lewis rats by immunization with guinea pig spinal cord tissue emulsified in complete Freund's adjuvant. This results in an acute disease within 11 days, followed by an almost complete remission around day 16 and a relapse at around days 26. On day 26 rats are thoracectomized after having been deeply anesthetized with Isoflurane (3%, 20 L / min) and perfused through the left ventricle of the heart. The left ventricle is punctured with a 19 gauge needle from a winged infusion set (SV-19BLK; Termudo, Elkton, MD), which is connected to an airtight pressurized syringe containing the rinsing solution (NaCl 0.9% with 250,000 U/l heparin at 35°C). The right atrium is punctured to provide outflow, and the perfusate is infused under a precise controlled pressure of 120 mm Hg. The perfusion is continued for 5 min (at a constant rate of 20 ml/min) followed by a pre-fixation solution (2% performaldehyde in PBS at 35°C). Finally, up to 30 ml of polyurethane resin (PUII4; Vasqtec, Zürich, Switzerland) is infused at the same rate. After 48 h, the resin-filled brain and spinal cord are excised from the animal and the soft tissue removed by maceration in 7.5% KOH during 24 hr at 50°C. The casts are then thoroughly cleaned with and stored in distilled water before drying by lyophilization. These vascular casts are quantitated using micro computer tomography.

In this assay, a S1P1 receptor modulator, e.g. Compound A significantly blocks disease-associated neo-angiogenesis when administered to the animals at a dose of from 0.1 to 20 mg/kg p.o. For example, Compound A, in the hydrochloride salt form, fully blocks disease-associated angiogenesis and completely inhibits the relapse phases when administered daily at a dose of 0.3 mg/kg p.o. The same effect is obtained when Compound A, in the hydrochloride salt form, is administered p.o. at 0.3 mg/kg every 2nd or 3rd day or once a week.

C. Clinical Trial

Investigation of clinical benefit of a S1P receptor agonist, e.g. a compound of formula I, e.g. Compound A.

20 patients with relapsing-remitting MS receive said compound at a daily dosage of 0.5, 1.25 or 2.5 mg p.o. The general clinical state of the patient is investigated weekly by physical and laboratory examination. Disease state and changes in disease progression are assessed every 2 months by radiological examination (MRI) and physical examination. Initially patients receive treatment for 2 to 6 months. Thereafter, they remain on treatment for as long as their disease does not progress and the drug is satisfactorily tolerated.

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Main variables for evaluation: Safety (adverse events), standard serum biochemistry and hematology, magnetic resonance imaging (MRI).

Daily dosages required in practicing the method of the present invention when a S1P receptor modulator alone is used will vary depending upon, for example, the compound used, the host, the mode of administration and the severity of the condition to be treated. A preferred daily dosage range is about from 0.1 to 100 mg as a single dose or in divided doses. Suitable daily dosages for patients are on the order of from e.g. 0.1 to 50 mg p.o. The S1P receptor modulator may be administered by any conventional route, in particular enterally, e.g. orally, e.g. in the form of tablets, capsules, drink solutions, nasally, pulmonary (by inhalation) or parenterally, e.g. in the form of injectable solutions or suspensions. Suitable unit dosage forms for oral administration comprise from ca. 0.1 to 30 mg, usually 0.25 to 30 mg S1P receptor modulator, together with one or more pharmaceutically acceptable diluents or carriers therefore. As already mentioned, the S1Preceptor modulator, e.g. Compound A, may alternatively be administered intermittently, e.g. at a dose of 0.5 to 30 mg every other day or once a week.

According to another embodiment of the invention, the S1P receptor modulator may be administered as the sole active ingredient or in conjunction with, e.g. as an adjuvant to, a VEGF-receptor antagonist.

Examples of suitable VEGF-receptor antagonist include e.g. compounds, proteins or antibodies which inhibit the VEGF receptor tyrosine kinase, inhibit a VEGF receptor or bind to VEGF, and are e.g. 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, WO 01/55114, WO 01/58899 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.

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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.

4-Pyridylmethyl-phthalazine derivatives are e.g. preferred inhibitors of VEGF receptor tyrosine kinase. Such derivatives and their preparation, pharmaceutical formulations thereof and methods of making such compounds are described in WO00/59509, EP02/04892, WO01/10859 and, in particular, in U.S. Patent No. 6,258,812, which are here incorporated by reference.

Where the S1P receptor modulator is administered in conjunction with a VEGF-receptor antagonist, dosages of the co-administered VEGF-receptor agonist 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 S1P receptor modulator and a VEGF-receptor antagonist, e.g. as indicated above.

6. A pharmaceutical combination, e.g. a kit, comprising a) a first agent which is a S1P receptor modulator as disclosed herein, in free form or in pharmaceutically acceptable salt form, and b) a VEGF-receptor antagonist, e.g. as indicated 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 S1P receptor modulator and a VEGF-receptor antagonist, 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 S1P receptor modulator and a VEGF-receptor antagonist, 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.

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CLAIMS

1. A method for preventing, inhibiting or treating neo-anglogenesis associated with a demyelinating disease, e.g. multiple sclerosis, in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of an S1P receptor modulator, e.g. a compound of formulae I to IXb as defined hereinabove.

2. A method according to claim 1, wherein the S1P receptor modulator is administered intermittently.

3. A pharmaceutical composition for use in a method according to claim 1 or 2, comprising an S1P receptor modulator, e.g. a compound of formulae I to IXb as defined hereinabove, together with one or more pharmaceutically acceptable diluents or carriers therefor.

4. Use of an S1P receptor modulator, e.g a compound of formula I to IXb as defined herein above, in a method according to claim 1 or 2.

5. Use of an S1P receptor modulator, e.g. a compound of formulae I to IXb as defined herein above, in the preparation of a medicament for use in a method according to claim 1 or 2.

6. A method according to claim 1 or 2 comprising co-administration, e.g. concomitantly or in sequence, of a therapeutically effective non-toxic amount of a S1P receptor modulator and a VEGF-receptor antagonist, e.g. as defined hereinabove.

7. A pharmaceutical combination, e.g. a kit, comprising a) a first agent which is a S1P receptor modulator e.g. a compound of formulae I to XIb as defined herein above, in free form or in pharmaceutically acceptable salt form, and b) a VEGF-receptor antagonist, e.g. as defined hereinabove.

8. A method, use, pharmaceutical composition or pharmaceutical combination according to any one of the preceding claims, wherein the S1P receptor modulator is 2-amino-2-[2-(4-octylphenyl) ethyl]propane-1,3-diol in free form or in a pharmaceutically acceptable salt form.

9. A method, use, pharmaceutical composition or pharmaceutical combination substantially as hereinbefore defined and described.

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PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

PCT/EP 2007 / 005597
International Application No.

25 JUN 2007 (25.06.07)
International Filing Date

RO/EP
Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* 50279-WO-PCT

Box No. I TITLE OF INVENTION

Organic Compounds

Box No. II APPLICANT ☐ This person is also inventor

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

Novartis AG
Lichtstrasse 35
4056 Basel
CH

Telephone No.
+41 61 324 11 11

Facsimile No.
+41 61 322 75 32

Applicant's registration No. with the Office

State *(that is, country)* of nationality: CH

State *(that is, country)* of residence: CH

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☒ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

JEFFRIES Charles
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Corporate Intellectual Property
4002 Basel
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Facsimile No.
+41 61 322 75 32

Agent's registration No. with the Office
9203830

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

Novartis Pharma GmbH
Brunner Strasse 59
1230 Vienna
AT

This person is:
- [X] applicant only
- [ ] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: AT

State *(that is, country)* of residence: AT

This person is applicant for the purposes of: [ ] all designated States [ ] all designated States except the United States of America [ ] the United States of America only [X] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

HIESTAND Peter C.
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This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: AT

State *(that is, country)* of residence: CH

This person is applicant for the purposes of: [ ] all designated States [ ] all designated States except the United States of America [X] the United States of America only [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

SCHNELL Christian
Rue de Buschwiller 9
68220 Hesingue
FR

This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: FR

State *(that is, country)* of residence: FR

This person is applicant for the purposes of: [ ] all designated States [ ] all designated States except the United States of America [X] the United States of America only [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- [ ] applicant only
- [ ] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: [ ] all designated States [ ] all designated States except the United States of America [ ] the United States of America only [ ] the States indicated in the Supplemental Box

[ ] Further applicants and/or (further) inventors are indicated on another continuation sheet.

Supplemental Box *If the Supplemental Box is not used, this sheet should not be included in the request.*

1. *If, in any of the Boxes, except Boxes Nos. VIII(i) to (v) for which a special continuation box is provided, the space is insufficient to furnish all the information: in such case, write "Continuation of Box No...." (indicate the number of the Box) and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:*

   (i) *if more than one person is to be indicated as applicant and/or inventor and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below;*

   (ii) *if, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;*

   (iii) *if, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;*

   (iv) *if, in addition to the agent(s) indicated in Box No. IV, there are further agents: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;*

   (v) *if, in Box No. VI, there are more than three earlier applications whose priority is claimed: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI.*

2. *If the applicant intends to make an indication of the wish that the international application be treated, in certain designated States, as an application for a patent of addition, certificate of addition, inventor's certificate of addition or utility certificate of addition: in such a case, write the name or two-letter code of each designated State concerned and the indication "patent of addition," "certificate of addition," "inventor's certificate of addition" or "utility certificate of addition," the number of the parent application or parent patent or other parent grant and the date of grant of the parent patent or other parent grant or the date of filing of the parent application (Rules 4.11(a)(iii) and 49bis.1(a) or (b)).*

3. *If the applicant intends to make an indication of the wish that the international application be treated, in the United States of America, as a continuation or continuation-in-part of an earlier application: in such a case, write "United States of America" or "US" and the indication "continuation" or "continuation-in-part" and the number and the filing date of the parent application (Rules 4.11(a)(iv) and 49bis.1(d)).*

Continuation of Box No. II
Novartis AG is applicant for all designated States with the exception of: AT (Austria) and US (USA)

Continuation of Box No. III
Novartis Pharma GmbH is applicant for AT (Austria) only.

Box No. V DESIGNATIONS

The filing of this request **constitutes under Rule 4.9(a), the designation** of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.

However,

- ☐ DE Germany **is not designated** for any kind of national protection
- ☐ JP Japan **is not designated** for any kind of national protection
- ☐ KR Republic of Korea **is not designated** for any kind of national protection
- ☐ RU Russian Federation **is not designated** for any kind of national protection

(The check-boxes above may only be used to exclude (irrevocably) the designations concerned if, at the time of filing or subsequently under Rule 26bis.1, the international application contains in Box No. VI a priority claim to an earlier national application filed in the particular State concerned, in order to avoid the ceasing of the effect, under the national law, of this earlier national application.)

Box No. VI PRIORITY CLAIM

The priority of the following earlier application(s) is hereby claimed:

Filing date of earlier application *(day/month/year)*	Number of earlier application	Where earlier application is:		
		national application: country or Member of WTO	regional application: regional Office	international application: receiving Office
item (1) 27 June 2006 (27.06.2006)	0612721.1	GB		
item (2)				
item (3)				

☐ Further priority claims are indicated in the Supplemental Box.

Transmit certified copy: the receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office)* identified above as:

☐ all items ☐ item (1) ☐ item (2) ☐ item (3) ☐ other, see Supplemental Box

Restore the right of priority: the receiving Office is requested to restore the right of priority for the earlier application(s) identified above or in the Supplemental Box as item(s) (_____). *(See also the Notes to Box No. VI; further information must be provided to support a request to restore the right of priority.)*

Incorporation by reference: where an element of the international application referred to in Article 11(1)(iii)(d) or (e) or a part of the description, claims or drawings referred to in Rule 20.5(a) is not otherwise contained in this international application but is completely contained in an earlier application whose priority is claimed on the date on which one or more elements referred to in Article 11(1)(iii) were first received by the receiving Office, that element or part is, subject to confirmation under Rule 20.6, incorporated by reference in this international application for the purposes of Rule 20.6.

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used)*:

ISA / EP

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority)*:

Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII DECLARATIONS

The following **declarations** are contained in Boxes Nos. VIII (i) to (v) *(mark the applicable check-boxes below and indicate in the right column the number of each type of declaration)*:			Number of declarations
☐	Box No. VIII (i)	Declaration as to the identity of the inventor :	
☒	Box No. VIII (ii)	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent :	1
☐	Box No. VIII (iii)	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application :	
☐	Box No. VIII (iv)	Declaration of inventorship (only for the purposes of the designation of the United States of America) :	
☐	Box No. VIII (v)	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty :	

Box No. IX CHECK LIST; LANGUAGE OF FILING

This international application **contains**:

(a) **on paper**, the following number of sheets:

request (including declaration and supplemental sheets)	:	6
description (excluding sequence listing and/or tables related thereto)	:	15
claims	:	2
abstract	:	
drawings	:	
Sub-total number of sheets	:	23
sequence listing	:	
tables related thereto	:	
(for both, actual number of sheets if filed on paper, whether or not also filed in electronic form; see (c) below)		
Total number of sheets	:	23

(b) ☐ **only in electronic form** (Section 801(a)(i))
- (i) ☐ sequence listing
- (ii) ☐ tables related thereto

(c) ☐ **also in electronic form** (Section 801(a)(ii))
- (i) ☐ sequence listing
- (ii) ☐ tables related thereto

Type and number of carriers (diskette, CD-ROM, CD-R or other) on which are contained the
- ☐ sequence listing: .....
- ☐ tables related thereto: .....

(additional copies to be indicated under items 9(ii) and/or 10(ii), in right column)

This international application is **accompanied by** the following item(s) *(mark the applicable check-boxes below and indicate in right column the number of each item)*:

		Number of items
1. ☒ fee calculation sheet	:	1
2. ☒ original separate power of attorney	:	1
3. ☐ original general power of attorney	:	
4. ☒ copy of general power of attorney; reference number, if any: AV 36671 + 46171	:	2
5. ☐ statement explaining lack of signature	:	
6. ☒ priority document(s) identified in Box No. VI as item(s): (1)	:	1
7. ☐ translation of international application into *(language)*:	:	
8. ☐ separate indications concerning deposited microorganism or other biological material	:	
9. ☐ sequence listing in electronic form *(indicate type and number of carriers)*		
(i) ☐ copy submitted for the purposes of international search under Rule 13*ter* only (and not as part of the international application)	:	
(ii) ☐ *(only where check-box (b)(i) or (c)(i) is marked in left column)* additional copies including, where applicable, the copy for the purposes of international search under Rule 13*ter*	:	
(iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing mentioned in left column	:	
10. ☐ tables in electronic form related to sequence listing *(indicate type and number of carriers)*		
(i) ☐ copy submitted for the purposes of international search under Section 802(b-*quater*) only (and not as part of the international application)	:	
(ii) ☐ *(only where check-box (b)(ii) or (c)(ii) is marked in left column)* additional copies including, where applicable, the copy for the purposes of international search under Section 802(b-*quater*)	:	
(iii) ☐ together with relevant statement as to the identity of the copy or copies with the tables mentioned in left column	:	
11. ☐ other *(specify)*:	:	

Figure of the drawings which should accompany the abstract:	**Language of filing** of the international application: English

Box No. X SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

In the name of the applicants, the representative

21.06.2007 JEFFRIES Charles AV 36671 + 46171

For receiving Office use only

1. Date of actual receipt of the purported international application:	(25.06.07) 25 JUN 2007	2. Drawings: ☐ received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:		☐ not received:
4. Date of timely receipt of the required corrections under PCT Article 11(2):		
5. International Searching Authority (if two or more are competent): ISA /	6. ☐ Transmittal of search copy delayed until search fee is paid	

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

Form PCT/RO/101 (last sheet) (April 2007) *See Notes to the request form*

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12/303,765

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 January 2008 (03.01.2008)

PCT

(10) International Publication Number
WO 2008/000419 A1

(51) International Patent Classification:
A61K 31/137 (2006.01) *A61K 31/397* (2006.01)
A61P 37/06 (2006.01)

(21) International Application Number:
PCT/EP2007/005597

(22) International Filing Date: 25 June 2007 (25.06.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0612721.1 27 June 2006 (27.06.2006) GB

(71) Applicant *(for all designated States except AT, US)*: **NOVARTIS AG** [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).

(71) Applicant *(for AT only)*: **NOVARTIS PHARMA GMBH** [AT/AT]; Brunner Strasse 59, A-1230 Vienna (AT).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **HIESTAND, Peter, C.** [CH/CH]; Schönenbuchstrasse 13a, CH-4123 Allschwil (CH). **SCHNELL, Christian** [FR/FR]; 9, Rue de Buschwiller, F-68220 Hesingue (FR).

(74) Agent: **JEFFRIES, Charles**; Novartis AG, CH-4002 Basel (CH).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, 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, IS, IT, LT, LU, LV, MC, MT, 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).

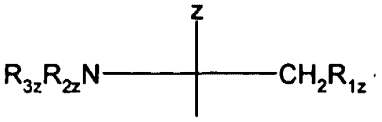
Declaration under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:
— *with international search 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 2008/000419 A1

(54) Title: S1P RECEPTOR MODULATORS FOR TREATING MULTIPLE SCLEROSIS



(X)

(57) Abstract: The present invention relates uses of an S1 P receptor modulator 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) for the treatment or prevention of neo-angiogenesis associated with a demyelinating disease, e.g. multiple sclerosis.

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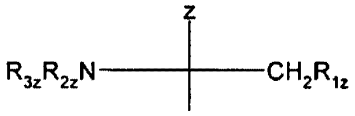
Organic Compounds

The present invention relates to the use of an S1P receptor modulator in the treatment or prevention of neo-angiogenesis associated with a demyelinating disease, e.g. multiple sclerosis.

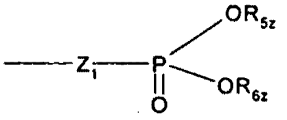
S1 P receptor modulators are typically sphingosine analogues, such as 2-substituted 2-amino- propane-1,3-diol or 2-amino-propanol derivatives, e. g. a compound comprising a group of formula X .

Sphingosine-1 phosphate (hereinafter "S1P") is a natural serum lipid. Presently there are eight known S1P receptors, namely S1P1 to S1P8. S1 P receptor modulators 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

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R_{1z} is or comprises a residue of formula (a), signals as an agonist at one of more sphingosine-1-phosphate receptor.

S1P receptor modulators 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.

The binding affinity of S1P receptor modulators to individual human S1P receptors may be determined in following assay:
S1P receptor 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 preferably have a binding affinity to S1P receptor <50 nM.

Preferred S1P receptor 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 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

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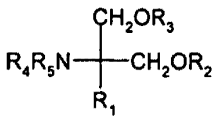
modulator depletes peripheral blood lymphocytes, e.g. by 50%, when administered at a dose of e.g. < 20 mg/kg.

Examples of appropriate S1P receptor 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

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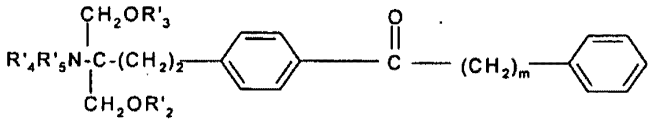
- in the carbon chain, a bond or a heteroatom selected from a double bond, a triple bond, O, S, sulfinyl, sulfonyl, or NR_6, wherein R_6 is as defined above, and
- as a substituent C_{1-4}alkoxy, C_{2-4}alkenyloxy, C_{2-4}alkynyloxy, arylC_{1-4}alkyloxy, acyl, C_{1-4}alkylamino, C_{1-4}alkylthio, acylamino, (C_{1-4}alkoxy)carbonyl, (C_{1-4}alkoxy)carbonylamino, acyloxy, (C_{1-4}alkyl)carbamoyl, nitro, halogen, amino, 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;

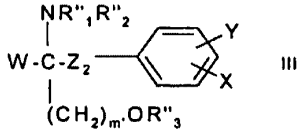
- Compounds as disclosed in EP 1002792A1, e.g. a compound of formula II



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,

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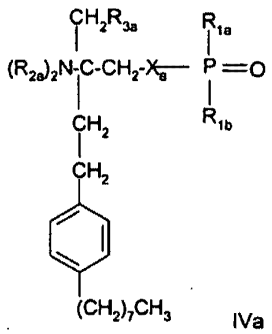
each of p and q, independently, is an integer of 1 to 20, with the proviso of $6 \leq p+q \leq 23$, m' is 1, 2 or 3, n is 2 or 3,

each of R''_1, R''_2, R''_3 and R''_4, independently, is H, C_{1-4}alkyl or acyl,

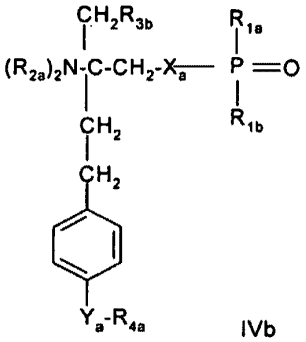
or a pharmaceutically acceptable salt or hydrate thereof,

- Compounds as disclosed in WO02/18395, e.g. a compound of formula IVa or IVb



IVa

or

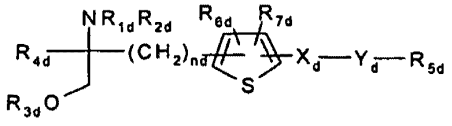


IVb

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 WO02/06268Al, e.g. a compound of formula V



V

wherein each of R_{1d} and R_{2d}, independently, is H or an amino-protecting group;

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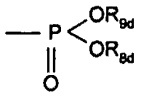
R_{3d} is hydrogen, a hydroxy-protecting group or a residue of formula



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;

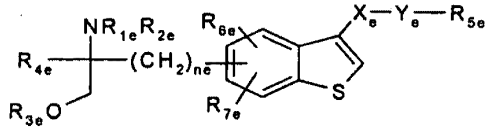
each of R_{8d} and R_{9d}, independently, is H or C_{1-4}alkyl optionally substituted by halogen;

<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 VI



VI

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 WO03/062252A1, e.g. a compound of formula VII

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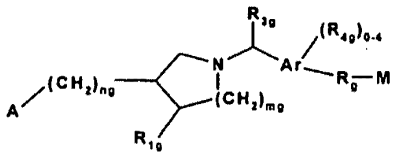
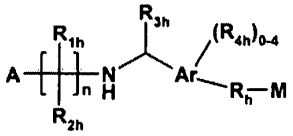


VII

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 VIII



VIII

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 optionally 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, $S(O)_{0,1\ or2}C_{1-3}$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 IXa or IXb

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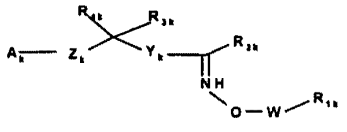
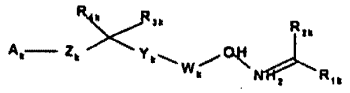


IXa



IXb

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_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-4}alkyl, C_{3-8}heterocycloalkyl or C_{3-8}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.

The compounds of formulae I to IXb may exist in free or salt form. Examples of pharmaceutically acceptable salts of the compounds of the formulae I to VI 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.

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Aryl may be phenyl or naphthyl, preferably phenyl.

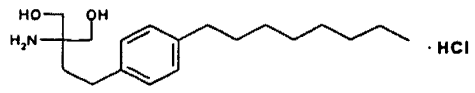
When in the compounds of formula I the carbon chain as R_1 is substituted, it is preferably substituted by halogen, nitro, amino, hydroxy or carboxy. When the carbon chain is interrupted by an optionally substituted phenylene, the carbon chain is preferably unsubstituted. When the phenylene moiety is 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 V "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 salt, 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.

Compounds may e in phosphorylated form. 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 VI is (2R)-2-amino-4-[3-(4-cyclohexyloxybutyl)-benzo[b]thien-6-yl]-2-methylbutan-1-ol.

A preferred compound of formula IXa is e.g. 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, or a prodrug thereof.

S1P receptor agonists or modulators are known as having immunosuppressive properties or anti-angiogenic properties in the treatment of tumors, e.g. as disclosed in EP627406A1, WO 04/103306, WO 05/000833, WO 05/103309, WO 05/113330 or WO 03/097028.

Multiple sclerosis (MS) is an immune-mediated disease of the central nervous system with chronic inflammatory demyelination leading to progressive decline of motor and sensory functions and permanent disability. The therapy of multiple sclerosis is only partially effective, and in most cases only offers a short delay in disease progression despite anti-inflammatory and immunosuppressive treatment. Accordingly, there is a need for agents which are effective in the inhibition or treatment of demyelinating diseases, e.g. multiple sclerosis or Guillain-Barré syndrome, including reduction of, alleviation of, stabilization of or relief from the symptoms which affect the organism.

Characteristic pathological features of demyelinating diseases include inflammation, demyelination and axonal and oligodendrocyte loss. In addition lesions can also have a significant vascular component. A firm link has recently been established between chronic inflammation and angiogenesis and neovascularization seems to have a significant role in the progression of disease.

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It has now been found that S1P receptor modulators have an inhibitory effect on neo-angiogenesis associated with demyelinating diseases, e.g. MS.

In a series of further specific or alternative embodiments, the present invention provides:

1.1 A method for preventing, inhibiting or treating neo-angiogenesis associated with a demyelinating disease, e.g. MS, in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of an S1P receptor modulator, e.g. a compound of formulae I to IXb.

1.2 A method for alleviating or delaying progression of the symptoms of a demyelinating disease, e.g. multiple sclerosis or Guillain-Barré syndrome, in a subject in need thereof, in which method neo-angiogenesis associated with said disease is prevented or inhibited, comprising administering to said subject a therapeutically effective amount of an S1P receptor modulator, e.g. a compound of formulae I to IXb.

1.3 A method for reducing or preventing or alleviating relapses in a demyelinating disease, e.g. multiple sclerosis or Guillain-Barré syndrome, in a subject in need thereof, in which method neo-angiogenesis associated with said disease is prevented or inhibited, comprising administering to said subject a therapeutically effective amount of an S1P receptor modulator, e.g. a compound of formulae I to IXb.

1.4 A method for slowing progression of a demyelinating disease, e.g. multiple sclerosis or Guillain-Barré syndrome, in a subject being in a relapsing-remitting phase of the disease, in which method neo-angiogenesis associated with said disease is prevented or inhibited, comprising administering to said subject a therapeutically effective amount of an S1P receptor modulator, e.g. a compound of formulae I to XIb.

1.5 A method as indicated above, wherein the S1P receptor modulator is administered intermittently.

For example, the S1P receptor modulator may be administered to the subject every 2nd or 3rd day or once a week.

2. A pharmaceutical composition for use in any one of the methods 1.1 to 1.5, comprising an S1P receptor modulator, e.g. a compound of formulae I to IXb as defined hereinabove, together with one or more pharmaceutically acceptable diluents or carriers therefor.

3. An S1P receptor modulator, e.g a compound of formula I to IXb as defined herein above, for use in any one of the methods 1.1 to 1.5.

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4 An S1P receptor modulator, e.g. a compound of formulae I to IXb as defined herein above, for use in the preparation of a medicament for use in any one of the methods 1.1 to 1.5.

Clinicians usually categorize patients having MS into four types of disease patterns:

- *Relapsing-remitting* (RR-MS): Discrete motor, sensory, cerebellar or visual attacks that occur over 1-2 weeks and often resolve over 1-2 months. Some patients accrue disability with each episode, yet remain clinically stable between relapses. About 85% of patients initially experience the RR form of MS, but within 10 years about half will develop the secondary progressive form.
- *Secondary-progressive* (SP-MS): Initially RR followed by gradually increasing disability, with or without relapses. Major irreversible disabilities appear most often during SP.
- *Primary-progressive* (PP-MS): Progression disease course from onset without any relapses or remissions, affecting about 15% of MS patients.
- *Progressive-relapsing* (PR-MS): Progressive disease from onset with clear acute relapses; periods between relapses characterized by continuing progression.

Accordingly, the S1P receptor modulators, e.g. a compound of formulae I to IXb as defined hereinabove, may be useful in the treatment of one or more of *Relapsing-remitting* (RR-MS), *Secondary-progressive* (SP-MS), *Primary-progressive* (PP-MS) and *Progressive-relapsing* (PR-MS).

In particular, the S1P receptor modulators as described herein, e.g. FTY720, i.e. 2-amino-2-[2-(4-octylphenyl) ethyl]propane-1,3-dio, are useful for treating PP-MS.

Utility of the S1P receptor modulators, e.g. the S1P receptor modulators comprising a group of formula X, in preventing or treating neo-angiogenesis associated with a demyelinating disease as hereinabove specified, may be demonstrated in animal test methods as well as in clinic, for example in accordance with the methods hereinafter described.

In vivo: Relapsing Experimental Autoimmune Encephalomyelitis (EAE)

Disease is induced in female Lewis rats by immunization with guinea pig spinal cord tissue emulsified in complete Freund's adjuvant. This results in an acute disease within 11 days, followed by an almost complete remission around day 16 and a relapse at around days 26.

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On day 26 rats are thoracectomized after having been deeply anesthetized with Isoflurane (3%, 20 L / min) and perfused through the left ventricle of the heart. The left ventricle is punctured with a 19 gauge needle from a winged infusion set (SV-19BLK; Termudo, Elkton, MD), which is connected to an airtight pressurized syringe containing the rinsing solution (NaCl 0.9% with 250,000 U/l heparin at 35°C). The right atrium is punctured to provide outflow, and the perfusate is infused under a precise controlled pressure of 120 mm Hg. The perfusion is continued for 5 min (at a constant rate of 20 ml/min) followed by a pre-fixation solution (2% performaldehyde in PBS at 35°C). Finally, up to 30 ml of polyurethane resin (PUI14; Vasqtec, Zürich, Switzerland) is infused at the same rate. After 48 h, the resin-filled brain and spinal cord are excised from the animal and the soft tissue removed by maceration in 7.5% KOH during 24 hr at 50°C. The casts are then thoroughly cleaned with and stored in distilled water before drying by lyophilization. These vascular casts are quantitated using micro computer tomography.

In this assay, a S1P1 receptor modulator, e.g. Compound A significantly blocks disease-associated neo-angiogenesis when administered to the animals at a dose of from 0.1 to 20 mg/kg p.o. For example, Compound A, in the hydrochloride salt form, fully blocks disease-associated angiogenesis and completely inhibits the relapse phases when administered daily at a dose of 0.3 mg/kg p.o. The same effect is obtained when Compound A, in the hydrochloride salt form, is administered p.o. at 0.3 mg/kg every 2nd or 3rd day or once a week.

C. Clinical Trial

Investigation of clinical benefit of a S1P receptor agonist, e.g. a compound of formula I, e.g. Compound A.

20 patients with relapsing-remitting MS receive said compound at a daily dosage of 0.5, 1.25 or 2.5 mg p.o. The general clinical state of the patient is investigated weekly by physical and laboratory examination. Disease state and changes in disease progression are assessed every 2 months by radiological examination (MRI) and physical examination. Initially patients receive treatment for 2 to 6 months. Thereafter, they remain on treatment for as long as their disease does not progress and the drug is satisfactorily tolerated.

Main variables for evaluation: Safety (adverse events), standard serum biochemistry and hematology, magnetic resonance imaging (MRI).

Daily dosages required in practicing the method of the present invention when a S1P receptor modulator alone is used will vary depending upon, for example, the compound used, the host, the mode of administration and the severity of the condition to be treated. A preferred daily dosage range is about from 0.1 to 100 mg as a single dose or in divided

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doses. Suitable daily dosages for patients are on the order of from e.g. 0.1 to 50 mg p.o. The S1P receptor modulator may be administered by any conventional route, in particular enterally, e.g. orally, e.g. in the form of tablets, capsules, drink solutions, nasally, pulmonary (by inhalation) or parenterally, e.g. in the form of injectable solutions or suspensions. Suitable unit dosage forms for oral administration comprise from ca. 0.1 to 30 mg, usually 0.25 to 30 mg S1P receptor modulator, together with one or more pharmaceutically acceptable diluents or carriers therefore. As already mentioned, the S1Preceptor modulator, e.g. Compound A, may alternatively be administered intermittently, e.g. at a dose of 0.5 to 30 mg every other day or once a week.

According to another embodiment of the invention, the S1P receptor modulator may be administered as the sole active ingredient or in conjunction with, e.g. as an adjuvant to, a VEGF-receptor antagonist.

Examples of suitable VEGF-receptor antagonist include e.g. compounds, proteins or antibodies which inhibit the VEGF receptor tyrosine kinase, inhibit a VEGF receptor or bind to VEGF, and are e.g. 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, WO 01/55114, WO 01/58899 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.

4-Pyridylmethyl-phthalazine derivatives are e.g. preferred inhibitors of VEGF receptor tyrosine kinase. Such derivatives and their preparation, pharmaceutical formulations thereof and methods of making such compounds are described in WO00/59509, EP02/04892, WO01/10859 and, in particular, in U.S. Patent No. 6,258,812, which are here incorporated by reference.

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Where the S1P receptor modulator is administered in conjunction with a VEGF-receptor antagonist, dosages of the co-administered VEGF-receptor agonist 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 S1P receptor modulator and a VEGF-receptor antagonist, e.g. as indicated above.

6. A pharmaceutical combination, e.g. a kit, comprising a) a first agent which is a S1P receptor modulator as disclosed herein, in free form or in pharmaceutically acceptable salt form, and b) a VEGF-receptor antagonist, e.g. as indicated 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 S1P receptor modulator and a VEGF-receptor antagonist, 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 S1P receptor modulator and a VEGF-receptor antagonist, 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.

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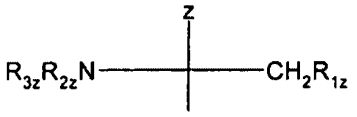
CLAIMS

1. Use of an S1P receptor modulator, e.g. a compound of formulae I to IXb as defined herein above, in the preparation of a medicament for preventing, inhibiting or treating neo-angiogenesis associated with a demyelinating disease, e.g. multiple sclerosis.

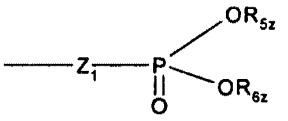
2. Use of an S1P receptor modulator, e.g. a compound of formulae I to IXb as defined herein above, in the preparation of a medicament for preventing, inhibiting or treating PP-MS.

3. Use of claim 1 or 2, wherein the S1P receptor modulator 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.

4. Use of any preceding claim, wherein the medicament is co-administered, e.g. concomitantly or in sequence, with a VEGF-receptor antagonist, e.g. as defined hereinabove.

5. A pharmaceutical composition for use of any preceding claim, comprising an S1P receptor modulator, e.g. a compound of formulae I to IXb as defined hereinabove, together with one or more pharmaceutically acceptable diluents or carriers therefor.

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6. A pharmaceutical combination, e.g. a kit, comprising a) a first agent which is a S1P receptor modulator e.g. a compound of formulae I to XIb as defined herein above, in free form or in pharmaceutically acceptable salt form, and b) a VEGF-receptor antagonist, e.g. as defined hereinabove.

7. A method for preventing, inhibiting or treating neo-angiogenesis associated with a demyelinating disease, e.g. multiple sclerosis, in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of an S1P receptor modulator, e.g. a compound of formulae I to IXb as defined hereinabove.

8. A method of preventing, inhibiting or treating PP-MS in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of an S1P receptor modulator, e.g. a compound of formulae I to IXb as defined hereinabove.

9. A method according to claim 8, wherein the S1P receptor modulator is administered intermittently.

10. A method, use, pharmaceutical composition or pharmaceutical combination of any preceding claim, 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, 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.

11. A method, use, pharmaceutical composition or pharmaceutical combination according to any one of the preceding claims, wherein the S1P receptor modulator is 2-amino-2-[2-(4-octylphenyl) ethyl]propane-1,3-diol in free form or in a pharmaceutically acceptable salt form.

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2007/005597

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/137 A61P37/06 A61K31/397

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

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, EMBASE, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2006/058316 A (NOVARTIS AG [CH]; NOVARTIS PHARMA GMBH [AT]; KOVARIK JOHN M [CH]; APPE) 1 June 2006 (2006-06-01) page 1, line 1 - line 3 page 1, line 9 - line 10 page 2, line 29 - line 31 page 3, paragraph 1 page 9, line 14 page 13, line 4 - line 5 page 13, line 23 - line 24 page 14, line 5 - line 8 claim 12	1-3,5, 7-11
Y	-----	1-11
	-/--	

[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
18 September 2007	08/10/2007

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	Terenzi, Carla

Form PCT/ISA/210 (second sheet) (April 2005)

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2007/005597

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 2004/113330 A1 (IRM LLC [US]; PAN SHIFENG [US]; GRAY NATHANAEL S [US]; MI YUAN [US]; F) 29 December 2004 (2004-12-29) page 8, line 27 - line 31 page 10, line 15 - line 18 page 11, line 7 - line 8 page 12, line 4 - line 5 page 13, line 26 - line 31 page 14, line 10 - line 25	1,2,5, 7-9
Y	-----	1-11
X	BRINKMANN VOLKER ET AL: "The immune modulator FTY720 targets sphingosine 1-phosphate receptors" JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY OF BIOLOCHEMICAL BIOLOGISTS, BIRMINGHAM,, US, vol. 277, no. 24, 14 June 2002 (2002-06-14), pages 21453-21457, XP002264445 ISSN: 0021-9258 abstract page 21457, column 1, line 44 - line 53	1-3,7-11
Y	-----	1-11

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2007/005597

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 7-11 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.

Form PCT/ISA/210 (continuation of first sheet (2)) (January 2004)

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2007/005597

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2006058316 A	01-06-2006	AU 2005309378 A1	01-06-2006
		CA 2589265 A1	01-06-2006
		EP 1819326 A1	22-08-2007
WO 2004113330 A1	29-12-2004	BR PI0410746 A	27-06-2006
		CA 2524027 A1	29-12-2004
		EP 1644367 A1	12-04-2006
		JP 2007501860 T	01-02-2007
		MX PA05012460 A	25-05-2006

Form PCT/ISA/210 (patent family annex) (April 2005)

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Sheet No. ...5...

Box No. VIII (ii) DECLARATION: ENTITLEMENT TO APPLY FOR AND BE GRANTED A PATENT

The declaration must conform to the standardized wording provided for in Section 212; see Notes to Boxes Nos. VIII, VIII (i) to (v) (in general) and the specific Notes to Box No. VIII (ii). If this Box is not used, this sheet should not be included in the request.

Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51*bis*.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate:

in relation to this international application,

Novartis AG is entitled to apply for and be granted a patent by virtue of the following:

an assignment from:

HIESTAND Peter C., Schönenbuchstrasse 13 a, 4123 Allschwil, CH / dated 03.04.2007
SCHNELL Christian, Rue de Buschwiller 9, 68220 Hesingue, FR / dated 04.04.2007

to Novartis AG.

☐ This declaration is continued on the following sheet, "Continuation of Box No. VIII (ii)".

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

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/EP2007/005597	25.06.2007	27.06.2006

International Patent Classification (IPC) or both national classification and IPC
INV. A61K31/137 A61P37/06 A61K31/397

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") except that 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 3 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:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Terenzi, Carla Telephone No. +49 89 2399-7707

Form (PCT/ISA/237) (Cover Sheet) (April 2005)

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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

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) 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:

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in electronic 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. 7-11 (I. A.)

because:

☒ the said international application, or the said claims Nos. 7-11 (I. A.) relate to the following subject matter which does not require an international search *(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 *(specify)*:

☐ no international search report has been established for the whole application or for said claims Nos.

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box 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	4,6
	No:	Claims	1-3,5,7-11
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-11
Industrial applicability (IA)	Yes:	Claims	
	No:	Claims	7-11

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III.

Claims 7-11 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.

1 Reference is made to the following documents:

D1: WO 2006/058316 A (NOVARTIS AG [CH]; NOVARTIS PHARMA GMBH [AT]; KOVARIK JOHN M [CH]; APPE) 1 June 2006 (2006-06-01)

D2: WO 2004/113330 A1 (IRM LLC [US]; PAN SHIFENG [US]; GRAY NATHANAEL S [US]; MI YUAN [US]; F) 29 December 2004 (2004-12-29)

D3: BRINKMANN VOLKER ET AL: "The immune modulator FTY720 targets sphingosine 1-phosphate receptors" JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY OF BIOLOCHEMICAL BIOLOGISTS, BIRMINGHAM,, US, vol. 277, no. 24, 14 June 2002 (2002-06-14), pages 21453-21457, XP002264445 ISSN: 0021-9258

For what concerns the most important passages of the above-mentioned documents, please see citations in the International search Report, unless otherwise stated.

Novelty

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-3, 5, 7-11 is not new in the sense of Article 33(2) PCT.

Document D1 describes pharmaceutical compositions comprising a S1P receptor modulator, including compounds comprising the group of formula X (i.e. the 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol, FTY720), the 2-amino-2-[4-(3-benzyloxyphenoxy)-2-chlorophenyl]ethyl-1,3-propane-diol and the 1-{4-[1(1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid. The use of said S1P receptor modulators for treating patients suffering from autoimmune diseases, i.e. multiple

sclerosis, is as well disclosed.
Therefore, claims 1-3,5,7,8,10 and 11 are not new.

D2 discloses pharmaceutical compositions comprising a S1P receptor modulator and their use in the treatment of diseases mediated by lymphocytes interactions, i.e. multiple sclerosis. Thus, the subject-matter of claims 1,2,5,7 and 8 is not novel over D2.

D3 reports on the beneficial effect of the S1P receptor agonist FTY20 in experimental autoimmune encephalomyelitis (EAE), which is the same model of human multiple sclerosis used in the present application. Therefore, D3 takes away the novelty of claims 1-3,7,8, 10 and 11.

Inventive step
The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 4 and 6 does not involve an inventive step in the sense of Article 33(3) PCT.

The document D1 is regarded as being the closest prior art to the subject-matter of claims 4 and 6, and as already pointed out above discloses pharmaceutical compositions comprising a S1P receptor modulator and their use in the treatment of autoimmune diseases, i.e. multiple sclerosis.

The subject-matter of claims 4 and 6 therefore differs from this known D1 in that the S1P receptor modulator has been used in combination with a VEGF-receptor antagonist.

The problem to be solved by the present invention may therefore be regarded as the provision of an alternative therapy for the above mentioned diseases.

However, document D2 teaches us that in the treatment of multiple sclerosis, the S1P receptor modulator can be used in combination with other therapeutic agents, i.a. "compounds targeting/decreasing a protein or lipid kinase activity or further anti-angiogenic compounds" and among them VEGF-receptor antagonists.

In view of documents D1 and D2, the skilled person would regarding as normal routine

procedure to try and use a VEGF-receptor antagonist in combination with a S1P receptor modulator in order to solve the problem posed.
Moreover, the applicant should note that no data has been provided in the present application showing any surprising or unexpected technical effect achieved by the combination of the present invention in comparison with the prior art.

Dependent claims 9 do not add any features which might establish novelty/inventive step of the subject-matter of the independent claims over the prior art.

Re Item VIII.
Claims 10 and 11 refer both to a method, an use and a pharmaceutical composition. The definition of the subject-matter of said claims is therefore unclear, contrary to the requirements of Article 6 PCT.

Industrial applicability
As stated above, no opinion is given on the question of whether present claims 7-11 are industrially applicable since their patentability is *inter alia* dependent upon their formulation as well as upon national and regional laws and no unifying criteria is provided in this field by the PCT.

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

JEFFRIES, Charles
Novartis AG
CH-4002 Basel
SUISSE

Date of mailing *(day/month/year)* 21 January 2008 (21.01.2008)	
Applicant's or agent's file reference 50279-WO-PCT	IMPORTANT NOTIFICATION
International application No. PCT/EP2007/005597	International filing date *(day/month/year)* 25 June 2007 (25.06.2007)

1. The following indications appeared on record concerning:

☒ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address	State of Nationality	State of Residence
NOVARTIS PHARMA GMBH Brunner Strasse 59 A-1230 Vienna Austria	AT	AT
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☒ the person ☐ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address	State of Nationality	State of Residence
NOVARTIS AG Lichtstrasse 35 CH-4056 Basel Switzerland	CH	CH
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:
NOVARTIS PHARMA GMBH has assigned all its rights to NOVARTIS AG. NOVARTIS AG is now recorded as applicant for all designated States except the United States of America.

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☐ the International Preliminary Examining Authority
☒ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Nissen Diana
Facsimile No. +41 22 338 82 70	e-mail Diana.Nissen@wipo.int Telephone No. +41 22 338 80 54

Form PCT/IB/306 (October 2005) 1/D12Z5YC10

PTO/SB/06 (07-06)
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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
12/303,765	12/08/2008	

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	
	12/08/2008	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
AMENDMENT	Total (37 CFR 1.16(i))	* 11	Minus	** 20	= 0	X $ =		OR	X $52=	0
	Independent (37 CFR 1.16(h))	* 2	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	0

		(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:
/ANDREW JAMES JR/

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.**

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 12/303,765	Filing Date 12/08/2008	☐ 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	
	12/08/2008	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
AMENDMENT	Total (37 CFR 1.16(i))	* 11	Minus	** 20	= 0	X $ =		OR	X $52=	0
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	☐ 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)					
		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".

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