Access DB# 22977

SEARCH REQUEST FORM

187

Scientific and Technical Information Center

Requester's Full Name: SUDHAKAR PATEL Examiner #: 77018 Date: 8/16/00
Art Unit: 1624 Phone Number 308-4259 Serial Number: 09/529,096
Mail Box and Bldg/Room Location: CM1 4E18 Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched: Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

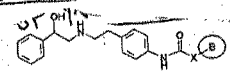
Title of Invention: AMIDE DERIVATIVES OR SALTS THEREOF.

Inventors (please provide full names): TATSUYA MARUYAMA et al.

Earliest Priority Filing Date: ASAP → Mr. J. Dittmann or Ms. B. O'Bryen or Ms. S. Henning please see THX

**For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

COMPOUNDS: claims: 1-6
COMPOSITION: Claim: 7
Method / USE: PHARMACEUTICAL: Claim 8
COMPOUNDS OF INTEREST PLEASE



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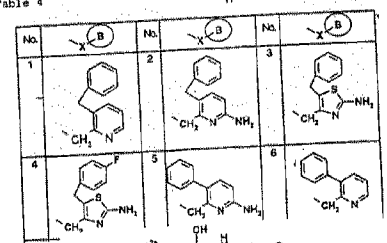

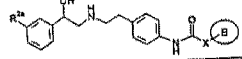

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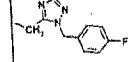
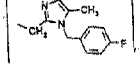
13	H		14	H	

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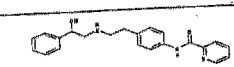
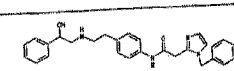
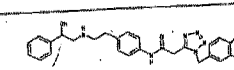
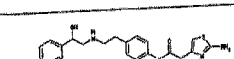
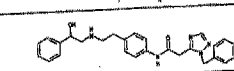
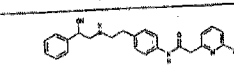
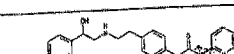
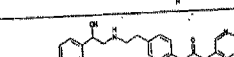
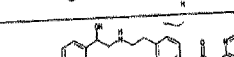
1	
23	
33	
41	
47	
56	
86	
93	
	

spy of claims 1-8 + Lots of structures enclosed 8/16

STAFF USE ONLY

Searcher: _____

Date Searcher Picked Up: _____

Date Completed: 8-21-00

Searcher Prep & Review Time: 40

Clerical Prep Time: _____

Online Time: 13

Type of Search

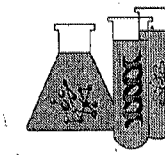
NA Sequence (#)_____ STN 104
AA Sequence (#)_____ Dialog
Bibliographic _____ Dr.Link _____
Litigation _____ Lexis/Nexis _____
Fulltext _____ Sequence Systems _____
Patent Family _____ WWW/Internet _____
Other _____ Other (specify) _____

PTO-1590 (1-2000)

Point of Contact:
Barb O'Bryen
Technical Info. Specialist
CM1 12C14 Tel: 308-4291

Biotechnology/Chemical Division

Scientific and Technical Information Center



Search Results Feedback Form

The results for your recent search request are attached. If you have any questions or comments about the scope or the results of the search, please contact the searcher whose name is stamped below.

Point of Contact:
Barb O'Bryen
Technical Info. Specialist
CM1 12C14 Tel: 308-4291

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Phone: 308-4259

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=> fil reg; d stat que l8; fil capl; d que nos 19

FILE 'REGISTRY' ENTERED AT 15:59:09 ON 21 AUG 2000
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STRUCTURE FILE UPDATES:   20 AUG 2000  HIGHEST RN 286833-04-3
DICTIONARY FILE UPDATES:  20 AUG 2000  HIGHEST RN 286833-04-3

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 11, 2000

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

Structure search limits have been increased.  See HELP SLIMIT
for details.

L6                STR
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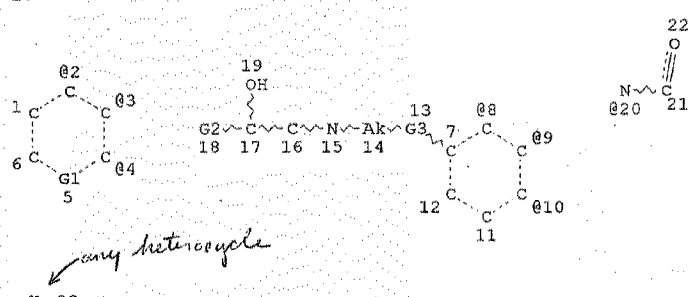


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NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  23

STEREO ATTRIBUTES: NONE
L8          172 SEA FILE=REGISTRY SSS FUL L6

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SEARCH TIME: 00.00.15



FILE 'CAPLUS' ENTERED AT 15:59:10 ON 21 AUG 2000
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PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
                        Searched by Barb O'Bryen, STIC 308-4291
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FILE COVERS 1967 - 21 Aug 2000 VOL 133 ISS 9
FILE LAST UPDATED: 20 Aug 2000 (20000820/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

This file supports REGISTRY for direct browsing and searching of all substance data from the REGISTRY file. Enter HELP FIRST for more information.

Now you can extend your author, patent assignee, patent information, and title searches back to 1907. The records from 1907-1966 now have this searchable data in CAOLD. You now have electronic access to all of CA: 1907 to 1966 in CAOLD and 1967 to the present in CAPLUS on STN.

L6 STR
L8 172 SEA FILE=REGISTRY SSS FUL L6
L9 6 SEA FILE=CAPLUS ABB=ON L8

=> d ibib abs hitstr l9 1-6; fil cao; d que nos l10

L9 ANSWER 1 OF 6 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1999:282201 CAPLUS
DOCUMENT NUMBER: 130:311793
TITLE: Preparation of amides as antidiabetics
INVENTOR(S): Maruyama, Tatsuya; Suzuki, Takayuki; Onda, Kenichi; Hayakawa, Masahiko; Moritomo, Hiroyuki; Kimizuka, Tetsuya; Matsui, Tetsuo
PATENT ASSIGNEE(S): Yamanouchi Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 45 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9920607	A1	19990429	WO 1998-JP4671	19981015
W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9889288	A1	19990506	AU 1998-89288	19981013
AU 9894621	A1	19990510	AU 1998-94621	19981015
EP 1028111	A1	20000816	EP 1998-947894	19981015
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				

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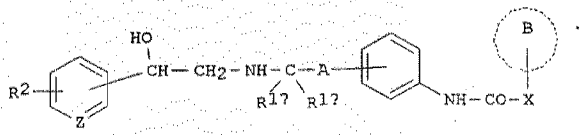
CN 1218045 A 19990602 CN 1998-121375 19981016
NO 2000001983 A 20000414 NO 2000-1983 20000414
PRIORITY APPLN. INFO.: JP 1997-285778 19971017
WO 1998-JP4671 19981015
OTHER SOURCE(S): MARPAT 130:311793
GI



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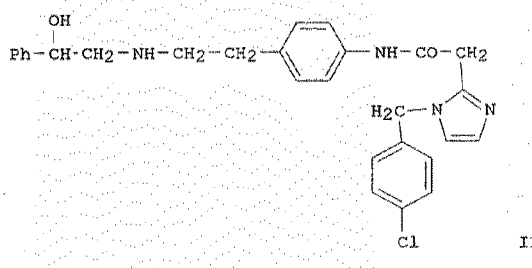

II

AB The title compds. I [ring B = an optionally substituted heteroaryl optionally fused with a benzene ring; X = a bond, lower alkylene or lower alkenylene (optionally substituted by hydroxy or lower alkyl), carbonyl, or NH (further details related to X are given); A = a lower alkylene or a group represented by (lower alkylene)-O; R1a and R1b = hydrogen or lower alkyl; R2 = hydrogen or halogeno; and Z = nitrogen or CH] are prepd. I are useful as diabetes remedies which not only function to accelerate the secretion of insulin and enhance insulin sensitivity but also have an anti-obesity action and an antihyperlipemic action based on their selective stimulative action on .beta.3 receptor. For example, imidazole deriv. II was prepd. Compds. of this invention significantly decreased blood sugar in mice.

IT **223672-09-1P 223672-10-4P 223672-11-5P**
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223672-15-9P 223672-16-0P 223672-17-1P
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Searched by Barb O'Bryen, STIC 308-4291

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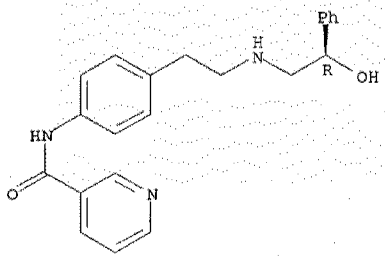
223673-66-3P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of amides as antidiabetics)

RN 223672-09-1 CAPLUS
CN 3-Pyridinecarboxamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



●2 HCl

RN 223672-10-4 CAPLUS
CN 8-Quinolinecarboxamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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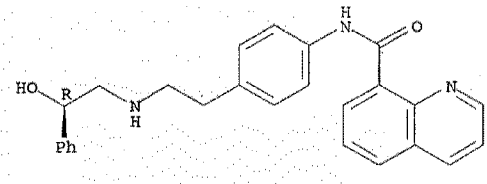
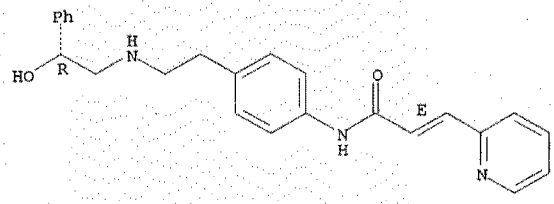


●2 HCl

RN 223672-11-5 CAPLUS
CN 2-Propenamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-3-(2-pyridinyl)-, dihydrochloride, (2E)- (9CI) (CA INDEX NAME)

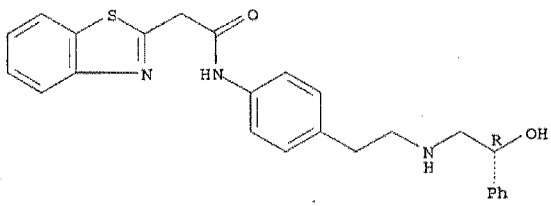
Absolute stereochemistry.
Double bond geometry as shown.



●2 HCl

RN 223672-12-6 CAPLUS
CN 2-Benzothiazoleacetamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

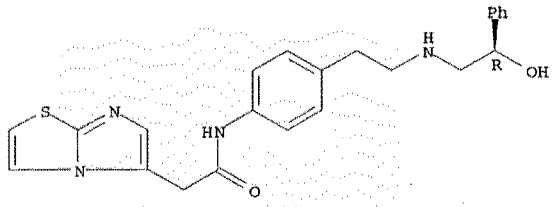


●2 HCl

RN 223672-13-7 CAPLUS

CN Imidazo[2,1-b]thiazole-5-acetamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

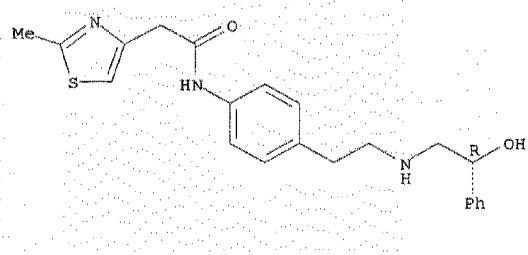
Absolute stereochemistry.



●2 HCl

RN 223672-14-8 CAPLUS
CN 4-Thiazoleacetamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-2-methyl-, dihydrochloride (9CI) (CA INDEX NAME)

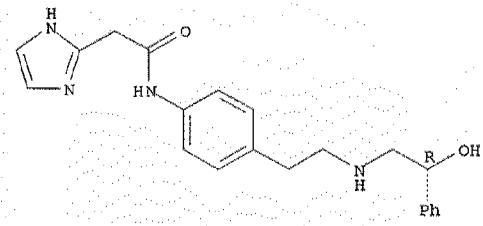
Absolute stereochemistry.



●2 HCl

RN 223672-15-9 CAPLUS
CN 1H-Imidazole-2-acetamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

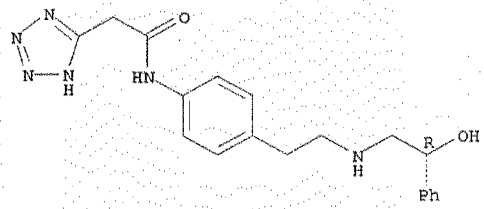
Absolute stereochemistry.



● 2 HCl

RN 223672-16-0 CAPLUS
CN 1H-Tetrazole-5-acetamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)

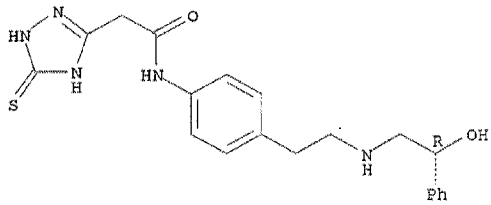
Absolute stereochemistry.



● HCl

RN 223672-17-1 CAPLUS
CN 1H-1,2,4-Triazole-3-acetamide, 2,5-dihydro-N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-5-thioxo-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

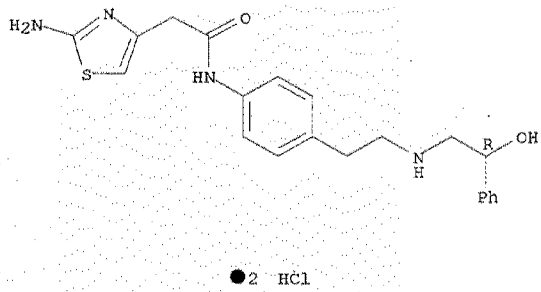


● HCl

Searched by Barb O'Bryen, STIC 308-4291

RN 223672-18-2 CAPLUS
CN 4-Thiazoleacetamide, 2-amino-N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

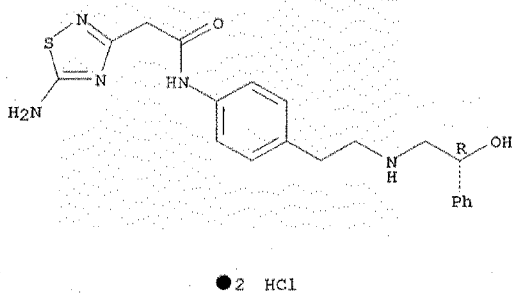
Absolute stereochemistry.



●2 HCl

RN 223672-19-3 CAPLUS
CN 1,2,4-Thiadiazole-3-acetamide, 5-amino-N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

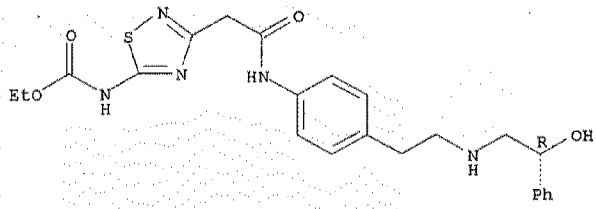


●2 HCl

RN 223672-20-6 CAPLUS
CN Carbamic acid, [3-[2-[[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]amino]-2-oxoethyl]-1,2,4-thiadiazol-5-yl]-, ethyl ester, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

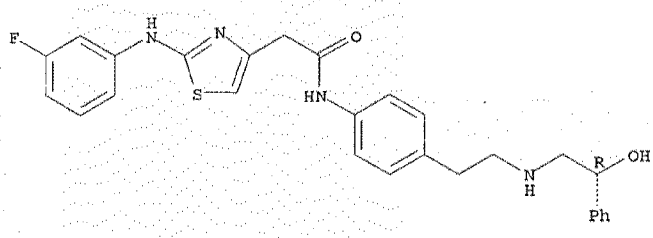
Searched by Barb O'Bryen, STIC 308-4291



● HCl

RN 223672-21-7 CAPLUS
CN 4-Thiazoleacetamide, 2-[(3-fluorophenyl)amino]-N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

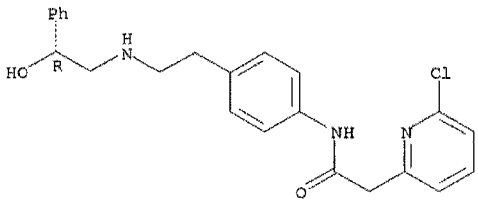
Absolute stereochemistry.



● 2 HCl

RN 223672-22-8 CAPLUS
CN 2-Pyridineacetamide, 6-chloro-N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

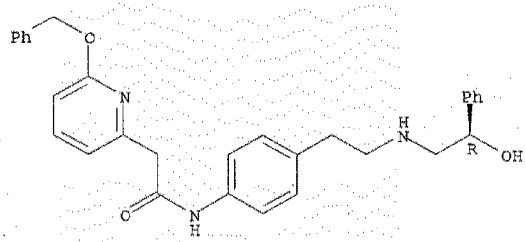


● HCl

Searched by Barb O'Bryen, STIC 308-4291

RN 223672-23-9 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-6-(phenylmethoxy)-, monohydrochloride (9CI) (CA INDEX NAME)

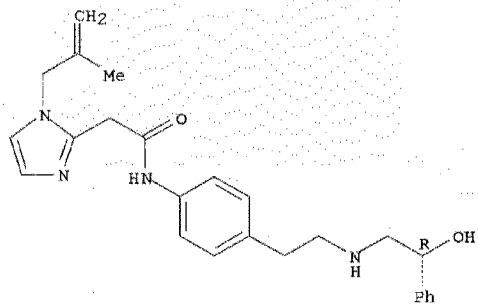
Absolute stereochemistry.



● HCl

RN 223672-24-0 CAPLUS
CN 1H-Imidazole-2-acetamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-1-(2-methyl-2-propenyl)-, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

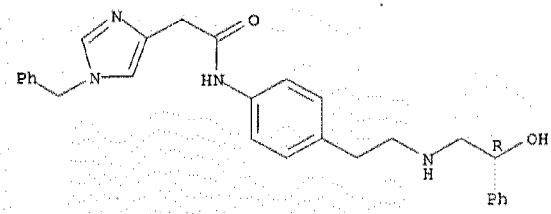


●2 HCl

RN 223672-25-1 CAPLUS
CN 1H-Imidazole-4-acetamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-1-(phenylmethyl)-, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

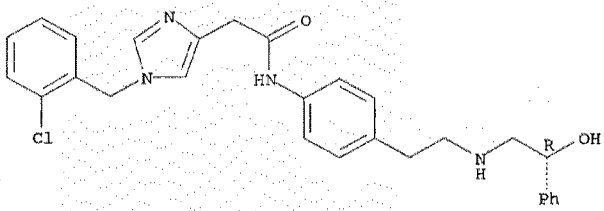
Searched by Barb O'Bryen, STIC 308-4291



●2 HCl

RN 223672-26-2 CAPLUS
CN 1H-Imidazole-4-acetamide, 1-[(2-chlorophenyl)methyl]-N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

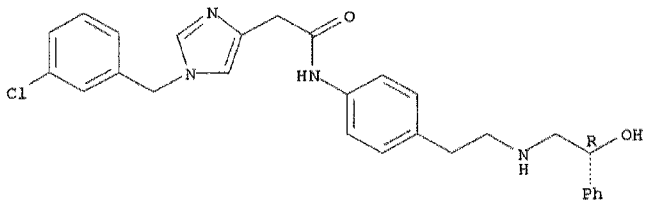
Absolute stereochemistry.



●2 HCl

RN 223672-27-3 CAPLUS
CN 1H-Imidazole-4-acetamide, 1-[(3-chlorophenyl)methyl]-N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

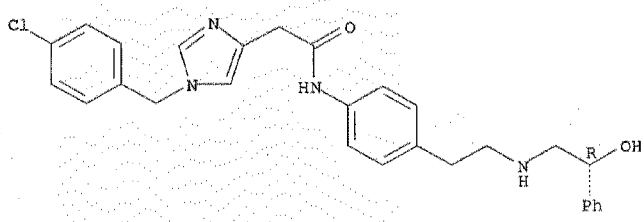
Absolute stereochemistry.



●2 HCl
Searched by Barb O'Bryen, STIC 308-4291

RN 223672-29-5 CAPLUS
CN 1H-Imidazole-4-acetamide, 1-[(4-chlorophenyl)methyl]-N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

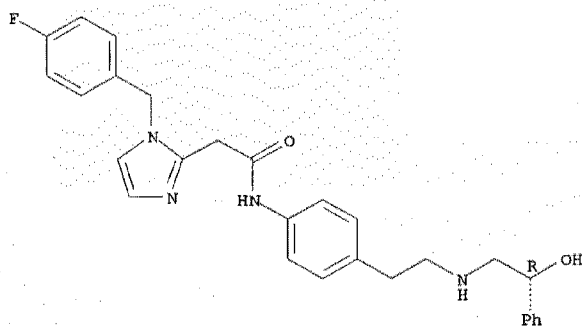
Absolute stereochemistry.



●2 HCl

RN 223672-30-8 CAPLUS
CN 1H-Imidazole-2-acetamide, 1-[(4-fluorophenyl)methyl]-N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

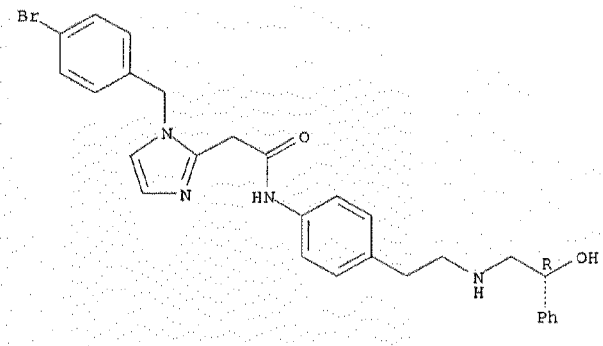


●2 HCl

RN 223672-31-9 CAPLUS
CN 1H-Imidazole-2-acetamide, 1-[(4-bromophenyl)methyl]-N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

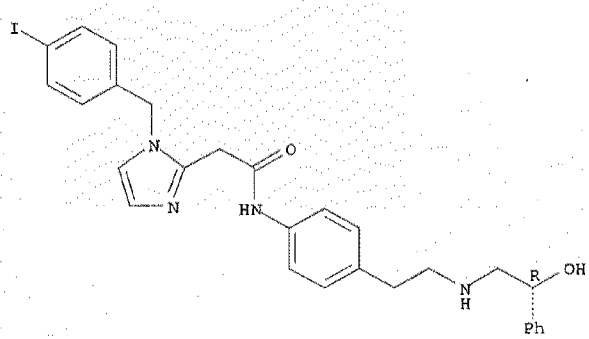
Searched by Barb O'Bryen, STIC 308-4291



●2 HCl

RN 223672-32-0 CAPLUS
CN 1H-Imidazole-2-acetamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-1-[(4-iodophenyl)methyl]-, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

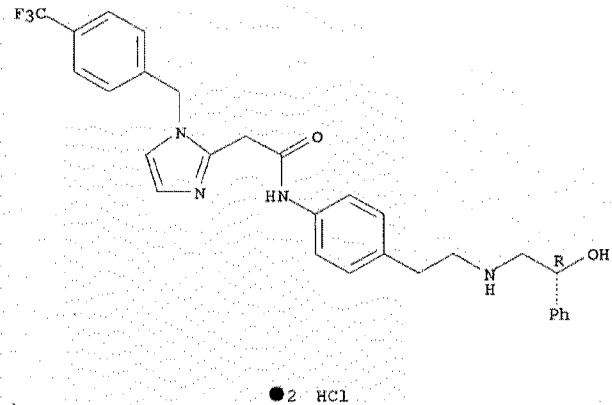


●2 HCl

RN 223672-34-2 CAPLUS
CN 1H-Imidazole-2-acetamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-1-[[4-(trifluoromethyl)phenyl]methyl]-, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

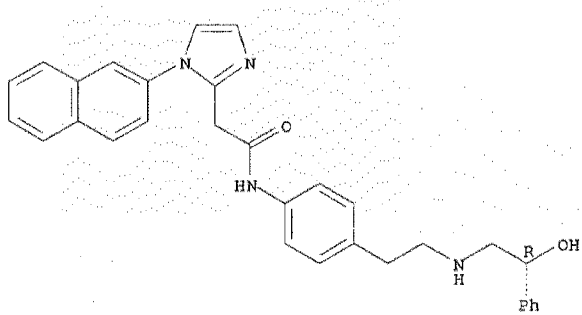
Searched by Barb O'Bryen, STIC 308-4291



●2 HCl

RN 223672-36-4 CAPLUS
CN 1H-Imidazole-2-acetamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-1-(2-naphthalenyl)-, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

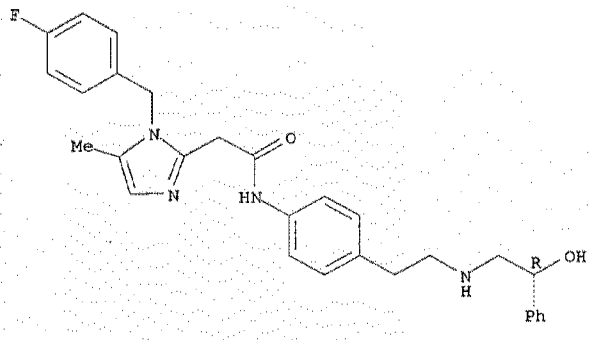


●2 HCl

RN 223672-38-6 CAPLUS
CN 1H-Imidazole-2-acetamide, 1-[(4-fluorophenyl)methyl]-N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-5-methyl-, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

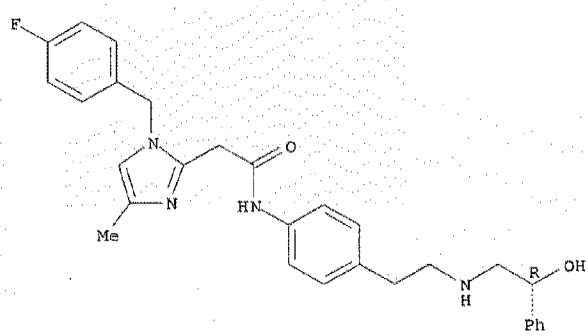
Searched by Barb O'Bryen, STIC 308-4291



●2 HCl

RN 223672-40-0 CAPLUS
CN 1H-Imidazole-2-acetamide, 1-[(4-fluorophenyl)methyl]-N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-4-methyl-, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

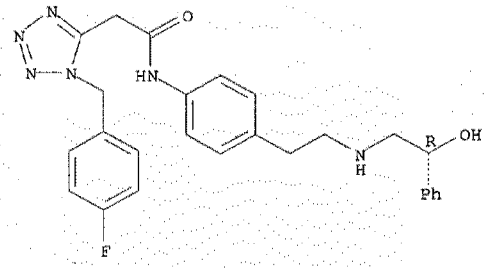


●2 HCl

RN 223672-42-2 CAPLUS
CN 1H-Tetrazole-5-acetamide, 1-[(4-fluorophenyl)methyl]-N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

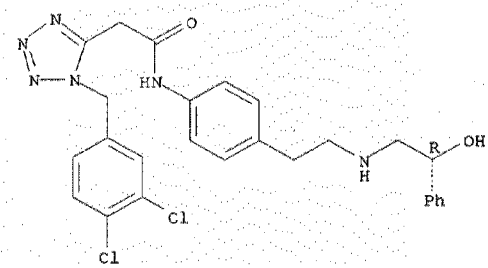
Searched by Barb O'Bryen, STIC 308-4291



● HCl

RN 223672-44-4 CAPLUS
CN 1H-Tetrazole-5-acetamide, 1-[(3,4-dichlorophenyl)methyl]-N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

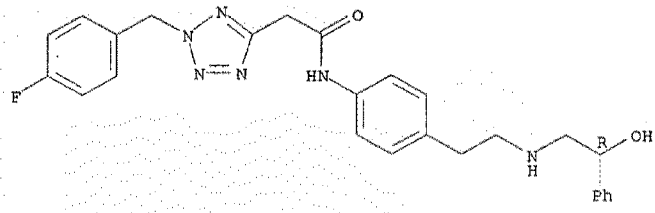


● HCl

RN 223672-46-6 CAPLUS
CN 2H-Tetrazole-5-acetamide, 2-[(4-fluorophenyl)methyl]-N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

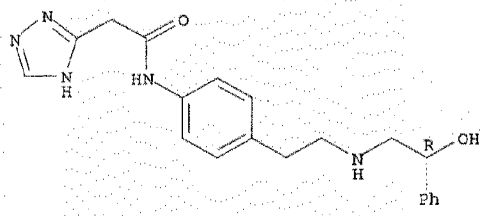
Searched by Barb O'Bryen, STIC 308-4291



● HCl

RN 223672-47-7 CAPLUS
CN 1H-1,2,4-Triazole-3-acetamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

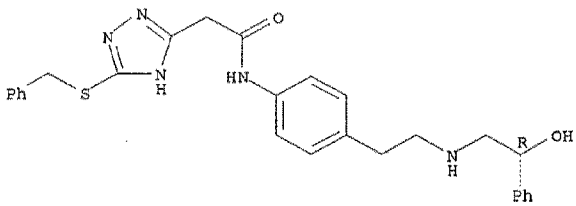
Absolute stereochemistry.



●2 HCl

RN 223672-48-8 CAPLUS
CN 1H-1,2,4-Triazole-3-acetamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-5-[(phenylmethyl)thio]-, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

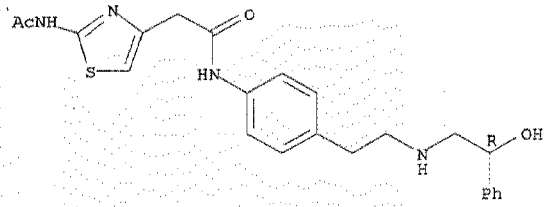


●2 HCl

Searched by Barb O'Bryen, STIC 308-4291

RN 223672-49-9 CAPLUS
CN 4-Thiazoleacetamide, 2-(acetylamino)-N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)

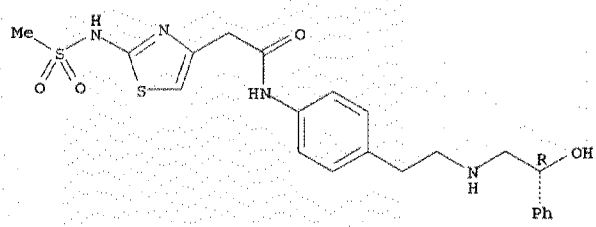
Absolute stereochemistry.



● HCl

RN 223672-50-2 CAPLUS
CN 4-Thiazoleacetamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-2-[(methylsulfonyl)amino]-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

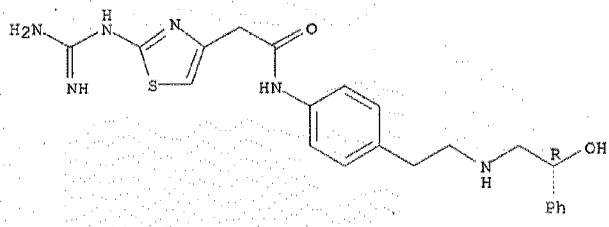


● HCl

RN 223672-51-3 CAPLUS
CN 4-Thiazoleacetamide, 2-[(aminoiminomethyl)amino]-N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

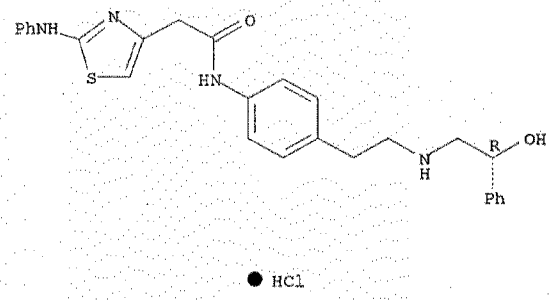
Searched by Barb O'Bryen, STIC 308-4291



● 2 HCl

RN 223672-52-4 CAPLUS
CN 4-Thiazoleacetamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-2-(phenylamino)-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

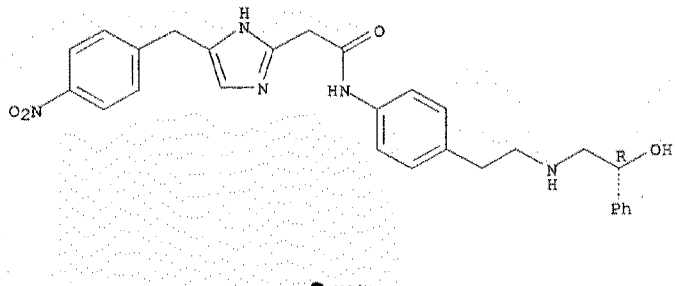


● HCl

RN 223672-53-5 CAPLUS
CN 1H-Imidazole-2-acetamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-4-[(4-nitrophenyl)methyl]-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

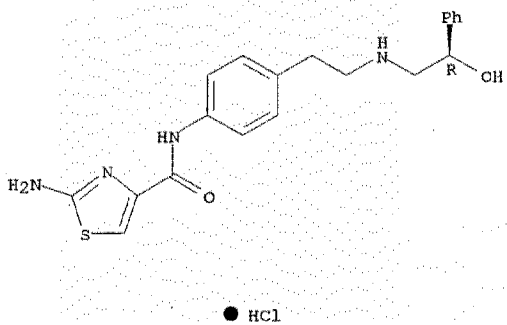
Searched by Barb O'Bryen, STIC 308-4291



● HCl

RN 223672-55-7 CAPLUS
CN 4-Thiazolecarboxamide, 2-amino-N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

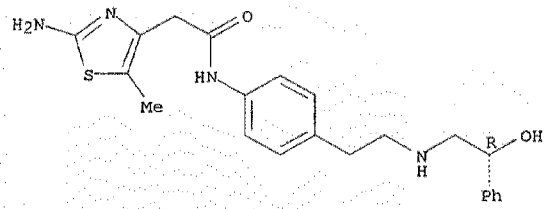


● HCl

RN 223672-58-0 CAPLUS
CN 4-Thiazoleacetamide, 2-amino-N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-5-methyl-, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

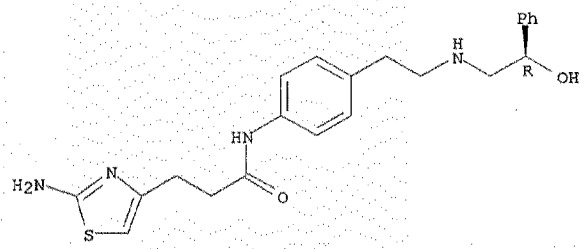
Searched by Barb O'Bryen, STIC 308-4291



●2 HCl

RN 223672-60-4 CAPLUS
CN 4-Thiazolepropanamide, 2-amino-N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)

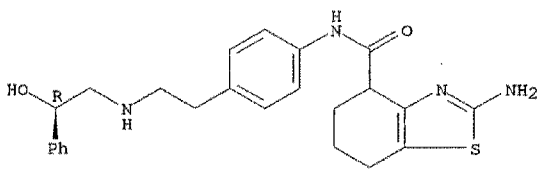
Absolute stereochemistry.



● HCl

RN 223672-63-7 CAPLUS
CN 4-Benzothiazolecarboxamide, 2-amino-4,5,6,7-tetrahydro-N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

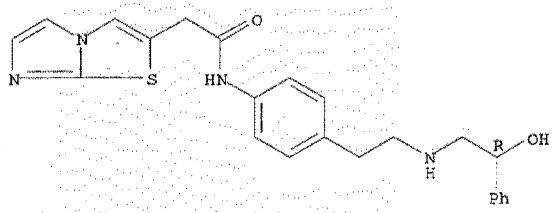


●2 HCl

Searched by Barb O'Bryen, STIC 308-4291

RN 223672-65-9 CAPLUS
CN Imidazo[2,1-b]thiazole-2-acetamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)

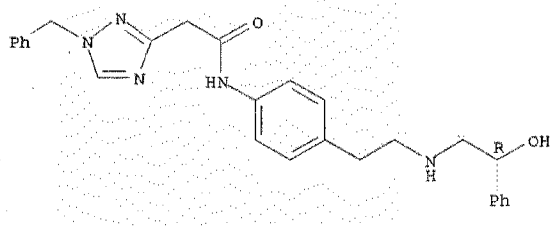
Absolute stereochemistry.



● HCl

RN 223672-66-0 CAPLUS
CN 1H-1,2,4-Triazole-3-acetamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-1-(phenylmethyl)- (9CI) (CA INDEX NAME)

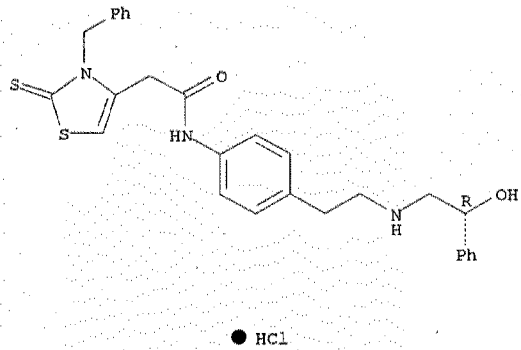
Absolute stereochemistry.



RN 223672-67-1 CAPLUS
CN 4-Thiazoleacetamide, 2,3-dihydro-N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-3-(phenylmethyl)-2-thioxo-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

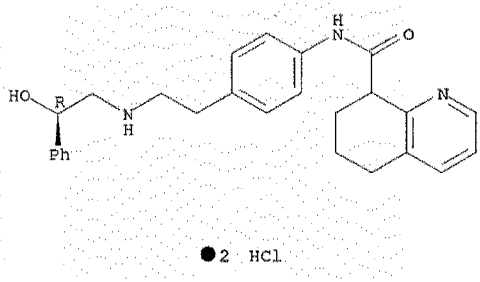
Searched by Barb O'Bryen, STIC 308-4291



● HCl

RN 223672-68-2 CAPLUS
CN 8-Quinolinecarboxamide, 5,6,7,8-tetrahydro-N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

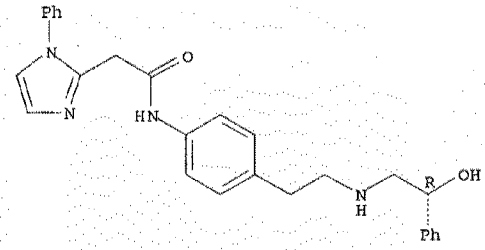


●2 HCl

RN 223672-69-3 CAPLUS
CN 1H-Imidazole-2-acetamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-1-phenyl-, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

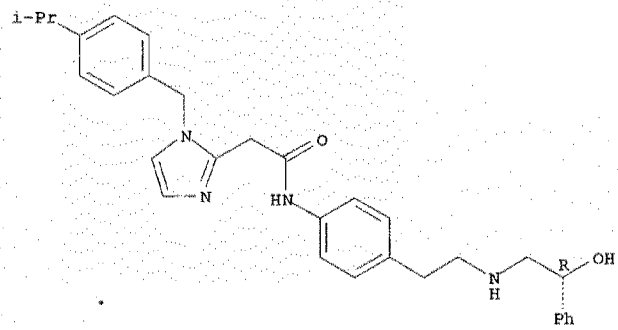
Searched by Barb O'Bryen, STIC 308-4291



●2 HCl

RN 223672-70-6 CAPLUS
CN 1H-Imidazole-2-acetamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-1-[[4-(1-methylethyl)phenyl]methyl]-, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

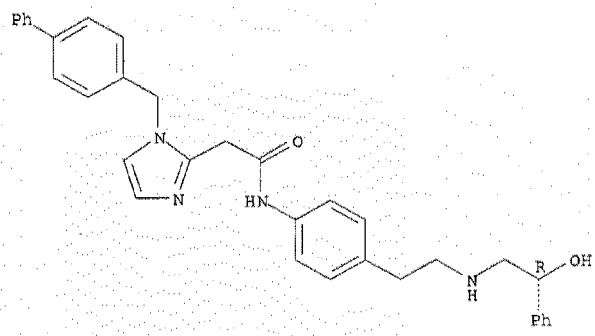


●2 HCl

RN 223672-71-7 CAPLUS
CN 1H-Imidazole-2-acetamide, 1-([1,1'-biphenyl]-4-ylmethyl)-N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

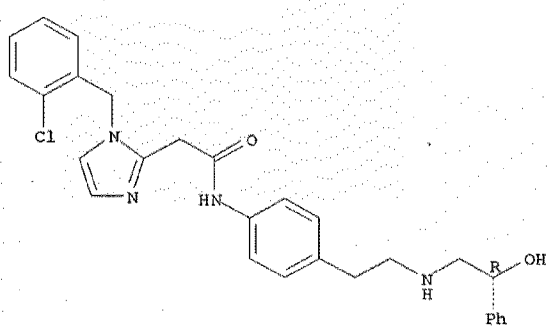
Searched by Barb O'Bryen, STIC 308-4291



●2 HCl

RN 223672-72-8 CAPLUS
CN 1H-Imidazole-2-acetamide, 1-[(2-chlorophenyl)methyl]-N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

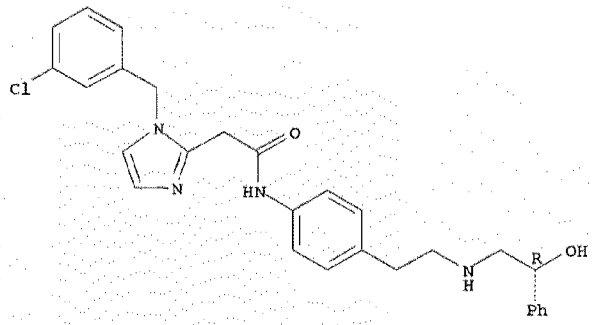


●2 HCl

RN 223672-73-9 CAPLUS
CN 1H-Imidazole-2-acetamide, 1-[(3-chlorophenyl)methyl]-N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

Searched by Barb O'Bryen, STIC 308-4291



●2 HCl

RN 223672-74-0 CAPLUS
CN 1H-Imidazole-2-acetamide, 1-[(3,4-dichlorophenyl)methyl]-N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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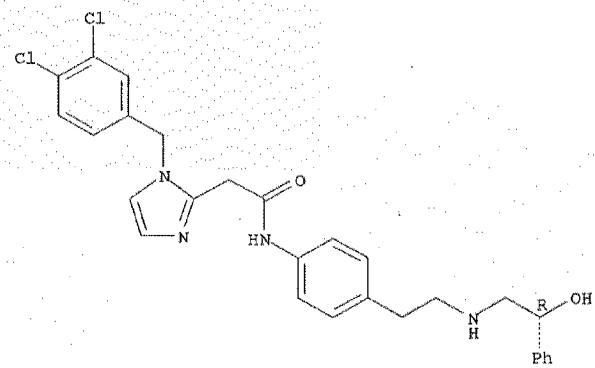

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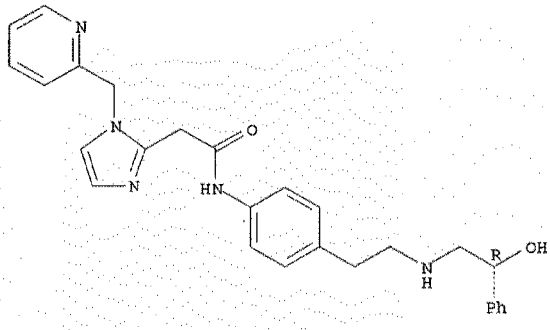
●2 HCl

RN 223672-75-1 CAPLUS
CN 1H-Imidazole-2-acetamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-1-(2-pyridinylmethyl)-, dihydrochloride (9CI) (CA INDEX NAME)

Searched by Barb O'Bryen, STIC 308-4291

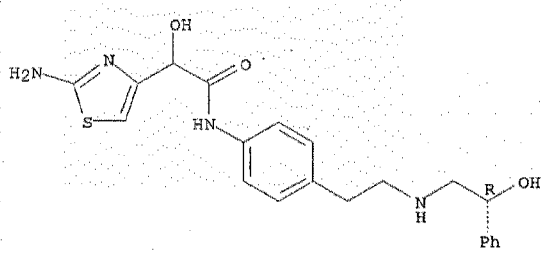
Absolute stereochemistry.



● 2 HCl

RN 223672-76-2 CAPLUS
CN 4-Thiazoleacetamide, 2-amino-.alpha.-hydroxy-N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

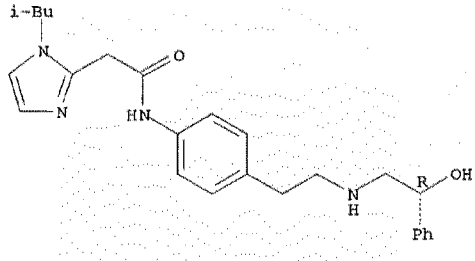


● HCl

RN 223672-77-3 CAPLUS
CN 1H-Imidazole-2-acetamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-1-(2-methylpropyl)-, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

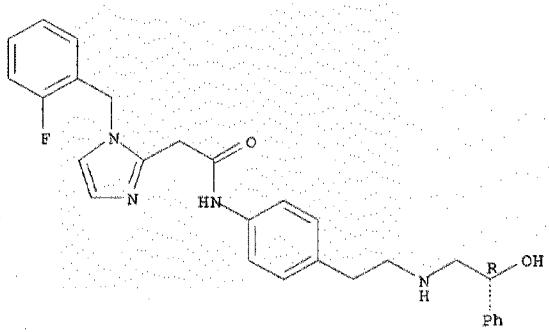
Searched by Barb O'Bryen, STIC 308-4291



●2 HCl

RN 223672-78-4 CAPLUS
CN 1H-Imidazole-2-acetamide, 1-[(2-fluorophenyl)methyl]-N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

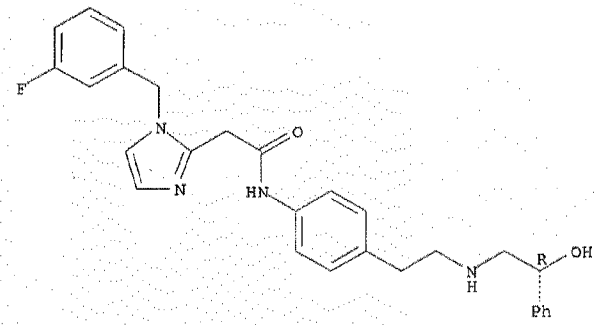


●2 HCl

RN 223672-79-5 CAPLUS
CN 1H-Imidazole-2-acetamide, 1-[(3-fluorophenyl)methyl]-N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

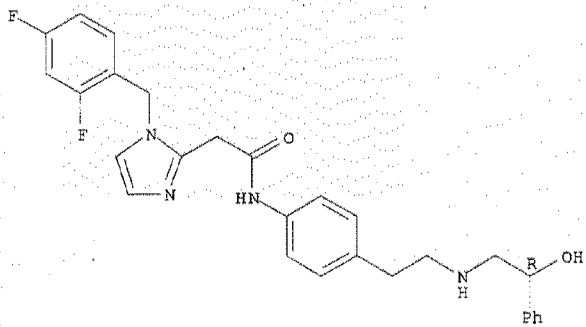
Searched by Barb O'Bryen, STIC 308-4291



●2 HCl

RN 223672-80-8 CAPLUS
CN 1H-Imidazole-2-acetamide, 1-[(2,4-difluorophenyl)methyl]-N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

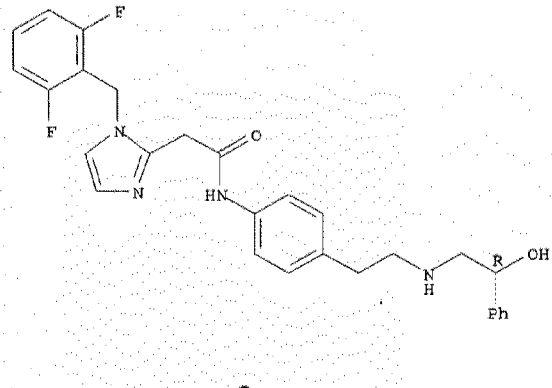


●2 HCl

RN 223672-81-9 CAPLUS
CN 1H-Imidazole-2-acetamide, 1-[(2,6-difluorophenyl)methyl]-N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

Searched by Barb O'Bryen, STIC 308-4291



●2 HCl

RN 223672-82-0 CAPLUS
CN 1H-Imidazole-2-acetamide, 1-[(3,5-difluorophenyl)methyl]-N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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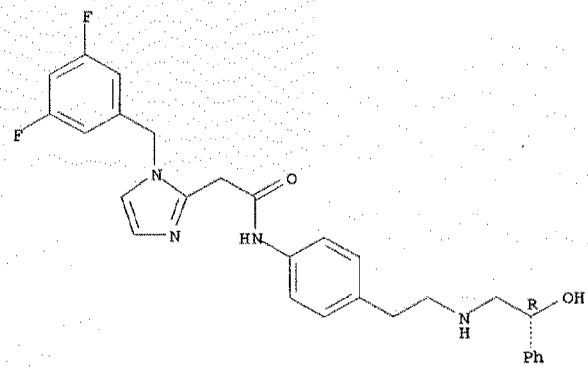

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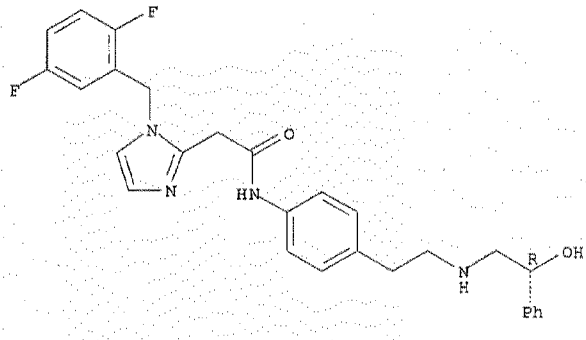
●2 HCl

RN 223672-83-1 CAPLUS
CN 1H-Imidazole-2-acetamide, 1-[(2,5-difluorophenyl)methyl]-N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

Searched by Barb O'Bryen, STIC 308-4291

Absolute stereochemistry.



●2 HCl

RN 223672-84-2 CAPLUS
CN 1H-Imidazole-2-acetamide, 1-[(3,4-difluorophenyl)methyl]-N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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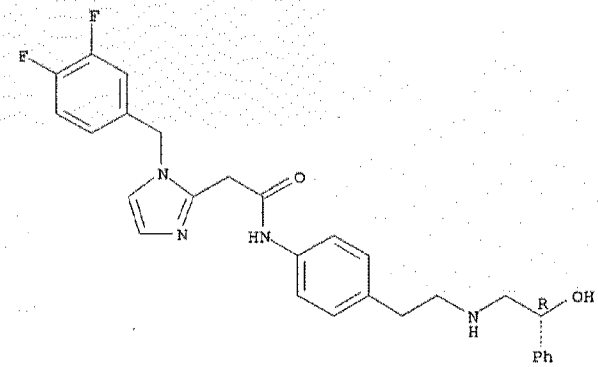

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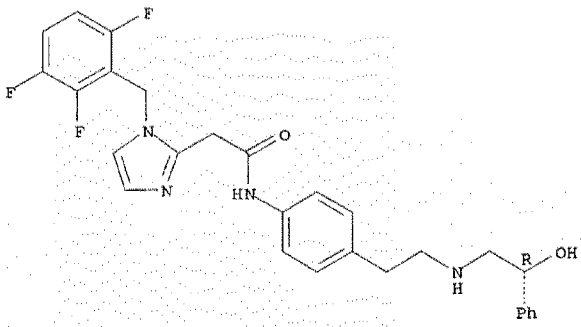
●2 HCl

RN 223672-85-3 CAPLUS
CN 1H-Imidazole-2-acetamide, N-[4-[2-[[(2R)-2-hydroxy-2-

Searched by Barb O'Bryen, STIC 308-4291

phenylethyl]amino]ethyl]phenyl]-1-[(2,3,6-trifluorophenyl)methyl]-, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



●2 HCl

RN 223672-86-4 CAPLUS
CN 1H-Imidazole-2-acetamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-1-[(2,4,5-trifluorophenyl)methyl]-, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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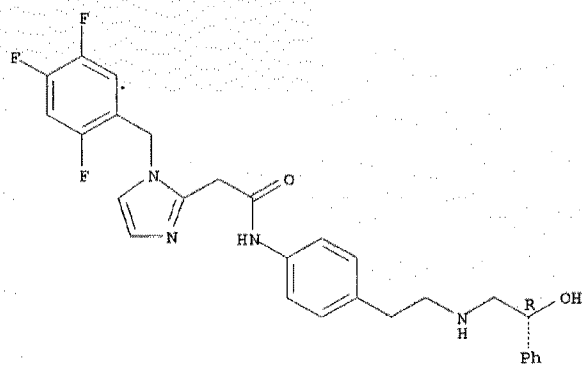

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●2 HCl

Searched by Barb O'Bryen, STIC 308-4291

RN 223672-87-5 CAPLUS
CN 1H-Imidazole-2-acetamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-1-[(3,4,5-trifluorophenyl)methyl]-, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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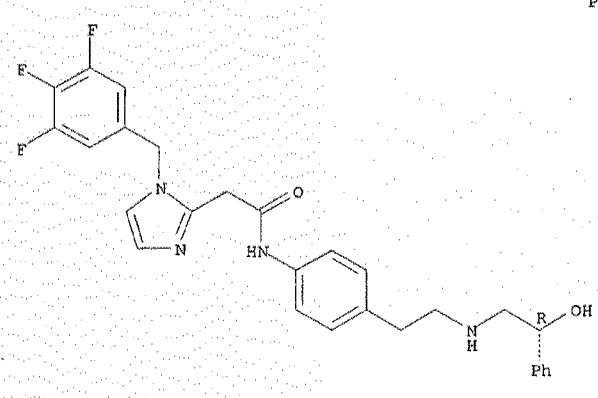

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●2 HCl

RN 223672-88-6 CAPLUS
CN 1H-Imidazole-2-acetamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-1-[(pentafluorophenyl)methyl]-, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

Searched by Barb O'Bryen, STIC 308-4291

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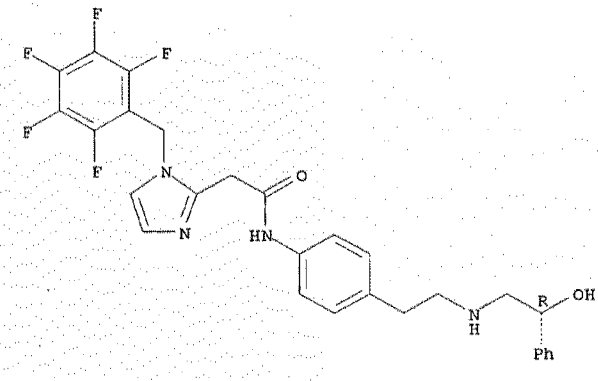

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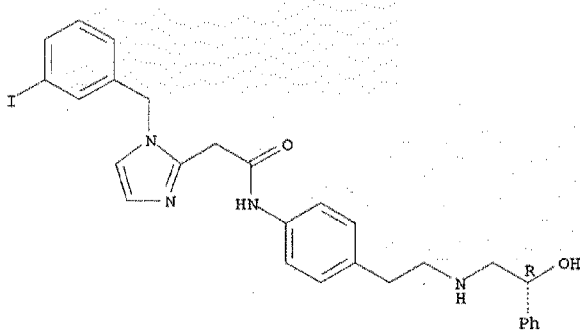
●2 HCl

RN 223672-89-7 CAPLUS
CN 1H-Imidazole-2-acetamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-1-[(3-iodophenyl)methyl]-, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

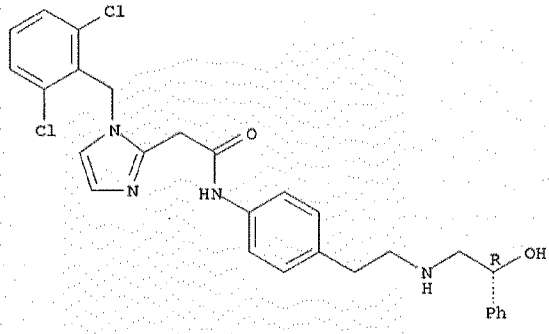


●2 HCl

RN 223672-90-0 CAPLUS
CN 1H-Imidazole-2-acetamide, 1-[(2,6-dichlorophenyl)methyl]-N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)

Searched by Barb O'Bryen, STIC 308-4291

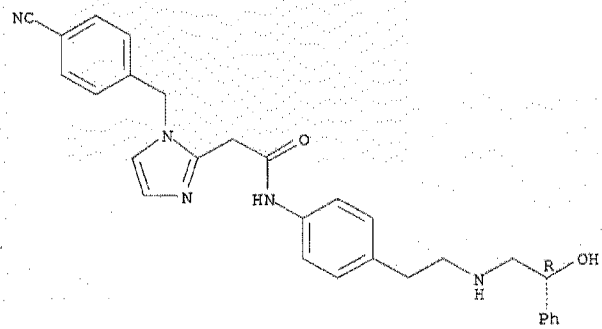
Absolute stereochemistry.



● HCl

RN 223672-91-1 CAPLUS
CN 1H-Imidazole-2-acetamide, 1-[(4-cyanophenyl)methyl]-N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

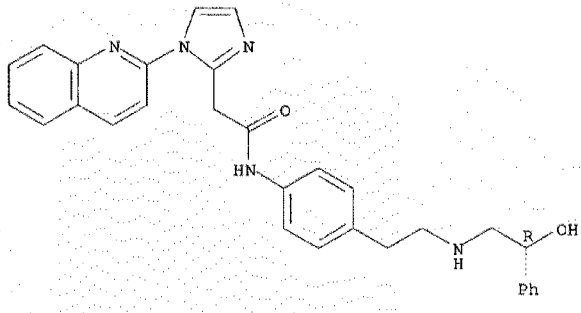


●2 HCl

RN 223672-92-2 CAPLUS
CN 1H-Imidazole-2-acetamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-1-(2-quinolinyl)-, trihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

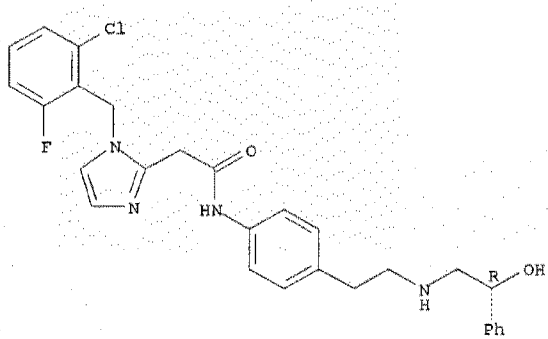
Searched by Barb O'Bryen, STIC 308-4291



●3 HCl

RN 223672-93-3 CAPLUS
CN 1H-Imidazole-2-acetamide, 1-[(2-chloro-6-fluorophenyl)methyl]-N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]- (9CI) (CA INDEX NAME)

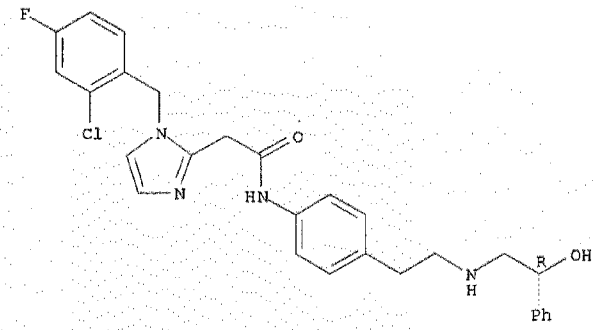
Absolute stereochemistry.



RN 223672-94-4 CAPLUS
CN 1H-Imidazole-2-acetamide, 1-[(2-chloro-4-fluorophenyl)methyl]-N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]- (9CI) (CA INDEX NAME)

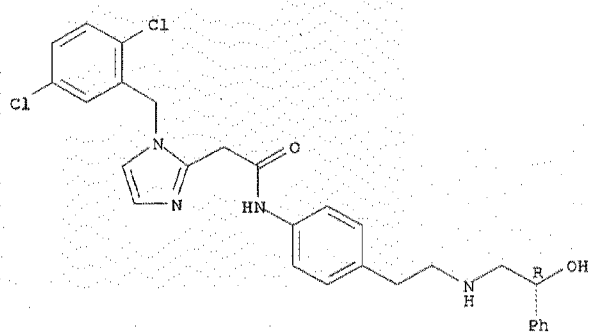
Absolute stereochemistry.

Searched by Barb O'Bryen, STIC 308-4291



RN 223672-95-5 CAPLUS
CN 1H-Imidazole-2-acetamide, 1-[(2,5-dichlorophenyl)methyl]-N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



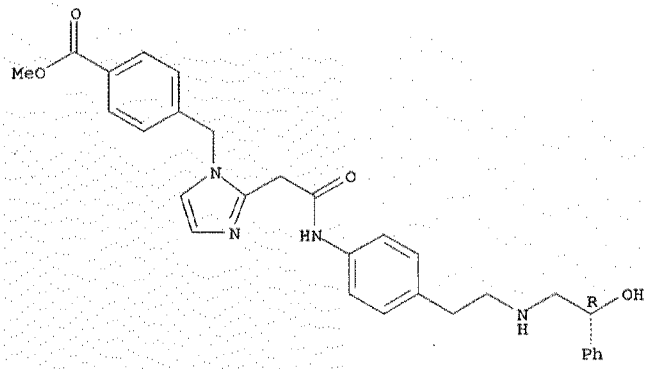
●2 HCl

RN 223672-96-6 CAPLUS
CN Benzoic acid, 4-[[2-[2-[[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]amino]-2-oxoethyl]-1H-imidazol-1-yl]methyl]-, methyl ester, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

Searched by Barb O'Bryen, STIC 308-4291

PAGE 1-A

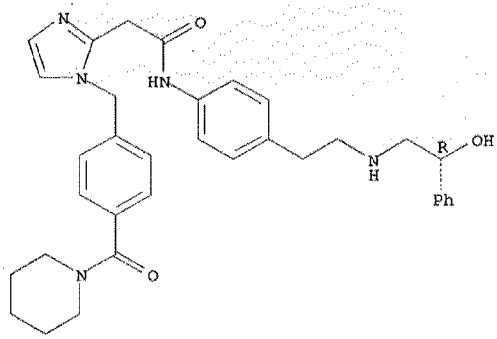


PAGE 2-A

●2 HCl

RN 223672-97-7 CAPLUS
CN 1H-Imidazole-2-acetamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-1-[[4-(1-piperidinylcarbonyl)phenyl]methyl]-, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

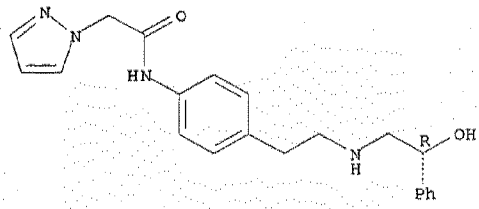


●2 HCl

RN 223672-98-8 CAPLUS
CN 1H-Pyrazole-1-acetamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)

Searched by Barb O'Bryen, STIC 308-4291

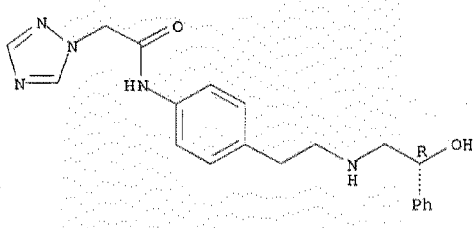
Absolute stereochemistry.



● HCl

RN 223672-99-9 CAPLUS
CN 1H-1,2,4-Triazole-1-acetamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

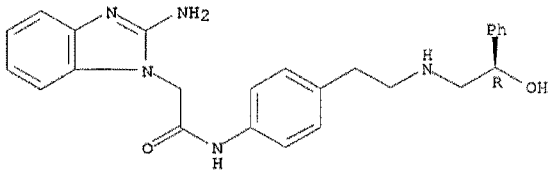
Absolute stereochemistry.



●2 HCl

RN 223673-00-5 CAPLUS
CN 1H-Benzimidazole-1-acetamide, 2-amino-N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

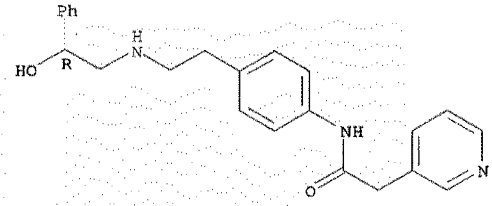


●2 HCl

Searched by Barb O'Bryen, STIC 308-4291

RN 223673-01-6 CAPLUS
CN 3-Pyridineacetamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)

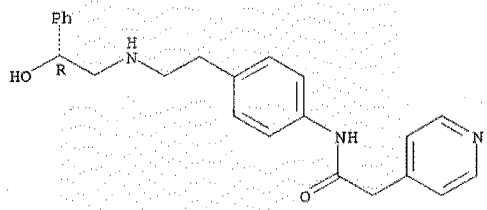
Absolute stereochemistry.



● HCl

RN 223673-02-7 CAPLUS
CN 4-Pyridineacetamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

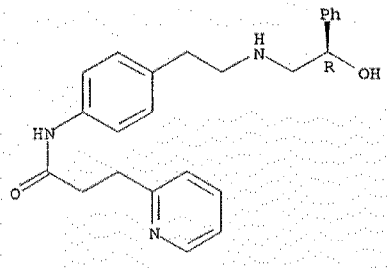


● HCl

RN 223673-03-8 CAPLUS
CN 2-Pyridinepropanamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

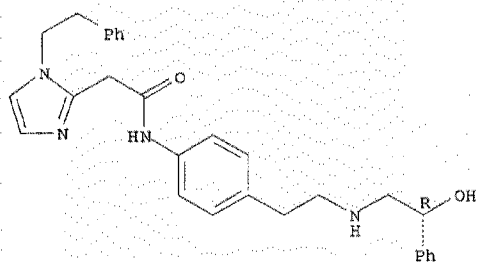
Searched by Barb O'Bryen, STIC 308-4291



● HCl

RN 223673-04-9 CAPLUS
CN 1H-Imidazole-2-acetamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-1-(2-phenylethyl)-, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

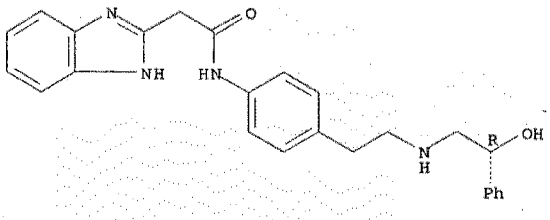


●2 HCl

RN 223673-05-0 CAPLUS
CN 1H-Benzimidazole-2-acetamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]- (9CI) (CA INDEX NAME)

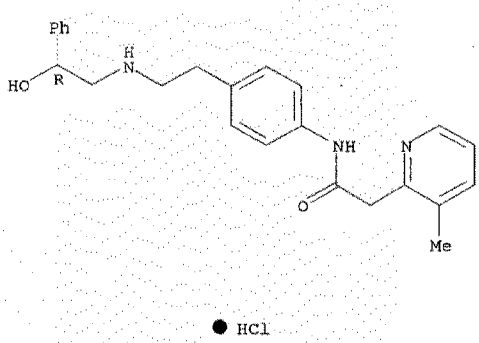
Absolute stereochemistry.

Searched by Barb O'Bryen, STIC 308-4291



RN 223673-06-1 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-3-methyl-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

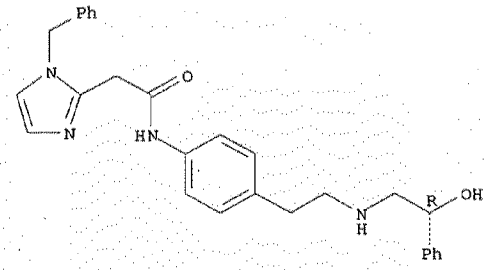


● HCl

RN 223673-07-2 CAPLUS
CN 1H-Imidazole-2-acetamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-1-(phenylmethyl)-, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

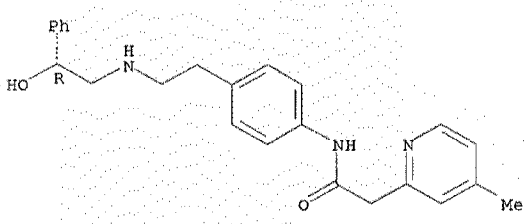
Searched by Barb O'Bryen, STIC 308-4291



●2 HCl

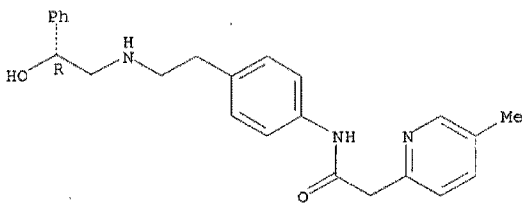
RN 223673-08-3 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-4-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 223673-09-4 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-5-methyl- (9CI) (CA INDEX NAME)

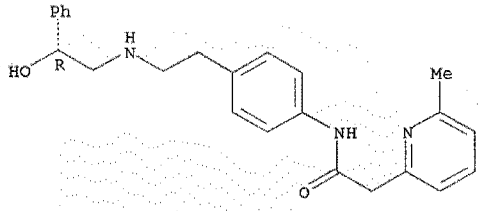
Absolute stereochemistry.



RN 223673-10-7 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-6-methyl- (9CI) (CA INDEX NAME)

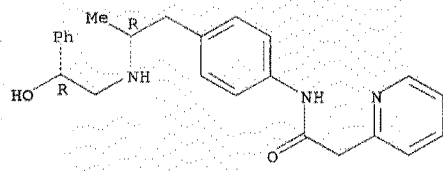
Absolute stereochemistry.

Searched by Barb O'Bryen, STIC 308-4291



RN 223673-11-8 CAPLUS
CN 2-Pyridineacetamide, N-[4-[(2R)-2-[[(2R)-2-hydroxy-2-phenylethyl]amino]propyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)

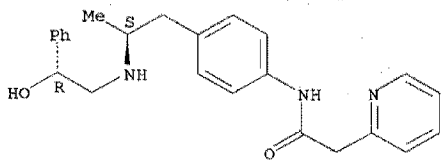
Absolute stereochemistry.



● HCl

RN 223673-12-9 CAPLUS
CN 2-Pyridineacetamide, N-[4-[(2S)-2-[[(2R)-2-hydroxy-2-phenylethyl]amino]propyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

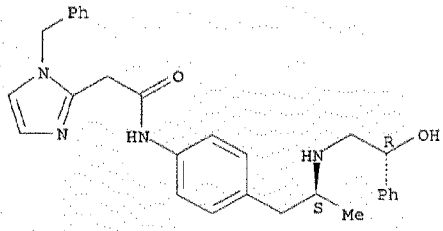


● HCl

RN 223673-13-0 CAPLUS
CN 1H-Imidazole-2-acetamide, N-[4-[(2S)-2-[[(2R)-2-hydroxy-2-phenylethyl]amino]propyl]phenyl]-1-(phenylmethyl)-, monohydrochloride (9CI) (CA INDEX NAME)

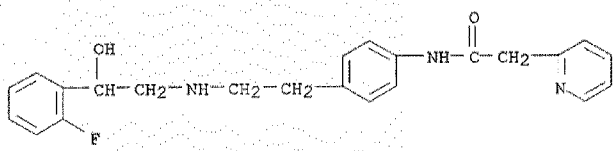
Absolute stereochemistry.

Searched by Barb O'Bryen, STIC 308-4291



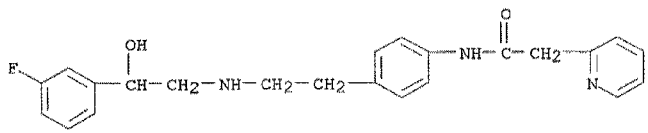
● HCl

RN 223673-14-1 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[2-(2-fluorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

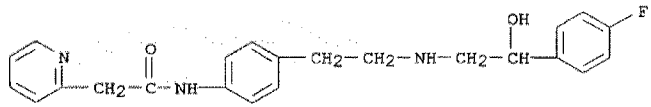
RN 223673-15-2 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[2-(3-fluorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

RN 223673-16-3 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[2-(4-fluorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)

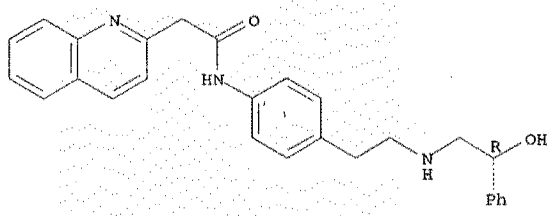
Searched by Barb O'Bryen, STIC 308-4291



● HCl

RN 223673-17-4 CAPLUS
CN 2-Quinolineacetamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)

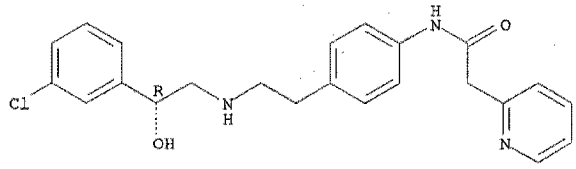
Absolute stereochemistry.



● HCl

RN 223673-18-5 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)

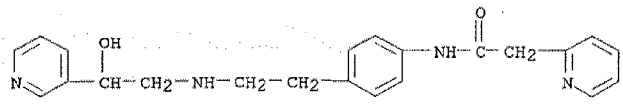
Absolute stereochemistry.



● HCl

RN 223673-19-6 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)

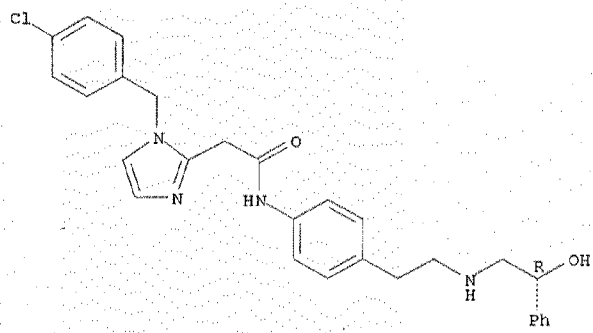
Searched by Barb O'Bryen, STIC 308-4291



● HCl

RN 223673-20-9 CAPLUS
CN 1H-Imidazole-2-acetamide, 1-[(4-chlorophenyl)methyl]-N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

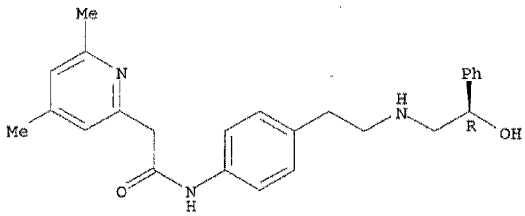
Absolute stereochemistry.



● 2 HCl

RN 223673-21-0 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-4,6-dimethyl- (9CI) (CA INDEX NAME)

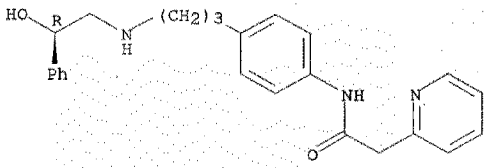
Absolute stereochemistry.



RN 223673-22-1 CAPLUS
CN 2-Pyridineacetamide, N-[4-[3-[[(2R)-2-hydroxy-2-phenylethyl]amino]propyl]phenyl]-, monohydrochloride (9CI) (CA INDEX

NAME)

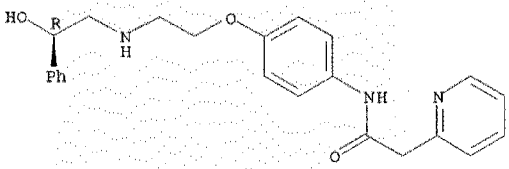
Absolute stereochemistry.



● HCl

RN 223673-23-2 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethoxy]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)

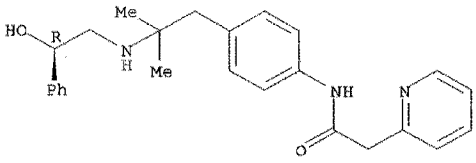
Absolute stereochemistry.



● HCl

RN 223673-25-4 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]-2-methylpropyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

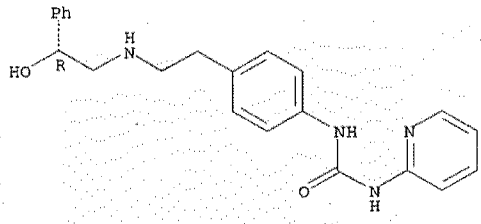


● HCl

RN 223673-26-5 CAPLUS
CN Urea, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-N'-2-pyridinyl-, dihydrochloride (9CI) (CA INDEX NAME)

Searched by Barb O'Bryen, STIC 308-4291

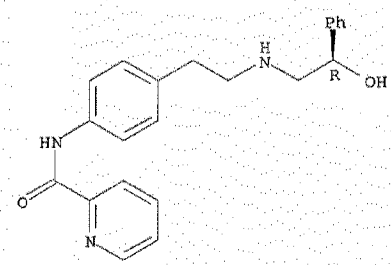
Absolute stereochemistry.



●2 HCl

RN 223673-27-6 CAPLUS
CN 2-Pyridinecarboxamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

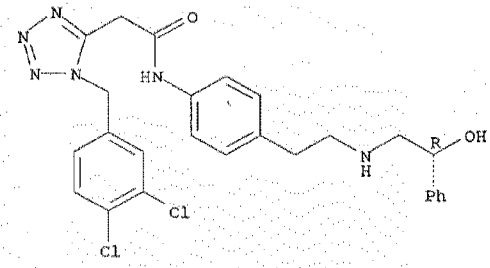


●2 HCl

RN 223673-28-7 CAPLUS
CN 1H-Tetrazole-5-acetamide, 1-[(3,4-dichlorophenyl)methyl]-N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

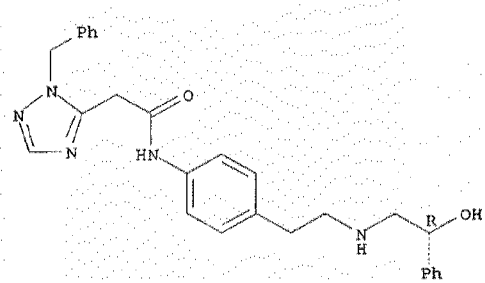
Searched by Barb O'Bryen, STIC 308-4291



●2 HCl

RN 223673-29-8 CAPLUS
CN 1H-1,2,4-Triazole-5-acetamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-1-(phenylmethyl)-, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

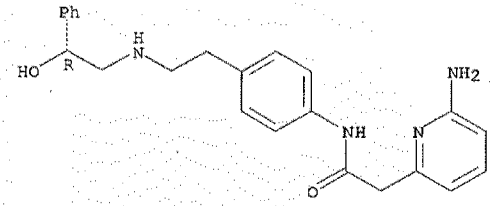


●2 HCl

RN 223673-30-1 CAPLUS
CN 2-Pyridineacetamide, 6-amino-N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

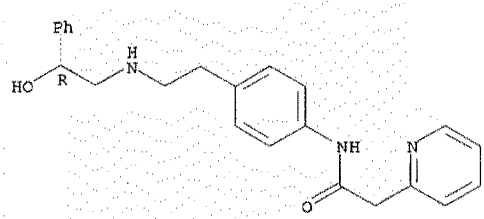
Searched by Barb O'Bryen, STIC 308-4291



●2 HCl

RN 223673-31-2 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

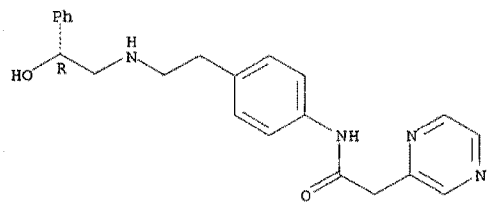
Absolute stereochemistry.



●2 HCl

RN 223673-32-3 CAPLUS
CN Pyrazineacetamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



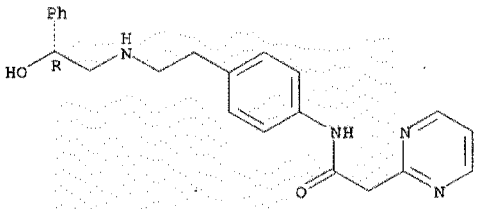
●2 HCl

RN 223673-33-4 CAPLUS

Searched by Barb O'Bryen, STIC 308-4291

CN 2-Pyrimidineacetamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

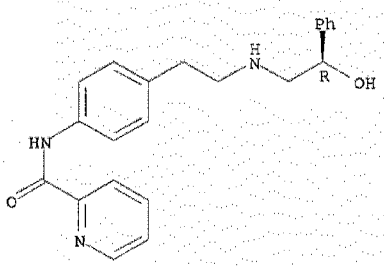
Absolute stereochemistry.



●2 HCl

RN 223673-58-3 CAPLUS
CN 2-Pyridinecarboxamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]- (9CI) (CA INDEX NAME)

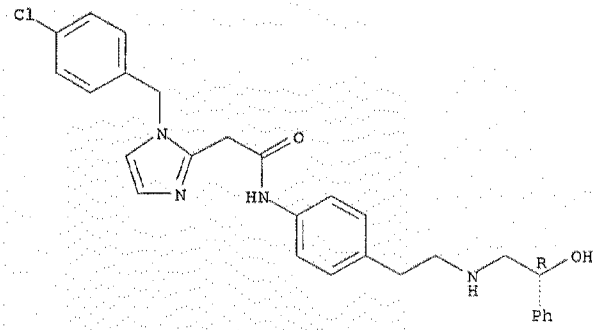
Absolute stereochemistry.



RN 223673-59-4 CAPLUS
CN 1H-Imidazole-2-acetamide, 1-[(4-chlorophenyl)methyl]-N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]- (9CI) (CA INDEX NAME)

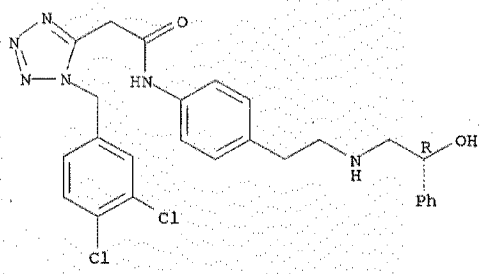
Absolute stereochemistry.

Searched by Barb O'Bryen, STIC 308-4291



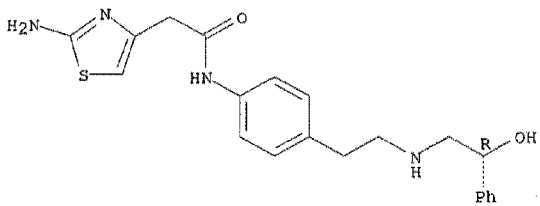
RN 223673-60-7 CAPLUS
CN 1H-Tetrazole-5-acetamide, 1-[(3,4-dichlorophenyl)methyl]-N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 223673-61-8 CAPLUS
CN 4-Thiazoleacetamide, 2-amino-N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]- (9CI) (CA INDEX NAME)

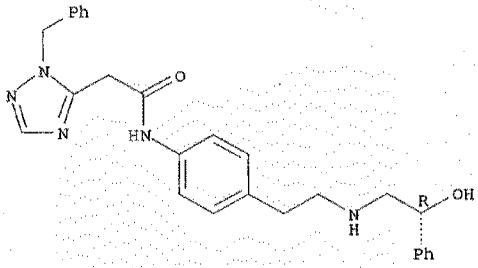
Absolute stereochemistry.



RN 223673-62-9 CAPLUS
CN 1H-1,2,4-Triazole-5-acetamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-1-(phenylmethyl)- (9CI) (CA INDEX NAME)

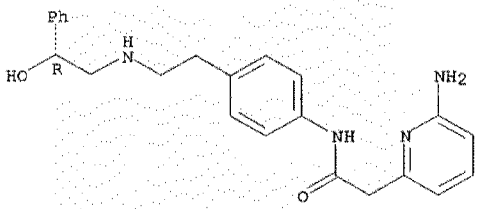
Searched by Barb O'Bryen, STIC 308-4291

Absolute stereochemistry.



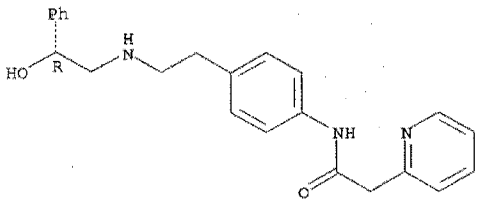
RN 223673-63-0 CAPLUS
CN 2-Pyridineacetamide, 6-amino-N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 223673-64-1 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]- (9CI) (CA INDEX NAME)

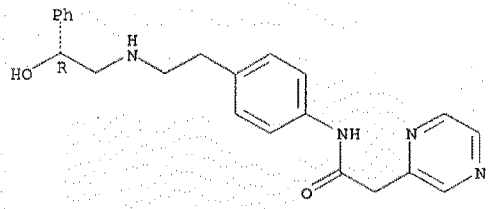
Absolute stereochemistry.



RN 223673-65-2 CAPLUS
CN Pyrazineacetamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]- (9CI) (CA INDEX NAME)

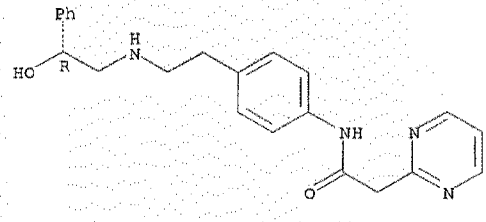
Absolute stereochemistry.

Searched by Barb O'Bryen, STIC 308-4291



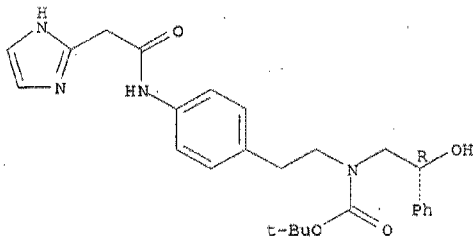
RN 223673-66-3 CAPLUS
CN 2-Pyrimidineacetamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **223673-45-8 223673-47-0 223673-48-1**
223673-49-2 223673-50-5 223673-51-6
223673-52-7 223673-53-8 223673-56-1
223673-57-2
RL: RCT (Reactant)
(prepn. of amides as antidiabetics)
RN 223673-45-8 CAPLUS
CN Carbamic acid, [(2R)-2-hydroxy-2-phenylethyl][2-[4-[(1H-imidazol-2-ylacetyl)amino]phenyl]ethyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

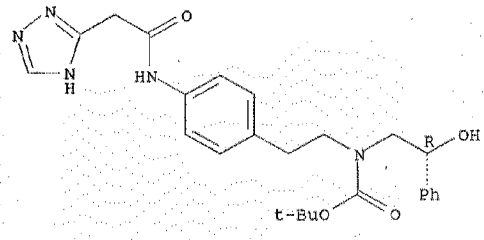
Absolute stereochemistry.



RN 223673-47-0 CAPLUS
CN Carbamic acid, [(2R)-2-hydroxy-2-phenylethyl][2-[4-[(1H-1,2,4-triazol-3-ylacetyl)amino]phenyl]ethyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

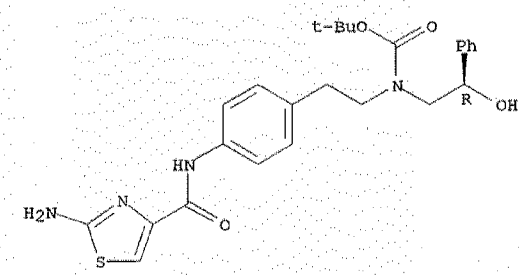
Searched by Barb O'Bryen, STIC 308-4291

Absolute stereochemistry.



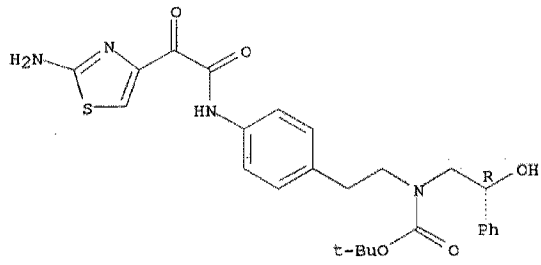
RN 223673-48-1 CAPLUS
CN Carbamic acid, [2-[4-[[(2-amino-4-thiazolyl)carbonyl]amino]phenyl]ethyl][(2R)-2-hydroxy-2-phenylethyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 223673-49-2 CAPLUS
CN Carbamic acid, [2-[4-[[(2-amino-4-thiazolyl)oxoacetyl]amino]phenyl]ethyl][(2R)-2-hydroxy-2-phenylethyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

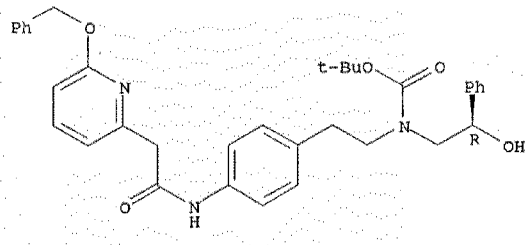
Absolute stereochemistry.



RN 223673-50-5 CAPLUS
CN Carbamic acid, [(2R)-2-hydroxy-2-phenylethyl][2-[4-[[[6-(phenylmethoxy)-2-

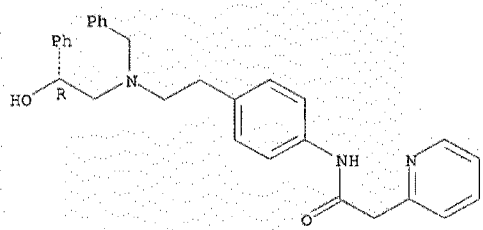
pyridinyl]acetyl]amino]phenyl]ethyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



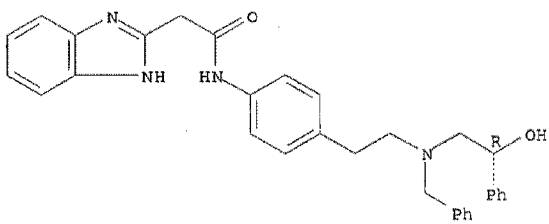
RN 223673-51-6 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl](phenylmethyl)amino]ethyl]phenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 223673-52-7 CAPLUS
CN 1H-Benzimidazole-2-acetamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl](phenylmethyl)amino]ethyl]phenyl]- (9CI) (CA INDEX NAME)

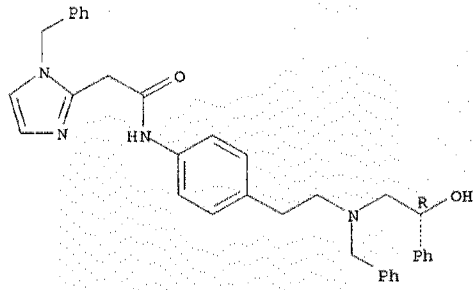
Absolute stereochemistry.



RN 223673-53-8 CAPLUS
CN 1H-Imidazole-2-acetamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl](phenylmethyl)amino]ethyl]phenyl]-1-(phenylmethyl)- (9CI) (CA INDEX NAME)

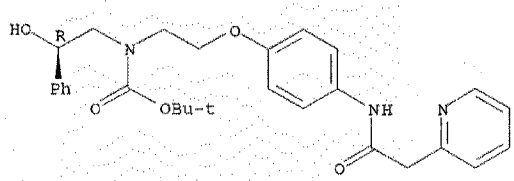
Searched by Barb O'Bryen, STIC 308-4291

Absolute stereochemistry.



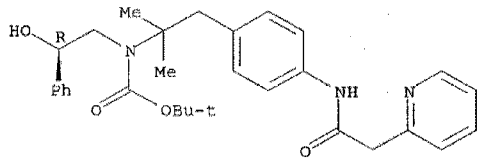
RN 223673-56-1 CAPLUS
CN Carbamic acid, [(2R)-2-hydroxy-2-phenylethyl][2-[4-[(2-pyridinylacetyl)amino]phenoxy]ethyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 223673-57-2 CAPLUS
CN Carbamic acid, [1,1-dimethyl-2-[4-[(2-pyridinylacetyl)amino]phenyl]ethyl][(2R)-2-hydroxy-2-phenylethyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

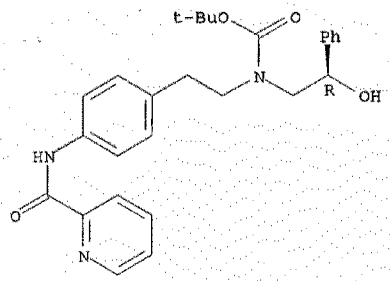
Absolute stereochemistry.



IT **223673-37-8P 223673-38-9P 223673-39-0P**
223673-41-4P 223673-44-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. of amides as antidiabetics)
RN 223673-37-8 CAPLUS
CN Carbamic acid, [(2R)-2-hydroxy-2-phenylethyl][2-[4-[(2-pyridinylcarbonyl)amino]phenyl]ethyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

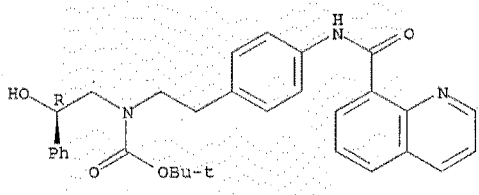
Absolute stereochemistry.

Searched by Barb O'Bryen, STIC 308-4291



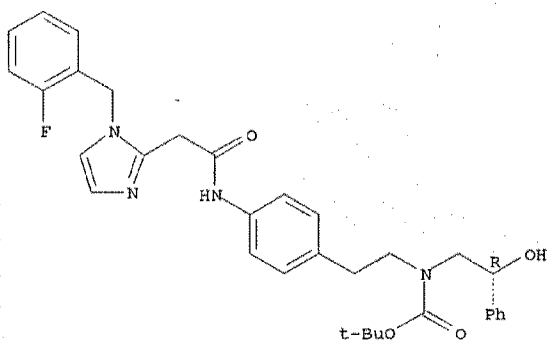
RN 223673-38-9 CAPLUS
CN Carbamic acid, [(2R)-2-hydroxy-2-phenylethyl][2-[4-[(8-quinolinylcarbonyl)amino]phenyl]ethyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 223673-39-0 CAPLUS
CN Carbamic acid, [2-[4-[[[1-[(2-fluorophenyl)methyl]-1H-imidazol-2-yl]acetyl]amino]phenyl]ethyl][(2R)-2-hydroxy-2-phenylethyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

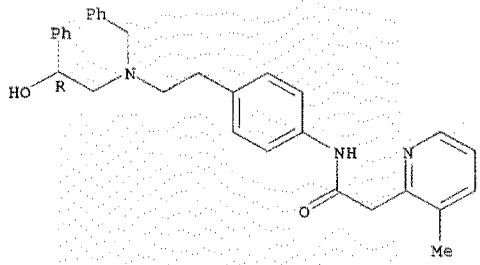


RN 223673-41-4 CAPLUS

Searched by Barb O'Bryen, STIC 308-4291

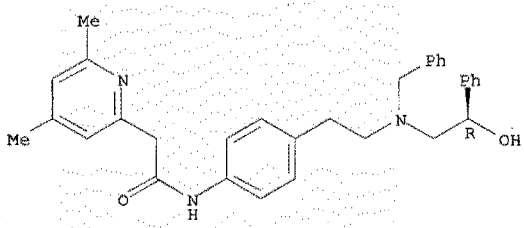
CN 2-Pyridineacetamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl](phenylmethyl)amino]ethyl]phenyl]-3-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 223673-44-7 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl](phenylmethyl)amino]ethyl]phenyl]-4,6-dimethyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 10
REFERENCE(S): (1) Merck & Co Inc; JP 07-10827 A 1995
(2) Merck & Co Inc; US 5553475 A 1995
(5) Merck & Co Inc; US 5541197 A 1997 CAPLUS
(7) Merck & Co Inc; WO 95/29159 A1 1997 CAPLUS
(10) Takeda Chem Ind Ltd; EP 643050 A1 1996 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1998:535771 CAPLUS
DOCUMENT NUMBER: 129:198012
TITLE: Preparation of phenethanol derivatives and their use as antidiabetic agents
INVENTOR(S): Maruyama, Tatsuya; Onta, Kenichi; Hayakawa, Akihiko; Matsui, Tetsuo
PATENT ASSIGNEE(S): Yamanouchi Pharmaceutical Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 20 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
Searched by Barb O'Bryen, STIC 308-4291

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 10218861	A2	19980818	JP 1997-21870	19970204

OTHER SOURCE(S): MARPAT 129:198012

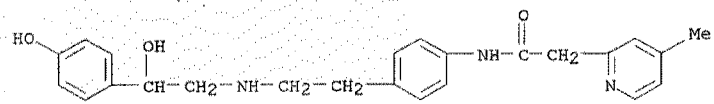
GI For diagram(s), see printed CA Issue.

AB The derivs. I [ring B = II, III, IV; X, Y = O, S, NR6; R1 = H, lower alkyl; R2 = H, lower alkyl, NHSO2Me, NHCOR3; R3 = H, lower alkyl, mono- or di(lower alkylamino), aryl, aralkyl; R4, R5 = H, lower alkyl, amino; R6 = H, lower alkyl, aralkyl] or their salts as .beta.3-adrenoceptor agonists are prepd. Antidiabetic agents contg. I or thir salts as active ingredients are also claimed. I decreased blood glucose of obese and hyperglycemic kk mice with insulin resistance upon both oral and percutaneous administrations. I also increased insulin secretion in normal rats. Prepn. of some of I was given.

IT **211636-04-3P 211636-05-4P 211636-06-5P**
211636-07-6P 211636-08-7P 211636-09-8P
211636-10-1P 211636-11-2P 211636-13-4P
211636-15-6P 211636-17-8P 211636-18-9P
211636-19-0P 211636-20-3P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of antidiabetic phenethanol derivs. as .beta.3-adrenoceptor agonists)

RN 211636-04-3 CAPLUS

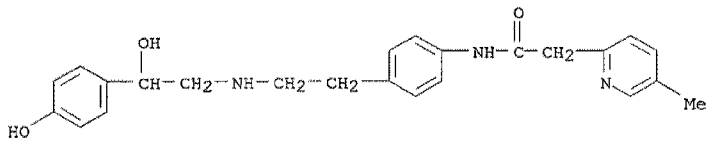
CN 2-Pyridineacetamide, N-[4-[2-[[2-hydroxy-2-(4-hydroxyphenyl)ethyl]amino]ethyl]phenyl]-4-methyl-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

RN 211636-05-4 CAPLUS

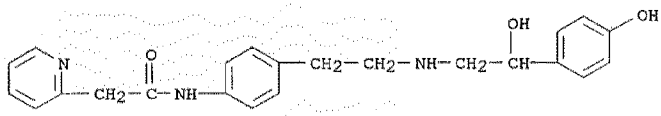
CN 2-Pyridineacetamide, N-[4-[2-[[2-hydroxy-2-(4-hydroxyphenyl)ethyl]amino]ethyl]phenyl]-5-methyl-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

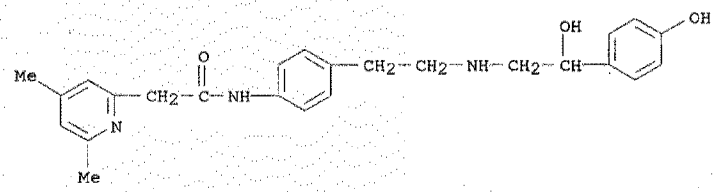
Searched by Barb O'Bryen, STIC 308-4291

RN 211636-06-5 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[2-hydroxy-2-(4-hydroxyphenyl)ethyl]amino]ethyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)



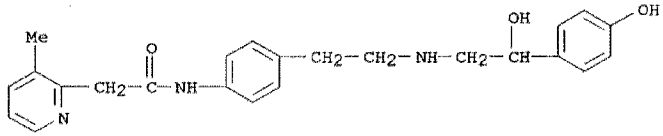
● HCl

RN 211636-07-6 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[2-hydroxy-2-(4-hydroxyphenyl)ethyl]amino]ethyl]phenyl]-4,6-dimethyl-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

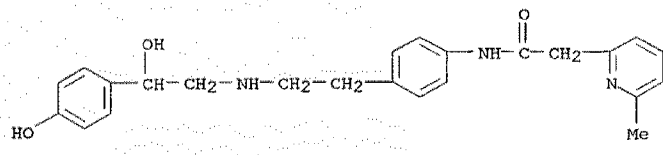
RN 211636-08-7 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[2-hydroxy-2-(4-hydroxyphenyl)ethyl]amino]ethyl]phenyl]-3-methyl-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

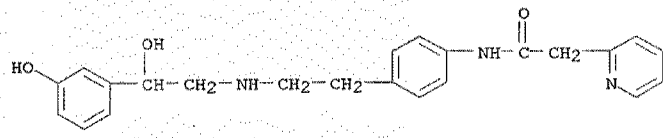
RN 211636-09-8 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[2-hydroxy-2-(4-hydroxyphenyl)ethyl]amino]ethyl]phenyl]-6-methyl-, monohydrochloride (9CI) (CA INDEX NAME)

Searched by Barb O'Bryen, STIC 308-4291



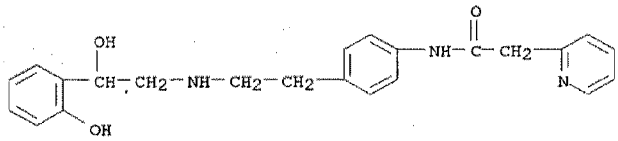
● HCl

RN 211636-10-1 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[2-hydroxy-2-(3-hydroxyphenyl)ethyl]amino]ethyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

RN 211636-11-2 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[2-hydroxy-2-(2-hydroxyphenyl)ethyl]amino]ethyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)



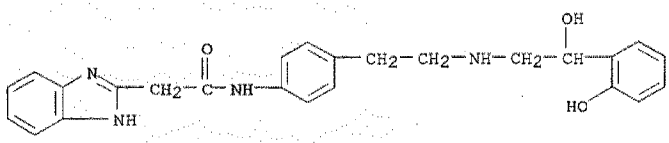
● HCl

RN 211636-13-4 CAPLUS
CN 1H-Benzimidazole-2-acetamide, N-[4-[2-[[2-hydroxy-2-(2-hydroxyphenyl)ethyl]amino]ethyl]phenyl]-, (2E)-2-butenedioate (2:1) (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 211636-12-3
CMF C25 H26 N4 O3

Searched by Barb O'Bryen, STIC 308-4291



CM 2

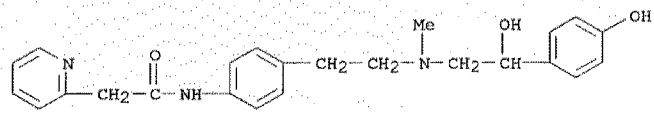
CRN 110-17-8
CMF C4 H4 O4
CDES 2:E

Double bond geometry as shown.

RN 211636-15-6 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[2-hydroxy-2-(4-hydroxyphenyl)ethyl]methylamino]ethyl]phenyl]-, (2E)-2-butenedioate (1:1) (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 211636-14-5
CMF C24 H27 N3 O3



CM 2

CRN 110-17-8
CMF C4 H4 O4
CDES 2:E

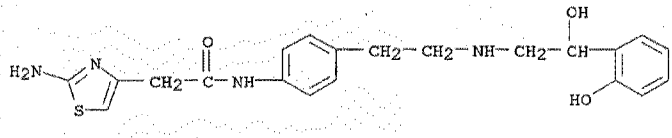
Double bond geometry as shown.

RN 211636-17-8 CAPLUS
CN 4-Thiazoleacetamide, 2-amino-N-[4-[2-[[2-hydroxy-2-(2-hydroxyphenyl)ethyl]amino]ethyl]phenyl]-, hydrochloride trifluoroacetate (2:1:3) (salt) (9CI) (CA INDEX NAME)

CM 1

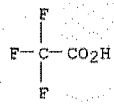
Searched by Barb O'Bryen, STIC 308-4291

CRN 211636-16-7
CMF C21 H24 N4 O3 S

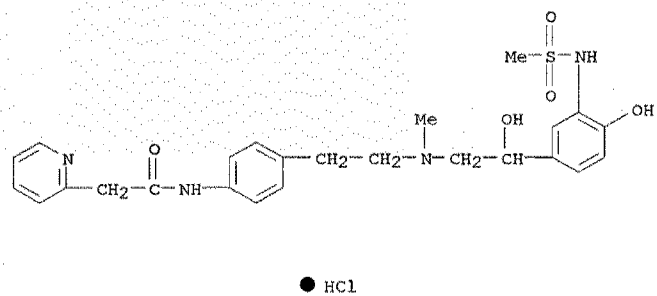


CM 2

CRN 76-05-1
CMF C2 H F3 O2



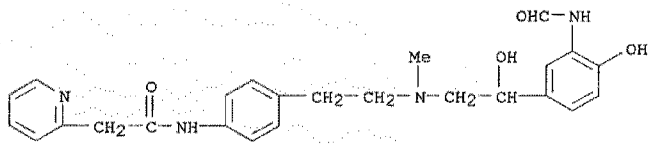
RN 211636-18-9 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[2-hydroxy-2-[4-hydroxy-3-[(methylsulfonyl)amino]phenyl]ethyl]methylamino]ethyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

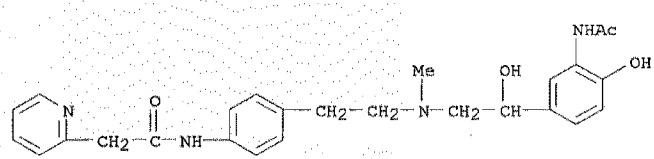
RN 211636-19-0 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[2-[3-(formylamino)-4-hydroxyphenyl]-2-hydroxyethyl]methylamino]ethyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)

Searched by Barb O'Bryen, STIC 308-4291



● HCl

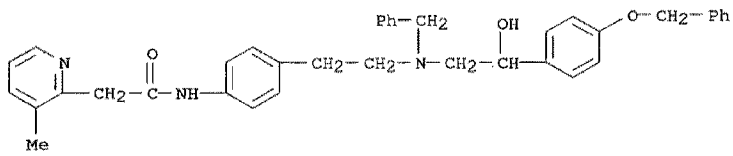
RN 211636-20-3 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[2-[3-(acetylamino)-4-hydroxyphenyl]-2-hydroxyethyl]methylamino]ethyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

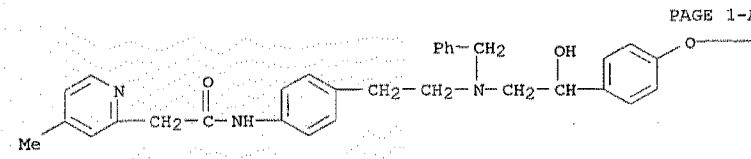
IT **211635-78-8P 211635-79-9P 211635-80-2P**
211635-81-3P 211635-86-8P 211635-87-9P
211635-88-0P 211635-89-1P 211635-92-6P
211635-93-7P 211635-94-8P 211635-95-9P
211635-96-0P 211635-97-1P 211636-00-9P
211636-03-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. of antidiabetic phenethanol derivs. as .beta.3-adrenoceptor agonists)

RN 211635-78-8 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[2-hydroxy-2-[4-(phenylmethoxy)phenyl]ethyl](phenylmethyl)amino]ethyl]phenyl]-3-methyl- (9CI) (CA INDEX NAME)

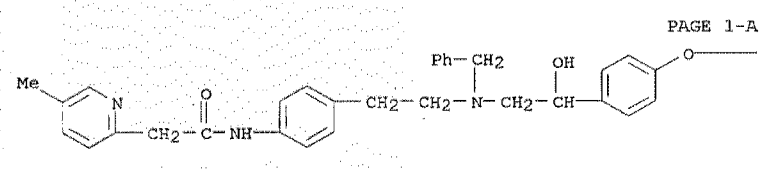


RN 211635-79-9 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[2-hydroxy-2-[4-

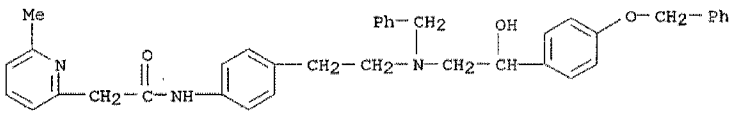
(phenylmethoxy)phenyl]ethyl](phenylmethyl)amino]ethyl]phenyl]-4-methyl-
(9CI) (CA INDEX NAME)



RN 211635-80-2 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[2-hydroxy-2-[4-
(phenylmethoxy)phenyl]ethyl](phenylmethyl)amino]ethyl]phenyl]-5-methyl-
(9CI) (CA INDEX NAME)

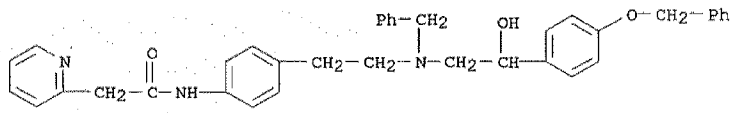


RN 211635-81-3 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[2-hydroxy-2-[4-
(phenylmethoxy)phenyl]ethyl](phenylmethyl)amino]ethyl]phenyl]-6-methyl-
(9CI) (CA INDEX NAME)



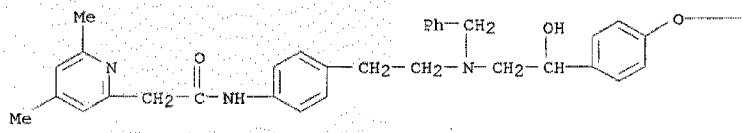
RN 211635-86-8 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[2-hydroxy-2-[4-
(phenylmethoxy)phenyl]ethyl](phenylmethyl)amino]ethyl]phenyl]- (9CI) (CA
INDEX NAME)

Searched by Barb O'Bryen, STIC 308-4291

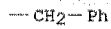


RN 211635-87-9 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[2-hydroxy-2-[4-(phenylmethoxy)phenyl]ethyl](phenylmethyl)amino]ethyl]phenyl]-4,6-dimethyl- (9CI) (CA INDEX NAME)

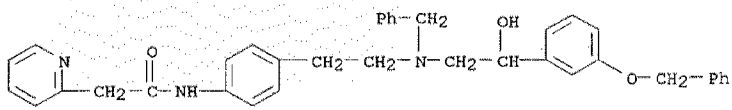
PAGE 1-A



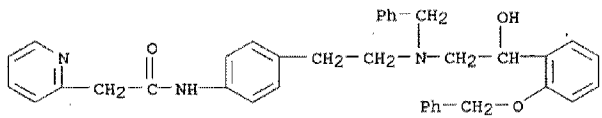
PAGE 1-B



RN 211635-88-0 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[2-hydroxy-2-[3-(phenylmethoxy)phenyl]ethyl](phenylmethyl)amino]ethyl]phenyl]- (9CI) (CA INDEX NAME)

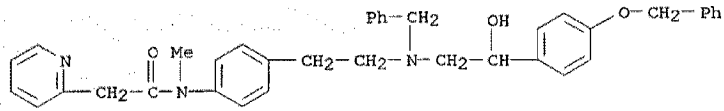


RN 211635-89-1 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[2-hydroxy-2-[2-(phenylmethoxy)phenyl]ethyl](phenylmethyl)amino]ethyl]phenyl]- (9CI) (CA INDEX NAME)

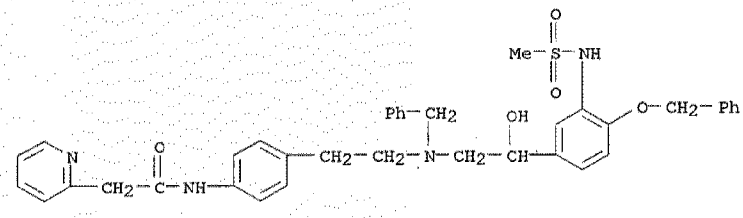


RN 211635-92-6 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[2-hydroxy-2-[4-(phenylmethoxy)phenyl]ethyl](phenylmethyl)amino]ethyl]phenyl]-N-methyl- (9CI) (CA INDEX NAME)

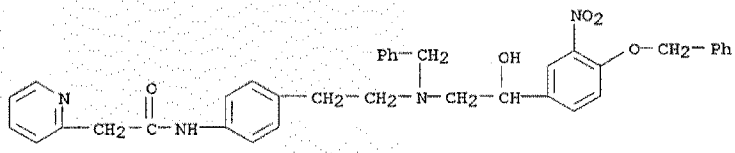
Searched by Barb O'Bryen, STIC 308-4291



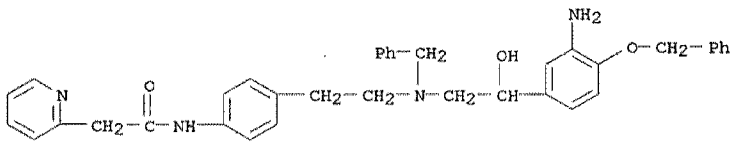
RN 211635-93-7 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[2-hydroxy-2-[3-[(methylsulfonyl)amino]-4-(phenylmethoxy)phenyl]ethyl](phenylmethyl)amino]ethyl]phenyl]- (9CI) (CA INDEX NAME)



RN 211635-94-8 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[2-hydroxy-2-[3-nitro-4-(phenylmethoxy)phenyl]ethyl](phenylmethyl)amino]ethyl]phenyl]- (9CI) (CA INDEX NAME)

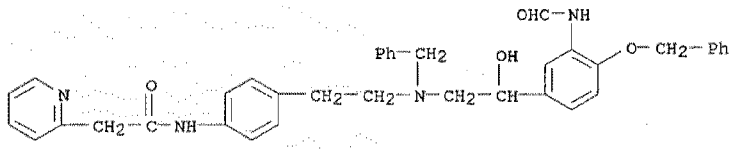


RN 211635-95-9 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[2-[3-amino-4-(phenylmethoxy)phenyl]-2-hydroxyethyl](phenylmethyl)amino]ethyl]phenyl]- (9CI) (CA INDEX NAME)

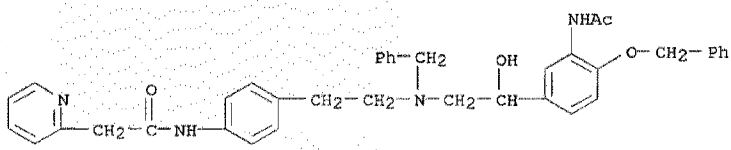


RN 211635-96-0 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[2-[3-(formylamino)-4-(phenylmethoxy)phenyl]-2-hydroxyethyl](phenylmethyl)amino]ethyl]phenyl]- (9CI) (CA INDEX NAME)

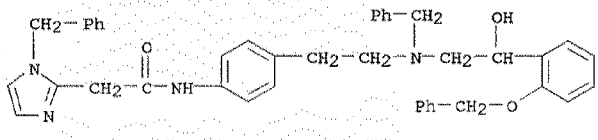
Searched by Barb O'Bryen, STIC 308-4291



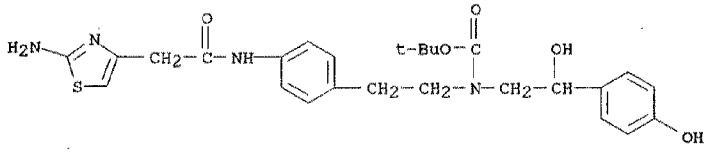
RN 211635-97-1 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[2-[3-(acetylamino)-4-(phenylmethoxy)phenyl]-2-hydroxyethyl](phenylmethyl)amino]ethyl]phenyl]- (9CI) (CA INDEX NAME)



RN 211636-00-9 CAPLUS
CN 1H-Imidazole-2-acetamide, N-[4-[2-[[2-hydroxy-2-[2-(phenylmethoxy)phenyl]ethyl](phenylmethyl)amino]ethyl]phenyl]-1-(phenylmethyl)- (9CI) (CA INDEX NAME)



RN 211636-03-2 CAPLUS
CN Carbamic acid, [2-[4-[[(2-amino-4-thiazolyl)acetyl]amino]phenyl]ethyl][2-hydroxy-2-(4-hydroxyphenyl)ethyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



L9 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1998:269995 CAPLUS
DOCUMENT NUMBER: 128:303693
TITLE: New Azole Antifungals. 3. Synthesis and Antifungal Activity of 3-Substituted-4(3H)-quinazolinones
AUTHOR(S): Bartroli, Javier; Turmo, Enric; Alguero, Monica; Boncompte, Eulalia; Vericat, Maria L.; Conte, Lourdes; Ramis, Joaquim; Merlos, Manuel; Garcia-Rafanell, Searched by Barb O'Bryen, STIC 308-4291

Julian; Forn, Javier
CORPORATE SOURCE: Research Center, J. Uriach Cia. S.A., Barcelona, 08026, Spain
SOURCE: J. Med. Chem. (1998), 41(11), 1869-1882
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
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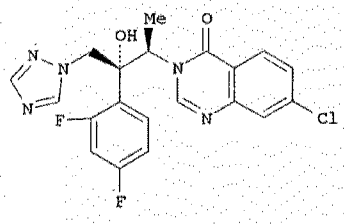


I

AB A series of azole antifungal agents featuring a quinazolinone nucleus have been subjected to studies of structure-activity relationships. In general, these compds. displayed higher in vitro activities against filamentous fungi and shorter half-lives than the structures described in our preceding paper. The most potent products in vitro carried a halogen (or an isostere) at the 7-position of the quinazolinone ring. Using a murine model of systemic candidosis, oral activity was found to be dependent on hydrophobicity, which, in turn, modulated the compd.'s half-life. The 7-Cl deriv., (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one [I, UR-9825], was selected for further testing due to its high in vitro activity, low toxicity, good pharmacokinetic profile, and ease of obtention. Compd. I is the (1R,2R) isomer of four possible stereoisomers. The other three isomers were also prepd. and tested. The enantiomer (1S,2S) and the (1R,2S) epimer were inactive, whereas the (1S,2R) epimer retained some activity. In vitro, I was superior to fluconazole, itraconazole, SCH-42427, and TAK-187 and roughly similar to voriconazole and ER-30346. In vivo, I was only moderately active in a mouse model of systemic candidosis when administration was limited to the first day. This was attributed to its short half-life in that species (t1/2 = 1 h po). Protection levels comparable to or higher than those of fluconazole, however, were obsd. in systemic candidosis models in rat and rabbit, where the half-life of the compd. was found to be 6 and 9 h, resp. Finally, I showed excellent protection levels in an immunocompromised rat model of disseminated aspergillosis. The compd. showed low toxicity signs when administered to rats at 250 mg/kg qd or at 100 mg/kg bid during 28 days.

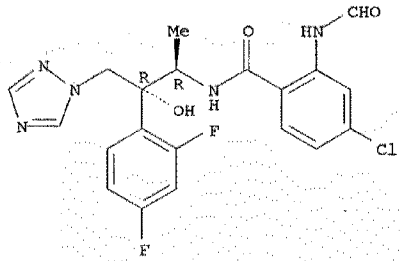
IT **206350-06-3P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(synthesis and antifungal activity of 3-substituted-4(3H)-quinazolinones)

RN 206350-06-3 CAPLUS

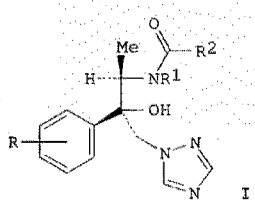
CN Benzamide, 4-chloro-N-[(1R,2R)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-2-(formylamino)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

Searched by Barb O'Bryen, STIC 308-4291



L9 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1992:426440 CAPLUS
DOCUMENT NUMBER: 117:26440
TITLE: Triazole antifungals. IV. Synthesis and antifungal activities of 3-acylamino-2-aryl-2-butanol derivatives
AUTHOR(S): Konosu, Toshiyuki; Tajima, Yawara; Takeda, Noriko; Miyaoka, Takeo; Kasahara, Mayumi; Yasuda, Hiroshi; Oida, Sadao
CORPORATE SOURCE: Med. Chem. Res. Lab., Sankyo Co., Ltd., Tokyo, 140, Japan
SOURCE: Chem. Pharm. Bull. (1991), 39(10), 2581-9
CODEN: CPBTAL; ISSN: 0009-2363
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB New triazoles, e.g., I (R = 4-Cl, 2,4-Cl2, 2,4-F2; R1 = H, Me; R2 = H, CMe3, Ph, substituted Ph, 2-furyl, 2-thienyl) were designed and synthesized as potential inhibitors of the fungal cytochrome P 450 14.alpha.-demethylase. In testing for antifungal activity against a mouse systemic Candida albicans infection, (2R,3R)-3-acylamino-2-aryl-2-butanol derivs. exhibited remarkably high efficacy after oral or parenteral administration. The structure-activity relationships of these amido alcs. were evaluated.

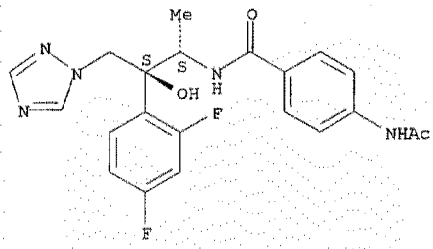
IT **126916-61-8P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. and antifungal activity of)

RN 126916-61-8 CAPLUS

CN Benzamide, 4-(acetylamino)-N-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-, (R*,R*)- (9CI) (CA INDEX NAME)

Searched by Barb O'Bryen, STIC 308-4291

Relative stereochemistry.

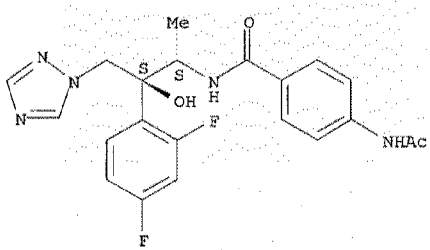


IT **138990-07-5P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)
RN 138990-07-5 CAPLUS
CN Benzamide, 4-(acetylamino)-N-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-, (R*,R*)-, ethanedioate (1:1) (salt) (9CI) (CA INDEX NAME)

CM 1

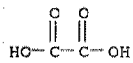
CRN 126916-61-8
CMF C21 H21 F2 N5 O3

Relative stereochemistry.



CM 2

CRN 144-62-7
CMF C2 H2 O4



L9 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1990:631379 CAPLUS
DOCUMENT NUMBER: 113:231379
Searched by Barb O'Bryen, STIC 308-4291

TITLE: Preparation and formulation of (halophenyl)-1H-1,2,4-triazol-1-ylalkanols as medical and agrochemical fungicides

INVENTOR(S): Oida, Sadao; Tajima, Yawara; Konosu, Toshiyuki; Iwata, Masayuki; Takeda, Noriko; Miyaoka, Takeo; Takeshiba, Hideo; Nakanishi, Toshiro

PATENT ASSIGNEE(S): Sankyo Co., Ltd., Japan

SOURCE: Eur. Pat. Appl., 160 pp.
CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 332387	A1	19890913	EP 1989-302244	19890306
EP 332387	B1	19931124		
R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
DK 8901051	A	19890905	DK 1989-1051	19890303
FI 8901021	A	19890905	FI 1989-1021	19890303
FI 97382	B	19960830		
FI 97382	C	19961210		
NO 8900926	A	19890905	NO 1989-926	19890303
NO 171272	B	19921109		
NO 171272	C	19930217		
JP 02191262	A2	19900727	JP 1989-51336	19890303
HU 53889	A2	19901228	HU 1989-1034	19890303
CN 1036759	A	19891101	CN 1989-101072	19890304
CN 1029962	B	19951011		
AU 8931051	A1	19890907	AU 1989-31051	19890306
AU 622639	B2	19920416		
ZA 8901678	A	19901128	ZA 1989-1678	19890306
AT 97662	E	19931215	AT 1989-302244	19890306
ES 2061975	T3	19941216	ES 1989-302244	19890306

PRIORITY APPLN. INFO.: JP 1988-51312 19880304
JP 1988-68681 19880323
JP 1988-250158 19881004
JP 1988-261211 19881017
EP 1989-302244 19890306

OTHER SOURCE(S): MARPAT 113:231379

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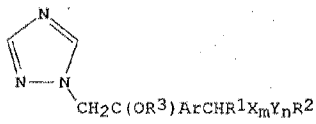


I

AB Title compds. I (Ar = (un)substituted Ph; R1 = H, C1-6 alkyl, etc.; R2 = C1-6 alkyl, halo-C1-6-alkyl, (un)substituted Ph, naphthyl, (un)substituted 5-6-membered heterocyclyl; R3 = H, substituted amino; X = C1-6 alkylene, C2-6 aliph. having 1 or 2 C-C double bonds, C2-6 aliph. having 1 or 2 C-C triple bonds, C3-6 cycloalkylene, etc.; Y = NR5CO, NR5COCH:CH, O2C, O2CCH:CH, SCO, SCOCH:CH, R5 = H, C1-4 alkyl; m, n = 0, 1; YR2 = N3, (un)substituted phthalimido, (un)substituted 1-oxo-2,3-dihydro-2-indolyl)

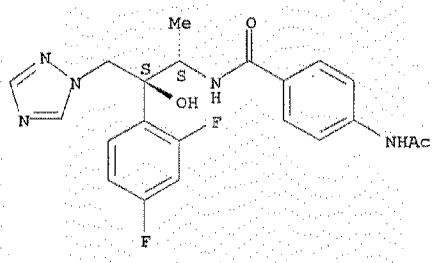
Searched by Barb O'Bryen, STIC 308-4291

and acid addn. salts thereof, are prepd. I are useful as medical and agrochem. fungicides. When used as agrochem. fungicides, I may be blended with other fungicides and insecticides for a broader fungicidal spectrum and synergistic effect. 4-ClC6H4COCl was added to (2R,3R)-3-amino-2-(2,4-dichlorophenyl)-1-(1H-1,2,4-triazol-1-yl)-2-butanol (prepn. given) to give (2R,3R)-I (Ar = 2,4-Cl2C6H3; R1 = Me; R3 = H; Xm = O; YR2 = 4-ClC6H4CONH) and converted to the oxalate salt (II). In rice seedlings inoculated with Rhizoctonia solani, II at 100 ppm (30 mL/3 pots), gave complete control. Mice inoculated with Candida albicans and administered orally II 20 mg/kg, showed 100% survival rate.

IT **126916-61-8P 126918-10-3P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. of, as fungicide)

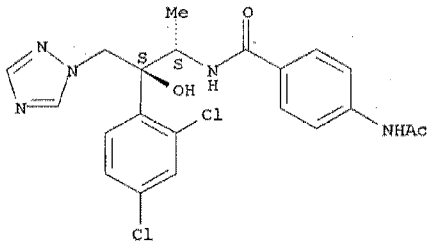
RN 126916-61-8 CAPLUS
CN Benzamide, 4-(acetylamino)-N-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-, (R*,R*)- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 126918-10-3 CAPLUS
CN Benzamide, 4-(acetylamino)-N-[2-(2,4-dichlorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-, (R*,R*)- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L9 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1990:98544 CAPLUS
DOCUMENT NUMBER: 112:98544
TITLE: Preparation and formulation of 5-hydroxy-8-[1-hydroxy-2-(2-methyl-2-propylamine)ethyl]-2H-1,4-benzoxazin-3-(4H)-ones and analogs containing a quaternary ammonium group as broncholytics
Searched by Barb O'Bryen, STIC 308-4291

INVENTOR(S): Schromm, Kurt; Mentrup, Anton; Renth, Ernst Otto; Muacevic, Gojko; Traunecker, Werner
PATENT ASSIGNEE(S): Boehringer Ingelheim International G.m.b.H., Fed. Rep. Ger.
SOURCE: Ger. Offen., 30 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 3743265	A1	19890629	DE 1987-3743265	19871219
EP 321864	A2	19890628	EP 1988-121011	19881215
EP 321864	A3	19901227		
R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
ZA 8809387	A	19900829	ZA 1988-9387	19881215
DK 8807007	A	19890620	DK 1988-7007	19881216
FI 8805811	A	19890620	FI 1988-5811	19881216
NO 8805598	A	19890620	NO 1988-5598	19881216
AU 8827022	A1	19890622	AU 1988-27022	19881216
AU 618302	B2	19911219		
DD 280099	A5	19900627	DD 1988-323312	19881216
SU 1628854	A3	19910215	SU 1988-4613149	19881216
JP 02000239	A2	19900105	JP 1988-320315	19881219
HU 53866	A2	19901228	HU 1988-6491	19881219
HU 207283	B	19930329		
PL 160685	B1	19930430	PL 1988-276549	19881219
US 5223614	A	19930629	US 1990-603585	19901025
PRIORITY APPLN. INFO.:			DE 1987-3743265	19871219
			US 1988-286442	19881219

OTHER SOURCE(S): MARPAT 112:98544
GI

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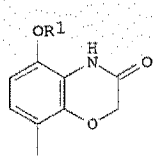


AB QCH(OH)CHR4NHCR5R6(CH2)nR (Q = Ph group of a broncholytically effective compd., e.g., Q1(R1 = H); R = quaternary ammonium group contg.-alkoxy, -heterocyclyl, -arylalkoxy, etc.; R4 = H, Me, Et; R5,R6 = H, Me; n = 1-5) were prepd. Thus, Q1COCH(OH)OEt (R1 = Bz) was condensed with 4-(Me2N)C6H4CH2CMe2NH2 and the product treated with NaBH4 to give Q1CH(OH)CH2NHCMe2CH21C6H4NMe2-4 (R1 = Bz) which was condensed with BrCH2CO2Et to give, after hydrolysi and hydrogenolysis, Q1CH(OH)CH2NHCMe2CH2C6H4R2-4 (I) (R1 = H; R2 = N+Me2CH2CO2-)(II). I [R1 = H; R2 = OCH2CH2N+Me2(CH2)3SO2-) gave 50% protection against acetylcholine-induced spasm in guinea pigs after inhalation of a 0.004% aq. soln. An aerosol was prepd. contg. II 0.1, sorbitan trioleate 0.5, and CFCl3 and CF2Cl2 (2:3) 99.4 wt. %.

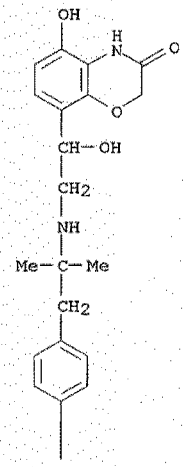
IT **124955-21-1P 124955-32-4P**
RL: SPN (Synthetic preparation); PREP (Preparation)
Searched by Barb O'Bryen, STIC 308-4291

(prepn. of, as broncholytic)

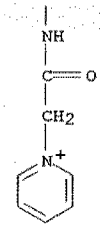
RN 124955-21-1 CAPLUS

CN Pyridinium, 1-[2-[[4-[2-[[2-(3,4-dihydro-5-hydroxy-3-oxo-2H-1,4-benzoxazin-8-yl)-2-hydroxyethyl]amino]-2-methylpropyl]phenyl]amino]-2-oxoethyl]-, chloride, monohydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A



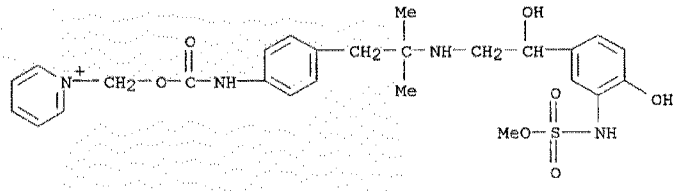
● Cl⁻

● HCl

RN 124955-32-4 CAPLUS

Searched by Barb O'Bryen, STIC 308-4291

CN Pyridinium, 1-[[[[[4-[2-[[2-hydroxy-2-[4-hydroxy-3-[(methoxysulfonyl)amino]phenyl]ethyl]amino]-2-methylpropyl]phenyl]amino]carbonyl]oxy]methyl]-, chloride, monohydrochloride (9CI) (CA INDEX NAME)



● Cl⁻

● HCl

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FILE LAST UPDATED: 01 May 1997 (19970501/UP)

This file contains CAS Registry Numbers for easy and accurate substance identification. Title keywords, authors, patent assignees, and patent information, e.g., patent numbers, are now searchable from 1907-1966. TIFF images of CA abstracts printed between 1907-1966 are available in the PAGE display formats.

This file supports REGISTRY for direct browsing and searching of all substance data from the REGISTRY file. Enter HELP FIRST for more information.

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Searched by Barb O'Bryen, STIC 308-4291

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FILE LAST UPDATED: 6 MAR 2000

FILE COVERS 1779 TO 2000.
*** CAS REGISTRY NUMBERS FOR 4,356,237 SUBSTANCES AVAILABLE ***
*** FILE CONTAINS 7,688,486 SUBSTANCES ***

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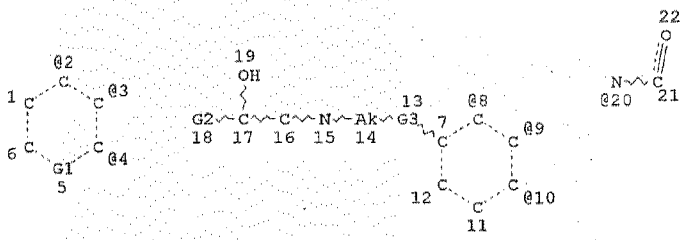

Hy 23

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VAR G2=2/3/4
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VPA 20-8/9/10 U
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DEFAULT MLEVEL IS ATOM
MLEVEL  IS CLASS  AT  14 23
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  23

STEREO ATTRIBUTES: NONE
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SEARCH TIME: 00.00.34
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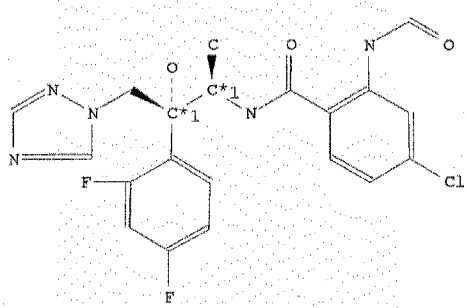
Searched by Barb O'Bryen, STIC 308-4291

=> d ide pre l15 1-2; fil hom

L15 ANSWER 1 OF 2 COPYRIGHT 2000 BEILSTEIN CDS MDL

Beilstein Reg. No. (BRN): 7956379 Beilstein
Molecular Formula (MF): C20 H18 Cl F2 N5 O3
Autonom Name (AUN): 4-chloro-N-<2-(2,4-difluoro-phenyl)-2-hydroxy-1-methyl-3-<1,2,4>triazol-1-yl-propyl>-2-formylamino-benzamide
Beilstein Reference (SO): 6-26
General Comments (NTE): Stereo compound
Formula Weight (FW): 449.84
Lawson Number (LN): 29971; 16524; 16039; 1145



Atom/Bond Notes:
1. CIP Descriptor: R

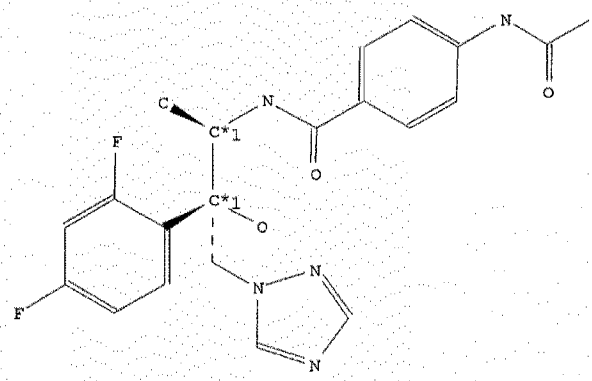
Preparation:
PRE
Start: BRN=7983052 (1R,2R)-7-chloro-3-<2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl>quinazolin-4(3H)-one
Reag: 0.1N aq. NaOH
Time: 3 hour(s)
Yield: 25.00 %
Solv: tetrahydrofuran
Ambient Temperature
Reference(s):
1. Bartroli, Javier; Turmo, Enric; Alugero, Monica; Boncompte, Eulalia; Vericat, Maria L.; et al., J.Med.Chem., 41 <1998> 11, 1869-1882, LA: EN, CODEN: JMCMAR

Same as CAPLUS answer # 3

L15 ANSWER 2 OF 2 COPYRIGHT 2000 BEILSTEIN CDS MDL

Beilstein Reg. No. (BRN): 4892790 Beilstein
Molecular Formula (MF): C21 H21 F2 N5 O3
Autonom Name (AUN): 4-acetylamino-N-<2-(2,4-difluoro-phenyl)-2-hydroxy-1-methyl-3-<1,2,4>triazol-1-yl-propyl>-benzamide
Beilstein Reference (SO): 6-26
General Comments (NTE): Stereo compound; racemate
Searched by Barb O'Bryen, STIC 308-4291

CAS Reg. No. (RN): 126916-61-8
Beilstein Pref. RN (BPR): 126916-61-8
Formula Weight (FW): 429.43
Lawson Number (LN): 29971; 16524; 16038; 1155



Atom/Bond Notes:
1. CIP Descriptor: R
Fragment Notes:
Additionally represents mirror image

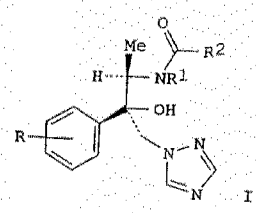
Preparation:
PRE
Start: BRN=4297530 (2R*,3R*)-3-Amino-2-(2,4-difluoropropyl)-1-(1H-1,2,4-triazol-1-yl)-2-butanol, BRN=513757 p-acetylaminobenzoyl chloride
Reag: pyridine
Yield: 51.00 %
Temp: 0.0 Cel
Reference(s):
1. Konosu, Toshiyuki; Tajima, Yawara; Takeda, Noriko; Miyaoka, Takeo; Kasahara, Mayumi; et al., Chem.Pharm.Bull., 39 <1991> 10, 2581-2589, LA: EN, CODEN: CPBTAL

same as CAPLUS answer #4

FILE 'HOME' ENTERED AT 16:01:34 ON 21 AUG 2000

Searched by Barb O'Bryen, STIC 308-4291

L9 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1992:426440 CAPLUS
DOCUMENT NUMBER: 117:26440
TITLE: Triazole antifungals. IV. Synthesis and antifungal activities of 3-acylamino-2-aryl-2-butanol derivatives
AUTHOR(S): Konosu, Toshiyuki; Tajima, Yawara; Takeda, Noriko; Miyaoka, Takeo; Kasahara, Mayumi; Yasuda, Hiroshi; Oida, Sadao
CORPORATE SOURCE: Med. Chem. Res. Lab., Sankyo Co., Ltd., Tokyo, 140, Japan
SOURCE: Chem. Pharm. Bull. (1991), 39(10), 2581-9
CODEN: CPBTAL; ISSN: 0009-2363
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

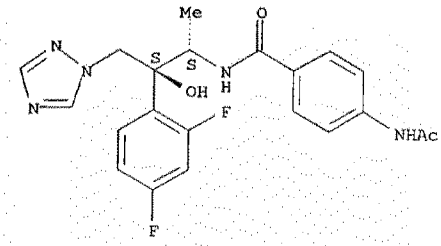
AB New triazoles, e.g., I (R = 4-Cl, 2,4-Cl2, 2,4-F2; R1 = H, Me; R2 = H, CMe3, Ph, substituted Ph, 2-furyl, 2-thienyl) were designed and synthesized as potential inhibitors of the fungal cytochrome P 450 14.alpha.-demethylase. In testing for antifungal activity against a mouse systemic Candida albicans infection, (2R,3R)-3-acylamino-2-aryl-2-butanol derivs. exhibited remarkably high efficacy after oral or parenteral administration. The structure-activity relationships of these amido alcs. were evaluated.

IT **126916-61-8P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. and antifungal activity of)

RN 126916-61-8 CAPLUS
CN Benzamide, 4-(acetylamino)-N-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-, (R*,R*)- (9CI) (CA INDEX NAME)

Searched by Barb O'Bryen, STIC 308-4291

Relative stereochemistry.

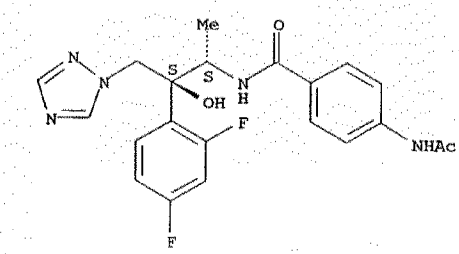


IT 138990-07-5P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)
RN 138990-07-5 CAPLUS
CN Benzamide, 4-(acetylamino)-N-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-, (R*,R*)-, ethanedioate (1:1) (salt) (9CI)
(CA INDEX NAME)

CM 1

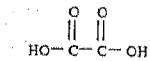
CRN 126916-61-8
CMF C21 H21 F2 N5 O3

Relative stereochemistry.



CM 2

CRN 144-62-7
CMF C2 H2 O4



L9 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1990:98544 CAPLUS
DOCUMENT NUMBER: 112:98544
TITLE: Preparation and formulation of 5-hydroxy-8-[1-hydroxy-2-(2-methyl-2-propylamine)ethyl]-2H-1,4-benzoxazin-3-(4H)-ones and analogs containing a quaternary ammonium group as broncholytics

INVENTOR(S): Schromm, Kurt; Mentrup, Anton; Renth, Ernst Otto; Muacevic, Gojko; Traunecker, Werner

PATENT ASSIGNEE(S): Boehringer Ingelheim International G.m.b.H., Fed. Rep. Ger.

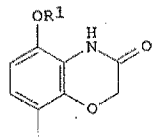
SOURCE: Ger. Offen., 30 pp.
CODEN: GWXXBX

DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 3743265	A1	19890629	DE 1987-3743265	19871219
EP 321864	A2	19890628	EP 1988-121011	19881215
EP 321864	A3	19901227		
R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
ZA 8809387	A	19900829	ZA 1988-9387	19881215
DK 8807007	A	19890620	DK 1988-7007	19881216
FI 8805811	A	19890620	FI 1988-5811	19881216
NO 8805598	A	19890620	NO 1988-5598	19881216
AU 8827022	A1	19890622	AU 1988-27022	19881216
AU 618302	B2	19911219		
DD 280099	A5	19900627	DD 1988-323312	19881216
SU 1628854	A3	19910215	SU 1988-4613149	19881216
JP 02000239	A2	19900105	JP 1988-320315	19881219
HU 53866	A2	19901228	HU 1988-6491	19881219
HU 207283	B	19930329		
PL 160685	B1	19930430	PL 1988-276549	19881219
US 5223614	A	19930629	US 1990-603585	19901025
PRIORITY APPLN. INFO.:			DE 1987-3743265	19871219
			US 1988-286442	19881219

OTHER SOURCE(S): MARPAT 112:98544
GI

Q1=



AB QCH(OH)CHR4NHCR5R6(CH2)nR (Q = Ph group of a broncholytically effective compd., e.g., Q1(R1 = H); R = quaternary ammonium group contg.-alkoxy, -heterocyclyl, -arylalkoxy, etc.; R4 = H, Me, Et; R5,R6 = H, Me; n = 1-5) were prepd. Thus, Q1COCH(OH)OEt (R1 = Bz) was condensed with 4-(Me2N)C6H4CH2CMe2NH2 and the product treated with NaBH4 to give Q1CH(OH)CH2NHCMe2CH2C6H4NMe2-4 (R1 = Bz) which was condensed with BrCH2CO2Et to give, after hydrolysi and hydrogenolysis, Q1CH(OH)CH2NHCMe2CH2C6H4R2-4 (I) (R1 = H; R2 = N+Me2CH2CO2-)(II). I [R1 = H; R2 = OCH2CH2N+Me2(CH2)3SO2-) gave 50% protection against acetylcholine-induced spasm in guinea pigs after inhalation of a 0.004% aq. soln. An aerosol was prepd. contg. II 0.1, sorbitan trioleate 0.5, and CFCl3 and CF2Cl2 (2:3) 99.4 wt. %.

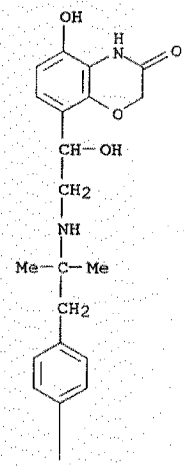
IT **124955-21-1P 124955-32-4P**
RL: SPN (Synthetic preparation); PREP (Preparation)
Searched by Barb O'Bryen, STIC 308-4291

(prepn. of, as broncholytic)

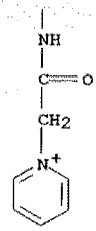
RN 124955-21-1 CAPLUS

CN Pyridinium, 1-[2-[[4-[2-[[2-(3,4-dihydro-5-hydroxy-3-oxo-2H-1,4-benzoxazin-8-yl)-2-hydroxyethyl]amino]-2-methylpropyl]phenyl]amino]-2-oxoethyl]-, chloride, monohydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A



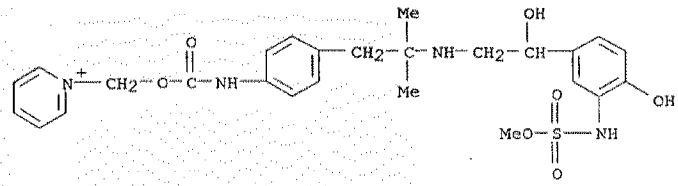
● Cl⁻

● HCl

RN 124955-32-4 CAPLUS

Searched by Barb O'Bryen, STIC 308-4291

CN Pyridinium, 1-[[[[[4-[2-[[2-hydroxy-2-[4-hydroxy-3-[(methoxysulfonyl)amino]phenyl]ethyl]amino]-2-methylpropyl]phenyl]amino]carbonyl]oxy]methyl]-, chloride, monohydrochloride (9CI) (CA INDEX NAME)



● Cl⁻

● HCl

L9 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER:	1998:535771 CAPLUS
DOCUMENT NUMBER:	129:198012
TITLE:	Preparation of phenethanol derivatives and their use as antidiabetic agents
INVENTOR(S):	Maruyama, Tatsuya; Onta, Kenichi; Hayakawa, Akihiko; Matsui, Tetsuo
PATENT ASSIGNEE(S):	Yamanouchi Pharmaceutical Co., Ltd., Japan
SOURCE:	Jpn. Kokai Tokkyo Koho, 20 pp. CODEN: JKXXAF
DOCUMENT TYPE:	Patent
LANGUAGE:	Japanese
FAMILY ACC. NUM. COUNT:	1 Searched by Barb O'Bryen, STIC 308-4291

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 10218861	A2	19980818	JP 1997-21870	19970204

OTHER SOURCE(S): MARPAT 129:198012

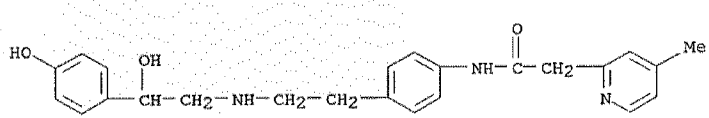
GI For diagram(s), see printed CA Issue.

AB The derivs. I [ring B = II, III, IV; X, Y = O, S, NR6; R1 = H, lower alkyl; R2 = H, lower alkyl, NHSO2Me, NHCOR3; R3 = H, lower alkyl, mono- or di(lower alkylamino), aryl, aralkyl; R4, R5 = H, lower alkyl, amino; R6 = H, lower alkyl, aralkyl] or their salts as .beta.3-adrenoceptor agonists are prepd. Antidiabetic agents contg. I or thir salts as active ingredients are also claimed. I decreased blood glucose of obese and hyperglycemic kk mice with insulin resistance upon both oral and percutaneous administrations. I also increased insulin secretion in normal rats. Prepn. of some of I was given.

IT **211636-04-3P 211636-05-4P 211636-06-5P**
211636-07-6P 211636-08-7P 211636-09-8P
211636-10-1P 211636-11-2P 211636-13-4P
211636-15-6P 211636-17-8P 211636-18-9P
211636-19-0P 211636-20-3P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of antidiabetic phenethanol derivs. as .beta.3-adrenoceptor agonists)

RN 211636-04-3 CAPLUS

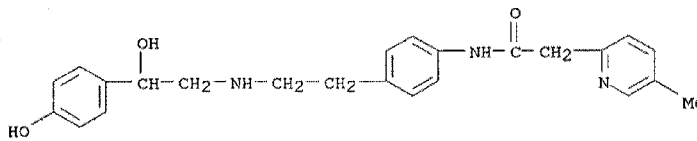
CN 2-Pyridineacetamide, N-[4-[2-[[2-hydroxy-2-(4-hydroxyphenyl)ethyl]amino]ethyl]phenyl]-4-methyl-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

RN 211636-05-4 CAPLUS

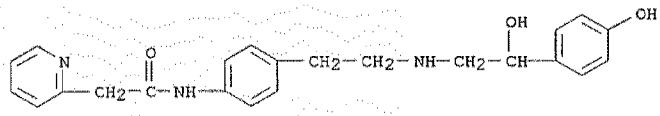
CN 2-Pyridineacetamide, N-[4-[2-[[2-hydroxy-2-(4-hydroxyphenyl)ethyl]amino]ethyl]phenyl]-5-methyl-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

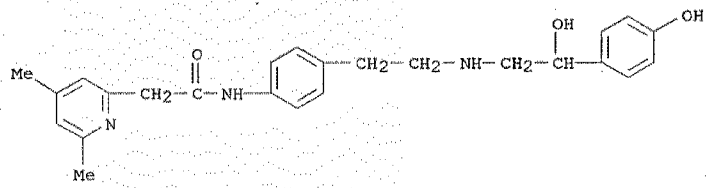
Searched by Barb O'Bryen, STIC 308-4291

RN 211636-06-5 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[2-hydroxy-2-(4-hydroxyphenyl)ethyl]amino]ethyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)



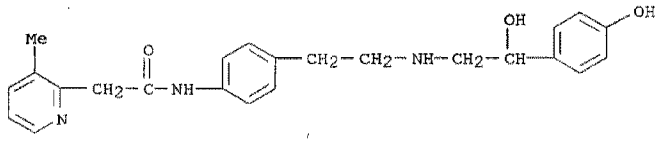
● HCl

RN 211636-07-6 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[2-hydroxy-2-(4-hydroxyphenyl)ethyl]amino]ethyl]phenyl]-4,6-dimethyl-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

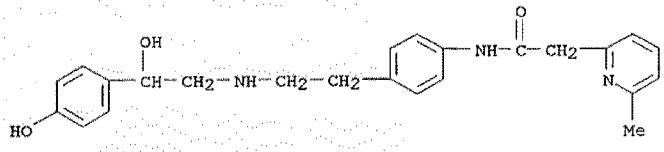
RN 211636-08-7 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[2-hydroxy-2-(4-hydroxyphenyl)ethyl]amino]ethyl]phenyl]-3-methyl-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

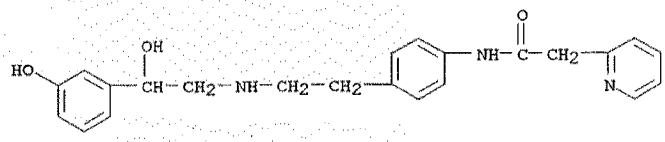
RN 211636-09-8 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[2-hydroxy-2-(4-hydroxyphenyl)ethyl]amino]ethyl]phenyl]-6-methyl-, monohydrochloride (9CI) (CA INDEX NAME)

Searched by Barb O'Bryen, STIC 308-4291



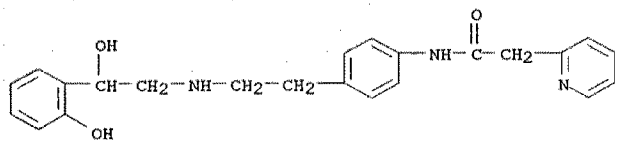
● HCl

RN 211636-10-1 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[2-hydroxy-2-(3-hydroxyphenyl)ethyl]amino]ethyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

RN 211636-11-2 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[2-hydroxy-2-(2-hydroxyphenyl)ethyl]amino]ethyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)



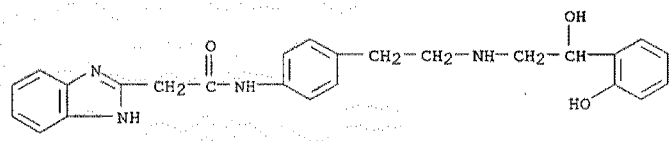
● HCl

RN 211636-13-4 CAPLUS
CN 1H-Benzimidazole-2-acetamide, N-[4-[2-[[2-hydroxy-2-(2-hydroxyphenyl)ethyl]amino]ethyl]phenyl]-, (2E)-2-butenedioate (2:1) (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 211636-12-3
CMF C25 H26 N4 O3

Searched by Barb O'Bryen, STIC 308-4291



CM 2

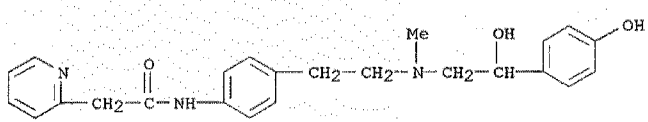
CRN 110-17-8
CMF C4 H4 O4
CDES 2:E

Double bond geometry as shown.

RN 211636-15-6 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[2-hydroxy-2-(4-hydroxyphenyl)ethyl]methylamino]ethyl]phenyl]-, (2E)-2-butenedioate (1:1) (salt) (9CI) (CA INDEX NAME)

CM 1

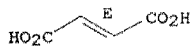
CRN 211636-14-5
CMF C24 H27 N3 O3



CM 2

CRN 110-17-8
CMF C4 H4 O4
CDES 2:E

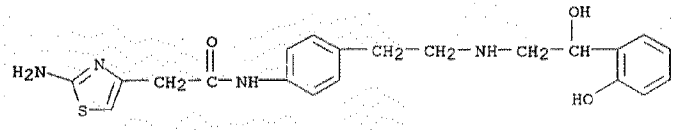
Double bond geometry as shown.



RN 211636-17-8 CAPLUS
CN 4-Thiazoleacetamide, 2-amino-N-[4-[2-[[2-hydroxy-2-(2-hydroxyphenyl)ethyl]amino]ethyl]phenyl]-, hydrochloride trifluoroacetate (2:1:3) (salt) (9CI) (CA INDEX NAME)

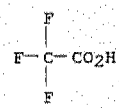
CM 1

CRN 211636-16-7
CMF C21 H24 N4 O3 S

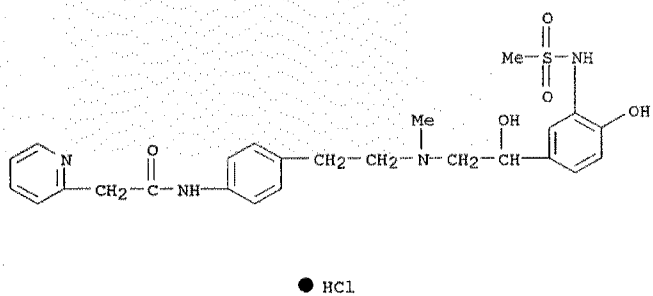


CM 2

CRN 76-05-1
CMF C2 H F3 O2



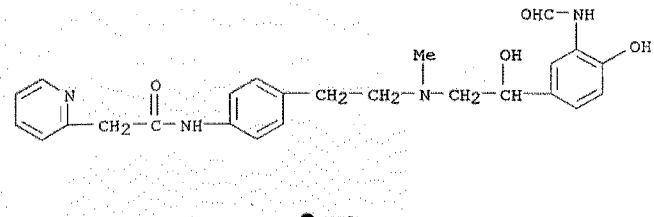
RN 211636-18-9 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[2-hydroxy-2-[4-hydroxy-3-[(methylsulfonyl)amino]phenyl]ethyl]methylamino]ethyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

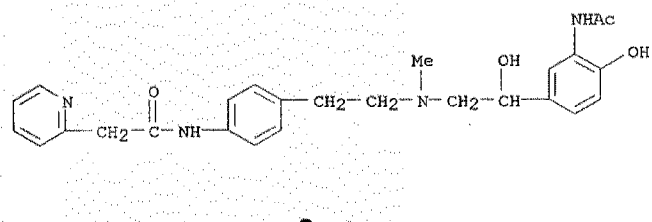
RN 211636-19-0 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[2-[3-(formylamino)-4-hydroxyphenyl]-2-hydroxyethyl]methylamino]ethyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)

Searched by Barb O'Bryen, STIC 308-4291



● HCl

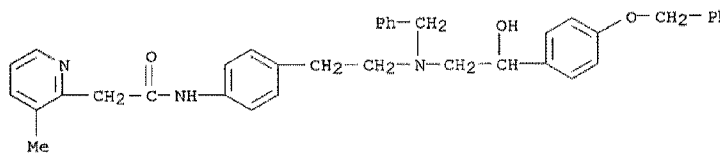
RN 211636-20-3 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[2-[3-(acetylamino)-4-hydroxyphenyl]-2-hydroxyethyl]methylamino]ethyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

IT **211635-78-8P 211635-79-9P 211635-80-2P**
211635-81-3P 211635-86-8P 211635-87-9P
211635-88-0P 211635-89-1P 211635-92-6P
211635-93-7P 211635-94-8P 211635-95-9P
211635-96-0P 211635-97-1P 211636-00-9P
211636-03-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. of antidiabetic phenethanol derivs. as .beta.3-adrenoceptor agonists)

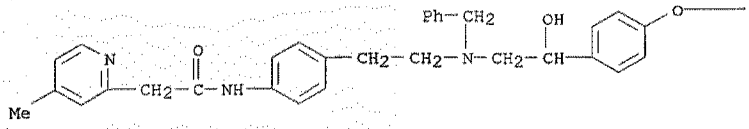
RN 211635-78-8 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[2-hydroxy-2-[4-(phenylmethoxy)phenyl]ethyl](phenylmethyl)amino]ethyl]phenyl]-3-methyl- (9CI) (CA INDEX NAME)



RN 211635-79-9 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[2-hydroxy-2-[4-

(phenylmethoxy)phenyl]ethyl](phenylmethyl)amino]ethyl]phenyl]-4-methyl-
(9CI) (CA INDEX NAME)

PAGE 1-A

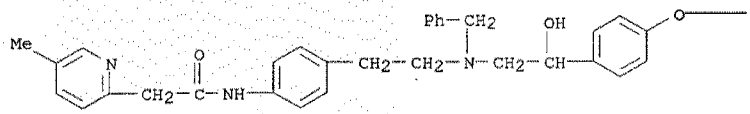


PAGE 1-B

—CH_2—Ph

RN 211635-80-2 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[2-hydroxy-2-[4-
(phenylmethoxy)phenyl]ethyl](phenylmethyl)amino]ethyl]phenyl]-5-methyl-
(9CI) (CA INDEX NAME)

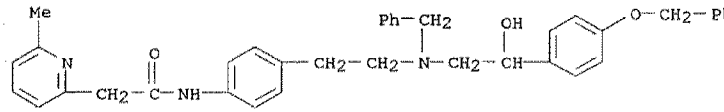
PAGE 1-A



PAGE 1-B

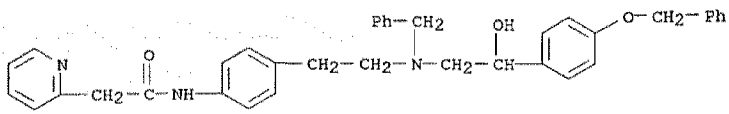
—CH_2—Ph

RN 211635-81-3 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[2-hydroxy-2-[4-
(phenylmethoxy)phenyl]ethyl](phenylmethyl)amino]ethyl]phenyl]-6-methyl-
(9CI) (CA INDEX NAME)



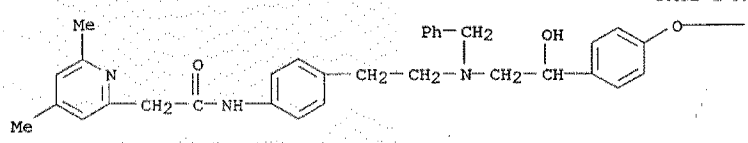
RN 211635-86-8 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[2-hydroxy-2-[4-
(phenylmethoxy)phenyl]ethyl](phenylmethyl)amino]ethyl]phenyl]- (9CI) (CA
INDEX NAME)

Searched by Barb O'Bryen, STIC 308-4291



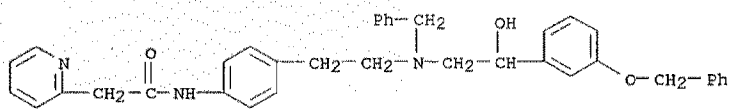
RN 211635-87-9 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[2-hydroxy-2-[4-(phenylmethoxy)phenyl]ethyl](phenylmethyl)amino]ethyl]phenyl]-4,6-dimethyl- (9CI) (CA INDEX NAME)

PAGE 1-A

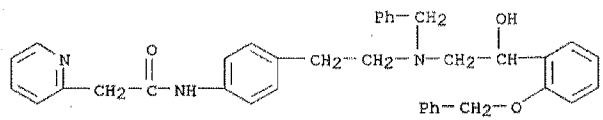


PAGE 1-B

RN 211635-88-0 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[2-hydroxy-2-[3-(phenylmethoxy)phenyl]ethyl](phenylmethyl)amino]ethyl]phenyl]- (9CI) (CA INDEX NAME)

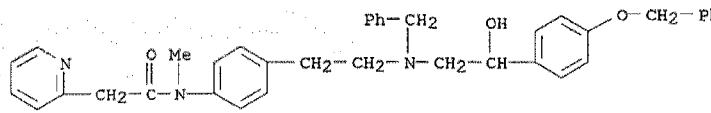


RN 211635-89-1 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[2-hydroxy-2-[2-(phenylmethoxy)phenyl]ethyl](phenylmethyl)amino]ethyl]phenyl]- (9CI) (CA INDEX NAME)

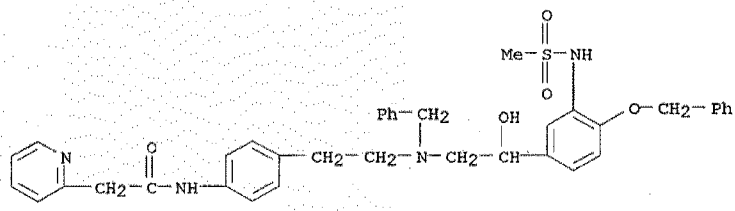


RN 211635-92-6 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[2-hydroxy-2-[4-(phenylmethoxy)phenyl]ethyl](phenylmethyl)amino]ethyl]phenyl]-N-methyl- (9CI) (CA INDEX NAME)

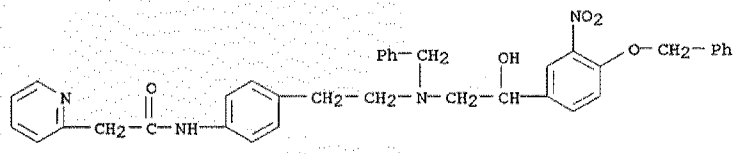
Searched by Barb O'Bryen, STIC 308-4291



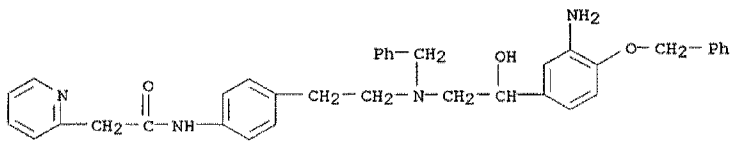
RN 211635-93-7 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[2-hydroxy-2-[3-[(methylsulfonyl)amino]-4-(phenylmethoxy)phenyl]ethyl](phenylmethyl)amino]ethyl]phenyl]- (9CI) (CA INDEX NAME)



RN 211635-94-8 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[2-hydroxy-2-[3-nitro-4-(phenylmethoxy)phenyl]ethyl](phenylmethyl)amino]ethyl]phenyl]- (9CI) (CA INDEX NAME)

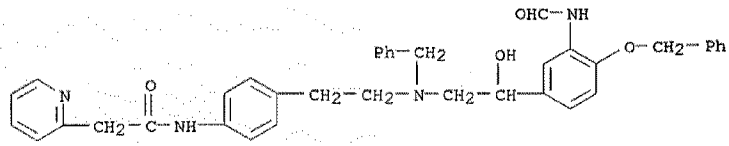


RN 211635-95-9 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[2-[3-amino-4-(phenylmethoxy)phenyl]-2-hydroxyethyl](phenylmethyl)amino]ethyl]phenyl]- (9CI) (CA INDEX NAME)

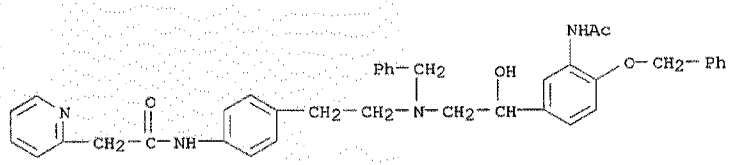


RN 211635-96-0 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[2-[3-(formylamino)-4-(phenylmethoxy)phenyl]-2-hydroxyethyl](phenylmethyl)amino]ethyl]phenyl]- (9CI) (CA INDEX NAME)

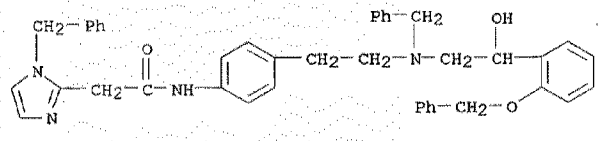
Searched by Barb O'Bryen, STIC 308-4291



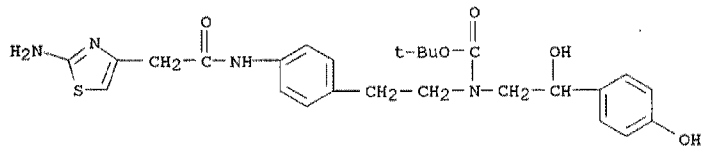
RN 211635-97-1 CAPLUS
CN 2-Pyridineacetamide, N-[4-[2-[[2-[3-(acetylamino)-4-(phenylmethoxy)phenyl]-2-hydroxyethyl](phenylmethyl)amino]ethyl]phenyl]- (9CI) (CA INDEX NAME)



RN 211636-00-9 CAPLUS
CN 1H-Imidazole-2-acetamide, N-[4-[2-[[2-hydroxy-2-[2-(phenylmethoxy)phenyl]ethyl](phenylmethyl)amino]ethyl]phenyl]-1-(phenylmethyl)- (9CI) (CA INDEX NAME)



RN 211636-03-2 CAPLUS
CN Carbamic acid, [2-[4-[[(2-amino-4-thiazolyl)acetyl]amino]phenyl]ethyl][2-hydroxy-2-(4-hydroxyphenyl)ethyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



L9 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1998:269995 CAPLUS
DOCUMENT NUMBER: 128:303693
TITLE: New Azole Antifungals. 3. Synthesis and Antifungal Activity of 3-Substituted-4(3H)-quinazolinones
AUTHOR(S): Bartroli, Javier; Turmo, Enric; Alguero, Monica; Boncompte, Eulalia; Vericat, Maria L.; Conte, Lourdes; Ramis, Joaquim; Merlos, Manuel; Garcia-Rafanell, Searched by Barb O'Bryen, STIC 308-4291

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/529,096	04/07/00	MARUYAMA T	07385.0007

HM12/1027
FINNEGAN HENDERSON FARABOW
GARRETT & DUNNER
1300 I STREET NW
WASHINGTON DC 20005-3315

EXAMINER	
PATEL, S	
ART UNIT	**PAPER NUMBER**
1624	4

DATE MAILED: 10/27/00

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

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant
09/529,096	Tatsuya Maruyama et al.
Examiner	**Group Art Unit**
Sudhaker Patel	1624

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL.**

☐ 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.

A shortened statutory period for response to this action is set to expire 1 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) 1-8 is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☐ Claim(s) _____ is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claims 1-8 are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

DETAILED ACTION

Election/Restrictions

1. Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in response to this action, to elect a single invention to which the claims must be restricted.

Group I, claim(s) 1-3,6-8, drawn to compounds, composition, and method of use for **Formula I** where in Z = N; B = 6-membered rings containing at least 1 N and one other heteroatom (0,N,S) e.g. 1,4-, 1,3- diazine, piperazine, morpholine, thiomorpholine etc.

Group II, claim(s) 1-3,6-8, drawn to compounds, composition, and method of use for **Formula I** where in Z = N; B= 6-membered rings containing 1 N & 5 carbons, e.g. pyridine, piperidine, quinoline etc..

Group III, claim(s)1-3,6-8, drawn to compounds, composition, and method of use for **Formula I** where in Z = N; B = 5-membered rings containing 1N and +0 to 3 heteroatoms (0,S,N) e.g. diazoles, triazoles, tetrazoles, Thiadiazoles, Thiazole etc..

Group IV, claim(s)1-1-4,5,6,7-8, drawn to compounds, composition, and method of use for Formula (I) wherein Z = CH If this group is elected, further restriction(s) will be required..

Group V, claim(s)1-8, drawn to compounds not included in above Groups I-IV.

In addition to election of one of the above groups, applicants are also required to elect a single species for the group.

2. The inventions listed as **Groups I-V** do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: They have different structures.

3. A telephone call was made to Mr. Hill on 10/24/00 to request an oral election to the above restriction requirement, but did not result in an election being made.

Applicants are advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

4. Applicants are reminded that upon the cancellation of claims to a non-elected invention, the inventor ship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventor ship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(I).

5.Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sudhaker Patel whose telephone number is (703) 308 4709. The examiner can normally be reached on Monday thru' Friday from 8:30 AM to 5:00 PM. If attempts to reach

the examiner by the phone are unsuccessful, the examiner's supervisor, Mukund Shah can be reached at (703) 308 4716.

A facsimile center has been established for Group 1600. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier numbers for accessing the facsimile machine are (703) 308-4556 or (703) 305-3592.

Any inquiry of general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308 1235.

sp

October 25, 2000

Mukund J. Shah

Mukund J. Shah

Supervisory Patent Examiner

Art Unit 1624

1624
#5
PATENT 11/28/00

187

Customer Number 22,852
Attorney Docket No. 7385.0007-00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
Tatsuya MARUYAMA et al.	)	
Serial No.: 09/529,096	)	Group Art Unit: 1624
Filed: April 7, 2000	)	Examiner: S. Patel
For: AMIDE DERIVATIVES OR SALTS THEREOF	)	

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

RESPONSE TO RESTRICTION REQUIREMENT

In a restriction requirement dated October 27, 2000, the Examiner required restriction under 35 U.S.C. §§ 121 and 372 between the following groups of claims:

Group I Claims 1-3, and 6-8, drawn to compounds, compositions, and methods of use for Formula I wherein Z is N and B is a six-membered ring which contains at least one nitrogen and one other heteroatom;

Group II Claims 1-3, and 6-8, drawn to compounds, compositions, and methods of use for Formula I wherein Z is N and B is a six-membered ring which contains one nitrogen and five carbon atoms;

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202-408-4000

Group III Claims 1-3, and 6-8, drawn to compounds, compositions, and methods of use for Formula I wherein Z is N and B is a five-membered ring containing one nitrogen and zero to three additional heteroatoms;

Group IV Claims 1-8, drawn to compounds, compositions, and methods of use for Formula I wherein Z is CH; and

Group V Claims 1-8 drawn to compounds not included in the above Groups I-IV.

See Office Action at 2.

The Examiner also required an election of species for the group elected. *See id* at 3.

A. Restriction Election with Traverse

Applicants provisionally elect to prosecute Group IV, claims 1-8 drawn to compounds, compositions, and methods of use for Formula I wherein Z is CH, with traverse. Applicants traverse on the ground that the claims would not be unduly burdensome to search as written. *See* MPEP § 803.

The Examiner indicated that election of Group IV would require additional restriction. *See* Office Action at 2. During a telephonic discussion with Applicants'

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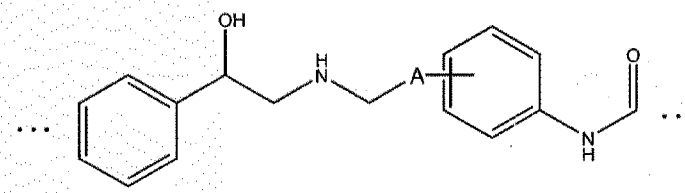
representative, Jeremy Stipkala, held November 20, 2000, the Examiner kindly agreed to reconsider whether further restrictions would be required.

Applicants respectfully request the Examiner to examine the claims of Group IV without further restriction. With the provisional election made above, the scope of the required search is limited to compounds, compositions and methods of use of compounds having the following appearance:



*Note: not all substituents shown

This, Applicants respectfully contend, represents a substantial and reasonable structure for the basis of a search that is not unduly burdensome on the Examiner. Therefore, further restrictions should not be required. In making this argument, Applicants reserve the right to argue the patentability of their claimed subject matter over any cited document which may allegedly anticipate or allegedly render obvious any portion of their claimed subject matter.

B. Species Election with Traverse

Applicants also provisionally elect, with traverse, the species of Example 7 on page 37, Example 12 on page 38, and Example 41 on page 44. Applicants traverse on

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the ground that the claims as written do not define an unreasonable number of species. *See* 37 C.F.R. § 1.141(a).

CONCLUSION

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

Dated: November 22, 2000

By: David W. Hill
David W. Hill
Reg. No. 28,220

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WASHINGTON, DC 20005
202-408-4000

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/529,096	04/07/00	MARUYAMA T	07385.0007

HM12/1207

FINNEGAN HENDERSON FARABOW
GARRETT & DUNNER
1300 I STREET NW
WASHINGTON DC 20005-3315

EXAMINER	
PATEL, S	
ART UNIT	**PAPER NUMBER**
1624	6

DATE MAILED: 12/07/00

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

Commissioner of Patents and Trademarks

PTO-90C (Rev. 2/95)

1- File Copy

Office Action Summary

Application No.	Applicant(s)
09/529,096	Tatsuya Maruyama et al.
Examiner	**Group Art Unit**
Sudhaker Patel	1624

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL.**

☐ 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.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-8* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-8* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☒ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 3

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

DETAILED ACTION

Claims 1-8 are pending in this application.

Applicants' communication paper # 5 dated 11/22/00 is acknowledged.

Applicants' various arguments and remarks have been considered, and found persuasive.

Accordingly Group IV will not be subjected to further restriction as indicated in previous Office Action paper # 4 dated 10/27/00. This is because the additional time required for search would be within the reasonable time spent for the prosecution during the present Office Action.

Applicants have provisionally elected with traverse invention of Group IV, claims 1-8, drawn to compounds, compositions, and method of use for Formula (I) wherein Z = CH, and have also elected species of Examples 7 on page 37, Example 12 on page 38, and Example 41 on page 44.Since Claims 1-8 link with other groups of inventions, the same will be examined bearing in mind the subject matter, and species as elected by the applicants only. Affirmation of this election must be made by the applicants in replying to this Office Action.

The requirement is still deemed proper for non-elected subject matter, and is therefore made ***FINAL***.

Improper Markush Rejection

Claims 1-8 are rejected under a judicially created doctrine as being drawn to an improper Markush group, that is, the claims lack unity of invention. The variables .Z, X, B, to gather with various values for other substituents are defined in a such a way that they keep changing the structure/core of the compound that determines the classification/subclassification. Additionally,

the physical properties e.g. solubility, melting point, appearance etc. are tremendously altered with the changing of the various variable as recited herein. By changing the values of these variables several patentably distinct and independent compounds are claimed.

In order to have unity of invention the compounds must have " a community of chemical or physical characteristics" which justify their inclusion in a common group, and that such inclusion is not repugnant to principles of scientific classification" In re Jones (CCPA) 74 USPQ 149 (see footnote 2).As already pointed out earlier, the structural formula (I) does not have a significant structural feature that is shared by all of its alternatives which is inventive. The structure has only a Formula (I) = Phenyl-CH(0H)-CH2-NH-C(R1a)(R1b)-A-Phenyl-NH-C0- common. . This feature is not inventive. Compounds embraced by Formula (I) are so diverse in nature that a prior art anticipating a claim with respect to one member under 35 U.S.C. 102 would not render obvious the same claim under 35 U.S.C. 103. This is evidentiary of patentably distinct and independent inventions.

Limiting the claims to the elected group would overcome this rejection.

Claim Rejections - 35 U.S.C. § 112

1. 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 1 , and claims dependent on these claims , namely, claims .2-8 are rejected because while enabling as therapeutic agent for diabetes mellitus which comprises of the amide derivative or its salt according to claims 1-6 as an effective ingredient, does not reasonably provide enablement for compounds, composition based on heteroaryl ring = isothiazolopyridine, imidazopyridyl or oxobenzofurayl etc. Whereas the claim language does not only include these cited compounds but many more compounds as represented by variables outlined in above mentioned Markush rejection in **Group IV** as elected, and rejected under 35 U.S.C. 112, para. one because the claims are open-ended, and broad.

In evaluating the enablement question, several factors are to be considered. In re Wands, 8 USPQ 2d 1400 (Fed. Cir. 1988); Ex parte Forman, 230 USPQ 546. The factors include:*(1).* The nature of invention;*(2).* the state of prior art ;*(3).* the predictability or lack thereof in the art; *(4).* the amount of direction or guidance present;*(5).* the presence or absence of working examples;*(6).* the breadth of the claims, and *(7).* the quantity of experimentation needed

1). The nature of the invention: The claims are drawn to compounds, composition(s), a method(s) of making a pharmaceutical agent to be used as a therapeutic agent for diabetes mellitus.

2). The state of prior art: There are no known compounds of similar structure(s) which have been demonstrated to treat diabetes mellitus.

3). The predictability or lack thereof in the art: "predictability" have been demonstrated to be sufficiently lacking in the instant case for the instant method(s) claims which include (but not

limited to) making therapeutic agent for diabetes mellitus.

4). The amount of direction or guidance present and 5): There are no doses present for a method of preparing a therapeutic agent for diabetes mellitus.. Such utilities are unbelievable on their face and therefore they must be supported by sufficient evidence demonstrating such utilities. All available drugs to treat diabetes could only be used in a limited way.

6). The breadth of the claims: The claims are drawn to making either a pharmaceutical agent or a therapeutic agent for diabetes mellitus comprising the amide derivative or the salt thereof according to claims 1-6 as an effective ingredient.

7). The quantity of experimentation need would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan for the many reasons stated above.

Claim Rejections - 35 U.S.C. § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-8 are rejected under 35 U.S.C. 102(a) reference JP 10218861 which claims the application date of 2/4/1997. See also CAPLUS 1998:535771 pages 61-70.

Claim Rejections - 35 U.S.C. § 103

3. 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 1, and claims dependent on these claims, 2-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schromm, Kurt et al.(DE 3743265) as applied to claims above, and further in view of Konosu Toshiyuki et al.,"Triazol Antifungal", Chem. Pharm. Bull., 39/10,2581-9 (1991) also cited as CAPLUS 1992:26440.

Claims are drawn to generic Formula (I) of claim 1 wherein the core is very similar to main core of '265. The reference '265 teaches the making of compounds with generic core(s) encompassed by Claim 1 which are drawn to compounds of Formula (I) and others as instantly claimed.

The reference '265 (See Examples on pages 77-78) differ from the instantly claimed compounds by not having --CH(0H)-CH2-NH- **CH2-CH2**-phenyl-NH-C0-CH2-pyridine, but -CH(0H)-CH2- NH- **C(Me)2- CH2-** phenyl-NH-C0-CH2-pyridinium quat. (See Ex. On page 78) as claimed herein. However, the reference '265 is not limited in teaching of making of

compounds based on above generic core(s)only, but also teaches the use of the compounds as broncholvtics i.e. use as pharmaceuticals as taught by the instant application.

The other reference Konosu, Toshiyuki et al. teaches making of compounds with a core also similar to instantly claimed compounds(see Formula I of CAPLUS pages 72-72). The reference has a core = Phenyl-CH(0H(heterocycle)-CH(Me)-NHC0-R2(R2+ H, Ph, substituted Ph, furyl, thienyl etc.) which is very similar to instant Example 47 cited on page 71. The reference differs from the instantly claimed compound by having triazole in place of H, and R2 (= -CH2PH) instead of -CH2-heterocycle. The instant compounds' claims have eliminated the reference by defining B= a heteroaryl group which may be substituted and may be fused with a benzene ring. However, the specific main core Phenyl-C(H/het)(0H)-CH(H/Alkyl)-NH-C0- remains the same as claimed instantly herein.

However, the reference is not limited to teaching of making of a part of the molecule of the instantly claimed invention, but also teaches it use as antifungal agents. (see CAPLUS page 72), that is to say the ref. Compounds have ability to control or prevent growth of living organisms. However, the difference in structural synthesis could be overcome by the teaching of Kurt et al. ' 265 as cited above.

Thus, one having ordinary skill in the art would have been motivated to modify Formula (I)of ref '265 and try out combination of ref. Konosu by using/reacting Benzene- substituted with-CH(0H)-CH2-NH-CH2-CH2-Ph-NH-C0-CH2- with pyridine or other heterocycle for example, triazole, tetrazol or thiazole as used in the instantly claimed invention, and one would

have expected still to maintain &/or find out pharmaceutical/pharmacological activity either same or different than the reference '265. Hence, at the time of the invention was made, it would have been obvious to a person of ordinary skill in the art to prepare compounds and pharmaceutical compositions of the claimed Formula (I) by combining the 2 arts which were available.

This application has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicants' cooperation is, therefore, requested in promptly correcting any errors of which they may become aware in the specification.

Preliminary computer assisted search revealed references: U.S.P. 5541197. However, this reference do claim pharmacologically active compounds having hypolipidemic and hypoglycemic activities. These reference are also available on CAPLUS, MARPAT etc. The references are cited but not applied herein at this time.

Applicants are also requested to note that Application Serial #s 09297762;09514637, and others involving either one or more of the inventors, and similar subject matter to current application are located thru' preliminary search. These references are in transit and are not accessible to the examiner at this time. Applicants are advised to provide the information related to similar &/or presently pending local or international applications, if any, related to the subject matter included in the instant application to avoid various issues arising out of question of either double patenting &/or priority claims and other related matters.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sudhaker Patel whose telephone number is (703) 308 4709. The examiner can normally be reached on Monday thru' Friday from 8:30 AM to 5:00 PM. If attempts to reach the examiner by the phone are unsuccessful, the examiner's supervisor, Mukund Shah can be reached at (703) 308 4716.

A facsimile center has been established for Group 1600. The hours of operation Monday through Friday, 8:45 AM to 4:45 PM. The telecopier numbers for accessing the facsimile machine are (703) 308-4556 or (703) 305-3592.

Any inquiry of general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308 1235.

Mukund J. Shah

Mukund Shah

Supervisory Patent Examiner

Art Unit 1624

sp

December 1 , 2000.

Notice of References Cited

Application No.	Applicant(s)		
09/529,096	Tatsuya Maruyama et al.		
Examiner		Group Art Unit	Page 1 of 1
Sudhaker Patel		1624	

U.S. PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	NAME	CLASS	SUBCLASS
x	A	5,541,197	7/1996	Fisher et al.	514	311
	B					
	C					
	D					
	E					
	F					
	G					
	H					
	I					
	J					
	K					
	L					
	M					

FOREIGN PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	COUNTRY	NAME	CLASS	SUBCLASS
	N	3,743,265	6/1989	DE	S. Kurt El Al.	—	—
	O	10,218,861	6/1989	JP	M.Tetsuo et al.	—	—
	P						
	Q						
	R						
	S						
	T						

NON-PATENT DOCUMENTS

*		DOCUMENT (Including Author, Title, Source, and Pertinent Pages)	DATE
	U	Konosu T. et al."Triazole antif.",Chem.Pharm.Bull.,39/10,2581-9	10/1991
	V		
	W		
	X		

* A copy of this reference is not being furnished with this Office action. (See Manual of Patent Examining Procedure, Section 707.05(a).)

INFORMATION DISCLOSURE CITATION
(Use several sheets if necessary)

OMB No. 0651-0011

Attorney Docket No. 7385.0007	Serial No. 09/529,096
Applicant Tatsuya Maruyama et al.	
Filing Date April 7, 2000	Group Art Unit Unassigned

U.S. PATENT DOCUMENTS

Examiner Initial	Document Number	Date	Name	Class	Subclass	Filing Date
	5,541,197	07/30/96	Fisher et al.	514	311	
	5,553,475	09/10/96	Hayashi et al.	72	225	
	5,614,544	03/25/97	Sohda et al.	514	378	

FOREIGN PATENT DOCUMENTS

Examiner Initial	Document Number	Date	Country	Class	Sub-Class	Trans. Yes	Trans. No

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

Examiner [signature] Date Considered 11/30/00

*Examiner: Initial if reference considered, whether or not citation is in conformance with MPEP 609; draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

Form PTO 1449 Patent and Trademark Office - U.S. DEPARTMENT OF COMMERCE

PATENT
Customer Number 22,852
Attorney Docket No. 7385.0007-00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Tatsuya MARUYAMA et al.

Serial No.: 09/529,096 — Group Art Unit: 1624

Filed: April 7, 2000 — Examiner: S. Patel

For: AMIDE DERIVATIVES OR SALTS THEREOF

HSA
5/11/01

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

AMENDMENT UNDER 37 C.F.R. § 1.111

In response to the Office Action dated December 7, 2000, the period for response having been extended to May 7, 2001 by the filing of a Petition for Extension of Time (Two Months) and appropriate fee herewith, please amend this application as follows:

IN THE CLAIMS:

Without prejudice, disclaimer, or acquiescence, please cancel claim 8, amend claims 1, 3, 5, 6, and 7, and add new claims 9, 10, 11, 12, and 13, as follows:

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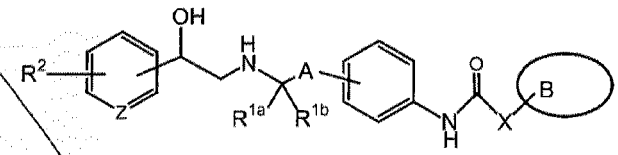
05/08/2001 MBERHE 00000073 09529096
01 FC:116 390.00 OP

1. (Once Amended) An amide derivative represented by the general formula (I):



(I)

in the formula, each of the symbols means as follows:

ring B is a heteroaryl group which is unsubstituted or substituted and is optionally fused with a benzene ring;

X is a bond, or a lower alkylene or an alkenylene, both of which are unsubstituted or substituted with hydroxy or a lower alkyl group, or X is a carbonyl or a group represented by -NH-, and when X is a lower alkylene which is substituted with a lower alkyl group, a carbon atom of the ring B optionally bonds with the lower alkyl group so that a ring is formed;

A is a lower alkylene or a group represented by -lower alkylene-O-;

R^{1a}, R^{1b} are the same or different and each is a hydrogen atom or a lower alkyl group;

R^2 is a hydrogen atom or a halogen atom; and

Z is a nitrogen atom or a group represented by =CH-;

or a salt thereof.

3. (Once Amended) The amide derivative or the salt thereof according to claim 2, wherein the ring B is a heteroaryl group which is substituted with a substituent chosen

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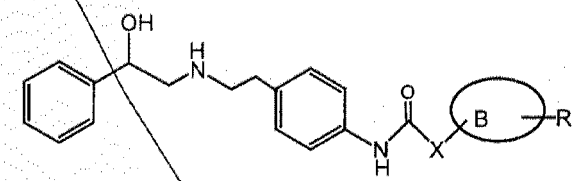
from a halogen atom, lower alkyl, lower alkenyl, lower alkynyl, hydroxy, sulfanyl, halogeno lower alkyl, lower alkyl-O-, lower alkyl-S-, lower alkyl-O-CO-, carboxy, sulfonyl, sulfinyl, lower alkyl-SO-, lower alkyl-SO_2-, lower alkyl-CO-, lower alkyl-CO-O-, carbamoyl, lower alkyl-NH-CO-, di-lower alkyl-N-CO-, nitro, cyano, amino, lower alkyl-NH-, di-lower alkyl-N-, aryl-lower alkyl, halogeno aryl-lower alkyl, guanidino, lower alkyl-CO-NH, and lower alkyl-SO_2-NH-.

5. (Once Amended) An amide derivative represented by the general formula (Ia):



(Ia)

in the formula, each of the symbols means as follows:

ring B is a heteroaryl group;

X is a bond or a lower alkylene group;

R is a hydrogen atom, a halogen atom, a lower alkyl group, amino group, an aryl lower alkyl group, or a halogeno aryl-lower alkyl group;

or a salt thereof.

6. (Once Amended)

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-pyridinecarboxyanilide, (R)-2-[1-(4-chlorobenzyl)-1H-imidazol-2-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]-

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acetanilide, (R)-2-[1-(3,4-dichlorobenzyl)-1H-tetrazol-5-yl]- 4'-[2-[(2-hydroxy -2-phenylethyl)amino]ethyl]acetanilide, (R)-2-(2-aminothiazol-4-yl)-4'-[2-(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide, (R)-2-(2-benzyl-1H-1,2,4-triazol-3-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)-amino] ethyl]acetanilide, (R)-2-(2-aminopyridin-6-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl)acetanilide, (R)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]-2-(2-pyridyl)acetanilide, (R)-4'-[2-[(2-hydroxy-2-phenylethyl)-amino]ethyl)-2-(2-pyrazinyl)acetanilide, (R)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl)-2-(2-pyrimidinyl)-acetanilide, or a salt of any of the foregoing.

7. (Once Amended) A composition comprising at least one amide derivative or the salt thereof as claimed in one of claims 1 through 6 in a pharmaceutically acceptable carrier.

9. (New) The composition as claimed in claim 7, wherein the amount of at least one amide derivative or the salt thereof is an amount effective for the treating diabetes mellitus in a human or animal patient in need of such treating.

10. (New) The amide derivative of general formula (I) as claimed in claim 1, wherein the amide derivative is an optical isomer, a hydrate, or a solvate of the amide derivative.

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11. (New) A composition comprising an amide derivative of general formula (I) as claimed in claim 1 in a pharmaceutically acceptable carrier, wherein the amide derivative is present as a polymorphic substance.

12. (New) A method for treating diabetes mellitus in a human or animal patient in need of such treatment comprising administering to the patient an amount of an amide derivative of general formula (I) as claimed in claim 1, wherein the amount is an amount effective for such treatment.

13. (New) A method for treating obesity in a human or animal patient in need of such treatment comprising administering to the patient an amount of an amide derivative of general formula (I) as claimed in claim 1, wherein the amount is an amount effective for such treatment.

REMARKS

I. Amendments to the Claims

Claims 1-7 and 9-13 are now pending. Claims 1, 3, 5, 6, and 7 have been amended, and claim 8 has been canceled, all without prejudice to pursuing canceled subject matter, if any, in a continuation application, without disclaimer of any subject matter, and without acquiescence to any rejection, objection, or requirement. New claim 9 has been added to replace canceled claim 8. New claims 10 and 11 have been added to point out that several forms of the amide derivative of claim 1 form part of the claimed invention. Claim 12 has been added to claim the method of treatment implicit in

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canceled claim 8. Claim 13 has been added to claim a method of treating obesity, as taught in the application as originally filed.

Claims 1, 3, and 5 have been amended to more particularly point out and distinctly claim the subject matter Applicants regard as their invention. In particular, the claim language has been adjusted to conform with accepted U.S. claim language practices. For example, parentheses were deleted, and language describing optional or alternative features of the claimed invention was clarified. Claim 6 was amended to clarify that each recited compound or its salt was claimed individually, and not necessarily in the form of a composition containing all recited compounds and salts thereof.

In claim 7, "agent" was changed to "composition" to recite the statutory term. *See* 35 U.S.C. § 101. Applicants have used "agent" and "composition" interchangeably throughout the application. *Compare, for example,* specification at page 5, lines 1-5, and page 26, line 10. Claim 7 was also modified to recite widely accepted multiply dependent claim language. Applicants note that, upon a review of their records, it appears that the fee for multiply dependent claims was not submitted yet in this application. Therefore, Applicants submit that fee with this Amendment.

Claim 8 was canceled and rewritten as claim 9. Claim 9 depends from claim 7, and merely presents the subject matter of canceled claim 8 in widely accepted claim language. Support for new claims 10 and 11, reciting forms of the amide derivatives of claim 1, find support throughout the specification and claims as originally filed, and in particular on page 8, line 24, to page 9, line 5, and page 19, lines 7-15. Claim 12, depending from claim 1 and reciting the method of treating diabetes mellitus in original

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claim 8, finds additional support in the specification generally, and in particular on pages 20-28. Claim 13 recites a method for treating obesity, and finds support in the application as filed, and in particular, in the specification on page 20, line 4, to page 21, line 11, and page 25, line 13, to page 28, line 22.

II. Certified Copies of Priority Document

The first page of the Office Action dated December 7, 2000, indicates that no certified copy of the priority document has been received by the Patent and Trademark Office (PTO). However, the Notification of Acceptance of Application under 35 U.S.C. 371 and 37 C.F.R. 1.494 or 1.495 mailed May 17, 2000 (a copy enclosed), indicates that a copy of the priority document *has* been received. Applicants respectfully request that the Examiner verify whether a certified copy of the priority application has been received by the PTO in this application.

III. Restriction and Election Requirements

The restriction requirement and species election requirement of record have been made final. *See* Office Action at page 2. While Applicants maintain their traverse of these requirements, they affirm their election with traverse of Group IV, claims 1-8 (now claims 1-7 and 9) drawn to compounds, compositions, and methods of use for Formula I wherein Z is CH, and also their election with traverse of the species of Example 7 on page 37, Example 12 on page 38, and Example 41 on page 44 of the specification. Applicants gratefully acknowledge the Examiner for refraining from restricting the claims further. *See* Office Action at page 2.

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IV. Improper Markush Group Rejection

Claims 1-8 have been rejected under the judicially created doctrine of improper Markush grouping, because these claims are allegedly drawn to an improper Markush group, that is, the claims allegedly lack unity of invention. *See* Office Action at page 2. The Office Action reasons that the "variables Z, X, and B, [together] with various values for other substituents are defined in such a way that they keep changing the structure/core of the compound that determines the classification/subclassification." *Id.* The Office Action has further asserted that the physical properties of the various compounds would be "tremendously altered" by the possible range of the claimed variables. In sum, the Office Action alleges an improper Markush group based on the alleged lack of unity. Applicants traverse, and disagree with the reasoning.

Among the many incorrect statements set forth in the Office Action at pages 2-3, Applicants disagree, in particular, with the statement that "[t]his feature is not inventive." *Id.* Moreover, Applicants traverse the unsupported statement that "the physical properties e.g. solubility, melting point, appearance etc. are tremendously altered with the changing of the various variable[s]," to the extent that foreseeable variation in these properties is used to support the improper Markush group rejection. Applicants request evidence on this point in accordance with MPEP § 2144.03.

Applicants respectfully request that the Examiner hold this rejection in abeyance until otherwise patentable subject matter has been identified. The Examiner kindly indicated that this rejection could be overcome by limiting the claimed invention to the elected subject matter. *See* Office Action at page 3. Applicants have traversed the

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restriction and election requirements, and if those requirements are not withdrawn, further argument now against the Markush rejection would be moot.

V. Claim Rejections under 35 U.S.C. § 112

Claims 1-8 have been rejected under 35 U.S.C. § 112, ¶ 1, as allegedly lacking enablement for compounds and compositions wherein "heteroaryl ring = isothiazolopyridine, imidazopyridinyl, or oxobenzofuranyl, etc." Office Action at pages 3-4. Specifically, the Office Action states "while [claims 1-8 are] enabl[ed] as therapeutic agent for diabetes mellitus which comprises of the amide derivative or its salt according to claims 1-6 as an effective ingredient, [the Applicants' disclosure] does not reasonably provide enablement for compounds, compositions based on heteroaryl ring = isothiazolopyridine, imidazopyridinyl, or oxobenzofuranyl, etc." *Id.* The Office Action then analyzes several factors for determining enablement from *In re Wands* to support the rejection. *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988); *ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Interf. 1986). Applicants respectfully traverse this rejection.

In stating the rejection, the Office Action asserts that "the claims are open-ended, and broad." This reasoning appears to suggest an indefiniteness rejection under 35 U.S.C. § 112, ¶ 2, which has not been made. Applicants traverse this assertion and ask for clarification whether the claims are rejected on this ground.

35 U.S.C. § 112, ¶ 1 requires:

> 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

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use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Given the statutory language, "enablement requires that the specification teach those in the art to make and use the invention without undue experimentation." *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. Moreover, "[t]he key word is 'undue,' not 'experimentation.' " *Id.* (internal quotations and citations omitted). To determine whether any needed experimentation is undue, the Federal Circuit listed eight factors to consider. *See id.* Applicants believe that the full scope of their claims is enabled, and set forth their counter-analysis of those eight factors below:

(1) The nature of the invention: Claims 1-6 recite compounds which are amide derivatives represented by the general formula (I), and salts thereof. Claim 6 names several amide derivatives and salts thereof. Claim 7 recites a composition which comprises at least one amide derivative as claimed in one of claims 1 to 6 in a pharmaceutically acceptable carrier. Claim 9 recites the composition of claim 7, wherein the amount of amide derivative is an amount effective for the treatment of diabetes mellitus. To the extent that the disclosed invention is broader than the scope of these claims, Applicants do not mean to limit the scope of their invention by this characterization. Also, Applicants point out that the claimed invention is more than just a treatment for diabetes.

(2) The state of the prior art: The specification describes some background of the present invention on pages 1-3. Applicants do not concede that any of the documents mentioned therein are "prior art" with respect to their invention.

(3) The predictability or lack thereof in the art: The Office Action asserts that a lack of predictability as to methods for making a therapeutic agent for diabetes

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mellitus has been demonstrated. Applicants traverse and ask for evidence of that demonstration. To the extent that the Office Action is correct, and yet Applicants' disclosure addresses that lack, this speaks of the patentability of Applicants' contribution to the art.

(4) The amount of direction or guidance present, and

(5) The presence or absence of working examples: The Office Action asserts: "There are no doses present for a method of preparing a therapeutic agent for diabetes mellitus." Office Action at page 5. Applicants disagree, and point to the dosage, adjuvant, and administration information on pages 26-28, among other places in the specification. The dose is "around 0.01 mg/kg to 100 mg/kg per day for adults in the case of oral administration, and that is administered at a time or by dividing into 2 to 4 times a day." Specification at page 26, lines 20-23. If the dose is given intravenously, the dosage changes to "around 0.001 mg/kg to 10 mg/kg per day for adults." *Id.*, at page 26, line 24, to page 27, line 1.

The Office Action continues: "Such utilities are unbelievable on their face and therefore they must be supported by sufficient evidence demonstrating such utilities." Office Action at page 5. To the contrary, some of many potential utilities are listed in the specification on pages 20-23, and operability is demonstrated in the specification on pages 23-26. Furthermore, if one of ordinary skill in the art sought to determine the efficacy of an amide derivative of general formula (I), that skilled artisan could follow the guidance provided in the specification for performing the hypoglycemic test in kk mice detailed on pages 23-24, the glucose tolerance test in normal rats beginning on page 24, and the test for stimulating human β_3-, β_2-, and β_1- receptors found on pages 24-25.

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The compounds of the present invention were shown to have a potentiating action to insulin sensitivity *ten times* greater than those compounds disclosed in WO 95/29159. *See* specification at page 24. Not only do the inventive amide derivatives of general formula (I) work, but they work surprisingly better.

The Office Action concludes this point of analysis by stating that "[a]ll available drugs to treat diabetes mellitus could only be used in a limited way." Office Action at page 5. Applicants respectfully point out that their invention is not limited to treating diabetes mellitus. *See* specification *generally, and in particular*, pages 20-23.

Moreover, Applicants assert that the compounds are enabled *per se*: the amide derivatives represented by the general formula (I) are described, among other places, on pages 4-9. General synthesis schemes appear in the Manufacturing Methods set forth on pages 9-20. Synthetic details for specific examples of amide derivatives represented by general formula (I) are shown on pages 36-63, and pages 64-70 tabulate physico-chemical properties of one hundred and thirteen (113) amide derivatives of the present invention actually prepared according to the disclosed syntheses.

To the extent that the rejection holds that certain heteroaryl rings are not enabled, Applicants point out the following examples actually synthesized and reported in the specification: Example 6 (imidazo[2,1-b]thiazolyl), Example 41 (aminothiazolyl), Example 60 (benzyloxypyridinyl), Example 90 (benzimidazolyl), Example 104 (pyrimidinyl), among many others.

(6) The breadth of the claims: Applicants believe that the breadth of their claims is fully supported by the large number of diverse amide derivatives prepared and

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described in the specification, and by the numerous tests showing efficacy of the amide derivatives, as discussed above.

(7) The quantity of experimentation: The Office Action asserts that there is inadequate guidance, and that the amount of experimentation required of one of ordinary skill in the art to practice the invention would be undue. *See* Office Action at 5. Applicants counter by referring again to the general and specific synthetic details provided in the specification on pages 9-20 and 36-63, the utilities listed on page 20-23, the efficacy tests described on pages 23-26, and the dosage and formulation information found on pages 26-28. To the extent that any experimentation would be needed, Applicants contend that it would be routine and not undue.

(8) Level of skill of those in the art: While the Office Action did not address this final *Wands* factor, it is accepted that those in the pharmaceutical, medical, and related arts possess a high level of skill.

In sum, Applicants respectfully contend that one of ordinary skill in the art finds copious enabling disclosure in the specification, and practicing the claimed invention does not require undue experimentation. Applicants therefore request that this rejection be withdrawn.

VI. Claim Rejections under 35 U.S.C. § 102

Claims 1-8 have been rejected under 35 U.S.C. § 102(a) without elaboration over JP 10-218861. *See* Office Action at page 6. Applicants traverse this rejection, for the reason, among many, that this Japanese document is not applicable as prior art by virtue of its publication date.

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Japanese application JP 10-218861 was published on August 18, 1998. Applicants filed their priority application on October 17, 1997. Therefore, Applicants respectfully request that this rejection be withdrawn.

Applicants perfect their claim for priority in accordance with 37 C.F.R. § 1.55(a) by submitting, a verified English translation of their priority document with this Amendment. Upon perfection of Applicants' priority date, this rejection should be withdrawn.

VII. Claim Rejections under 35 U.S.C. § 103

Claims 1-8 have been rejected as allegedly unpatentable over Schromm et al. (DE 3743265) in view of Toshiyuki et al. (Chem. Pharm. Bull. 39(10) 2581-2589 (1991)). See Office Action at page 6. The Office Action points out alleged structural similarities between the compounds disclosed and the present claimed amide derivatives of general formula (I), while acknowledging structural differences between them. The disclosed use of Schromm's compounds as broncholytics allegedly motivates one with knowledge of Toshiyuki's compounds, useful as antifungals, to modify Schromm's compounds to obtain Applicants' amide derivatives. Therefore, the Office Action concludes, one of ordinary skill in the art would find the amide derivatives of the present invention obvious. Applicants respectfully traverse.

> To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

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MPEP § 2143. Applicants assert that a prima facie case of obviousness has not been established here.

The Office Action finds motivation to combine one document teaching broncholytics with another document teaching antifungals. That both disclosed classes of chemicals are useful "as pharmaceuticals" is insufficient. One prevents bronchospasm, while the other kills fungus. No motivation has been offered, besides alleged structural similarity and general use in the pharmaceutical arts, to combine these molecules, to obtain either a better broncholytic or a better antifungal. Moreover, the compounds are structurally very different. Toshiyuki et al. teaches a molecule with a phenyl group just two carbon atoms away from a triazole ring at the same end of the molecule. On the other hand, Schromm et al. discloses a molecule in which a phenyl ring attaches the *opposite end* of a substantial 5- to 9-atom amino-hydrocarbon chain, far away from any possible heterocyclic groups.

No reasonable expectation of success can be found in either cited document. The molecules disclosed by Schromm et al. on the one hand are so structurally different, and in a different field of endeavor, from those taught by Toshiyuki et al., that there is no predictability in their combination. The Office Action states that "one [making this modification] would have expected still to maintain &/or find out pharmaceutical/pharmacological activity either [the] same or different than the reference '265 [Schromm et al.]." Applicants respectfully assert that this statement reflects the unpredictable nature of the proposed modification, and thus, the modification would be merely obvious to try at best. "Obvious to try" is not the legal standard to render the present claims unpatentable. *See* MPEP § 2141.

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For at least these reasons, Applicants respectfully contend that the rejection under 35 U.S.C. § 103(a) over Schromm et al. in view of Toshiyuki et al. be withdrawn.

To the extent that the rejection relies on Schromm et al. in combination with alleged common knowledge in the art or allegedly "well-known" prior art, Applicants traverse and request that support be provided in accordance with MPEP § 2144.03.

VIII. Documents Made of Record but Not Cited

The Office Action makes of record US 5,541,197. *See* Office Action at page 8. The Office Action also mentions Application No. 09/297,762 (now US 6,048,884) and its division, Application No. 09/514,637 (now US 6,177,454). Applicants note that both patents are assigned to the same Assignee as the present application, and submit a copy of the '884 patent in a Supplemental Information Disclosure Statement accompanying this Amendment. The '637 application is a division of the '884 patent, and so submission of the patent obviates the need to submit a copy of the division. Applicants contend that the present claims are patentable over the referenced patent and its division, at least because the present application claims an earlier priority date than the filing date of the patent. Moreover, Applicants submit US 5,223,614 to Schromm et al., since this document appears to be an English language equivalent of Schromm et al., discussed above.

Applicants believe that the claims are patentable over these documents, and reserve the right to argue that patentability should the need arise.

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CONCLUSION

Applicants respectfully request that all rejections be withdrawn, the application be reconsidered, and the claims allowed in a timely manner.

A Petition for Extension of Time (Two Months) and fee therefor accompany this Amendment. Please grant any further extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

Dated: May 4, 2001

By: David W. Hill
David W. Hill
Reg. No. 28,220

Enclosures:

- Appendix
- Verified Translation of Priority Document

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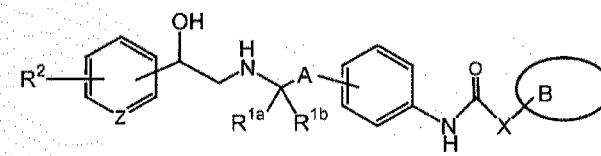
APPENDIX

Claims 1, 3, 5, 6, and 7 (each once amended) and claims 9, 10, and 11 (new) are set forth below in marked-up form to aid the Examiner in identifying amendments to the claims. Additions are underlined, and deletions are shown with bold square brackets and strikethrough text **[~~like this~~]**.

1. (Once Amended) An amide derivative represented by the **[~~following~~]** general formula (I):



(I)

[(] in the formula, each of the symbols means as follows:

ring B**[,]** is a heteroaryl group which **[~~may be~~]** is unsubstituted or substituted and **[~~may be~~]** is optionally fused with a benzene ring;

X**[,]** is a bond, or a lower alkylene or an alkenylene, both of which **[~~may be~~]** are unsubstituted or substituted with hydroxy or a lower alkyl group, or X is a carbonyl**[,]** or a group represented by -NH-, **[(]** and when X is a lower alkylene **[~~group~~]** which **[~~may be~~]** is substituted with a lower alkyl group, **[~~the hydrogen atoms bonded to the~~]** a carbon atom **[~~constituting~~]** of the ring B **[~~may form a lower alkylene group together~~]** optionally bonds with the lower alkyl group so that a ring is formed**[)]**;

A**[,]** is a lower alkylene or a group represented by -lower alkylene-O-;

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R^{1a} , R^{1b}[: ~~they may be~~] are the same or different and each is a hydrogen atom or a lower alkyl group;

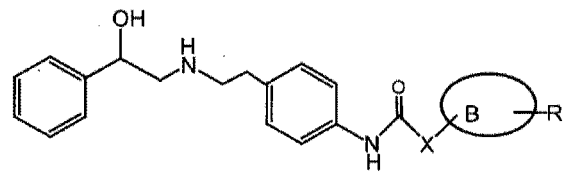
R^2[:] is a hydrogen atom or a halogen atom; and

Z[:] is a nitrogen atom or a group represented by =CH-[)];

or a salt thereof.

3. (Once Amended) The amide derivative or the salt thereof according to claim 2, wherein the ring B is a heteroaryl group which [~~may be~~] is substituted with a substituent [~~selected~~] chosen from a halogen atom, lower alkyl, lower alkenyl, lower alkynyl, hydroxy, sulfanyl, halogeno lower alkyl, lower alkyl-O-, lower alkyl-S-, lower alkyl-O-CO-, carboxy, sulfonyl, sulfinyl, lower alkyl-SO-, lower alkyl-SO_2-, lower alkyl-CO-, lower alkyl-CO-O-, carbamoyl, lower alkyl-NH-CO-, di-lower alkyl-N-CO-, nitro, cyano, amino, lower alkyl-NH-, di-lower alkyl-N-, aryl-lower alkyl, halogeno aryl-lower alkyl, guanidino, lower alkyl-CO-NH, and lower alkyl-SO_2-NH-.

5. (Once Amended) An amide derivative represented by the [~~following~~] general formula (Ia):



(Ia)

[(]in the formula, each of the symbols means as follows:

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ring B[;] is a heteroaryl group;

X[;] is a bond or a lower alkylene group;

R[;] is a hydrogen atom, a halogen atom, a lower alkyl group, amino group, an aryl lower alkyl group, or a halogeno aryl-lower alkyl group[;];

or a salt thereof.

6. (Once Amended)

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-pyridinecarboxyanilide, (R)-2-[1-(4-chlorobenzyl)-1H-imidazol-2-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]-acetanilide, (R)-2-[1-(3,4-dichlorobenzyl)-1H-tetrazol-5-yl]- 4'-[2-[(2-hydroxy -2-phenylethyl)amino]ethyl]acetanilide, (R)-2-(2-aminothiazol-4-yl)-4'-[2-(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide, (R)-2-(2-benzyl-1H-1,2,4-triazol-3-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)-amino] ethyl]acetanilide, (R)-2-(2-aminopyridin-6-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl)acetanilide, (R)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]-2-(2-pyridyl)acetanilide, (R)-4'-[2-[(2-hydroxy-2-phenylethyl)-amino]ethyl)-2-(2-pyrazinyl)acetanilide, (R)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl)-2-(2-pyrimidinyl)-acetanilide, [and salts thereof] or a salt of any of the foregoing.

7. (Once Amended) A [pharmaceutical agent] composition comprising [the] at least one amide derivative or the salt thereof [according to] as claimed in one of claims 1 through 6 in a pharmaceutically acceptable carrier.

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9. (New) The composition as claimed in claim 7, wherein the amount of at least one amide derivative or the salt thereof is an amount effective for the treating diabetes mellitus in a human or animal patient in need of such treating.

10. (New) The amide derivative of general formula (I) as claimed in claim 1, wherein the amide derivative is an optical isomer, a hydrate, or a solvate of the amide derivative.

11. (New) A composition comprising an amide derivative of general formula (I) as claimed in claim 1 in a pharmaceutically acceptable carrier, wherein the amide derivative is present as a polymorphic substance.

12. (New) A method for treating diabetes mellitus in a human or animal patient in need of such treatment comprising administering to the patient an amount of an amide derivative of general formula (I) as claimed in claim 1, wherein the amount is an amount effective for such treatment.

13. (New) A method for treating obesity in a human or animal patient in need of such treatment comprising administering to the patient an amount of an amide derivative of general formula (I) as claimed in claim 1, wherein the amount is an amount effective for such treatment.

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PATENT
Customer No. 22,852
Attorney Docket No. 07385.0007-00

#9 PS
5/15/01

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	
Tatsuya MARUYAMA et al.	
Serial No.: 09/529,096	Group Art Unit: 1624
Filed: April 7, 2000	Examiner: S. Patel
For: AMIDE DERIVATIVES OR SALTS THEREOF	

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT UNDER 37 C.F.R. § 1.97(c)

Pursuant to 37 C.F.R. §§ 1.56 and 1.97(c), applicants bring to the attention of the Examiner the documents listed on the attached PTO 1449. This Information Disclosure Statement is being filed after the events recited in Section 1.97(b) but, to the undersigned's knowledge, before the mailing date of either a Final action, Quayle action, or a Notice of Allowance. Under the provisions of 37 C.F.R. § 1.97(c), this Information Disclosure Statement is accompanied by a fee of $180.00 as specified by Section 1.17(p).

Copies of the listed documents are attached. Applicants respectfully request that the Examiner consider the listed documents and indicate that they were considered by making appropriate notations on the attached form.

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Applicants call the Examiner's attention to the following copending U.S. patent applications:

Application No.: 09/297,762 - now U.S. Patent No. 6,048,884
Filing Date: May 7, 1999
Attorney Docket No.: 7385.0004-00

Application No.: 09/514,637 - now U.S. Patent No. 6,177,454
Filing Date: February 29, 2000
Attorney Docket No.: 7385.0004-01

This submission does not represent that a search has been made or that no better art exists and does not constitute an admission that each or all of the listed documents are material or constitute "prior art." If the Examiner applies any of the documents as prior art against any claims in the application and applicants determine that the cited documents do not constitute "prior art" under United States law, applicants reserve the right to present to the office the relevant facts and law regarding the appropriate status of such documents.

Applicants further reserve the right to take appropriate action to establish the patentability of the disclosed invention over the listed documents, should one or more of the documents be applied against the claims of the present application.

If there is any fee due in connection with the filing of this Statement, please charge the fee to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

Dated: May 4, 2001

By: David W. Hill
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PATENT
Customer Number 22,852
Attorney Docket No. 7385.0007-00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)
Tatsuya MARUYAMA et al.	)
Application No.: 09/529,096	) Group Art Unit: 1624
Filed: April 7, 2000	) Examiner: S. Patel
For: AMIDE DERIVATIVES OR SALTS THEREOF	)

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

SUBMISSION OF TRANSLATION OF PRIORITY DOCUMENT

Applicants submit herewith a translation of Japanese patent application Hei-9-285778, filed October 17, 1997. In accordance with 37 C.F.R. § 1.55(a), Applicants hereby perfect their claim of priority under 35 U.S.C. § 119 by filing this certified translation.

Please grant any extensions of time required to enter this translation and charge any required fees to our deposit account 06-0916.

Respectfully submitted,

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VERIFICATION OF TRANSLATION

APPLICATION No. Pat. Hei -9-285778

I, Tsuyoshi UDAGAWA, of c/o Yamanouchi Pharmaceutical Co., Ltd., Patent Dept., 17-1, Hasune 3-chome, Itabashi-ku, Tokyo 174-8612 Japan, am the translator of the document attached and I state that the following is a true translation to the best of my knowledge and belief.

Signature of translator

Tsuyoshi Udagawa

Tsuyoshi Udagawa

Dated: April 19, 2001

PATENT OFFICE
JAPANESE GOVERNMENT

This is to certify that the annexed is a true copy of the following application as filed with this Office.

Date of Application: October 17, 1997

Application Number: Patent Appln. Hei-9-285778

Applicant(s): Yamanouchi Pharmaceutical Co., Ltd.

September 11, 1998

Commissioner, Patent Office Takeshi Isayama

Issuance No. Hei-10-

[Document Name] Patent Application

[Reference Number] 0000002773

[Filing Date] October 17, 1997

[Addressee] Commissioner of Patent Office
Hisamitsu ARAI

[International Patent Classification] C07C233/54
A61K 31/165 ACN
A61K 31/165 ADN
A61K 31/165 ADP

[Title of the Invention]
AMIDE DERIVATIVES OR SALTS THEREOF

[Number of Claims] 3

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[Name or Appellation] Emiko YANO

[Phone Number] 0298-52-5111

[Indication of fees]

[Prepayment book number] 005348

[Amount of payment] 21000 yen

[List of submitted article]

[Article name] Specification 1 copy

[Article name] Abstract 1 copy

[General Power of Attorney Number] 9704254

[Requirement for proof] Yes

[Document Name] Specification

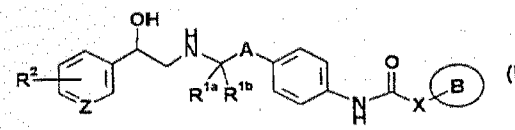
[Title of the Invention]

AMIDE DERIVATIVES OR SALTS THEREOF

[Scope of the Claims for Patent]

[Claim 1] An amide derivative represented by the following formula:

[Formula 1]



(I)

(In the above formula, each of the symbols means as follows:

ring B: a nitrogen-containing heteroaryl group which may be substituted and may be fused with a benzene ring;

X: a bond, an optionally hydroxy- or lower alkyl-substituted linear lower alkylene, lower alkenylene or carbonyl, or a group represented by a formula -NH- (when X is a linear lower alkylene group which may be substituted with a lower alkyl group, the hydrogen atom bonded to the carbon atom constituting a ring B may form a lower alkylene group together with said lower alkyl group so that a ring is formed);

A: methylene, ethylene or a group represented by a formula $-CH_2O-$;

R^{1a}, R^{1b}: they may be same or different and each is a hydrogen atom or a lower alkyl group;

R^2: a hydrogen atom or a halogen atom; and

Z: a nitrogen atom or a group represented by a formula =CH-)

or a salt thereof.

[Claim 2] A pharmaceutical agent comprising the amide derivative or the salt thereof according to claim 1.

[Claim 3] A therapeutic agent for diabetes mellitus comprising the amide derivative or the salt thereof according to claim 1 as an effective ingredient.

[Detailed Description of the Invention]

[0001]

[Technical Field to which the Invention Belongs]

The present invention relates to pharmaceuticals and, more particularly, it relates to novel amide derivatives or salts thereof and also to therapeutic agents for diabetes mellitus containing them as effective components.

[0002]

[Prior Art]

Diabetes mellitus is a disease accompanied by continuous hyperglycemic state and is said to be resulted by action of many environmental factors and genetic factors. The main controlling factor for blood sugar is insulin, and it has been known that hyperglycemia is resulted by deficiency of insulin

or by excess of factors which inhibit its action (such as genetic cause, lack of exercise, obesity and stress).

Diabetes mellitus is classified into two main types. One is insulin-dependent diabetes mellitus (IDDM) caused by a lowering of insulin-secreting function of pancreas due to autoimmune diseases, and another is non-insulin-dependent diabetes mellitus (NIDDM) caused by a lowering of insulin-secreting function of pancrease due to pancreatic fatigue accompanied by continuous high insulin secretion. 95% or more of diabetic patients in Japan are said to suffer from NIDDM, and an increase in the patients due to a change in daily life style is becoming a problem.

As to the therapy of diabetes mellitus, dietetic treatment, therapeutic exercise and remedy of obesity are mainly conducted in mild cases while, when the disease progresses, oral antidiabetic drugs (for example, insulin secretion promoters such as sulfonyl urea compounds and insulin sensitivity potentiators which potentiate the sensitivity of insulin) are administered. In severe cases, an insulin preparation is administered. However, there has been a brisk demand for creation of the drugs whereby higher control for blood sugar is possible, and development of antidiabetic drugs having a new mechanism and having high usefulness has been demanded.

[0003]

U.S. Patents 4,396,627 and 4,478,849 describe phenylethanolamine derivatives and disclose that those compounds are useful as drugs for obesity and for hyperglycemia. Action of those compounds is reported to be due to a stimulating action to β_3-receptors.

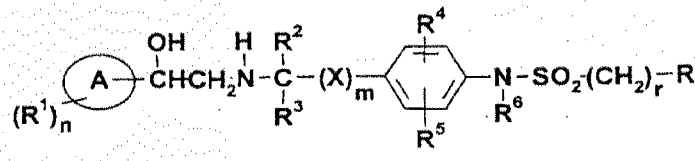
Incidentally, it has been known that β-adrenaline receptors are classified into β_1, β_2 and β_3 subtypes, that stimulation of β_1-receptor causes an increase in heart rate, that stimulation of β_2-receptor stimulates decomposition of glycogen in muscles, whereby synthesis of glycogen is inhibited, causing an action such as muscular tremor, and that stimulation of β_3-receptor shows an anti-obesity and an anti-hyperglycemia action (such as decrease in triglyceride, decrease in cholesterol and increase in HDL-cholesterol).

However, those β_3-agonists also have actions caused by stimulation of β_1- and β_2-receptors such as increase in heart rate and muscular tremor, and they have a problem in terms of side effects. In addition, recently, it was ascertained that β-receptors have differences to species, and it has been reported that even compounds having been confirmed to have a β_3-receptor selectivity in rodential animals such as rats show an action due to stimulating action to β_1- and β_2-receptors in human being. In view of the above, investigations for compounds having a stimulating action which is selective to β_3-receptor in human being have been conducted recently using human cells

or cells where human receptors are expressed. For example, WO 95/29159 describes substituted sulfonamide derivatives represented by the formula set forth below and discloses that due to their selective stimulating action to β_3-receptors in human being, they are useful against obesity, hyperglycemia, etc. However, this patent does not specifically disclose an insulin secretion promoting action and an insulin sensitivity potentiating action of those compounds.

[0004]

[Formula 2]



(In the formula, the symbols should be referred to in the specification of this patent.)

[0005]

[Problems to be Solved by the Invention]

As such, there has been still a demand for creation of therapeutic agents for diabetes mellitus of a new type which have a highly clinical usefulness.

[0006]

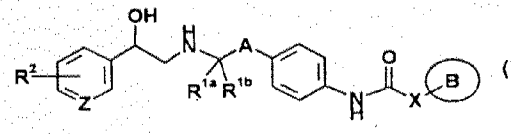
[Means to Solve the Problems]

The present inventors have conducted an intensive investigation on compounds having both an insulin secretion promoting action and an insulin sensitivity potentiating action and found that novel amide derivatives show both a good insulin secretion promoting action and a good insulin sensitivity potentiating action and furthermore show a selective stimulating action to β_3-receptors, leading to accomplishment of the present invention.

That is, the present invention relates to an amide derivative represented by the formula (I) set forth below or a salt thereof, having both an insulin secretion promoting action and an insulin sensitivity potentiating action and further having anti-obesity and anti-hyperlipemia actions due to a selective stimulating action to β_3-receptors. The present invention also relates to a pharmaceutical agent, particularly to a therapeutic agent for diabetes mellitus containing the amide derivative or the salt thereof as an effective ingredient.

[0007]

[Formula 3]



(I)

(In the formula, each of the symbols means as follows:

ring B: a nitrogen-containing heteroaryl group which may be substituted and may be fused with a benzene ring;

X: a bond, an optionally hydroxy- or lower alkyl-substituted linear lower alkylene, lower alkenylene or carbonyl, or a group represented by a formula -NH- (when X is a linear lower alkylene group which may be substituted with a lower alkyl group, the hydrogen atom bonded to the carbon atom constituting a ring B may form a lower alkylene group together with the lower alkyl group so that a ring is formed);

A: methylene, ethylene or a group represented by a formula $-CH_2O-$;

R^{1a}, R^{1b}: they may be same or different and each is a hydrogen atom or a lower alkyl group;

R^2: a hydrogen atom or halogen atom; and

Z: a nitrogen atom or a group represented by a formula =CH-.)

[0008]

[Embodiments of the Invention]

The compound of the formula (I) is further illustrated as follows.

In the definitions used in the formula in this specification, the term "lower" means a linear or branched hydrocarbon chain having from 1 to 6 carbon atoms unless otherwise specified.

Examples of the "lower alkyl group" are methyl, ethyl and linear or branched propyl, butyl, pentyl or hexyl, preferably an alkyl group having from 1 to 4 carbon atoms, and particularly preferably methyl, ethyl, propyl or isopropyl.

Examples of the "lower alkylene group" is a divalent group obtained by removing a hydrogen atom from the above "lower alkyl group", preferably an alkylene group having from 1 to 4 carbon atoms, and particularly preferably methylene, ethylene, propylene or butylene.

[0009]

The term "nitrogen-containing heteroaryl group which may be fused with a benzene ring" in "a nitrogen-containing heteroaryl group which may be substituted and may be fused with a benzene ring" means a ring group where a benzene ring is fused with a heteroaryl group as mentioned later or a non-fused heteroaryl group.

Specific examples of the "ring group where the benzene ring is fused with a heteroaryl group" are fused-ring heteroaryl groups such as quinolyl, isoquinolyl, quinazolinyl,

quinolidinyl, quinoxalinyl, cinnolinyl, benzimidazolyl, imidazopyridyl, benzofuranyl, benzoisoxazolyl, benzoxazolyl, benzothiazolyl, oxazolopyridyl, isothiazolopyridyl and benzothienyl groups; and oxo-added rings such as oxobenzofurayl group.

Examples of the "heteroaryl group" are monocyclic heteroaryl groups such as furyl, thienyl, pyrrolyl, imidazolyl, thiazolyl, pyrazolyl, isothiazolyl, isoxazolyl, pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, thiadiazolyl, triazolyl and tetrazolyl; and bicyclic heteroaryl groups such as naphthylidinyl and pyridopyrimidinyl.

[0010]

The substituent in the "nitrogen-containing heteroaryl group which may be substituted and may be fused with a benzene ring" may be any group which can be usually substituted in this ring group. Preferred examples are a halogen atom and lower alkyl, lower alkenyl, lower alkynyl, hydroxyl, sulfanyl, halogeno lower alkyl, lower alkyl-O-, lower alkyl-S-, lower alkyl-O-CO-, carboxy, sulfonyl, sulfinyl, lower alkyl-SO_2-, lower alkyl-SO-, lower alkyl-CO-, lower alkyl-CO-O-, carbamoyl, lower alkyl-NH-CO-, di-lower alkyl-N-CO-, nitro, cyano, amino, lower alkyl-NH-, di-lower alkyl-N-, and -O-lower alkylene-O- groups.

The "lower alkenyl group" is a linear or branched alkenyl group having 2 to 6 carbon atoms, and its specific examples are vinyl, propenyl, butenyl, pentenyl and hexenyl groups.

The "lower alkynyl group" is a linear or branched alkynyl group having 2 to 6 carbon atoms, and its specific examples are ethynyl, propynyl, butynyl, pentynyl and hexynyl groups.

"Halogen atom" means fluorine atom, chlorine atom, bromine atom or iodine atom, and the "halogeno lower alkyl group" means a group where a hydrogen atom or atoms in the above-mentioned alkyl group is/are substituted with a halogen atom or atoms.

The case when X is a bond means that a carbon atom of the group -CO- is directly bonded to the ring B.

[0011]

The compound (I) of the present invention has at least one asymmetric carbon atom and therefore, there are optical isomers such as (R)-compounds and (S)-compounds, racemates, diastereomers, etc. The present invention includes all and each of isolated isomers and mixtures thereof. The present invention also includes hydrates, solvates (such as those with ethanol) and polymorphic substances of the compound (I).

The compound (I) of the present invention may form a salt with an acid. Examples of the salt are acid addition salts with mineral acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid and phosphoric

acid; and those with organic acids such as formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric aid, maleic acid, lactic acid, malic acid, citric acid, tartaric acid, carbonic acid, picric acid, methanesulfonic acid, ethanesulfonic acid and glutamic acid.

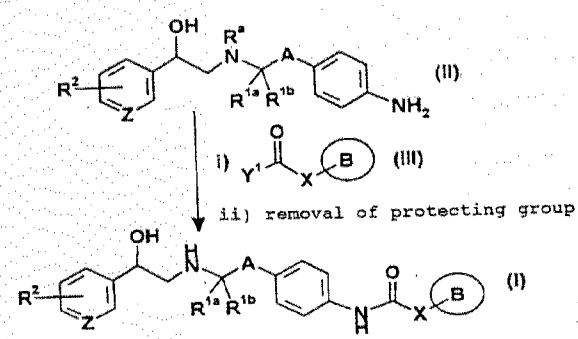
[0012]

(Manufacturing Method)

The compound of the present invention or the salt thereof may be manufactured by application of various synthetic methods utilizing the characteristics of its fundamental skeleton or type of the substituent. Representative manufacturing methods are illustrated as hereunder.

First Manufacturing Method

[Formula 4]



(In the formulae, R^{1a}, R^{1b}, R^2, A, B, X and Z have the same meanings as defined already; R^a is a protective group for amino group; and Y^1 is a leaving group, and more specifically hydroxyl, a lower alkoxy group or a halogen atom.)

[0013]

In this method, the compound (II) and the compound (III) are subjected to amidation, and the protective group is then removed therefrom to synthesize the compound (I) of the present invention.

The amidation in this manufacturing method can be conducted by conventional means.

The solvent may vary depending upon Y^1 of the compound (III) and mostly, an inert solvent or an alcoholic solvent (such as isopropanol) may be applied.

When Y^1 is a hydroxyl group, a method where the reaction is conducted in the above-mentioned solvent in the presence of a condensing agent may be applied. Examples of the condensing agent are N,N'-dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI), 1,1'-carbonyldiimidazole (CDI), diphenylphosphoryl azide (DPPA) and diethylphosphoryl cyanide (DEPC).

When Y^1 is a lower alkoxy group, a method where the reaction is conducted under heating or refluxing as it is or in the above-mentioned inert solvent may be applied.

When Y^1 is a halogen atom, a method where the reaction is conducted in the above-mentioned inert solvent in the presence of a base may be applied.

[0014]

Examples of the inert solvent are dimethylformamide (DMF), dimethylacetamide, tetrachloroethane, dichloromethane, dichloroethane, chloroform, carbon tetrachloride, tetrahydrofuran, dioxane, dimethoxyethane, ethyl acetate, benzene, toluene, xylene, acetonitrile, dimethyl sulfoxide and a mixed solvent thereof, and they may be appropriately selected depending upon each reaction condition. Examples of the base are inorganic bases such as sodium hydroxide, potassium

hydroxide, sodium carbonate and potassium carbonate; and organic bases such as N-methylmorpholine, triethylamine, diisopropylethylamine and pyridine.

The protective group of the amino group represented by R^a is a protective group which is commonly used for amino group by those skilled in the art, and its representative examples are acyl groups such as formyl, acetyl, propionyl, methoxyacetyl, methoxypropionyl, benzoyl, thienylacetyl, thiazolylacetyl, tetrazolylacetyl, thiazolylglyoxyloyl and thienylglyoxyloyl groups; lower alkoxycarbonyl groups such as methoxycarbonyl, ethoxycarbonyl and tert-butoxycarbonyl groups; aralkyloxycarbonyl groups such as benzyloxycarbonyl and p-nitrobenzyloxycarbonyl groups; lower alkanesulfonyl groups such as methanesulfonyl and ethanesulfonyl groups; aralkyl groups such as benzyl, p-nitrobenzyl, benzhydryl and trityl groups ; and tri-(lower alkyl)silyl groups such as trimethylsilyl group.

[0015]

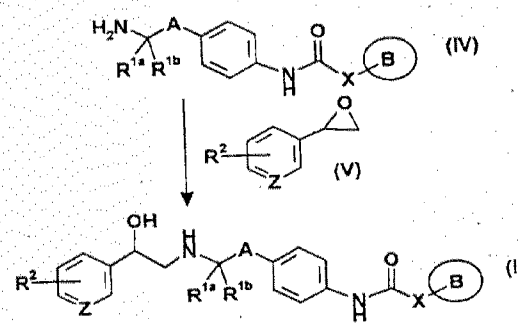
Removal of the protective group in this manufacturing method may be conducted by conventional means. For example, the protective group for the amino group represented by R^a may be easily removed, for example, by i) a method where in case that the protective group is benzhydryl, p-methoxybenzyl, trityl, tert-butoxycarbonyl, formyl, etc., treatment with an acid such as formic acid, trifluoroacetic acid, a mixture of

trifluoroacetic acid and anisole, a mixture of hydrobromic acid and acetic acid, a mixture of hydrochloric acid and dioxane, etc. is conducted; ii) a method where in case that the protective group is benzyl, p-nitrobenzyl, benzhydryl, trityl, etc., catalytic reduction using palladium-carbon or palladium hydroxide-carbon is conducted; and iii) a method where in case that the protective group is a tri-(lower alkyl)silyl group or the like, treatment with water, fluoride anion (tetra-n-butylammonium fluoride, sodium fluoride, potassium fluoride or hydrofluoric acid), etc. is conducted.

[0016]

Second Manufacturing Method

[Formula 5]



(In the formulae, R^{1a}, R^{1b}, R^2, A, B, X and Z have the same meanings as defined already.)

[0017]

In this manufacturing method, the compound (IV) is reacted with the compound (V) to give the compound (I) of the present invention.

The amine compound (IV) and the compound (V) are reacted with each other under heating or refluxing for 1 to 24 hours as they are or in an inert solvent, to give the compound (I) of the present invention.

Examples of the inert solvent are acetonitrile, tetrahydrofuran, 2-butanone, dimethyl sulfoxide and N-

methylpyrrolidone. In the reaction, a base such as sodium bicarbonate, potassium carbonate or diisopropylethylamine may be added to the reaction mixture.

[0018]

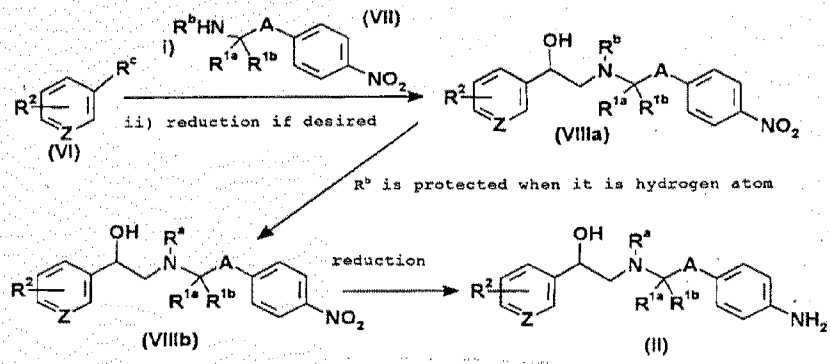
Incidentally, in the above manufacturing methods, it is possible to purify the resulting substance by removing undesired by-products by means of recrystallization, pulverization, preparative thin layer chromatography, silica gel flash chromatography (as mentioned in W. C. Still, et al.; *J. Org. Chem.*, **43**, 2923 (1978)), medium-pressure liquid chromatography and HPLC. The compound produced by means of HPLC can be isolated as a corresponding salt.

The starting material used in the above-mentioned manufacturing methods may be easily manufactured by the methods which are known to those skilled in the art. One of the representative methods is shown as hereunder.

[0019]

(Manufacturing Method for the Starting Compound (II))

[Formula 6]



(In the formulae, R^{1a}, R^{1b}, R^2, A and Z have the same meanings as defined already; R^b is hydrogen atom or a protective group of an aralkyl type for the amino group; and R^c is epoxy, 2-haloacetyl or 1-carboxymethan-1-ol group.)

[0020]

This manufacturing method is composed of from step (a) to step (c) in which the step (a) is a step where the compound (VI) is reacted with the compound (VII), followed by subjecting to reduction to give the compound (VIIIa) depending upon the type of R^c,; the step (b) is a step where protection is conducted when R^b of the compound (VIIIa) is hydrogen atom; and the step

(c) is a step where a nitro group is reduced to an amino group to give the compound (II).

Examples of the protective group of an aralkyl type for the amino group used in the above manufacturing method are benzyl, p-nitrobenzyl, benzhydryl groups, etc.

[0021]

Step (a):

Illustration is made for the following three cases.

1) When R^c is an epoxy group, the compound (VI) may be reacted with the compound (VII) by the same manner as in the above-mentioned second manufacturing method. Reaction conditions such as reaction temperature, solvent, etc. are the same as well.

2) When R^c is 2-haloacetyl group, the compound (VI) is reacted with the compound (VII) in the presence of a base, followed by subjecting to reduction to prepare the compound (VIIIa). The base is the same as that mentioned in the first manufacturing method. The reduction may be conducted in the above-mentioned inert solvent or in a solvent of an alcohol type with stirring in the presence of a reducing agent. Examples of the reducing agent are sodium borohydride, sodium cyanoborohydride, lithium aluminum hydride and borane.

3) When R^c is 1-carboxymethan-1-ol group, the compound (VI) is reacted with the compound (VII) in the presence of a condensing agent, followed by subjecting to reduction in the

same manner as in 2) to prepare the compound (VIIIa). The condensing agent is the same as that mentioned in the first manufacturing method.

[0022]

Step (b):

When R^b in the compound (VIIIa) is hydrogen atom, the amino group is protected by conventional means using, for example, di-tert-butyl dicarbonate or the like, to prepare the compound (VIIIa).

Step (c):

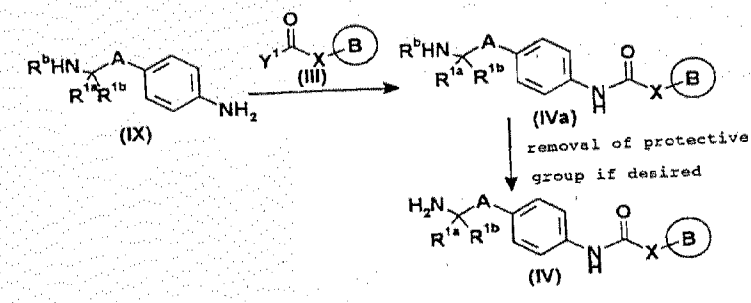
A method for the reduction of nitro group to amino group may be conducted by conventional means such as metallic reduction using iron, zinc, etc. and catalytic reduction using a catalyst such as palladium-carbon, palladium hydroxide-carbon, Raney nickel, etc. R^a becomes hydrogen atom depending upon the reducing condition, but it may be protected again by conventional means.

[0023]

(Manufacturing Method for Starting Compound (IV))

A)

[Formula 7]



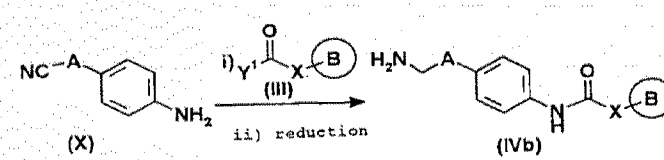
(In the formulae, R^{1a}, R^{1b}, R^b, A, B, X and Y^1 have the same meanings as defined already.)

This reaction is a reaction where the compound (IX) and the compound (III) are subjected to amidation reaction to give a compound (IVa) and, when R^b is a protective group for amino group, the protective group is removed to give a compound (IV). The amidation reaction can be conducted by the same manner as in the above-mentioned first manufacturing method, and the reaction conditions such as reaction temperature and solvent are the same as well.

[0024]

B)

[Formula 8]



This reaction is a reaction where the compound (X) and the compound (III) are subjected to amidation reaction and then to reduction reaction to give a compound (IVa). The amidation reaction can be conducted by the same manner as in the above-mentioned first manufacturing method, and the reaction conditions such as reaction temperature and solvent are the same as well. In the reduction reaction, the above-mentioned catalytic reduction or a method where cobalt chloride and sodium borohydride is used may be applied.

[0025]

With regard to other compounds such as the compound (III), the compound (IV), the compound (V), the compound (VI) and the compound (VII), those which are available in the market or are appropriately synthesized by known methods (such as N-alkylation, cyclization and hydrolysis) from the commercially available compounds may be used.

[0026]

The compound (I) of the present invention which is manufactured as such is isolated and purified as a free compound, a salt thereof obtained by means of salt formation by conventional means, a hydrate, a solvate with various solvents such as ethanol, or polymorphic crystals. The isolation and purification may be conducted by applying common chemical operations such as extraction, concentration, evaporation, crystallization, filtration, recrystallization and various chromatographic means.

Various isomers may be isolated by conventional means utilizing the physico-chemical differences between the isomers. For example, the racemate can be converted to stereochemically pure isomers by common recemic resolution (such as a method where the racemate is changed to diastereomer salts with conventional optically active acid [for example, tartaric acid], followed by subjecting to optical resolution). Incidentally, a mixture of diastereomers may be separated by conventional method such as fractional crystallizaiton or chromatography. In the case of an optically active compound, it may be manufactured starting from an appropriate optically active material.

[0027]

[Effects of the Invention]

The phenethanol derivative of the present invention represented by the formula (I) or the salt thereof has both an insulin secretion promoting action and an insulin sensitivity

potentiating action and also has a selective β_3-receptor stimulating action, so that it is useful as a therapeutic agent for diabetes mellitus.

As confirmed by a glucose tolerance test and a hypoglycemic test in insulin-resisting model animals as described later, the compound of the present invention has both a good insulin secretion promoting action and a good insulin sensitivity potentiating action, so that its usefulness in diabetes mellitus is expected. Although the β_3-receptor stimulating action may have a possibility of participating in expression of the insulin secretion promoting action and the insulin sensitivity potentiating action, other mechanism might also possibly participate therein, and the details thereof have been still unknown yet.

The β_3-receptor stimulating action of the compound of the present invention is selective to β_3-receptors in human being. It has been known that the stimulation of β_3-receptor stimulates decomposition of fat (decomposition of the fat tissue triglyceride into glycerol and free fatty acid), whereby a disappearance of fat mass is promoted. Therefore, the compound of the present invention has an anti-obesity action and an anti-hyperlipemia action (such as triglyceride lowering action, cholesterol lowering action and HDL cholesterol increasing action) and is useful as a preventive and therapeutic agent for obesity and hyperlipemia (such as hypertriglyceridemia,

hypercholesterolemia and hypo-HDL-lipoproteinemia). Those diseases have been known as animus factors in diabetes mellitus, and amelioration of those diseases is useful for prevention and therapy of diabetes mellitus as well.

[0028]

The compound of the present invention is also useful as a preventive and therapeutic agent for other diseases where the improvement of symptom can be achieved by reducing the symptoms of obesity and hyperlipemia such as ischemic coronary diseases (for example, arteriosclerosis, myocardial infarction and angina pectoris), cerebral arteriosclerosis (for example, cerebral infarction) or aneurysm.

Further, the selective β_3-receptor stimulating action of the compound of the present invention is useful for prevention and therapy of several diseases which have been reported to be improved by the stimulation of β_3-receptor. Examples of those diseases are shown as follows.

It has been mentioned that the β_3-receptor mediates the motility of non-sphincteral smooth muscle contraction, and because it is believed that the selective β_3-receptor stimulating action assists the pharmacological control of intestinal motility without being accompanied by cardiovascular action, the compound of the present invention has a possibility of being useful in therapy of the diseases caused by abnormal intestinal motility such as various

gastrointestinal diseases including irritable colon syndrome. It is also useful as the therapy for peptic ulcer, esophagitis, gastritis and duodenitis (including that induced by *H. pylori*), enterelcosis (such as inflammatory intestinal diseases, ulcerative colitis, clonal disease and proctitis).

It is further shown that the β_3-receptor affects the inhibition of release of neuropeptide of some sensory fibers in lung. The sensory nerve plays an important role in neurogenic inflammation of respiratory tract including cough, and therefore, the specific β_3-agonist of the present invention is useful in the therapy of neurogenic inflammation and in addition, has little action to cariopulmonary system.

Moreover, the β_3-adrenaline receptor is capable of resulting in a selective antidepressant action due to stimulation of the β_3-receptor in brain, and accordingly, the compound of the present invention has a possibility of being useful as an antidepressant.

The action of the compound of the present invention has been ascertained to be selective to β_3-receptors as a result of experiments using human cells, and the adverse action caused by other β_3-receptor stimulation is low or none.

[0029]

Effects of the compound of the present invention have been ascertained by the following tests.

1. Hypoglycemic test in kk mice (insulin-resisting model; obesity and hyperglycemia):

Male kk mice (blood sugar level: not lower than 200 mg/dl) were subjected to a measurement of blood sugar level under feeding and then randomly classified into groups. The drug to be tested was compulsorily administered orally or subcutaneously once daily for four days, and the blood sugar level after 15-18 hours from the final administration was compared with that before the administration (n = 6). The blood was collected from a tail vein of the mice using a glass capillary (previously treated with heparin), the protein was removed therefrom, and the amount of glucose in the supernatant liquid (mg/dl) was measured by colorimetric determination by means of a glucose oxidase method.

The compound of the present invention significantly lowered the blood sugar level as compared with that prior to the administration of a comparative drug in both cases of oral and subcutaneous administrations. From this result, it is shown that the compound of the present invention has a good potentiating action to insulin sensitivity.

[0030]

2. Glucose tolerance test in normal rats:

Male rats of SD strain of seven weeks age were fasted for a whole day and night, then randomly classified into groups and subjected to an oral glucose tolerance test (OGTT) (n = 4). The

compound to be tested was administered orally or subcutaneously at 30 minutes before administration of glucose (2 g/kg by oral administration). The blood was collected from an abdominal aorta using a heparin-treated glass syringe from the rats which were anesthetized with pentobarbital (65 mg/kg), the protein was removed therefrom, and the amount of glucose in the supernatant liquid (mg/dl) was measured by colorimetric determination by means of a glucose oxidase method. The insulin value in blood was determined by measuring the amount of insulin in plasma (ng/ml) by means of radioimmunoassay (RIA).

In a group where the compound of the present invention was administered orally or subcutaneously, a significant increase in the insulin value in blood was observed as compared with the group to which no drug was given. An increase in the sugar blood level after administration of glucose was significantly inhibited as well. From those results, it is apparent that the compound of the present invention has a good insulin secretion promoting action and a good hyperglycemia inhibiting action.

[0031]

3. Stimulating test to human β_3-, β_2- and β_1-receptors:

Human β_3-stimulating action was investigated using an SK-N-MC cell system (cells in which human β_3-receptor and human β_1-receptor were permanently expressed were purchased) while human β_2- and β_1-stimulating actions were investigated using a

CHO cell system (cells in which each of human β_2- and β_1-receptors was compulsorily expressed were purchased). Stimulating action of the compound (10^{-10} to 10^{-4} M) were investigated by incubating 10^5 cells/well of each of the cells on a 24-well plate and checking under a subconfluent state after two days using a producing activity of cyclic AMP (cAMP) as an index. Incidentally, the human β_3-stimulating action was investigated in the presence of a β_1-receptor blocker (CGP20712A, 10^{-6} M). Amount of production of cAMP in each cell (pmol/ml) was measured by an RIA method using ^{125}I-cAMP. Intensity of action of each compound was compared by calculating the pD2 value and the maximum activity (I.A. (%) where the maximum reaction of 10^{-5} M isoproterenol was defined as 100%) from the resulting dose-reaction curve.

It has been ascertained that the compound of the present invention has a selective stimulating action to human β_3-receptor.

A pharmaceutical composition containing one or more of the compound of the present invention or the salt thereof as an effective ingredient is prepared using common pharmaceutically acceptable vehicles. Administration of the pharmaceutical composition according to the present invention may be either by oral administration or by parenteral administration by, for example, injection, suppository, subcutaneous agent, inhaling agent or intracystic infusion.

The dose may be appropriately decided depending upon each particular case while taking into consideration symptom, age, sex, etc. of the patient but usually, is around 0.01 mg/kg to 100 mg/kg per day for adults in the case of oral administration, and that is administered at a time or by dividing into 2 to 4 times a day. When intravenous injection is conducted depending upon the symptom, the dose is usually around 0.001 mg/kg to 10 mg/kg per day for adults, and that is administered at a time or by dividing into two or more times a day.

With regard to a vehicle for the preparation, nontoxic solid or liquid substances for pharmaceuticals may be used.

[0032]

Examples of the solid composition for use by means of oral administration according to the present invention are tablets, pills, capsules, diluted powder and granules. In such a solid composition, one or more active substances are mixed with at least one inert excipient such as lactose, mannitol, glucose, hydroxypropyl cellulose, microcrystalline cellulose, starch, polyvinylpyrrolidone, agar, pectin, magnesium metasilicate aluminate and magnesium aluminate. The composition may also contain additives other than the inert excipient such as lubricant (for example, magnesium stearate), disintegrant (for example, calcium cellulose glycolate), stabilizer (for example, lactose) and auxiliary solubilizer (for example, glutamic acid or aspartic acid) by conventional means. Tablets and pills may,

if necessary, be coated with sugar coat such as sucrose, gelatin, hydroxypropyl cellulose and hydroxypropylmethyl cellulose phthalate or with film of gastric or enteric coating substances.

The liquid composition for oral administration includes pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs and contains commonly used inert excipients such as purified water or ethanol. In addition to the inert excipient, the composition may further contain auxiliary agents such as moisturizing or suspending agents, sweeteners, tasting agents, aromatic agents and antiseptic agents.

The injection for parenteral administration includes aseptic aqueous or non-aqueous solutions, suspensions and emulsions. The non-aqueous solutions and suspensions include, for example, distilled water for injection and a physiological saline solution. Examples of the solvent for non-aqueous solution and suspension are propylene glycol, polyethylene glycol, plant oils (such as cacao butter, olive oil and sesame oil), alcohols (such as ethanol), gum arabic and Polysolvate 80 (trade name). Such a composition may further contain auxiliary agents such as isotonizing agents, antiseptic agents, moisturizing agents, emulsifiers, dispersing agents, stabilizers (for example, lactose) and auxiliary solubilizers (for example, glutamic acid and aspartic acid). These may be sterilized, for example, by filtration passing through a bacteria-preserving filter or by compounding of or irradiation

with a bactericide. These may also be used by manufacturing a sterile solid composition, followed by dissolving in sterile water or a sterile solvent for injection before use.

[0033]

[Examples]

The present invention is further illustrated by way of Examples as hereunder. Compounds of the present invention are not limited to those mentioned in the following Examples but cover all of the compounds represented by the above formula (I), salts thereof, hydrates thereof, geometric and optical isomers thereof and polymorphic forms thereof. Incidentally, the case where the material which is used in the present invention is novel is illustrated by way of the following Referential Example.

[0034]

Referential Example 1

Into a solution of 781 mg of 2-pyrazinylacetonitrile in 30 ml of ethanol was passed hydrochloric acid gas at 55°C for one hour. The solvent was evaporated, and the resulting residue was dissolved in ethyl acetate and a saturated aqueous solution of sodium hydrogen carbonate. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated therefrom. The resulting residue was purified by silica gel column chromatography (eluent: hexane/ethyl acetate = 1/1) to give 941 mg of ethyl 2-(2-pyrazinyl)acetate.

[0035]

Referential Example 2

To a solution of 1.00 g of ethyl 2-(1H-benzimidazol-2-yl)acetate in 30 ml of acetonitrile were added 812 mg of potassium carbonate and 1.21 g of 4-chlorobenzyl bromide, and the reaction mixture was stirred at room temperature for 15 hours. The mixture was filtered, and the solvent was evaporated *in vacuo* from the filtrate. The resulting residue was purified by silica gel column chromatography (eluent: hexane/ethyl acetate = 2/1) to give 464 mg of ethyl [1-(4-chlorobenzyl)-1H-benzimidazol-3-yl]acetate.

[0036]

Referential Example 3

Ethyl 2-(1-benzyl-1H-imidazol-2-yl)acetate hydrochloride (21.4 g) was dissolved in 300 ml of ethanol and 100 ml of tetrahydrofuran, and 4.50 g of 10% palladium-carbon was added to the mixture, followed by stirring for 15 hours in a hydrogen atmosphere under atmospheric pressure. The catalyst was filtered off, and the solvent was evaporated *in vacuo* from the filtrate to give 14.9 g of ethyl 2-(1H-imidazol-2-yl)acetate hydrochloride.

[0037]

Referential Example 4

To 8.80 g of ethyl 2-(1H-imidazol-2-yl)acetate hydrochloride was added 160 ml of 10% hydrochloric acid, and

the mixture was heated to reflux for 50 minutes. The solvent was evaporated *in vacuo* therefrom, and the resulting crystals were washed with 100 ml of acetone and dried to give 6.89 g of 2-(1H-imidazol-2-yl)acetic acid hydrochloride.

[0038]

Referential Example 5

To an ethanolic solution of 1.46 g of ethyl 2-(2-chloropyridin-6-yl)acetate was added 7.5 ml of a 1N aqueous solution of sodium hydroxide at room temperature. The mixture was stirred at room temperature, and 7.5 ml of 1N hydrochloric acid was added thereto. An aqueous solution obtained by evaporation of ethanol was extracted with ethyl acetate. The resulting organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated therefrom to give 1.07 g of 2-(2-chloropyridin-6-yl)acetic acid.

[0039]

The compounds of Referential Examples 6 and 7 were prepared by the same manner as mentioned in Referential Example 5; and the compound of Referential Example 8 was prepared by the same manner as mentioned in Referential Example 4.

Referential Example 6

2-(2-Acetylaminothiazol-2-yl)acetic acid

Referential Example 7

2-(3-Benzyl-2-thioxathiazol-4-yl)acetic acid

Referential Example 8

2-Methyl-2-(2-aminothiazol-4-yl)propionic acid hydrochloride

[0040]

Referential Example 9

To a solution of 1.18 g of guanyl thiourea in 20 ml of methanol was added 1.65 g of methyl 4-chloroacetoacetate. The mixture was heated to reflux for four hours, the solvent was concentrated, and the concentrate was crushed by adding ethyl acetate thereto. The powder obtained by filtering off the solvent was washed with ethyl acetate and dried to give 2.25 g of methyl 2-(2-guanidinothiazol-4-yl)acetate.

[0041]

The compounds of Referential Examples 10 and 12 were prepared by the same manner as in Referential Example 4; and the compound of Referential Example 11 was prepared by the same manner as mentioned in Referential Example 9.

Referential Example 10

2-(2-Guanidinothiazol-2-yl)acetic acid hydrochloride

Referential Example 11

Ethyl 2-[2-(3-fluoroanilino)thiazol-4-yl]acetate

Referential Example 12

2-[2-(3-Fluoroanilino)thiazol-4-yl]acetic acid hydrochloride

[0042]

Referential Example 13

To a solution of 0.96 g of ethyl 3-oxovalerate in 4 ml of acetic acid was added 2.1 g of pyridinium tribromide. The mixture was stirred at room temperature for three hour, then diethyl ether and water were added thereto, and the organic layer was washed with water and a saturated saline solution. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated therefrom to give 1.24 g of a crude bromine compound. To a solution of 1.24 g of the crude bromine compound in ethanol was added 0.5 g of thiourea. After heating to reflux for 12 hours, the solvent was concentrated, and the concentrate was recrystallized from ethanol-ethyl acetate to give 1.05 g of ethyl 2-(2-amino-5-methylthiazol-4-yl)acetate.

[0043]

The compound of Referential Example 14 was prepared by the same manner as in Referential Example 4.

Referential Example 14

2-(2-Amino-5-methylthiazol-4-yl)acetic acid hydrochloride

Referential Example 15

To a solution of 0.8 g of methyl 2-(5-sulfanyl-1H-1,2,4-triazol-3-yl)acetate in 16 ml of acetonitrile were added 0.79 g of benzyl bromide and 1.5 g of cesium carbonate. The mixture was stirred at room temperature for 30 minutes, insoluble matters were filtered off, and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel

column chromatography (eluent: chloroform/methanol = 50/1) to give 0.79 g of ethyl 2-(5-benzylsulfanyl-1H-1,2,4-triazol-3-yl)acetate.

[0044]

The compounds of Referential Examples 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47 and 49 were prepared by the same manner as in Referential Example 2; and the compounds of Referential Examples 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48 and 50 were prepared by the same manner as in Referential Example 4.

Referential Example 16

2-(5-Benzylsulfanyl-1H-1,2,4-triazol-3-yl)acetic acid hydrochloride

Referential Example 17

Ethyl 2-[1-(4-fluorobenzyl)-1H-imidazol-2-yl]acetate

Referential Example 18

2-[1-(4-Fluorobenzyl)-1H-imidazol-2-yl]acetic acid hydrochloride

Referential Example 19

Ethyl 2-[1-(4-chlorobenzyl)-1H-imidazol-2-yl]acetate

Referential Example 20

2-[1-(4-Chlorobenzyl)-1H-imidazol-2-yl]acetic acid hydrochloride

[0045]

Referential Example 21

Ethyl 2-[1-(3-chlorobenzyl)-1H-imidazol-2-yl]acetate

Referential Example 22

2-[1-(3-Chlorobenzyl)-1H-imidazol-2-yl]acetic acid hydrochloride

Referential Example 23

Ethyl 2-[1-(2-chlorobenzyl)-1H-imidazol-2-yl]acetate

Referential Example 24

2-[1-(2-Chlorobenzyl)-1H-imidazol-2-yl]acetic acid hydrochloride

Referential Example 25

Ethyl 2-[1-(3,4-dichlorobenzyl)-1H-imidazol-2-yl]-acetate

Referential Example 26

2-[1-(3,4-Dichlorobenzyl)-1H-imidazol-2-yl]acetic acid hydrochloride

Referential Example 27

Ethyl 2-[1-(4-bromobenzyl)-1H-imidazol-2-yl]acetate

Referential Example 28

2-[1-(4-Bromobenzyl)-1H-imidazol-2-yl]acetic acid hydrochloride

Referential Example 29

Ethyl 2-[1-(4-iodobenzyl)-1H-imidazol-2-yl]acetate

Referential Example 30

2-[1-(4-Iodobenzyl)-1H-imidazol-2-yl]acetic acid hydrochloride

[0046]

Referential Example 31

Ethyl 2-[1-(4-trifluoromethylbenzyl)-1H-imidazol-2-yl]acetate

Referential Example 32

2-[1-(4-Trifuoromethylbenzyl)-1H-imidazol-2-yl]acetic acid hydrochloride

Referential Example 33

Ethyl 2-[1-(4-isopropylbenzyl)-1H-imidazol-2-yl]-acetate

Referential Example 34

2-[1-(4-Isopropylbenzyl)-1H-imidazol-2-yl]acetic acid hydrochloride

Referential Example 35

Ethyl 2-[1-(4-phenylbenzyl)-1H-imidazol-2-yl]acetate

Referential Example 36

2-[1-(4-Phenylbenzyl)-1H-imidazol-2-yl]acetic acid hydrochloride

Referential Example 37

Ethyl 2-[1-(2-naphthyl)-1H-imidazol-2-yl]acetate

Referential Example 38

2-[1-(2-Naphthyl)-1H-imidazol-2-yl]acetic acid hydro-chloride

Referential Example 39

Ethyl 2-[1-(2-pyridyl)methyl-1H-imidazol-2-yl]acetate

Referential Example 40

2-[1-(2-Pyridyl)methyl-1H-imidazol-2-yl]acetic acid hydrochloride

[0047]

Referential Example 41

Ethyl 2-[1-(2-methyl-2-propenyl)-1H-imidazol-2-yl]-acetate

Referential Example 42

2-[1-(2-Methyl-2-propenyl)-1H-imidazol-2-yl]acetic acid hydrochloride

Referential Example 43

Ethyl 2-[1-benzyl-1H-imidazol-4-yl]acetate

Referential Example 44

2-(1-Benzyl-1H-imidazol-4-yl)acetic acid hydrochloride

Referential Example 45

Ethyl 2-[1-(2-chlorobenzyl)-1H-imidazol-4-yl]acetate

Referential Example 46

2-[1-(2-Chlorobenzyl)-1H-imidazol-4-yl]acetic acid hydrochloride

Referential Example 47

Ethyl 2-[1-(3-chlorobenzyl)-1H-imidazol-4-yl]acetate

Referential Example 48

2-[1-(3-chlorobenzyl)-1H-imidazol-4-yl]acetic acid hydrochloride

Referential Example 49

Ethyl 2-[1-(4-chlorobenzyl)-1H-imidazol-4-yl]acetate

Referential Example 50

2-[1-(4-Chlorobenzyl)-1H-imidazol-4-yl]acetic acid hydrochloride

[0048]

Referential Example 51

To a solution of 0.66 g of ethyl 2-(1H-1,2,4-triazol-3-yl)acetate in 10 ml of acetonitrile were added 0.59 g of potassium carbonate and 0.73 g of benzyl bromide. The mixture was heated to reflux for two hours, insoluble matters were filtered off, and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (eluent: hexane/ethyl acetate = 3/2) to give 289 mg of ethyl 2-(2-benzyl-1H-1,2,4-triazol-3-yl)acetate (Referential Example 51a) and 311 mg of ethyl 2-(1-benzyl-1H-1,2,4-triazol-3-yl)acetate (Referential Example 51b).

[0049]

The compounds of Referential Examples 52 and 53 were prepared by the same manner as in Referential Example 4.

Referential Example 52

2-(2-Benzyl-1H-1,2,4-triazol-3-yl)acetic acid hydrochloride

Referential Example 53

2-(1-Benzyl-1H-1,2,4-triazol-3-yl)acetic acid hydrochloride

[0050]

The compounds of Referential Examples 54(a) and 54(b) were prepared by the same manner as in Referential Example 51.

Referential Example 54(a)

Ethyl 2-[1-(4-fluorobenzyl)-1H-tetrazol-5-yl]acetate

Referential Example 54(b)

Ethyl 2-[2-(4-fluorobenzyl)-1H-tetrazol-5-yl]acetate

[0051]

The compounds of Referential Examples 55 and 56 were prepared by the same manner as in Referential Example 5.

Referential Example 55

2-[1-(4-Fluorobenzyl)-1H-tetrazol-5-yl]acetic acid

Referential Example 56

2-[2-(4-Fluorobenzyl)-1H-tetrazol-5-yl]acetic acid

[0052]

The compounds of Referential Examples 57(a) and 57(b) were prepared by the same manner as in Referential Example 51.

Referential Example 57(a)

Ethyl 2-[1-(3,4-dichlorobenzyl)-1H-tetrazol-5-yl]-acetate

Referential Example 57(b)

Ethyl 2-[2-(3,4-dichlorobenzyl)-1H-tetrazol-5-yl]-acetate

[0053]

The compounds of Referential Examples 58 and 59 were prepared by the same manner as in Referential Example 5.

Referential Example 58

2-[1-(3,4-Dichlorobenzyl)-1H-tetrazol-5-yl]acetic acid

Referential Example 59

2-[2-(3,4-Dichlorobenzyl)-1H-tetrazol-5-yl]acetic acid

[0054]

Referential Example 60

Into a mixture of 3.67 g of 1-phenyl-2-methyl-1H-imidazole with 50 ml of acetonitrile and 6.50 ml of triethylamine was dropped 4.40 ml of ethyl chloroformate with ice cooling and stirring in an argon atmosphere. After 2.5 hours, water and ethyl acetate were added to the reaction mixture, and the organic layer was washed with a saturated saline solution and dried over anhydrous magnesium sulfate. The solvent was evaporated, and the residue was purified by silica gel column chromatography (eluent: chloroform/methanol = 50/1) to give 2.26 g of ethyl 2-(1-phenyl-1H-imidazol-2-yl)acetate.

[0055]

The compounds of Referential Examples 61, 63 and 65 were prepared by the same manner as in Referential Example 4; and the compounds of Referential Examples 60 and 64 were prepared by the same manner as in Referential Example 60.

Referential Example 61

2-(1-Phenyl-1H-imidazol-2-yl)acetic acid hydrochloride

Referential Example 62

Ethyl 2-[1-(4-nitrobenzyl)-1H-imidazol-2-yl]acetate

Referential Example 63

2-[1-(4-Nitrobenzyl)-1H-imidazol-2-yl]acetic acid hydrochloride

Referential Example 64

Ethyl 2-[1-(2-phenylethyl)-1H-imidazol-2-yl]acetate

Referential Example 65

2-[1-(2-Phenylethyl)-1H-imidazol-2-yl]acetic acid hydrochloride

[0056]

Referential Example 66

Into a mixture of 3.69 g of 2,4-dimethyl-1H-imidazole, 4.27 g of triethylamine and 25 ml of acetonitrile was dropped 3.00 g of acetyl chloride with ice cooling and stirring. The reaction mixture was stirred at room temperature for 15 minutes, insoluble matters were filtered off, and the solvent was evaporated *in vacuo*. To the residue were added 7.11 g of 4-fluorobenzyl bromide and 30 ml of acetonitrile, and the mixture was heated to reflux for 3.5 hours. The solvent was evaporated *in vacuo*, ethanol and ethyl acetate were added to the residue, and the deposited crystals were collected by filtration and washed with ethyl acetate. To the resulting

crystals were added 100 ml of chloroform and 40 ml of a 0.5N aqueous solution of sodium hydroxide, and the organic layer was washed with a saturated saline solution and dried over anhydrous magnesium sulfate. The solvent was evaporated *in vacuo* to give 3.40 g of 1-(4-fluorobenzyl)-2,5-dimethyl-1H-imidazole.

[0057]

The compounds of Referential Examples 67 and 68 were prepared by the same manner as in Referential Examples 60 and 4, respectively.

Referential Example 67

Ethyl 2-[1-(4-fluorobenzyl)-5-methyl-1H-imidazol-2-yl]acetate

Referential Example 68

2-[1-(4-Fluorobenzyl)-5-methyl-1H-imidazol-2-yl]-acetic acid hydrochloride

[0058]

Referential Example 69

To a solution of 1.00 g of 2,4-dimethyl-1H-imidazole in 10 ml of dimethyl formamide was added 1.30 g of potassium tert-butoxide with stirring at room temperature. Into the mixture was dropped 2.20 g of 4-fluorobenzyl bromide, followed by stirring for one hour. After insoluble matters were filtered off, the solvent was evaporated *in vacuo*, and ethyl acetate and water were added to the residue. The organic layer was washed with a saturated saline solution and dried over anhydrous

magnesium sulfate. The solvent was evaporated *in vacuo*, and the residue was purified by silica gel column chromatography (eluent: chloroform/methanol = 50/1) to give 1.17 g of 1-(4-fluorobenzyl)-2,4-dimethyl-1H-imidazole.

[0059]

The compounds of Referential Examples 70 and 71 were prepared by the same manner as in Referential Examples 60 and 4, respectively.

Referential Example 70

Ethyl 2-[1-(4-fluorobenzyl)-4-methyl-1H-imidazol-2-yl]acetate

Referential Example 71

2-[1-(4-Fluorobenzyl)-4-methyl-1H-imidazol-2-yl]-acetic acid hydrochloride

[0060]

Referential Example 72

Into a solution of 3.11 g of 2-benzyloxy-6-methylpyridine in 50 ml of tetrahydrofuran was dropped 16 ml of 1.03M sec-butyl lithium/cyclohexane at -78°C. Then, 0.95 ml of diethyl carbonate was added thereto at -78°C, the dry ice-methanol bath was removed, and the reaction solution was stirred until it rose to room temperature. The solvent was evaporated, and the residue was diluted with water and extracted with ethyl acetate. The resulting organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated. The resulting residue

was purified by silica gel column chromatography (eluent: hexane/ethyl acetate = 10/1) to give ethyl 2-(2-benzyloxypyridin-6-yl)acetate.

[0061]

The compounds of Referential Examples 73 and 75 were prepared by the same manner as in Referential Example 5; and the compound of Referential Example 74 was prepared by the same manner as in Referential Example 72.

Referential Example 73

2-(2-Benzyloxypyridin-6-yl)acetic acid

Referential Example 74

Ethyl 2-(2-tert-butoxycarbonylaminopyridin-6-yl)-acetate

Referential Example 75

2-(2-tert-Butoxycarbonylaminopyridin-6-yl)acetic acid

[0062]

Referential Example 76

Into a solution of 3.11 g of 5,6,7,8-tetrahydroquinoline in 15 ml of tetrahydrofuran was dropped 15 ml of 1.59M n-butyl lithium/hexane at not higher than -65°C. Then, 1.4 ml of diethyl carbonate was added thereto at -70°C, the dry ice-methanol bath was removed, and the reaction solution was stirred until it rose to room temperature. To the reaction solution were added water and ethyl acetate successively. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was

evaporated therefrom. The resulting residue was purified by silica gel column chromatography (eluent: hexane/ethyl acetate = 2/1) to give 3.0 g of a mixture of ethyl 8-(5,6,7,8-tetrahydro-quinoline)carboxylate and 5,6,7,8-tetrahydro-quinoline. To an ethanolic solution of 1.02 g of this mixture was added 5 ml of a 1N aqueous sodium hydroxide solution at room temperature. The reaction solution was stirred at room temperature for 12 hours, and the reaction solution was washed with diethyl ether twice to remove the 5,6,7,8-tetrahydro-quinoline. The reaction mixture was neutralized by adding 1N hydrochloric acid thereto, and the solvent was evaporated to give 750 mg of 8-(5,6,7,8-tetrahydroquinoline)carboxylic acid.

[0063]

Referential Example 77

To a mixed solution of ethyl acetate and a 1N aqueous solution of sodium hydroxide was added 25.2 g of 4-nitrophenyl ethylamine hydrochloride, and the mixture was vigorously stirred. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated. To the resulting residue were added 100 ml of 2-propanol and 15.0 g of (R)-styrene oxide successively, and the reaction mixture was heated to reflux for 12 hours. The solvent was evaporated *in vacuo*, and the residue was purified by silica gel column chromatography (eluent: chloroform/methanol = 100/1 → 10/1). The resulting residue was again subjected to silica gel column chromatography

(eluent: hexane/ethyl acetate/triethylamine = 1/5/trace) to give 8.05 g of (R)-1-phenyl-2-[[2-(4-nitrophenyl)ethyl]-amino]ethanol.

[0064]

Referential Example 78

A solution of 6.30 g of (R)-1-phenyl-2-[[2-(4-nitrophenyl)ethyl]amino]ethanol and 6.30 g of di-tert-butyl dicarbonate in 80 ml of tetrahydrofuran was stirred for 12 hours at room temperature. The residue obtained by evaporation of the solvent was purified by silica gel column chromatography (eluent: hexane/ethyl acetate = 3/1) to give 10.8 g of tert-butyl (R)-N-(2-hydroxy-2-phenylethyl)-N-[2-(4-nitrophenyl)ethyl]-carbamate.

[0065]

Referential Example 79

To a solution of tert-butyl (R)-N-(2-hydroxy-2-phenylethyl)-N-[2-(4-nitrophenyl)ethyl]carbamate in 200 ml of ethanol was added 1.03 g of 10% palladium-carbon and the mixture was stirred for two hours at room temperature in a hydrogen atmosphere under atmospheric pressure. Insoluble matters were removed using Celite, and the filtrate was concentrated *in vacuo* to give 9.54 g of tert-butyl (R)-N-[2-(4-aminophenyl)-N-(2-hydroxy-2-phenylethyl)ethyl]carbamate.

[0066]

Referential Example 80

To a solution of 7.62 g of (R)-mandelic acid in 100 ml of dimethylformamide were added 10.15 g of 4-nitrophenethylamine hydrochloride, 7.11 g of 1-hydroxybenzotriazole, 7.3 ml of triethylamine and 1.01 g of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, and the reaction mixture was stirred at room temperature for 18 hours. To the mixture were added water and ethyl acetate, and the organic layer was washed with 1N hydrochloric acid, a saturated aqueous solution of sodium hydrogen carbonate, water and a saturated saline solution successively and dried over anhydrous magnesium sulfate. The solvent was evaporated to give 14.94 g of (R)-2-hydroxy-N-[(2-(4-nitrophenyl)ethyl]-2-phenylacetamide.

[0067]

Referential Example 81

To a solution of 14.94 g of (R)-2-hydroxy-N-[(2-(4-nitrophenyl)ethyl]-2-phenylacetamide in 80 ml of tetrahydrofuran was added 15.4 ml of a 10M borane-methyl sulfide complex, and the mixture was heated to reflux for 1.5 hours. This was cooled down to room temperature, stirred for one hour after addition of 20 ml of methanol, then 150 ml of 1N hydrochloride acid was added, and the mixture was heated to reflux for one hour. To the residue obtained by concentrating the solvent *in vacuo* were added 200 ml of 1N sodium hydroxide

and ethyl acetate, and the organic layer was washed with water and a saturated saline solution successively and dried over anhydrous magnesium sulfate. The solvent was evaporated *in vacuo*, the residue was dissolved in 100 ml of ethanol, and 12.3 ml of a 4N hydrogen chloride-ethyl acetate solution was added thereto. The deposited crystals were filtered to give 12.13 g of (R)-2-[2-(4-nitrophenyl)ethylamine]-1-phenylethanol hydrochloride.

[0068]

Referential Example 82

To a solution of 448 mg of tert-butyl (R)-N-[2-(4-aminophenyl)-N-(2-hydroxy-2-phenylethyl)ethyl]carbamate and 330 mg of triethylamine in 4 ml of chloroform was added 146 mg of 2-pyridinecarbonyl chloride. The reaction solution was stirred at room temperature for two hours, and the solvent was evaporated *in vacuo*. The residue was diluted with chloroform, and the organic layer was washed with a saturated aqueous solution of sodium hydrogen carbonate and dried over anhydrous magnesium sulfate. The residue obtained by evaporating the solvent *in vacuo* was purified by silica gel column chromatography (eluent: hexane/ethyl acetate = 1/3) to give 321 mg of tert-butyl (R)-N-(2-hydroxy-2-phenylethyl)-N-[2-[4-[(2-pyridinecarbonyl)amino]phenyl]ethyl]carbamate.

[0069]

The compound of Referential Example 83 was prepared by the same manner as in Referential Example 82.

Referential Example 83

tert-Butyl (R)-N-(2-hydroxy-2-phenylethyl)-N-[2-[4-[(3-pyridinecarbonyl)amino]phenyl]ethyl]carbamate

Referential Example 84

To a solution of 377 mg of tert-butyl (R)-N-[2-(4-aminophenyl)-N-(2-hydroxy-2-phenylethyl)ethyl]carbamate in 10 ml of tetrahydrofuran were added 203 mg of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, 143 mg of 1-hydroxybenzotriazole and 202 mg of 8-quinolinecarboxylic acid successively. The reaction solution was stirred at room temperature for 18.5 hours, and the solvent was evaporated *in vacuo*. The residue was diluted with ethyl acetate, and the organic layer was washed with a saturated aqueous solution of sodium hydrogen carbonate and dried over anhydrous magnesium sulfate. The residue obtained by evaporation of the solvent was purified by silica gel column chromatography (eluent: hexane/ethyl acetate = 2/1) to give 302 mg of tert-butyl (R)-N-(2-hydroxy-2-phenylethyl)-N-[2-[4-[(8-quinoline-carbonyl)amino]phenyl]ethyl]carbamate.

[0070]

The compounds of Referential Examples 85 to 139 were prepared by the same manner as in Referential Example 84.

Referential Example 85

tert-Butyl (R)-N-(2-hydroxy-2-phenylethyl)-(E)-N-[2-[4-[3-(2-pyridyl)acryloylamino]phenyl]ethyl]carbamate

Referential Example 86

tert-Butyl (R)-N-[2-[4-[(2-benzothiazol-2-ylacetyl)-amino]phenyl]ethyl]-N-(2-hydroxy-2-phenylethyl)carbamate

Referential Example 87

tert-Butyl (R)-N-(2-hydroxy-2-phenylethyl)-N-[2-[4-[[2-(imidazo[2,1-b]thiazol-3-yl)acetyl]amino]phenyl]ethyl]-carbamate

Referential Example 88

tert-Butyl (R)-N-(2-hydroxy-2-phenylethyl)-N-[2-[4-[2-(2-methylthiazol-4-yl)acetylamino]phenyl]ethyl]carbamate

Referential Example 89

tert-Butyl (R)-N-(2-hydroxy-2-phenylethyl)-N-[2-[4-[2-(1H-imidazol-2-yl)acetamino]phenyl]ethyl]carbamate

Referential Example 90

tert-Butyl (R)-N-(2-hydroxy-2-phenylethyl)-N-[2-[4-[(2-1H-tetrazol-5-yl)acetamino]phenyl]ethyl]carbamate

Referential Example 91

tert-Butyl (R)-N-(2-hydroxy-2-phenylethyl)-N-[2-[4-[2-(5-sulfanyl-1H-1,2,4-triazol-3-yl)acetylamino]phenyl]-ethyl]carbamate

Referential Example 92

tert-Butyl (R)-N-[2-[4-[[2-(2-aminothiazol-4-yl)-2-oxoacetyl]amino]phenyl]ethyl]-N-(2-hydroxy-2-phenylethyl)-carbamate

Referential Example 93

tert-Butyl (R)-N-[2-[4-[2-(5-amino-1,2,4-thiadiazol-3-yl)acetylamino]phenyl]ethyl]-N-(2-hydroxy-2-phenylethyl)-carbamate

Referential Example 94

tert-Butyl (R)-N-[2-[4-[2-(5-ethoxycarbonylamino-1,2,4-thiadiazol-3-yl)acetylamino]phenyl]ethyl]-N-(2-hydroxy-2-phenylethyl)carbamate

Referential Example 95

tert-Butyl (R)-N-[2-[4-[2-[(3-fluorophenylamino)-thiazol-4-yl]acetylamino]phenyl]ethyl]-N-(2-hydroxy-2-phenylethyl)carbamate

Referential Example 96

tert-Butyl (R)-N-[2-[4-[2-[(2-chloropyridin-6-yl)-acetyl]amino]phenyl]ethyl]-N-(2-hydroxy-2-phenylethyl)-carbamate

Referential Example 97

tert-Butyl (R)-N-[2-[4-[[2-(2-benzyloxypyridin-6-yl)-acetyl]amino]phenyl]ethyl]-N-(2-hydroxy-2-phenylethyl)-carbamate

Referential Example 98

tert-Butyl (R)-N-(2-hydroxy-2-phenylethyl)-N-[2-[4-[2-[1-(2-methyl-3-propenyl)-1H-imidazol-2-yl)acetamino]-phenyl]ethyl]carbamate

Referential Example 99

tert-Butyl (R)-N-[2-[4-[2-(1-benzyl-1H-imidazol-4-yl)acetylamino]phenyl]ethyl]-N-(2-hydroxy-2-phenylethyl)-carbamate

Referential Example 100

tert-Butyl (R)-N-[2-[4-[2-[1-(2-chlorobenzyl)-1H-imidazol-4-yl]acetylamino]phenyl]ethyl]-N-(2-hydroxy-2-phenylethyl)carbamate

[0071]

Referential Example 101

tert-Butyl (R)-N-[2-[4-[2-[1-(3-chlorobenzyl)-1H-imidazol-4-yl]acetylamino]phenyl]ethyl]-N-(2-hydroxy-2-phenylethyl)carbamate

Referential Example 102

tert-Butyl (R)-N-[2-[4-[2-[1-(4-chlorobenzyl)-1H-imidazol-4-yl]acetylamino]phenyl]ethyl]-N-(2-hydroxy-2-phenylethyl)carbamate

Referential Example 103

tert-Butyl (R)-N-[2-[4-[2-[1-(4-fluorobenzyl)-1H-imidazol-2-yl]acetamino]phenyl]ethyl]-N-(2-hydroxy-2-phenylethyl)carbamate

Referential Example 104

tert-Butyl (R)-N-[2-[4-[2-[1-(4-chlorobenzyl)-1H-imidazol-2-yl]acetamino]phenyl]ethyl]-N-(2-hydroxy-2-phenylethyl)carbamate

Referential Example 105

tert-Butyl (R)-N-[2-[4-[2-[1-(4-bromobenzyl)-1H-imidazol-2-yl]acetamino]phenyl]ethyl]-N-(2-hydroxy-2-phenylethyl)carbamate

Referential Example 106

tert-Butyl (R)-N-(2-hydroxy-2-phenylethyl)-N-[2-[4-[2-[1-(4-iodobenzyl)-1H-imidazol-2-yl]acetamino]phenyl]-ethyl]carbamate

Referential Example 107

tert-Butyl (R)-N-(2-hydroxy-2-phenylethyl)-N-[2-[4-[2-[1-(4-trifluoromethylbenzyl)-1H-imidazol-2-yl]-acetamino]phenyl]ethyl]carbamate

Referential Example 108

tert-Butyl (R)-N-(2-hydroxy-2-phenylethyl)-N-[2-[4-[2-[1-(2-naphthyl)-1H-imidazol-2-yl]acetamino]phenyl]-ethyl]carbamate

Referential Example 109

tert-Butyl (R)-N-[2-[4-[2-[3-(4-fluorobenzyl)-4-methyl-1H-imidazol-2-yl]acetamino]phenyl]ethyl]-N-(2-hydroxy-2-phenylethyl)carbamate

Referential Example 110

tert-Butyl (R)-N-[2-[4-[2-[1-(4-fluorobenzyl)-4-methyl-1H-imidazol-2-yl]acetamino]phenyl]ethyl]-N-(2-hydroxy-2-phenylethyl)carbamate

[0072]

Referential Example 111

tert-Butyl (R)-N-[2-[4-[2-[1-(4-fluoromobenzyl)-1H-tetrazol-5-yl]acetamino]phenyl]ethyl]-N-(2-hydroxy-2-phenylethyl)carbamate

Referential Example 112

tert-Butyl (R)-N-[2-[4-[2-[2-(3,4-dichlorobenzyl)-1H-tetrazol-5-yl]acetamino]phenyl]ethyl]-N-(2-hydroxy-2-phenylethyl)carbamate

Referential Example 113

tert-Butyl (R)-N-[2-[4-[2-[2-(4-fluorobenzyl)-1H-tetrazol-5-yl]acetamino]phenyl]ethyl]-N-(2-hydroxy-2-phenylethyl)carbamate

Referential Example 114

tert-Butyl (R)-N-[2-[4-[2-[2-(3,4-dichlorobenzyl)-1H-tetrazol-5-yl]acetamino]phenyl]ethyl]-N-(2-hydroxy-2-phenylethyl)carbamate

Referential Example 115

tert-Butyl (R)-N-[2-[4-[2-(1H-1,2,4-triazol-3-yl]-acetylamino]phenyl]ethyl]-N-(2-hydroxy-2-phenylethyl)-carbamate

Referential Example 116

tert-Butyl (R)-N-[2-[4-[2-(5-benzylsulfanyl-1H-1,2,4-triazol-3-yl]acetylamino]phenyl]ethyl]-N-(2-hydroxy-2-phenylethyl)carbamate

Referential Example 117

tert-Butyl (R)-N-[2-[4-[2-(2-acetamidothiazol-4-yl)-acetylamino]phenyl]ethyl]-N-(2-hydroxy-2-phenylethyl)-carbamate

Referential Example 118

tert-Butyl (R)-N-(2-hydroxy-2-phenylethyl)-N-[2-[4-[2-(2-methanesulfonamidothiazol-4-yl]acetylamino]phenyl]-ethyl]carbamate

Referential Example 119

tert-Butyl (R)-N-[2-[4-[2-(2-guanidinothiazol-4-yl)-acetylamino]phenyl]ethyl]-N-(2-hydroxy-2-phenylethyl)-carbamate

Referential Example 120

tert-Butyl (R)-N-(2-hydroxy-2-phenylethyl)-N-[2-[4-[2-[1-(2-phenylaminothiazol-4-yl)]acetamino]phenyl]ethyl]-carbamate

[0073]

Referential Example 121

tert-Butyl (R)-N-(2-hydroxy-2-phenylethyl)-N-[2-[4-[2-[1-(4-nitrobenzyl)-1H-imidazol-2-yl]acetamino]phenyl]-ethyl]carbamate

Referential Example 122

tert-Butyl (R)-N-[2-[4-[2-(2-aminothiazol-4-yl)-acetamino]phenyl]ethyl]-N-(2-hydroxy-2-phenylethyl)-carbamate

Referential Example 123

tert-Butyl (R)-N-[2-[4-[(2-aminothiazol-4-yl)-carboxyamino]phenyl]ethyl]-N-(2-hydroxy-2-phenylethyl)-carbamate

Referential Example 124

tert-Butyl (R)-N-[2-[4-[2-(2-amino-5-methylthiazol-4-yl)acetylamino]phenyl]ethyl]-N-(2-hydroxy-2-phenylethyl)-carbamate

Referential Example 125

tert-Butyl (R)-N-[2-[4-[2,2-dimethyl-2-(2-amino-thiazol-4-yl)acetylamino]phenyl]ethyl]-N-(2-hydroxy-2-phenylethyl)carbamate

Referential Example 126

tert-Butyl (R)-N-[2-[4-[(2-amino-4,5,6,7-tetrahydro-benzothiazol-4-yl)carboxyamino]phenyl]ethyl]-N-(2-hydroxy-2-phenylethyl)carbamate

Referential Example 127

tert-Butyl (R)-N-(2-hydroxy-2-phenylethyl)-N-[2-[4-[[2-(imidazo[2,1-b]thiazol-6-yl)acetyl]amino]phenyl]ethyl]-carbamate

Referential Example 128

tert-Butyl (R)-N-[2-[4-[2-(2-benzyl-1,2,4-triazol-3-yl)acetylamino]phenyl]ethyl]-N-(2-hydroxy-2-phenylethyl)-carbamate

Referential Example 129

tert-Butyl (R)-N-[2-[4-[2-(1-benzyl-1,2,4-triazol-3-yl)acetylamino]phenyl]ethyl]-N-(2-hydroxy-2-phenylethyl)-carbamate

Referential Example 130

tert-Butyl (R)-N-[2-[4-[2-(3-benzyl-2-thioxothiazol-4-yl)acetylamino]phenyl]ethyl]-N-(2-hydroxy-2-phenylethyl)-carbamate

[0074]

Referential Example 131

tert-Butyl (R)-N-(2-hydroxy-2-phenylethyl)-N-[2-[4-[[(5,6,7,8-tetrahydroquinolin-8-yl)carbonyl]amino]phenyl]-ethyl]carbamate

Referential Example 132

tert-Butyl (R)-N-(2-hydroxy-2-phenylethyl)-N-[2-[4-[2-[(1-phenyl)-1H-imidazol-2-yl]acetamino]phenyl]ethyl]-carbamate

Referential Example 133

tert-Butyl (R)-N-(2-hydroxy-2-phenylethyl)-N-[2-[4-[2-[1-(4-isopropylbenzyl)-1H-imidazol-2-yl]acetamino]-phenyl]ethyl]carbamate

Referential Example 134

tert-Butyl (R)-N-(2-hydroxy-2-phenylethyl)-N-[2-[4-[2-[1-(4-phenylbenzyl)-1H-imidazol-2-yl]acetamino]phenyl]-ethyl]carbamate

Referential Example 135

tert-Butyl (R)-N-[2-[4-[2-[1-(2-chlorobenzyl)-1H-imidazol-2-yl]acetylamino]phenyl]ethyl]-N-(2-hydroxy-2-phenylethyl)carbamate

Referential Example 136

tert-Butyl (R)-N-[2-[4-[2-[1-(3-chlorobenzyl)-1H-imidazol-2-yl]acetylamino]phenyl]ethyl]-N-(2-hydroxy-2-phenylethyl)carbamate

Referential Example 137

tert-Butyl (R)-N-[2-[4-[2-[1-(3,4-dichlorobenzyl)-1H-imidazol-2-yl]acetylamino]phenyl]ethyl]-N-(2-hydroxy-2-phenylethyl)carbamate

Referential Example 138

tert-Butyl (R)-N-(2-hydroxy-2-phenylethyl)-N-[2-[4-[2-[1-(2-pyridyl)methyl-1H-imidazol-2-yl]acetylamino]-phenyl]ethyl]carbamate

Referential Example 139

tert-Butyl (R)-N-[2-[4-[[2-[2-(tert-butoxycarbonyl-amino)pyridin-6-yl]acetyl]amino]phenyl]ethyl]-N-(2-hydroxy-2-phenylethyl)carbamate

[0075]

Referential Example 140

To a solution of 1.1 g of tert-butyl (R)-N-[2-[4-[[2-[2-(tert-butoxycarbonylamino)pyridin-6-yl]acetylamino]-phenyl]ethyl]-N-(2-hydroxy-2-phenylethyl)carbamate in 10 ml of methanol was added 20 ml of a 4N hydrogen chloride-ethyl acetate solution. The reaction solution was stirred at room temperature for two hours. The solvent was evaporated, and to the resulting residue were added 5.2 g of triethylamine, 2.2 g of di-tert-butyl carbonate, 15 ml of tetrahydrofuran and 1 ml of methanol, and the mixture was stirred for 13 hours. The reaction mixture was diluted with ethyl acetate and washed with a saturated aqueous solution of sodium chloride and a saturated aqueous solution of sodium hydrogen carbonate successively. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated *in vacuo*. The resulting residue was purified by silica gel column chromatography (eluent: chloroform/methanol = 100/1) to give 260 mg of tert-butyl (R)-N-[2-[4-[[2-(2-aminopyridin-6-yl)acetyl]amino]phenyl]-ethyl]-N-(2-hydroxy-2-phenylethyl)carbamate.

[0076]

Referential Example 141

tert-butyl (R)-N-(2-hydroxy-2-phenylethyl)-N-[2-[4-[2-[1-(2-methyl-2-propenyl)-1H-imidazol-2-yl]acetamino]-phenyl]ethyl]carbamate (314 mg) was dissolved in 15 ml of ethanol, 90 mg of 10% palladium-carbon was added, and the mixture

was stirred for 5.5 hours in a nitrogen atmosphere under atmospheric pressure. The catalyst was filtered off, the solvent was evaporated *in vacuo*, and the residue was purified by silica gel column chromatography (eluent: chloroform/methanol = 30/1) to give 230 mg of tert-butyl (R)-N-[(2-hydroxy-2-phenyl)ethyl]-N-[2-[4-[1-(2-methyl-propyl)-1H-imidazol-2-yl]acetamino]phenyl]ethyl]carbamate.

[0077]

Referential Example 142

To a solution of 403 mg of tert-butyl (R)-N-(2-hydroxy-2-phenylethyl)-N-[2-[4-[(2-1H-imidazol-2-ylacetyl)-amino]phenyl]ethyl]carbamate in 10 ml of acetonitrile were added 120 mg of potassium carbonate and 164 mg of 2-fluorobenzyl bromide successively at room temperature. The reaction solution was stirred at 50°C for 12 hours. Insoluble matters were filtered off using Celite, and the solvent was evaporated. The resulting residue was purified by silica gel column chromatography to give 253 mg of tert-butyl (R)-N-[2-[4-[[2-[1-(2-fluorobenzyl)-1H-imidazol-2-yl]acetyl]amino]-phenyl]ethyl]-N-(2-hydroxy-2-phenylethyl)carbamate.

[0078]

The compounds of Referential Examples 143 to 162 were prepared by the same manner as in Referential Example 142.

Referential Example 143

tert-Butyl (R)-N-[2-[4-[2-[1-(3-fluorobenzyl)-1H-imidazol-2-yl]acetamino]phenyl]ethyl]-N-(2-hydroxy-2-phenylethyl)carbamate

Referential Example 144

tert-Butyl (R)-N-[2-[4-[2-[1-(2,4-difluorobenzyl)-1H-imidazol-2-yl]acetylamino]phenyl]ethyl]-N-(2-hydroxy-2-phenylethyl)carbamate

Referential Example 145

tert-Butyl (R)-N-[2-[4-[2-[1-(2,6-difluorobenzyl)-1H-imidazol-2-yl]acetylamino]phenyl]ethyl]-N-(2-hydroxy-2-phenylethyl)carbamate

Referential Example 146

tert-Butyl (R)-N-[2-[4-[[2-[1-(3,5-difluorobenzyl)-1H-imidazol-2-yl]acetyl]amino]phenyl]ethyl]-N-(2-hydroxy-2-phenylethyl)carbamate

Referential Example 147

tert-Butyl (R)-N-[2-[4-[2-[1-(2,5-difluorobenzyl)-1H-imidazol-2-yl]acetylamino]phenyl]ethyl]-N-(2-hydroxy-2-phenylethyl)carbamate

Referential Example 148

tert-Butyl (R)-N-[2-[4-[2-[1-(3,4-difluorobenzyl)-1H-imidazol-2-yl]acetamino]phenyl]ethyl]-N-(2-hydroxy-2-phenylethyl)carbamate

Referential Example 149

tert-Butyl (R)-N-(2-hydroxy-2-phenylethyl)-N-[2-[4-[2-[1-(2,3,5-trifluorobenzyl)-1H-imidazol-2-yl]acetamino]-phenyl]ethyl]carbamate

Referential Example 150

tert-Butyl (R)-N-(2-hydroxy-2-phenylethyl)-N-[2-[4-[[2-[1-(2,4,5-trifluorobenzyl)-1H-imidazol-2-yl]acetyl]-amino]phenyl]ethyl]carbamate

Referential Example 151

tert-Butyl (R)-N-(2-hydroxy-2-phenylethyl)-N-[2-[4-[2-[1-(3,4,5-trifluorobenzyl)-1H-imidazol-2-yl]acetamino]-phenyl]ethyl]carbamate

[0079]

Referential Example 152

tert-Butyl (R)-N-(2-hydroxy-2-phenylethyl)-N-[2-[4-[[2-[1-(2,3,4,5,6-pentafluorobenzyl)-1H-imidazol-2-yl]-acetylamino]phenyl]ethyl]carbamate

Referential Example 153

tert-Butyl (R)-N-(2-hydroxy-2-phenylethyl)-N-[2-[4-[[2-[1-(3-iodobenzyl)-1H-imidazol-2-yl]acetyl]amino]phen-yl]ethyl]carbamate

Referential Example 154

tert-Butyl (R)-N-[2-[4-[2-[1-(2,6-dichlorobenzyl)-1H-imidazol-2-yl]acetylamino]phenyl]ethyl]-N-(2-hydroxy-2-phenylethyl)carbamate

Referential Example 155

tert-Butyl (R)-N-[2-[4-[2-[1-(4-cyanobenzyl)-1H-imidazol-2-yl]acetylamino]phenyl]ethyl]-N-(2-hydroxy-2-phenylethyl)carbamate

Referential Example 156

tert-Butyl (R)-N-(2-hydroxy-2-phenylethyl)-N-[2-[4-[2-[1-(quinolin-2-yl)methyl-1H-imidazol-2-yl]acetylamino]-phenyl]ethyl]carbamate

Referential Example 157

tert-Butyl (R)-N-[2-[4-[2-[1-(2-chloro-6-fluoro-benzyl)-1H-imidazol-2-yl]acetylamino]phenyl]ethyl]-N-(2-hydroxy-2-phenylethyl)carbamate

Referential Example 158

tert-Butyl (R)-N-[2-[4-[2-[1-(2-chloro-4-fluoro-benzyl)-1H-imidazol-2-yl]acetylamino]phenyl]ethyl]-N-(2-hydroxy-2-phenylethyl)carbamate

Referential Example 159

tert-Butyl (R)-N-[2-[4-[2-[1-(2,5-dichlorobenzyl)-1H-imidazol-2-yl]acetylamino]phenyl]ethyl]-N-(2-hydroxy-2-phenylethyl)carbamate

Referential Example 160

tert-Butyl (R)-N-(2-hydroxy-2-phenylethyl)-N-[2-[4-[2-[1-(2,3,4-trifluorobenzyl)-1H-imidazol-2-yl]acetyl-amino]phenyl]ethyl]carbamate

Referential Example 161

tert-Butyl (R)-N-(2-hydroxy-2-phenylethyl)-N-[2-[4-[[2-[1-(4-methoxycarbonylbenzyl)-1H-imidazol-2-yl]acetyl]-amino]phenyl]ethyl]carbamate

Referential Example 162

tert-Butyl (R)-N-(2-hydroxy-2-phenylethyl)-N-[2-[4-[2-[1-[4-(piperidin-1-carnbonyl)benzyl]-1H-imidazol-2-yl]-acetylamino]phenyl]ethyl]carbamate

[0080]

Referential Example 163

Into a solution of 1.87 g of tert-butyl (R)-N-(2-hydroxy-2-phenylethyl)-N-[2-(4-nitrophenyl)ethyl]carbamate and 1.05 g of diisopropyl ethylamine in 40 ml of chloroform was dropped a solution of 1.07 g of bromoacetyl bromide in 3 ml of chloroform with ice cooling. The reaction mixture was stirred for one hour with ice cooling and washed with 1N hydrochloric acid and a saturated saline solution successively. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated *in vacuo*. The resulting residue was purified by silica gel column chromatography (eluent: chloroform/methanol = 30:1) to give 2.15 g of tert-butyl (R)-N-[2-[4-(2-bromoacetylamino)phenyl]ethyl]-N-(2-hydroxy-2-phenylethyl)carbamate.

[0081]

The compounds of Referential Examples 164 to 166 were prepared by the same manner as in Referential Example 147, and the compound of Referential Example 167 was prepared by the same manner as in Referential Example 77.

Referential Example 164

tert-Butyl (R)-N-(2-hydroxy-2-phenylethyl)-N-[2-[4-[2-(1-pyrazolyl)acetylamino]phenyl]ethyl]carbamate

Referential Example 165

tert-Butyl (R)-N-(2-hydroxy-2-phenylethyl)-N-[2-[4-[2-(1,2,4-triazol-1-yl)acetylamino]phenyl]ethyl]carbamate

Referential Example 166

tert-Butyl (R)-N-[2-[4-[2-(2-aminobenzimidazol-1-yl)-acetylamino]phenyl]ethyl]-N-(2-hydroxy-2-phenylethyl)-carbamate

Referential Example 167

(R)-2-[N-Benzyl-N-[2-(4-nitrophenyl)ethyl]amino]-1-phenylethanol

[0082]

Referential Example 168

To a solution of (R)-2-[N-benzyl-N-[2-(4-nitrophenyl)ethyl]amino]-1-phenylethanol in 150 ml of methanol were added 8.6 g of iron powder and 40 ml of 2N hydrochloric acid. The reaction mixture was heated to reflux for two hours, 1N sodium hydroxide was added thereto, and the insoluble matters thus produced were filtered off using Celite. The filtrate was

concentrated *in vacuo* to remove the methanol. The resulting aqueous phase was extracted with chloroform, the organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated *in vacuo*. The resulting residue was purified by silica gel column chromatography (eluent: hexane/ethyl acetate = 1/1) to give 11.45 g of (R)-2-[N-[2-(4-aminophenyl)-ethyl]-N-benzylamino]-1-phenylethanol.

[0083]

The compounds of Referential Examples 169 to 174 were prepared by the same manner as in Referential Example 84.

Referential Example 169

(R)-4'-[2-[N-Benzyl-N-(2-hydroxy-2-phenylethyl)-amino]ethyl]-2-(2-pyridyl)acetanilide

Referential Example 170

(R)-4'-[2-[N-Benzyl-N-(2-hydroxy-2-phenylethyl)-amino]ethyl]-2-(3-pyridyl)acetanilide

Referential Example 171

(R)-4'-[2-[N-Benzyl-N-(2-hydroxy-2-phenylethyl)-amino]ethyl]-2-(4-pyridyl)acetanilide

Referential Example 172

(R)-4'-[2-[N-Benzyl-N-(2-hydroxy-2-phenylethyl)-amino]ethyl]-(E)-3-(2-pyridyl)acrylic anilide

Referential Example 173

(R)-4'-[4-[2-[N-Benzyl-N-(2-hydroxy-2-phenylethyl)-amino]ethyl]phenyl]-2-[1-(2-phenylethyl)-1H-imidazol-2-yl]acetanilide

Referential Example 174

(R)-4'-[4-[2-[N-Benzyl-N-(2-hydroxy-2-phenylethyl)-amino]ethyl]phenyl]-2-(1H-benzimidazol-2-yl]acetanilide

[0084]

Referential Example 175

To 502 mg of (R)-2-[N-[2-(4-aminophenyl)ethyl]-N-benzylamino]-1-phenylethanol were added 336 g of ethyl 2-(3-methylpyridin-2-yl)acetate and 10 ml of xylene. The reaction mixture was refluxed for nine hours, and the solvent was evaporated *in vacuo*. The resulting residue was purified by silica gel column chromatography (eluent: hexane/ethyl acetate = 1/3) to give 222 mg of (R)-4'-[2-[N-benzyl-N-(2-hydroxy-2-phenylethyl)amino]ethyl]-2-(3-methylpyridin-2-yl)-acetanilide.

[0085]

The compounds of Referential Examples 176 to 180 were prepared by the same manner as Referential Example 175.

Referential Example 176

(R)-4'-[2-[N-Benzyl-N-(2-hydroxy-2-phenylethyl)-amino]ethyl-2-(2-pyrazinyl)acetanilide

Referential Example 177

(R)-4'-[4-[2-[N-Benzyl-N-(2-hydroxy-2-phenylethyl)-amino]ethyl]phenyl]-2-(1-benzyl-1H-imidazol-2-yl)acetanilide

Referential Example 178

(R)-4'-[2-[N-Benzyl-N-(2-hydroxy-2-phenylethyl)-amino]ethyl]-2-(4-methyl-2-pyridyl)acetanilide

Referential Example 179

(R)-4'-[2-[N-Benzyl-N-(2-hydroxy-2-phenylethyl)-amino]ethyl-2-(5-methyl-2-pyridyl)acetanilide

Referential Example 180

(R)-4'-[2-[N-Benzyl-N-(2-hydroxy-2-phenylethyl)-amino]ethyl-2-(6-methyl-2-pyridyl)acetanilide

[0086]

Referential Example 181

To 5.22 g of 4-nitrophenylacetone were added 3.43 g of benzylamine and 50 ml of toluene. The reaction solution was heated to reflux for two hours while dehydration using a Dean-Starke apparatus. The solvent was evaporated *in vacuo*, the residue was dissolved in 100 ml of methanol and 30 ml of tetrahydrofuran, and 1.52 g of sodium borohydride was added to this solution at room temperature. The reaction solution was stirred for two hours at the same temperature, the solvent was evaporated *in vacuo*, and ethyl acetate and water were added to the residue. After separation of the liquid, the organic layer

was dried over anhydrous magnesium sulfate, and the solvent was evaporated *in vacuo*. The residue was purified by silica gel column chromatography (eluent: chloroform/methanol = 100/1) to give 5.35 g of N-benzyl-N-[1-methyl-2-(4-nitrophenyl)-ethyl]amine.

[0087]

Referential Example 182

To 6.34 g of N-benzyl-N-[1-methyl-2-(4-nitrophenyl)-ethyl]amine was added (R)-styrene oxide. The reaction mixture was stirred for two hours at 150°C which was a temperature of the oil bath. The resulting mixture was purified by silica gel column chromatography (eluent: hexane/ethyl acetate = 10/1) to give 2.98 g of 2-[benzyl-N-[(R)-1-methyl-2-(4-nitro-phenyl)ethyl]amino]-(R)-1-phenylethanol (Referential Example 182a) as a yellow oil and 2.69 g of 2-[benzyl-N-[(S)-1-methyl-2-(4-nitrophenyl)ethyl]amino]-(R)-1-phenylethanol (Referential Example 182b) as pale yellow crystals.

[0088]

The compounds of Referential Examples 183 and 184 were prepared by the same manner as in Referential Example 168; and the compounds of Referential Example 185 to 187 were prepared by the same manner in Referential Example 175.

Referential Example 183

2-[N-[2-(4-Aminophenyl)-(R)-1-methylethyl]-N-benzyl-amino]-(R)-1-phenylethanol

Referential Example 184

2-[N-[2-(4-Aminophenyl)-(S)-1-methylethyl]-N-benzyl-amino]-(R)-1-phenylethanol

Referential Example 185

4'-[(R)-2-[N-Benzyl-N-((R)-2-hydroxy-2-phenylethyl)-amino]propyl]-2-(2-pyridyl)acetanilide

Referential Example 186

4'-[(S)-2-[N-Benzyl-N-((R)-2-hydroxy-2-phenylethyl)-amino]propyl]-2-(2-pyridyl)acetanilide

Referential Example 187

4'-[(S)-2-[N-Benzyl-N-((R)-2-hydroxy-2-phenylethyl)-amino]propyl]-2-(1-benzyl-1H-imidazol-2-yl)acetanilide

[0089]

Referential Example 188

To a solution of 0.96 g of 2-fluoroacetophenone in 20 ml of tetrahydrofuran was added 2.65 g of benzyltrimethylammonium tribromide. The reaction mixture was stirred at room temperature for 30 minutes, insoluble matters were filtered off, and the solvent was concentrated *in vacuo*. The resulting residue was dissolved in 40 ml of 2-butanone, then 1.81 g of N-benzyl-N-nitrophenethylamine and 0.92 g of diisopropyl ethylamine were added, and the reaction mixture was heated to reflux for one hour. The solvent was evaporated *in vacuo*, ethyl acetate was added thereto, and the mixture was washed with water and a saturated saline solution successively. The organic

layer was dried over anhydrous magnesium sulfate and evaporated *in vacuo*. The resulting residue was dissolved in 40 ml of methanol, 0.34 g of sodium borohydride was added thereto, and the reaction mixture was stirred at room temperature for one hour. The solvent was evaporated *in vacuo*, ethyl acetate was added, and the mixture was washed with water and a saturated saline solution successively. The organic layer was dried over anhydrous magnesium sulfate and evaporated *in vacuo*. The resulting residue was purified by silica gel column chromatography (eluent: chloroform) to give 1.95 g of 2-[N-benzyl-N-[2-(4-nitrophenyl)ethyl]amino]-1-(2-fluorophenyl)-ethanol.

[0090]

The compounds of Referential Examples 189 and 190 were prepared by the same manner as in Referential Example 188; the compounds of Referential Examples 191 to 193 were prepared by the same manner as in Referential Example 168; the compound of Referential Example 194 was prepared by the same manner as in Referential Example 84; and the compounds of Referential Examples 195 and 196 were prepared by the same manner as in Referential Example 175.

Referential Example 189

2-[N-Benzyl-N-[2-(4-nitrophenyl)ethyl]amino]-1-(3-fluorophenyl)ethanol

Referential Example 190

2-[N-Benzyl-N-[2-(4-nitrophenyl)ethyl]amino]-1-(4-fluorophenyl)ethanol

Referential Example 191

2-[N-[2-(4-Aminophenyl)ethyl]-N-benzylamino]-1-(2-fluorophenyl)ethanol

Referential Example 192

2-[N-[2-(4-Aminophenyl)ethyl]-N-benzylamino]-1-(3-fluorophenyl)ethanol

Referential Example 193

2-[N-[2-(4-Aminophenyl)ethyl]-N-benzylamino]-1-(4-fluorophenyl)ethanol

Referential Example 194

4'-[2-[N-Benzyl-N-[2-(2-fluorophenyl)-2-hydroxy-ethyl]amino]ethyl]-2-(2-pyridyl)acetanilide

Referential Example 195

4'-[2-[N-Benzyl-N-[2-(3-fluorophenyl)-2-hydroxy-ethyl]amino]ethyl]-2-(2-pyridyl)acetanilide

Referential Example 196

4'-[2-[N-Benzyl-N-[2-(4-fluorophenyl)-2-hydroxy-ethyl]amino]ethyl]-2-(2-pyridyl)acetanilide

[0091]

Referential Example 197

A reaction mixture of 5.12 g of methyl 2-pyridylacetate, 5.14 g of 4-aminobenzyl cyanide and 50 ml of xylene was heated

to reflux for 24 hours. An appropriate amount of the solvent was evaporated, diethyl ether was added to the residue, and the resulting crystals were taken by filtration to give 5.65 g of 4'-cyanomethyl-2-(2-pyridyl)acetanilide.

[0092]

The compounds 198 to 201 were prepared by the same manner as in Referential Example 197.

Referential Example 198

4'-Cyanomethyl-2-(2-pyrimidinyl)acetanilide

Referential Example 199

4'-Cyanomethyl-2-(2-quinolyl)acetanilide

Referential Example 200

4'-Cyanomethyl-2-(2,4-dimethylpyridin-6-yl)acetanilide

Referential Example 201

2-[1-(4-Chlorobenzyl)-1H-benzimidazol-2-yl]-4'-cyanomethylacetanilide

[0093]

Referential Example 202

To a solution of 640 mg of 4'-cyanomethyl-2-(4,6-dimethyl-2-pyridyl)acetanilide in 15 ml of tetrahydrofuran was added 15 ml of an ethanolic suspension of a Raney nickel, and concentrated aqueous ammonia was added to adjust the pH of the mixture to about 10. The mixture was stirred at room temperature for one hour in a hydrogen atmosphere under

atmospheric pressure. The reaction mixture was filtered using Celite, and the solvent was evaporated *in vacuo* to give 640 mg of 4'-(2-aminomethyl)-2-(4,6-dimethyl-2-pyridyl)acetanilide.

[0094]

Referential Example 203

To a solution of 630 mg of 4'-(2-aminomethyl)-2-(4,6-dimethyl-2-pyridyl)acetanilide in 20 ml of toluene was added 0.27 ml of benzaldehyde, and the mixture was heated to reflux for three hours using a Dean-Starke apparatus. The reaction mixture was filtered, and the solvent was evaporated *in vacuo*. A solution of the resulting residue in 30 ml of methanol was cooled at 0°C, 63 mg of sodium borohydride was added, and the mixture was stirred at 0°C for one hour. About one-half of the solvent of the reaction mixture was evaporated *in vacuo*, water and ethyl acetate were added to the residue, the organic layer was washed with a saturated saline solution twice and dried *in vacuo* and the solvent was evaporated *in vacuo*. To a solution of the resulting residue in 50 ml of isopropanol was added 0.26 ml of (R)-styrene oxide, and the mixture was heated to reflux for 12 hours. The solvent was evaporated *in vacuo*, and the resulting residue was purified by silica gel column chromatography (eluent: chloroform/methanol = 100/3) to give 920 mg of (R)-4'-[2-[N-benzyl-N-(2-hydroxy-2-phenylethyl)-amino]ethyl]-2-(4,6-dimethyl-2-pyridyl)acetanilide.

[0095]

The compounds of Referential Examples 204 to 206 were prepared by the same manner as in Referential Example 84.

Referential Example 204

tert-Butyl N-[3-[4-[[2-(2-pyridyl)acetyl]amino]phenyl]propyl]carbamate

Referential Example 205

tert-Butyl N-[2-[4-[[2-(2-pyridyl)acetyl]amino]phenoxy]ethyl]carbamate

Referential Example 206

tert-Butyl N-[1,1-dimethyl-2-[4-[[2-(2-pyridyl)acetyl]amino]phenylethyl]carbamate

[0096]

Referential Example 207

To a solution of 1.54 g of tert-Butyl N-[3-[4-[[2-(2-pyridyl)acetyl]amino]phenyl]propyl]carbamate in 10 ml of methanol was added 10 ml of a 4N hydrogen chloride-ethyl acetate solution. The reaction mixture was stirred for two hours at room temperature, and the solvent was evaporated *in vacuo*. The residue was dissolved in a mixture of chloroform and 1N sodium hydroxide. The organic layer was dried over anhydrous magnesium sulfate, the solvent was evaporated *in vacuo*, and the resulting residue was dried to give 610 mg of 4'-(3-aminopropyl)-2-(2-pyridyl)acetanilide.

[0097]

Referential Example 208

To a solution of 1.1 g of tert-butyl (R)-N-[2-(4-aminophenyl)ethyl]-N-(2-hydroxy-2-phenylethyl)carbamate in 20 ml of 1,2-dichloroethane were added 0.35 g of triethylamine and 0.64 g of 4-nitrophenyl chloroformate. The reaction mixture was stirred at room temperature for one hour, and the solvent was evaporated *in vacuo*. The resulting residue was dissolved in 15 ml of dimethylformamide, and 0.31 g of 2-aminopyridine was added thereto. The reaction mixture was stirred at room temperature for four hours, and ethyl acetate and water were added thereto. The organic layer was washed with water, a saturated sodium hydrogen carbonate solution and a saturated saline solution successively and dried over anhydrous magnesium sulfate. The solvent was evaporated *in vacuo*, and the resulting residue was purified by silica gel column chromatography (eluent: chloroform/methanol = 30/1) to give 0.19 g of tert-butyl (R)-N-(2-hydroxy-2-phenylethyl)-N-[2-[4-[3-(2-pyridyl)ureido]phenyl]ethyl]carbamate.

[0098]

Example 1

A 4N hydrogen chloride-ethyl acetate solution (10 ml) was added to 10 ml of an ethanolic solution of 458 mg of tert-butyl (R)-N-(2-hydroxy-2-phenylethyl)-N-[2-[4-[(2-pyridinecarbonyl)amino]phenyl]ethyl]carbamate. The reaction solution was stirred at room temperature for three hours, and the solvent

was then evaporated *in vacuo*. The obtained crude crystals were recrystallized from methanol-ethanol-ethyl acetate to give 289 mg of (R)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]-2-pyridinecarboxanilide dihydrochloride.

[0099]

The compounds of Examples 2 to 4 were prepared by the same manner as in Example 1.

Example 2

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-3-pyridinecarboxanilide dihydrochloride

Example 3

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-8-quinolinecarboxanilide dihydrochloride

Example 4

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-(E)-3-(2-pyridyl)acrylic anilide dihydrochloride

Example 5

(R)-2-(Benzothiazol-2-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)-amino]ethyl]acetanilide dihydrochloride

Example 6

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(imidazo[2,1-b]thiazol-3-yl)acetanilide dihydrochloride

Example 7

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(2-methylthiazol-4-yl)acetanilide hydrochloride

Example 8

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(1H-imidazol-2-yl)acetanilide dihydrochloride

Example 9

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(1H-tetrazol-5-yl)acetanilide hydrochloride

Example 10

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(5-sulfanyl-1H-1,2,4-triazol-3-yl)acetanilide hydrochloride

[0100]

Example 11

(R)-2-(2-Aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]-2-oxoacetanilide dihydrochloride

Example 12

(R)-2-(5-Amino-1,2,4-thiadiazol-3-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

Example 13

(R)-2-(5-Ethoxycarbonylamino-1,2,4-thiadiaol-3-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide hydrochloride

Example 14

(R)-2-[(2-(3-Fluorophenylamino)thiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

Example 15

(R)-2-(2-Chloropyridin-6-yl)-4'-[2-[(2-hydroxy-2-phenyl-ethyl)amino]ethyl]acetanilide hydrochloride

Example 16

(R)-2-(2-Benzyloxypyridin-6-yl)-4'-[2-[(2-hydroxy-2-phenyl-ethyl)amino]ethyl]acetanilide hydrochloride

Example 17

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-[1-(2-methyl-3-propenyl)-1H-imidazol-2-yl)acetanilide dihydro-chloride

Example 18

(R)-2-(1-Benzyl-1H-imidazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

Example 19

(R)-2-[1-(2-Chlorobenzyl)-1H-imidazol-4-yl]-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydro-chloride

Example 20

(R)-2-[1-(3-Chlorobenzyl)-1H-imidazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydro-chloride

[0101]

Example 21

(R)-2-[1-(4-Chlorobenzyl)-1H-imidazol-4-yl]-4'-[2-[(2-hydr-oxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

Example 22

(R)-2-[1-(4-Fluorobenzyl)-1H-imidazol-2-yl]-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

Example 23

(R)-2-[1-(4-Chlorobenzyl)-1H-imidazol-2-yl]-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

Example 24

(R)-2-[1-(4-Bromobenzyl)-1H-imidazol-2-yl]-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

Example 25

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-[1-(4-iodobenzyl)-1H-imidazol-2-yl]acetanilide dihydrochloride

Example 26

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-[1-(4-trifluoromethylbenzyl)-1H-imidazol-2-yl]acetanilide dihydrochloride

Example 27

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-[1-(2-naphthyl)-1H-imidazol-2-yl]acetanilide dihydrochloride

Example 28

(R)-2-[1-(4-Fluorobenzyl)-5-methyl-1H-imidazol-2-yl]-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

Example 29

(R)-2-[1-(4-Fluorobenzyl)-4-methyl-1H-imidazol-2-yl]-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

Example 30

(R)-2-[1-(4-Fluorobenzyl)-1H-tetrazol-5-yl]-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide hydrochloride

[0102]

Example 31

(R)-2-[2-(3,4-Dichlorobenzyl)-1H-tetrazol-5-yl]-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide hydrochloride

Example 32

(R)-2-[2-(4-Fluorobenzyl)-1H-tetrazol-5-yl]-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide hydrochloride

Example 33

(R)-2-[1-(3,4-Dichlorobenzyl)-1H-tetrazol-5-yl]-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide hydrochloride

[0103]

Example 34

To a solution of 75 mg of tert-butyl (R)-N-[2-[4-[2-(1H-1,2,4-triazol-3-yl)acetylamino]phenyl]ethyl]-N-(2-hydroxy-2-phenylethyl)carbamate in 5 ml of methanol was added 4 ml of a solution of 4N hydrogen chloride in ethyl acetate. The mixture was stirred at room temperature for three hours, the solvent was filtered off, and the resulting powder was washed with ethanol. The resulting powder was dried to give 125 mg

of (R)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]-2-(1H-1,2,4-triazol-3-yl)acetanilide dihydrochloride.

[0104]

The compounds of Examples 35 to 40 were prepared by the same manner as in Example 34.

Example 35

(R)-2-(5-Benzylsulfanyl-1H-1,2,4-triazol-3-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

Example 36

(R)-2-(2-Acetamidothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide hydrochloride

Example 37

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(2-methanesulfonamidothiazol-4-yl)acetanilide hydrochloride

Example 38

(R)-2-(2-Guanidinothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

Example 39

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(2-phenylaminothiazol-4-yl)acetanilide hydrochloride

Example 40

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-[1-(4-nitrobenzyl)-1H-imidazol-2-yl]acetanilide hydrochloride

[0105]

Example 41

To 690 mg of tert-butyl (R)-N-[2-[4-[2-(2-amino-thiazol-4-yl)acetamino]phenyl]ethyl]-N-[(2-hydroxy-2-phenyl)ethyl]carbamate were added 30 ml of methanol and 15 ml of a solution of 4N hydrogen chloride in ethyl acetate, and the mixture was stirred at room temperature for two hours. The solvent was evaporated *in vacuo*, and the residue was purified by a reverses phase column chromatography (eluent: water/methanol = 2/1) to give 310 mg of (R)-2-(2-aminothiazol-4-yl)-4'-[2-(2-hydroxy-2-phenylethyl)amino]-ethyl]acetanilide dihydrochloride.

[0106]

The compounds of Examples 42 to 57 were prepared by the same manner as in Example 41.

Example 42

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-(2-amino-thiazol-4-yl)carboxylic acid anilide hydrochloride

Example 43

(R)-2-(2-Amino-5-methylthiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

Example 44

(R)-2-(2-Aminothiazol-4-yl)-2-methyl-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]propionanilide hydrochloride

Example 45

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-(2-amino-4,5,6,7-tetrahydrobenzothiazol-4-yl)carboxylic acid anilide dihydrochloride

Example 46

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(imidazo[2,1-b]thiazol-6-yl)acetanilide hydrochloride

Example 47

(R)-2-(2-Benzyl-1H-1,2,4-triazol-3-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide hydrochloride

Example 48

(R)-2-(1-Benzyl-1H-1,2,4-triazol-3-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide hydrochloride

Example 49

(R)-2-(3-Benzyl-2-thioxothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide hydrochloride

Example 50

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-(5,6,7,8-tetrahydroquinolin-8-yl)carboxylic acid dihydrochloride

[0107]

Example 51

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(1-phenyl-1H-imidazol-2-yl)acetanilide dihydrochloride

Example 52

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-[(1-(4-isopropylbenzyl)-1H-imidazol-2-yl)acetanilide dihydrochloride

Example 53

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-[(1-(4-phenylbenzyl)-1H-imidazol-2-yl)acetanilide dihydrochloride

Example 54

(R)-2-[1-(2-Chlorobenzyl)-1H-imidazol-2-yl]-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

Example 55

(R)-2-[1-(3-Chlorobenzyl)-1H-imidazol-2-yl]-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

Example 56

(R)-2-[1-(3,4-Dichlorobenzyl)-1H-imidazol-2-yl]-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

Example 57

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-[(1-(2-pyridyl)methyl-1H-imidazol-2-yl)acetanilide dihydrochloride

The compound of Example 58 was prepared by the same manner as in Example 1.

Example 58

(R)-2-(2-aminopyridin-6-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

[0108]

Example 59

To a solution of tert-butyl (R)-N-[2-[4-[[2-(2-aminothiazol-4-yl)-2-oxoacetyl]amino]phenyl]ethyl]-N-(2-hydroxy-2-phenylethyl)carbamate in 30 ml of methanol was added 130 mg of sodium borohydride at room temperature. The reaction mixture was stirred at room temperature for three hours, and the solvent was evaporated *in vacuo*. The residue was dissolved in 5 ml of methanol, and to this reaction solution was added 10 ml of a solution of 4N hydrogen chloride-ethyl acetate. The reaction solution was stirred at room temperature for eight hours and the solvent was evaporated *in vacuo*. The residue was purified by silica gel column chromatography (eluent: chloroform/methanol = 5/1). The resulting residue was purified by reversed phase column chromatography (eluent: water/methanol = 2/1) to give 77 mg of (R)-2-(2-aminothiazol-4-yl)-2-hydroxy-4'-[2-(2-hydroxy-2-phenylethyl)-amino]acetanilide hydrochloride.

[0109]

Example 60

To 349 mg of tert-butyl (R)-N-[2-[4-[[2-(2-benzyloxypyridin-6-yl)acetyl]amino]phenyl]ethyl]-N-(2-hydroxy-2-phenylethyl)carbamate were added 478 mg of pentamethylbenzene

and 5 ml of trifluoroacetic acid successively. The reaction solution was stirred at room temperature for four hours, and the solvent was evaporated *in vacuo*. To the residue were added water and potassium carbonate to make the solution basic, and the aqueous phase was extracted with a mixed solvent of chloroform and tetrahydrofuran. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated *in vacuo*. The residue was purified by silica gel column chromatography (eluent: chloroform/methanol = 10/1 → 5/1). To an ethanolic solution of the resulting residue was added 100 μl of a 4N hydrogen chloride-ethyl acetate solution, and then the solvent was evaporated *in vacuo*. The resulting crude crystals were recrystallized from ethanol-ethyl acetate to give 65 mg of (R)-2-(2-benzyloxypyridin-6-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide hydrochloride.

[0110]

The compounds of Examples 61 to 76, 83 and 85 were prepared by the same manner as in Example 1; and the compounds of Examples 77 to 82 were prepared by the same manner as in Example 41.

Example 61

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(2-methylpropyl-1H-imidazol-2-yl)acetanilide dihydrochloride

Example 62

(R)-2-[1-(2-Fluorobenzyl)-1H-imidazol-2-yl]-4'-[2-(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

Example 63

(R)-2-[1-(3-Fluorobenzyl)-1H-imidazol-2-yl]-4'-[2-(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

Example 64

(R)-2-[1-(2,4-Difluorobenzyl)-1H-imidazol-2-yl]-4'-[2-(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

Example 65

(R)-2-[1-(2,6-Difluorobenzyl)-1H-imidazol-2-yl]-4'-[2-(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

Example 66

(R)-2-[1-(3,5-Difluorobenzyl)-1H-imidazol-2-yl]-4'-[2-(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

Example 67

(R)-2-[1-(2,5-Difluorobenzyl)-1H-imidazol-2-yl]-4'-[2-(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

Example 68

(R)-2-[1-(3,4-Difluorobenzyl)-1H-imidazol-2-yl]-4'-[2-(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

Example 69

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-[1-(2,3,6-trifluorobenzyl)-1H-imidazol-2-yl]acetanilide dihydrochloride

Example 70

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-[1-(2,4,5-trifluorobenzyl)-1H-imidazol-2-yl]acetanilide dihydrochloride

[0111]

Example 71

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-[1-(3,4,5-trifluorobenzyl)-1H-imidazol-2-yl]acetanilide dihydrochloride

Example 72

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-[1-(2,3,4,5,6-pentafluorobenzyl)-1H-imidazol-2-yl]acetanilide dihydrochloride

Example 73

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-[1-(3-iodobenzyl)-1H-imidazol-2-yl]acetanilide dihydrochloride

Example 74

(R)-2-[1-(2,6-Dichlorobenzyl)-1H-imidazol-2-yl]-4'-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide hydrochloride

Example 75

(R)-2-[1-(4-Cyanobenzyl)-1H-imidazol-2-yl]-4'-[2-(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

Example 76

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-[1-(quinolin-2-yl)-1H-imidazol-2-yl]acetanilide trihydrochloride

Example 77

(R)-2-[1-(2-Chloro-6-fluorobenzyl)-1H-imidazol-2-yl]-4'-[2-(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide

Example 78

(R)-2-[1-(2-Chloro-4-fluorobenzyl)-1H-imidazol-2-yl]-4'-[2-(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide

Example 79

(R)-2-[1-(2,5-Dichlorobenzyl)-1H-imidazol-2-yl]-4'-[2-(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

Example 80

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-[1-(2,3,4-trifluorobenzyl)-1H-imidazol-2-yl]acetanilide dihydrochloride

[0112]

Example 81

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-[1-(4-methoxycarbonylbenzyl)-1H-imidazol-2-yl]acetanilide dihydrochloride

Example 82

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-[1-[(piperidine-1-carbonyl)benzyl]-1H-imidazol-2-yl]acetanilide dihydrochloride

Example 83

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(1-pyrazolyl)acetanilide hydrochloride

Example 84

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(1,2,4-triazol-1-yl)acetanilide dihydrochloride

Example 85

(R)-2-(2-Aminobenzimidazol-1-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

[0113]

Example 86

To a solution of 20.1 g of 4'-[2-[N-benzyl-N-(2-hydroxy-2-phenylethyl)amino]ethyl]-2-(2-pyridyl)acetanilide in 400 ml of methanol was added 5.96 g of 10% palladium-carbon. The reaction solution was stirred for six hours in a hydrogen atmosphere under atmospheric pressure. Insoluble matters were filtered off using Celite and the filtrate was concentrated *in vacuo*. To a methanolic solution of the resulting residue was

added 10.8 ml of a 4N hydrogen chloride-ethyl acetate solution, and the solvent was evaporated *in vacuo*. The resulting crude crystals were recrystallized from methanol-ethanol to give (R)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]-2-(2-pyridyl)acetanilide hydrochloride.

[0114]

The compounds of 87 to 90 were prepared by the same manner as in Example 86.

Example 87

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(3-pyridyl)acetanilide hydrochloride

Example 88

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(4-pyridyl)acetanilide hydrochloride

Example 89

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-3-(2-pyridyl)propionanilide hydrochloride

Example 90

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-[(1-phenylethyl)-1H-imidazol-2-yl]acetanilide dihydrochloride

[0115]

Example 91

(R)-2-(1H-Benzimidazol-2-yl)-4'-[4-[2-[N-benzyl-N-(2-hydroxy-2-phenylethyl)amino]ethyl]phenyl]acetanilide (240 mg) was dissolved in 30 ml of ethanol, then 170 mg of 10%

palladium-carbon was added thereto and the mixture was stirred for nine hours in a hydrogen atmosphere under atmospheric pressure. The catalyst was filtered off, the solvent was evaporated *in vacuo*, and the residue was washed with ethanol-ethyl acetate to give 200 mg of (R)-2-(1H-benzimidazol-2-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide.

[0116]

The compounds of Examples 92 and 93 were prepared by the same manner as in Example 86.

Example 92

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(3-methylpyridin-2-yl]acetanilide hydrochloride

Example 93

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(2-pyrazinyl)acetanilide hydrochloride

[0117]

Example 94

(R)-4'-[4-[2-[N-Benzyl-N-(2-hydroxy-2-phenylethyl)-amino]ethyl]phenyl]-2-(1-benzyl-1H-imidazol-2-yl)acetanilide (350 mg) was dissolved in 20 ml of ethanol, then 130 mg of 10% palladium-carbon was added thereto, and the mixture was stirred for 17.5 hours in a hydrogen atmosphere under atmospheric pressure. The catalyst was filtered off, the solvent was evaporated *in vacuo*, and the residue was purified

by silica gel column chromatography (eluent: chloroform/methanol/ concentrated aqueous ammonia = 200/10/1). The resulting oily substance was dissolved in methanol, and 280 µl of a 4N hydrogen chloride-ethyl acetate solution was added thereto. The mixture was filtered after adding active carbon was added thereto, and the solvent was evaporated *in vacuo* to give 200 mg of (R)-2-(1-benzyl-1H-imidazol-2-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride.

[0118]

The compounds of Examples 95 and 97 were prepared by the same manner as in Example 91; the compounds of Examples 98 and 100 were prepared by the same manner as in Example 94; and the compounds of Examples 99 and 101 to 103 were prepared by the same manner as in Example 86.

Example 95

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(4-methyl-2-pyridyl)acetanilide

Example 96

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(5-methyl-2-pyridyl)acetanilide

Example 97

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(6-methyl-2-pyridyl)acetanilide

Example 98

4'-[(R)-2-[((R)-Hydroxy-2-phenylethyl)amino]propyl]-2-(2-pyridyl)acetanilide hydrochloride

Example 99

4'-[(S)-2-[((R)-Hydroxy-2-phenylethyl)amino]propyl]-2-(2-pyridyl)acetanilide hydrochloride

Example 100

2-(1-Benzyl-1H-imidazol-2-yl)-4'-[(S)-2-[((R)-2-hydroxy-2-phenylethyl)amino]propyl]acetanilide hydrochloride

Example 101

4'-[2-[[2-Hydroxy-2-(2-fluorophenyl)ethyl]amino]ethyl]-2-(2-pyridyl)acetanilide hydrochloride

Example 102

4'-[2-[[2-Hydroxy-2-(3-fluorophenyl)ethyl]amino]ethyl]-2-(2-pyridyl)acetanilide hydrochloride

Example 103

4'-[2-[[2-Hydroxy-2-(4-fluorophenyl)ethyl]amino]ethyl]-2-(2-pyridyl)acetanilide hydrochloride

[0119]

Example 104

To a solution of 805 mg of 4'-cyanomethyl-2-(2-pyrimidinyl)acetanilide in 30 ml of tetrahydrofuran were added 30 ml of an ethanolic solution of a Raney nickel and 3 ml of concentrated aqueous ammonia. The reaction solution was stirred for four hours in a hydrogen atmosphere under atmospheric pressure, then insoluble matters were filtered off

using Celite, and the solvent was evaporated. To the resulting residue were added 10 ml of 2-propanol, 300 mg of (R)-styrene oxide and 2 ml of methanol successively. The reaction mixture was heated to reflux for ten hours, and the solvent was evaporated. The residue was purified by silica gel column chromatography (eluent: chloroform/methanol = 10/1). To a methanolic solution of the resulting residue was added 150 µl of 4N hydrogen chloride-ethyl acetate solution, and the solvent was evaporated *in vacuo*. The resulting residue was crystallized from methanol-ethanol-ethyl acetate and then recrystallized from ethanol-diethyl ether to give 160 mg of (R)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]-2-(2-pyrimidinyl]acetanilide hydrochloride.

[0120]

The compounds of Examples 105 to 108 were prepared by the same manner as in Example 104; and the compound of Example 109 was prepared by the same manner as in Example 91.

Example 105

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(2-quinolyl)acetanilide hydrochloride

Example 106

(R)-4'-[2-[[2-Hydroxy-2-(3-chlorophenyl)ethyl]amino]ethyl]-2-(2-pyridyl)acetanilide hydrochloride

Example 107

4'-[2-[[2-Hydroxy-2-(3-pyridyl)ethyl]amino]ethyl]-2-(2-pyridyl)acetanilide hydrochloride

Example 108

(R)-2-[1-(4-Chlorobenzyl)-1H-benzimidazol-2-yl]-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

Example 109

(R)-2-(4,6-Dimethyl-2-pyridyl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide

[0121]

Example 110

To 4'-(3-aminopropyl)-2-(2-pyridyl)acetanilide were added 10 ml of 2-propanol and 600 mg of (R)-styrene oxide successively. The reaction mixture was heated to reflux for four hours, and the solvent was evaporated. The residue was purified by silica gel column chromatography (eluent: chloroform/methanol = 30/1 → 10/1). To a methanolic solution of the resulting residue was added 100 µl of a 4N hydrogen chloride-ethyl acetate solution, and the solvent was evaporated *in vacuo*. The resulting crude crystals were recrystallized from ethanol-diethyl ether to give 71 mg of (R)-4'-[3-[(2-hydroxy-2-phenylethyl)amino]propyl]-2-(2-pyridyl)acetanilide hydrochloride.

[0122]

Example 111

To a solution of 3.62 g of tert-butyl N-[2-[4-[[2-(2-pyridyl)acetyl]amino]phenoxy]ethyl]carbamate in 30 ml of methanol was added 50 ml of a 4N hydrochloride-ethyl acetate solution. After the reaction solution was stirred at room temperature for eight hours, the solvent was evaporated *in vacuo*. To the residue were added an aqueous solution of sodium hydrogen carbonate and potassium carbonate to adjust to pH about 12. The resulting aqueous phase was extracted with a mixed solvent of chloroform and tetrahydrofuran. The organic layer was dried over anhydrous magnesium sulfate and concentrated, the resulting residue was dissolved in 40 ml of methanol, and 1.02 g of (R)-styrene oxide was added thereto. After the reaction solution was heated to reflux for 26 hours, the solvent was evaporated *in vacuo*. The resulting residue was purified by silica gel column chromatography (eluent: chloroform/methanol = 30/1 → 10/1) and dissolved in methanol, 0.59 ml of a 4N hydrogen chloride-ethyl acetate solution was added, and the solvent was evaporated *in vacuo*. The resulting crude crystals were recrystallized from methanol-ethanol to give 320 mg of (R)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethoxy]-2-(2-pyridyl)acetanilide hydrochloride

[0123]

Example 112

To a solution of 490 mg of tert-butyl N-[1,1-dimethyl-2-[4-[[2-(2-pyridyl)acetyl]amino]phenyl]ethyl]-

carbamate in 10 ml of methanol was added 30 ml of a 4N hydrochloride-ethyl acetate solution. After the reaction solution was stirred at room temperature for eight hours, the solvent was evaporated *in vacuo*. To the residue were added an aqueous solution of sodium hydrogen carbonate and potassium carbonate to adjust to pH about 12. The resulting aqueous phase was extracted with a mixed solvent of chloroform and tetrahydrofuran. The organic layer was dried over anhydrous magnesium sulfate and concentrated, the resulting residue was dissolved in 2 ml of 2-propanol and 2 ml of methanol, and 120 mg of (R)-styrene oxide was added thereto. After the reaction solution was heated to reflux for 24 hours, the solvent was evaporated *in vacuo*. The resulting residue was purified by silica gel column chromatography (eluent: chloroform/methanol = 30/1 → 5/1) and dissolved in methanol, 0.1 ml of a 4N hydrogen chloride-ethyl acetate solution was added, and the solvent was evaporated *in vacuo*. The resulting residue was purified by silica gel column chromatography (eluent: chloroform/methanol = 5/1) and a reversed phase column chromatography (eluent: water/methanol = 2/1 → 1/1) to give 35 mg of (R)-4'-[2,2-dimethyl-2-[(2-hydroxy-2-phenylethyl)amino]ethyl]-2-(2-pyridyl)acetanilide hydrochloride

[0124]

The compound of Example 113 was prepared by the same manner as in Example 1.

Example 113

(R)-1-[4-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]phenyl]-3-(2-pyridyl)urea dihydrochloride

[0125]

As hereunder, physical and chemical properties of the compounds of the Referential Examples are given in Tables 1 to 13 and those of the compounds of the Examples are given in Tables 14 to 25.

The symbols in the tables have the following meanings.

Rex.: Referential Example No.

Ex.: Example No.

DATA: Physico-chemical properties

NMR: Nucleomagnetic resonance spectrum (TMS internal standard; DMSO-d_6 was used as a solvent unless otherwise specified)

mp: melting point

dec: decomposition

MS (m/z): mass spectrographic data (m/z)

[0126]

[Table 1]

Rex.	DATA
1	NMR ($CDCl_3$) δ: 1.28(3H,t,J=7.2Hz), 3.88(2H,s), 4.21(2H,q,J=7.2Hz), 7.56-7.71(1H,m), 8.53-8.56(1H,m), 8.60-8.62(1H,m)
2	NMR ($CDCl_3$) δ: 1.22(3H,t,J=7.1Hz), 3.95(2H,s), 4.12(2H,q,J=7.1Hz), 5.39(2H,s), 7.00(2H,d,J=8.7Hz), 7.17-7.30(5H,m), 7.78(1H,dd,J=7.1, 2.0Hz)
3	NMR δ: 1.22(3H,t,J=6.9Hz), 4.16(2H,q,J=6.9Hz), 4.26(2H,s), 7.62(2H,s)
4	NMR δ: 4.16(2H,s), 7.61(2H,s)
5	NMR ($CDCl_3$) δ: 3.89(2H,s), 7.20-7.32(2H,m), 7.63-7.71(1H,m), 11.03(1H,brs)
6	NMR δ: 2.11(3H,s), 3.58(2H,s), 6.91(1H,s), 11.90-12.50(2H,m)
7	NMR δ: 3.56(2H,s), 5.48(2H,s), 7.13(2H,d,J=6.9Hz), 7.24-7.39(3H,m), 12.90(1H,s)
8	NMR δ: 1.46(6H,s), 6.64(1H,s), 9.00(1H,brs)
9	NMR ($CDCl_3$) δ: 3.70(2H,s), 3.73(3H,s), 6.81(1H,s)
10	NMR δ: 3.66(2H,s), 7.11(1H,s), 8.28(4H,brs), 12.46(1H,brs)
11	NMR ($CDCl_3$) δ: 1.34(3H,t,J=7.2Hz), 3.77(2H,s), 4.28(2H,q,J=7.2Hz), 6.59(1H,s), 6.98-7.22(3H,m), 7.39-7.49(1H,m)
12	NMR δ: 3.58(2H,s), 6.72(1H,s), 6.73-6.79(1H,m), 7.22-7.37(2H,m), 7.64-7.71(1H,m), 10.59(1H,brs)
13	NMR ($CDCl_3$) δ: 1.21(3H,t,J=7.2Hz), 2.16(3H,s), 3.67(2H,s), 4.11(2H,q,J=7.2Hz)
14	NMR δ: 2.16(3H,s), 3.60(2H,s), 9.16(2H,brs)
15	NMR ($CDCl_3$) δ: 3.78(3H,s), 3.91(2H,s), 4.34(2H,s), 7.20-7.39(5H,m)
16	NMR δ: 3.74(2H,s), 4.33(2H,s), 7.20-7.39(5H,m)
17	NMR ($CDCl_3$) δ: 1.23(3H,t,J=7.2Hz), 3.75(2H,s), 4.13(2H,q,J=7.2Hz), 5.10(2H,s), 6.84(1H,d,J=1.2Hz), 7.00-7.12(5H,m)
18	NMR δ: 4.33(2H,s), 5.43(2H,s), 7.21-7.27(2H,m), 7.42-7.47(2H,m), 7.68-7.69(2H,m)
19	NMR ($CDCl_3$) δ: 1.23(3H,t,J=7.3Hz), 3.73(2H,s), 4.12(2H,q,J=7.3Hz), 5.11(2H,s), 6.84(1H,d,J=1.4Hz), 7.02-7.06(3H,m), 7.30-7.34(2H,m)
20	NMR δ: 4.32(2H,s), 5.45(2H,s), 7.39(2H,d,J=8.8Hz), 7.46(2H,d,J=8.8Hz), 7.70(2H,s), 14.00(1H,brs)
21	NMR ($CDCl_3$) δ: 1.23(3H,t,J=7.1Hz), 3.74(2H,s), 4.12(2H,q,J=7.1Hz), 5.12(2H,s), 6.87(1H,d,J=1.4Hz), 6.96-6.99(1H,m), 7.04(1H,d,J=1.4Hz), 7.08(1H,brs), 7.25-7.31(2H,m)
22	NMR δ: 4.35(2H,s), 5.46(2H,s), 7.32-7.35(1H,m), 7.43-7.44(2H,m), 7.48(1H,brs), 7.70(1H,d,J=1.8Hz), 7.72(1H,d,J=1.8Hz)
23	NMR ($CDCl_3$) δ: 1.22(3H,t,J=7.1Hz), 3.77(2H,s), 4.06(2H,q,J=7.1Hz), 5.23(2H,s), 6.78(1H,dd,J=7.5, 1.5Hz), 6.86(1H,d,J=1.5Hz), 7.05(1H,d,J=1.5Hz), 7.19-7.30(2H,m), 7.41(1H,dd,J=7.5, 1.5Hz)
24	NMR δ: 4.32(2H,s), 5.55(2H,s), 7.15-7.73(6H,m)

【0127】

[Table 2]

Rex.	DATA
25	NMR (CDCl3) δ: 1.24(3H,t,J=7.1Hz), 3.74(2H,s), 4.15(2H,q,J=7.1Hz), 5.10 (2H,s), 6.85(1H,d,J=1.5Hz), 6.94(1H,dd,J=8.4, 2.1Hz), 7.04(1H,d,J=1.5Hz), 7.20(1H,d,J=2.1Hz), 7.42(1H,d,J=8.4Hz)
26	NMR δ: 4.38(2H,s), 5.48(2H,s), 7.39(1H,dd,J=8.4, 1.8Hz), 7.67-7.72(3H,m), 7.76(1H,d,J=2.4Hz)
27	NMR (CDCl3) δ: 1.13(3H,t,J=6.7Hz), 4.01(2H,q,J=6.7Hz), 4.42(2H,s), 5.46 (2H,s), 7.31(2H,d,J=8.4Hz), 7.60(2H,d,J=8.4Hz), 7.73(1H,d,J=1.5Hz), 7.77(1H,d,J=1.5Hz)
28	NMR δ: 4.31(2H,s), 5.43(2H,s), 7.32(2H,d,J=8.4Hz), 7.61(2H,d,J=8.4Hz), 7.70(2H,s)
29	NMR (CDCl3) δ: 1.23(3H,t,J=6.9Hz), 3.73(2H,s), 4.12(2H,q,J=6.9Hz), 5.08 (2H,s), 6.83-6.86(3H,m), 7.02(1H,d,J=1.5Hz), 7.67(2H,d,J=8.4Hz)
30	NMR δ: 4.31(2H,s), 5.41(2H,s), 7.16(2H,d,J=8.3Hz), 7.55-7.61(2H,m), 7.7 6(2H,d,J=8.3Hz)
31	NMR (CDCl3) δ: 1.22(3H,t,J=7.0Hz), 3.74(2H,s), 4.10(2H,q,J=7.0Hz), 5.21 (2H,s), 6.86(1H,d,J=1.4Hz), 7.05(1H,d,J=1.4Hz), 7.20(2H,d,J=9.5Hz), 7.60(2H,d,J=9.5Hz)
32	NMR δ: 4.32(2H,s), 5.57(2H,s), 7.54(2H,d,J=8.0Hz), 7.70-7.75(2H,m), 7.7 7(2H,d,J=8.0Hz)
33	NMR (CDCl3) δ: 1.20-1.26(9H,m), 2.89(1H,sep,J=7.2Hz), 3.75(2H,s), 4.11(2H,q,J=6.9Hz), 5.09(2H,s), 6.86(1H,d,J=1,2Hz), 7.02(2H,d,J=7.2Hz), 7.19(2H,d,J=7.2Hz), 7.26(1H,d,J=1.2Hz)
34	NMR δ: 1.18(6H,d,J=6.6Hz), 2.88(1H,sep,6.6Hz), 4.32(2H,s), 5.38(2H,s), 7.27(2H,s), 7.66-7.68(4H,m)
35	NMR (CDCl3) δ: 1.17(3H,t,J=7.2Hz), 3.43(2H,s), 4.03(2H,q,J=7.2Hz), 4.99 (2H,s), 6.70(1H,d,J=1.2Hz), 6.94(1H,d,J=1.2Hz), 7.03-7.44(9H,m)
36	NMR δ: 3.91(2H,s), 5.38(2H,s), 7.21(1H,d,J=7.2Hz), 7.29-7.50(9H,m), 7.5 9(1H,d,J=1.5Hz)
37	NMR (CDCl3) δ: 1.20(3H,t,7.3Hz), 3.76(2H,s), 4.09(2H,q,J=7.3Hz), 5.29(2 H,s), 6.92(1H,d,J=1.4Hz), 7.05(1H,d,J=1.4Hz), 7.21-7.26(1H,m), 7.46-7.52(3H,m), 7.75-7.85(3H,m)
38	NMR δ: 4.37(2H,s), 5.61(2H,s), 7.45-7.50(1H,m), 7.52-7.60(2H,m), 7.70-7. 76(2H,m), 7.80-7.90(4H,m)
39	NMR (CDCl3) δ: 1.22(3H,t,J=7.1Hz), 3.82(2H,s), 4.11(2H,q,J=7.1Hz), 5.26 (2H,s), 6.93(1H,d,J=7.8Hz), 6.96(1H,d,J=1.4Hz), 7.05(1H,d,J=1.4Hz), 7.23(1H,dd,J=6.8, 5.0Hz), 7.66(1H,td,J=7.8, 1.9Hz), 8.58(1H,d,J=5.0Hz)
40	NMR δ: 4.35(2H,s), 5.70(2H,s), 7.53(1H,dd,J=7.5, 4.8Hz), 7.58(1H,d,J=7.5 Hz), 7.71(1H,d,J=1.9Hz), 7.82(1H,d,J=1.9Hz), 8.03(1H,td,J=4.8, 1.9Hz), 8. 61(1H,d,J=4.2Hz)
41	NMR (CDCl3) δ: 1.26(3H,dt,J=7.3, 1.4Hz), 1.70(3H,s), 3.77(2H,d,J=1.3Hz), 4.13(2H,dq,J=7.3, 1.4Hz), 4.45(2H,s), 4.64(1H,s), 4.90-4.95(1H,m), 6.85-7.28(2H,m)

[0128]

[Table 3]

Rex.	D A T A
42	NMR δ: 1.66(3H,s), 4.21(2H,s), 4.73(1H,s), 4.81(2H,s), 4.99(1H,s), 7.66(1H,d,J=1.8Hz), 7.71(1H,d,J=1.8Hz)
43	NMR ($CDCl_3$) δ: 1.26(3H,t,J=7.2Hz), 3.63(2H,d,J=0.6Hz), 4.17(2H,q,J=7.2Hz), 5.07(2H,s), 6.87(1H,d,J=1.1Hz), 7.15-7.18(2H,m), 7.31-7.37(3H,m), 7.46(1H,d,J=1.1Hz)
44	NMR δ: 3.78(2H,s), 5.42(2H,s), 7.38-7.44(6H,m), 7.58(1H,brs), 9.26(1H,brs)
45	NMR ($CDCl_3$) δ: 1.26(3H,t,J=7.2Hz), 3.64(2H,d,J=0.6Hz), 4.17(2H,q,J=7.2Hz), 5.18(2H,s), 6.91(1H,s), 6.99(1H,dd,J=8.4, 2.0Hz), 7.21-7.31(2H,m), 7.41(1H,dd,J=8.4, 2.0Hz), 7.49(1H,d,J=1.5Hz)
46	NMR δ: 3.79(2H,s), 5.43(2H,s), 7.42-7.58(6H,m), 9.26(1H,brs)
47	NMR ($CDCl_3$) δ: 1.26(3H,t,J=7.1Hz), 3.64(2H,d,J=0.6Hz), 4.17(2H,q,J=7.1Hz), 5.05(2H,s), 6.87(1H,s), 7.02-7.05(1H,m), 7.15(1H,d,J=0.9Hz), 7.28-7.30(2H,m), 7.47(1H,d,J=0.9Hz)
48	NMR δ: 3.78(2H,s), 5.54(2H,s), 7.39-7.47(4H,m), 7.58(1H,brs), 7.61(1H,brs), 9.27(1H,brs)
49	NMR ($CDCl_3$) δ: 1.26(3H,t,J=7.1Hz), 3.63(2H,s), 4.17(2H,q,J=7.1Hz), 5.04(2H,s), 6.69(1H,s), 7.08(1H,s), 7.11(1H,s), 7.31(1H,t,J=2.3Hz), 7.34(1H,t,J=2.3Hz), 7.45(1H,d,J=1.2Hz)
50	NMR δ: 3.78(2H,s), 5.41(2H,s), 7.45-7.52(5H,m), 7.58(1H,brs), 9.20(1H,brs)
51a	NMR ($CDCl_3$) δ: 1.22(3H,t,J=7.2Hz), 3.78(2H,s), 4.12(2H,q,J=7.2Hz), 5.37(2H,s), 7.15-7.21(2H,m), 7.28-7.39(3H,m), 7.90(1H,s)
51b	NMR ($CDCl_3$) δ: 1.26(3H,t,J=7.2Hz), 3.81(2H,s), 4.20(2H,q,J=7.2Hz), 5.30(2H,s), 7.23-7.29(2H,m), 7.34-7.39(3H,m), 7.96(1H,s)
52	NMR δ: 4.04(3H,s), 5.41(2H,s), 7.24-7.38(5H,m), 8.49(1H,s)
53	NMR δ: 3.62(3H,s), 5.37(2H,s), 7.25-7.41(5H,m), 8.65(1H,s)
54a	NMR ($CDCl_3$) δ: 1.25(3H,t,J=7.2Hz), 3.85(2H,s), 4.16(2H,q,J=7.2Hz), 5.59(2H,s), 7.07(2H,t,J=8.4Hz), 7.20-7.27(2H,m)
54b	NMR ($CDCl_3$) δ: 1.25(3H,t,J=7.2Hz), 3.95(2H,s), 4.19(2H,q,J=7.2Hz), 5.72(2H,s), 7.06(2H,t,J=8.4Hz), 7.35-7.39(2H,m)
55	NMR δ: 4.19(2H,s), 5.63(2H,s), 7.10-7.50(4H,m), 13.10(1H,brs)
56	NMR δ: 3.93(2H,s), 5.91(2H,s), 7.23(2H,t,J=8.7Hz), 7.43-7.47(2H,m), 12.79(2H,brs)
57a	NMR ($CDCl_3$) δ: 1.26(3H,t,J=7.0Hz), 3.89(2H,s), 4.17(2H,q,J=7.0Hz), 5.57(2H,s), 7.00-7.10(1H,m), 7.35-7.47(2H,m)
57b	NMR ($CDCl_3$) δ: 1.26(3H,t,J=7.0Hz), 3.96(2H,s), 4.20(2H,q,J=7.0Hz), 5.71(2H,s), 7.20-7.22(1H,m), 7.44-7.48(2H,m)
58	NMR δ: 4.23(2H,s), 5.66(2H,s), 7.32-7.35(1H,m), 7.64-7.67(2H,m), 7.70(2H,s), 13.14(1H,brs)

[0129]

[Table 4]

Rex.	D A T A
59	NMR δ: 3.95(2H,s), 5.97(2H,s), 7.33-7.39(1H,m), 7.66-7.71(2H,m), 12.81(1H,brs)
60	NMR ($CDCl_3$) δ: 1.19(3H,t,J=7.3Hz), 3.75(2H,s), 4.12(2H,q,J=7.3Hz), 7.06(1H,d,J=1.5Hz), 7.12(1H,d,J=1.5Hz), 7.32-7.52(5H,m)
61	NMR δ: 4.16(2H,s), 7.55-7.70(5H,m), 7.88-7.91(1H,m), 7.98-8.00(1H,m)
62	NMR ($CDCl_3$) δ: 1.23(3H,t,J=6.8Hz), 3.75(2H,s), 4.12(2H,q,J=6.8Hz), 5.28(2H,s), 6.87(1H,d,J=1.2Hz), 7.08(1H,d,J=1.2Hz), 7.26(2H,d,J=8.4Hz), 8.22(2H,d,J=8.4Hz)
63	NMR δ: 4.32(2H,s), 5.64(2H,s), 7.58(2H,d,J=8.9Hz), 7.73-7.78(2H,m), 8.25(2H,d,J=8.9Hz), 14.00(1H,brs)
64	NMR ($CDCl_3$) δ: 1.25(3H,t,J=6.9Hz), 3.02(2H,t,J=6.9Hz), 3.51(2H,s), 4.09-4.19(4H,m), 6.81(1H,d,J=1.5Hz), 6.96(1H,d,J=1.5Hz), 7.03-7.32(5H,m)
65	NMR δ: 3.08(2H,t,J=7.5Hz), 4.14(2H,s), 4.44(2H,t,J=7.5Hz), 7.20-7.35(5H,m), 7.64(1H,d,J=1.5Hz), 7.68(1H,d,J=1.5Hz)
66	NMR ($CDCl_3$) δ: 2.09(3H,s), 2.30(3H,s), 4.99(2H,s), 6.72(1H,s), 6.88-7.04(4H,m)
67	NMR ($CDCl_3$) δ: 1.21(3H,t,J=6.9Hz), 2.09(3H,d,J=0.6Hz), 3.69(2H,s), 4.08(2H,q,J=6.9Hz), 5.09(2H,s), 6.80(1H,d,J=0.6Hz), 6.86-7.04(4H,m)
68	NMR δ: 2.12(3H,s), 4.31(2H,s), 5.45(2H,s), 7.18-7.28(4H,m), 7.50(1H,s)
69	NMR ($CDCl_3$) δ: 2.18(3H,d,J=2.0Hz), 2.30(3H,s), 4.94(2H,s), 6.51(1H,d,J=1.5Hz), 6.88-7.04(4H,m)
70	NMR ($CDCl_3$) δ: 1.23(3H,t,J=7.2Hz), 2.19(3H,d,J=0.6Hz), 3.71(2H,s), 4.12(2H,q,J=7.2Hz), 5.03(2H,s), 6.54(1H,d,J=0.6Hz), 7.00-7.12(4H,m)
71	NMR δ: 2.24(3H,s), 4.27(2H,s), 5.35(2H,s), 7.21-7.45(5H,m)
72	NMR ($CDCl_3$) δ: 1.26(3H,t,J=6.8Hz), 3.87(2H,s), 4.18(2H,q,J=6.8Hz), 5.36(2H,s), 6.73(1H,d,J=6.8Hz), 6.85(1H,d,J=6.8Hz), 7.20-7.65(6H, m)
73	NMR ($CDCl_3$) δ: 3.41(2H,s), 5.40(2H,s), 6.70-7.00(2H,s), 7.20-7.70(6H,m)
74	NMR ($CDCl_3$) δ: 1.25(3H,t,J=7.2Hz), 1.48(9H,s), 3.69(2H,s), 4.17(2H,q,J=7.2Hz), 6.93(1H,d,J=7.9Hz), 7.58-7.65(1H,m), 7.82(1H,d,J=8.3Hz)
75	NMR ($CDCl_3$) δ: 1.51(9H,s), 3.68(2H,s), 6.80-7.00(1H,s), 7.50-7.90(2H,m)
76	NMR ($CDCl_3$) δ: 1.30-2.20(4H,s), 2.60-3.10(2H,s), 3.70-4.00(1H,m), 7.00-8.00(2H,s), 8.20-8.60(1H,m)
77	NMR ($CDCl_3$) δ: 2.75(1H,dd,J=12.4, 8.8Hz), 2.85-3.04(5H,m), 4.70(1H,dd,J=8.8, 3.7Hz), 7.24-7.40(7H,m), 8.10-8.20(2H,m)
78	NMR ($CDCl_3$) δ: 1.44(9H,s), 2.75-3.10(2H,m), 3.20-3.70(4H,m), 4.93(1H,br), 7.25-7.40(7H,m), 8.14(2H,d,J=8.4Hz)
79	NMR ($CDCl_3$) δ: 1.47(9H,s), 2.55-2.80(2H,m), 3.20-3.40(2H,m), 3.45-3.65(2H,m), 4.87(1H,m), 6.57-6.65(2H,m), 6.83-7.04(2H,m), 7.25-7.40(5H,m)
80	NMR ($CDCl_3$) δ: 2.87(2H,dt,J=6.6, 2.4Hz), 3.44-3.65(3H,m), 4.97(1H,s), 6.27(1H,brs), 7.16(2H,d,J=8.9Hz), 7.29-7.37(5H,m), 8.05(2H,d,J=8.9Hz)

[0130]

[Table 5]

Rex.	DATA
81	NMR δ: 3.04(1H,dd,J=12.3, 10.2Hz), 3.16-3.29(5H,m), 5.10(1H,brd,J=9.9Hz), 6.21(1H,brd,J=3.6Hz), 7.29-7.37(1H,m), 7.39-7.41(4H,m), 7.57(2H,d,J=8.6Hz), 8.21(2H,d,J=8.6Hz), 9.15(1H,brs),
82	NMR ($CDCl_3$) δ: 1.47(9H,s), 2.62-2.93(2H,m), 3.14-3.58(4H,m), 4.35(1H,brs), 4.90(1H,br), 7.06-7.40(7H,m), 7.45-7.50(1H,m), 7.67-7.72(2H,m), 7.90(1H,dt,J=2.0, 8.0Hz), 8.25-8.31(1H,m), 8.58-8.63(1H,m), 9.98(1H,brs)
83	NMR ($CDCl_3$) δ: 1.47(9H,s), 2.60-2.90(2H,m), 3.15-3.70(4H,m), 4.32(1H,brs), 4.85-4.94(1H,m), 7.05-7.46(8H,m), 7.55-7.61(2H,m), 8.16-8.23(1H,m), 8.75(1H,br), 9.05(1H,br)
84	NMR ($CDCl_3$) δ: 1.49(9H,s), 2.64-2.90(2H,m), 3.16-3.60(4H,m), 4.38(1H,brs), 4.91(1H,br), 7.10-7.42(7H,m), 7.55(1H,dd,J=8.0, 4.4Hz), 7.74(1H,t,J=8.0Hz), 7.77-7.84(2H,m), 8.01(1H,d,J=8.0, 1.2Hz), 8.34(1H,d,J=8.4, 1.6Hz), 8.96(1H,d,J=7.6, 1.6Hz), 9.02(1H,d,J=4.4, 2.0Hz), 13.61(1H,brs)
85	NMR ($CDCl_3$) δ: 1.47(9H,s), 2.60-2.90(2H,m), 3.20-3.55(4H,m), 4.35(1H,brs), 4.90(1H,br), 7.06-7.18(3H,m), 7.23-7.56(9H,m), 7.66-7.77(2H,m), 8.62(1H,d,J=4.0Hz)
86	NMR ($CDCl_3$) δ: 1.47(9H,s), 2.60-2.85(2H,m), 3.15-3.55(4H,m), 4.31(1H,brs), 4.88(1H,br), 7.01-7.20(2H,m), 7.22-7.56(9H,m), 7.90(1H,d,J=8.0Hz), 8.05(1H,d,J=8.0Hz), 9.54(1H,brs)
87	NMR ($CDCl_3$) δ: 1.45(9H,s), 2.60-2.85(2H,m), 3.10-3.50(4H,m), 3.80(2H,s), 4.40(1H,brs), 4.80-4.90(1H,m), 6.71(1H,s), 6.97-7.14(2H,m), 7.22-7.49(8H,m), 8.01(1H,s), 8.48(1H,brs)
88	NMR ($CDCl_3$) δ: 1.34(9H,s), 2.89(3H,s), 3.06-3.36(6H,m), 3.73(2H,s), 4.72(1H,s), 7.06-7.57(10H,m), 10.10(1H,s)
89	NMR ($CDCl_3$) δ: 1.46(9H,s), 2.52-2.80(2H,m), 3.10-3.60(4H,m), 3.89(2H,s), 4.85-4.95(1H,m), 6.95-7.40(9H,m), 7.49(2H,d,J=8.4Hz), 10.15(1H,brs)
90	NMR ($CDCl_3$) δ: 1.45(9H,s), 2.50-3.50(6H,m), 4.23(2H,s), 4.65-4.75(1H,m), 7.07(2H,d,J=8.0Hz), 7.20-7.80(7H,m), 9.26(1H,brs)
91	NMR ($CDCl_3$) δ: 1.46(9H,s), 2.56-3.40(6H,m), 3.73(2H,s), 4.75-4.91(1H,m), 7.00-7.47(9H,m), 9.15(1H,brs), 12.61(1H,brs)
92	NMR ($CDCl_3$) δ: 1.47(9H,s), 2.60-2.90(2H,m), 3.15-3.60(4H,m), 4.27(1H,brs), 4.91(1H,br), 5.31(2H,brs), 7.00-7.50(7H,m), 7.60(2H,d,J=8.0Hz), 8.80(1H,s), 9.12(1H,brs)
93	NMR ($CDCl_3$) δ: 1.45(9H,s), 2.60-2.75(2H,m), 3.10-3.55(4H,m), 3.81(2H,s), 4.81-4.87(1H,m), 6.40-6.55(2H,m), 7.03(2H,d,J=7.3Hz), 7.22-7.45(7H,m), 9.26(1H,s)
94	NMR ($CDCl_3$) δ: 1.44(3H,t,J=7.1Hz), 1.47(9H,s), 2.65-2.80(2H,m), 3.15-3.50(4H,m), 4.04(2H,s), 4.43(2H,q,J=7.1Hz), 4.83-4.90(1H,m), 7.02-7.15(2H,m), 7.30-7.35(5H,m), 7.45(2H,d,J=8.3Hz), 9.21(1H,s)
95	NMR ($CDCl_3$) δ: 1.45(9H,s), 2.60-2.75(2H,m), 3.10-3.50(4H,m), 3.64(2H,s), 4.82-4.91(1H,m), 6.43(1H,s), 6.70-7.44(13H,m), 9.14(1H,brs)

[0131]

[Table 6]

Rex.	D A T A
96	NMR (CDCl3) δ: 1.46(9H,s), 2.60-2.80(2H,m), 3.15-3.55(4H,m), 3.82(2H,s), 4.35(1H,brs), 4.88(1H,br), 6.97-7.16(2H,m), 7.22-7.38(7H,m), 7.42-7.48(2H,m), 7.66(1H,t,J=8.0Hz), 9.18(1H,brs)
97	NMR (CDCl3) δ: 1.46(9H,s), 2.60-2.85(2H,m), 3.15-3.55(4H,m), 3.77(2H,s), 4.33(1H,brs), 4.87(1H,br), 5.64(2H,s), 6.77(1H,d,J=8.4Hz), 6.89(1H,d,J=7.2Hz), 6.94-7.12(2H,m), 7.21-7.41(10H,m), 7.43-7.48(2H,m), 7.59(1H,dd,J=8.4, 7.2Hz), 9.05(1H,brs)
98	NMR (CDCl3) δ: 1.47(9H,s), 1.71(3H,s), 2.60-2.80(2H,m), 3.20-3.60(4H,m), 3.73(2H,s), 4.47(2H,s), 4.56(1H,s), 4.85-4.92(1H,m), 4.94(1H,s), 6.88(1H,s), 7.00-7.20(3H,m), 7.35-7.40(4H,m), 7.48(2H,d,J=8.3Hz), 10.33(1H,brs)
99	NMR (CDCl3) δ: 1.47(9H,s), 2.69(2H,brs), 3.11-3.43(4H,m), 3.61(2H,s), 4.42(1H,brs), 4.88(1H,brs), 5.08(2H,s), 6.80(1H,s), 7.03(2H,brs), 7.17(2H,dd,J=7.5, 2.1Hz), 7.33-7.41(8H,m), 7.45(2H,d,J=8.4Hz), 7.54(1H,d,J=1.2Hz), 9.44(1H,brs)
100	NMR (CDCl3) δ: 1.47(9H,s), 2.68(2H,brs), 3.11-3.43(4H,m), 3.62(2H,s), 4.39(1H,brs), 4.88(1H,brs), 5.19(2H,s), 6.83(1H,s), 7.03-7.06(3H,m), 7.24-7.35(7H,m), 7.42-7.47(3H,m), 7.58(1H,d,J=1.2Hz), 9.41(1H,brs)
101	NMR (CDCl3) δ: 1.47(9H,s), 2.69(2H,brs), 3.11-3.43(4H,m), 3.63(2H,s), 4.37(1H,brs), 4.87(1H,brs), 5.06(2H,s), 6.80(1H,s), 7.03(2H,brs), 7.17(1H,s), 7.30-7.35(8H,m), 7.45(2H,d,J=8.4Hz), 7.55(1H,d,J=1.2Hz), 9.37(1H,brs)
102	NMR (CDCl3) δ: 1.47(9H,s), 2.69(2H,brs), 3.11-3.43(4H,m), 3.62(2H,s), 4.337(1H,brs), 4.87(1H,brs), 5.06(2H,s), 6.78(1H,s), 7.05(2H,brs), 7.11(2H,d,J=8.4Hz), 7.33-7.36(7H,m), 7.45(2H,d,J=8.4Hz), 7.54(1H,brs), 9.38(1H,brs)
103	NMR (CDCl3) δ: 1.47(9H,s), 2.60-2.80(2H,m), 3.10-3.50(4H,m), 3.90(2H,s), 4.85-4.95(1H,m), 5.30(2H,s), 6.88(1H,s), 7.00-7.45(12H,m), 7.57(2H,d,J=8.3Hz), 7.70-7.76(1H,m), 7.87-7.96(1H,m), 9.98(1H,brs)
104	NMR (CDCl3) δ: 1.47(9H,s), 2.50-2.70(2H,m), 3.10-3.50(4H,m), 3.70(2H,s), 4.84-4.92(1H,m), 5.12(2H,s), 6.92-7.08(6H,m), 7.26-7.45(9H,m), 10.14(1H,s)
105	NMR (CDCl3) δ: 1.47(9H,s), 2.60-2.80(2H,m), 3.10-3.50(4H,m), 3.70(2H,s), 4.85-4.92(1H,m), 5.10(2H,s), 6.91-6.97(4H,m), 7.25-7.47(11H,m), 10.13(1H,brs)
106	NMR (CDCl3) δ: 1.47(9H,s), 2.50-3.00(2H,m), 3.10-3.60(4H,m), 3.82(2H,s), 4.85-4.92(1H,m), 6.83-6.91(3H,m), 7.00-7.20(3H,m), 7.30-7.40(5H,m), 7.51(2H,d,J=8.8Hz), 7.67(2H,d,J=8.3Hz), 9.95(1H,m)
107	NMR (CDCl3) δ: 1.47(9H,s), 2.50-2.70(2H,m), 3.10-3.60(4H,m), 3.70(2H,s), 4.30-4.40(1H,m), 4.88(1H,brs), 5.22(2H,s), 6.88-7.35(9H,m), 7.42(2H,d,J=8.3Hz), 7.59(2H,d,J=8.3Hz), 10.05(1H,brs)
108	NMR (CDCl3) δ: 1.47(9H,s), 2.60-2.80(2H,m), 3.10-3.50(4H,m), 4.19(2H,s), 4.80-4.90(1H,m), 5.60(2H,s), 6.93(1H,s), 6.94-7.90(17H,m), 10.05(1H,brs)
109	NMR (CDCl3) δ: 1.47(9H,s), 2.03(3H,s), 2.60-2.70(2H,m), 3.10-3.60(4H,m), 3.66(2H,s), 4.35(1H,brs), 4.87-4.89(1H,m), 5.08(2H,s), 6.84-7.20(7H,m), 7.70-7.90(5H,m), 7.44(2H,d,J=8.3Hz), 10.21(1H,brs)

[0132]

[Table 7]

Rex.	DATA
110	NMR ($CDCl_3$) δ: 1.48(9H,s), 2.23(3H,s), 2.60-2.80(2H,m), 3.10-3.60(4H,m), 3.68(2H,s), 4.35(1H,brs), 4.85-4.89(1H,m), 5.05(2H,s), 6.60(1H,s), 7.00-7.35(11H,m), 7.44(2H,d,J=8.3Hz), 10.17(1H,brs)
111	NMR ($CDCl_3$) δ: 1.46(9H,s), 2.60-2.90(2H,m), 3.10-3.55(4H,m), 3.89(2H,s), 4.85-4.95(1H,m), 5.66(2H,s), 7.00-7.10(4H,m), 7.50-7.90(9H,m), 8.66(1H,brs)
112	NMR ($CDCl_3$) δ: 1.46(9H,s), 2.60-2.80(2H,m), 3.20-3.50(4H,m), 4.02(2H,s), 4.83-4.91(1H,m), 5.71(2H,s), 7.00-7.51(12H,m), 8.41(1H,brs)
113	NMR ($CDCl_3$) δ: 1.46(9H,s), 2.10-2.30(2H,m), 3.10-3.55(4H,m), 4.02(2H,s), 4.85-4.95(1H,m), 5.73(2H,s), 7.00-7.20(4H,m), 7.30-7.45(9H,m), 8.85(1H,brs)
114	NMR ($CDCl_3$) δ: 1.46(9H,s), 2.60-2.80(2H,m), 3.10-3.60(4H,m), 3.92(2H,s), 4.27(1H,brs), 4.80-4.90(1H,m), 5.65(2H,s), 7.00-7.45(12H,m), 8.47(1H,brs)
115	NMR ($CDCl_3$) δ: 1.46(9H,s), 2.60-3.36(6H,m), 3.98(2H,m), 4.81-4.89(1H,m), 7.02-7.12(2H,m), 7.29-7.50(7H,m), 8.09(1H,brs), 9.24(1H,brs)
116	NMR ($CDCl_3$) δ: 1.46(9H,s), 2.60-3.40(6H,m), 3.88(2H,s), 4.37(2H,s), 4.80-4.95(1H,m), 7.00-7.45(14H,m), 8.02(1H,s)
117	NMR ($CDCl_3$) δ: 1.43(9H,s), 2.20(3H,s), 2.50-3.55(6H,m), 3.67(2H,s), 4.78-4.87(1H,m), 6.71(1H,s), 6.98(2H,d,J=8.5Hz), 7.24-7.45(7H,m), 8.89(1H,brs), 10.38(1H,brs)
118	NMR ($CDCl_3$) δ: 1.46(9H,s), 2.60-2.84(2H,m), 3.00(3H,s), 3.20-3.50(4H,m), 3.71(2H,s), 4.81-4.89(1H,m), 6.51(1H,s), 7.00-7.09(2H,m), 7.22-7.35(5H,m), 7.49(2H,d,J=8.4Hz), 8.84(1H,brs)
119	NMR ($CDCl_3$) δ: 1.40(9H,s), 2.28-2.75(2H,m), 3.10-3.64(6H,m), 4.81(1H,brs), 6.34(1H,brs), 6.98(2H,d,J=8.1Hz), 7.18-7.42(7H,m), 8.76(1H,brs)
120	NMR ($CDCl_3$) δ: 1.47(9H,s), 2.60-2.80(2H,m), 3.10-3.50(4H,m), 3.69(2H,s), 4.30(1H,brs), 4.87-4.88(1H,m), 6.44(1H,m), 7.00-7.50(13H,m), 9.11(1H,s)
121	NMR ($CDCl_3$) δ: 1.47(9H,s), 2.50-2.80(2H,m), 3.10-3.50(4H,m), 3.70(2H,s), 4.85-4.90(1H,m), 5.30(2H,s), 6.96-7.36(11H,m), 7.41(2H,d,J=8.3Hz), 8.18(2H,d,J=8.3Hz)
122	NMR ($CDCl_3$) δ: 2.20-3.50(6H,m), 3.63(2H,s), 4.87-4.88(1H,m), 5.54(1H,brs), 6.38(1H,s), 7.26-7.45(9H,m), 8.93(1H,brs)
123	NMR ($CDCl_3$) δ: 1.46(9H,s), 2.60-3.60(6H,m), 4.87-4.91(1H,m), 5.03(2H,brs), 7.02-7.38(7H,m), 7.46(1H,s), 7.55-7.60(2H,m), 8.93(1H,brs)
124	NMR ($CDCl_3$) δ: 1.47(9H,s), 2.25(3H,s), 2.60-3.50(6H,m), 3.52(2H,s), 4.83(1H,s), 7.27-7.45(9H,m), 9.01(1H,brs)
125	NMR ($CDCl_3$) δ: 1.47(9H,s), 1.59(6H,s), 2.55-3.60(6H,m), 5.01(1H,s), 6.34(1H,s), 6.95-7.50(9H,m), 9.25(1H,brs)
126	NMR ($CDCl_3$) δ: 1.47(9H,s), 1.75-3.80(13H,m), 4.86(1H,brs), 6.99-7.50(9H,m)

[0133]

[Table 8]

Rex.	DATA
127	NMR ($CDCl_3$) δ: 1.47(9H,s), 2.55-2.75(2H,m), 3.15-3.55(4H,m), 3.75(2H,s), 4.33(1H,brs), 4.87(1H,br), 6.86(1H,d,J=4.4Hz), 6.97-7.15(2H,m), 7.23-7.48 (9H,m), 9.28(1H,brs)
128	NMR ($CDCl_3$) δ: 1.43(9H,s), 2.55-3.50(6H,m), 3.78(2H,s), 4.89(1H,brs), 5.41(2H,s), 6.98-7.44(14H,m), 7.86(1H,s), 9.87(1H,brs)
129	NMR ($CDCl_3$) δ: 1.45(9H,s), 2.55-3.51(6H,m), 3.85(2H,s), 4.87(1H,brs), 5.29(2H,s), 7.04(2H,brs), 7.22-7.43(12H,m), 8.02(1H,s), 9.27(1H,brs)
130	NMR ($CDCl_3$) δ: 1.46(9H,s), 2.60-3.40(6H,m), 3.50(2H,s), 4.79-4.85(1H,m), 5.63(2H,s), 6.57(1H,s), 7.01-7.46(14H,m)
131	NMR ($CDCl_3$) δ: 1.46(9H,s), 1.77-1.98(3H,m), 2.56-2.88(5H,m), 3.10-3.55(4H,m), 3.82-3.90(1H,m), 4.35(1H,brs), 4.80-4.93(1H,m), 6.97-7.10(2H,m), 7.15(1H,dd,J=7.6, 4.8Hz), 7.24-7.37(5H,m), 7.43-7.48(3H,m), 8.45(1H,dd,J=4.4, 1.6Hz), 10.01(1H,brs)
132	NMR ($CDCl_3$) δ: 1.47(9H,s), 2.52-2.80(2H,m), 3.20-3.52(4H,m), 3.73(2H,s), 4.88(1H,brs), 7.00-7.40(11H,m), 7.45-7.51(5H,m), 10.41(1H,brs)
133	NMR ($CDCl_3$) δ: 1.22(6H,d,J=6.9Hz), 1.47(9H,s), 2.50-3.50(7H,m), 3.89(2H,s), 4.85-4.94(1H,m), 5.27(2H,s), 6.91(1H,s), 7.00-7.45(10H,m), 7.57(2H,d,J=8.3Hz), 10.12(1H,brs)
134	NMR ($CDCl_3$) δ: 1.47(9H,s), 2.50-2.80(2H,m), 3.20-3.60(6H,m), 4.30(1H,brs), 4.88(1H,brs), 4.99(2H,s), 6.70(1H,s), 6.97-7.52(28H,m)
135	NMR ($CDCl_3$) δ: 1.47(9H,s), 2.69(2H,brs), 3.11-3.43(4H,m), 3.74(2H,s), 4.37(1H,brs), 4.88(1H,brs), 5.22(2H,s), 6.72(1H,brd,J=7.2Hz), 6.91(1H,d,J=4.5Hz), 7.05(2H,brs), 7.10(1H,d,J=4.5Hz), 7.16-7.35(7H,m), 7.42(1H,d,J=8.1Hz), 7.48(2H,d,J=8.4Hz), 10.40(1H,brs)
136	NMR ($CDCl_3$) δ: 1.47(9H,s), 2.69(2H,brs), 3.20-3.50(4H,m), 3.71(2H,s), 4.81(1H,brs), 4.88(1H,brs), 5.14(2H,s), 6.93(2H,brs), 7.06(3H,brd,J=8.4Hz), 7.26-7.35(8H,m), 7.45(2H,d,J=8.4Hz), 10.20(1H,brs)
137	NMR ($CDCl_3$) δ: 1.47(9H,s), 2.70(2H,brs), 3.15-3.40(4H,m), 3.71(2H,s), 4.88(1H,brs), 5.13(2H,s), 6.72(1H,brd,J=7.2Hz), 6.90-7.44(14H,m), 10.01(1H,brs)
138	NMR ($CDCl_3$) δ: 1.46(9H,s), 2.70(2H,brs), 3.36(4H,brs), 4.40(2H,s), 4.89(1H,brs), 5.58(2H,s), 7.03-7.37(10H,m), 7.55-7.77(5H,m), 10.19(1H,brs)
139	NMR ($CDCl_3$) δ: 1.46(9H,s), 1.55(9H,s), 2.55-2.85(2H,m), 3.15-3.55(4H,m), 3.76(2H,s), 4.86(1H,dd,J=8.0, 3.2Hz), 6.94-7.15(3H,m), 7.21-7.48(6H,m), 7.63-7.84(3H,m), 9.03(1H,brs)
140	NMR ($CDCl_3$) δ: 1.47(9H,s), 2.55-2.85(2H,m), 3.12-3.54(4H,m), 3.67(2H,s), 4.56(2H,brs), 4.81-4.92(1H,m), 6.42(1H,d,J=8.4Hz), 6.63(1H,d,J=7.2Hz), 6.97-7.15(2H,m), 7.21-7.46(8H,m), 9.66(1H,brs)
141	NMR ($CDCl_3$) δ: 0.97(6H,d,J=6.3Hz), 1.46(9H,s), 2.06-2.17(1H,m), 2.50-3.50(6H,m), 4.00(2H,d,J=7.8Hz), 4.11(2H,s), 4.83-4.92(1H,m), 6.95(1H,d,J=1.5Hz), 7.00-7.10(2H,m), 7.14(1H,d,J=1.5Hz), 7.22-7.40(9H,m), 7.59(2H,d,J=8.0Hz), 10.11(1H,brs)

[0134]

[Table 9]

Rex.	DATA
142	NMR (CDCl3) δ: 1.47(9H,s), 2.60-2.80(2H,m), 3.15-3.55(4H,m), 3.78(2H,s), 4.36(1H,brs), 4.82-4.94(1H,m), 5.18(2H,s), 6.92-6.99(2H,m), 7.00-7.13(5H,m), 7.25-7.38(6H,m), 7.42-7.48(2H,m), 10.34(1H,brs)
143	NMR (CDCl3) δ: 1.47(9H,s), 2.60-2.80(2H,m), 3.10-3.55(4H,m), 3.70(2H,s), 4.40(1H,brs), 4.87-4.89(1H,m), 5.16(2H,s), 6.75(1H,d,J=10.2Hz), 6.86(1H,d,J=8.3Hz), 6.90-7.40(11H,m), 7.45(2H,d,J=8.3Hz), 10.22(1H,brs)
144	NMR (CDCl3) δ: 1.47(9H,s), 2.60-2.77(2H,m), 3.20-3.54(4H,m), 3.78(2H,s), 4.33-4.42(1H,m), 4.84-4.94(1H,m), 5.14(2H,s), 6.80-7.10(8H,m), 7.31-7.37(4H,m), 7.46(2H,d,J=8.3Hz), 10.19(1H,s)
145	NMR (CDCl3) δ: 1.47(9H,s), 2.70(2H,brs), 3.35(4H,brs), 3.92(2H,s), 4.36(1H,brs), 4.89(1H,brs), 5.17(2H,s), 6.92-7.07(6H,m), 7.26-7.35(6H,m), 7.48(2H,d,J=8.7Hz), 10.29(1H,brs)
146	NMR (CDCl3) δ: 1.47(9H,s), 2.60-2.80(2H,m), 3.15-3.55(4H,m), 3.69(2H,s), 4.35(1H,brs), 4.83-4.94(1H,m), 5.15(2H,s), 6.53-6.62(2H,m), 6.75(1H,tt,J=8.8, 2.0Hz), 6.94(1H,s), 7.00-7.15(3H,m), 7.25-7.39(5H,m), 7.42-7.48(2H,m), 10.09(1H,brs)
147	NMR (CDCl3) δ: 1.47(9H,s), 2.70(2H,brs), 3.36(4H,brs), 3.77(2H,s), 4.87(1H,brs), 5.17(2H,s), 6.60(1H,m), 6.95(1H,s), 6.95-7.09(5H,m), 7.25-7.35(5H,m), 7.46(2H,d,J=8.4Hz), 10.21(1H,brs)
148	NMR (CDCl3) δ: 1.47(9H,s), 2.60-2.70(2H,m), 3.10-3.60(4H,m), 3.70(2H,s), 4.85-4.90(1H,m), 5.12(2H,s), 6.80-6.95(3H,m), 7.00-7.20(4H,m), 7.50-7.90(5H,m), 7.44(2H,d,J=8.4Hz), 10.05(1H,brs)
149	NMR (CDCl3) δ: 1.47(9H,s), 2.60-2.80(2H,m), 3.10-4.05(4H,m), 3.92(2H,s), 4.35(1H,brs), 4.85-4.94(1H,m), 5.20(2H,s), 6.90-7.25(7H,m), 7.30-7.40(4H,m), 7.48(2H,d,J=8.4Hz), 10.25(1H,brs)
150	NMR (CDCl3) δ: 1.47(9H,s), 2.60-2.80(2H,m), 3.15-3.55(4H,m), 3.77(2H,s), 4.37(1H,brs), 4.82-4.94(1H,m), 5.15(2H,s), 6.74-6.82(1H,m), 6.90-7.14(5H,m), 7.24-7.37(5H,m), 7.42-7.48(2H,m), 10.04(1H,brs)
151	NMR (CDCl3) δ: 1.51(9H,s), 2.60-2.75(2H,m), 3.10-3.65(4H,m), 3.70(2H,s), 4.36(1H,brs), 4.85-4.93(1H,m), 5.12(2H,s), 6.69(2H,t,J=6.8Hz), 6.92(1H,s), 7.00-7.15(3H,m), 7.25-7.40(5H,m), 7.43(2H,d,J=8.3Hz), 9.91(1H,brs)
152	NMR (CDCl3) δ: 1.47(9H,s), 2.60-2.77(2H,m), 3.20-3.50(4H,m), 3.90(2H,s), 4.33-4.42(1H,m), 4.84-4.92(1H,m), 5.25(2H,s), 6.93(1H,s), 7.00-7.08(2H,m), 7.30-7.37(5H,m), 7.46(2H,d,J=8.3Hz), 10.03(1H,s)
153	NMR (CDCl3) δ: 1.47(9H,s), 2.60-2.80(2H,m), 3.15-3.55(4H,m), 3.71(2H,s), 4.38(1H,brs), 4.82-4.94(1H,m), 5.10(2H,s), 6.93(1H,s), 6.99-7.11(5H,m), 7.23-7.48(8H,m), 7.62-7.67(2H,m), 10.18(1H,brs)
154	NMR (CDCl3) δ: 1.47(9H,s), 2.69(2H,brs), 3.36(4H,brs), 3.98(2H,s), 4.41(1H,brs), 4.89(1H,brs), 5.35(2H,s), 6.68(1H,d,J=1.5Hz), 7.00(1H,d,J=1.5Hz), 7.07(2H,m), 7.26-7.41(8H,m), 7.49(2H,d,J=8.4Hz), 10.29(1H,brs)
155	NMR (CDCl3) δ: 1.47(9H,s), 2.70(2H,brs), 3.36(4H,brs), 3.69(2H,s), 4.89(1H,brs), 5.27(2H,s), 6.92(1H,brd,J=1.2Hz), 7.05-7.35(10H,m), 7.40(2H,d,J=8.4Hz), 7.61(2H,d,J=8.1Hz), 9.93(1H,brs)

[0135]

[Table 10]

Rex.	D A T A
156	NMR (CDCl3) δ: 1.47(9H,s), 2.69(2H,brs), 3.36(4H,brs), 3.84(2H,s), 4.43(1H,brs), 4.88(1H,brs), 5.43(2H,s), 7.04-7.06(4H,m), 7.11(1H,d,J=1.2Hz), 7.26-7.35(5H,m), 7.45(2H,d,J=8.4Hz), 7.55(1H,t,J=6.9Hz), 7.69-7.74(1H,m), 7.79(1H,d,J=8.1Hz), 8.01(1H,d,J=8.6Hz), 8.11(1H,d,J=8.6Hz), 10.36(1H,brs)
157	NMR (CDCl3) δ: 1.47(9H,s), 2.70(2H,brs), 3.36(4H,brs), 3.96(2H,s), 4.40(1H,brs), 4.89(1H,brs), 5.25(2H,d,J=1.5Hz), 6.87(1H,s), 6.99(1H,s), 7.03-7.10(3H,m), 7.25-7.35(7H,m), 7.49(2H,d,J=8.4Hz), 10.28(1H,brs)
158	NMR (CDCl3) δ: 1.47(9H,s), 2.70(2H,brs), 3.36(4H,brs), 3.74(2H,s), 4.42(1H,brs), 4.88(1H,brs), 5.19(2H,s), 6.74(1H,dd,J=8.4, 8.0Hz), 6.89-6.94(2H,m), 7.09-7.35(9H,m), 7.46(2H,d,J=8.4Hz), 10.26(1H,brs)
159	NMR (CDCl3) δ: 1.47(9H,s), 2.60-2.77(2H,m), 3.20-3.60(4H,m), 3.73(2H,s), 4.30-4.40(1H,m), 4.84-4.94(1H,m), 5.20(2H,s), 6.66(1H,d,J=2.5Hz), 6.92(1H,s), 7.00-7.20(3H,m), 7.22-7.52(9H,m), 10.25(1H,s)
160	NMR (CDCl3) δ: 1.47(9H,s), 2.60-2.75(2H,m), 3.25-3.55(4H,m), 3.77(2H,s), 4.30-4.40(1H,m), 4.84-4.92(1H,m), 5.18(2H,s), 6.67-6.75(1H,m), 6.88-6.96(2H,m), 7.02-7.12(3H,m), 7.31-7.36(5H,m), 7.45(2H,d,J=8.3Hz), 10.06(1H,s)
161	NMR (CDCl3) δ: 1.47(9H,s), 2.60-2.80(2H,m), 3.20-3.60(4H,m), 3.70(2H,s), 3.91(3H,s), 4.82-4.95(1H,m), 5.23(2H,s), 6.94(1H,s), 6.99-7.50(13H,m), 7.94-8.03(2H,m), 10.18(1H,brs)
162	NMR (CDCl3) δ: 1.47(9H,s), 1.60-1.70(6H,m), 2.60-2.80(2H,m), 3.20-3.40(5H,m), 3.60-3.75(3H,m), 3.71(2H,s), 4.30-4.40(1H,m), 4.80-4.90(1H,m), 5.17(2H,s), 6.95(1H,s), 7.00-7.20(5H,m), 7.30-7.50(10H,m), 10.28(1H,s)
163	NMR (CDCl3) δ: 1.47(9H,s), 2.60-2.90(2H,m), 3.16-3.56(4H,m), 4.01(2H,s), 4.20-4.30(1H,m), 4.80-4.95(1H,m), 7.00-7.20(2H,m), 7.25-7.38(5H,m), 7.44(2H,d,J=8.4Hz), 8.07(1H,s)
164	NMR (CDCl3) δ: 1.47(9H,s), 2.60-2.88(2H,m), 3.10-3.54(4H,m), 4.20-4.35(1H,m), 4.85-4.90(1H,m), 4.93(2H,s), 6.38-6.40(1H,m), 7.00-7.15(2H,m), 7.30-7.40(7H,m), 7.53(1H,d,J=2.0Hz), 7.71(1H,d,J=2.0Hz), 8.34(1H,s)
165	NMR (CDCl3) δ: 1.46(9H,s), 2.60-2.84(2H,m), 3.10-3.50(4H,m), 4.14-4.28(1H,m), 4.84-4.92(1H,m), 5.00(2H,s), 7.02-7.10(2H,m), 7.30-7.40(7H,m), 8.12(1H,s), 8.24(2H,s)
166	NMR (CDCl3) δ: 1.43(9H,s), 2.60-2.80(2H,m), 3.10-3.50(4H,m), 4.64(2H,s), 4.75-4.85(1H,m), 6.90-7.00(4H,m), 7.20-7.35(9H,m), 8.50-8.80(1H,m)
167	NMR (CDCl3) δ: 2.62-3.00(6H,m), 3.50-3.65(2H,m), 3.95(1H,d,J=13.2Hz), 4.67(1H,dd,J=10.4, 4.0Hz), 7.18-7.40(12H,m), 8.05-8.15(2H,m)
168	NMR (CDCl3) δ: 2.56-2.94(6H,m), 3.40-3.65(2H,m), 3.80(1H,brs), 3.95(1H,d,13.6Hz), 4.62(1H,dd,J=10.0, 3.2Hz), 6.57-6.66(2H,m), 6.87-6.98(2H,m), 7.20-7.37(10H,m)
169	NMR (CDCl3) δ: 2.54-2.98(6H,m), 3.50-4.02(5H,m), 4.62(1H,dd,J=10.0, 3.6Hz), 6.80-7.70(17H,m), 8.60(1H,d,J=5.6Hz), 9.73(1H,br)

[0136]

[Table 11]

Rex.	D A T A
170	NMR (CDCl3) δ: 2.54-2.98(6H,m), 3.50-3.74(3H,m), 3.96(1H,d,J=13.6Hz), 4.59(1H,dd,J=10.0, 3.6Hz), 7.00-7.80(16H,m), 8.50-8.62(2H,m)
171	NMR (CDCl3) δ: 2.54-3.02(6H,m), 3.50-3.75(3H,m), 3.96(1H,d,J=13.6Hz), 4.59(1H,dd,J=10.4, 4.0Hz), 7.00-7.60(16H,m), 8.55-8.65(2H,m)
172	NMR (CDCl3) δ: 2.54-3.02(6H,m), 3.50-4.04(3H,m), 3.65(1H,d,J=13.6Hz), 4.59(1H,dd,J=10.0, 4.0Hz), 7.00-8.00(19H,m), 8.61(1H,d,J=4.4Hz)
173	NMR (CDCl3) δ: 1.22(6H,d,J=6.9Hz), 1.47(9H,s), 2.50-3.50(7H,m), 3.89(2H,s), 4.85-4.94(1H,m), 5.27(2H,s), 6.91(1H,s), 7.00-7.45(10H,m), 7.57(2H,d,J=8.3Hz), 10.12(1H,brs)
174	NMR (CDCl3) δ: 2.57-2.96(3H,m), 3.58(1H,d,J=14.0Hz), 3.97(1H,d,J=4.0Hz), 4.04(2H,d,J=1.2Hz), 4.58(1H,dd,J=10.0, 3.2Hz), 7.10(2H,d,J=8.4Hz), 7.21-7.33(14H,m), 7.50(2H,d,J=8.4Hz), 9.82(1H,brs)
175	NMR (CDCl3) δ: 2.40(3H,s), 2.54-3.00(6H,m), 3.57(1H,d,J=13.6Hz), 3.88(2H,s), 3.95(1H,d,J=13.6Hz), 4.62(1H,dd,J=10.4, 3.6Hz), 7.00-7.75(16H,m), 8.44(1H,d,J=4.4Hz), 9.66(1H,brs)
176	NMR (CDCl3) δ: 2.54-3.00(6H,m), 3.57(1H,d,J=13.6Hz), 3.89(2H,s), 3.95(1H,d,J=13.6Hz), 4.61(1H,dd,J=10.0, 3.6Hz), 7.00-7.50(14H,m), 8.45-8.70(3H,m), 8.91(1H,brs)
177	NMR (CDCl3) δ: 2.59-2.94(6H,m), 3.57(1H,d,J=14.6Hz), 3.72(2H,s), 3.96(1H,d,J=14.6Hz), 4.63(1H,dd,J=10.4, 4.0Hz), 5.14(2H,s), 6.90(1H,s), 7.04-7.10(4H,m), 7.24-7.36(14H,m), 7.46(2H,d,J=8.4Hz), 10.27(1H,s)
178	NMR (CDCl3) δ: 2.31(3H,s), 2.89-3.19(6H,m), 3.98(2H,s), 3.72(2H,s), 4.96(1H,dt,J=3.2, 10.4Hz), 7.03-7.40(17H,m), 10.30(1H,s)
179	NMR (CDCl3) δ: 2.24(3H,s), 2.82-3.20(6H,m), 3.81(2H,s), 3.99(2H,s), 5.01(1H,dt,J=10.0, 3.6Hz), 7.14-7.61(17H,m), 10.36(1H,s)
180	NMR (CDCl3) δ: 2.42(3H,s), 2.70-3.19(6H,m), 3.69(2H,s), 3.93(2H,s), 4.94(1H,dt,J=3.2, 10.0Hz), 7.05-7.69(17H,m), 10.26(1H,s)
181	NMR (CDCl3) δ: 1.10(3H,d,J=6.4Hz), 2.73(1H,dd,J=13.2, 6.4Hz), 2.89(1H,dd,J=13.2, 6.8 Hz), 2.95-3.06(1H,m), 3.76 (1H,d,J=13.2Hz), 3.86(1H,d,J=13.2Hz), 7.16-7.40(7H,m), 8.01-8.22(2H,m)
182a	NMR (CDCl3) δ: 1.07(3H,d,J=6.4Hz), 2.50-2.75(3H,m), 2.88(1H,dd,J=13.6, 8.8Hz), 3.15-3.30(1H,m), 3.51(1H,d,J=13.2Hz), 3.88(1H,d,J=13.2Hz), 4.62(1H,dd,J=10.4, 4.0Hz), 6.80-7.60(12H,m), 8.00-8.15(2H,m)
182b	NMR (CDCl3) δ: 1.05(3H,d,J=6.4Hz), 2.47(1H,dd,J=14.4, 10.4Hz), 2.62-2.85(2H,m), 3.03-3.18(2H,m), 3.62(1H,brs), 3.75(1H,d,J=13.2Hz), 3.89(1H,d,J=13.2Hz), 4.51(1H,dd,J=9.6, 3.2Hz), 7.14-7.44(12H,m), 8.05-8.20(2H,m)
183	NMR (CDCl3) δ: 1.00(3H,d,J=6.8Hz), 2.45-2.77(4H,m), 3.13-3.18(1H,m), 3.40-3.78(4H,m), 3.91(1H,d,J=13.6Hz), 4.56(1H,dd,J=10.4, 3.6Hz), 6.55-6.68(2H,m), 6.80-6.93(2H,m), 7.13-7.40(10H,m)
184	NMR (CDCl3) δ: 1.04(3H,d,J=6.8Hz), 2.27(1H,dd,J=13.2, 9.6Hz), 2.62(1H,dd,J=13.2, 10.4Hz), 2.75(1H,dd,J=13.2, 4.0Hz), 3.30-4.10(5H,m), 4.42(1H,dd,J=10.0, 4.0Hz), 6.55-6.68(2H,m), 6.83-6.95(2H,m), 7.20-7.40(10H,m)

[0137]

[Table 12]

Rex.	DATA
185	NMR ($CDCl_3$) δ: 1.00(3H,d,J=6.8Hz), 2.54-2.65(3H,m), 2.70-2.82(1H,m), 3.08-3.20(1H,m), 3.44-3.98(5H,m), 4.55(1H,dd,J=10.4, 3.6Hz), 6.80-7.60(16H,m), 7.64-7.74(1H,m), 8.50-8.70(1H,m), 9.72(1H,brs)
186	NMR ($CDCl_3$) δ: 1.02(3H,d,J=6.8Hz), 2.32(1H,dd,J=12.8, 8.8Hz), 2.63(1H,dd,J=13.2, 10.4Hz), 2.75(1H,dd,J=13.2, 3.6Hz), 2.95-3.10(2H,m), 3.70-3.92(4H,m), 4.44(1H,dd,J=9.6, 3.6Hz), 7.00-7.06(2H,m), 7.16-7.38(11H,m), 7.62-7.72(2H,m), 8.61(1H,d,J=4.4Hz), 9.74(1H,brs)
187	NMR ($CDCl_3$) δ: 1.03(3H,d,J=6.8Hz), 2.32(1H,dd,J=13.2, 9.2Hz), 2.64(1H,dd,J=13.2, 10.4Hz), 2.75(1H,dd,J=13.2, 3.6Hz), 2.95-3.10(2H,m), 3.65-3.93(4H,m), 4.45(1H,dd,J=10.4, 4.0Hz), 5.14(2H,s), 6.92-7.50(21H,m), 10.30(1H,brs)
188	NMR ($CDCl_3$) δ: 2.58-2.65(1H,m), 2.75-3.00(5H,m), 3.59(1H,d,J=13.2Hz), 3.95(1H,d,J=13.2Hz), 5.01(1H,dd,J=10.0, 3.2Hz), 6.97-7.03(1H,m), 7.12-7.35(9H,m), 7.48-7.56(1H,m), 8.04-8.13(2H,m)
189	NMR ($CDCl_3$) δ: 2.65(1H,d,J=10.0, 12.4Hz), 2.72-3.00(5H,m), 3.57(1H,d,J=13.2Hz), 3.94(1H,d,J=13.2Hz), 4.64(1H,dd,J=10.0, 3.2Hz), 6.92-7.08(3H,m), 7.20-7.36(8H,m), 8.11(2H,d,J=8.8Hz)
190	NMR ($CDCl_3$) δ: 2.57-3.00(6H,m), 3.56(1H,d,J=13.2Hz), 3.95(1H,d,J=13.2Hz), 4.63(1H,dd,J=10.0, 3.2Hz), 6.99-7.04(2H,m), 7.21-7.35(9H,m), 8.12(2H,d,J=8.4Hz)
191	NMR ($CDCl_3$) δ: 2.52-2.59(1H,m), 2.64-2.93(5H,m), 3.58(1H,d,J=13.6Hz), 3.72-3.76(1H,m), 3.96(1H,d,J=13.6Hz), 4.98(1H,dd,J=2.8, 10.4Hz), 6.60-6.64(2H,m), 6.61-7.35(10H,m), 7.47-7.59(1H,m)
192	NMR ($CDCl_3$) δ: 2.51-2.59(1H,m), 2.64-2.90(5H,m), 3.57(1H,d,J=13.2Hz), 3.94(1H,d,J=13.2Hz), 4.59(1H,dd,J=10.0, 3.2Hz), 6.60-6.64(2H,m), 6.90-6.94(3H,m), 7.00-7.05(2H,m), 7.23-7.35(6H,m)
193	NMR ($CDCl_3$) δ: 2.52-2.92(6H,m), 3.57(1H,d,J=13.6Hz), 3.80(1H,s), 3.96(1H,d,J=13.6Hz), 4.58(1H,dd,J=10.2, 3.6Hz), 6.60-6.64(2H,m), 6.91-7.02(4H,m), 7.22-7.35(7H,m)
194	NMR ($CDCl_3$) δ: 2.53-2.60(1H,m), 2.68-2.94(5H,m), 3.58(1H,d,J=13.2Hz), 3.86(2H,s), 3.95(1H,d,J=13.2Hz), 4.97(1H,dd,J=2.8, 10.0Hz), 6.94-7.35(12H,m), 7.44-7.51(3H,m), 7.67-7.72(1H,m), 8.60-8.63(1H,m), 9.72(1H,s)
195	NMR ($CDCl_3$) δ: 2.52-2.59(1H,m), 2.66-2.94(5H,m), 3.57(1H,d,J=13.2Hz), 3.86(2H,s), 3.94(1H,d,J=13.2Hz), 4.58(1H,dd,J=10.4, 3.6Hz), 6.89-7.07(4H,m), 7.19-7.35(9H,m), 7.45-7.48(2H,m), 7.62-7.72(1H,m), 8.60-8.64(1H,m), 9.74(1H,s)
196	NMR ($CDCl_3$) δ: 2.52-2.94(6H,m), 3.56(1H,d,J=13.2Hz), 3.86(2H,s), 3.94(1H,d,J=13.2Hz), 4.57(1H,dd,J=10.0, 3.2Hz), 6.96-7.08(4H,m), 7.21-7.35(9H,m), 7.45-7.48(2H,m), 7.66-7.72(1H,m), 8.60-8.64(1H,m), 9.73(1H,s)
197	NMR ($CDCl_3$) δ: 3.70(2H,s), 3.88(2H,s), 7.23-7.32(4H,m), 7.54-7.62(2H,m), 7.71(1H,dt,J=7.6, 1.6Hz), 8.63(1H,d), 10.04(1H,brs)

【0138】

[Table 13]

Rex.	D A T A
198	NMR ($CDCl_3$) δ: 3.72(2H,s), 4.13(2H,s), 7.26-7.31(3H,m), 7.58-7.63(2H,m), 8.78(2H,d,J=5.2Hz), 9.82(1H,brs)
199	NMR ($CDCl_3$) δ: δ:3.71(2H,s), 4.08(2H,s), 7.25-7.30(2H,m), 7.40(1H,d,J=8.4Hz), 7.57-7.66(3H,m), 7.77-7.89(2H,m), 8.12(1H,d,J=8.4Hz), 8.20(1H,d,J=8.4Hz), 10.60(1H,brs)
200	NMR ($CDCl_3$) δ: 2.31(3H,s), 2.59(3H,s), 3.71(2H,s), 3.77(2H,s), 6.91(1H,s), 6.93(1H,s), 7.24-7.28(2H,m), 7.55-7.60(2H,m), 10.60(1H,brs)
201	NMR ($CDCl_3$) δ: 3.70(2H,s), 3.97(2H,s), 5.42(2H,s), 3.74(2H,s), 7.01(1H,d,J=8.5Hz), 6.89-6.94(2H,m), 7.22-7.37(7H,m), 7.56(2H,d,J=8.5Hz), 7.78-7.81(1H,m), 10.68(1H,brs)
202	NMR ($CDCl_3$) δ: 2.26(3H,s), 2.39(3H,s), 2.57(2H,t,J=7.2Hz), 2.72(2H,t,J=7.2Hz), 3.72(2H,s), 6.95(1H,s), 7.01(1H,s), 7.11(2H,d,J=8.8Hz), 7.51(2H,d,J=8.8Hz), 10.17(1H,s)
203	NMR δ: 2.32(3H,s), 2.41(3H,s), 2.90-3.19(6H,m), 3.75(2H,s), 4.01(2H,s), 4.89(1H,dt,J=7.6, 3.2Hz), 6.99-7.71(16H,m), 10.26(1H,s)
204	NMR ($CDCl_3$) δ: 1.47(9H,s), 1.70-1.82(2H,m), 2.59(2H,t,d,J=8.0Hz), 3.04-3.20(2H,m), 3.86(2H,s), 4.52(1H,brs), 7.05-7.15(2H,m), 7.20-7.33(2H,m), 7.40-7.50(2H,m), 7.69(1H,dt,J=2.0, 8.0Hz), 8.55-8.65(1H,m), 9.70(1H,brs)
205	NMR ($CDCl_3$) δ: 1.45(9H,s), 3.42-3.60(2H,m), 3.86(2H,s), 3.98(2H,t,J=5.2Hz), 5.00(1H,brs), 6.77-6.88(2H,m), 7.21-7.28(1H,m), 7.22(1H,d,J=8.0Hz), 7.40-7.50(2H,m), 7.70(1H,dt,J=8.0, 2.0Hz), 8.57-8.65(1H,m), 9.68(1H,brs)
206	NMR ($CDCl_3$) δ: 1.24(6H,s), 1.46(9H,s), 2.93(2H,s), 3.87(2H,s), 4.24(1H,brs), 7.05-7.13(2H,m), 7.18-7.33(2H,m), 7.42-7.50(2H,m), 7.66-7.73(1H,m), 8.58-8.66(1H,m), 9.73(1H,brs)
207	NMR ($CDCl_3$) δ: 1.65-1.85(2H,m), 2.55-2.64(2H,m), 2.66-2.74(2H,m), 3.86(2H,s), 7.07-7.15(2H,m), 7.20-7.35(4H,m), 7.40-7.50(2H,m), 7.65-7.73(1H,m), 8.54-8.64(1H,m), 9.70(1H,brs)
208	NMR ($CDCl_3$) δ: 1.48(9H,s), 2.60-2.85(2H,m), 3.15-3.60(4H,m), 4.30-4.40(1H,m), 4.80-4.95(1H,m), 6.77(1H,d,J=8.3Hz), 6.92-6.97(1H,m), 7.05-7.15(2H,m), 7.31-7.36(4H,m), 7.51(2H,d,J=8.3Hz), 7.60-7.68(2H,m), 8.26(1H,dt,J=4.9, 1.0Hz), 11.71(1H,s)

[0139]

[Table 14]

Ex.	DATA
1	mp : 223-225℃ NMR δ: 2.95-3.28(6H,m), 4.98-5.07(1H,m), 7.23-7.44(6H,m), 7.65-7.75(1H,m), 7.88(2H,d,J=8.4Hz), 8.05-8.22(2H,m), 8.75(1H,d,J=4.4Hz), 8.97(1H,brs), 9.43(1H,brs), 10.65(1H,brs)
2	mp : 263-265℃ NMR δ: 2.92-3.10(3H,m), 3.13-3.27(3H,m), 5.00(1H,dd,J=10.8, 2.8Hz), 7.24-7.44(8H,m), 7.74-7.81(3H,m), 8.57(1H,d,J=8.0Hz), 8.81-8.96(2H,m), 9.20-9.30(2H,m), 10.71(1H,brs)
3	mp : 145-147℃ NMR δ: 2.94-3.10(3H,m), 3.14-3.30(3H,m), 4.97-5.05(1H,m), 7.27-7.46(7H,m), 7.77-7.90(4H,m), 8.30(1H,dd,J=8.4, 1.6Hz), 8.60-8.71(2H,m), 8.89(1H,brs), 9.10-9.30(2H,m), 13.12(1H,brs)
4	mp : 246-248℃ (dec) NMR δ: 2.92-3.09(3H, m), 3.11-3.26(3H,m), 5.01(1H,dd,J=10.4, 2.8Hz), 7.24(2H,d,J=8.4Hz), 7.29-7.47(6H,m), 7.56-7.75(4H,m), 7.85(1H,d,J=8.0Hz), 8.11(1H,t,J=7.6Hz), 8.73(1H,d,J=4.4Hz), 8.92(1H,brs), 9.32(1H,brs), 10.69(1H,brs)
5	mp : 228-233℃ (dec) NMR δ: 2.88-3.09(3H,m), 3.10-3.24(3H,m), 4.30(2H,s), 4.93-5.01(1H,m), 6.19(1H,d,J=3.6Hz), 7.18-7.27(2H,m), 7.28-7.53(7H,m), 7.57-7.62(2H,m), 7.97(1H,d,J=7.6Hz), 8.08(1H,d,J=8.0Hz), 8.83(1H,brs), 9.11(1H,brs), 10.57(1H,brs)
6	mp : 161-162℃ NMR δ: 2.86-3.24(6H,m), 4.24(2H,s), 4.97(1H,dd,J=9.6, 2.8Hz), 7.16-7.23(2H,m), 7.27-7.44(5H,m), 7.55(1H,s), 7.61(2H,d,J=8.4Hz), 7.85(1H,s), 8.27(1H,d,J=2.4Hz), 8.97(1H,brs), 9.47(1H,brs), 10.94(1H,brs)
7	MS (m/z) : 396[(M+H)$^+$] NMR δ: 2.70(3H,s), 2.86-3.27(6H,m), 3.85(2H,s), 5.00-5.05(1H,m), 7.18-7.60(10H,m), 10.43(1H,s)
8	mp : 203-207℃ NMR δ: 2.92-3.08(3H,m), 3.10-3.22(3H,m), 4.28(2H,s), 5.01(1H,d,J=7.8Hz), 6.21(1H,brs), 7.22(2H,d,J=8.3Hz), 7.25-7.63(4H,m), 8.93(1H,brs), 9.38(1H,brs), 10.86(1H,s)
9	mp : 259-261℃ NMR δ: 2.90-3.10(3H,m), 3.10-3.25(3H,m), 4.15(2H,s), 4.97(1H,d,J=10.8Hz), 6.20(1H,d,J=3.9Hz), 7.21(2H,d,J=8.8Hz), 7.30-7.42(5H,m), 7.57(2H,d,J=8.8Hz), 8.85(1H,brs), 9.14(1H,brs), 10.58(1H,s)
10	mp : 210-213℃ NMR δ: 2.86-3.08(3H,m), 3.12-3.22(3H,m), 3.73(2H,s), 4.91-4.98(1H,m), 6.19(1H,d,J=3.9Hz), 7.21(2H,d,J=8.3Hz), 7.29-7.42(5H,m), 7.54(2H,d,J=8.3Hz), 8.78(1H,brs), 8.99(1H,brs), 10.35(1H,s), 13.21(1H,brs), 13.34(1H,brs)

[0140]

[Table 15]

Ex.	DATA
11	mp : 205-210°C (dec) NMR δ: 2.90-3.25(6H,m), 4.95-5.04(1H,m), 7.23-7.44(7H,m), 7.67-7.75(2H,m), 8.15(1H,s), 8.88(1H,brs), 9.25(1H,brs), 10.83(1H,brs)
12	mp : 244-246°C NMR δ: 2.90-3.08(3H,m), 3.10-3.20(3H,m), 3.67(2H,s), 5.00(1H,dd,J=2.4,10.02Hz), 7.19(2H,d,J=8.3Hz), 7.28-7.42(5H,m), 7.57(2H,d,J=8.3Hz), 8.90(1H,s), 9.31(1H,s), 10.31(1H,s)
13	mp : 205-208°C NMR δ: 1.27(3H,t,J=7.1Hz), 2.88-3.08(3H,m), 3.12-3.22(3H,m), 3.86(2H,s), 4.27(2H,q,J=7.1Hz), 4.96(1H,d,J=8.3Hz), 6.20(1H,s), 7.19(2H,d,J=8.3Hz), 7.30-7.42(5H,m), 7.57(2H,d,J=8.3Hz), 8.81(1H,s), 9.10(1H,s), 10.33(1H,s), 12.53(1H,s)
14	mp : 169-173°C NMR δ: 2.88-3.22(6H,m), 3.66(2H,s), 4.98(1H,dd,J=2.9, 13.1Hz), 6.72(1H,s), 7.19(2H,d,J=8.3Hz), 7.23-7.42(8H,m), 7.59(2H,d,J=8.3Hz), 7.72-7.78(1H,m), 8.85(1H,s), 9.18(1H,brs), 10.24(1H,brs), 10.55(1H,s)
15	mp : 248-251°C NMR δ: 2.90-3.08(3H,m), 3.09-3.21(3H,m), 3.88(2H,s), 5.02(1H,dd,J=10.0, 2.4Hz), 6.20(1H,brs), 7.16-7.22(2H,m), 7.28-7.46(7H,m), 7.57-7.63(2H,m), 7.84(1H,t,J=7.2Hz), 8.95(1H,brs), 9.40(1H,brs), 10.48(1H,brs)
16	mp : 237-238°C NMR δ: 2.87-3.24(6H,m), 3.77(2H,s), 4.93-5.03(1H,m), 5.32(2H,s), 6.20(1H,d,J=4.0Hz), 6.73(1H,d,J=8.0Hz), 6.99(1H,d,J=7.2Hz), 7.16-7.22(2H,m), 7.25-7.46(10H,m), 7.57-7.63(2H,s), 7.67(1H,dd,J=8.4, 7.2Hz), 8.87(1H,brs), 9.24(1H,brs), 10.30(1H,brs)
17	mp : 190-193°C NMR δ: 1.68(3H,m), 2.90-3.10(3H,m), 3.10-3.20(3H,m), 4.32(2H,s), 4.67(1H,s), 4.83(2H,s), 4.94(1H,s), 4.99(1H,d,J=8.3Hz), 6.21(1H,brs), 7.21(2H,d,J=8.7Hz), 7.24-7.42(5H,m), 7.56(2H,d,J=8.8Hz), 7.66(2H,d,J=1.9Hz), 7.71(1H,d,J=1.9Hz), 8.89(1H,brs), 9.30(1H,brs), 10.92(1H,s)
18	mp : 139-141°C NMR δ: 3.01(3H,brs), 3.15(3H,brs), 3.92(2H,s), 5.05(1H,d,J=10.3Hz), 5.44(2H,s), 6.19(1H,brs), 7.19(2H,d,J=8.3Hz), 7.31-7.47(10H,m), 7.60(2H,d,J=8.3Hz), 7.66(1H,s), 9.05(1H,brs), 9.35(1H,s), 9.60(1H,brs), 10.76(1H,s)
19	mp : 140-143°C NMR δ: 2.99-3.09(3H,m), 3.16(3H,brs), 3.95(2H,s), 5.06(1H,d,J=10.4Hz), 5.57(2H,s), 6.19(1H,brs), 7.19(2H,d,J=8.6Hz), 7.29-7.35(1H,m), 7.37-7.48(8H,m), 7.55-7.57(1H,m), 7.61(2H,d,J=8.6Hz), 9.09(1H,brs), 9.31(1H,d,J=1.5Hz), 9.65(1H,brs), 10.79(1H,s)

[0141]

[Table 16]

Ex.	DATA
20	mp : 140-143℃ NMR δ: 3.01-3.09(3H,m), 3.16(3H,brs), 3.93(2H,s), 5.06(1H,d,J=10.3Hz), 5.47(2H,s), 6.15(1H,brs), 7.19(2H,d,J=8.6Hz), 7.29-7.33(1H,m), 7.38-7.46(7H,m), 7.61(2H,d,J=8.6Hz), 7.63(1H,s), 7.70(1H,s), 9.08(1H,brs), 9.38(1H,s), 9.63(1H,brs), 10.78(1H,s)
21	mp : 141-146℃ NMR δ: 2.96-3.14(3H,m), 3.15(3H,brs), 3.91(2H,s), 5.04(1H,d,J=10.3Hz), 5.45(2H,s), 6.22(1H,brs), 7.19(2H,d,J=8.6Hz), 7.29-7.42(6H,m), 7.50(3H,s), 7.59(2H,d,J=8.6Hz), 7.65(1H,s), 9.02(1H,brs), 9.32(1H,d,J=1.5Hz), 9.55(1H,brs), 10.73(1H,s)
22	mp : 230-235℃ NMR δ: 2.59-3.10(3H,m), 3.10-3.25(3H,m), 4.47(2H,s), 5.01(1H,dd,J=10.3, 2.4Hz), 5.45(2H,s), 6.21(1H,brs), 7.16-7.22(4H,m), 7.28-7.50(7H,m), 7.54(2H,d,J=8.3Hz), 7.68(2H,dd,J=5.8, 1.9Hz), 8.94(1H,brs), 9.42(1H,brs), 10.98(1H,s)
23	mp : 203-209℃ NMR δ: 2.90-3.10(3H,m), 3.10-3.20(3H,m), 4.41-4.48(2H,m), 4.95-5.05(1H,m), 5.46(2H,s), 6.21(1H,brs), 7.20(2H,d,J=8.6Hz), 7.30-7.42(6H,m), 7.50-7.54(2H,m), 7.70(2H,s), 8.92(1H,brs), 9.39(1H,brs), 10.88-10.95(1H,m)
24	mp : 221-223℃ NMR δ: 2.90-3.08(3H,m), 3.10-3.22(3H,m), 4.04(2H,s), 4.97(1H,d,J=9.1Hz), 5.44(2H,s), 6.20(1H,brs), 7.20(2H,d,J=8.1Hz), 7.30-7.41(9H,m), 7.49(2H,d,J=8.6Hz), 7.55(2H,d,J=8.6Hz), 8.83(1H,brs), 9.16(1H,brs), 10.76(1H,s)
25	mp : 222-225℃ NMR δ: 2.60-3.05(3H,m), 3.10-3.20(3H,m), 4.43(2H,s), 5.01(1H,d,J=7.6Hz), 5.44(2H,s), 6.21(1H,brs), 7.15-7.23(4H,m), 7.26-7.46(5H,m), 7.51(2H,d,J=8.8Hz), 7.65-7.72(4H,m), 8.94(1H,brs), 9.41(1H,brs), 10.93(1H,s), 14.72(1H,brs)
26	mp : 197-203℃ NMR δ: 2.80-3.10(3H,m), 3.10-3.25(3H,m), 4.44(2H,s), 4.99(1H,d,J=8.0Hz), 5.61(2H,s), 6.21(1H,brs), 7.17(2H,d,J=8.6Hz), 7.30-7.42(5H,m), 7.48(2H,d,J=8.5Hz), 7.54(2H,d,J=8.0Hz), 7.70(2H,d,J=8.1Hz), 7.72-7.77(2H,m), 8.90(1H,brs), 9.34(1H,brs), 10.90(1H,s)
27	mp : 208-214℃ NMR δ: 2.90-3.10(3H,m), 3.10-3.22(3H,m), 4.44(2H,s), 4.97(1H,d,J=9.7Hz), 5.62(2H,s), 6.20(1H,brs), 7.16(2H,d,J=8.0Hz), 7.30-7.55(10H,m), 7.70-7.94(6H,m), 8.82(1H,brs), 9.14(1H,brs), 10.76(1H,s)
28	mp : 219-223℃ NMR δ: 2.11(3H,s), 2.92-3.08(3H,m), 3.10-3.20(3H,m), 4.43(2H,s), 5.02(1H,dd,J=10.2, 2.4Hz), 5.51(2H,s), 6.22(1H,brs), 7.14-7.34(7H,m), 7.36-7.42(4H,m), 7.48-7.53(3H,m), 8.95(1H,brs), 9.43(1H,brs), 10.94(1H,s), 14.61(1H,brs)

[0142]

[Table 17]

Ex.	DATA
29	mp : 204-207°C NMR δ: 2.24(3H,s), 2.80-3.10(3H,m), 3.10-3.50(3H,m), 4.43(2H,s), 5.01(1H,dd,J=10.3, 2.5Hz), 5.39(2H,s), 6.21(1H,brs), 7.17-7.24(2H,m), 7.30-7.42(7H,m), 7.47(2H,dd,J=8.8, 5.4Hz), 7.55(2H,d,J=8.3Hz), 8.94(1H,brs), 9.40(1H,brs), 11.00(1H,s), 14.70(1H,brs)
30	mp : 225-228°C NMR δ: 2.90-3.07(3H,m), 3.10-3.23(3H,m), 4.28(2H,s), 4.97(1H,d,J=10.3Hz), 5.68(2H,s), 6.20(1H,d,J=3.4Hz), 7.16-7.23(4H,m), 7.30-7.46(7H,m), 7.53(2H,d,J=8.8Hz), 8.82(1H,brs), 9.11(1H,brs), 10.63(1H,s)
31	mp : 232-235°C NMR δ: 2.90-3.10(3H,m), 3.10-3.25(3H,m), 4.03(2H,s), 4.98(1H,d,J=10.3Hz), 5.97(2H,s), 6.20(1H,brs), 7.19(2H,d,J=8.3Hz), 7.29-7.42(6H,m), 7.55(2H,d,J=8.3Hz), 7.67-7.77(2H,m), 8.87(1H,brs), 9.22(1H,brs), 10.49(1H,s), 14.61(1H,brs)
32	mp : 233-235°C NMR δ: 2.90-3.10(3H,m), 3.10-3.25(3H,m), 4.01(2H,s), 4.98(1H,d,J=10.3Hz), 5.91(2H,s), 6.19(1H,brs), 7.17-7.48(11H,m), 7.55(2H,d,J=8.3Hz), 8.85(1H,brs), 9.18(1H,brs), 10.47(1H,s)
33	mp : 240-242°C NMR δ: 2.90-3.10(3H,m), 3.10-3.25(3H,m), 4.32(2H,s), 4.98(1H,dt,J=10.3, 3.4Hz), 5.72(2H,s), 6.20(1H,d,J=3.9Hz), 7.20(2H,d,J=8.3Hz), 7.30-7.40(6H,m), 7.51(2H,d,J=8.8Hz), 7.62(1H,d,J=8.3Hz), 7.67(1H,d,J=2.0Hz), 8.86(1H,brs), 9.17(1H,brs), 10.67(1H,s)
34	mp : 221-224°C NMR δ: 2.90-3.07(3H,m), 3.10-3.20(3H,m), 4.05(2H,s), 5.00(2H,dd,J=2.7, 10.2Hz), 7.21(2H,d,J=8.6Hz), 7.29-7.42(5H,m), 7.58(2H,d,J=8.6Hz), 8.83(1H,s), 8.91(1H,brs), 9.32(1H,brs), 10.62(1H,s)
35	mp : 222-224°C NMR δ: 2.89-3.07(3H,m), 3.12-3.21(3H,m), 3.84(2H,s), 4.33(2H,s), 4.98(1H,dd,J=2.4, 10.2Hz), 7.20(2H,d,J=8.3Hz), 7.22-7.42(10H,m), 7.58(2H,d,J=8.3Hz), 8.87(1H,brs), 9.22(1H,brs), 10.44(1H,s)
36	mp : 242-245°C NMR δ: 2.11(3H,s), 2.99-3.06(3H,m), 3.09-3.21(3H,m), 3.68(2H,s), 5.00(1H,dd,J=2.1, 10.2Hz), 6.02(1H,brs), 6.98(1H,s), 7.18(2H,d,J=8.1Hz), 7.28-7.42(5H,m), 7.58(2H,d,J=8.1Hz), 8.89(1H,brs), 9.30(1H,brs), 10.25(1H,s), 12.10(1H,s)
37	mp : 252-256°C NMR δ: 2.89(3H,s), 2.91-3.07(3H,m), 3.11-3.21(3H,m), 3.65(2H,s), 4.95-5.02(1H,m), 6.20(1H,brs), 6.58(1H,s), 7.20(2H,d,J=8.6Hz), 7.28-7.42(5H,m), 7.57(2H,d,J=8.6Hz), 8.87(1H,brs), 9.24(1H,brs), 10.39(1H,s), 12.56(1H,s)

[0143]

[Table 18]

Ex.	DATA
38	mp : >230°C(dec.) NMR δ: 2.88-3.22(6H,m), 3.73(2H,s), 3.65(2H,s), 5.00(1H,dd,J=2.0, 10.0Hz), 6.20(1H,brs), 7.12(1H,s), 7.18(2H,d,J=8.8Hz), 7.28-7.42(5H,m), 7.59(2H,d,J=8.8Hz), 8.39(4H,brs), 8.91(1H,brs), 9.32(1H,brs), 10.41(1H,s), 12.60(1H,s)
39	mp : 177-181°C NMR δ: 2.90-3.10(3H,m), 3.10-3.25(3H,m), 3.67(2H,s), 5.00(1H,dd,J1=10.0, 2.0Hz), 6.68(1H,s), 6.97(1H,t,J=7.2Hz), 7.19(2H,d,J=8.4Hz), 7.27-7.42(9H,m), 7.59(2H,d,J=8.0Hz), 8.90(1H,brs), 9.29(1H,brs), 10.29(1H,s), 10.54(1H,brs)
40	mp : 237-243°C NMR δ: 2.90-3.06(3H,m), 3.06-3.20(3H,m), 4.45(2H,s), 5.01(1H,dd,J=7.8, 2.0Hz), 5.70(2H,s), 6.21(1H,brs), 7.14(2H,d,J=8.8Hz), 7.29-7.42(5H,m), 7.46(2H,d,J=8.8Hz), 7.54(2H,d,J=8.8Hz), 7.77(2H,dd,J=14.4, 2.0Hz), 8.13(2H,d,J=8.4Hz), 8.94(1H,brs), 9.41(1H,brs), 10.95(1H,s)
41	mp : 151-159°C NMR δ: 2.90-3.10(3H,m), 3.10-3.20(3H,m), 3.76(2H,s), 5.02(1H,dd,J=10.2, 2.7Hz), 6.70(1H,s), 7.20(2H,d,J=8.8Hz), 7.25-7.40(5H,m), 7.59(2H,d,J=8.8Hz), 8.96(1H,brs), 9.21(1H,brs), 9.43(1H,brs), 10.58(1H,s)
42	mp : 205-209°C NMR δ: 2.90-3.08(3H,m), 3.13-3.23(3H,m),4.92-4.97(1H,m), 6.20(1H,brs), 7.19-7.42(10H,m), 7.71(2H,d,J=8.8Hz), 8.76(1H,brs), 8.92(1H,brs), 9.65(1H,s)
43	MS (m/z) : 411[(M+H)$^+$] NMR δ: 2.20(3H,s), 2.90-3.07(3H,m), 3.10-3.20(3H,m), 3.74(2H,s), 5.00(1H,dd,J=2.5, 10.3Hz), 7.20(2H,d,J=8.8Hz), 7.28-7.42(5H,m), 7.59(2H,d,J=8.8Hz), 8.91(1H,brs), 9.13(1H,brs), 9.33(1H,brs), 10.58(1H,s)
44	MS (m/z) : 425[(M+H)$^+$] NMR δ: 1.48(6H,s), 2.86-3.22(6H,m), 4.90-4.96(1H,m), 6.19(1H,brs), 6.40(1H,brs), 7.17(2H,d,J=8.8Hz), 7.27-7.41(5H,m), 7.56(2H,d,J=8.8Hz), 8.74(1H,brs), 8.90(1H,brs), 9.53(1H,brs)
45	MS (m/z) : 437[(M+H)$^+$] NMR δ: 1.68-2.12(4H,m), 2.43-2.59(2H,m), 2.91-3.07(3H,m), 3.11-3.20(3H,m), 3.76-3.81(1H,m), 5.00(1H,dd,J=2.5, 10.3Hz), 6.20(1H,brs), 7.19(2H,d,J=8.3Hz), 7.27-7.42(5H,m), 7.60(1H,d,J=8.3Hz), 8.90(1H,brs), 9.33(1H,brs), 10.43(1H,s)
46	MS (m/z) : 421 [(M+H)$^+$] NMR δ: 2.88-3.24(6H,m), 3.83(2H,s), 4.95-5.04(1H,m), 6.19(1H,brs), 7.16-7.22(2H,m), 7.26-7.45(6H,m), 7.55-7.63(2H,m), 7.87(1H,s), 8.04(1H,d,J=3.6Hz), 8.91(1H,brs), 9.32(1H,brs), 10.42(1H,brs)
47	MS (m/z) : 456[(M+H)$^+$] NMR δ: 2.84-3.19(6H,m), 4.03(2H,s), 4.87-4.97(1H,m), 5.43(2H,s), 6.12(2H,s), 7.20(2H,d,J=8.3Hz), 7.25-7.41(11H,m), 7.53(2H,d,J=8.3Hz), 7.90(1H,s), 10.38(1H,s)

[0144]

[Table 19]

Ex.	DATA
48	MS (m/z) : 456[(M+H)$^+$] NMR δ: 2.88-3.18(6H,m), 3.69(2H,s), 4.87-4.95(1H,m), 5.36(2H,s), 6.15-6.21(1H,m), 7.18(2H,d,J=8.3Hz), 7.27-7.41(11H,m), 7.54(2H,d,J=8.3Hz), 8.57(1H,s), 8.72(1H,brs), 8.82(1H,brs), 10.20(1H,s)
49	MS (m/z) : 504[(M+H) $^+$] NMR δ: 2.88-3.07(3H,m), 3.11-3.21(3H,m), 3.67(2H,s), 4.93-4.99(1H,m), 5.53(2H,s), 6.20(1H,d,J=3.9Hz), 7.00(1H,s), 7.13(2H,d,J=7.3Hz), 7.18(2H,d,J=8.3Hz), 7.24-7.42(8H,m), 7.49(2H,d,J=8.3Hz), 8.82(1H,brs), 9.11(1H,brs), 10.35(1H,s)
50	MS (m/z) : 416 [(M+H)$^+$] NMR δ: 1.76-1.87(2H,m), 2.18-2.26(2H,m), 2.80-3.22(8H,m), 4.39-4.47(1H,m), 4.95-5.07(1H,m), 7.15-7.22(2H,m), 7.27-7.43(5H,m), 7.54-7.63(2H,m), 7.74-7.82(1H,m), 8.27(1H,d,J=7.2Hz), 8.67(1H,d,J=4.8Hz), 8.97(1H,brs), 9.47(1H,brs), 10.74(1H,brs)
51	MS (m/z) : 441[(M+H)$^+$] NMR δ: 2.90-3.10(3H,m), 3.10-3.20(3H,m), 4.18(2H,s), 4.96(1H,d,J=8.0Hz), 6.20(1H,brs), 7.18(2H,d,J=8.6Hz), 7.20-7.60(12H,m), 7.84(1H,s), 7.97(1H,s), 8.83(1H,brs), 9.17(1H,brs), 10.55(1H,s)
52	MS (m/z) : 497[(M+H)$^+$] NMR δ: 1.14(6H,d,J=12.9Hz), 2.83(1H,sep,J=12.9Hz), 2.90-3.22(6H,m), 4.38(2H,s), 4.97(1H,d,J=4.1Hz), 5.39(2H,s), 6.20(1H,brs), 7.07-7.42(10H,m), 7.52(2H,d,J=8.8Hz), 7.67(2H,d,J=3.9Hz), 8.84(1H,brs), 9.17(1H,brs), 10.76(1H,s)
53	MS (m/z) : 497[(M+H)$^+$] NMR δ: 1.14(6H,d,J=12.9Hz), 2.83(1H,sep,J=12.9Hz), 2.90-3.22(6H,m), 4.38(2H,s), 4.97(1H,d,J=4.1Hz), 5.39(2H,s), 6.20(1H,brs), 7.07-7.42(10H,m), 7.52(2H,d,J=8.8Hz), 7.67(2H,d,J=3.9Hz), 8.84(1H,brs), 9.17(1H,brs), 10.76(1H,s)
54	MS (m/z) : 489[M$^+$] NMR δ: 2.95-3.02(3H,m), 3.15(3H,brs), 4.44(2H,s), 5.01(1H,dd,J=10.3, 2.5Hz), 5.58(2H,s), 6.21(1H,brs), 7.19(2H,d,J=8.6Hz), 7.27-7.42(6H,m), 7.51(2H,d,J=8.6Hz), 7.58-7.60(1H,m), 7.69(1H,d,J=2.4Hz), 7.72(1H,d,J=2.0Hz), 7.75(1H,d,J=2.0Hz), 8.96(1H,brs), 9.44(1H,brs), 10.91(1H,s)
55	MS (m/z) : 489[M$^+$] NMR δ: 2.94-3.04(3H,m), 3.15(3H,brs), 3.94(2H,s), 5.01(1H,d,J=10.3Hz), 5.31(2H,s), 6.21(1H,d,J=3.9Hz), 7.01(1H,s), 7.17-7.41(12H,m), 7.54(2H,d,J=8.3Hz), 8.98(1H,brs), 9.35(1H,brs), 10.55(1H,s)
56	MS (m/z) : 523[M$^+$] NMR δ: 2.95-3.05(3H,m), 3.15(3H,brs), 4.44(2H,s), 5.01(1H,dd,J=10.3, 2.5Hz), 5.51(2H,s), 6.20(1H,brs), 7.19(3H,d,J=8.6Hz), 7.26-7.42(7H,m), 7.50-7.54(3H,m), 7.58(1H,d,J=2.0Hz), 7.73(1H,d,J=2.0Hz), 8.95(1H,brs), 9.43(1H,brs), 10.98(1H,s)

[0145]

[Table 20]

Ex.	DATA
57	MS (m/z) : 456[(M+H)$^+$] NMR δ: 2.92-3.05(3H,m), 3.15(3H,brs), 4.43(2H,s), 5.01(1H,dd,J=10.2, 2.6 Hz), 5.65(2H,s), 7.20(2H,d,J=8.4Hz), 7.29-7.48(5H,m), 7.50-7.53(3H,m), 7.70(1H,d,J=2.0Hz), 7.78(1H,d,J=2.0Hz), 7.85(1H,dt,J=8.0, 2.0Hz), 8.49(1H,d,J=8.0Hz), 8.94(1H,brs), 9.42(1H,brs), 10.86(1H,s)
58	mp : 150-152℃ NMR δ: 2.88-3.07(3H,m), 3.08(3H,m), 3.95(2H,s), 5.00(1H,dd,J=2.8, 10.0 Hz), 6.21(1H,s), 6.82(1H,d,J=7.6Hz), 6.91(1H,d,J=8.0Hz), 7.17-7.23(2H,m), 7.28-7.43(5H,m), 7.55-7.62(2H,m), 7.82-8.04(3H,m), 8.90(1H,brs), 9.31(1H,brs), 10.67(1H,brs), 14.07(1H,brs)
59	MS (m/z) : 413 [(M+H)$^+$] NMR δ: 2.90-3.25(6H,m), 4.95-5.04(1H,m), 5.20(1H,s), 6.22(1H,brs), 6.78(1H,s), 7.17-7.24(2H,m), 7.27-7.44(5H,m), 7.67-7.75(2H,m), 8.50-9.10(3H,br), 9.45(1H,br), 10.22(1H,brs)
60	mp : 214-216℃ NMR δ: 2.86-3.24(6H,m), 3.65(2H,s), 4.98(1H,dd,J=2.8, 10.4Hz), 6.18(1H,d,J=6.8Hz), 6.28 (1H,d,J=8.8Hz), 7.16-7.22(2H,m), 7.28-7.45(6H,m), 7.53-7.59(2H,s), 8.85(1H,brs), 9.18 (1H,brs), 10.36(1H,brs)
61	mp : 180-182℃ NMR δ: 0.87(6H,d,J=6.8Hz), 2.05-2.15(1H,m), 2.59-3.10(3H,m), 3.10-3.20(3H,m), 4.03(2H,d,J=7.8Hz), 4.41(2H,s), 5.01(1H,d,J=8.3Hz), 6.20(1H,brs), 7.21(2H,d,J=8.3Hz), 7.29-7.42(9H,m), 7.60(2H,d,J=8.8Hz), 7.69(1H,d,J=1.9 Hz), 7.75(1H,d,J=2.0Hz)
62	mp : 226-228℃ NMR δ: 2.87-3.23(6H,m), 4.45(2H,s), 5.02(1H,dd,J=2.4, 10.0Hz), 5.55(2H,s), 6.21(1H,brs), 7.16-7.46(11H,m), 7.49-7.55(2H,m), 7.66(1H,d,J=2.0Hz), 7.71(1H,d,J=2.0Hz), 8.95(1H,brs), 9.44(1H,brs), 10.93(1H,brs), 14.82(1H,brs)
63	mp : 224-225℃ NMR δ: 2.90-3.05(3H,m), 3.05-3.25(3H,m), 4.46(2H,s), 5.01(1H,d,J=8.0Hz), 5.50(2H,s), 6.21(1H,brs), 7.14-7.50(11H,m), 7.54(2H,d,J=8.8Hz), 7.70-7.73(2H,m), 8.93(1H,brs), 9.39(1H,brs), 10.95(1H,s)
64	mp : 205-208℃ NMR δ: 2.90-3.06(3H,m), 3.10-3.21(3H,m), 4.41(2H,s), 4.99(1H,d,J=8.3Hz), 5.51(2H,s), 6.21(1H,s), 7.06-7.12(1H,m), 7.20(2H,d,J=8.3Hz), 7.28-7.42(6H,m), 7.69(2H,dd,J=2.0, 8.3Hz), 8.87(1H,s), 9.26(1H,s), 10.81(1H,s)
65	mp : 211-216℃ NMR δ: 3.00(3H,brs), 3.15(3H,brs), 4.44(2H,s), 5.05(1H,dd,J=10.2, 1.9Hz), 5.58(2H,s), 6.22(1H,brs), 7.14-7.22(4H,m), 7.29-7.32(1H,m), 7.37-7.42(4H,m), 7.47-7.54(3H,m), 7.65(1H,s), 7.69(1H,d,J=1.9Hz), 9.02(1H,brs), 9.55(1H,brs), 10.97(1H,s)

[0146]

[Table 21]

Ex.	DATA
66	mp : 199-201°C NMR δ: 2.87-3.23(6H,m), 4.45(2H,s), 4.95-5.04(1H,m), 5.51(2H,s), 6.20(1H,brs), 7.10-7.43(10H,m), 7.49-7.55(2H,m), 7.71(1H,d,J=2.0Hz), 7.74(1H,d,J=2.0Hz), 8.89(1H,brs), 9.30(1H,brs), 10.90(1H,brs), 14.73(1H,brs)
67	mp : 131-135°C NMR δ: 3.00(3H,brs), 3.16(3H,brs), 4.49(2H,s), 5.04(1H,d,J=10.0Hz), 5.56(2H,s), 6.23(1H,brs), 7.20(2H,d,J=8.2Hz), 7.23-7.34(4H,m), 7.37-7.42(4H,m), 7.53(2H,d,J=8.2Hz), 7.72(2H,s), 9.01(1H,brs), 9.54(1H,brs), 11.00(1H,s)
68	mp : 217-219°C NMR δ: 2.90-3.05(3H,m), 3.05-3.20(3H,m), 4.46(2H,s), 5.00(1H,d,J=8.0Hz), 5.47(2H,s), 6.21(1H,brs), 7.20(2H,d,J=8.0Hz), 7.25-7.50(7H,m), 7.50-7.60(3H,m), 7.70(1H,d,J=1.9Hz), 7.71(1H,d,J=2.0Hz), 8.91(1H,brs), 9.33(1H,brs), 10.93(1H,s)
69	mp : 213-217°C NMR δ: 2.90-3.05(3H,m), 3.05-3.20(3H,m), 4.42(2H,s), 5.02(1H,dd,J=10.2, 2.4Hz), 5.62(2H,s), 6.21(1H,brs), 7.20(2H,d,J=8.3Hz), 7.29-7.42(6H,m), 7.49(2H,d,J=8.3Hz), 7.51-7.60(1H,m), 7.68-7.73(2H,m), 8.95(1H,brs), 9.42(1H,brs), 10.89(1H,s)
70	mp : 212-213°C NMR δ: 2.87-3.23(6H,m), 4.47(2H,s), 5.02(1H,dd,J=2.4, 10.0Hz), 5.53(2H,s), 6.21(1H,brs), 7.16-7.23(2H,m), 7.28-7.34(1H,m), 7.36-7.43(4H,m), 7.48-7.55(2H,m), 7.57-7.67(2H,m), 7.69-7.74(2H,m), 8.95(1H,brs), 9.43(1H,brs), 10.95(1H,brs), 14.86(1H,brs)
71	mp : 209-213°C NMR δ: 2.90-3.05(3H,m), 3.05-3.20(3H,m), 4.47(2H,s), 4.98-5.01(1H,m), 5.49(2H,s), 6.21(1H,brs), 7.21(2H,d,J=8.3Hz), 7.28-7.34(1H,m), 7.36-7.44(6H,m), 7.53(2H,d,J=8.8Hz), 7.71(1H,d,J=1.9Hz), 7.74(1H,d,J=1.9Hz), 8.91(1H,brs), 9.34(1H,brs), 10.97(1H,s)
72	mp : 190-193°C NMR δ: 2.90-3.08(3H,m), 3.10-3.21(3H,m), 4.38(2H,s), 4.99(1H,dd,J=2.5, 10.2Hz), 5.69(2H,s), 6.20(1H,s), 7.21(2H,d,J=8.8Hz), 7.29-7.42(5H,m), 7.48(2H,d,J=8.3Hz), 7.70(1H,d,J=1.9Hz), 7.77(1H,s), 8.88(1H,s), 9.27(1H,s), 10.84(1H,s)
73	mp : 233-234°C NMR δ: 2.90-3.23(6H,m), 4.47(2H,s), 5.02(1H,dd,J=2.4, 10.0Hz), 5.44(2H,s), 6.21(1H,brs), 7.12-7.23(3H,m), 7.28-7.34(1H,m), 7.36-7.44(5H,m), 7.52-7.58(2H,m), 7.66-7.73(3H,m), 7.79-7.81(1H,m), 8.96(1H,brs), 9.44(1H,brs), 10.96(1H,brs), 14.79(1H,brs)
74	mp : 180-183°C NMR δ: 2.67-2.76(4H,m), 2.78-2.86(2H,m), 4.00(2H,s), 4.66(1H,dd,J=8.3, 3.9Hz), 5.39(2H,s), 5.42(1H,brs), 6.57(1H,d,J=0.9Hz), 6.78(1H,s), 7.03(2H,d,J=8.3Hz), 7.21-7.26(1H,m), 7.27-7.34(4H,m), 7.46-7.50(1H,m), 7.52(2H,d,J=8.3Hz), 7.56(1H,s), 7.58(1H,s), 8.32(1H,s), 10.32(1H,s)

[0147]

[Table 22]

Ex.	DATA
75	mp : 210-215°C NMR δ: 2.91-3.03(3H,m), 3.15(3H,brs), 4.44(2H,s), 5.01(1H,dd,J=10.4, 2.6 Hz), 5.53(2H,s), 6.21(1H,brs), 7.18(2H,d,J=8.3Hz), 7.30-7.32(1H,m), 7.37-7.42(4H,m), 7.48(2H,d,J=8.3Hz), 7.49(2H,d,J=8.3Hz), 7.74(1H,d,J=2.0Hz), 7.75(1H,d,J=2.0Hz), 7.79(2H,d,J=8.3Hz), 8.94(1H,brs), 9.39(1H,brs), 10.93 (1H,s)
76	mp : 162-165°C NMR δ: 2.93-3.05(3H,m), 3.14(3H,brs), 4.47(2H,s), 5.03(1H,dd,J=10.3, 2.5 Hz), 5.62(1H,brs), 5.89(2H,s), 7.12(2H,d,J=8.3Hz), 7.30-7.37(1H,m), 7.39-7.43(6H,m), 7.61(2H,d,J=8.8Hz), 7.69(1H,t,J=7.5Hz), 7.75(1H,d,J=1.9Hz), 7.83-7.86(2H,m), 7.97(1H,d,J=8.3Hz), 8.44(1H,d,J=8.3Hz), 8.99(1H,brs), 9. 52(1H,brs), 10.84(1H,s)
77	MS (m/z) : 507[M^+] NMR δ: 2.64-2.74(4H,m), 2.77-2.82(2H,m), 3.93(2H,s), 4.63(1H,dd,J=7.8, 4.4Hz), 5.33(2H,s), 6.80(2H,d,J=6.3Hz), 7.14(2H,d,J=8.8Hz), 7.20-7.24(1H, m), 7.28-7.35(5H,m), 7.43(1H,d,J=7.8Hz), 7.47-7.52(3H,m), 10.27(1H,s)
78	MS (m/z) : 507[M^+] NMR δ: 2.63-2.72(4H,m), 2.75-2.81(2H,m), 3.79(2H,s), 4.62(1H,dd,J=7.8, 4.4Hz), 5.30(1H,brs), 5.33(2H,s), 6.68(1H,d,J=1.0Hz), 6.91(1H,dd,J=8.8, 5. 9Hz), 7.06(1H,d,J=1.0Hz), 7.12(2H,d,J=8.8Hz), 7.19-7.24(2H,m), 7.28-7.33 (4H,m), 7.43(2H,d,J=8.3Hz), 7.49(1H,dd,J=8.3, 2.5Hz), 8.32(1H,s), 10.21(1 H,s)
79	MS (m/z) : 523 [(M+H)$^+$] NMR δ: 2.88-3.08(3H,m), 3.10-3.22(3H,m), 4.40(2H,s), 4.97(1H,d,J=8.3Hz) , 5.56(2H,s), 6.20(1H,s), 7.19(2H,d,J=8.3Hz), 7.24(1H,d,J=2.5Hz), 7.30-7.6 0(9H,m), 7.64(1H,d,J=2.0Hz), 7.72(1H,s), 8.83(1H,s), 9.14(1H,s), 10.71(1H ,s)
80	MS (m/z) : 509 [(M+H)$^+$] NMR δ: 2.90-3.08(3H,m), 3.10-3.22(3H,m), 4.44(2H,s), 5.02(1H,d,J=8.8Hz) , 5.59(2H,s), 6.21(1H,s), 7.20(2H,d,J=8.0Hz), 7.24-7.42(7H,m), 7.50(2H,d,J =8.8Hz), 7.72(2H,d,J=6.8Hz), 8.94(1H,s), 9.42(1H,s), 10.93(1H,s)
81	MS (m/z) : 513 [(M+H)$^+$] NMR δ: 2.87-3.23(6H,m), 3.85(3H,s), 4.30(2H,s), 4.94-5.01(1H,m), 5.55(2 H,s), 6.17-6.22(1H,br), 7.14-7.23(2H,m), 7.28-7.50(9H,m), 7.57-7.64(2H,m), 7.87-7.93(2H,m), 8.83(1H,brs), 9.10(1H,brs), 10.68(1H,brs), 14.86(1H,brs)
82	MS (m/z) : 566 [(M+H)$^+$] NMR δ: 1.30-1.64(6H,m), 2.88-3.22(8H,m), 3.45-3.65(2H,m), 4.39(2H,s), 4 .97(1H,d,J=9.8Hz), 5.50(2H,s), 6.21(1H,s), 7.20(2H,d,J=8.3Hz), 7.30-7.42(9H,m), 7.51(2H,d,J=8.7Hz), 7.71(2H,d,J=7.8Hz), 8.81(1H,s), 9.14(1H,s), 1 0.77(1H,s)

[0148]

[Table 23]

Ex.	DATA
83	mp : 229-232℃ NMR δ: 2.90-3.00(3H,m), 3.10-3.18(3H,m), 5.00(1H,dd,J=2.8, 10.1Hz), 5.03(2H,s), 6.27(1H,t,J=2.0Hz), 7.20(2H,d,J=8.8Hz), 7.29-7.42(5H,m), 7.46(1H,d,J=2.4Hz), 7.58(2H,d,J=8.8Hz), 7.77(1H,d,J=2.0Hz), 8.91(1H,s), 9.32(1H,s), 10.53(1H,s)
84	mp : 237-240℃ NMR δ: 2.90-3.08(3H,m), 3.10-3.22(3H,m), 4.96(1H,dd,J=2.0, 10.0Hz), 5.15(2H,s), 7.21(2H,d,J=8.0Hz), 7.28-7.42(5H,m), 7.56(2H,d,J=8.4Hz), 8.03(1H,s), 8.61(1H,s), 8.82(1H,s), 9.09(1H,s), 10.57(1H,s)
85	mp : 244-248℃ NMR δ: 2.90-3.06(3H,m), 3.10-3.20(3H,m), 5.00(1H,d,J=7.6Hz), 5.20(2H,s), 6.20(1H,s), 7.20-7.50(11H,m), 7.59(2H,d,J=7.2Hz), 8.94(3H,s), 9.36(1H,s), 10.95(1H,s), 12.92(1H,s)
86	mp : 223-224℃ NMR δ: 2.86-3.22(6H,m), 3.49(2H,s), 4.93-5.03(1H,m), 6.20(1H,d,J=4.0Hz), 7.15-7.43(9H,m), 7.55-7.62(2H,m), 7.75(1H,dt,J=1.6, 8.0Hz), 8.45-8.53(1H,m), 8.06-9.50(2H,br), 10.35(1H,brs)
87	mp : 236-238℃ NMR δ: 2.86-3.23(6H,m), 3.72(2H,s), 4.91-5.02(1H,m), 6.20(1H,d,J=4.0Hz), 7.15-7.22(2H,m), 7.27-7.45(6H,m), 7.53-7.62(2H,m), 7.73-7.82(1H,m), 8.40-8.60(2H,m), 8.84(1H,brs), 9.16(1H,brs), 10.35-10.50(1H,br)
88	mp : 195-198℃ NMR δ: 2.86-3.22(6H,m), 3.73(2H,s), 4.93-5.04(1H,m), 6.15-6.25(1H,br), 7.14-7.22(2H,m), 7.28-7.43(7H,m), 7.54-7.63(2H,m), 8.47-8.53(2H,m), 9.07(2H,brs), 10.50(1H,brs)
89	mp : 202-204℃ NMR δ: 2.71-2.81(2H,m), 2.88-3.24(8H,m), 3.49(2H,s), 4.93-5.05(1H,m), 6.20(1H,brd,J=3.2Hz), 7.15-7.23(3H,m), 7.26-7.44(6H,m), 7.52-7.60(2H,m), 7.69(1H,dt,J=1.6, 7.6Hz), 8.45-8.51(1H,m), 9.07(2H,brs), 10.07(1H,brs)
90	mp : 220-227℃ NMR δ: 2.80-3.20(8H,m), 4.31(2H,s), 4.42(2H,t,J=8.0Hz), 5.00(1H,d,J=1.0Hz), 6.21(1H,brs), 7.20-7.40(12H,m), 7.59(2H,d,J=8.6Hz), 7.65(2H,dd,J=12.9, 0.9Hz), 8.91(1H,brs), 9.34(1H,brs), 10.98(1H,s)
91	mp : 158-165℃ NMR δ: 2.51-2.78(6H,m), 3.96(2H,s), 4.59(1H,t,J=5.2Hz), 5.20(1H,brs), 7.13-7.32(9H,m), 7.50-7.53(4H,m), 10.33(1H,s), 12.37(1H,brs)
92	mp : 216-217℃ NMR δ: 2.31(3H,s), 2.86-3.24(6H,m), 3.89(2H,s), 4.92-5.07(1H,m), 6.20(1H,d,J=4.0Hz), 7.12-7.22(3H,m), 7.28-7.45(5H,m), 7.50-7.64(2H,m), 8.30(1H,d,J=4.4Hz), 8.60-9.50(2H,br), 10.32(1H,brs)

[0149]

[Table 24]

Ex.	DATA
93	mp : 236-238℃ NMR δ: 2.86-3.24(6H,m), 3.95(2H,s), 4.91-5.01(1H,m), 5.44(2H,s), 6.19(1H,d,J=4.4Hz), 7.15-7.22(2H,m), 7.27-7.43(5H,m), 7.52-7.62(2H,m), 8.50-8.69(3H,m), 8.83(1H,br), 9.12(1H,brs), 10.41(1H,brs)
94	MS (m/z) : 455[(M+H)$^+$] NMR δ: 2.90-3.10(3H,m), 3.10-3.20(3H,m), 4.38(2H,s), 4.98(1H,t,J=10.4Hz), 5.44(2H,s), 6.20(1H,d,J=3.2Hz), 7.20(2H,d,J=8.4Hz), 7.30-7.45(9H,m), 7.53(2H,d,J=8.8Hz), 7.64(2H,s), 8.85(1H,brs), 9.21(1H,brs), 10.79(1H,s)
95	MS (m/z) : 390[(M+H)$^+$] NMR δ: 2.31(3H,s), 2.89-3.17(6H,m), 3.79(2H,s), 4.98(1H,dt,J=3.2, 10.4Hz), 7.10-7.41(12H,m), 10.32(1H,s)
96	MS (m/z) : 390[(M+H)$^+$] NMR δ: 2.27(3H,s), 2.89-3.17(6H,m), 3.79(2H,s), 4.99(1H,dt,J=3.6, 10.0Hz), 7.17-7.59(12H,m), 10.31(1H,s)
97	MS (m/z) : 390[(M+H)$^+$] NMR δ: 2.44(3H,s), 2.78-3.20(6H,m), 3.80(2H,s), 4.97(1H,dt,J=3.2, 10.4Hz), 7.12-7.66(12H,m), 10.33(1H,s)
98	MS (m/z) : 513 [(M+H)$^+$] NMR δ: 1.06(3H,d,J=6.4Hz), 2.50-2.65(2H,m), 2.90-3.15(3H,m), 3.83(2H,s), 4.80-4.94(1H,m), 7.10-7.18(2H,m), 7.23-7.45(7H,m), 7.52-7.60(2H,m), 7.71-7.80(1H,m), 8.41-8.52(1H,m), 10.25(1H,brs)
99	mp : 203-204℃ NMR δ: 1.13(3H,d,J=6.4Hz), 2.55-2.64(1H,m), 3.00-3.50(4H,m), 3.84(2H,s), 4.92-5.02(1H,m), 6.20(1H,d,J=4.0Hz), 7.13-7.20(2H,m), 7.24-7.46(7H,m), 7.54-7.60(2H,m), 7.73-7.80(1H,m), 8.51(1H,brs), 8.67(1H,brs), 9.13(1H,brs), 10.31(1H,brs)
100	MS (m/z) : 513 [(M+H)$^+$] NMR δ: 1.06(3H,d,J=6.4Hz), 2.50-2.65(1H,m), 2.57-3.50(4H,m), 3.78(2H,s), 4.77-4.92(1H,m), 5.25(2H,s), 6.85(1H,s), 7.10-7.55(15H,m), 10.33(1H,brs)
101	mp : 194-196℃ NMR δ: 2.88-3.25(6H,m), 3.89(2H,s), 5.20-5.26(1H,m), 6.30(1H,s), 7.17-7.48(7H,m), 7.54-7.60(3H,m), 7.81-7.88(1H,m), 8.54(1H,d,J=4.0Hz), 8.82(1H,s), 9.16(1H,s), 10.35(1H,s)
102	mp : 214-215℃ NMR δ: 2.88-3.25(6H,m), 3.85(2H,s), 4.96-5.02(1H,m), 6.33(1H,d,J=3.8Hz), 7.12-7.31(6H,m), 7.39-7.48(2H,m), 7.58(2H,d,J=8.3Hz), 7.74-7.80(1H,m), 8.50(1H,s), 8.82(1H,s), 9.01(1H,s), 10.30(1H,s)
103	mp : 223-225℃ NMR δ: 2.88-3.06(3H,m), 3.10-3.20(3H,m), 3.84(2H,s), 4.94-5.01(1H,m), 6.24(1H,d,J=4.0Hz), 7.16-7.30(5H,m), 7.38-7.46(3H,m), 7.58(2H,d,J=8.8Hz), 7.76(1H,dt,J=1.6, 7.6Hz), 8.50(1H,d,J=8.8Hz), 8.83(1H,s), 9.08(1H,s), 10.31(1H,s)

[0150]

[Table 25]

Ex.	DATA
104	mp : 208-210℃ NMR δ: 2.88-3.24(6H,m), 3.99(2H,s), 4.90-5.01(1H,m), 6.20(1H,d,J=3.6Hz), 7.15-7.24(2H,m), 7.28-7.44(6H,m), 7.53-7.62(2H,m), 8.50-9.30(4H,m), 10.33(1H,brs)
105	mp : 234-235℃ NMR δ: 2.94-3.25(6H,m), 4.07(2H,s), 4.90-5.02(1H,m), 6.20(1H,d,J=4.0Hz), 7.16-7.23(2H,m), 7.27-7.44(5H,m), 7.53-7.65(4H,m), 7.71-7.78(1H,m), 7.94-8.00(2H,m), 8.33(1H,d,J=8.0Hz), 8.50-9.25(2H,m), 10.46(1H,brs)
106	mp : 221-222℃ NMR δ: 2.90-3.25(6H,m), 3.85(2H,s), 4.92-5.08(1H,m), 6.35(1H,d,J=3.6Hz), 7.14-7.23(2H,m), 7.23-7.31(1H,m), 7.33-7.50(5H,m), 7.54-7.64(2H,m), 7.76(1H,dt,J=1.6, 7.6Hz), 8.43-8.55(1H,m), 8.80-9.40(2H,br), 10.36(1H,brs)
107	mp : 204-205℃ NMR δ: 2.85-3.28(6H,m), 3.85(2H,s), 5.02-5.14(1H,m), 6.37(1H,d,J=4.0Hz), 7.14-7.32(3H,m), 7.36-7.46(2H,m), 7.55-7.64(2H,m), 7.70-7.86(2H,m), 8.46-8.56(2H,m), 8.57-8.65(1H,m), 9.13(2H,brs), 10.37(1H,brs)
108	MS (m/z) : 539[M^+] NMR δ: 2.63-2.67(4H,m), 2.73-2.78(2H,m), 4.07(2H,s), 4.60(1H,dd,J=7.4, 4.9Hz), 5.24(1H,brs), 5.57(2H,s), 7.12-7.23(7H,m), 7.27-7.31(4H,m), 7.37(3H,d,J=8.3Hz), 7.46(2H,d,J=8.3Hz), 7.60-7.61(1H,m), 8.31(1H,s), 10.31(1H,s)
109	MS (m/z) : 404[$(M+H)^+$] NMR δ: 2.26(3H,s), 2.40(3H,s), 2.90-3.17(6H,m), 3.75(2H,s), 4.99(1H,dt,J=3.2, 6.8Hz), 6.97-7.60(11H,m), 10.35(1H,s)
110	mp : 183-184℃ NMR δ: 1.85-2.05(2H,m), 2.53-2.65(2H,m), 2.83-3.03(3H,m), 3.05-3.16(1H,m), 3.88(2H,s), 4.95(1H,d,J=9.6Hz), 6.15(1H,brs), 7.10-7.18(2H,m), 7.22-7.43 (7H,m), 7.50-7.60(2H,m), 7.75(1H,dt,J=1.6, 7.2Hz), 8.45-8.53(1H,m), 8.91(2H,brs), 10.29(1H,brs)
111	mp : 225-226℃ NMR δ: 3.02-3.14(1H,m), 3.18-3.46(3H,m), 3.84(2H,s), 4.22-4.35(2H,m), 4.98-5.08(1H,m), 6.21(1H,d,J=3.6Hz), 6.90-6.97(2H,m), 7.23-7.44(7H,m), 7.53-7.62(2H,m), 7.76(1H,dt,J=1.6, 7.2Hz), 8.45-8.54(1H,m), 8.80-9.50(2H,br), 10.29(1H,brs)
112	MS (m/z) : 404 [$(M+H)^+$] NMR δ: 1.21(6H,s), 2.85-3.23(4H,m), 3.89(2H,s), 4.90-5.00(1H,m), 6.21(1H,brs), 7.11-7.19(2H,m), 7.28-7.50(7H,m), 7.53-7.62(2H,m), 7.78-7.90(1H,m), 8.45-8.60(2H,m), 9.00-9.10(1H,br), 10.35(1H,brs)
113	mp : 132-133℃ NMR δ: 2.90-3.10(3H,m), 3.13-3.23(3H,m), 4.96(1H,dd,J=2.5, 10.2Hz), 7.06-7.11(1H,m,), 7.21(2H,d,J=8.7Hz), 7.30-7.42(5H,m), 7.47-7.53(3H,m), 7.81-7.87(1H,m), 8.29(1H,d,J=4.9Hz), 8.78(1H,s), 9.00(1H,s), 9.88(1H,s), 10.51(1H,s)

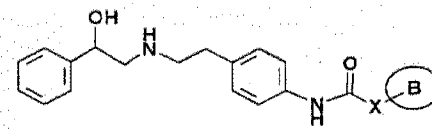
[0151]

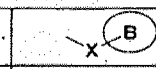
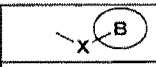
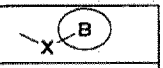
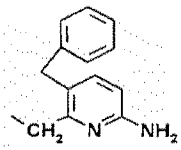
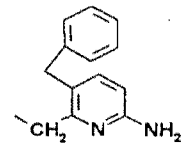
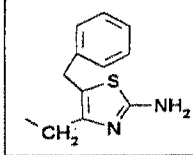
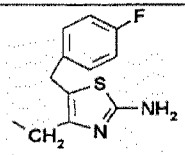
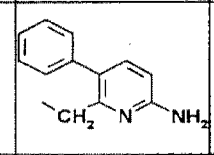
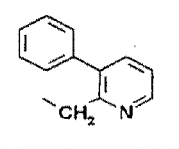
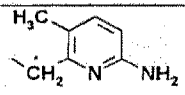
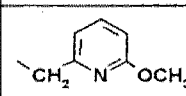
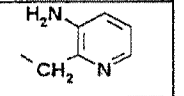
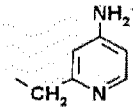
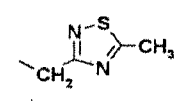
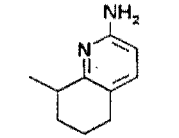
The compounds shown in Tables 26 and 27 together with chemical structural formulae can be easily manufactured by almost the same method as mentioned in the above Examples or Manufacturing Methods or by the method to which some modifications known to the persons skilled in the art are applied.

Incidentally, in some cases, there are tautomeric, geometric or optical isomers for the compounds mentioned in Tables 26 and 27, and the compounds of the present invention cover each of the isolated isomers of the above-mentioned ones or a mixture thereof.

[0152]

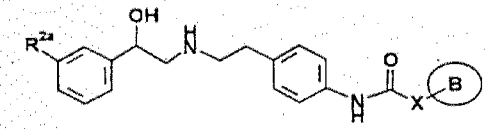
[Table 26]



No.		No.		No.	
1		2		3	
4		5		6	
7		8		9	
10		11		12	

[0153]

[Table 27]



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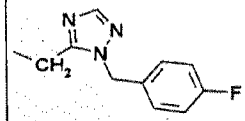
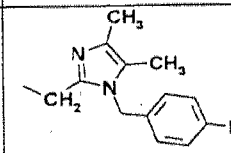
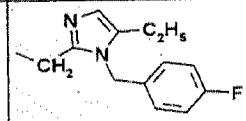
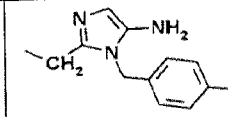
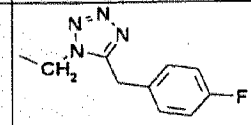
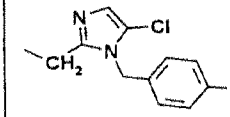
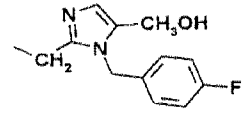
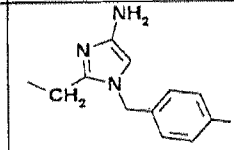
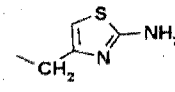
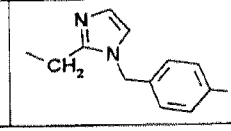
13	H		14	H	
15	H		16	H	
17	H		18	H	
19	H		20	H	
21	Cl		22	Cl	

[Document Name] Abstract

[Abstract]

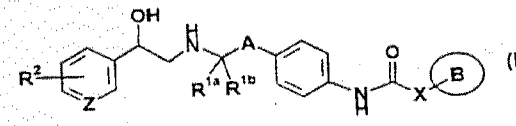
[Matters to be Solved]

Creation of a therapeutic agent for diabetes mellitus having both an insulin secretion promoting action and an insulin sensitivity potentiating action and also having a selective stimulating action to β_3-receptors

[Means to Solve the Matters]

An amide derivative represented by the following formula:

[Formula 1]



(In the above formula, each of the symbols means as follows:

ring B: a nitrogen-containing heteroaryl group which may be substituted and may be fused with a benzene ring;

X: a bond, an optionally hydroxy- or lower alkyl-substituted linear lower alkylene, lower alkenylene or carbonyl, or a group represented by a formula -NH- (when X is a linear lower alkylene group which may be substituted with a lower alkyl group, the hydrogen atom bonded to the carbon atom constituting a ring B may form a lower alkylene group together with the lower alkyl group so that a ring is formed);

A: methylene, ethylene or a group represented by a formula $-CH_2O-$;

R^{1a}, R^{1b}: they may be same or different and each is a hydrogen atom or a lower alkyl group;

R^2: a hydrogen atom or a halogen atom; and

Z: a nitrogen atom or a group represented by a formula =CH-)

or a salt thereof.

[Selective Drawing] No

1624

PATENT

Customer No. 22,852
Attorney Docket No. 7385.0007-00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Tatsuya MARUYAMA et al.

Group Art Unit: 1624

Serial No.: 09/529,096

Examiner: S. Patel

Filed: April 7, 2000

For: AMIDE DERIVATIVES OR SALTS THEREOF

#9
5/11/01
MW

TRANSMITTAL LETTER

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

Enclosed is a reply to the Office Action of December 7, 2000. The item(s) checked below are appropriate:

☒ Applicant(s) hereby petition(s) for a two month(s) extension of time to respond to the above Office Action. The fee of $390.00 for the Extension is enclosed.

The claims are calculated below:

	Claims Remaining After Amendment		Highest Number Previously Paid	Present Extra	Rate	Additional Fee
Total	12	-	20	0	x $ 18	$ 0
Indep.	3	-	3	0	x $ 80	0
☐ First Presentation of Multiple Dep. Claim(s)					+$270	0
					Subtotal	$ 0
					Reduction by ½ if small entity	- 0
					TOTAL	$ 0

☐ A fee of $___ to cover the cost of the additional claims added by this reply is enclosed.

☒ A fee of $180.00 to cover Supplemental Information Disclosure Statement is enclosed.

☒ A check for $570.00 to cover the above fee(s) is enclosed.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Dated: May 4, 2001

By: David W. Hill
David W. Hill
Reg. No. 28,220

05/08/2001 MBERHE 00000073 09529096
02 FC:126 180.00 OP

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1300 I STREET, N.W.
WASHINGTON, DC 20005
202-408-4000

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/529,096	04/07/00	MARUYAMA T	07385.0007

HM12/0619

FINNEGAN HENDERSON FARABOW
GARRETT & DUNNER
1300 I STREET NW
WASHINGTON DC 20005-3315

EXAMINER	
PATEL, S	
ART UNIT	PAPER NUMBER
1624	10

DATE MAILED: 06/19/01

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

Commissioner of Patents and Trademarks

PTO-90C (Rev.11/00)

1- File Copy

Office Action Summary

Application No.	Applicant(s)
09/529,096	Tatsuya Maruyama et al.
Examiner	**Art Unit**
Sudhaker Patel	1624

-- 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) 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 the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- 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 May 7, 2001

2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 1-7 and 9-13 is/are pending in the applica

4a) Of the above, claim(s) _____ is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 1-7 and 9-13 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

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.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 9

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

The claims pending in this application are claims 1-7,9-13.

Applicants' communication paper #8 dated 5/7/01 is acknowledged.

This application has been found to lack unity of invention. Applicants traverse on the grounds that the allowable claims and compounds of the elected Group are not identified and therefore, the restriction requirement is inappropriate.

This is not found persuasive because the claims lack unity of invention. The claims lack unity of invention because compounds of generic Formula of claim 1 and its intermediates as recited do not possess single structural element that is shared by all of the alternatives that is inventive. The Formulae arrived at by computing values of Z, R2 A, R1a,R1b, B etc. which simultaneously represent multiples of compounds including heterocycles. Additionally the change(s) in heterocycle size simultaneously vary the molecule because of optionally fused feature with a benzene ring.. Therefore, these compounds do not share a common structural feature(s) , and only common properties shared by all the compounds is presence of : ***Heterocycle-C(H)OH-CH2-CH2-O-PH-NH-CO-X-B bridge*** which does not represent patentable advances over the prior art already known(see U.S.P. 5223614;WO 9529159)

Note that compounds, corresponding compositions, a method of use and the first recited process of making composition(s) that are of the same scope are considered to form a single inventive concept under PCT Rule 13.1, 37 CFR 1.475(d). The species as presented by various groups and either compounds or their derivatives as recited by generic Formulae are not so

linked as to form a single inventive concept. The compounds are so diverse in scope that a prior art of making it or its composition and using the same further as a pharmaceutical which is anticipated under 35 U.S.C. 102 would not render obvious another compound of the same claim 35 U.S.C. 103.

The Examiner finds Applicant's arguments not persuasive concerning traversal of the restriction; therefore, the finding is maintained and made **FINAL.** Applicants are required to confirm their election, and also to cancel the non elected subject matter in the next communication.

Furthermore, according to 37 CFR 1.499(see MPEP 1893.03(d)), the examiner may in office action require the applicant in the response to that action to elect the invention to which the claims shall be restricted, if the Examiner finds that a national stage application lacks unity of invention under CFR 1.475.

Applicants' various remarks and arguments have been favorably considers, and the rejections under 35 U.S.C. 102 are withdrawn as the JP 10218861 publication date is 8/18/98 which is after the instant application' filing date 10/17/97.

The rejections made under U.S.C. 35 103(a) ref. Toshiyuki et al. are also withdrawn because the ref. does not teach pharmaceutical use.

However, following new grounds of rejections are still maintained.

Claim Rejections - 35 U.S.C. § 112

1. 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.

Claim 1-7,9-13 are rejected under 35 U.S.C. 112, second para. as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regards as the invention.

A). The generic claim 1 presents group B as: " heteroaryl group which may be substituted or unsubstituted and is optionally fused with a benzene ring". This is indefinite and vague because we are not told about the various substituents and their exact position for attachment to the ring.

Also, we do know exactly which kind of rings with which size, and the heteroatoms if any how many are involved by such indefinite definition.

B). The claims usually begin with " An amide derivative". This is indefinite because we do not know exactly which derivative.

"A compounds of Formula(I)" is suggested.

C). E claims' language also often recites the word "optionally" which is indefinite because we do not know exact point of attachment and connection to the ring carbon atom where applicable.

Claim Rejections - 35 U.S.C. § 103

2. 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.

Claims 1-7,9-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S.P. 5223614 to Schromm et al.

The applicants claim generically substituted amides of Formula(I) wherein B + heteroaryl group which is (UN) substituted and is optionally fused with a benzene ring., and further ring B optionally bonding with the lower alkyl group.

Applicants further claim composition comprising these compounds or the salt thereof in a pharmaceutically acceptable carrier, and a method for treating diabetes mellitus, obesity etc, in a human or animal patient in need of such treatment. The ref. '614 teaches generic compounds of the general Formula (I) (see abstract), and also Formula (Ia) (see column 1 lines 47-68, and column 2 lines 1-68) where in Formula (Ia) -R7- = -Ar-B-E (B =-NH-CO-C1-4 alkylene; E = -Het N+-; see column 3 lines 30-45), useful as pharmaceuticals, particularly for inhalation.. Claim 1 in the instant application differ from the reference by reciting more limited subgenus, however it is obvious to a chemist skilled in the art to select any species of the genus that will have reasonably similar properties and equal or better pharmaceutical use. The requisite motivation

stems from the expectation that compounds so structurally similar would be expected to possess similar properties(in re Wood, 199 USPQ 137).

It has been held that a prior art disclosed compounds is sufficient to render a prima facie case of obviousness as species falling within a genus. See In re SUSI, 440 F 2d 442, 169 USPQ 423, 425 (CCPA 1971), followed by Federal Circuit in Merck & co. V. Biocraft Laboratories, 847 F 2d 804, 10 USPQ 2d 1843, 1846 (Fed. Cir.1989).See In re Dillon 16 USPQ 2nd. 1897, 1923 regarding a prima facie case of obvious ness of structurally similar compounds disclosed by prior art" regardless lo the properties disclosed in the inventor's application.

All this is especially considered so in the absence of timely, verified, comparative data, commensurate in scope to the claims sought, clearly and convincingly proving obvious ness over the art(s) as applied above. If applicants intend to rely on unusual or unforseen results demonstrate patentability, attention is drawn to MPEP 716. It is also pointed out that arguments of patentability to differences either not in, or not made clear by, claim language will be of no avail as it is the claims, per se, that are the measure of the invention.

Any inquiry of general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308 1235.

This application has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicants' cooperation is, therefore, requested in promptly correcting any errors of which they may become aware in the specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sudhaker Patel,D.Sc.Tech. whose telephone number is (703) 308 4709.

The examiner can normally be reached on Monday thru' Friday from 8:30 AM to 5:00 PM. If attempts to reach the examiner by the phone are unsuccessful, the examiner's supervisor, Dr.Mukund Shah can be reached at (703) 308 4716.

A facsimile center has been established for Group 1600. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier numbers for accessing the facsimile machine are (703) 308-4556 or (703) 305-3592.

S.p.

June 18, 2001.

Mukund J. Shah

Mukund Shah

SUPERVISORY PATENT EXAMINER

ART UNIT 1624

Notice of References Cited

Applicant/Patent	Application/Control No.	
Tatsuya Maruyama et al.	09/529,096	
Examiner	Art Unit	Page 1 of 1
Sudhaker Patel	1624	

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY[1]	Name	Classification[2]	
X	A	5,223,614	6/1993	K.Schromm et al.	544	105
	B					
	C					
	D					
	E					
	F					
	G					
	H					
	I					
	J					
	K					
	L					
	M					

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY[1]	Country	Name	Classification[2]	
X	N	9,529,159	11/1995	WIPO	Fisher et al.	—	—
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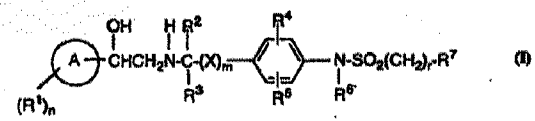
(54) Title: SUBSTITUTED SULFONAMIDES AS SELECTIVE β_3 AGONISTS FOR THE TREATMENT OF DIABETES AND OBESITY



(57) Abstract

Substituted sulfonamides having formula (I), are selective β_3 adrenergic receptor agonists with very little β_1 and β_2 adrenergic receptor activity and as such the compounds are capable of increasing lipolysis and energy expenditure in cells. The compounds thus have potent activity in the treatment of Type II diabetes and obesity. The compounds can also be used to lower triglyceride levels and cholesterol levels or raise high density lipoprotein levels or to decrease gut motility. In addition, the compounds can be used to reduce neurogenic inflammation or as antidepressant agents. The compounds are prepared by coupling an aminoalkylphenyl-sulfonamide with an appropriately substituted epoxide. Compositions and methods for the use of the compounds in the treatment of diabetes and obesity and for lowering triglyceride levels and cholesterol levels or raising high density lipoprotein levels or for increasing gut motility are also disclosed.

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TITLE OF THE INVENTION

SUBSTITUTED SULFONAMIDES AS SELECTIVE β_3 AGONISTS FOR THE TREATMENT OF DIABETES AND OBESITY

CROSS REFERENCE

This is a continuation-in-part of co-pending application U.S.S.N. 08/233,166 filed April 26, 1994, which is hereby incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

β-Adrenoceptors have been subclassified as β_1 and β_2 since 1967. Increased heart rate is the primary consequence of β_1-receptor stimulation, while bronchodilation and smooth muscle relaxation typically result from β_2 stimulation. Adipocyte lipolysis was initially thought to be solely a β_1-mediated process. However, more recent results indicate that the receptor-mediating lipolysis is atypical in nature. These atypical receptors, later called β_3-adrenoceptors, are found on the cell surface of both white and brown adipocytes where their stimulation promotes both lipolysis (breakdown of fat) and energy expenditure.

Early developments in this area produced compounds with greater agonist activity for the stimulation of lipolysis (β_3 activity) than for stimulation of atrial rate (β_1) and tracheal relaxation (β_2). These early developments disclosed in Ainsworth et al., U.S. Patents 4,478,849 and 4,396,627, were derivatives of phenylethanolamines.

Such selectivity for β_3-adrenoceptors could make compounds of this type potentially useful as antiobesity agents. In addition, these compounds have been reported to show antihyperglycemic effects in animal models of non-insulin-dependent diabetes mellitus.

A major drawback in treatment of chronic diseases with β_3 agonists is the potential for stimulation of other β-receptors and subsequent side effects. The most likely of these include muscle tremor (β_2) and increased heart rate (β_1). Although these phenylethanolamine

derivatives do possess some β_3 selectivity, side effects of this type have been observed in human volunteers. It is reasonable to expect that these side effects resulted from partial β_1 and/or β_2 agonism.

More recent developments in this area are disclosed in Ainsworth et al., U.S. Patent 5,153,210, Caulkett et al., U.S. Patent 4,999,377, Alig et al., U.S. Patent 5,017,619, Lecount et al., European Patent 427480 and Bloom et al., European Patent 455006.

Even though these more recent developments purport to describe compounds with greater β_3 selectivity over the β_1 and β_2 activities, this selectivity was determined using rodents, in particular, rats as the test animal. Because even the most highly selective compounds, as determined by these assays, still show signs of side effects due to residual β_1 and β_2 agonist activity when the compounds are tested in humans, it has become apparent that the rodent is not a good model for predicting human β_3 selectivity.

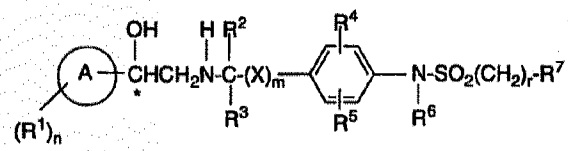
Recently, assays have been developed which more accurately predict the effects that can be expected in humans. These assays utilize cloned human β_3 receptors which have been expressed in Chinese hamster ovary cells. See Emorine et al, Science, 1989, 245:1118-1121; and Liggett, Mol. Pharmacol., 1992, 42:634-637. The agonist and antagonist effects of the various compounds on the cultivated cells provide an indication of the antiobesity and antidiabetic effects of the compounds in humans.

SUMMARY OF THE INVENTION

The instant invention is concerned with substituted sulfonamides which are useful as antiobesity and antidiabetic compounds. Thus, it is an object of this invention to describe such compounds. It is a further object to describe the specific preferred stereoisomers of the substituted sulfonamides. A still further object is to describe processes for the preparation of such compounds. Another object is to describe methods and compositions which use the compounds as the active ingredient thereof. Further objects will become apparent from reading the following description.

DESCRIPTION OF THE INVENTION

The present invention provides compounds having the formula I:



I

where

n is 0 to 5;

m is 0 or 1;

r is 0 to 3;

A is (1) a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen,
(2) a benzene ring fused to a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen,
(3) a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen fused to a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen,
(4) phenyl, or
(5) a benzene ring fused to a C3-C8 cycloalkyl ring;

R1 is (1) hydroxy,
(2) oxo,
(3) halogen,
(4) cyano,
(5) NR^8R^8,

(6) SR^8,
(7) trifluoromethyl,
(8) C_1-C_{10} alkyl,
(9) OR^8,
(10) SO_2R^9,
(11) $OCOR^9$,
(12) NR^8COR^9,
(13) COR^9,
(14) $NR^8SO_2R^9$,
(15) $NR^8CO_2R^8$, or
(16) C_1-C_{10} alkyl substituted by hydroxy, halogen, cyano, NR^8R^8, SR^8, trifluoromethyl, OR^8, C_3-C_8 cycloalkyl, phenyl, NR^8COR^9, COR^9, SO_2R^9, $OCOR^9$, $NR^8SO_2R^9$ or $NR^8CO_2R^8$;

R^2 and R^3 are independently
(1) hydrogen,
(2) C_1-C_{10} alkyl or
(3) C_1-C_{10} alkyl with 1 to 4 substituents selected from hydroxy, C_1-C_{10} alkoxy, and halogen;

X is (1) $-CH_2-$,
(2) $-CH_2-CH_2-$,
(3) $-CH=CH-$ or
(4) $-CH_2O-$;

R^4 and R^5 are independently
(1)hydrogen,
(2) C_1-C_{10} alkyl,
(3) halogen,
(4) NHR^8,
(5) OR^8,
(6) SO_2R^9 or
(7) $NHSO_2R^9$;

R^6 is (1) hydrogen or
(2) C_1-C_{10} alkyl;

R^7 is $Z-(R^{1a})_n$;

R^{1a} is (1) R^1, with the proviso that when A is phenyl, R^{1a} is not C_1-C_{10} alkyl,
(2) C_3-C_8 cycloalkyl,
(3) phenyl optionally substituted with up to 4 groups independently selected from R^8, NR^8R^8, OR^8, SR^8 and halogen, or
(4) 5 or 6-membered heterocycle with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen, optionally substituted with up to four groups independently selected from oxo, R^8, NR^8R^8, OR^8, SR^8, and halogen;

Z is (1) phenyl,
(2) naphthyl,
(3) a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen,
(4) a benzene ring fused to a C_3-C_8 cycloalkyl ring,
(5) a benzene ring fused to a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen,
(6) a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen fused to a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen, or
(7) a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen fused to a C_3-C_8 cycloalkyl ring;

R^8 is (1) hydrogen,
(2) C_1-C_{10} alkyl,
(3) C_3-C_8 cycloalkyl,
(4) Z optionally having 1 to 4 substituents selected from halogen, nitro, oxo, $NR^{10}R^{10}$, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, C_1-C_{10} alkylthio, and C_1-C_{10} alkyl having 1 to 4 substituents selected from hydroxy, halogen, CO_2H, CO_2-C_1-C_{10} alkyl, SO_2-C_1-C_{10} alkyl, C_3-C_8 cycloalkyl, C_1-

C_{10} alkoxy, and Z optionally substituted by from 1 to 3 of halogen, C_1-C_{10} alkyl or C_1-C_{10} alkoxy, or

(5) C_1-C_{10} alkyl having 1 to 4 substituents selected from hydroxy, halogen, CO_2H, CO_2-C_1-C_{10} alkyl, SO_2-C_1-C_{10} alkyl, C_3-C_8 cycloalkyl, C_1-C_{10} alkoxy, C_1-C_{10} alkyl, and Z optionally substituted by from 1 to 4 of halogen, C_1-C_{10} alkyl or C_1-C_{10} alkoxy;

R^9 is (1) R^8 or

(2) NR^8R^8;

R^{10} is (1) C_1-C_{10} alkyl, or

(2) two R^{10} groups together with the N to which they are attached formed a 5 or 6-membered ring optionally substituted with C_1-C_{10} alkyl; or

a pharmaceutically acceptable salt thereof.

In one embodiment of the instant invention A is a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen, a benzene ring fused to a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen, or a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen fused to a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen.

In another embodiment of the instant invention A is phenyl or benzene fused to a C_3-C_8 cycloalkyl ring.

Preferred compounds of the instant invention are realized when in the above structural formula I:

R^2 and R^3 are hydrogen or methyl;

X is $-CH_2-$;

n is 0 to 3;

m is 1;

r is 0 to 2; and

R^4, R^5 and R^6 are hydrogen.

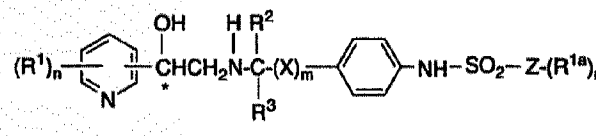
Other preferred compounds of the instant invention are realized when in the above structural formula I:

A is phenyl or a 6-membered heterocyclic ring with 1 or 2 heteroatoms selected from nitrogen and sulfur;

R^1 is hydroxy, halogen, cyano, trifluoromethyl, NR^8R^8, $NR^8SO_2R^9$, NR^8COR^9, $NR^8CO_2R^8$, C_1-C_6 alkyl optionally substituted by hydroxy; and

r is 0 or 2.

More preferred compounds are represented by the formula Ia:



Ia

wherein

n is 0 to 3;

m is 1

R^1 is (1) halogen or
(2) NR^8R^8;

R^2, R^3 are independently hydrogen or methyl;

R^{1a} is (1) halogen,
(2) C_1-C_{10} alkyl,
(3) NR^8R^8,
(4) NR^8COR^9,
(5) $NR^8CO_2R^8$,
(6) COR^9,
(7) $OCOR^9$, or
(8) a 5 or 6-membered heterocycle with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen, optionally substituted with up to four groups independently selected from oxo, halogen, R^8, NR^8R^8, OR^8, and SR^8;

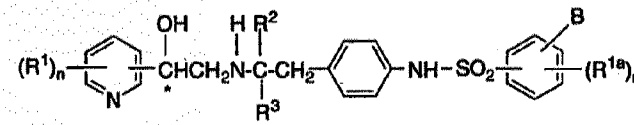
Z is (1) phenyl,
(2) naphthyl,

(3) a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen,
(4) benzene ring fused to a 5 or 6-membered heterocyclic ring with from 1 to 3 heteroatoms selected from oxygen, sulfur and nitrogen, or
(5) a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen fused to a C_3-C_8 cycloalkyl ring;

X is $-CH_2-$; and

R^8 and R^9 are as defined under formula I.

Even more preferred compounds are those represented by formula Id:



Id

n is 0 or 1;

R^1 is NR^8R^8;

R^2 and R^3 are independently
(1) hydrogen, or
(2) methyl;

B is (1) hydrogen,
(2) benzene fused to the benzene ring to form naphthyl, or
(3) a 5 or 6-membered heterocycle with 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen atom fused to the benzene ring;

R^{1a} is (1) halogen,
(2) C_1-C_{10} alkyl,
(3) NR^8R^8,
(4) NR^8COR^9,
(5) $NR^8CO_2R^8$,

(6) COR^9, or
(7) a 5 or 6-membered heterocycle with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen, optionally substituted with up to four groups independently selected from oxo, R^8, SR^8, OR^8, and NR^8R^8;
when B and the benzene ring form a fused ring system, R^{1a} is attached to either ring;

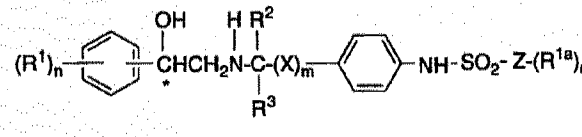
R^8 is (1) hydrogen,
(2) C_1-C_{10} alkyl,
(3) Z optionally having 1 to 4 substituents selected from nitro, oxo, and $NR^{10}R^{10}$, or
(5) C_1-C_{10} alkyl having 1 to 4 substituents selected from hydroxy, halogen, C_1-C_{10} alkyl, C_3-C_8 cycloalkyl, and Z optionally substituted by from 1 to 4 of halogen, C_1-C_{10} alkyl or C_1-C_{10} alkoxy;

R^9 is (1) R^8 or
(2) NR^8R^8;

R^{10} is (1) C_1-C_{10} alkyl, or
(2) two R^{10} groups together with the N to which they are attached formed a 5 or 6-membered ring optionally substituted with C_1-C_{10} alkyl; and

Z is (1) phenyl,
(2) a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen,
(3) a benzene ring fused to a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen, or
(4) a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen fused to a C_3-C_8 cycloalkyl ring.

Other more preferred compounds are represented by formula Ib:



Ib

wherein

n is 0 to 3;

m is 1

R^1 is (1) hydroxy,
(2) cyano,
(3) NR^8R^8 or
(4) halogen;

R^{1a} is (1) halogen,
(2) NR^8R^8,
(3) NR^8COR^9,
(4) $NR^8CO_2R^8$,
(5) $OCOR^9$, or
(6) a 5 or 6-membered heterocycle with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen, optionally substituted with up to three groups independently selected from oxo, halogen, R^8, NR^8R^8, OR^8 and SR^8;

Z is (1) phenyl,
(2) naphthyl or
(3) benzene ring fused to a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen;

X is $-CH_2-$; and

R^2 and R^3 are independently hydrogen or methyl.

Representative antiobesity and antidiabetic compounds of the present invention include the following:

N-[4-[2-[[2-hydroxy-2-(6-aminopyridin-3-yl)ethyl]amino]ethyl]phenyl]-4-(hexylaminocarbonylamino)benzenesulfonamide

N-[4-[2-[[2-hydroxy-2-(6-aminopyridin-3-yl)ethyl]amino]ethyl]phenyl]-4-iodobenzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(6-aminopyridin-3-yl)ethyl]amino]ethyl]phenyl]-benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(6-aminopyridin-3-yl)ethyl]amino]ethyl]phenyl]-2-naphthalenesulfonamide
N-[4-[2-[[2-hydroxy-2-(6-aminopyridin-3-yl)ethyl]amino]ethyl]phenyl]-3-quinolinesulfonamide
N-[4-[2-[[2-hydroxy-2-(6-aminopyridin-3-yl)ethyl]amino]ethyl]phenyl]-5-benzisoxazolesulfonamide
N-[4-[2-[[2-hydroxy-2-(6-aminopyridin-3-yl)ethyl]amino]ethyl]phenyl]-4-[(hexylmethylaminocarbonyl)amino]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(6-aminopyridin-3-yl)ethyl]amino]ethyl]phenyl]-4-[(dimethylaminocarbonyl)amino]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(6-aminopyridin-3-yl)ethyl]amino]ethyl]phenyl]-4-(3-hexyl-2-imidazolidon-1-yl)benzenesulfonamide
N-[4-[3-[[2-hydroxy-2-(6-aminopyridin-3-yl)ethyl]amino]propyl]-phenyl]-4-(hexylaminocarbonylamino)benzenesulfonamide
N-[4-[3-[[2-hydroxy-2-(6-aminopyridin-3-yl)ethyl]amino]propyl]-phenyl]-4-iodobenzenesulfonamide
N-[4-[3-[[2-hydroxy-2-(6-aminopyridin-3-yl)ethyl]amino]propyl]-phenyl]benzenesulfonamide
N-[4-[3-[[2-hydroxy-2-(6-aminopyridin-3-yl)ethyl]amino]propyl]-phenyl]-2-naphthalenesulfonamide
N-[4-[3-[[2-hydroxy-2-(6-aminopyridin-3-yl)ethyl]amino]propyl]-phenyl]-3-quinolinesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(hexylaminocarbonylamino)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-isopropylbenzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-2-naphthalenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-3-quinolinesulfonamide

N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[(hexylmethylaminocarbonyl)amino]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(3-hexyl-2-imidazolidinon-1-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-iodobenzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[5-(3-cyclopentylpropyl)-[1,2,4]-oxadiazol-3-yl]benzensulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[(1-oxoheptyl)amino]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[(1-oxo-4-phenylbutyl)amino]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[(propoxycarbonyl)amino]benzenesulfonamide
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N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[[[(2-indol-3-ylethyl)amino]carbonyl]amino]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[[(octylamino)carbonyl]amino]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-[(hexylamino)carbonyl]-5-indolinesulfonamide
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N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(1-oxononyl)-5-indolinesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(4-methylthiazol-2-yl)-5-indolinesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(4-octylthiazol-2-yl)-5-indolinesulfonamide

N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(4-ethyl-5-methylthiazol-2-yl)-5-indolinesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(3-octyl-2-imidazolidinon-1-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[3-(4,4,4-trifluorobutyl)-2-imidazolidinon-1-yl]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[3-(3-phenylpropyl)-2-imidazolidinon-1-yl]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[3-(4,4,5,5,5-pentafluoropentyl)-2-imidazolidinon-1-yl]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[3-(2-cyclohexylethyl)-2-imidazolidinon-1-yl]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[3-[3-(4-chlorophenyl)propyl]-2-imidazolidinon-1-yl]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(3-pentyl-2-imidazolidinon-1-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[3-(3-cyclopentylpropyl)-2-imidazolidinon-1-yl]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[3-(2-cyclopentylethyl)-2-imidazolidinon-1-yl]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[3-(3-cyclohexylpropyl)-2-imidazolidinon-1-yl]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[3-(2,2-dimethylhexyl)-2-imidazolidinon-1-yl]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(3-hexyl-2-imidazolon-1-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[3-(4,4,4-trifluorobutyl)-2-imidazolon-1-yl]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(3-octyl-2-imidazolon-1-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[3-(3-cyclopentylpropyl)-2-imidazolon-1-yl]benzenesulfonamide

N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(2-octyl-3-oxo-[1,2,4]-triazol-4-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(4-hexyl-5-tetrazolon-1-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(4-octyl-5-tetrazolon-1-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[(3-cyclopentylpropyl)-5-tetrazolon-1-yl]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(2-pentyloxazol-5-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(2-octyloxazol-5-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[2-(2-cyclopentylethyl)oxazol-5-yl]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[(4-ethyl-5-methylthiazol-2-yl)amino]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[(4,5,6,7-tetrahydrobenzothiazol-2-yl)amino]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(2-hexylimidazol-4-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(1-methyl-2-octylimidazol-5-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[1-methyl-2-(2-cyclopentylethyl)imidazol-5-yl]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[1-methyl-2-[2-(4-fluorophenyl)ethyl]imidazol-5-yl]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(5-pentyl-[1,2,4]-oxadiazol-3-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[5-(2-cyclopentylethyl)-[1,2,4]-oxadiazol-3-yl]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(5-heptyl-[1,2,4]-oxadiazol-3-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(5-octyl-[1,2,4]-oxadiazol-3-yl)benzenesulfonamide

N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(5-hexylthio-[1,2,4]-triazol-3-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[[4-(4-propylpiperidin-1-yl)-1,1-dioxo-[1,2,5]-thiadiazol-3-yl]amino]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[[4-(hexylmethylamino)-1,1-dioxo-[1,2,5]-thiadiazol-3-yl]amino]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[[4-(N-heptyl, N-methylamino)-1,1-dioxo-[1,2,5]-thiadiazol-3-yl]amino]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(1-octyl-2,4-imidazolidinedion-3-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[3-(3-nitrophenyl)-5-pyrazolon-1-yl]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[4-(1-hydroxy-1-hexylheptyl)-5-methyl-[1,2,3]-triazol-2-yl]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[4-(1-hydroxyheptyl)-5-methyl-[1,2,3]-triazol-2-yl]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]-2-methylpropyl]-phenyl]-4-(3-hexyl-2-imidazolidinon-1-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]-2-methylpropyl]-phenyl]-4-iodobenzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]-2-methylpropyl]-phenyl]-4-[[(hexylamino)carbonyl]amino]benzenesulfonamide
N-[4-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]phenyl]-4-iodobenzenesulfonamide
N-[4-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]phenyl]-2-naphthalenesulfonamide
N-[4-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]phenyl]-3-quinolinesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-chlorophenyl)ethyl]amino]ethyl]phenyl]-3-isopropylbenzenesulfonamide

N-[4-[2-[[2-hydroxy-2-(3-chlorophenyl)ethyl]amino]ethyl]phenyl]-2-naphthalenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-chlorophenyl)ethyl]amino]ethyl]phenyl]-3-quinolinesulfonamide
N-[4-[2-[[2-hydroxy-2-(4-amino-3,5-dichlorophenyl)ethyl]amino]ethyl]-phenyl]-4-(hexylaminocarbonylamino)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(4-amino-3,5-dichlorophenyl)ethyl]amino]ethyl]-phenyl]-1-[(octylamino)carbonyl]-5-indolinesulfonamide
N-[4-[2-[[2-hydroxy-2-(4-amino-3,5-dichlorophenyl)ethyl]amino]ethyl]-phenyl]-4-(3-hexyl-2-imidazolidinon-1-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(4-amino-3,5-dichlorophenyl)ethyl]amino]ethyl]-phenyl]-4-(3-octyl-2-imidazolidinon-1-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(4-hydroxyphenyl)ethyl]amino]ethyl]phenyl]-benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(4-hydroxyphenyl)ethyl]amino]ethyl]phenyl]-4-iodobenzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-cyanophenyl)ethyl]amino]ethyl]phenyl]-4-(hexylaminocarbonylamino)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-cyanophenyl)ethyl]amino]ethyl]phenyl]-3-quinolinesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(5-hexyl-[1,2,4]-oxadiazol-3-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(4-heptyl-5-methyl-[1,2,3]-triazol-2-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(3-hexyl-2,4-imidazolidinedion-1-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(3-octyl-2,4-imidazolidinedion-1-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[3-(3-cyclopentylpropyl)-2,4-imidazolidinedion-1-yl]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(3-pentyl-[1,2,4]-oxadiazol-5-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(3-hexyl-[1,2,4]-oxadiazol-5-yl)benzenesulfonamide

N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(3-heptyl-[1,2,4]-oxadiazol-5-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(3-octyl-[1,2,4]-oxadiazol-5-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[3-(2-cyclopentylethyl)-[1,2,4]-oxadiazol-5-yl]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[3-(3-cyclopentylpropyl)-[1,2,4]-oxadiazol-5-yl]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(3-pentyl-[1,2,4]-thiadiazol-5-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(3-hexyl-[1,2,4]-thiadiazol-5-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(3-heptyl-[1,2,4]-thiadiazol-5-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(3-octyl-[1,2,4]-thiadiazol-5-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[3-(2-cyclopentylethyl)-[1,2,4]-thiadiazol-5-yl]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[3-(3-cyclopentylpropyl)-[1,2,4]-thiadiazol-5-yl]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(5-pentyl-[1,2,4]-thiadiazol-3-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(5-hexyl-[1,2,4]-thiadiazol-3-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(5-heptyl-[1,2,4]-thiadiazol-3-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(5-octyl-[1,2,4]-thiadiazol-3-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[5-(2-cyclopentylethyl)-[1,2,4]-thiadiazol-3-yl]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[5-(3-cyclopentylpropyl)-[1,2,4]-thiadiazol-3-yl]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(4-pentyl-3-oxo-[1,2,4]-triazol-2-yl)benzenesulfonamide

N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(4-hexyl-3-oxo-[1,2,4]-triazol-2-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(4-heptyl-3-oxo-[1,2,4]-triazol-2-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(4-octyl-3-oxo-[1,2,4]-triazol-2-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[4-(2-cyclopentylethyl)-3-oxo-[1,2,4]-triazol-2-yl]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[4-(3-cyclopentylpropyl)-3-oxo-[1,2,4]-triazol-2-yl]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(5-pentyloxazol-2-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(5-hexyloxazol-2-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(5-heptyloxazol-2-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(5-octyloxazol-2-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[5-(2-cyclopentylethyl)oxazol-2-yl]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[5-(3-cyclopentylpropyl)oxazol-2-yl]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(4-pentyloxazol-2-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(4-hexyloxazol-2-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(4-heptyloxazol-2-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(4-octyloxazol-2-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[4-(2-cyclopentylethyl)oxazol-2-yl]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[4-(3-cyclopentylpropyl)oxazol-2-yl]benzenesulfonamide

N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(2-hexyloxazol-5-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(2-heptyloxazol-5-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[2-(3-cyclopentylpropyl)oxazol-5-yl]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[2-(4-cyclohexylbutyl)oxazol-5-yl]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[2-[2-(4-fluorophenyl)ethyl]oxazol-5-yl]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(2-pentyloxazol-4-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(2-hexyloxazol-4-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(2-heptyloxazol-4-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(2-octyloxazol-4-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[2-(2-cyclopentylethyl)oxazol-4-yl]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[2-(3-cyclopentylpropyl)oxazol-4-yl]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(5-pentylthiazol-2-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(5-hexylthiazol-2-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(5-heptylthiazol-2-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(5-octylthiazol-2-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[5-(2-cyclopentylethyl)thiazol-2-yl]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[5-(3-cyclopentylpropyl)thiazol-2-yl]benzenesulfonamide

N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(4-pentylthiazol-2-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(4-hexylthiazol-2-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(4-heptylthiazol-2-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(4-octylthiazol-2-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[4-(2-cyclopentylethyl)thiazol-2-yl]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[4-(3-cyclopentylpropyl)thiazol-2-yl]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(2-pentylthiazol-4-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(2-hexylthiazol-4-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(2-heptylthiazol-4-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(2-octylthiazol-4-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[2-(2-cyclopentylethyl)thiazol-4-yl]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[2-(3-cyclopentylpropyl)thiazol-4-yl]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(2-pentylthiazol-5-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(2-hexylthiazol-5-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(2-heptylthiazol-5-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(2-octylthiazol-5-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[2-(2-cyclopentylethyl)thiazol-5-yl]benzenesulfonamide

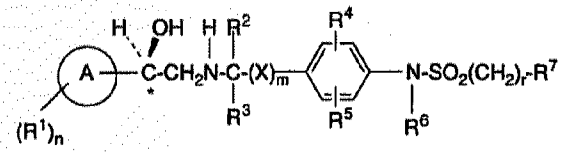
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[2-(3-cyclopentylpropyl)thiazol-5-yl]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(5-methylthiazol-2-yl)-5-indolinesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(5-pentylthiazol-2-yl)-5-indolinesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(5-hexylthiazol-2-yl)-5-indolinesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(5-heptylthiazol-2-yl)-5-indolinesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(5-octylthiazol-2-yl)-5-indolinesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-[5-(2-cyclopentylethyl)thiazol-2-yl]-5-indolinesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-[5-(3-cyclopentylpropyl)thiazol-2-yl]-5-indolinesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(4-pentylthiazol-2-yl)-5-indolinesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(4-hexylthiazol-2-yl)-5-indolinesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(4-heptylthiazol-2-yl)-5-indolinesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-[4-(2-cyclopentylethyl)thiazol-2-yl]-5-indolinesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-[4-(3-cyclopentylpropyl)thiazol-2-yl]-5-indolinesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(5-methyloxazol-2-yl)-5-indolinesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(5-pentyloxazol-2-yl)-5-indolinesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(5-hexyloxazol-2-yl)-5-indolinesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(5-heptyloxazol-2-yl)-5-indolinesulfonamide

N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(5-octyloxazol-2-yl)-5-indolinesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-[5-(2-cyclopentylethyl)oxazol-2-yl]-5-indolinesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-[5-(3-cyclopentylpropyl)oxazol-2-yl]-5-indolinesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(4-methyloxazol-2-yl)-5-indolinesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(4-pentyloxazol-2-yl)-5-indolinesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(4-hexyloxazol-2-yl)-5-indolinesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(4-heptyloxazol-2-yl)-5-indolinesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(4-octyloxazol-2-yl)-5-indolinesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-[4-(2-cyclopentylethyl)oxazol-2-yl]-5-indolinesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-[4-(3-cyclopentylpropyl)oxazol-2-yl]-5-indolinesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(3-methyl-[1,2,4]-oxadiazol-5-yl)-5-indolinesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(3-pentyl-[1,2,4]-oxadiazol-5-yl)-5-indolinesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(3-hexyl-[1,2,4]-oxadiazol-5-yl)-5-indolinesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(3-heptyl-[1,2,4]-oxadiazol-5-yl)-5-indolinesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(3-octyl-[1,2,4]-oxadiazol-5-yl)-5-indolinesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-[3-(2-cyclopentylethyl)-[1,2,4]-oxadiazol-5-yl]-5-indolinesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-[3-(3-cyclopentylpropyl)-[1,2,4]-oxadiazol-5-yl]-5-indolinesulfonamide

N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(5-methyl-[1,2,4]-oxadiazol-3-yl)-5-indolinesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(5-pentyl-[1,2,4]-oxadiazol-3-yl)-5-indolinesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(5-hexyl-[1,2,4]-oxadiazol-3-yl)-5-indolinesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(5-heptyl-[1,2,4]-oxadiazol-3-yl)-5-indolinesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(5-octyl-[1,2,4]-oxadiazol-5-yl)-3-indolinesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-[5-(2-cyclopentylethyl)-[1,2,4]-oxadiazol-3-yl]-5-indolinesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-[5-(3-cyclopentylpropyl)-[1,2,4]-oxadiazol-3-yl]-5-indolinesulfonamide

The compounds of the instant invention all have at least one asymmetric center as noted by the asterisk in structural Formula I. Additional asymmetric centers may be present on the molecule depending upon the nature of the various substituents on the molecule, in particular, R^2 and R^3. Each such asymmetric center will produce two optical isomers and it is intended that all such optical isomers, as separated, pure or partially purified optical isomers or racemic mixtures thereof, be included within the ambit of the instant invention. In the case of the asymmetric center represented by the asterisk in Formula I, it has been found that the compound in which the hydroxy substituent is above the plane of the structure, as seen in Formula Ic, is more active and thus more preferred over the compound in which the hydroxy substituent is below the plane of the structure.

The following stereospecific structure represents the preferred stereoisomers of the instant invention:



Ic

where n, m, r, A, R^1, R^2, R^3, R^4, R^5, R^6, R^7 and X are as defined above under formula I.

Throughout the instant application, the following terms have the indicated meanings:

The alkyl groups specified above are intended to include those alkyl groups of the designated length in either a straight or branched configuration. Exemplary of such alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tertiary butyl, pentyl, isopentyl, hexyl, isohexyl, and the like.

The alkoxy groups specified above are intended to include those alkoxy groups of the designated length in either a straight or branched configuration. Exemplary of such alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tertiary butoxy, pentoxy, isopentoxy, hexoxy, isohexoxy and the like.

The term "halogen" is intended to include the halogen atoms fluorine, chlorine, bromine and iodine.

Examples of 5 and 6-membered heterocycles and fused heterocycles of A, Z and R^{1a} include pyridyl, quinolinyl, pyrimidinyl, pyrrolyl, thienyl, imidazolyl, thiazolyl, benzimidazolyl, thiadiazolyl, benzothiadiazolyl, indolyl, indolinyl, benzodioxolyl, benzodioxanyl, benzothiophenyl, benzofuranyl, benzoxazinyl, benzisoxazolyl, benzothiazolyl, tetrahydronaphthyl, dihydrobenzofuranyl, tetrahydroquinolinyl, furopyridine and thienopyridine.

The preferred values of A and Z are phenyl, naphthyl, benzene ring fused to a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen, or

heterocycles with from 1 to 4 heteroatoms independently selected from one of oxygen or sulfur, and/or 1 to 4 nitrogen atoms.

The more preferred values of A are phenyl, pyridyl, quinolinyl, pyrimidinyl, pyrrolyl, thienyl, imidazolyl, and thiazolyl.

The more preferred values of Z are phenyl, naphthyl, quinolinyl, thienyl, benzimidazolyl, thiadiazolyl, benzothiadiazolyl, indolyl, indolinyl, benzodioxolyl, benzodioxanyl, benzothiophenyl, benzofuranyl, benzoxazinyl, benzisoxazolyl, benzothiazolyl, tetrahydronaphthyl, dihydrobenzofuranyl, triazolyl, tetrazolyl, oxadiazolyl, imidazolyl, oxazolyl, thiazolyl, imidazolidinyl, pyrazolyl, isoxazolyl, pyridyl, pyrimidyl, pyrazolyl, tetrahydrobenzothiazolyl and tetrahydroquinolinyl. When Z is attached to $-NSO_2(CH_2)_r-$, it is preferably phenyl, naphthyl or a benzene ring fused to a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen. When Z is part of the definition of R^8, it is preferably phenyl, a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen, a benzene ring fused to a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen, or a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen fused to a C_3-C_8 cycloalkyl ring.

The preferred heterocycles of R^{1a} are thienyl, thiadiazolyl, triazolyl, tetrazolyl, oxadiazolyl, imidazolyl, oxazolyl, thiazolyl, imidazolidinyl, pyrazolyl, isoxazolyl, pyridyl, pyrimidyl, and pyrazolyl.

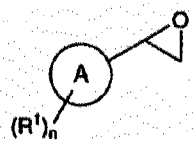
Certain of the above defined terms may occur more than once in the above formula and upon such occurrence each term shall be defined independently of the other; thus for example, NR^8R^8 may represent NH_2, $NHCH_3$, $N(CH_3)CH_2CH_3$, and the like.

The following abbreviations are used throughout the specification:

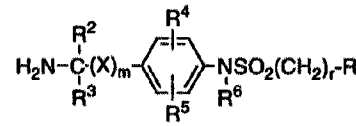
Boc	: tert-butyloxycarbonyl
Cbz	: carbobenzyloxy
DIP-Cl	: diisopinocampheylchloroborane
DMF	: dimethylformamide

DMSO	: dimethylsulfoxide
HPLC	: high pressure liquid chromatography
Me	: methyl
MPLC	: medium pressure liquid chromatography
Ms	: methanesulfonyl (mesyl)
NBS	: N-bromosuccinimide
NCS	: N-chlorosuccinimide
nHex	: n-hexyl
TBAF	: tetrabutylammonium fluoride
TBS (TBDMS)	: t-butyldimethylsilyl
TFA	: trifluoroacetic acid
THF	: tetrahydrofuran

The compounds (I) of the present invention can be prepared from epoxide intermediates such as those of formula II and amine intermediates such as those of formula III. The preparation of these intermediates is described in the following schemes.



II



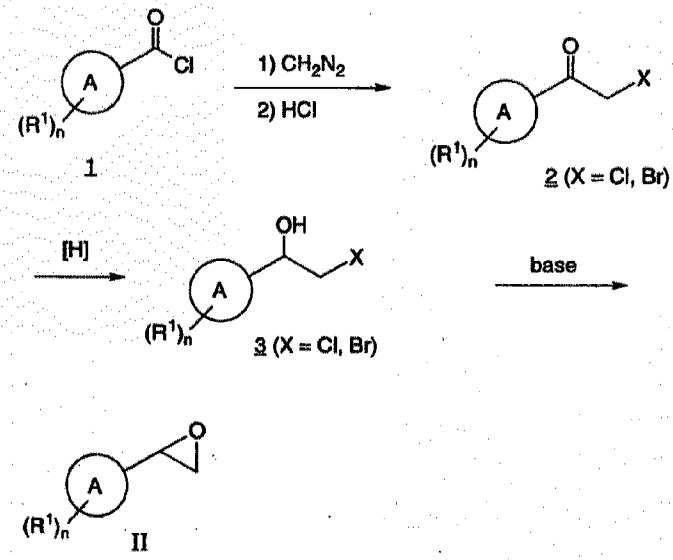
III

where n, m, r, A, R^1, R^2, R^3, R^4, R^5, R^6, R^7 and X are as defined above.

Compounds II are known in the literature or may be conveniently prepared by a variety of methods familiar to those skilled in the art. One common route is illustrated in Scheme 1. Acid chloride 1, which may be commercially available or readily prepared from the corresponding acid by treatment with, for example, thionyl chloride or oxalyl chloride, is treated with diazomethane in a solvent such as diethyl ether. The resultant diazoketone is then treated with hydrogen chloride to give chloroketone 2 (X = Cl). The haloketone 2 is then reduced with a reducing agent such as sodium borohydride. The resultant alcohol 3 is

treated with base such as potassium carbonate in refluxing acetone to provide the desired epoxide II. The enantiomerically enriched (*R*) and (*S*) epoxides II are readily available by asymmetric reduction of haloketones 2 using chiral reducing agents such as (-) or (+)-DIP-Cl, (*R*) or (*S*)-Alpine borane or (*R*) or (*S*)-tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo[1,2-*c*][1,3,2]oxazaborole-borane ((*R*) or (*S*)-OAB•BH_3).

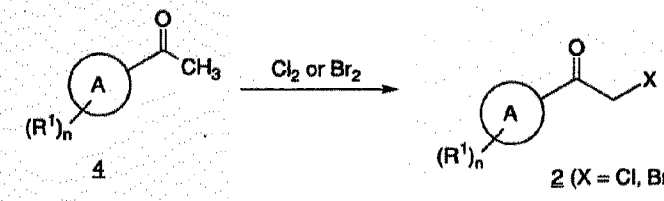
SCHEME 1



An alternate route to the desired haloketones 2 is illustrated in Scheme 2. Methylketone 4 may be converted to the corresponding haloketone using a variety of reagents known to those in the art and summarized in Larock *Comprehensive Organic Transformations*; VCH: New York, 1989, 369-372. Conveniently, methylketone 4 is treated

with chlorine or *N*-chlorosuccinimide in acetic acid with an additional acid source such as hydrogen chloride or aluminum chloride. For the synthesis of 2 (X = Br), bromine, dibromobarbituric acid or NBS with hydrogen bromide or aluminum bromide may be used. In some cases, the chloro or bromoketones 2 may be commercially available.

SCHEME 2



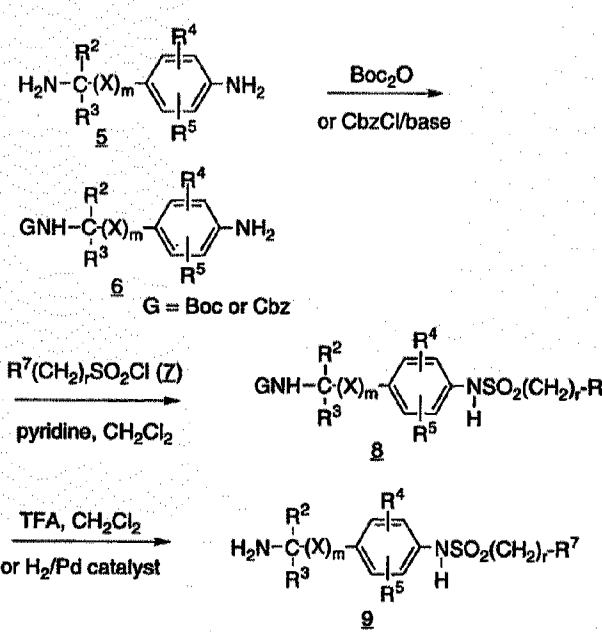
4 2 (X = Cl, Br)

Many of the methylketones 4 are commercially available or readily prepared by methods described in the literature and known to those skilled in the art. R^1 substituents on the acid chlorides 1 or methylketones 4 may need to be protected during the subsequent procedures. A description of such protecting groups may be found in: Protective Groups in Organic Synthesis, 2nd Ed., T. W. Greene and P. G. M. Wuts, John Wiley and Sons, New York, 1991.

Compounds III can be conveniently prepared by a variety of methods familiar to those skilled in the art. A convenient route for their preparation when R^6 is hydrogen is illustrated in Scheme 3. Compound 5 is selectively protected as a suitable carbamate derivative 6 with, for example, di-*tert*-butyl dicarbonate or carbobenzyloxy chloride. This compound is then treated with a sulfonyl halide, preferably the sulfonyl chloride 7, and a base such as pyridine in an anhydrous solvent such as dichloromethane or chloroform for 0.5 to 24 hours at temperatures of -20 to 50°C, preferably 0°C, to provide the sulfonamide 8. The protecting group is then removed with, for

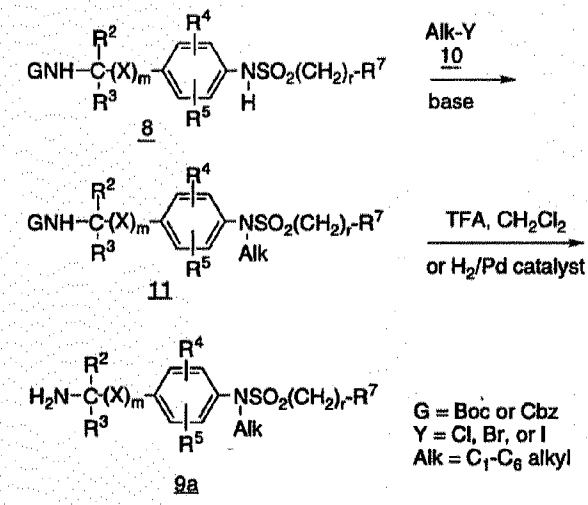
example, trifluoracetic acid in the case of Boc or catalytic hydrogenation in the case of Cbz, to give the desired amine 9.

SCHEME 3.



Compounds III where R^6 is not hydrogen may be conveniently prepared as illustrated in Scheme 4. Sulfonamide 8, prepared as described above, is alkylated with an appropriate alkylating agent 10 in the presence of base to provide sulfonamide 11. Removal of the protecting group as above gives the desired compound 9a.

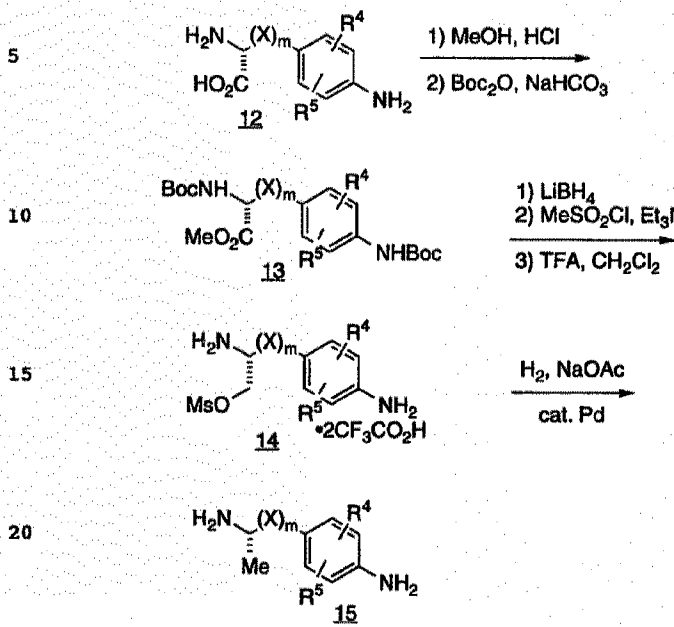
SCHEME 4



The sulfonyl chlorides 7, many of which are commercially available, can also be readily prepared by a number of methods familiar to those skilled in the art. One suitable method involves the addition of an organolithium reagent or a Grignard reagent to sulfuryl chloride following the procedure of S. N. Bhattacharya, et. al., J. Chem. Soc. (C), 1265-1267 (1969). Another convenient method involves the treatment of a thiol with sulfuryl chloride and a metal nitrate according to the procedure of Y. J. Park, et. al., Chemistry Letters, 1483-1486 (1992). Sulfonic acids are also conveniently converted to the corresponding sulfonyl chloride by treatment with PCl_5, PCl_3 or $SOCl_2$ (J. March, Advanced Organic Chemistry, 4th Ed., John Wiley and Sons, New York: 1992, p1297 and references sited therein). Aromatic and heteroaromatic compounds may be chlorosulfonylated directly by treatment with Vilsmeier's reagent or chorosulfonic acid (Organic Synthesis, I, 8).

The diamines 5 are commercially available or readily prepared by methods described in the literature or known to those skilled in the art. Compound 5 where R^2 or R^3 is methyl can be prepared from the corresponding amino acid following the method of J. D. Bloom, et. al., J. Med. Chem., 35, 3081-3084 (1992). As illustrated in Scheme 5 for R^3 = methyl, the appropriate (*R*) amino acid 12 is esterified, conveniently by treatment with methanolic hydrochloric acid, and then treated with di-*tert*-butyl dicarbonate to give compound 13. The ester group is reduced with a hydride source such as lithium borohydride and the resultant alcohol is converted to a leaving group such as a mesylate. Removal of the Boc protecting groups gives diamine 14. This compound is subjected to catalytic hydrogenation in the presence of base such as sodium acetate to give the desired α-methyl amine 15. The other enantiomer is available through an analogous sequence starting with the corresponding (*S*) amino acid.

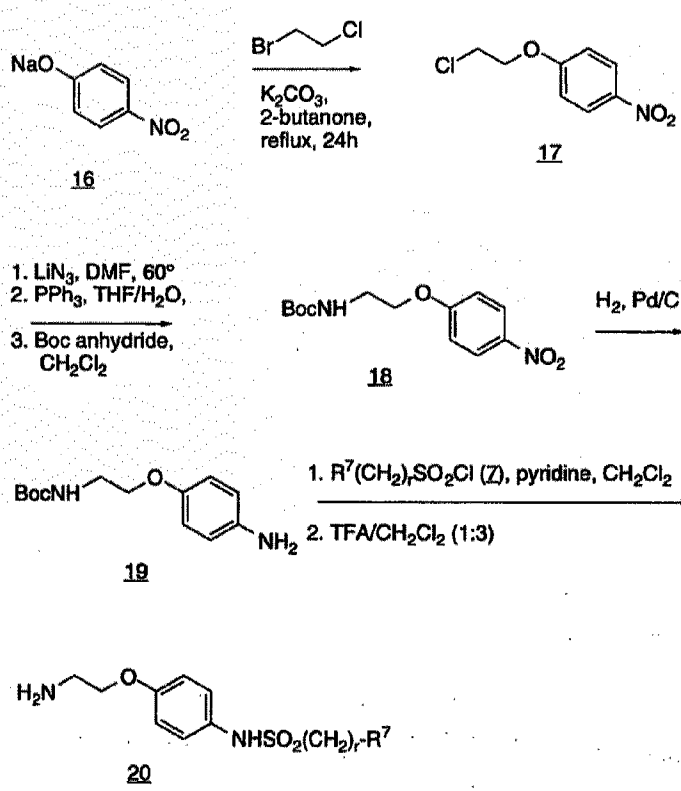
SCHEME 5



Diamines 5 or sulfonamide amines 9 where X is $-CH_2O-$ and m is 1 are also readily prepared by methods described in the literature or known to those skilled in the art. For example, as shown in Scheme 6, the sodium salt of 4-nitrophenol 16 is alkylated with 1-bromo-2-chloroethane, conveninetly in refluxing 2-butanone with a base such as potassium carbonate to give chloro derivative 17. The chloride is converted to the corresponding amine by treatment with lithium azide followed by reduction with, for example, triphenylphosphine in aqueous tetrahydrofuran. Protection of the resultant amine, conveniently as its t-butyl carbamate by treatment with di-tert-butyldicarbonate, gives derivative 18. The nitro group is then reduced, for example, by

catalytic hydrogenation to provide amine 19. Acylation of intermediate 19 with sulfonyl chloride 7, followed by deprotection with acid such as trifluoroacetic acid gives the desired intermediate 20.

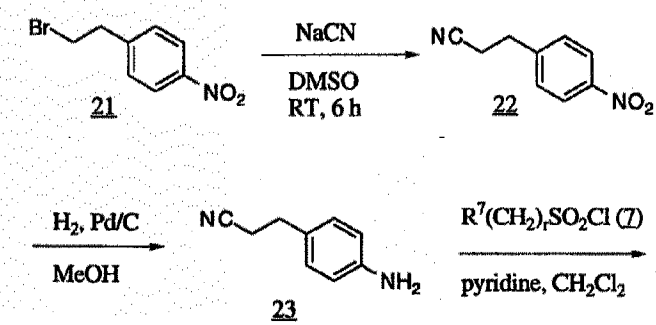
SCHEME 6



Alternatively, diamine 5 where X is -CH_2O- and m is 1 is available from intermediate 19 by treatment with trifluoroacetic acid. This diamine may then be modified as illustrated in Scheme 3.

Diamines 5 and sulfonamide amines 9 where X is $-CH_2CH_2-$ and m is 1 are also readily prepared by methods described in the literature or known to those skilled in the art. For example, as shown in Scheme 7, bromo derivative 21 is treated with sodium cyanide to provide nitrile 22. The nitro group is selectively reduced by treatment with hydrogen and catalytic palladium to provide amine 23. Amine 23 is acylated with sulfonyl chloride 7 to give the corresponding sulfonamide 24. Reduction of compound 24 with cobalt chloride and sodium borohydride provides the desired amine 25.

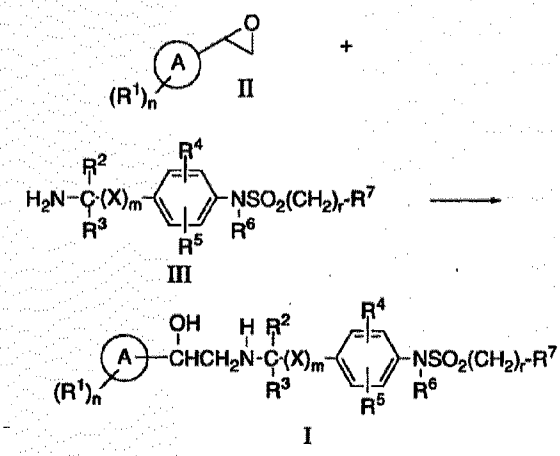
SCHEME 7



Alternatively, diamine 5 where X is $-CH_2CH_2-$ and m is 1 is available from intermediate 23 by reduction of the nitrile group with, for example, cobalt chloride and sodium borohydride. This diamine may then be modified as illustrated in Scheme 3.

Intermediates II and III are coupled by heating them neat or as a solution in a polar solvent such as methanol, acetonitrile, tetrahydrofuran, dimethylsulfoxide or *N*-methyl pyrrolidinone for 1 to 24 hours at temperatures of 30 to 150°C to provide compounds I as shown in Scheme 8. The reaction is conveniently conducted in refluxing methanol. Alternatively, a salt of amine III, such as the trifluoroacetate or hydrochloride salt, may be used. In these cases, a base such as sodium bicarbonate or diethylisopropylamine is added to the reaction mixture. The product is purified from unwanted side products by recrystallization, trituration, preparative thin layer chromatography, flash chromatography on silica gel as described by W. C. Still, et. al., J. Org. Chem. 43, 2923 (1978), medium pressure liquid chromatography, or HPLC. Compounds which are purified by HPLC may be isolated as the corresponding salt. Purification of intermediates is achieved in the same manner.

SCHEME 8

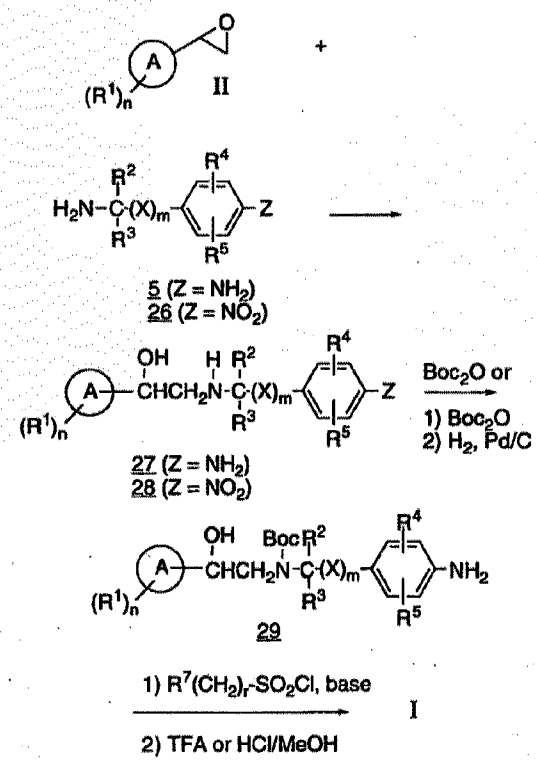


In some cases, the coupling product I from the reaction described in Scheme 8 may be further modified, for example, by the removal of protecting groups or the manipulation of substituents on, in particular, R^1 and R^7. These manipulations may include, but are not limited to, reduction, oxidation, alkylation, acylation, and hydrolysis reactions which are commonly known to those skilled in the art.

An alternate method for the synthesis of compound I is illustrated in Scheme 9. Epoxide II is coupled to amine 5 as described above for coupling intermediates II and III (Scheme 8) to give aniline derivative 27. The secondary amine is selectively protected, for example, as a carbamate by treatment with di-*tert*-butyldicarbonate to provide carbamate 29. Alternatively, nitro amine 26 is used in the coupling reaction to provide 28. Following protection as described above, the nitro group is reduced, for example, by catalytic hydrogenation with palladium catalyst or raney nickel, to provide intermediate 29. In some cases, other group may be reduced concomitantly. For example, if R^1 is halogen in intermediate 28, it may

be converted to hydrogen in intermediate 29. Treatment with a sulfonyl chloride in the presence of a base such as pyridine followed by removal of the protecting group with, in the case of a *tert*-butylcarbamate, acid such as trifluoroacetic acid or methanolic hydrogen chloride, provides the sulfonamide I.

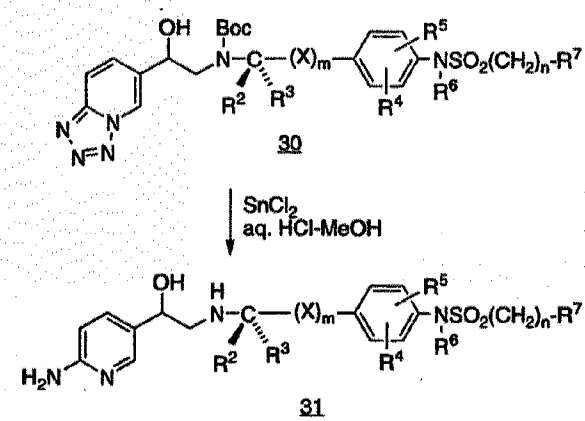
SCHEME 9



In some cases, compound I from the reaction sequence illustrated in Scheme 9 may be further modified, for example, by the

removal of protecting groups or the manipulation of substituents on, in particular, R^1 and R^7, as described above. In addition, manipulation of substituents on any of the intermediates in the reaction sequence illustrated in Scheme 9 may occur. One such example is illustrated in Scheme 10. Compound 30, which is prepared as outlined in Scheme 9 from the corresponding epoxide, is subjected to reduction using tin(II) chloride to provide compound 31. Other examples of substituents on compound I which may be reduced to the corresponding amine by methods commonly known to those skilled in the art include nitro groups, nitriles, and azides.

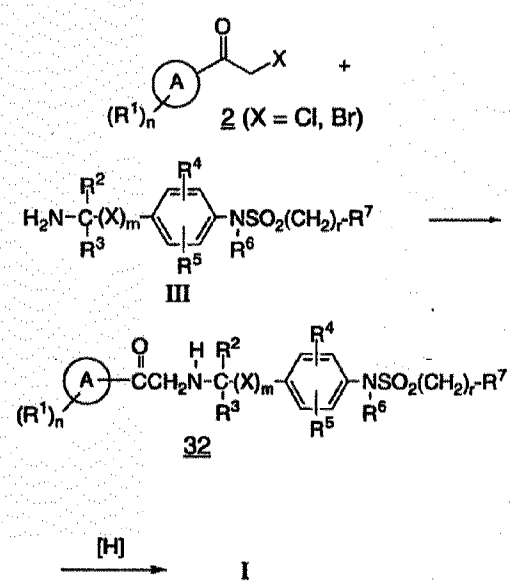
SCHEME 10



The compounds (I) of the present invention can also be prepared from amine intermediates such as those of formula III and haloketone intermediates such as those of formula 2, as shown in Scheme 11. Amine III is alkylated with haloketone derivative 2, conveniently by treatment of a mixture of III and 2 with base such as potassium carbonate or triethylamine in a polar solvent such as acetonitrile, acetone or dimethylformamide. The resultant aminoketone

32 is reduced with, for example, sodium borohydride in methanol to give the desired aminoalcohol I.

SCHEME 11

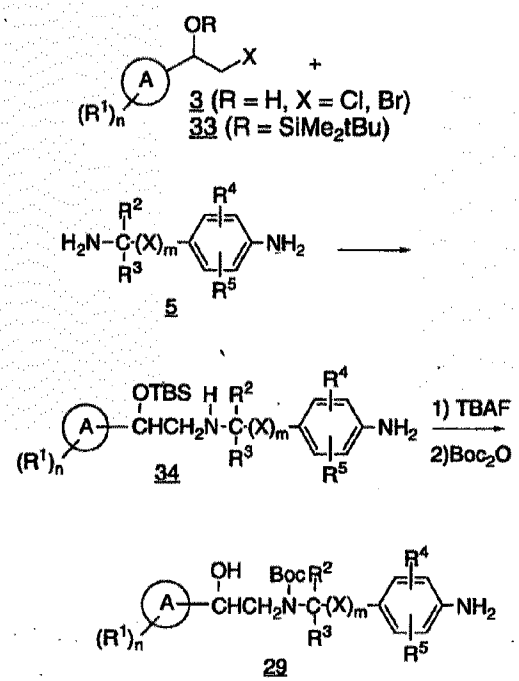


In some cases, the product I from the reaction described in Scheme 11 may be further modified, for example, by the removal of protecting groups or the manipulation of substituents on, in particular, R^1 and R^7. These manipulations may include, but are not limited to, reduction, oxidation, alkylation, acylation, and hydrolysis reactions which are commonly known to those skilled in the art.

An alternate synthesis of key intermediate 29 is shown is Scheme 12. The alcohol of intermediate 3 is protected, for example, as its t-butyldimethylsilyl ether to give TBS derivative 33. This compound is then treated with amine 5 and a base such as diisopropylethylamine in a solvent, typically polar aprotic such as acetonitrile, at temperatures of

25 to 150 °C for 1 to 72 hours. Typically, an iodide source such as sodium iodide is added to facilitate the reaction. The protecting group is then removed, in the case of silyl ether, by treatment of the resultant amine 34 with a fluoride source such as tetrabutylammonium fluoride. Protection of the secondary amine as before gives key intermediate 29.

SCHEME 12

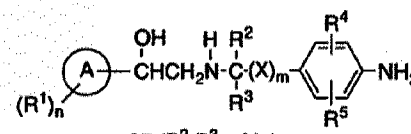


In some cases, compound I may be synthesized directly from intermediate 27 without protection of the secondary amine. For example, when R^2 and R^3 are both methyl, aniline derivative 27 is treated with sulfonyl chloride 7 and a base such as pyridine in a solvent

such as dichloromethane at a temperature of -30 to 50 °C, typically 0 °C, to provide compound I.

In some cases, the product I from the reaction described in Scheme 13 may be further modified, for example, by the removal of protecting groups or the manipulation of substituents on, in particular, R^1 and R^7, as described above.

SCHEME 13



27 (R^2,R^3 = Me)

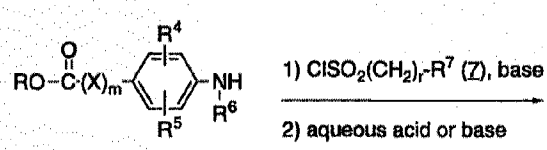
$R^7(CH_2)_r$-SO_2Cl (7)

base

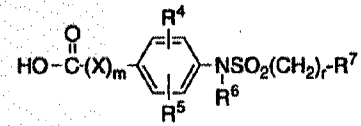
I

The compounds (I) of the present invention where R^2 and R^3 are hydrogen can also be prepared from acid intermediates of formula 36 and aminoalcohols of formula 37, as shown in Scheme 14. Acid 36 is available from the corresponding ester 35, typically a methyl or ethyl ester, by treatment with sulfonyl chloride 7 and a base such as pyridine, followed by hydrolysis of the ester with aqueous acid or base. Acid 36 is coupled to amine 37, which is known in the literature or readily prepared by methods known to those skilled in the art, using a coupling agent such as benzotriazolyl-N-oxy-tris(dimethylamino)phosphonium hexafluorophosphate or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide methiodide to provide the amide 38. This is treated with a reducing agent, typically borane, to provide the desired compound I.

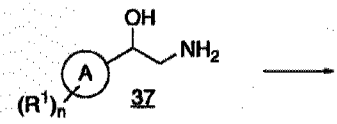
SCHEME 14



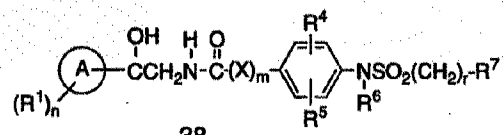
35 R = Me or Et, etc.



36



37



38

I

Compounds of the general Formula I may be separated into diastereoisomeric pairs of enantiomers by, for example, fractional crystallization from a suitable solvent, for example methanol or ethyl acetate or a mixture thereof. The pair of enantiomers thus obtained

may be separated into individual stereoisomers by conventional means, for example by the use of an optically active acid as a resolving agent.

Alternatively, any enantiomer of a compound of the general Formula I may be obtained by stereospecific synthesis using optically pure starting materials of known configuration.

The instant compounds can be isolated in the form of their pharmaceutically acceptable acid addition salts, such as the salts derived from using inorganic and organic acids. Examples of such acids are hydrochloric, nitric, sulfuric, phosphoric, formic, acetic, trifluoroacetic, propionic, maleic, succinic, malonic and the like. In addition, certain compounds containing an acidic function such as a carboxy or tetrazole, can be isolated in the form of their inorganic salt in which the counterion can be selected from sodium, potassium, lithium, calcium, magnesium and the like, as well as from organic bases.

As previously indicated, the compounds of the present invention have valuable pharmacological properties.

The present invention also provides a compound of the general Formula I or a pharmaceutically acceptable salt thereof for use as an active therapeutic substance.

In one aspect, the present invention provides a compound of the general Formula I or a pharmaceutically acceptable ester thereof: or a pharmaceutically acceptable salt thereof for use in the treatment of obesity in human or non-human animals.

The present invention further provides a compound of the general Formula I, or a pharmaceutically acceptable ester thereof; or pharmaceutically acceptable salt thereof, for use in the treatment of hyperglycemia (diabetes) in human or non-human animals.

The disease diabetes mellitus is characterized by metabolic defects in production and utilization of glucose which result in the failure to maintain appropriate blood sugar levels. The result of these defects is elevated blood glucose or hyperglycemia. Research on the treatment of diabetes has centered on attempts to normalize fasting and postprandial blood glucose levels. Treatments have included parenteral

administration of exogenous insulin, oral administration of drugs and dietary therapies.

Two major forms of diabetes mellitus are now recognized. Type I diabetes, or insulin-dependent diabetes, is the result of an absolute deficiency of insulin, the hormone which regulates glucose utilization. Type II diabetes, or insulin-independent diabetes, often occurs in the face of normal, or even elevated levels of insulin and appears to be the result of the inability of tissues to respond appropriately to insulin. Most of the Type II diabetics are also obese.

In addition the compounds of the present invention lower triglyceride levels and cholesterol levels and raise high density lipoprotein levels and are therefore of use in combatting medical conditions wherein such lowering (and raising) is thought to be beneficial. Thus they may be used in the treatment of hyper-triglyceridaemia, hypercholesterolaemia and conditions of low HDL (high density lipoprotein) levels in addition to the treatment of atherosclerotic disease such as of coronary, cerebrovascular and peripheral arteries, cardiovascular disease and related conditions.

Accordingly, in another aspect the present invention provides a method of lowering triglyceride and/or cholesterol levels and/or increasing high density lipoprotein levels which comprises administering, to an animal in need thereof, a therapeutically effective amount of a compound of the formula (I) or pharmaceutically acceptable salt thereof. In a further aspect the present invention provides a method of treating atherosclerosis which comprises administering, to an animal in need thereof; a therapeutically effective amount of a compound of the formula (I) or pharmaceutically acceptable salt thereof. The compositions are formulated and administered in the same general manner as detailed below for treating diabetes and obesity. They may also contain other active ingredients known for use in the treatment of atherosclerosis and related conditions, for example fibrates such as clofibrate, bezafibrate and gemfibrozil; inhibitors of cholesterol biosynthesis such as HMG-CoA reductase inhibitors for example lovastatin, simvastatin and pravastatin; inhibitors

of cholesterol absorption for example beta-sitosterol and (acyl CoA:cholesterol acyltransferase) inhibitors for example melinamide; anion exchange resins for example cholestyramine, colestipol or a dialkylaminoalkyl derivatives of a cross-linKed dextran; nicotinyl alcohol, nicotinic acid or a salt thereof; vitamin E; and thyromimetics.

The compounds of the instant invention also have the effect of reducing intestinal motility and thus find utility as aiding in the treatment of various gastrointestinal disorders such as irritable bowel syndrome. It has been proposed that the motility of non-sphincteric smooth muscle contraction is mediated by activity at β_3 adrenoreceptors. The availability of a β_3 specific agonist, with little activity at β_1 and β_2 receptors will assist in the pharmacologic control of intestinal motility without concurrent cardiovascular effects. The instant compounds are administered generally as described below with dosages similar to those used for the treatment of diabetes and obesity.

It has also been found unexpectedly that the compounds which act as agonists at β3 adrenoreceptors may be useful in the treatment of gastrointestinal disorders, especially peptic ulcerations, esophagitis, gastritis and duodenitis, (including that induced by H. pylori), intestinal ulcerations (including inflammatory bowel disease, ulcerative colitis, Crohn's disease and proctitis) and gastrointestinal ulcerations.

In addition, β_3 receptors have been indicated to have an effect on the inhibition of the release of neuropeptides in certain sensory fibers in the lung. As sensory nerves may play an important role in the neurogenic inflammation of airways, including cough, the instant specific β_3 agonists may be useful in the treatment of neurogenetic inflammation , such as asthma, with minimal effects on the cardio-pulmonary system.

β_3 adrenoreceptors are also able to produce selective antidepressant effects by stimulating the β_3 receptors in the brain and thus an additional contemplated utility of the compounds of this invention are as antidepressant agents.

The active compounds of the present invention may be orally administered as a pharmaceutical composition, for example, with an inert diluent, or with an assimilable edible carrier, or they may be enclosed in hard or soft shell capsules, or they may be compressed into tablets, or they may be incorporated directly with the food of the diet. For oral therapeutic administration, which includes sublingual administration, these active compounds may be incorporated with excipients and used in the form of tablets, pills, capsules, ampules, sachets, elixirs, suspensions, syrups, and the like. Such compositions and preparations should contain at least 0.1 percent of active compound. The percentage of active compound in these compositions may, of course, be varied and may conveniently be between about 2 percent to about 60 percent of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that an effective dosage will be obtained. The active compounds can also be administered intranasally as, for example, liquid drops or spray.

The effective dosage of active ingredient employed may vary depending on the particular compound employed, the mode of administration, the condition being treated and the severity of the condition being treated.

When treating diabetes mellitus and/or hyperglycemia generally satisfactory results are obtained when the compounds of the present invention are administered at a daily dosage of from about 0.1 milligram to about 100 milligram per kilogram of animal body weight, preferably given in divided doses two to six times a day, or in sustained release form. For most large mammals, the total daily dosage is from about 1.0 milligrams to about 1000 milligrams, preferably from about 1 milligrams to about 50 milligrams. In the case of a 70 kg adult human, the total daily dose will generally be from about 7 milligrams to about 350 milligrams. This dosage regimen may be adjusted to provide the optimal therapeutic response.

When treating obesity, in conjunction with diabetes and/or hyperglycemia, or alone, generally satisfactory results are obtained when the compounds of the present invention are administered at a daily

dosage of from 1 milligram to about 1000 milligrams per kilogram of animal body weight, preferably given in divided doses two to six times a day, or in sustained release form. For most large mammals, the total daily dosage is from about 10 milligrams to about 10,000 milligrams, preferably from about 10 milligrams to about 500 milligrams. In the case of a 70 kg adult human, the total daily dose will generally be from about 70 milligrams to about 3500 milligrams. This dosage regimen may be adjusted to provide the optimal therapeutic response.

The tablets, pills, capsules, and the like may also contain a binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin. When a dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil.

Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain, in addition to the active ingredient, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

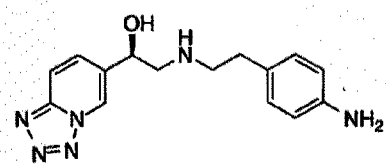
These active compounds may also be administered parenterally. Solutions or suspensions of these active compounds can be prepared in water suitably mixed with a surfactant such as hydroxy-propylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the

contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g. glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

The following examples are provided so that the invention might be more fully understood. They should not be construed as limiting the invention in any way.

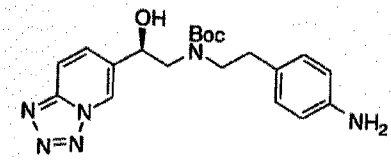
EXAMPLE 1



(R)-N-[2-[4-(aminophenyl)]ethyl]-2-hydroxy-2-(tetrazolo[1,5-a]pyrid-6-yl)ethylamine

A solution of 1.62 g (10 mmol) of (R)-2-(tetrazolo[1,5-a]pyrid-6-yl)oxirane (See Fisher and Wyvratt, European Patent Application 0 318 092 A2 for the synthesis of this compound.) and 4.1 g (30 mmol) of 2-(4-aminophenyl)ethylamine in 30 mL of methanol was heated at reflux for 5h. The reaction mixture was concentrated and the residue chromatographed on silica gel (2% methanol/98% methylene chloride) to give 1.69 g (56%) of the title compound: ^{1}H NMR (400 MHz, CD_3OD) δ 9.01 (d, 1H, J =1.3 Hz), 8.02 (d,1 H, J = 9.2 Hz), 7.82 (dd, 1H, J = 1.3, 9.2 Hz), 6.94 (d, 2H, J = 6.3 Hz), 6.63 (d, 2H, J = 6.3 Hz), 4.91 (m, 1H), 2.82 (m, 4H), 2.67 (t, 2 H, J = 7.1Hz).

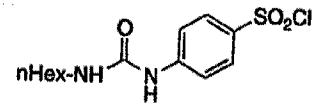
EXAMPLE 2



(R)-N-[2-[4-(aminophenyl)]ethyl]-2-hydroxy-2-(tetrazolo[1,5-a]pyrid-6-yl)ethylcarbamic acid 1,1-dimethylethyl ester

A solution of 1.69 g (56.7 mmol) of the amine from Example 1 and 1.23 g (56.7 mmol) of di-tert-butyl dicarbonate in 10 mL of tetrahydrofuran (THF) at 0° C was stirred for 2 h. The reaction mixture was concentrated and the residue chromatographed on silica gel (4% methanol/96% methylene chloride) to afford 2.2 g (97%) of the title compound: ^{1}H NMR (400 MHz, CD_3OD) δ 8.96 (s, 1H), 8.05 (m, 2H), 7.85 (m, 2H), 6.93 (dd, 2H, J = 7.7, 8.3 Hz), 6.66 (d, 2H, J = 8.3 Hz), 4.99 (m, 1H), 3.49 (m, 4H), 2.70 (t, 2H, J =6.5 Hz), 1.26 (s, 9H).

EXAMPLE 3



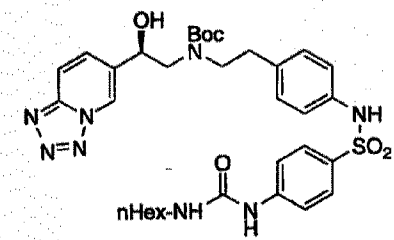
4-(Hexylaminocarbonylamino)benzenesulfonyl chloride

Hexylamine, 12.15 ml (9.2 mmol), was added dropwise to a solution of 10 ml (9.2 mmol) of phenyl isocyanate in THF (150 ml) at 0°C, and stirring was continued for 1 h. The solvent was removed *in vacuo*, and the resultant hexyl phenyl urea was used without further purification.

A 6-g (2.7 mmol) portion was added over 20 min to chlorosulfonic acid at 0°C, followed by heating at 60°C for 2h. After cooling, the mixture was added to ice/water (100ml) and the aqueous

phase extracted with EtOAc (3x100 ml). The combined organic phase was washed with brine (50 ml), dried with $MgSO_4$, concentrated, and purified by flash chromatography (silica gel, 75% hexane/ 25% ethyl acetate) to give 6 g (70%) of the title compound: ^1H NMR ($CDCl_3$) δ 7.85 (d, 2H, J = 9.6 Hz), 7.54 (d, 2H, J = 9.6 Hz), 6.79 (br.s, 1H), 4.71(br. s, 1H), 3.23 (t, 2H, J = 8 Hz), 1.54-1.44 (m, 2H), 1.33-1.20 (m, 6H), 0.91-0.79 (m, 3H).

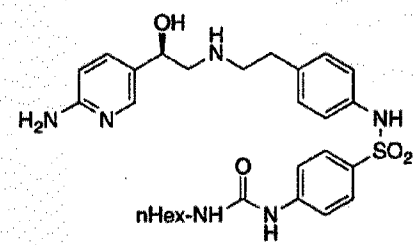
EXAMPLE 4



(R)-N-[4-[2-[N-(1,1-dimethylethoxycarbonyl)-N-[2-hydroxy-2-(tetrazolo[1,5-a]pyrid-6-yl)]ethyl]amino]ethyl]phenyl]-4-(hexylaminocarbonylamino)benzenesulfonamide

To a stirred solution of 0.200 g (0.502 mmol) of the Boc-compound from Example 2 in 3 mL of methylene chloride was added 80 mg (1.00 mmol) of pyridine followed by 0.16 g (0.75 mmol) of the sulfonyl chloride from Example 3. After being stirred for 5h, the reaction mixture was concentrated and the residue chromatographed on silica gel (10% methanol/90% methylene chloride) to afford 0.303 g (88%) of the title compound: ^1H NMR (400 Hz, CD_3OD) δ 8.95 (s, 1H), 8.0-8.08 (m, 1H), 7.75-7.87 (m, 1H), 7.40-7.62 (m, 4H), 7.00 (m, 4H), 4.95 (m, 2H), 3.47 (m, 2H), 3.15 (m, 2H), 2.75 (m, 2H), 1.52 (t, 2H, J = 6.0 Hz), 1.33 (m, 8H), 1.21 (s, 9H), 0.90 (t, 3H, J = 6.0 Hz).

EXAMPLE 5

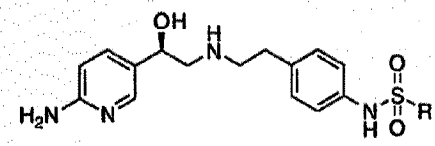


(R)-N-[4-[2-[[2-hydroxy-2-(6-aminopyridin-3-yl)ethyl]amino]ethyl]-phenyl]-4-(hexylaminocarbonylamino)benzenesulfonamide

A mixture of 0.302 g (0.44 mmol) of the tetrazine from Example 4, 0.20 g (0.88mol) of tin(II) chloride dihydrate and 0.3 ml of concentrated aqueous hydrochloric acid in 2 mL of methanol was heated at reflux for 5 h. The reaction mixture was concentrated and the residue purified by reverse-phase MPLC (C8, 47%methanol/53 0.1% trifluoroacetic acid buffer) to give 0.32 g (78%) of the title compound as its bistrifluoroacetate salt: ^{1}H NMR (400 MHz, CD_3OD) δ 7.96 (dd, 1H, J = 2.0, 9.2 Hz), 7.86 (d, 1H, J = 2.0 Hz), 7.59 (d, 2H, J = 8.8 Hz), 7.43 (d, 2H, J = 8.8 Hz), 7.14 (d, 2H, J = 8.4 Hz), 7.07 (d, 2H, J = 8.4 Hz), 7.03 (d, 1H, J = 9.2 Hz), 4.92 (m, 1H), 3.23 (m, 2H), 3.15 (m, 2H), 2.93 (m, 2H, 4.0 Hz), 1.49 (t, 2H, J = 6.0Hz), 1.32 (m, 8H), 0.91 (t, 3H, J = 6.0 Hz); CI MS *m/z* 555(M+1).

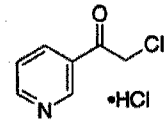
Following the procedures outlined for Examples 1-5, the compounds listed in Table 1 were prepared.

TABLE 1



Example	R	Selected ^{1}H NMR (CD_3OD) Data
6	Ph, trifluoroacetate salt	7.74 (m,2H), 7.53 (m, 1H), 7.45 (m, 2H).
7	2-naphthyl, trifluoroacetate salt	7.93 (m, 4H), 7.75 (d, 1H, J = 1.7 Hz), 7.61 (m, 2H)
8	3-quinolinyl, trifluoroacetate salt	9.00 (d, 1H, J = 2.3 Hz), 8.06 (m, 2H), 7.94 (m, 2H), 7.72 (t, 1H, J = 7.2 Hz)
9	1,2-benzisoxazol-5-yl, trifluoroacetate salt	9.02 (s, 1H), 8.30 (d, 1H, J = 1.3 Hz), 7.90 (m, 1H), 7.77 (m, 1H)
10	4-iodophenyl, trifluoroacetate salt	7.83 (d, 2H, J = 8.6 Hz), 7.46 (d, 2H, J = 8.6 Hz)
11	4-[(N-hexyl,N-methyl-aminocarbonyl)amino]-phenyl, trifluoroacetate salt	7.62 (d, 2H, J = 4.6 Hz), 7.48 (d, 2H, J = 4.6Hz), 2.99 (s, 3H)
12	4-[(N,N-dimethyl-aminocarbonyl)amino]-phenyl, trifluoroacetate salt	3.0 (s, 6H)
13	4-(3-hexyl-2-imidazolidinon-1-yl)phenyl, trifluoroacetate salt	3.88-3.83 (m, 2H), 3.57-3.50 (m, 2H), 2.89-2.95 (m, 2H), 1.61-1.52 (m, 2H), 1.37-1.30 (m, 6H), and 0.93-0.88 (m,3H)

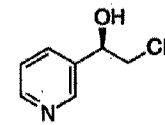
EXAMPLE 14



3-(2-Chloroacetyl)pyridine hydrochloride

To a solution of 12 g (11 mL, 100 mmol) of 3-acetylpyridine in 100 mL of ethyl ether was added 100 mL of 1 M ethereal hydrogen chloride. The resultant precipitate was filtered and 15.0 g (95.2 mmol) was collected and placed in a 500-mL round bottom flask equipped with a magnetic stir bar. To this was added 95 mL of 1 M hydrogen chloride in acetic acid. After the mixture was stirred until all the solid had dissolved, 12.7 g (95.2 mmol) of N-chlorosuccinimide (NCS) was added in one portion. The solution turned yellow and the NCS gradually dissolved. After 4 h, a white precipitate had formed. The mixture was allowed to stir for 2.5 days. It was then filtered. The solid collected was washed with 10 mL of acetic acid and 200 mL of ethyl ether to give 15.2 g (83%) of the title compound as a white solid: ^{1}H NMR (200 MHz, d_6-DMSO) δ 9.22 (t, 1H, J = 1 Hz), 8.29 (dd, 1H, J = 1.6, 5.1 Hz), 8.55 (td, 1H, J = 2, 8.1 Hz), 7.82 (ddd, 1H, J = 0.8, 5.1, 8.1 Hz), 5.27 (s, 2H).

EXAMPLE 15

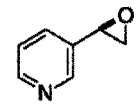


(R)–α–Chloromethyl-3-pyridinemethanol

To a stirred solution of 3.67 g (11.5 mmol) of (-)-B-chlorodiisopinocampheylborane [(-)-DIP-Cl] in 11 mL of THF at -25 °C was added a slurry of 1.00 g (5.21 mmol) of the product from

Example 14 in 5 mL of THF via a cannula. Following the addition of 0.80 mL (5.79 mmol) of triethylamine, the reaction mixture was stirred at -25 °C for 4 days. To the mixture was added 10 mL of water which was then allowed to warm to room temperature. To the mixture was added 20 mL of ethyl acetate and the organic phase separated. The aqueous phase was neutralized with saturated $NaHCO_3$ solution then extracted six times with ethyl acetate. The combined organic phase was concentrated in vacuo to afford a yellow oil. Flash chromatography (silica gel, 75 - 100% ethyl acetate-hexanes) afforded 561 mg (68%) of the title compound as a pale yellow oil: ^1H NMR (400 MHz, CD_3OD) δ 8.58 (d, 1H, J = 1.8 Hz), 8.46 (dd, 1H, J = 4.9, 1.5 Hz), 7.90 (d, 1H, J = 7.9 Hz), 7.44 (dd, 1H, J = 7.9, 4.9 Hz), 4.93 (m, 1H), 3.75 (m, 2H).

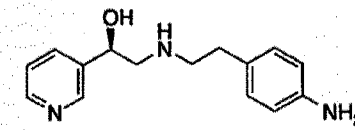
EXAMPLE 16



(R)-(Pyrid-3-yl)oxirane

To a solution of 557 mg (3.55 mmol) of the product from Example 15 in 16 mL of acetone was added 1.80 g of potassium carbononate. The mixture was heated at reflux for 20 h then cooled to room temperature. The mixture was filtered and the filtrate evaporated in vacuo. Flash chromatography (silica gel, 2% methanol-methylene chloride) afforded 262 mg (61%) of the title compound as a pale yellow oil: ^1H NMR (200 MHz, $CDCl_3$) δ 8.54 (m, 2H), 7.52 (m, 1H), 7.24 (m, 1H), 3.86 (dd, 1H, J = 4.0, 2.5 Hz), 3.17 (dd, 1H, J = 5.4, 4.0 Hz), 2.80 (dd, 1H, J = 5.4, 2.5 Hz).

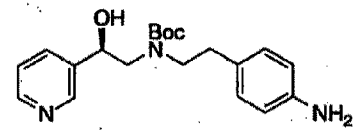
EXAMPLE 17



(R)-N-[2-[4-(Aminophenyl)]ethyl]-2-hydroxy-2-(pyrid-3-yl)ethylamine

To a stirred solution of 377 mg (2.44 mmol) of 4-aminophenethylamine in 10 mL of methanol was added a solution of 300 mg (2.48 mmol) of the product from Example 16 in 15 mL of methanol. The mixture was heated at reflux for 16 h then cooled to room temperature. The methanol was removed in vacuo and the residue chromatographed (silica gel, 6 - 8% methanol, 1% ammonia-methylene chloride) to afford 101 mg (16%) of the title compound together with 279 mg of a mixture that was rechromatographed (5% methanol, 1% ammonia-methylene chloride) to give a further 54 mg (9%) of the title compound as an off-white solid: ^{1}H NMR (500 MHz, CD_3OD) δ 8.52 (d, 1H, J = 1.8 Hz), 8.43 (dd, 1H, J = 4.8, 1.4 Hz), 7.81 (m, 1H), 7.40 (m, 1H), 6.95 (d, 2H, J = 8.3 Hz), 6.67 (d, 2H, J = 8.3 Hz), 4.81 (m, 1H), 2.90-2.65 (m, 6H).

EXAMPLE 18



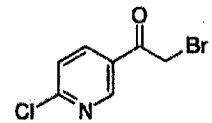
(R)-N-[2-[4-(aminophenyl)]ethyl]-2-hydroxy-2-(pyrid-3-yl)ethylcarbamic acid 1,1-dimethylethyl ester

A solution of 386 mg (1.77 mmol) of di-tert-butyl dicarbonate in 3.5 mL of THF was added, via a cannula, to a stirred slurry of 456 mg (1.77 mmol) of the product from Example 17 in 3.6

mL of THF cooled to 0 °C. The yellow solution was stirred at 0 °C for 3 h, then the THF was removed in vacuo. Flash chromatography (silica gel, 10% methanol, 1% ammonia-methylene chloride) afforded 549 mg (87%) of the title compound as an off white solid: ^{1}H NMR (500 MHz, CD_3OD, mixture of rotomers) δ 8.45 (m, 2H), 7.83 (d, 0.6H, J = 7.4 Hz), 7.78 (d, 0.4H, J = 6.9 Hz), 7.41 (m, 1H), 6.94 (d, 0.8H, J = 8.0 Hz), 6.89 (d, 1.2H, J = 7.8 Hz), 6.66 (d, 2H, J = 7.3 Hz), 4.89 (m, 1H), 3.42-3.21 (m, 4H), 2.67 (m, 2H), 1.39 (s, 5.4H), 1.36 (s, 3.6H).

An alternative synthesis of the aniline derivative in Example 18 is illustrated in Examples 19-23:

EXAMPLE 19

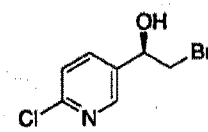


2-Chloro-5-(2-bromoacetyl)pyridine hydrochloride

A solution of 784 mg of 2-chloro-5-acetylpyridine in 10 mL of THF was added via canula to a solution of 1.44 g of dibromobarbituric acid (DBBA) in 10 mL of THF. The resultant solution was heated at 50-55 °C for 12 h, and then an additional 0.72 g DBBA was added. After stirring at 50-55 °C for 2.5 more hours, 0.36 g DBBA was added. The mixture was allowed to stir for 2 h at which point NMR analysis of an aliquot indicated 87% conversion. The reaction mixture was cooled, diluted with ethyl acetate, washed with two portions of saturated aqueous sodium bicarbonate, water, and brine, dried over magnesium sulfate and concentrated. Purification by flash chromatography (silica gel, 15% ethyl acetate/hexane) provided 0.86 g (73%) of the title compound as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 (d, 1H, J = 2.6 Hz), 8.21 (dd, 1H, J = 2.5, 8.3 Hz), 7.46 (d, 1H, J = 8.4 Hz), 4.37 (s, 2H). The NMR also indicated the presence

of the corresponding 2-bromo derivative. The ~4:1 mixture was carried on through the synthesis.

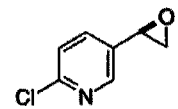
EXAMPLE 20



(R)-α-Bromomethyl-3-(6-chloropyridine)methanol

To a solution of 602 mg (1.88 mmol) of (-)-DIP-Cl in 0.5 mL of THF at -25 °C was added via canula 200 mg of ketone from Example 19 in 1.5 mL of THF at -25 °C. The reaction mixture was allowed to stir at -25 °C for 17 h. It was then quenched by the addition of water and extracted with ether. The ether phase was diluted with ethyl acetate, washed with two portions of saturated aqueous sodium bicarbonate, water, and brine, dried over magnesium sulfate and concentrated. Purification by flash chromatography (silica gel, 15 and 25% ethyl acetate/hexane) gave 170 mg (84%) of the title compound: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, 1H), 7.70 (dd, 1H), 7.32 (d, 1H), 4.97 (m, 1H), 3.61 (dd, 1H), 3.50 (dd, 1H), 2.85 (d, 1H).

EXAMPLE 21

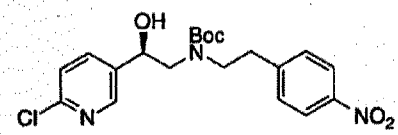


(R)-(2-chloropyrid-5-yl)oxirane

To a solution of 100 mg of bromoalcohol from Example 20 in 2 mL of 1:1 THF:water was added 1 mL of 5 N aqueous sodium hydroxide solution. The mixture was allowed to stir for 10 min. It was then extracted with three portions of dichloromethane. The combined

organic phases were washed with two portions of water and brine, dried over magnesium sulfate, and concentrated to give 98 mg (93%) of the title compound which was used without further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, 1H), 7.48 (dd, 1H), 7.29 (d, 1H), 3.86 (dd, 1H), 3.18 (dd, 1H), 2.78 (dd, 1H).

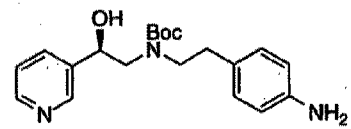
EXAMPLE 22



(R)-N-[2-[4-(Nitrophenyl)]ethyl]-2-hydroxy-2-(2-chloropyrid-5-yl)ethylcarbamic acid 1,1-dimethylethyl ester

Following the procedure outlined in Examples 17 and 18, the title compound was prepared from the epoxide from Example 21 and 4-nitrophenylethylamine: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, 1H, J = 1.3 Hz), 8.13 (d, 2H, J = 8.6 Hz), 7.66 (br m, 1H), 7.30 (d, 2H, J = 8.1 Hz), 7.27 (br m, 1H), 4.94 (br m), 3.38 (br m, 4H), 2.84 (br m, 2H), 1.40 (s, 9H).

EXAMPLE 23

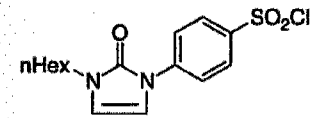


(R)-N-[2-[4-(aminophenyl)]ethyl]-2-hydroxy-2-(pyrid-3-yl)ethylcarbamic acid 1,1-dimethylethyl ester

To a solution of 80 mg (0.19 mmol) of the nitro compound from Example 22 in 2 mL of ethanol was added 0.114 mL (0.57 mmol) of 5 N aqueous sodium hydroxide solution and 20 mg of raney nickel.

The reaction mixture was shaken at room temperature under 45 psi hydrogen for 16 h. The mixture was neutralized with saturated aqueous sodium phosphate monobasic and extracted with three portions of ethyl acetate. The combined organic phases were washed with water and brine, dried (magnesium sulfate), and concentrated to give 40 mg (59%) of the title compound which was identical to the sample prepared in Example 18.

EXAMPLE 24

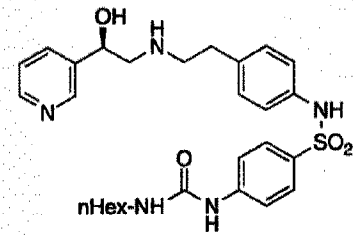


4-(3-Hexyl-2-imidazolon-1-yl)phenylsulphonyl chloride

Hexyl iodide (50mmol, 7.38ml) was added to a mixture of 2-amino acetaldehyde dimethyl acetal (100mmol, 11ml) and potassium carbonate (50mmol, 6.9g) in DMF (10ml) at 0°C. Stirring was continued for 16h before diluting with ethyl acetate (200ml), and filtering the solution through a plug of celite. Concentration *in vacuo* was follwed by column chromatography (eluant ethyl acetate) to give N-hexyl 2-amino acetaldehyde dimethyl acetal (7.39g, 78%) as a colourless oil.

To the amine (38.6mmol, 7.3g) in methylene chloride (100ml) at 0°C was added 4-(chlorosulphonyl) phenyl isocyanate (38.6mmol, 8.4g). The reaction mixture was stirred for 20mins until a clear solution had formed, and 1:1 water: trifluoroacetic acid (100ml total) was added. Vigorous stirring was continued for 16h., the layers separated, the organic layer was diluted with ethyl acetate (500ml) and washed with saturated sodium bicarbonate solution (4x50ml), brine (50ml), dried with anhydrous magnesium sulphate, and concentrated *in vacuo*. Column chromatrography (eluant 3 hexane/ 1 ethyl acetate) yielded the title compound as pale yellow crystals (8.8g, 67%).

EXAMPLE 25

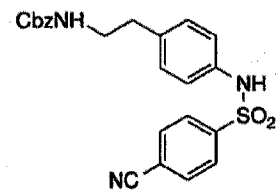


(R)-N-[4-[2-[[2-Hydroxy-2-(pyridin-3-yl)ethyl]amino]ethyl]phenyl]-4-(hexylaminocarbonylamino)benzenesulfonamide

To a solution of 302 mg (0.845 mmol) of the product from Example 18 and 137 mL (1.69 mmol) of pyridine in 10 mL of methylene chloride was added 296 mg (0.928 mmol) of 4-(hexylaminocarbonylamino)benzenesulfonyl chloride from Example 3. The reaction was stirred for 12 h then the solvent removed in vacuo. Flash chromatography (silica gel, 6% methanol, 0.5% ammonia-methylene chloride) afforded 468 mg (87%) of the BOC-protected title compound.

A solution of 468 mg (0.731 mmol) of BOC-protected title compound in 5 mL of methylene chloride and 5 mL of trifluoroacetic acid was stirred for 30 min then the volatile components removed in vacuo. The residue was azeotroped twice with 10% methanol/toluene, twice with methanol, then dried in vacuo to give 521 mg (93%) of the title compound as its trifluroracetate salt: ^{1}H NMR (400 MHz, CD_3OD) δ 8.88 (s, 1H), 8.79 (d, 1H, J = 5.5 Hz), 8.53 (d, 1H, J = 8.2 Hz), 7.99 (m, 1H), 7.59 (dd, 2H, J = 6.9, 1.9 Hz), 7.43 (dd, 2H, J = 6.9, 1.9 Hz), 7.15 (dd, 2H, J = 8.6, 2.1 Hz), 7.08 (dd, 2H, J = 8.6, 2.1 Hz), 5.23 (m, 1H), 3.40-3.10 (m, 6H), 2.94 (m, 2H), 1.49 (m, 2H), 1.32 (m, 6H), 0.90 (m, 2H).

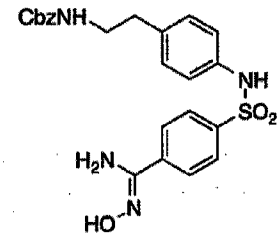
EXAMPLE 26



(N)-[4-[2-[(phenylmethoxycarbonyl)amino]ethyl]phenyl]-4-cyanobenzensulfonamide

Following the procedure outlined in Example 4, the title compound was prepared from 2-(4-aminophenyl)ethylcarbamic acid phenylmethyl ester (see Fisher, et. al., Eur. Pat. Appl. 0 611 003 A1, 1994) and 4-cyanobenzenesulfonyl chloride: ^{1}H NMR (400 MHz, CD_3OD) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, 2H, J=8.7Hz), 7.69 (d, 2H, J=8.7Hz), 7.32 (m, 5H), 7.06 (d, 2H, J=8.4Hz), 6.96 (d, 2H, J=8.4Hz), 6.75 (s, 1H), 5.06 (s, 2H), 4.71 (t, br, 1H), 3.38 (q, 2H, J=6.9Hz), 2.74 (t, 2H, J=7.0Hz).

EXAMPLE 27

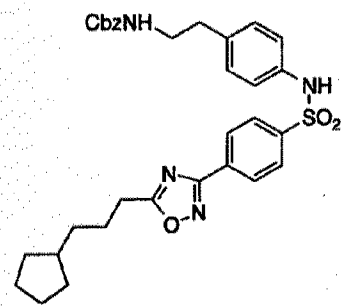


(N)-[4-[2-[(phenylmethoxycarbonyl)amino]ethyl]phenyl]-4-aminooximidomethyl)benzensulfonamide

A mixture of the nitrile from Example 26 (2.71g, 6.23mmol), absolute ethanol (65ml), finely divided K_2CO_3 (5.17g,

37.4mmol), and hydroxylamine hydrochloride (2.17g, 31.2mmol) was refluxed for 6 h. The ethanol was removed under reduced pressure. The resulting solid was dissolved in ethyl acetate and washed with water 3 times. The organic phase was concentrated in vacuo to 2.87g (98%) of the title compound as a white powder which was of sufficient purity to be used in subsequent steps: ^{1}H NMR (400 MHz, CD_3OD) δ 7.71 (s, 4H), 7.31 (m, 5H), 7.04 (d, 2H, J=8.4Hz), 6.99 (d, 2H, J=8.4Hz), 5.02 (s, 2H), 3.25 (t, 2H, J=6.8Hz), 2.67 (t, 2H, J=6.7Hz).

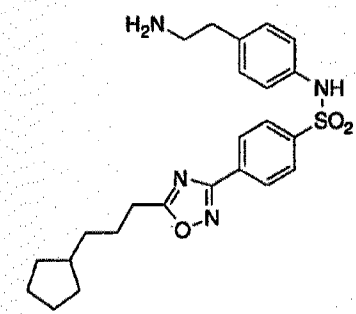
EXAMPLE 28



(N)-[4-[2-[(phenylmethoxycarbonyl)amino]ethyl]phenyl]-4-[5-(3-cyclopentylpropyl)-[1,2,4]-oxadiazol-3-yl]benzensulfonamide

To a solution of compound from Example 27 (0.468g, 1.00mmol) in dry pyridine (5.0ml) was added 4-cyclopentylbutyryl chloride (0.175g, 1.00mmol). The mixture was refluxed for 3.5 h. The pyridine was removed under reduced pressure. The resulting residue was purified by silica gel chromatography (35% ethyl acetate in hexanes) to give 0.152g (26%) of the title compound: ^{1}H NMR (400 MHz, $CDCL_3$) δ 8.12 (d, 2H, J=8.7Hz), 7.81 (d, 2H, J=8.7Hz), 7.31 (m, 5H), 7.03 (d, 2H, J=8.1Hz), 6.97 (d, 2H, J=8.4Hz), 6.67 (s, 1H), 5.05 (s, 2H), 4.70 (t, br, 1H), 3.37 (q, 2H, J=6.5Hz), 2.91 (t, 2H, J=7.6Hz), 2.72 (t, 2H, J=7.0), 1.90-1.70 (m, 5H), 1.65-1.30 (m, 6H), 1.06 (m, 2H).

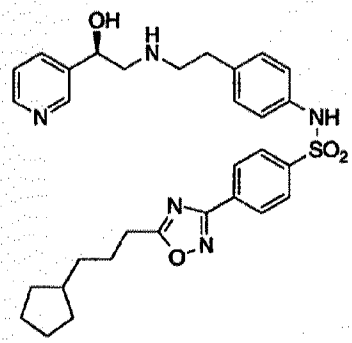
EXAMPLE 29



N-[4-(2-aminoethyl)phenyl]-4-[5-(3-cyclopentylpropyl)-[1,2,4]-oxadiazol-3-yl]benzensulfonamide

A mixture of Cbz amine from Example 28 (0.145g, 0.246mmol), palladium hydroxide on carbon (0.02g), and glacial acetic acid (5.0ml) was hydrogenated for 2 h. The acetic acid was removed under reduced pressure. The residue was purified by silica gel chromatography (1 : 9 of 10% ammonium hydroxide in methanol : methylene chloride) to give 0.058g (52%) of the title compound: ^{1}H NMR (400 MHz, CD_3OD) δ 8.11 (d, 2H, J=8.6Hz), 7.87 (d, 2H, J=8.5Hz), 7.06 (d, 2H, J=8.6Hz), 7.02 (d, 2H, J=8.7Hz), 2.97 (t, 2H, J=7.5Hz), 2.84 (t, 2H, J=6.9Hz), 2.67 (t, 2H, J=7.5Hz), 1.90-1.75 (m, 5H), 1.70-1.40 (m, 6H), 1.12 (m, 2H).

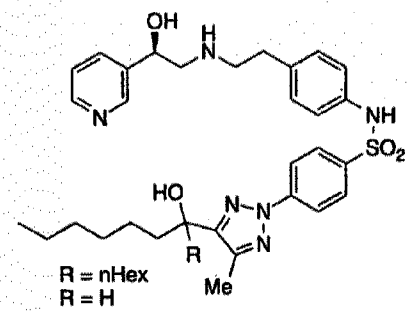
EXAMPLE 30



(R)-N-[4-[2-[[2-Hydroxy-2-(pyridin-3-yl)ethyl]amino]ethyl]phenyl]-4-[5-(3-cyclopentylpropyl)-[1,2,4]-oxadiazol-3-yl]benzensulfonamide

To a solution of amine from Example 29 (0.053g, 0.117mmol) in dry methanol (30.0ml) was added 3-pyridine epoxide from Example 16 (0.021g, 0.175mmol). The resulting solution was refluxed overnight. After concentration, the residue was purified by silica gel chromatography (13% methanol in methylene chloride) to give 0.01g (15%) of the title compound: ^{1}H NMR (400 MHz, CD_3OD) δ 8.52 (d, 1H, J=1.9Hz), 8.42 (dd, 1H, J=1.5, 4.8Hz), 8.13 (d, 2H, J=8.6Hz), 7.85 (m, 3H), 7.40 (dd, 1H, J=4.8, 7.8Hz), 7.10 (d, 1H, J=8.6Hz), 7.03 (d, 2H, J=8.6Hz), 4.81 (dd, 1H, J=4.9, 8.1Hz), 2.96 (t, 2H, J=7.5Hz), 2.93-2.70 (m, 6H), 1.90-1.72 (m, 5H), 1.68-2.48 (m, 4H), 1.42 (m, 2H), 1.11 (m, 2H).

EXAMPLE 31



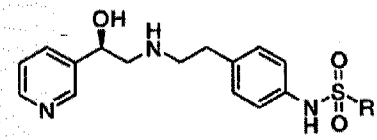
(R)-N-[4-[2-[[2-Hydroxy-2-(pyridin-3-yl)ethyl]amino]ethyl]phenyl]-4-[4-(1-hydroxy-1-hexylheptyl)-5-methyl-[1,2,3]-triazol-2-yl]benzenesulfonamide and (R)-N-[4-[2-[[2-Hydroxy-2-(pyridin-3-yl)ethyl]amino]ethyl]phenyl]-4-[4-(1-(R,S)-hydroxyheptyl)-5-methyl-[1,2,3]-triazol-2-yl]benzenesulfonamide

To a solution of 180 mg of (R)-N-[4-[2-[[2-Hydroxy-2-(pyridin-3-yl)ethyl]amino]ethyl]phenyl]-4-(4-methoxycarbonyl-5-methyl-[1,2,3]-triazol-2-yl)benzenesulfonamide (prepared according to the procedures outlined in examples 14-19) in 2 mL of distilled THF under argon at 0°C was added, dropwise, 2 mL of a 2.0M solution of n-hexylmagnesium bromide in ether. After 5 min, the reaction was quenched with cautious addition of 5 mL of aqueous ammonium chloride followed by ethyl acetate extraction of the aqueous layer. The combined organic extracts were dried over sodium sulfate, filtered, and concentrated in vacuo to yield the crude products. Preparative layer chromatography (PLC) on 2X0.5 mm thick silica gel plates eluted in 9:1 (v/v) dichloromethane:methanol gave two bands A (20 mg) and B (60mg). ^{1}H NMR (500 MHz, CD_3OD) of A: δ 8.51 (d, 1H, J=2 Hz), 8.41 (dd, 1H, J=1.5, 5 Hz), 8.01 (dd, 2H, J=2.5, 6.5Hz), 7.81 (m, 1H), 7.78 (dd, 2H, J=2.0, 9.0 Hz), 7.37 (m, 1H), 7.07;7.02 (ABq, 4H, Jab= 8.5 Hz), 4.86 (s, CD_3OH), 4.79 (dd, 1H, J= 7.5, 8 Hz), 2.9-2.7 (m, 6H), 2.44 (s, 3H), 1.85 (m, 4H), 1.40-1.15 (m, 16H), 0.83 (t, 6H, J=7 Hz)

indicating the dihexyl tertiary alcohol adduct, mass spec. expected 677 found 677. ^{1}H NMR (500 MHz, CD_3OD) of B: 8.51 (d, 1H, J=2 Hz), 8.41 (dd, 1H, J=1.5, 5 Hz), 8.03 (d, 2H, J=9 Hz), 7.78 (d, 2H, J=9 Hz), 7.37 (dd, 1H, J= 4.8, 7.7 Hz), 7.07;7.02 (ABq, 4H, Jab=8 Hz), 4.86 (s, CD_3OH), 4.80 (m, 2H), 2.9-2.7 (m, 6H), 2.38 (s, 3H), 1.87 (m, 2H), 1.44 (m, 1H), 1.4-1.2 (m, 7H), 0.87 (t, 3H, J=7 Hz) indicating the mono-hexyl adduct. Mass spec expected 591 (for the hexyl ketone) found 593 (hexyl alcohol, intermediate ketone reduced by Grignard reagent in situ).

Following the procedures outlined for Examples 14-31, the compounds listed in Table 2 were prepared.

TABLE 2



Example	R	Selected ^{1}H NMR (CD_3OD) Data
32	4-isopropylphenyl	7.64 (d, 2H, J = 8.0 Hz), 7.33 (d, 2H, J = 8.0 Hz), 4.80 (m, 1H), 2.95-2.70 (m, 7H), 1.22 (d, 6H, J = 6.7 Hz)
33	4-iodophenyl, bistrifluoroacetate salt	7.84 (d, 2H, J = 8.6 Hz), 7.47 (d, 2H, J = 8.6 Hz), 5.19 (dd, 1H, J = 10.1, 3.0 Hz), 3.40-3.20 (m, 4H), 2.96 (m, 2H)
34	2-naphthyl	8.28 (s, 1H), 7.94 (m, 3H), 7.72 (dd, 1H, J = 8.7, 1.9 Hz), 7.60 (m, 2H)
35	3-quinolinyl, bistrifluoroacetate salt	9.01 (d, 1H, J = 2.3 Hz), 8.76 (d, 1H, 1.8 Hz), 8.08 (d, 1H, J = 8.7 Hz), 8.04 (d, 1H, J = 8.0 Hz), 7.93 (m, 1H), 7.73 (m, 1H)

36	4-[(N-hexyl,N-methyl-aminocarbonyl)-amino]phenyl, bistrifluoroacetate salt	5.12 (d, 1H, J = 8.7 Hz), 3.40-3.10 (m, 6H), 2.99 (s, 3H), 2.95 (m, 2H), 1.56 (m, 2H), 1.31 (m, 6H), 0.88 (m, 3H)
37	4-(3-hexyl-2-imidazolidinon-1-yl)phenyl, bistrifluoroacetate salt	5.15 (m, 1H), 3.85 (m, 2H), 3.53 (m, 2H), 3.40-3.15 (m, 6H), 2.94 (m, 2H), 1.55 (m, 2H), 1.32 (m, 6H), 0.89 (m, 3H).
38	4-[(1-oxoheptyl)-amino]phenyl, bistrifluoroacetate salt	2.35 (tr, 2H, J=7.5 Hz), 1.65 (quint., 2H, J=7.1 Hz), 1.32 (m, 6H), 0.892 (tr, 3H, J=6.8Hz).
39	4-[(1-oxo-4-phenyl-butyl)amino]phenyl, bistrifluoroacetate salt	7.34-7.25 (m, 4H), 7.15-7.05 (m, 5H), 2.71 (tr, 2H, J=7.7Hz), 2.36 (tr, 2H, J-7.4 Hz), 1.96 (m, 2H).
40	4-[(propoxycarbonyl)-amino]phenyl	4.07 (tr, 2H, J=6.6 Hz), 1.67 (sextet, 2H, J=7.0 Hz). 0.968 (tr, 3H, J=7.4 Hz).
41	4-[[[(fur-2-ylmethyl)amino]carbonyl]amino]phenyl, bistrifluoroacetate salt	7.40 (d, 1H, J = 0.9 Hz), 6.32 (dd, 1H, J = 2.9, 1.8 Hz), 6.23 (d, 1H, J = 2.9 Hz), 4.34 (s, 2H)
42	4-[[[(2-phenylethyl)amino]carbonyl]amino]phenyl, bistrifluoroacetate salt	7.38-7.02 (m, 9H), 3.50-3.15 (m, 6H), 2.80 (m, 2H)
43	4-[[[(2-indol-3-ylethyl)amino]carbonyl]amino]phenyl	7.58-7.53 (m, 3 H), 7.42-7.30 (m, 4 H), 7.08-6.94 (m, 7H), 3.48 (tr, 2 H, J=6.9 Hz) 2.94 (tr, 2H, J=6.8 Hz).
44	4-[[(octylamino)carbonyl]amino]phenyl, bistrifluoroacetate salt	2.94 (m, 2H), 1.51 (tr, 2H, J=6.8 Hz), 1.30 (m, 10H), 0.884 (tr, 3H, J=6.9 Hz).

45	1-[(hexylamino)carbonyl] indolin-5-yl	7.83 (d, 2H, J = 9.2 Hz), 7.48 (m, 2H), 3.92 (t, 2H, J = 8.8 Hz), 3.1-3.2 (two overlap-ping t, 4H), 1.54 (m, 2H), 1.30 (m, 6H), 0.90 (t, 3H, J = 6.8 Hz).
46	1-[(octylamino)carbonyl]-indolin-5-yl	7.83 (d, 2H, J = 9.2 Hz), 7.48 (m, 2H), 3.92 (t, 2H, J = 8.8 Hz), 3.1-3.2 (two overlap-ping t, 4H), 1.63 (m, 2H), 1.30 (m, 10H), 0.89 (t, 3H, J = 6.9 Hz).
47	1-[(N-methyl-N-octylamino)carbonyl]-indolin-5-yl	7.53 (m, 2H), 6.90 (d, 1H, J = 8.3 Hz), 3.89 (t, 2H, J = 8.4 Hz), 3.26 (t, 2H, J = 7.6 Hz), 3.04 (t, 2H, J = 8.4 Hz), 2.91 (s, 3H), 1.60 (m, 2H), 1.27 (m, 10H), 0.87 (t, 3H, J = 6.8).
48	1-(1-oxononyl)indolin-5-yl	7.49 (m, 2H), 8.09 (d, 1H, J=9.1), 4.04 (t, 2H, J=8.5), 3.07 (t, 2H, J=8.5), 2.41 (t, 2H, J=7.5), 1.62 (m, 2H), 1.30 (m, 10H), 0.88 (t, 3H, J=6.8)
49	1-(4-methylthiazol-2-yl)indolin-5-yl	7.87 (d, 1H, J= 8.6 Hz), 7.58 (1H, dd, J = 2.0, 8.6 Hz), 7.52 (d, 1H, J = 2.0 Hz), 6.48 (s, 1H), 4.08 (t, 2H, J = 8.7 Hz), 3.25 (t, 2H, J = 8.7 Hz), 2.30 (s, 3H).
50	1-(4-octylthiazol-2-yl)indolin-5-yl	7.97 (d, 1H, J= 8.6 Hz), 7.57 (1H, dd, J = 2.0, 8.6 Hz), 7.53 (d, 1H, J = 2.0 Hz), 6.49 (s, 1H), 4.06 (t, 2H, J = 8.8 Hz), 3.24 (t, 2H, J = 8.8 Hz), 2.62 (t, 2H, J = 7.5 Hz), 1.68 (m, 2H), 1.2-1.4 (m, 10H), 0.88 (t, 3H, J = 7.0 Hz).

51	1-(4-ethyl-5-methylthiazol-2-yl)indolin-5-yl	7.87 (d, 1H, J= 8.5 Hz), 7.54 (1H, dd, J = 2.0, 8.5 Hz), 7.50 (d, 1H, J = 2.0 Hz), 4.02 (t, 2H, J = 8.7 Hz), 3.20 (t, 2H, J = 8.7 Hz), 2.56 (q, 2H, J = 7.7 Hz), 2.26 (s, 3H), 1.20 (t, 3H, J = 7.7 Hz).
52	4-(3-octyl-2-imidazolidinon-1-yl)phenyl	4.78 (m, 1H), 3.83 (m, 2H), 3.52 (m, 2H), 3.24 (t, 2H, 8Hz), 1.60-1.51 (m, 2H), 1.35-1.25 (m, 10H), 0.88 (t, 2H, 8Hz).
53	4-[3-(4,4,4-trifluorobutyl)-2-imidazolidinon-1-yl]phenyl, bistrifluoroacetate salt	3.86 (m, 2H), 3.54 (m, 2H), 3.40-3.20 (m, 6H), 2.19 (m, 2H), 1.82 (quin, J = 7.9 Hz, 2H)
54	4-[3-(3-phenylpropyl)-2-imidazolidinon-1-yl]phenyl, bistrifluoroacetate salt	7.20 (m, 4H), 7.10 (m, 1H), 5.15 (dd, 1H, 9.6,4Hz), 3.75 (m, 2H), 3.46 (m, 2H), 3.36-3.20 (m, 6H), 2.95-2.91 (m, 2H), 2.65 (t, 2H, 8Hz), 1.90 (qu, 2H, 8Hz).
55	4-[3-(4,4,5,5,5-pentafluoropentyl)-2-imidazolidinon-1-yl]phenyl, bistrifluoroacetate salt	3.87 (m, 2H), 3.56 (m, 2H), 3.40-3.20 (m, 6H), 2.14 (m, 2H), 1.86 (quin, J = 7.8 Hz, 2H)
56	4-[3-(2-cyclohexylethyl)-2-imidazolidinon-1-yl]phenyl, bistrifluoroacetate salt	3.82 (m, 2H), 3.50 (m, 2H), 2.87-2.70 (m, 6H), 1.78-1.63 (m, 5H), 1.41 (quartet, 2H, J=7.2 Hz), 1.30-1.18 (m, 4H), 0.949 (m, 2H).
57	4-[3-[3-(4-chlorophenyl)propyl]-2-imidazolidinon-1-yl]phenyl	7.19 (s, 4H), 4.79 (m, 1H), 3.74 (m, 2H), 3.47 (m, 2H), 3.30 (m, 2H), 2.63 (t, 2H, 7.6Hz), 1.91-1.83 (m, 2H).

58	4-(3-pentyl-2-imidazolidinon-1-yl)phenyl, bistrifluoroacetate salt	3.82 (m, 2 H), 3.53 (m, 2H), 2.94 (m, 2H), 1.57 (quintet, 2H, J=7.4 Hz), 1.39-1.28 (m, 4H), 0.916, (tr, 3H, J=7.1 Hz).
59	4-[3-(3-cyclopentylpropyl)-2-imidazolidinon-1-yl]phenyl	3.81 (m, 2H), 3.51 (m, 2H), 3.23 (t, J = 7.3 Hz, 2H), 1.78 (m, 3H), 1.57 (m, 6H), 1.33 (m, 2H), 1.17 (m, 2H)
60	4-[3-(2-cyclopentylethyl)-2-imidazolidinon-1-yl]phenyl, bistrifluoroacetate salt	3.83 (m. 2H), 3.53 (m, 2H), 2.94 (m, 2H), 1.81 (m, 4H), 1.65-1.53 (m, 5H), 1.16 (m, 2H).
61	4-[3-(3-cyclohexylpropyl)-2-imidazolidinon-1-yl]phenyl	3.83 (m, 2H), 3.51 (m, 2H), 3.22 (t, J = 7.3 Hz, 2H), 1.71 (m, 5H), 1.56 (m, 2H), 1.20 (m, 6H), 0.88 (m, 2H)
62	4-[3-(2,2-dimethylhexyl)-2-imidazolidinon-1-yl]phenyl	3.82 (m, 2H), 3.60 (m, 2H), 3.03 (s, 2H), 1.28 (m, 6H), 0.93 (m, 3H), 0.91 (s, 6H)
63	4-(3-hexyl-2-imidazolon-1-yl)phenyl	6.93 (d, 1H, 4Hz), 6.70 (d, 1H, 4Hz), 4.79 (m,1H), 3.64 (t, 2H, 8Hz), 1.71-1.64 (m, 2H), 1.35-1.28 (m, 6H), 0.91-0.86 (m, 3H).
64	4-[3-(4,4,4-trifluorobutyl)-2-imidazolon-1-yl]phenyl	6.97 (d, 1H, 3Hz), 6.73 (d, 1H, 3Hz), 3.73 (t, 2H, 7Hz), 2.23-2.19 (m, 2H), 1.98-1.92 (m, 2H).
65	4-(3-octyl-2-imidazolon-1-yl)phenyl	6.93 (d, 1H, 4Hz), 6.69 (d, 1H, 4Hz), 3.64 (t, 2H, 7Hz), 1.70-1.63 (m, 2H), 1.33-1.23 (m, 10H), 0.90-0.85 (m, 3H).

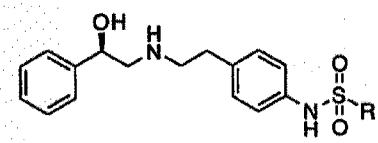
66	4-[3-(3-cyclopentylpropyl)-2-imidazolon-1-yl]phenyl	6.93 (d, 1H, 3Hz), 6.69 (d, 1H, 3Hz), 3.63 (t, 2H, 7Hz), 1.80-1.47 (m, 11H), 1.35-1.29 (m, 2H), 1.13-1.02 (m, 2H).
67	4-(2-octyl-3-oxo-[1,2,4]-triazol-4-yl)phenyl	8.25 (s, 1H), 3.79 (t, 2H, 7Hz), 1.80-1.70 (m, 2H), 1.36-1.25 (m, 10H), 0.91-0.86 (m, 3H).
68	4-(4-hexyl-5-tetrazolon-1-yl)phenyl	3.98 (t, 2H, J=7.1Hz), 2.9-2.7 (m, 6H), 1.82 (q, 2H, J=7 Hz), 1.4-1.27 (m, 6H), 0.89 (t, 3H, J=7Hz)
69	4-(4-octyl-5-tetrazolon-1-yl)phenyl	3.98 (t, 2H, J=7.1Hz), 2.9-2.7 (m, 6H), 1.83 (m, 2H), 1.4-1.2 (m, 10H), 0.87 (t, 3H, J=7 Hz)
70	4-[(3-cyclopentylpropyl)-5-tetrazolon-1-yl]phenyl	3.97 (t, 2H, J=7.1Hz), 2.9-2.7 (m, 9H), 1.9-1.7 (m, 5H), 1.6 (m, 1H), 1.5 (m, 1H), 1.37(m, 2H), 1.07(m, 1H)
71	4-(2-pentyloxazol-5-yl)phenyl	7.48 (s, 1H), 4.82 (m, 1H), 2.92-2.70 (m, 8H), 1.80 (m, 2H), 1.39 (m, 4H), 0.92 (m, 4H)
72	4-(2-octyloxazol-5-yl)phenyl	7.52 (s, 1H), 5.09 (m, 1H), 3.01-2.82 (m, 8H), 1.77 (m, 2H), 1.37-1.27 (m, 10H), 0.87 (m, 1H)
73	4-[2-(2-cyclopentylethyl)oxazol-5-yl]phenyl	7.52 (s, !H), 4.80 (m, 1H), 2.94-2.70 (m, 8H), 1.79 (m, 5H), 1.62 (m, 2H), 1.54 (m, 2H), 1.12 (m, 2H)
74	4-[(4-ethyl-5-methylthiazol-2-yl)amino]phenyl	7.62 (d, 2H, J = 9 Hz), 7.58 (d, 2H, J = 9 Hz), 2.53 (q, 2H, J = 7.5 Hz), 2.23 (s, 3H), 1.18 (t, 3H, J = 7.5 Hz)

75	4-[(4,5,6,7-tetrahydrobenzo-thiazol-2-yl)amino]phenyl	7.54 (d, 2H, J = 9 Hz), 7.48 (d, 2H, J = 9 Hz), 2.54 (m, 2H), 2.50 (m, 2H), 1.75 (m, 4H)
76	4-(2-hexylimidazol-4-yl)phenyl	7.75 (s, 1H), 5.04 (m, 1H), 3.29-3.20 (m, 4H), 2.97-2.90 (m, 4H), 1.82 (m, 2H), 1.40-1.30 (m, 6H), 0.9 (m, 3H)
77	4-(1-methyl-2-octylimidazol-5-yl)-phenyl	7.92 (s, 1H), 5.30 (m, 1H), 4.84 (s, 3H), 3.48-3.25 (m, 4H), 3.05-2.95 (m, 4H), 1.80 (m, 2H), 1.50-1.26 (m, 10H), 0.89 (m, 3H)
78	4-[1-methyl-2-(2-cyclopentylethyl)-imidazol-5-yl]phenyl	7.41 (s, 1H), 3.64 (s, 3H), 2.96-2.68 (m, 8H), 1.90-1.79 (m, 9H), 1.16 (m, 2H)
79	4-[1-methyl-2-[2-(4-fluorophenyl)ethyl]-imidazol-5-yl]phenyl	7.40 (s, 1H), 7.10-6.95 (m, 4H), 4.91 (m, 1H), 3.39 (s, 3H), 3.0 (bs, 4H)
80	4-(5-pentyl-[1,2,4]-oxadiazol-3-yl)phenyl	2.96 (t, 2H, J=7.6Hz), 1.84 (t, 2H, J=7.4Hz), 1.39 (m, 4H), 0.92 (t, 3H, J=7.1)
81	4-[5-(2-cyclopentylethyl)-[1,2,4]-oxadiazol-3-yl]phenyl	2.98 (t, 2H, J=7.5Hz), 1.84 (m, 5H), 1.70-1.50 (m, 4H), 1.16 (m, 2H)
82	4-(5-hexyl-[1,2,4]-oxadiazol-3-yl)phenyl	2.96 (t, 2H, J=7.5Hz), 1.84 (quin, 2H, J=7.4Hz), 1.48-1.28 (m, 6H), 0.90 (t, 3H, J=7.0Hz)
83	4-(5-heptyl-[1,2,4]-oxadiazol-3-yl)phenyl	2.96 (t, 2H, J=7.5Hz), 1.84 (quin, 2H, J=7.0Hz), 1.46-1.26 (m, 8H), 0.89 (t, 3H, J=6.9Hz)

84	4-(5-hexylthio-[1,2,4]-triazol-3-yl)phenyl	3.11(t,2H,J=7.3Hz), 2.98-2.84 (m,4H), 2.76 (t,2H,J=7.3Hz), 1.65 (q,2H,J=7.3Hz), 1.37 (q,2H,J=7.1Hz), 1.28-1.23 (m,4H), 0.84 (t,3H,J=6.9Hz)
85	4-[[4-(4-propylpiperidin-1-yl)-1,1-dioxo-[1,2,5]-thiadiazol-3-yl]amino]phenyl	8.84 (s, 1H), 8.75(d, 1H, J=5.07 Hz), 8.46(d, 1H, J=8Hz), 7.15 & 7.08 each (d, 2H, J=8Hz), 0.92(t, 3H, J=7Hz)
86	4-[[4-(hexylmethylamino)-1,1-dioxo-[1,2,5]-thiadiazol-3-yl]amino]phenyl	7.15(d, 2H, J=8.5Hz), 7.12(d, 2H, J=8.5Hz), 5.19(dd, 1H, 3.1Hz, 9Hz), 2.93(m, 2H), 0.90(t, 3H, 6.8Hz)
87	4-[[4-(heptylmethylamino)-1,1-dioxo-[1,2,5]-thiadiazol-3-yl]amino]phenyl	7.16(d, 2H, J=8.8Hz), 7.11(d, 2H, J=8.8 Hz), 5.01(dd, J=3.2Hz, 9.9Hz), 2.92(m, 2H), 1.68(m, 2H)
88	4-(1-octyl-2,4-imidazolidinedion-3-yl)phenyl	4.09 (s, 2H), 3.41 (t, 2H, 7hz), 1.65-1.56 (m, 2H), 1.30-1.25 (m, 10H), 0.91-0.86 (m, 3H).
89	4-[3-(3-nitrophenyl)-5-pyrazolon-1-yl]phenyl	8.55 (t,1H,J=1.9Hz), 8.47 (d, 1H,J=2.0Hz), 8.37 (dd,1H, J=3.2Hz), 8.14 (d,2H,J=8.9Hz), 8.08 (t,2H,J=8.5Hz), 7.74(d, 3H,J=8.9Hz), 7.56 (t,1H,J=8.0 Hz), 7.33 (dd,1H,J=4.8Hz), 7.04 (dd,4H,J=6.6Hz), 4.75 (t, 1H,J=2.1Hz), 2.83-2.69 (m,6H)

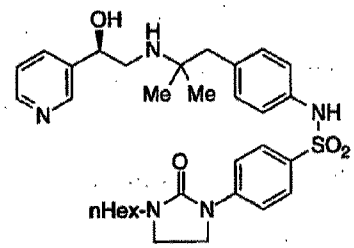
Starting with commercially available (R)-styrene epoxide and following the procedures outlined for Examples 17,18 and 25, the compounds listed in Table 3 were prepared.

TABLE 3



Example	R	Selected ^{1}H NMR (CD_3OD) Data
90	4-iodophenyl, trifluoroacetate salt	7.84 (d, 2H, J = 8.6 Hz), 7.45 (d, 2H, J = 8.5 Hz)
91	2-naphthyl, trifluoroacetate salt	8.31 (s, 1H), 7.96-7.90 (m, 3H), 7.74 (dd, 1H, J = 1.8, 8.7 Hz), 7.63 (t, 1H), 7.58 (t, 1H)
92	3-quinolinyl, trifluoroacetate salt	9.01 (d, 1H, J = 2.2 Hz), 8.75 (d, 1H, J = 2.1 Hz), 8.07 (d, 1H, J = 8.4 Hz), 8.03 (d, 1H, J = 8.3 Hz), 7.92 (t, 1H, J = 7.0 Hz), 7.72 (t, 1H, J = 7.1 Hz)

EXAMPLE 93



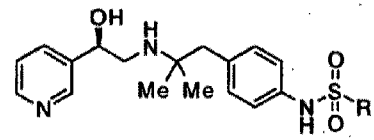
(R)-N-[4-[2-[[2-Hydroxy-2-(pyridin-3-yl)ethyl]amino]-2-methylpropyl]phenyl]-4-(3-hexyl-2-imidazolidinon-1-yl)benzenesulfonamide

A solution of pyridine epoxide (160mg,1.32 mmol) from example 16 and 4-amino-a,a-dimethylphenethylamine (1.2g, 7.3 mmol), prepared according to *J. Biol. Chem.* 1981, 256, 11944-50, in methanol (8 ml) was warmed at reflux for 16 hours. After cooling, the reaction mixture was concentrated and purified by flash chromatography (silica gel, 95:5 CH_2Cl_2: 10% NH_4OH/CH_3OH) to give 23 mg (0.080 mmol) of product as an oil.

The above product (18 mg, 0.063 mmol) was dissolved in CH_2Cl_2 (1 mL) and pyridine (0.05 mL). The resulting solution was cooled to 0°C and treated with 4-(3-hexyl-2-imidazolidinon-1-yl)benzenesulfonyl chloride (22 mg, 0.063 mmol). The mixture was allowed to stir at 0°C for 20 hours and was then purified by flash chromatography (silica gel, 95:5 CH_2Cl_2: 10% NH_4OH/CH_3OH) to give the desired product (21 mg, 0.035mmol) as an oil: ^{1}HNMR (CD_3OD) δ 8.53 (s, 1H), 8.44 (d,1H, J=5.0), 7.83 (d, 1H, J=7.9), 7.63 (m, 4H), 7.40 (dd, 1H, J=5.0, 7.9), 6.98 (m, 4H), 4.72 (dd, 1H, J=4.0, 8.4), 3.80 (m, 2H), 3.49 (m, 2H), 3.22 (t, 2H, J=7.2), 2.78 (m, 2H), 2.62 (m, 2H), 1.55 (m, 2H), 1.31 (m, 6H), 1.01 (s, 3H), 0.99 (s, 3H), 0.89 (m, 3H).

Following the procedure outlined above, the compounds in Table 4 were prepared.

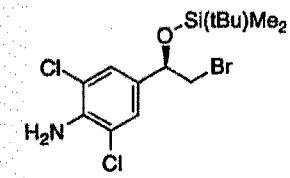
TABLE 4



Example	R	Selected ^{1}H NMR (CD_3OD) Data

94	4-iodophenyl	7.82 (d, 2H, J=8.6), 7.42 (d, 2H, J=8.6)
95	4-[[(hexylamino)carbonyl]amino]phenyl	7.55 (d, 2H, J=8.8), 7.42 (d, 2H, J=8.8), 3.11 (t, 2H, J=7.0), 1.49 (m, 2H), 1.30 (m, 6H), .089 (m, 3H)

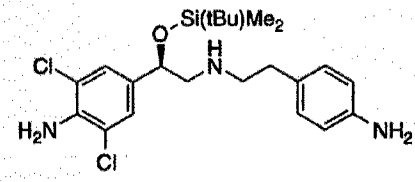
EXAMPLE 96



(R)-4-amino-α-(bromomethyl)-3,5-dichlorobenzenemethanol, dimethyl-1,1-dimethylethylsilyl ether

A solution of t-butyldimethylsilyl chloride (1.67 g, 11.1 mmol) in DMF (15 mL) was added slowly to a stirred solution of (R)-4-amino-α-(bromomethyl)-3,5-dichlorobenzenemethanol (2.1 g, 7.4 mmol, see Judkins, et. al, European Patent Application 0 460 924) and imidazole (0.75 g, 11.1 mmol) in DMF (6 mL) with an ice-water bath cooling. After being stirred at RT for 3h, the reaction mixture was poured into water (300 mL) and the product was extracted with ether. The organic phase was washed with saturated aqueous sodium bicarbonate solution, brine, dried($MgSO_4$) and evaporated to dryness. The crude product was purified on silica (95/5 hexane/ethyl acetate) to give the title compound (2.73 g, 93 %): ^1H NMR (400 MHz, $CDCl_3$) δ 7.14 (s, 2H), 4.67 (dd, 1H, J=2.1, 6.4 Hz), 3.33 (m, 2H), 0.87 (s, 9H), 0.89(s, 6H)

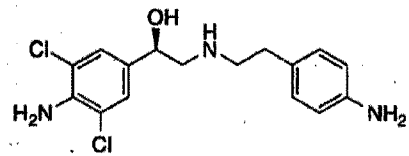
EXAMPLE 97



(R)-N-[2-[4-(Aminophenyl)]ethyl]-2-[(dimethyl-1,1-dimethylethylsilyl)oxy]-2-(4-amino-3,5-dichlorophenyl)ethylamine

O-TBDMS bromo compound from Example 96 (2.73g, 6.86 mmol) was dissolved in CH_3CN (50 mL) and 4-amino-phenethylamine (1.86 g, 13.72 mmol) was added, followed by the addition of N,N'-diisopropylethylamine (3.58 mL, 20.6 mmol) and sodium iodide (1.03 g, 6.86 mmol). After being heated at reflux for 48 h, the reaction mixture was concentrated and the residue chromatographed on silica (50/50 ethyl acetate/hexane) to provide the title compound (2.3 g, 75 %): ^1H NMR (400 MHz, $CDCl_3$) δ 7.08 (s, 2H), 6.94 (AA', 2H, J=8.4 Hz), 6.60 (BB', 2H, J=8.4 Hz), 4.63 (m, 1H), 4.37 (s, 2H), 3.53 (br s, 2H), 2.87-2.60 (m, 6H), 0.80 (s, 9H), -0.03 (s, 6H)

EXAMPLE 98

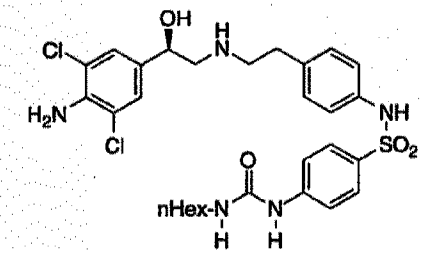


(R)-N-[2-[4-(Aminophenyl)]ethyl]-2-hydroxy-2-(4-amino-3,5-dichlorophenyl)ethylamine

To a stirred solution of silyl compound from Example 97 (2.2 g, 4.8 mmol) in THF (20 mL) at RT was added

tetrabutylammonium fluoride (10 mL of 1.0 M solution in THF) in one portion. After being stirred at RT for 2h, the reaction mixture was concentrated and chromatographed on silica (10/90 CH_3OH/CH_2Cl_2) to give the title compound (1.59 g, 97 %): ^1H NMR (400 MHz, CD_3OD) δ 7.15 (s, 2H), 6.92 (AA', 2H, J=8.3 Hz), 6.60 (BB', 2H, 8.3 Hz), 4.58 (m,1H), 2.83-2.65 (m, 6H)

EXAMPLE 99

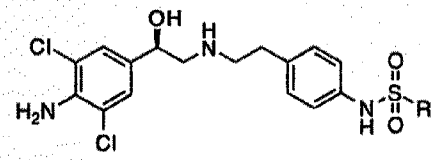


(R)-N-[4-[2-[[2-Hydroxy-2-(4-amino-3,5-dichlorophenyl)ethyl]amino]ethyl]-phenyl]-4-(hexylaminocarbonylamino)benzenesulfonamide

Following the procedure outlined in Example 18 and 25, the title compound was prepared from the aniline derivative from Example 98: NMR (400 MHz, CD_3OD) 7.57 (AA', 2H, J=2.7 Hz), 7.42 (BB', 2H, J=2.7 Hz), 7.16 (s, 2H), 7.04 (AA', 2H, J=2.0 Hz), 7.00 (BB', 2H, J=2.0 Hz), 4.58 (t, 1H, j=7.1 Hz), 3.14 (t, 1H, J=7.0 Hz), 2.80 (m, 2H), 2.73 (m, 4H), 1.49 (m, 2H), 1.32 (m, 6H), 0.90 (t, 3H, J=6.7 Hz). ESI MS *m/z* 622 (M).

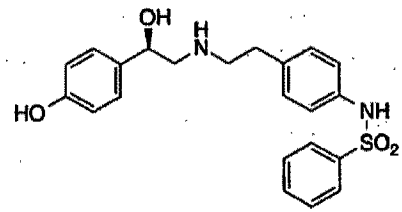
Following the procedure outlined in Examples 96-99, the compounds in Table 5 were prepared.

TABLE 5



Example	R	Selected ^{1}H NMR (CD_3OD) Data
100	1-[(octylamino)carbonyl]-indolin-5-yl	7.82 (d, 1H, J=9.2 Hz), 7.47 (m, 2H), 3.93 (t, 2H, J=9.0 Hz), 3.18 (m, 4H), 1.53 (m, 2H), 1.31 (m, 10H), 0.88 (t, 3H, J=7.1 Hz)
101	4-(3-hexyl-2-imidazolidinon-1-yl)phenyl	7.68-7.60 (AA'BB', 4H), 3.82 (t, 2H, J=6.2 Hz), 3.52 (t, 2H, J=6.2 Hz), 3.30 (t, 2H, J=6.0 Hz), 1.54 (m, 2H), 1.31 (m, 6H), 0.89 (t, 3H J=6.0 Hz)
102	4-(3-octyl-2-imidazolidinon-1-yl)phenyl	7.65-7.60 (AA'BB', 4H), 3.82 (t, 2H, J=6.2 Hz), 3.52 (t, 2H, J=6.2 Hz), 3.29 (t, 2H, J=6.0 Hz), 1.54 (m, 2H), 1.30 (m, 10H), 0.87 (t, 3H, J=6.1 HZ)

EXAMPLE 103



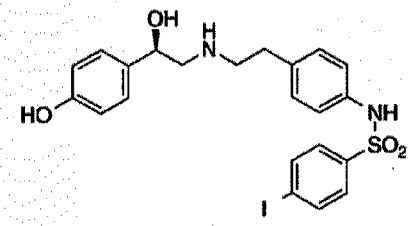
(R)-N-[4-[2-[[2-Hydroxy-2-(4-hydroxyphenyl)ethyl]amino]ethyl]phenyl]-benzenesulfonamide

A solution of 5 g of 4-aminophenethyl alcohol in 50 mL of DMF was silylated with 5.5 g of t-butyldimethylsilyl chloride (TBDMS-Cl) and 2.5 g of imidazole overnight at room temperature. Extraction of the product following an aqueous ammonium chloride workup afforded 6.6 g of the O-TBDMS ether. This aniline derivative was then coupled to benzenesulfonyl chloride in pyridine-dichloromethane to give the sulfonamide in greater than 80% yield after chromatographic purification. The TBDMS group of the sulfonamide was removed with methanolic HCl at room temperature for 30 min. The crude alcohol was oxidized to the corresponding carboxylic acid with Jones reagent in acetone (RT 30 min, ethyl acetate extraction).

To a solution of 180 mg of (R)-octopamine and 300 mg of the resultant 4-N-benzenesulfonamidophenylacetic acid in 7 mL of DMF was added 0.5 mL of triethylamine and 490 mg of benzotriazolyl-N-oxy-tris(dimethylamino)phosphonium hexafluorophosphate. The reaction mixture was stirred at RT 2h, flash chromatography over silica gel eluting with 95:5 chloroform-methanol gave 322 mg of purified amide.

A solution of 220 mg of this amide in 13 mL of 1.0 M borane-THF was refluxed under argon for 2h followed by the addition of 3 mL of N,N-dimethylaminoethanol and further reflux for another hour. The solvent and excess volatiles were removed in vacuo and the residual solid was taken up in acetone and purified by PLC on silica gel (9:1 ethyl acetate:methanol) to yield 61 mg of the title compound: ^1H NMR (500 MHz, CD_3OD) δ 7.73 (dt, 2H, J=2.1, 8.2Hz), 7.53 (tt, 1H, J=1.4, 7.6Hz), 7.44 (t, 2H, J=8 Hz), 7.18 (d, 2H, J=8.4 Hz), 7.05 (ABq, 4H, Jab=8.5 Hz), 6.76 (d, 2H, J=8.4Hz), 4.75 (dd, 1H, J=7.5, 7.6 Hz), 3.05-2.90 (m, 4H), 2.81 (t, 2H, J=7.6 Hz). Mass spec calcd. 412.5 found 413.2.

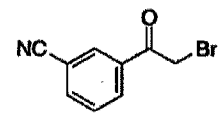
EXAMPLE 104



(R)-N-[4-[2-[[2-Hydroxy-2-(4-hydroxyphenyl)ethyl]amino]ethyl]phenyl]-4-iodobenzenesulfonamide

Following the procedure outlined in Example 103, the title compound was prepared: ^{1}H NMR (500 MHz, CD_3OD) δ 7.77 (d, 2H, J=8.5 Hz), 7.43 (d, 2H, J=8.5 Hz), 7.15 (d, 2H, J=8.5 Hz), 7.02 (ABq, 4H, Jab=8.7 Hz), 6.75 (d, 2H, J=8.5 Hz), 4.67 (dd, 1H, J=4.4, 6.6 Hz), 2.90-2.66 (m, 6H). Mass spec calcd. 538.4 found 538.9.

EXAMPLE 105

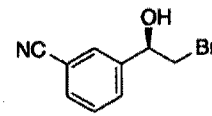


3-(2-bromoacetyl)benzonitrile

To a solution of 1.02 g (7.04 mmol) of 3-acetylbenzonitrile in 70 mL of ethyl ether was added 1.02 g (3.52 mmol, 0.5 equiv) of dibromobarbituric acid. The mixture was allowed to stir at room temperature overnight. The resultant white slurry was filtered and the filtrate was concentrated. Purification by flash chromotography (silica gel, 20% ethyl acetate/hexane) gave 1.28 g (81%) of the title compound as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ .8.26 (t, 1H, J = 1.4

Hz), 8.20 (td, 1H, J = 1.5, 8.0 Hz), 7.87 (dd, 1H, J = 1.3, 7.8 Hz), 7.64 (t, 1H, J = 7.9 Hz), 4.40 (s, 2H).

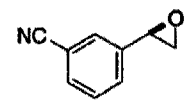
EXAMPLE 106



(R)-α-Bromomethyl-3-cyanophenylmethanol

To a suspension of 181 mg (0.623 mmol) of (R)-tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo[1,2c][1,3,2]oxazaborole-borane (R-OAB catalyst) in 6 mL of THF at 0 °C was added dropwise 6.24 mL (6.24 mmol) of a 1 M solution of borane in THF. The resultant clear solution was allowed to stir for 5 min, and then a solution of 1.27 g (5.67 mmol) of bromoketone from Example 105 in 6 mL of THF was added slowly over 1 h. After the reaction was allowed to stir for 30 min more, it was quenched by the dropwise addition of 6 mL of methanol and concentrated. Purification by flash chromatography (silica gel, 20-25% ethyl acetate/hexane) provided 944 mg (74%) of the title compound as a clear oil which crystallized: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, 1H, J = 1.5 Hz), 7.62-7.60 (m, 2H), 7.48 (t, 1H, J = 7.7 Hz), 4.95 (dd, 1H, J = 3.4, 8.4 Hz), 3.63 (dd, 1H, J = 3.4 Hz), 3.49 (dd, 1H, J = 8.4 Hz).

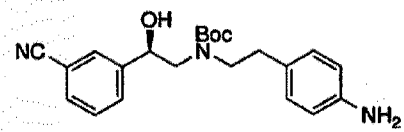
EXAMPLE 107



(R)-(3-cyanophenyl)oxirane

To a solution of 937 mg (4.14 mmol) of bromohydrin from Example 106 in 8 mL of methanol was added 601 mg (4.35 mmol, 1.05 equiv) of potassium carbonate. The reaction mixture was allowed to stir at room temperature for 7 h. It was then diluted with ethyl acetate, washed with water, dried over magnesium sulfate, and concentrated. Purification by flash chromatography (silica gel, 20% ethyl acetate/hexane) provided 573 mg (95%) of the title compound: ^{1}H NMR (400 MHz, $CDCl_3$) δ .7.59-7.55 (m, 2H), 7.49 (dd, 1H, J = 1.6, 7.9 Hz), 7.44 (t, 1H, J = 7.7 Hz), 3.87 (dd, 1H, J = 2.5, 4.0 Hz), 3.17 (dd, 1H, J = 4.1, 5.5 Hz), 2.74 (dd, 1H, J = 2.5, 5.4 Hz).

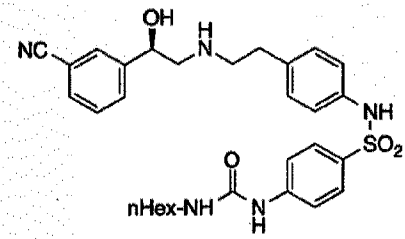
EXAMPLE 108



(R)-N-[2-[4-(aminophenyl)]ethyl]-2-hydroxy-2-(3-cyanophenyl)ethylcarbamic acid 1,1-dimethylethyl ester

Following the procedures outlined in Examples 17 and 18, the title compound was prepared from the epoxide from Example 107: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58-7.52 (br m, 3H), 7.41 (t, 1H, J = 7.5 Hz), 6.89 (br d, 2H, J = 7.6 Hz), 6.65 (br d, 2H, J = 7.8 Hz), 4.82 (br dd, 1H, J = 2.7, 7.9 Hz), 3.42-3.05 (br m, 4H), 2.75-2.55 (br m, 2H).

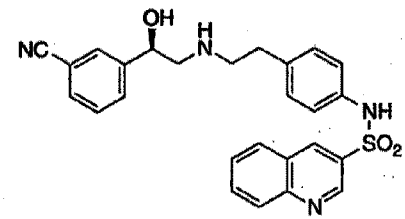
EXAMPLE 109



(R)-N-[4-[2-[[2-Hydroxy-2-(3-cyanophenyl)ethyl]amino]ethyl]phenyl]-4-(hexylaminocarbonylamino)benzenesulfonamide

Following the procedure outlined in Example 25, the title compound was prepared from the Boc aniline derivative from Example 108: ^{1}H NMR (400 MHz, CD_3OD) δ 7.70 (s, 1H), 7.63-7.57 (m, 4H), 7.48 (t, 1H, J = 7.7 Hz), 7.43 (d, 2H, J = 8.9 Hz), 7.06 (d, 2H, J = 8.5 Hz), 6.99 (d, 2H, J = 8.5 Hz), 4.77 (dd, 1H, J = 3.9, 8.5 Hz), 3.15 (t, 2H, J = 7.0 Hz), 2.86-2.69 (m, 6H), 1.49 (br m, 2H), 1.31 (br m, 6H), 0.90 (br t, 3H).

EXAMPLE 110



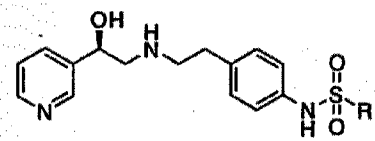
(R)-N-[4-[2-[[2-Hydroxy-2-(3-cyanophenyl)ethyl]amino]ethyl]phenyl]-3-quinolinesulfonamide

Following the procedure outlined in Example 25, the title compound was prepared from the Boc aniline derivative from Example

108 and 3-quinolinesulfonyl chloride: ^{1}H NMR (400 MHz, CD_3OD) δ 9.02 (d, 1H, J = 2.3 Hz), 8.68 (d, 1H, J = 1.9 Hz), 8.06 (d, 1H, J = 8.3 Hz), 8.02 (d, 1H, J = 7.9 Hz), 7.90 (ddd, 1H, J = 1.4, 7.0, 8.4 Hz), 7.72-7.69 (m, 2H), 7.62-7.58 (m, 2H), 7.47 (t, 1H, J = 7.7 Hz), 7.07 (d, 2H, J = 8.7 Hz), 7.03 (d, 2H, J = 8.7 Hz), 4.76 (dd, 1H, J = 4.0, 8.5 Hz), 2.85-2.68 (m, 6H).

Following the procedures outlined for Examples 14-31, the compounds listed in Table 6 were prepared.

TABLE 6

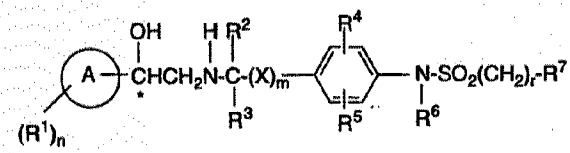


Example	R	Selected ^{1}H NMR (CD_3OD) Data
111	4-(3-hexyl-2,4-imidazolidinedion-1-yl)phenyl	4.40 (s,2H), 3.54 (m, 2H), 1.68-1.59 (m, 2H), 1.37-1.28 (m, 6H), 0.91 (m, 3H).
112	4-(3-octyl-2,4-imidazolidinedion-1-yl)phenyl	4.40 (s,2H), 3.52 (m, 2H), 1.68-1.59 (m, 2H), 1.38-1.23 (m, 10H), 0.89 (m, 3H).
113	4-[2-(4-cyclohexylbutyl)-oxazol-5-yl]phenyl, trihydrochloride	7.66 (s, 1H), 5.35 (m, 1H), 3.22-3.32 (m, 5H), 2.95 (m, 2H), 2.90 (t, J=6.5Hz, 2H), 1.8 (m, 2H), 1.69 (m, 5H), 1.45 (m, 2H), 1.24 (m, 6H), 0.89 (m. 2H)
114	4-[2-[2-(4-fluorophenyl)ethyl]-oxazol-5-yl]phenyl	7.49 (s, 1H), 7.2 (m, 2H), 6.99 (m, 2H), 4.90 (m, 1H), 3.05 (m, 4H), 2.70-2.85 (m, 6H)

115	4-[2-(3-cyclopentylpropyl)-oxazol-5-yl]phenyl	7.51 (s, 1H), 4.90 (m, 1H), 2.65-2.90 (m, 8H), 1.80 (m, 5H), 1.46-1.62 (m, 4H), 1.05 (m, 2H)
116	4-(4-hexyl-3-oxo-[1,2,4]-triazol-2-yl)phenyl	8.04 (s, 1H), 3.69 (m , 2H), 1.78-1.69 (m, 2H), 1.39-1.28 (m, 6H), 0.90 (m, 3H).
117	4-(4-octyl-3-oxo-[1,2,4]-triazol-2-yl)phenyl	8.03 (s, 1H), 3.69 (m , 2H), 1.77-1.69 (m, 2H), 1.38-1.25 (m, 10H), 0.89 (m, 3H).
118	4-(4-heptyl-5-methyl-[1,2,3]-triazol-2-yl)phenyl	2.28 (s,3H), 1.67 (t, 2H, J=6.9 Hz), 1.36-1.34 (m, 4H), 1.31-1.29 (m, 2H), 1.18 (d, 4H, J=2.5 Hz), 0.88 (t, 3H, J=7.0 Hz)

WHAT IS CLAIMED IS:

1. A compound having the formula I:



I

where

n is 0 to 5;

m is 0 or 1;

r is 0 to 3;

A is (1) a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen,
(2) a benzene ring fused to a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen,
(3) a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen fused to a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen,
(4) phenyl, or
(5) a benzene ring fused to a C3-C8 cycloalkyl ring;

R^1 is (1) hydroxy,
(2) oxo,
(3) halogen,
(4) cyano,
(5) NR^8R^8,
(6) SR^8,
(7) trifluoromethyl,

(8) C_1-C_{10} alkyl,
(9) OR^8,
(10) SO_2R^9,
(11) $OCOR^9$,
(12) NR^8COR^9,
(13) COR^9,
(14) $NR^8SO_2R^9$,
(15) $NR^8CO_2R^8$, or
(16) C_1-C_{10} alkyl substituted by hydroxy, halogen, cyano, NR^8R^8, SR^8, trifluoromethyl, OR^8, C_3-C_8 cycloalkyl, phenyl, NR^8COR^9, COR^9, SO_2R^9, $OCOR^9$, $NR^8SO_2R^9$ or $NR^8CO_2R^8$;

R^2 and R^3 are independently
(1) hydrogen,
(2) C_1-C_{10} alkyl or
(3) C_1-C_{10} alkyl with 1 to 4 substituents selected from hydroxy, C_1-C_{10} alkoxy, and halogen;

X is (1) $-CH_2-$,
(2) $-CH_2-CH_2-$,
(3) $-CH=CH-$ or
(4) $-CH_2O-$;

R^4 and R^5 are independently
(1)hydrogen,
(2) C_1-C_{10} alkyl,
(3) halogen,
(4) NHR^8,
(5) OR^8,
(6) SO_2R^9 or
(7) $NHSO_2R^9$;

R^6 is (1) hydrogen or
(2) C_1-C_{10} alkyl;

R^7 is $Z-(R^{1a})_n$;

R^{1a} is (1) R^1, with the proviso that when A is phenyl, R^{1a} is not C_1-C_{10} alkyl,

(2) C_3-C_8 cycloalkyl,
(3) phenyl optionally substituted with up to 4 groups independently selected from R^8, NR^8R^8, OR^8, SR^8 and halogen, or
(4) 5 or 6-membered heterocycle with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen, optionally substituted with up to four groups independently selected from oxo, R^8, NR^8R^8, OR^8, SR^8, and halogen;

Z is (1) phenyl,
(2) naphthyl,
(3) a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen,
(4) a benzene ring fused to a C_3-C_8 cycloalkyl ring,
(5) a benzene ring fused to a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen,
(6) a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen fused to a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen, or
(7) a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen fused to a C_3-C_8 cycloalkyl ring;

R^8 is (1) hydrogen,
(2) C_1-C_{10} alkyl,
(3) C_3-C_8 cycloalkyl,
(4) Z optionally having 1 to 4 substituents selected from halogen, nitro, oxo, $NR^{10}R^{10}$, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, C_1-C_{10} alkylthio, and C_1-C_{10} alkyl having 1 to 4 substituents selected from hydroxy, halogen, CO_2H, CO_2-C_1-C_{10} alkyl, SO_2-C_1-C_{10} alkyl, C_3-C_8 cycloalkyl, C_1-C_{10} alkoxy, and Z optionally substituted by from 1 to 3 of halogen, C_1-C_{10} alkyl or C_1-C_{10} alkoxy, or

(5) C_1-C_{10} alkyl having 1 to 4 substituents selected from hydroxy, halogen, CO_2H, CO_2-C_1-C_{10} alkyl, SO_2-C_1-C_{10} alkyl, C_3-C_8 cycloalkyl, C_1-C_{10} alkoxy, C_1-C_{10} alkyl, and Z optionally substituted by from 1 to 4 of halogen, C_1-C_{10} alkyl or C_1-C_{10} alkoxy;

R^9 is (1) R^8 or
(2) NR^8R^8;

R^{10} is (1) C_1-C_{10} alkyl, or
(2) two R^{10} groups together with the N to which they are attached formed a 5 or 6-membered ring optionally substituted with C_1-C_{10} alkyl; or

a pharmaceutically acceptable salt thereof.

2. A compound of Claim 1 where

n is 0 to 3;

m is 1;

r is 0 to 2;

A is phenyl or a 5- or 6-membered heterocyclic ring with from 1 to 4 nitrogen atoms;

X is $-CH_2-$;

R^1 is (1) hydroxy,
(2) halogen,
(3) cyano,
(4) trifluoromethyl,
(5) NR^8R^8,
(6) $NR^8SO_2R^9$,
(7) NR^8COR^9,
(8) $NR^8CO_2R^8$, or
(9) C_1-C_{10} alkyl optionally substituted by hydroxy;

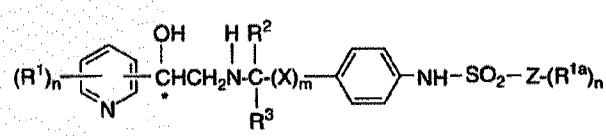
R^2, R^3 are independently
(1) hydrogen or
(2) methyl;

R^4, R^5 and R^6 are each hydrogen;

R^7 is $Z-(R^{1a})_n$; and

R^8, R^9, Z and R^{1a} are as defined in Claim 1, and when R^1 is part of the definition of R^{1a} has the meaning defined in Claim 1.

3. A compound of Claim 1 having the formula Ia:



Ia

wherein

n is 0 to 3;

m is 1

R^1 is (1) halogen or
(2) NR^8R^8;

R^2, R^3 are independently hydrogen or methyl;

R^{1a} is (1) halogen,
(2) C_1-C_{10} alkyl,
(3) NR^8R^8,
(4) NR^8COR^9,
(5) $NR^8CO_2R^8$,
(6) COR^9,
(7) $OCOR^9$, or
(8) a 5 or 6-membered heterocycle with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen, optionally substituted with up to four groups independently selected from oxo, halogen, R^8, NR^8R^8, OR^8, and SR^8;

Z is (1) phenyl,
(2) naphthyl,
(3) a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen,

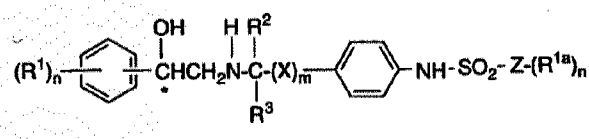
(4) benzene ring fused to a 5 or 6-membered heterocyclic ring with from 1 to 3 heteroatoms selected from oxygen, sulfur and nitrogen, or
(5) a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen fused to a C_3-C_8 cycloalkyl ring;

X is $-CH_2-$; and

R^8 and R^9 are as defined in Claim 1.

4. A compound of Claim 3 wherein R^2 and R^3 are each hydrogen.

5. A compound of Claim 1 having the formula Ib:



Ib

wherein

n is 0 to 3;

m is 1

R^1 is (1) hydroxy,
(2) cyano,
(3) NR^8R^8 or
(4) halogen;

R^{1a} is (1) halogen,
(2) NR^8R^8,
(3) NR^8COR^9,
(4) $NR^8CO_2R^8$,
(5) $OCOR^9$, or

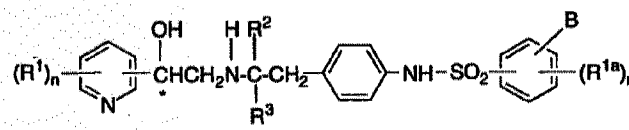
(6) a 5 or 6-membered heterocycle with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen, optionally substituted with up to three groups independently selected from oxo, halogen, R^8, NR^8R^8, OR^8 and SR^8;

Z is (1) phenyl,
(2) naphthyl or
(3) benzene ring fused to a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen;

X is $-CH_2-$; and

R^2 and R^3 are independently hydrogen or methyl.

6. A compound of Claim 1 having the formula Id



Id

n is 0 or 1;

R^1 is NR^8R^8;

R^2 and R^3 are independently
(1) hydrogen, or
(2) methyl;

B is (1) hydrogen,
(2) benzene fused to the benzene ring to form naphthyl, or
(3) a 5 or 6-membered heterocycle with 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen atom fused to the benzene ring;

R^{1a} is (1) halogen,
(2) C_1-C_{10} alkyl,
(3) NR^8R^8,
(4) NR^8COR^9,

(5) $NR^8CO_2R^8$,
(6) COR^9, or
(7) a 5 or 6-membered heterocycle with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen, optionally substituted with up to four groups independently selected from oxo, R^8, SR^8, OR^8, and NR^8R^8;
when B and the benzene ring form a fused ring system, R^{1a} is attached to either ring;

R^8 is (1) hydrogen,
(2) C_1-C_{10} alkyl,
(3) Z optionally having 1 to 4 substituents selected from nitro, oxo, and $NR^{10}R^{10}$, or
(5) C_1-C_{10} alkyl having 1 to 4 substituents selected from hydroxy, halogen, C_1-C_{10} alkyl, C_3-C_8 cycloalkyl, and Z optionally substituted by from 1 to 4 of halogen, C_1-C_{10} alkyl or C_1-C_{10} alkoxy;

R^9 is (1) R^8 or
(2) NR^8R^8;

R^{10} is (1) C_1-C_{10} alkyl, or
(2) two R^{10} groups together with the N to which they are attached formed a 5 or 6-membered ring optionally substituted with C_1-C_{10} alkyl; and

Z is (1) phenyl,
(2) a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen,
(3) a benzene ring fused to a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen, or
(4) a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen fused to a C_3-C_8 cycloalkyl ring.

7. A compound of Claim 1 selected from the group consisting of:

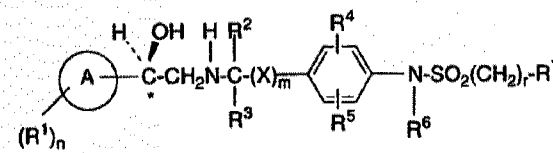
N-[4-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]phenyl]-4-iodobenzenesulfonamide;
N-[4-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]phenyl]-2-naphthalenesulfonamide; and
N-[4-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]phenyl]-3-quinolinesulfonamide.
N-[4-[2-[[2-hydroxy-2-(4-amino-3,5-dichlorophenyl)ethyl]amino]-ethyl]-phenyl]-4-(hexylaminocarbonylamino)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(4-amino-3,5-dichlorophenyl)ethyl]amino]-ethyl]-phenyl]-1-[(octylamino)carbonylamino]-5-indolinesulfonamide
N-[4-[2-[[2-hydroxy-2-(4-amino-3,5-dichlorophenyl)ethyl]amino]-ethyl]-phenyl]-4-(3-hexyl-2-imidazolidon-1-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(4-amino-3,5-dichlorophenyl)ethyl]amino]-ethyl]-phenyl]-4-(3-octyl-2-imidazolidon-1-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(4-hydroxyphenyl)ethyl]amino]-ethyl]phenyl]-benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(4-hydroxyphenyl)ethyl]amino]-ethyl]phenyl]-4-iodobenzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-cyanophenyl)ethyl]amino]ethyl]phenyl]-4-(hexylaminocarbonylamino)benzenesulfonamide, and
N-[4-[2-[[2-hydroxy-2-(3-cyanophenyl)ethyl]amino]ethyl]phenyl]-3-quinolinesulfonamide

8. A compound of Claim 1 selected from the group consisting of:
N-[4-[2-[[2-hydroxy-2-(6-aminopyridin-3-yl)ethyl]amino]ethyl]phenyl]-4-(hexylaminocarbonylamino)benzenesulfonamide;
N-[4-[2-[[2-hydroxy-2-(6-aminopyridin-3-yl)ethyl]amino]ethyl]phenyl]-4-iodobenzenesulfonamide;
N-[4-[2-[[2-hydroxy-2-(6-aminopyridin-3-yl)ethyl]amino]ethyl]phenyl]-benzenesulfonamide;
N-[4-[2-[[2-hydroxy-2-(6-aminopyridin-3-yl)ethyl]amino]ethyl]phenyl]-2-naphthalenesulfonamide;
N-[4-[2-[[2-hydroxy-2-(6-aminopyridin-3-yl)ethyl]amino]ethyl]phenyl]-3-quinolinesulfonamide;

N-[4-[2-[[2-hydroxy-2-(6-aminopyridin-3-yl)ethyl]amino]ethyl]phenyl]-5-benzisoxazolesulfonamide;
N-[4-[2-[[2-hydroxy-2-(6-aminopyridin-3-yl)ethyl]amino]ethyl]phenyl]-4-[(hexylmethylaminocarbonyl)amino]benzenesulfonamide;
N-[4-[2-[[2-hydroxy-2-(6-aminopyridin-3-yl)ethyl]amino]ethyl]phenyl]-4-[(dimethylaminocarbonyl)amino]benzenesulfonamide;
N-[4-[2-[[2-hydroxy-2-(6-aminopyridin-3-yl)ethyl]amino]ethyl]phenyl]-4-(3-hexyl-2-imidazolidon-1-yl)benzenesulfonamide;
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(hexylaminocarbonylamino)benzenesulfonamide;
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-isopropylbenzenesulfonamide;
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-2-naphthalenesulfonamide;
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-3-quinolinesulfonamide;
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[(hexylmethylaminocarbonyl)amino]benzenesulfonamide;
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(3-hexyl-2-imidazolidon-1-yl)benzenesulfonamide;
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-iodobenzenesulfonamide;
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[3-(3-cyclopentylpropyl)-2-imidazolidon-1-yl]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(3-octyl-2-imidazolidinon-1-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(3-hexyl-2-imidazolon-1-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(3-octyl-2-imidazolon-1-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[3-(3-cyclopentylpropyl)-2-imidazolon-1-yl]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(4-octylthiazol-2-yl)-5-indolinesulfonamide

N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(5-pentyl-[1,2,4]-oxadiazol-3-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(5-hexyl-[1,2,4]-oxadiazol-3-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(5-heptyl-[1,2,4]-oxadiazol-3-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(5-octyl-[1,2,4]-oxadiazol-3-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[5-(2-cyclopentylethyl)-[1,2,4]-oxadiazol-3-yl]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]pbenyl]-4-[5-(3-cyclopentylpropyl)-[1,2,4]-oxadiazol-3-yl]benzensulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(2-pentyloxazol-5-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(2-hexyloxazol-5-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(2-heptyloxazol-5-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(2-octyloxazol-5-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[2-(2-cyclopentylethyl)oxazol-5-yl]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[2-(3-cyclopentylpropyl)oxazol-5-yl]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(4-hexyl-5-tetrazolon-1-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(4-octyl-5-tetrazolon-1-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[(3-cyclopentylpropyl)-5-tetrazolon-1-yl]benzenesulfonamide

9. A compound of Claim 1 with the structural formula Ic:



Ic

where n, m, r, A, R^1, R^2, R^3, R^4, R^5, R^6, R^7 and X are as defined in Claim 1.

10 A method for the treatment of diabetes which comprises administering to a diabetic patient an effective amount of a compound of Claim 1.

11. A method for the treatment of obesity which comprises administering to an obese patient an effective amount of a compound of Claim 1.

12. A method for lowering triglyceride levels and cholesterol levels or raising high density lipoprotein levels which comprises administering to a patient needing lower triglyceride and cholesterol levels or higher high density lipoprotein levels an effective amount of a compound of Claim 1.

13. A method for decreasing gut motility which comprises administering to a patient in need of decreased gut motility, an effective amount of a compound of Claim 1.

14. A method for reducing neurogenic inflammation of airways which comprises administering to a patient in need of reduced neurogenic inflammation, an effective amount of a compound of Claim 1.

15. A method for reducing depression which comprises administering to a depressed patient an effective amount of a compound of Claim 1.

16. A method for treating gastrointestinal disorders which comprises administering to a patient with gastrointestinal disorders an effective amount of a compound of Claim 1.

17. A composition for the treatment of diabetes or obesity or for lowering triglyceride or cholesterol levels or increasing high density lipoprotein levels or for decreasing gut motility or for reducing neurogenic inflammation or for treating depression or for treating gastrointestinal disorders which comprises an inert carrier and an effective amount of a compound of Claim 1.

INTERNATIONAL SEARCH REPORT

Inten al Application No
PCT/US 95/04956

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D213/30 C07D413/12 C07D401/12 C07D417/14 C07C311/21
C07D417/12 C07D209/08 C07D233/36 C07D215/36 A61K31/44
A61K31/47 A61K31/18

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)
IPC 6 C07D C07C 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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	EP-A-0 611 003 (MERCK & CO INC) 17 August 1994 see the whole document	1-17
A	EP-A-0 091 749 (BEECHAM GROUP PLC) 19 October 1983 see the whole document	1-17

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in 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
4 August 1995	11. 08. 95

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	Bosma, P

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter nal Application No
PCT/US 95/04956

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0611003	17-08-94	AU-B-	5498694	29-06-95
		CA-A-	2114712	10-08-94
		JP-A-	7010827	13-01-95
		WO-A-	9418161	18-08-94
EP-A-0091749	19-10-83	JP-A-	58185554	29-10-83

Form PCT/ISA/210 (patent family annex) (July 1992)

INFORMATION DISCLOSURE CITATION
(Use several sheets if necessary)

OMB No. 0651-0011

Atty. Docket No.	0007-00	Serial No.	09/529,096
Applicant	Tatsuya MARUYAMA et al.		
Filing Date	April 7, 2000	Group:	1624

U.S. PATENT DOCUMENTS

Examiner Initial*		Document Number	Issue Date	Name	Class	Sub Class	Filing Date If Appropriate
		5,223,614	Jun 29, 1993	Schromm et al.	544	105	
		6,048,884	Apr 11, 2000	Maruyama et al.	514	370	
		6,177,454	Jan 23, 2001	Maruyama et al.	514	394	

FOREIGN PATENT DOCUMENTS

		Document Number	Publication Date	Country	Class	Sub Class	Translation Yes or No

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

Examiner		Date Considered	6/18/01

*Examiner: Initial if reference considered, whether or not citation is in conformance with MPEP 609; draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Form PTO 1449 — Patent and Trademark Office - U.S. Department of Commerce

1624
#11B
9/25

PATENT
Customer Number 22,852
Attorney Docket No. 7385.0007-00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

re Application of:

Tatsuya MARUYAMA et al.

Application No.: 09/529,096 — Group Art Unit: 1624

Filed: April 7, 2000 — Examiner: S. Patel

For: AMIDE DERIVATIVES OR SALTS THEREOF

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

SECOND AMENDMENT UNDER 37 C.F.R. § 1.111

In response to the Office Action dated June 19, 2001, Applicants amend this application as follows:

IN THE CLAIMS:

Without prejudice, disclaimer, or acquiescence, please amend claims 1-7 and 9-13, and add new claims 14-15 as follows:

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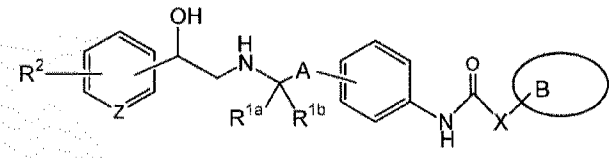
T0760
B1

1. (Twice Amended) A compound of formula (I):



(I)

in the formula, each of the symbols means as follows:

ring B is a heteroaryl group which is unsubstituted or substituted and is optionally fused with a benzene ring;

X is a bond, or a lower alkylene or an alkenylene, both of which are unsubstituted or substituted with hydroxy or a lower alkyl group, or X is a carbonyl or a group represented by -NH-, and when X is a lower alkylene which is substituted with a lower alkyl group, a carbon atom of the ring B optionally bonds with the lower alkyl group so that a ring is formed;

A is a lower alkylene or a group represented by -lower alkylene-O-;

R^{1a}, R^{1b} are the same or different and each is a hydrogen atom or a lower alkyl group;

R^2 is a hydrogen atom or a halogen atom; and

Z is a group represented by =CH-;

or a salt thereof.

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B2

2. (Once Amended) The compound of formula (I) or the salt thereof according to claim 1, wherein A is methylene, ethylene, or a group represented by $-CH_2O-$.

76

B

B3

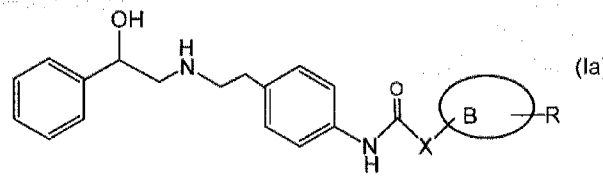
3. (Twice Amended) The compound of formula (I) or the salt thereof according to claim 2, wherein the ring B is a heteroaryl group which is substituted with a substituent chosen from a halogen atom, lower alkyl, lower alkenyl, lower alkynyl, hydroxy, sulfanyl, halogeno lower alkyl, lower alkyl-O-, lower alkyl-S-, lower alkyl-O-CO-, carboxy, sulfonyl, sulfinyl, lower alkyl-SO-, lower alkyl-SO_2-, lower alkyl-CO-, lower alkyl-CO-O-, carbamoyl, lower alkyl-NH-CO-, di-lower alkyl-N-CO-, nitro, cyano, amino, lower alkyl-NH-, di-lower alkyl-N-, aryl-lower alkyl, halogeno aryl-lower alkyl, guanidino, lower alkyl-CO-NH, and lower alkyl-SO_2-NH-.

B4

4. (Once Amended) The compound of formula (I) or the salt thereof according to claim 3, wherein R^2, R^{1a} and R^{1b} are each a hydrogen atom, and Z is =CH-.

B5

5. (Twice Amended) A compound of formula (Ia):



(Ia)

T0770

in the formula, each of the symbols means as follows:

ring B is a heteroaryl group;

X is a bond or a lower alkylene group;

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R is a hydrogen atom, a halogen atom, a lower alkyl group, amino group, an aryl lower alkyl group, or a halogeno aryl-lower alkyl group;

or a salt thereof.

6. (Once Amended) A compound:

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-pyridinecarboxyanilide,

(R)-2-[1-(4-chlorobenzyl)-1H-imidazol-2-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]-acetanilide, (R)-2-[1-(3,4-dichlorobenzyl)-1H-tetrazol-5-yl]- 4'-[2-[(2-hydroxy -2-phenylethyl)amino]ethyl]acetanilide,

(R)-2-(2-aminothiazol-4-yl)-4'-[2-(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide,

(R)-2-(2-benzyl-1H-1,2,4-triazol-3-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)-amino] ethyl]acetanilide,

(R)-2-(2-aminopyridin-6-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl)acetanilide, (R)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]-2-(2-pyridyl)acetanilide,

(R)-4'-[2-[(2-hydroxy-2-phenylethyl)-amino]ethyl)-2-(2-pyrazinyl)acetanilide, (R)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl)-2-(2-pyrimidinyl)-acetanilide, or a salt of any of the foregoing.

7. (Twice Amended) A composition comprising at least one compound of formula (I) or the salt thereof as claimed in one of claims 1 through 4 in a pharmaceutically acceptable carrier.

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8. (Once Amended) The composition as claimed in claim 7, wherein the at least one compound of formula (I) or the salt thereof is present in an amount effective for the treating of diabetes mellitus in a human or animal patient in need of such treating.

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9. (Once Amended) The compound of formula (I) as claimed in claim 1, wherein the compound of formula (I) is an optical isomer, a hydrate, or a solvate of the compound of formula (I).

10. (Once Amended) A composition comprising a compound of formula (I) as claimed in claim 1 in a pharmaceutically acceptable carrier, wherein the compound of formula (I) is present as a polymorphic substance.

13. (Once Amended) A method for treating diabetes mellitus in a human or animal patient in need of such treatment comprising administering to the patient an amount of a compound of formula (I) as claimed in claim 1, wherein the amount is an amount effective for such treatment.

14. (Once Amended) A method for treating obesity in a human or animal patient in need of such treatment comprising administering to the patient an amount of a compound of formula (I) as claimed in claim 1, wherein the amount is an amount effective for such treatment.

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~~14.~~ (New) A composition comprising at least one compound of formula (I) or the salt thereof as claimed in claim 5, in a pharmaceutically acceptable carrier.

12
~~15.~~ (New) A composition comprising at least one compound or the salt of any of the foregoing as claimed in claim 6, in a pharmaceutically acceptable carrier.

REMARKS

I. Amendments to the Claims

Claims 1-7 and 9-15 are now pending. Claims 1-7 and 9-13 have been amended, without prejudice to pursuing canceled subject matter, if any, in a continuation application, without disclaimer of any subject matter, and without acquiescence to any rejection, objection, or requirement.

Claims 1-7 and 9-13 were amended to recite "a compound" instead of "an amide derivative," in accordance with the Examiner's suggestion. *See* Office Action at page 4. The claims were also amended to remove non-elected subject matter: specifically, in claim 1, Z is no longer claimed to be a nitrogen atom. These amendments simply clarify the meaning of the claims, and support may be found throughout the application and claims as originally filed.

Claim 6 was amended by adding the words "a compound." Support for this amendment can be found, among other places, in claim 6 as originally filed. Claim 7 now depends in the alternative from one of claims 1 to 4. New claims 14 and 15 have been added to claim those compositions comprising at least one compound of claim 5 and claim 6, respectively. Support for this amendment may be found, among other

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places, in claim 7 as originally filed. To the extent that claim 7 has been rejected, claims 14 and 15 should be deemed allowable for the same reasons as claim 7 set forth below.

Care has been taken so that no new matter has been introduced into this application. With the exception of the deletion of non-elected subject matter, these amendments are not intended to alter the scope of the claims.

II. Restriction Requirement

The restriction requirement of record has been made final, on the ground that the claims lack unity of invention. *See* Office Action at pages 2-3. While Applicants maintain their traverse of this requirement, they affirm their election with traverse of Group IV, now claims 1-7 and 9-15, drawn to compounds, compositions, and methods of use for Formula I wherein Z is =CH-. Accordingly, and without prejudice or disclaimer, the claims have been amended to exclude non-elected subject matter. Specifically, claim 1 no longer recites that Z can be a nitrogen atom.

III. Rejections Under 35 U.S.C. §112, ¶2

Claims 1-7 and 9-13 have been rejected under 35 U.S.C. § 112, ¶2, as indefinite for allegedly failing to particularly point out and distinctly claim the subject matter Applicants regard as their invention. *See* Office Action at page 4. Applicants respectfully traverse, and respond as follows.

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A. In the definition of group B, the claim language "heteroaryl group which may be substituted or unsubstituted and is optionally fused with a benzene ring" has been rejected for being indefinite. Applicants respectfully disagree with the rejection.

Claim 1, reciting the definition of group B, is not indefinite. The claim language satisfies the two separate requirements of 35 U.S.C. § 112, ¶ 2. First, "the claims must set forth the subject matter that applicants regard as their invention." MPEP § 2171. Second, "the claims must particularly point out and distinctly define the metes and bounds of the subject matter that will be protected by the patent grant." *Id.*

> [b]readth of a claim is not to be equated with indefiniteness. If the scope of the subject matter embraced by the claims is clear, and if applicants have not otherwise indicated that they intend the invention to be of a scope different from that defined in the claims, then the claims comply with 35 U.S.C. 112, second paragraph.

MPEP § 2173.04 (citations omitted). Applicants contend that the rejected claim language is broad, but it is not indefinite.

Applicants give specific, but nonlimiting, examples of the heteroaryl group, heteroaryl group fused with a benzene ring, and optional substituents, on pages 7-8 in the specification. Taking the disclosure as a whole and these examples, one of ordinary skill in the art would be able to determine the metes and bounds of the claimed invention. B may be, for example, pyridopyrimidinyl; and B may not be a hydrogen atom.

To require the claims to list every single heteroaryl group would be to deprive the Applicants of substantial value of their invention. An unscrupulous copyist could easily select a heteroaryl group not listed, and thereby steal the essence of Applicants'

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invention without fear of infringement. For these reasons, Applicants respectfully request that this rejection be withdrawn.

B. Claims reciting, "an amide derivative" have been rejected for being indefinite. *See* Office Action at page 4. Without acquiescing in the allegation that the claims were indefinite, Applicants have amended the claims to conform to the Examiner's suggestion. The claims now recite, "a compound of formula (I)" or similar language where appropriate. Applicants therefore request that this rejection be withdrawn.

C. The term "optionally" has been rejected for being indefinite. *See* Office Action at page 4. Applicants respectfully assert that "optionally" is not an indefinite term *per se*, and that the claim as it was written, was not indefinite. *See* MPEP § 2173.05(h)(III). One possible alternative expression is "ring B . . . is not fused or is fused with a benzene ring." Applicants assert that the present expression employing "optionally" is clear and satisfies 35 U.S.C. § 112, ¶2, discussed above. Applicants respectfully request that this rejection be withdrawn.

IV. Claim Rejections Under 35 U.S.C. § 103

Claims 1-7 and 9-13 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over *Schromm et al.* (US 5,223,614). *See* Office Action at page 5. Applicants respectfully traverse this rejection.

To establish a prima facie case of obviousness,

> First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of

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> ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

MPEP § 2143. The present rejection falls short of establishing a prima facie case, at least because *Schromm et al.* fails to teach or suggest all of the claim limitations.

Schromm et al. shows a generic formula containing, among other radicals, a radical Q. *See Schromm et al.* at col. 1, line 30. "Q represents a substituted phenyl group[.]" *Id.*, at col. 1, line 36. Throughout the disclosure of *Schromm et al.*, this substituted phenyl group shows an hydroxyl or an ether substitution on the phenyl ring corresponding to radical Q. This hydroxyl or ether substitution does not teach or suggest Applicants' claimed invention. In present claim 1, to the extent that the ring comprising Z and binding R^2 remotely corresponds to *Schromm's* radical Q, the two structures differ: Applicants' "R^2 is a hydrogen atom or a halogen atom," not an hydroxyl or ether radical. The Office Action provides no motivation to modify *Schromm's* substituted phenyl group Q to obtain anything resembling Applicants' Z ring and R^2. Even if such modification were made, no reasonable expectation of success can be shown that such molecules would work for Schromm's intended purpose. Therefore, Applicants respectfully request that the rejection be withdrawn as to all claims rejected.

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CONCLUSION

Applicants respectfully request that all rejections be withdrawn, the application be reconsidered, and the claims allowed in a timely manner.

Please grant any extensions of time required to enter this response and charge any required extension fees to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

Dated: September 18, 2001

By: David W. Hill
David W. Hill
Reg. No. 28,220

Enclosure:

- Appendix

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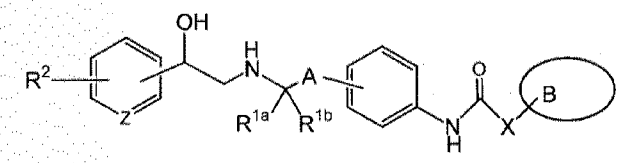
APPENDIX

In accordance with 37 C.F.R. § 1.121, claims 1-7 and 9-13 are set forth below in marked-up form to aid the Examiner in identifying amendments to the claims. Additions are underlined, and deletions are shown with bold square brackets and strikethrough text [~~like this~~]. If a discrepancy is found between the version of the claims set forth above and the version set forth below, then the version set forth above controls.

1. (Twice Amended) [~~An amide derivative represented by the general~~] A compound of formula (I):



(I)

in the formula, each of the symbols means as follows:

ring B is a heteroaryl group which is unsubstituted or substituted and is optionally fused with a benzene ring;

X is a bond, or a lower alkylene or an alkenylene, both of which are unsubstituted or substituted with hydroxy or a lower alkyl group, or X is a carbonyl or a group represented by -NH-, and when X is a lower alkylene which is substituted with a lower alkyl group, a carbon atom of the ring B optionally bonds with the lower alkyl group so that a ring is formed;

A is a lower alkylene or a group represented by -lower alkylene-O-;

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R^{1a}, R^{1b} are the same or different and each is a hydrogen atom or a lower alkyl group;

R^2 is a hydrogen atom or a halogen atom; and

Z is [~~a nitrogen atom or~~] a group represented by =CH-;

or a salt thereof.

2. (Once Amended) The [~~amide derivative~~] compound of formula (I) or the salt thereof according to claim 1, wherein A is methylene, ethylene, or a group represented by $-CH_2O-$.

3. (Twice Amended) The [~~amide derivative~~] compound of formula (I) or the salt thereof according to claim 2, wherein the ring B is a heteroaryl group which is substituted with a substituent chosen from a halogen atom, lower alkyl, lower alkenyl, lower alkynyl, hydroxy, sulfanyl, halogeno lower alkyl, lower alkyl-O-, lower alkyl-S-, lower alkyl-O-CO-, carboxy, sulfonyl, sulfinyl, lower alkyl-SO-, lower alkyl-SO_2-, lower alkyl-CO-, lower alkyl-CO-O-, carbamoyl, lower alkyl-NH-CO-, di-lower alkyl-N-CO-, nitro, cyano, amino, lower alkyl-NH-, di-lower alkyl-N-, aryl-lower alkyl, halogeno aryl-lower alkyl, guanidino, lower alkyl-CO-NH, and lower alkyl-SO_2-NH-.

4. (Once Amended) The [~~amide derivative~~] compound of formula (I) or the salt thereof according to claim 3, wherein R^2, R^{1a} and R^{1b} are each a hydrogen atom, and Z is =CH-.

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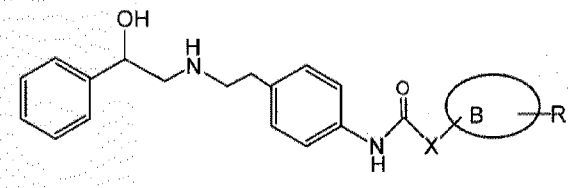
5. (Twice Amended) ~~[An amide derivative represented by the general]~~ A compound of formula (Ia):



(Ia)

in the formula, each of the symbols means as follows:

ring B is a heteroaryl group;

X is a bond or a lower alkylene group;

R is a hydrogen atom, a halogen atom, a lower alkyl group, amino group, an aryl lower alkyl group, or a halogeno aryl-lower alkyl group;

or a salt thereof.

6. (Once Amended) A compound:

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-pyridinecarboxyanilide,

(R)-2-[1-(4-chlorobenzyl)-1H-imidazol-2-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]-acetanilide, (R)-2-[1-(3,4-dichlorobenzyl)-1H-tetrazol-5-yl]- 4'-[2-[(2-hydroxy -2-phenylethyl)amino]ethyl]acetanilide,

(R)-2-(2-aminothiazol-4-yl)-4'-[2-(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide,

(R)-2-(2-benzyl-1H-1,2,4-triazol-3-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)-amino] ethyl]acetanilide,

(R)-2-(2-aminopyridin-6-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl)acetanilide, (R)-

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4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]-2-(2-pyridyl)acetanilide, (R)-4'-[2-[(2-hydroxy-2-phenylethyl)-amino]ethyl)-2-(2-pyrazinyl)acetanilide, (R)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl)-2-(2-pyrimidinyl)-acetanilide, or a salt of any of the foregoing.

7. (Twice Amended) A composition comprising at least one [~~amide derivative~~] compound of formula (I) or the salt thereof as claimed in one of claims 1 through [~~6~~] 4 in a pharmaceutically acceptable carrier.

9. (Once Amended) The composition as claimed in claim 7, wherein the [~~amount of~~] at least one [~~amide derivative~~] compound of formula (I) or the salt thereof is present in an amount effective for the treating of diabetes mellitus in a human or animal patient in need of such treating.

10. (Once Amended) The [~~amide derivative of general~~] compound of formula (I) as claimed in claim 1, wherein the [~~amide derivative~~] compound of formula (I) is an optical isomer, a hydrate, or a solvate of the [~~amide derivative~~] compound of formula (I).

11. (Once Amended) A composition comprising [~~an amide derivative of general~~] a compound of formula (I) as claimed in claim 1 in a pharmaceutically acceptable carrier, wherein the [~~amide derivative~~] compound of formula (I) is present as a polymorphic substance.

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12. (Once Amended) A method for treating diabetes mellitus in a human or animal patient in need of such treatment comprising administering to the patient an amount of ~~[an amide derivative of general]~~ a compound of formula (I) as claimed in claim 1, wherein the amount is an amount effective for such treatment.

13. (Once Amended) A method for treating obesity in a human or animal patient in need of such treatment comprising administering to the patient an amount of ~~[an amide derivative of general]~~ a compound of formula (I) as claimed in claim 1, wherein the amount is an amount effective for such treatment.

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UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

NOTICE OF ALLOWANCE AND ISSUE FEE DUE

HM22/1001
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1300 I STREET NW
WASHINGTON DC 20005-3315

APPLICATION NO.	FILING DATE	TOTAL CLAIMS	EXAMINER AND GROUP ART UNIT	DATE MAILED
09/529,096	04/07/00	014	PATEL, S 1624	10/01/01

First Named Applicant	MARUYAMA,	35 USC 154(b) term ext. =	0 Days.

TITLE OF INVENTION: AMIDE DERIVATIVES OR SALTS THEREOF

ATTY'S DOCKET NO.	CLASS-SUBCLASS	BATCH NO.	APPLN. TYPE	SMALL ENTITY	FEE DUE	DATE DUE
1 07385.0007	514-252.010	M82	UTILITY	NO	$1240.00	01/02/02

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED.

THE ISSUE FEE MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED.

HOW TO RESPOND TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.
If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is changed, pay twice the amount of the FEE DUE shown above and notify the Patent and Trademark Office of the change in status, or
B. If the status is the same, pay the FEE DUE shown above.

If the SMALL ENTITY is shown as NO:

A. Pay FEE DUE shown above, or

B. File verified statement of Small Entity Status before, or with, payment of 1/2 the FEE DUE shown above.

II. Part B-Issue Fee Transmittal should be completed and returned to the Patent and Trademark Office (PTO) with your ISSUE FEE. Even if the ISSUE FEE has already been paid by charge to deposit account, Part B Issue Fee Transmittal should be completed and returned. If you are charging the ISSUE FEE to your deposit account, section "4b" of Part B-Issue Fee Transmittal should be completed and an extra copy of the form should be submitted.

III. All communications regarding this application must give application number and batch number.
Please direct all communications prior to issuance to Box ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PATENT AND TRADEMARK OFFICE COPY

PTOL-85 (REV. 10-96) Approved for use through 08/30/99. (0651-0033)

Notice of Allowability

Application No.	Applicant(s)
09/529,096	Taqtsuya Maruyama et al.
Examiner	**Art Unit**
Sudhaker Patel	1624

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

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance and Issue Fee Due or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *paper # 11 dated 9/18/01*

2. ☒ The allowed claim(s) is/are *1-7 and 9-15*

3. ☐ The drawings filed on _____ are acceptable as formal drawings.

4. ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

   a) ☐ All b) ☐ Some* c) ☒ None of the:

   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)).

   *Certified copies not received: _____

5. ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application. **THIS THREE-MONTH PERIOD IS NOT EXTENDABLE FOR SUBMITTING NEW FORMAL DRAWINGS, OR A SUBSTITUTE OATH OR DECLARATION.** ~~**This three-month period for complying with the REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL is extendable under 37 CFR 1.136(a).**~~

6. ☐ Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient. A SUBSTITUTE OATH OR DECLARATION IS REQUIRED.

7. ☐ Applicant MUST submit NEW FORMAL DRAWINGS

   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached

   1) ☐ hereto or 2) ☐ to Paper No. _____.

   (b) ☐ including changes required by the proposed drawing correction filed _____, which has been approved by the examiner.

   (c) ☐ including changes required by the attached Examiner's Amendment/Comment or in the Office action of Paper No. _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

8. ☐ Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Any reply to this letter should include, in the upper right hand corner, the APPLICATION NUMBER (SERIES CODE/SERIAL NUMBER). If applicant has received a Notice of Allowance and Issue Fee Due, the ISSUE BATCH NUMBER and DATE of the NOTICE OF ALLOWANCE should also be included.

Attachment(s)

1 ☐ Notice of References Cited (PTO-892)
2 ☐ Notice of Informal Patent Application (PTO-152)
3 ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
4 ☐ Interview Summary (PTO-413), Paper No. _____.
5 ☐ Information Disclosure Statement(s) (PTO-1449), Paper No(s). _____
6 ☐ Examiner's Amendment/Comment
7 ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
8 ☒ Examiner's Statement of Reasons for Allowance
9 ☐ Other

REASONS FOR ALLOWANCE

1. The following is an examiner's statement of reasons for allowance:

Applicants' communication paper # 11 dated 9/18/01 is acknowledged.

Applicants have canceled claim 8, amended claims 1-7,9-13, and added new claims to add clarity by limiting the scope of the claims to elected invention of Group IV.

Applicants various arguments and remarks have been considered favorably, and rejections made under 35 U.S.C. 112 para. Second are now withdrawn.

Rejections made under 35 U.S.C. 103(a) are also with drawn because reference Schromm et al.(U.S.P. 5223614) does not indicate or disclose substituent Q(which is in ref.= hydroxy phenol or its ether) equivalent to applicants' instantly claimed compounds having ring Z and binding R2 = hydrogen or a halogen. Additionally, the instant compounds have a different utility related to diabetes v.s. ref. Bronchospasm.

Therefore, applicants' compounds having substituted phenyl-C(OH)H-NH-CH2-CH2-Phenyl-NH-CO-X-Heterocycle-R core deem to be novel and patentably distinct.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sudhaker Patel,D.Sc.Tech. whose telephone number is (703) 308 4709.

The examiner can normally be reached on Monday thru' Friday from 8:30 AM to 5:00 PM. If attempts to reach the examiner by the phone are unsuccessful, the examiner's supervisor, Dr.Mukund Shah can be reached at (703) 308 4716.

A facsimile center has been established for Group 1600. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier numbers for accessing the facsimile machine are (703) 308-4556 or (703) 305-3592.

Any inquiry of general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308 1235.

RICHARD L. RAY
PRIMARY E
ART UNIT 1624

S.p.

September 29, 2001

Best Available Copy

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Complete and mail this form, together with applicable fees, to: Box ISSUE FEE
Assistant Commissioner for Patents
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CURRENT CORRESPONDENCE ADDRESS (Note: Legibly mark-up with any corrections or use Block 1)

HM22/1001
FINNEGAN HENDERSON FARABOW
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1300 I STREET NW
WASHINGTON DC 20005-3315

Note: The certificate of mailing below can only be used for domestic mailings of the Issue Fee Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing.

Certificate of Mailing

I hereby certify that this Issue Fee Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Box Issue Fee address above on the date indicated below.

(Depositor's name)

(Signature)

(Date)

APPLICATION NO.	FILING DATE	TOTAL CLAIMS	EXAMINER AND GROUP ART UNIT	DATE MAILED
09/529,096	04/07/00	014	PATEL, S 1624	10/01/01

First Named Applicant: MARUYAMA, — 35 USC 154(b) term ext. = 0 Days.

TITLE OF INVENTION: AMIDE DERIVATIVES OR SALTS THEREOF

ATTY'S DOCKET NO.	CLASS-SUBCLASS	BATCH NO.	APPLN. TYPE	SMALL ENTITY	FEE DUE	DATE DUE
1 07385.0007	514-252.010	M82	UTILITY	NO	$1240.00	01/02/02

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363). Use of this form(s) and Customer Number are recommended, but not required.
   - ☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
   - ☐ "Fee Address" indication (or "Fee Address" indication form PTO/SB/47) attached.

2. For printing on the patent front page, list (1) the names of up to 3 registered patent attorneys or agents OR, alternatively, (2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
   1 FINNEGAN, HENDERSON,
   2 FARABOW, GARRETT & DUNNER, L.L.P.
   3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)
   PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. Inclusion of assignee data is only appropriate when an assignment has been previously submitted to the USPTO or is being submitted under separate cover. Completion of this form is NOT a substitute for filing an assignment.
   (A) NAME OF ASSIGNEE: YAMANOUCHI PHARMACEUTICAL CO., LTD.
   (B) RESIDENCE: (CITY & STATE OR COUNTRY): Tokyo, Japan
   Please check the appropriate assignee category indicated below (will not be printed on the patent)
   ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. The following fees are enclosed (make check payable to Commissioner of Patents and Trademarks):
   - ☒ Issue Fee
   - ☐ Advance Order - # of Copies

4b. The following fees or deficiency in these fees should be charged to:
   DEPOSIT ACCOUNT NUMBER 06-0916
   (ENCLOSE AN EXTRA COPY OF THIS FORM)
   - ☒ Issue Fee
   - ☐ Advance Order - # of Copies

The COMMISSIONER OF PATENTS AND TRADEMARKS is requested to apply the Issue Fee to the application identified above.

(Authorized Signature) David W. Hill
Date: 12/21/01

David W. Hill, Reg. No. 28,220

12/26/2001 EABUBNK2 00000142 09529096
01 FC:142 1280.00 OP

NOTE: The Issue Fee will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the Patent and Trademark Office.

Burden Hour Statement: This form is estimated to take 0.2 hours to complete. Time will vary depending on the needs of the individual case. Any comments on the amount of time required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, D.C. 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND FEES AND THIS FORM TO: Box Issue Fee, Assistant Commissioner for Patents, Washington D.C. 20231

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

TRANSMIT THIS FORM WITH FEE

#14 CA 1-4-02

BOX IF
PATENT
Customer Number 22,852
Attorney Docket No. 7385.0007-00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
Tatsuya MARUYAMA et al.	)	
Application No.: 09/529,096	)	Group Art Unit: 1624
Filed: April 7, 2000	)	Examiner: S. Patel
For: AMIDE DERIVATIVES OR SALTS THEREOF	)	

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

COMMENTS ON STATEMENT OF REASONS FOR ALLOWANCE

Applicants gratefully acknowledge the withdrawal of all rejections and allowance of the claims. *See* Notice of Allowability dated October 1, 2001.

In the Statement of Reasons for Allowance, the Examiner referred to Applicants' claimed invention as including a "substituted phenyl-C(OH)H-NH-CH2-CH2-Phenyl-NH-CO-X-Heterocycle-R core." *See* Statement of Reasons for Allowance at page 2. Applicants respectfully traverse this restatement of their claimed invention, at least because it contains structural errors. Applicants rely, instead, upon the allowed claims as defining their patented invention.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

CONCLUSION

Please grant any extensions of time required to enter these Comments and charge any required extension fees to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

Dated: December 21, 2001

By: Jeremy M. Stipkala
Jeremy M. Stipkala
Reg. No. 44,359

FINNEGAN
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DUNNER LLP

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Fax 202.408.4400
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PATENT
Customer No. 22,852
Attorney Docket No. 07385.0007-00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent No.: 6,346,532 B1
Inventors: Tatsuya MARUYAMA et al.
Issue Date.: February 12, 2002
For: AMIDE DERIVATIVES OR SALTS THEREOF

Certificate of Correction Branch

Commissioner for Patents
Washington, DC 20231

Sir:

REQUEST FOR CERTIFICATE OF CORRECTION

Pursuant to 35 U.S.C. §§ 254 and 255, and 37 C.F.R. §§ 1.322 and 1.323, this is a request for a Certificate of Correction in the above-identified patent. The mistakes identified in the appended Form occurred through the fault of both the Patent Office and the Patentees' representatives. A check in the amount of $100 (the fee set forth in 37 C.F.R. § 1.20(a)) is attached.

Two (2) copies of PTO Form 1050 are appended. The complete Certificate of Correction involves five (5) pages. Issuance of the Certificate of Correction containing the correction is earnestly requested.

Should a check not be appended or should any additional fees be needed, authorization is hereby given to charge any fees due in connection with the filing of this request to Deposit Account No. 06-0916.

04/19/2002 MAHMED2 00000057 6346532
01 FC:145 100.00 OP

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

By: Reg# 27932
Jeremy M. Stipkala
Reg. No. 44,359

Dated: April 17, 2002

FINNEGAN
HENDERSON
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GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. 6,346,532 B1

DATED: February 12, 2002

INVENTORS: T. MARUYAMA et al.

It is hereby certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 16, lines 29-30, (Example 3) should read:

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-8-quinolinecarboxanilide dihydrochloride

Column 17, lines 40-41, (Example 16) should read:

(R)-2-(2-Benzyloxypyridin-6-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide hydrochloride

Column 19, lines 58-60, (Example 39) should read:

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(2-phenylaminothiazol-4-yl)acetanilide hydrochloride

Column 23, lines 3-5, (Example 66) should read:

(R)-2-[1-(3,5-Difluorobenzyl)-1H-imidazol-2-yl]-4'-[2-(2-hydroxy-2-phenylethyl)amino]ethyl] acetanilide dihydrochloride

Column 26, lines 47-49, (Example 99) should read:

4'[(S)-2-[((R)-2-Hydroxy-2-phenylethyl) amino]propyl]-2-(2-pyridyl)acetanilide hydrochloride

MAILING ADDRESS OF SENDER

Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P.
1300 I Street, N.W.
Washington, D.C. 20005-3315

Patent No. 6,346,532 B1

No. of additional copies @ .30¢ per page

Column 28, line 2, change "30/1 Δ 10/1)." to --30/1 → 10/1).--.

line 7, should read:

[(2-hydroxy-2-phenylethyl)amino]propyl]-2-(2-pyridyl)

lines 62-63, (Example 113) should read:

(R)-1-[4-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl] phenyl]-3-(2-pyridyl)urea dihydrochloride

Column 45, Claim 6, line 4 should read:

(R)-2-[1-(4-chlorobenzyl)-1H-imidazol-2-yl]-4'-[2-[(2-

MAILING ADDRESS OF SENDER

Finnegan, Henderson, Farabow,
Garrett & Dunner, L.L.P.
1300 I Street, N.W.
Washington, D.C. 20005-3315

Patent No. 6,346,532 B1

No. of additional copies
@ .30¢ per page

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. 6,346,532 B1

DATED: February 12, 2002

INVENTORS: T. MARUYAMA et al.

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Finnegan, Henderson, Farabow,
Garrett & Dunner, L.L.P.
1300 I Street, N.W.
Washington, D.C. 20005-3315

Patent No. 6,346,532 B1

No. of additional copies
@ .30¢ per page

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Column 45, ~~Claim 6,~~ line 4 should read:

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MAILING ADDRESS OF SENDER

Finnegan, Henderson, Farabow,
Garrett & Dunner, L.L.P.
1300 I Street, N.W.
Washington, D.C. 20005-3315

Patent No. 6,346,532 B1

No. of additional copies
@ .30¢ per page

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,346,532 B1
DATED : February 12, 2002
INVENTOR(S) : T. Maruyama et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 16,
Lines 29-30, (Example 3) should read: -- (R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino] ethyl]-8-quinolinecarboxanilide dihydrochloride

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Lines 40-41, (Example 16) should read:
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Column 26,
Lines 47-49, (Example 99) should read: -- 4'[(S)-2-[((R)-2-Hydroxy-2-phenylethyl) amino]propyl]-2-(2-pyridyl)acetanilide hydrochloride --

NOTICE RE: CERTIFICATES OF CORRECTION

DATE : 05,17,02 Paper No.: 16

TO : Supervisor, Art Unit 1600 1624

SUBJECT : Certificate of Correction Request in Patent No.: 6,326,532

A response to the following question is requested with respect to the accompanying request for a certificate of correction.

With respect to the change(s) requested, correcting Office and/or Applicant's errors, should the patent read as shown in the certificate of correction? No new matter should be introduced, nor should the scope or meaning of the claims be changed.

PLEASE COMPLETE THIS FORM AND
RETURN WITH FILE, WITHIN 7 DAYS,
TO CERTIFICATES OF CORRECTION BRANCH - PK 3-915/922
PALM LOCATION 7580 - TEL. N0. 305-8309

THANK YOU FOR YOUR ASSISTANCE!

Note your decision, regarding the changes requested in the Request for Certificate of Correction, by placing a check mark (+) in the box that reflects your decision, which corresponds to the question checked above.

☒ **YES** ☐ **NO** ☐ **Comments below**

☐ **Comments:**

Murkund J. Shah — **Supervisor**

1624 — **Art Unit**

PTOL-306 (REV. 2/02) U.S. DEPARTMENT OF COMMERCE Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,346,532 B1
DATED : February 12, 2002
INVENTOR(S) : T. Maruyama et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 28,
Line 2, change "30/1 Δ 10/1)." to -- 30/1 → 10/1). --.
Line 7, should read: -- [(2-hydroxy-2-phenylethyl)amino]propyl]-2-(2-pyridyl) --
Lines 62-63, (Example 113) should read: -- (R)-1-[4-[2-[(2-Hydroxy-2-phenylethyl) amino]ethyl] phenyl]-3-(2-pyridyl)urea dihydrochloride --

Column 45,
Line 4, should read: -- (R)-2-[1-(4-chlorobenzyl)-1H-imidazol-2-yl]-4'-[2-[(2- --

Signed and Sealed this

Thirtieth Day of July, 2002

Attest:

Attesting Officer

JAMES E. ROGAN
Director of the United States Patent and Trademark Office

02213.003400. PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re: U.S. Patent No. 6,346,532 B1

Issued: February 12, 2002

To: Tatsuya Maruyama, Takayuki Suzuki, Kenichi Onda, Masahiko Hayakawa, Hiroyuki Moritomo, Tetsuya Kimizuka, and Tetsuo Matsui

For: AMIDE DERIVATIVES OR SALTS THEREOF

Mail Stop Hatch-Waxman PTE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL LETTER FOR PATENT TERM EXTENSION APPLICATION

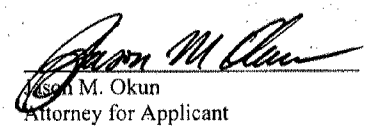
Madam:

Attached in triplicate is an Application for Extension of Patent Term under 35 U.S.C. § 156 of U.S. Patent No. 6,346,532 B1.

The Commissioner is hereby authorized to charge the $1,120 fee prescribed in 37 C.F.R. § 1.20(j)(1), as well as any additional fees that may be necessitated in connection with the filing of this Application for Extension of Patent Term under 35 U.S.C. § 156, to Deposit Account No. 50-3939. Two additional copies of this transmittal letter are being submitted for charging papers.

Applicant's undersigned attorney may be reached in our New York office by telephone at (212) 218-2100. All correspondence should be directed to our address given below.

Respectfully submitted,



Jason M. Okun
Attorney for Applicant
Reg. No. 48,512

Date: August 21, 2012

FITZPATRICK, CELLA, HARPER & SCINTO
1290 Avenue of the Americas
New York, New York 10104-3800
Telephone: (212) 218-2100
Facsimile: (212) 218-2200

Attachs.: Three copies of Application for Extension of Patent Term under 35 U.S.C. § 156
Two additional copies of this transmittal letter

02213.003400. PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re: U.S. Patent No. 6,346,532 B1

Issued: February 12, 2002

To: Tatsuya Maruyama, Takayuki Suzuki, Kenichi Onda, Masahiko Hayakawa, Hiroyuki Moritomo, Tetsuya Kimizuka, and Tetsuo Matsui

For: AMIDE DERIVATIVES OR SALTS THEREOF

Mail Stop Hatch-Waxman PTE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156

Madam:

Applicant, Astellas Pharma Inc., a company organized and existing under the laws of Japan, represents that it is the owner of the entire title and interest in and to U.S. Patent No. 6,346,532 B1, which was granted on February 12, 2002 to Tatsuya Maruyama, Takayuki Suzuki, Kenichi Onda, Masahiko Hayakawa, Hiroyuki Moritomo, Tetsuya Kimizuka, and Tetsuo Matsui for "AMIDE DERIVATIVES OR SALTS THEREOF" by virtue of the Assignment recorded on April 7, 2000 at Reel 010808, Frame 0313, from the inventors to Yamanouchi Pharmaceutical Co., Ltd., and the change of name recorded on November 16, 2005 at Reel 016784, Frame 0361, from Yamanouchi Pharmaceutical Co., Ltd., to Astellas Pharma Inc. Extension of the term of this patent under 35 U.S.C. § 156 is hereby respectfully requested.

By the Power of Attorney and the Statement Under 37 C.F.R. § 3.73(b), attached hereto as "Appendix A", Applicant appoints attorneys associated with Customer No. 05514 to transact all business in the U.S. Patent and Trademark Office in connection with U.S. Patent No. 6,346,532 B1.

I. Applicant submits this Application for Extension of Patent Term under 35 U.S.C. § 156 by providing the following information as required by 37 C.F.R. § 1.710 through 1.785, especially 1.740.

(1) A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics.

The complete identification of the approved product is:

chemical name: 2-(2-aminothiazol-4-yl)-N-[4-(2-{[(2R)-2-hydroxy-2-phenylethyl]amino}ethyl)phenyl]acetamide

alternative chemical names:

4-thiazoleacetamide, 2-amino-N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]

(R)-2-(2-aminothiazol-4-yl)-4'-[2-(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide

(R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetic acid anilide

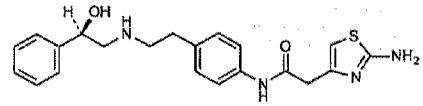
Tradename: Myrbetriq

generic name: mirabegron

empirical formula: $C_{21}H_{24}N_4O_2S$

molecular weight: 396.51

chemical structure:



A copy of the product label is attached hereto as "Appendix B".

(2) **A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred.**

The approved product was subject to regulatory review under the Federal Food, Drug, and Cosmetic Act, Section 505 (21 U.S.C. § 355).[1]

(3) **An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred.**

The approved product received permission for commercial marketing or use under Section 505 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355) on June 28, 2012. A copy of the approval letter is attached as "Appendix C".[2]

(4) **In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved.**

The sole active ingredient in Myrbetriq™ is mirabegron, which has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, Section 505 (21 U.S.C. § 355) prior to the approval of NDA 202611 by the United States Food and Drug Administration on June 28, 2012.

---

[1] The Investigational New Drug Application was submitted pursuant to Section 505(i) of the Federal Food, Drug, and Cosmetic Act. The New Drug Application was submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act.

[2] Astellas Pharma Global Development, Inc. is owned by Astellas Pharma Inc.

(5) **A statement that the application is being submitted within the sixty day period permitted for submission pursuant to § 1.720(f) and an identification of the date of the last day on which the application could be submitted.**

This Application for Extension of the term of U.S. Patent No. 6,346,532 B1 under 35 U.S.C. § 156 is being submitted within the permitted 60 day period set forth in 37 C.F.R. § 1.720(f), which period expires on August 26, 2012 (Sunday).

(6) **A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration.**

The patent, the term of which this Application seeks to extend, is U.S. Patent No. 6,346,532 B1, which issued on February 12, 2002 to Tatsuya Maruyama, Takayuki Suzuki, Kenichi Onda, Masahiko Hayakawa, Hiroyuki Moritomo, Tetsuya Kimizuka, and Tetsuo Matsui. The term of U.S. Patent No. 6,346,532 B1, as calculated in accordance with 35 U.S.C. § 154, would otherwise expire on October 15, 2018.

(7) **A copy of the patent for which an extension is being sought, including the entire specification (including claims) and drawings.**

A complete copy of U.S. Patent No. 6,346,532 B1, identified in paragraph 6 above, is attached as "Appendix D".

(8) **A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent.**

No Terminal Disclaimer, Re-Examination Certificate, or Re-Issue has been issued or requested with respect to U.S. Patent No. 6,346,532 B1. The first maintenance fee for U.S. Patent No. 6,346,532 B1 in the amount of $900.00 was paid on July 20, 2005. The second maintenance fee for U.S. Patent No. 6,346,532 B1 in the amount of $2,480.00 was paid on July 15, 2009. Copies of the Maintenance Fee Statements for the first and second maintenance fees are attached hereto as "Appendix E". A copy of Certificate of Correction granted July 30, 2002, is attached hereto as "Appendix F".

(9) **A statement that the patent claims the approved product, or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which at least one such patent claim reads on: (i) the approved product, if the listed claims include any claim to the approved product; (ii) the method of using the approved product, if the listed claims include any claim to the method of using the approved product; and (iii) the method of manufacturing the approved product, if the listed claims include any claim to the method of manufacturing the approved product.**

U.S. Patent No. 6,346,532 B1 claims the approved product and a method of using the approved product. Claims 1-12 read on the approved product (claims 1-6 and 9 read on the approved product per se and claims 7, 8, and 10-12 read on compositions that include the approved product); and claims 13 and 14 read on a method of using the approved product.

Approved Product:

Claim 6 reads as follows:

6. A compound:

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-pyridinecarboxyanilide,

(R)-2-[1-(4-chlorobenzyl)-1H-imidazol-2-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]-acetanilide,

(R)-2-[1-(3,4-dichlorobenzyl)-1H-tetrazol-5-yl]-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide,

(R)-2-(2-aminothiazol-4-yl)-4'-[2-(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide,

(R)-2-(2-benzyl-1H-1,2,4-triazol-3-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)-amino]ethyl]acetanilide,

(R)-2-(2-aminopyridin-6-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide,

(R)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]-2-(2-pyridyl)acetanilide,

(R)-4'-[2-[(2-hydroxy-2-phenylethyl)-amino]ethyl)-2-(2-pyrazinyl)acetanilide,

(R)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl)-2-(2-pyrimidinyl)-acetanilide,

or a salt of any of the foregoing.

Claim 6 reads on the approved product as follows:

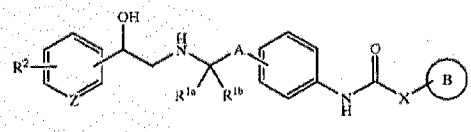
Claim 6 reads on the approved product when the compound is (R)-2-(2-aminothiazol-4-yl)-4'-[2-(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide, which is one of the alternative chemical names of mirabegron.

Method of Using Approved Product:

Claim 13 reads as follows:

13. A method for treating diabetes mellitus in a human or animal patient in need of such treatment comprising administering to the patient an amount of a compound of formula (I) as claimed in claim 1, wherein the amount is an amount effective for such treatment.

Claim 13 reads on a method of using the approved product when, in the compound of formula (I):



R^2 is a hydrogen atom

R^{1a} is a hydrogen atom

R^{1b} is a hydrogen atom

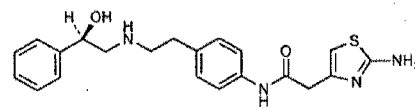
Z is =CH–

A is a lower alkylene

B is a heteroaryl group, which is substituted

X is a lower alkylene, which is unsubstituted.

Mirabegron:



(10) A statement beginning on a new page of the relevant dates and information pursuant to 35 U.S.C. 156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period as follows:

(i) For a patent claiming a human drug, antibiotic, or human biological product:
(A) The effective date of the investigational new drug (IND) application and the IND number;
(B) The date on which a new drug application (NDA) or Product License Application (PLA) was initially submitted and the NDA or PLA number; and
(C) The date on which the NDA was approved or the Product License issued.

The relevant dates and information pursuant to 35 U.S.C. § 156(g) to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

a. An Investigational New Drug Application (IND) for mirabegron was submitted on May 9, 2006, was received by the Department of Health and Human Services on May 10, 2006, and the IND number assigned was 69,416. A copy of the FDA letter confirming receipt of the IND is attached hereto as "Appendix G."

b. A New Drug Application (NDA) was received by the Department of Health and Human Services on August 29, 2011 and the NDA number assigned was 202611.

c. The date on which NDA 202611 was approved is June 28, 2012.

(11) A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities.

As a brief description of the significant activities undertaken by the Applicant during the applicable regulatory review period, attached hereto as "Appendix H" is a chronology including a list of communications from the Applicant to the U.S. Food and Drug Administration in connection with the IND and NDA during the periods mentioned in paragraph 10 above.

(12) A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension.

Applicant is of the opinion that U.S. Patent No. 6,346,532 B1 is eligible for extension under 35 U.S.C. § 156 and 37 C.F.R. § 1.720 because it satisfies all of the requirements for such extension as follows:

a. 35 U.S.C. § 156(a) and 37 C.F.R. § 1.720(a)

U.S. Patent No. 6,346,532 B1 claims a human drug product, mirabegron and a method of using this human drug product.

b. 35 U.S.C. § 156(a)(1) and 37 C.F.R. § 1.720(g)

The term of U.S. Patent No. 6,346,532 B1 (expiring October 15, 2018) has not expired before the submission of this Application.

c. 35 U.S.C. § 156(a)(2) and 37 C.F.R. § 1.720(b)

The term of U.S. Patent No. 6,346,532 B1 has never been extended under 35 U.S.C. § 156.

d. 35 U.S.C. § 156(a)(3) and 37 C.F.R. § 1.720(c)

The Application for extension of the term of U.S. Patent No. 6,346,532 B1 is submitted by the owner of record thereof in accordance with the requirements of 35 U.S.C. § 156(d)(1) and 37 C.F.R. § 1.740.

e. 35 U.S.C. § 156(a)(4) and 37 C.F.R. § 1.720(d)

The approved product, Myrbetriq™, has been subjected to

a regulatory review period before its commercial marketing or use.

f. 35 U.S.C. § 156(a)(5)(A) and 37 C.F.R. § 1.720(e)

The approved product, Myrbetriq™, has received permission for commercial marketing or use, and the permission for the commercial marketing or use of the product is the first such permission received under the Federal Food, Drug, and Cosmetic Act, Section 505 (21 U.S.C. § 355).

g. 35 U.S.C. § 156(a)(5)(A) and 37 C.F.R. § 1.720(h)

No other patent term has been extended for the same regulatory review period for the approved product, Myrbetriq™.

(13) A statement as to the length of extension claimed, including how the length of extension was determined.

The length of the extension of the patent term of U.S. Patent No. 6,346,532 B1 requested by Applicant is 1259 days, i.e., to March 27, 2022, which length was calculated in accordance with 37 C.F.R. § 1.775 as follows:

a. The regulatory review period under 35 U.S.C. § 156(g)(1)(B) began on June 9, 2006 (30 days after the receipt date of the IND) and ended on June 28, 2012, amounting to a total of 2213 days, which is the sum of (i) and (ii) below:

   i) The period of review under 35 U.S.C. § 156(g)(1)(B)(i), the "Testing Period", began on June 9, 2006 and ended on August 29, 2011, which is 1908 days;

   ii) The period for review under 35 U.S.C. § 156(g)(1)(B)(ii) the "Application Period", began on August 29, 2011 and ended on June 28, 2012, which is 305 days;

b. The regulatory review period upon which the period for extension is calculated is the entire regulatory review period as determined in sub-paragraph (13)(a) above (2213 days) less:

   i) The number of days in the regulatory review period which were on and before the date on which the patent issued (February 12, 2002), i.e. 0 days, and

   ii) The number of days during which the Applicant did not act with due diligence, i.e. zero days, and

   iii) One half of the number of days remaining in the period in subparagraph (13)(a)(i) after subtracting the number of days in subparagraphs (13)(b)(i) and

(13)(b)(ii), which is one half of (1908 - 0) or 954 days;

which results in a period of 2213 - [0 + 0 + 954] = 1259 days.

c. The number of days as determined in sub-paragraph (13)(b), when added to the original term, would result in the date of March 27, 2022.

d. Fourteen (14) years, when added to the date of the NDA Approved Letter (June 28, 2012), would result in the date of June 28, 2026.

e. The earlier date as determined by sub-paragraphs (13)(c) and (13)(d) is March 27, 2022.

f. Since the original patent was issued after September 24, 1984, the extension otherwise obtainable is limited to not more than five years. Five years, when added to the original expiration of U.S. Patent No. 6,346,532 B1 (October 15, 2018), results in the date of October 15, 2023.

g. The earlier date as determined in sub-paragraphs (13)(e) and (13)(f) is March 27, 2022, i.e., 1259 days from the October 15, 2018 expiration date under 35 U.S.C. § 154.

(14) A statement that the applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought (see § 1.765).

Applicant acknowledges a duty to disclose to the U.S. Patent and Trademark Office and the Secretary of Health and Human Services any information, which is material to the determination of entitlement to the extension sought. In that connection, Applicant advises that Patent Term Extension applications in connection with the approval of Myrbetriq™ (mirabegron) are being concurrently filed for U.S. Patent Nos. 7,342,117 B2 and 7,750,029 B2.

(15) The prescribed fee for receiving and acting upon the application for extension (see §1.20(j)).

The Commissioner is authorized to charge the prescribed fee for receiving and acting upon this application to Deposit Account 50-3939. Any overpayment should be credited to the same Deposit Account.

(16) The name, address, and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed.

All correspondence relating to this application for patent term extension should be addressed to:

Jason M. Okun
FITZPATRICK, CELLA, HARPER & SCINTO
1290 Avenue of the Americas
New York, New York 10104-3800
Telephone: (212) 218-2100
Facsimile: (212) 218-2200

(17) Certification under 37 C.F.R. § 1.740(b)

The undersigned hereby certifies that the instant application, including its attachments and supporting papers, is being submitted with two additional copies thereof (for a total of three copies) in accordance with 37 C.F.R. § 1.740(b).

Respectfully submitted,

Jason M. Okun
Attorney for Applicant
Reg. No. 48,512

Date: August 21, 2012

FITZPATRICK, CELLA, HARPER & SCINTO
1290 Avenue of the Americas
New York, New York 10104-3800
Telephone: (212) 218-2100
Facsimile: (212) 218-2200

Appendix A

PTO/SB/81A (12-08)
Approved for use through 11/30/2011. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT - POWER OF ATTORNEY OR REVOCATION OF POWER OF ATTORNEY WITH A NEW POWER OF ATTORNEY AND CHANGE OF CORRESPONDENCE ADDRESS

Patent Number	6,346,532 B1
Issue Date	February 12, 2002
First Named Inventor	Tatsuya Maruyama et al.
Title	AMIDE DERIVATIVES OR SALTS THEREOF
Attorney Docket Number	02213.003400

I hereby revoke all previous powers of attorney given in the above-identified patent.

☐ A Power of Attorney is submitted herewith.

OR

☒ I hereby appoint Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s) with respect to the patent identified above, and to transact all business in the United States Patent and Trademark Office connected therewith: 05514

OR

☐ I hereby appoint Practitioner(s) named below as my/our attorney(s) or agent(s) with respect to the patent identified above, and to transact all business in the United States Patent and Trademark Office connected therewith:

Practitioner(s) Name	Registration Number

Please recognize or change the correspondence address for the above-identified patent to:

☐ The address associated with the above-mentioned Customer Number.

OR

☒ The address associated with Customer Number: 05514

OR

☐ Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the:

☐ Inventor, having ownership of the patent.

OR

☒ Patent owner.

Statement under 37 CFR 3.73(b) (Form PTO/SB/96) submitted herewith or filed on _____.

SIGNATURE of Inventor or Patent Owner

Signature		Date	8/10/2012
Name	Hiroshi MORITA	Telephone	+81-3-3244-3051
Title and Company	Vice President Intellectual Property, Astellas Pharma Inc		

NOTE: Signatures of all the inventors or patent owners of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☒ *Total of 1 forms are submitted.

This collection of information is required by 37 CFR 1.31, 1.32 and 1.33. 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 1.11 and 1.14. This collection is estimated to take 3 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.

PTO/SB/96 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Tatsuya Maruyama et al.

Application No./Patent No.: 6,346,532 B1 Filed/Issue Date: February 12, 2002

Titled: AMIDE DERIVATIVES OR SALTS THEREOF

Astellas Pharma Inc., a Corporation
(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.

states that it is:

1. [X] the assignee of the entire right, title, and interest in;

2. [ ] an assignee of less than the entire right, title, and interest in (The extent (by percentage) of its ownership interest is _____ %); or

3. [ ] the assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made)

the patent application/patent identified above, by virtue of either:

A. [ ] An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy therefore is attached.

OR

B. [X] A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: Inventors To: Yamanouchi Pharmaceutical Co., Ltd.
The document was recorded in the United States Patent and Trademark Office at
Reel 010808, Frame 0313, or for which a copy thereof is attached.

2. From: Yamanouchi Pharmaceutical Co., Ltd. To: Astellas Pharma Inc.
The document was recorded in the United States Patent and Trademark Office at
Reel 016784, Frame 0361, or for which a copy thereof is attached.

3. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

[ ] Additional documents in the chain of title are listed on a supplemental sheet(s).

[ ] As required by 37 CFR 3.73(b)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (*i.e.*, a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

Signature — Date: 8/20/2012

Hiroshi MORITA — Vice President Intellectual Property
Printed or Typed Name — Title

Appendix B

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use MYRBETRIQ™ safely and effectively. See full prescribing information for MYRBETRIQ.

MYRBETRIQ™ (mirabegron) extended-release tablets, for oral use
Initial U.S. Approval: 2012

----------INDICATIONS AND USAGE----------

Myrbetriq is a beta-3 adrenergic agonist indicated for the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency (1)

----------DOSAGE AND ADMINISTRATION----------

- Recommended starting dose is 25 mg once daily, with or without food (2.1)
- 25 mg is effective within 8 weeks. Based on individual efficacy and tolerability, may increase dose to 50 mg once daily (2.1, 14)
- Swallow whole with water, do not chew, divide or crush (2.1)
- *Patients with Severe Renal Impairment or Patients with Moderate Hepatic Impairment:* Maximum dose is 25 mg once daily (2.2, 8.6, 8.7, 12.3)
- *Patients with End Stage Renal Disease (ESRD) or Patients with Severe Hepatic Impairment:* Not recommended (2.2, 8.6, 8.7, 12.3)

----------DOSAGE FORMS AND STRENGTHS----------

Extended-release tablets: 25 mg and 50 mg (3)

----------CONTRAINDICATIONS----------

None (4)

----------WARNINGS AND PRECAUTIONS----------

- *Increases in Blood Pressure*: Myrbetriq can increase blood pressure. Periodic blood pressure determinations are recommended, especially in hypertensive patients. Myrbetriq is not recommended for use in severe uncontrolled hypertensive patients (5.1).
- *Urinary Retention in Patients With Bladder Outlet Obstruction and in Patients Taking Antimuscarinic Drugs for Overactive Bladder:* Administer with caution in these patients because of risk of urinary retention (5.2).
- *Patients Taking Drugs Metabolized by CYP2D6*: Myrbetriq is a moderate inhibitor of CYP2D6. Appropriate monitoring is recommended and dose adjustment may be necessary for narrow therapeutic index CYP2D6 substrates (5.3, 7.1, 12.3)

----------ADVERSE REACTIONS----------

Most commonly reported adverse reactions (> 2% and > placebo) were hypertension, nasopharyngitis, urinary tract infection and headache (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Astellas Pharma US, Inc. at 1-800-727-7003 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------

- *Drugs Metabolized by CYP2D6 (e.g. Metoprolol and Desipramine):* Mirabegron is CYP2D6 inhibitor and when used concomitantly with drugs metabolized by CYP2D6, especially narrow therapeutic index drugs, appropriate monitoring and possible dose adjustment of those drugs may be necessary (5.3, 7.1, 12.3).
- *Digoxin.* When initiating a combination of Myrbetriq and digoxin, prescribe the lowest dose of digoxin; monitor serum digoxin concentrations to titrate digoxin dose to desired clinical effect (7.2, 12.3).

----------USE IN SPECIFIC POPULATIONS----------

- *Pregnancy:* Use only if the benefit to the mother outweighs the potential risk to the fetus (8.1)
- *Nursing mothers:* Myrbetriq is predicted to be excreted in human milk and is not recommended for use by nursing mothers (8.3)
- *Pediatric use:* The safety and effectiveness of Myrbetriq in pediatric patients have not been established (8.4)
- *Geriatric use:* No dose adjustment is recommended for elderly patients (8.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: June 2012

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Myrbetriq™ is a beta-3 adrenergic agonist indicated for the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The recommended starting dose of Myrbetriq is 25 mg once daily with or without food. Myrbetriq 25 mg is effective within 8 weeks. Based on individual patient efficacy and tolerability the dose may be increased to 50 mg once daily *[see Clinical Studies (14)]*.

Myrbetriq should be taken with water, swallowed whole and should not be chewed, divided, or crushed.

2.2 Dose Adjustments in Specific Populations

The daily dose of Myrbetriq should not exceed 25 mg once daily in the following populations:

- Patients with severe renal impairment (CL_{cr} 15 to 29 mL/min or eGFR 15 to 29 mL/min/1.73 m^2) *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.
- Patients with moderate hepatic impairment (Child-Pugh Class B) *[see Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)]*.

Myrbetriq is not recommended for use in patients with end stage renal disease (ESRD), or in patients with severe hepatic impairment (Child-Pugh Class C) *[see Use in Specific Populations (8.6, 8.7) and Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

Myrbetriq extended-release tablets are supplied in two different strengths as described below:

- 25 mg oval, brown, film coated tablet, debossed with the (Astellas logo) and "325"
- 50 mg oval, yellow, film coated tablet, debossed with the (Astellas logo) and "355"

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Increases in Blood Pressure

Myrbetriq can increase blood pressure. Periodic blood pressure determinations are recommended, especially in hypertensive patients. Myrbetriq is not recommended for use in patients with severe uncontrolled hypertension (defined as systolic blood pressure greater than or equal to 180 mm Hg and/or diastolic blood pressure greater than or equal to 110 mm Hg) *[see Clinical Pharmacology (12.2)]*.

In two, randomized, placebo-controlled, healthy volunteer studies, Myrbetriq was associated with dose-related increases in supine blood pressure. In these studies, at the maximum recommended dose of 50 mg, the mean maximum increase in systolic/diastolic blood pressure was approximately 3.5/1.5 mmHg greater than placebo.

In contrast, in OAB patients in clinical trials, the mean increase in systolic and diastolic blood pressure at the maximum recommended dose of 50 mg was approximately 0.5 - 1 mmHg greater than placebo. Worsening of pre-existing hypertension was reported infrequently in Myrbetriq patients.

5.2 Urinary Retention in Patients with Bladder Outlet Obstruction and in Patients Taking Antimuscarinic Medications for OAB

Urinary retention in patients with bladder outlet obstruction (BOO) and in patients taking antimuscarinic medications for the treatment of OAB has been reported in postmarketing experience in patients taking mirabegron. A controlled clinical safety study in patients with BOO did not demonstrate increased urinary retention in Myrbetriq patients; however, Myrbetriq should be administered with caution to patients with clinically significant BOO. Myrbetriq should also be administered with caution to patients taking antimuscarinic medications for the treatment of OAB *[see Clinical Pharmacology (12.2)]*.

5.3 Patients Taking Drugs Metabolized by CYP2D6

Since mirabegron is a moderate CYP2D6 inhibitor, the systemic exposure to CYP2D6 substrates such as metoprolol and desipramine is increased when co-administered with mirabegron. Therefore, appropriate monitoring and dose adjustment may be necessary, especially with narrow therapeutic index drugs metabolized by CYP2D6, such as thioridazine, flecainide, and propafenone *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In three, 12 week, double-blind, placebo-controlled, safety and efficacy studies in patients with overactive bladder (Studies 1, 2, and 3), Myrbetriq was evaluated for safety in 2736 patients *[see Clinical Studies (14)]*. Study 1 also included an active control. For the combined Studies 1, 2, and 3, 432 patients received Myrbetriq 25 mg, 1375 received Myrbetriq 50 mg, and 929 received Myrbetriq 100 mg once daily. In these studies, the majority of the patients were Caucasian (94%), and female (72%) with a mean age of 59 years (range 18 to 95 years).

Myrbetriq was also evaluated for safety in 1632 patients who received Myrbetriq 50 mg once daily (n=812 patients) or Myrbetriq 100 mg (n=820 patients) in a 1 year, randomized, fixed dose, double-blind, active controlled, safety study in patients with overactive bladder (Study 4). Of these patients, 731 received Myrbetriq in a previous 12 week study. In Study 4, 1385 patients received Myrbetriq continuously for at least 6 months, 1311 patients received Myrbetriq for at least 9 months, and 564 patients received Myrbetriq for at least 1 year.

The most frequent adverse events (0.2%) leading to discontinuation in Studies 1, 2 and 3 for the 25 mg or 50 mg dose were nausea, headache, hypertension, diarrhea, constipation, dizziness and tachycardia.

Atrial fibrillation (0.2%) and prostate cancer (0.1%) were reported as serious adverse events by more than 1 patient and at a rate greater than placebo.

Table 1 lists adverse reactions, derived from all adverse events, that were reported in Studies 1, 2 and 3 at an incidence greater than placebo and in 1% or more of patients treated with Myrbetriq 25 mg or 50 mg once daily for up to 12 weeks. The most commonly reported adverse reactions (greater than 2% of Myrbetriq patients and greater than placebo) were hypertension, nasopharyngitis, urinary tract infection and headache.

Table 1: Percentages of Patients with Adverse Reactions, Derived from All Adverse Events, Exceeding Placebo Rate and Reported by 1% or More Patients Treated With Myrbetriq 25 mg or 50 mg Once Daily in Studies 1, 2, and 3

	Placebo (%)	Myrbetriq 25 mg (%)	Myrbetriq 50 mg (%)
Number of Patients	**1380**	**432**	**1375**
Hypertension*	7.6	11.3	7.5
Nasopharyngitis	2.5	3.5	3.9
Urinary Tract Infection	1.8	4.2	2.9
Headache	3.0	2.1	3.2
Constipation	1.4	1.6	1.6
Upper Respiratory Tract Infection	1.7	2.1	1.5
Arthralgia	1.1	1.6	1.3
Diarrhea	1.3	1.2	1.5
Tachycardia	0.6	1.6	1.2
Abdominal Pain	0.7	1.4	0.6
Fatigue	1.0	1.4	1.2

*Includes reports of blood pressure above the normal range, and BP increased from baseline, occurring predominantly in subjects with baseline hypertension.

Other adverse reactions reported by less than 1% of patients treated with Myrbetriq in Studies 1, 2, or 3 included:

Cardiac disorders: palpitations, blood pressure increased *[see Clinical Pharmacology (12.2)]*
Eye Disorders: glaucoma *[see Clinical Pharmacology (12.2)]*
Gastrointestinal disorders: dyspepsia, gastritis, abdominal distension
Infections and Infestations: sinusitis, rhinitis
Investigations: GGT increased, AST increased, ALT increased, LDH increased
Renal and urinary disorders: nephrolithiasis, bladder pain
Reproductive system and breast disorders: vulvovaginal pruritis, vaginal infection
Skin and subcutaneous tissue disorders: urticaria, leukocytoclastic vasculitis, rash, pruritus, purpura, lip edema

Table 2 lists the rates of the most commonly reported adverse reactions, derived from all adverse events in patients treated with Myrbetriq 50 mg for up to 52 weeks in Study 4. The most commonly reported adverse reactions (>3% of Myrbetriq patients) were hypertension, urinary tract infection, headache, and nasopharyngitis.

Table 2: Percentages of Patients with Adverse Reactions, Derived from all Adverse Events, Reported by Greater Than 2% of Patients Treated With Myrbetriq 50 mg Once Daily in Study 4

	Myrbetriq 50 mg (%)	Active Control (%)
Number of Patients	**812**	**812**
Hypertension	9.2	9.6
Urinary Tract Infection	5.9	6.4
Headache	4.1	2.5
Nasopharyngitis	3.9	3.1
Back Pain	2.8	1.6
Constipation	2.8	2.7
Dry Mouth	2.8	8.6
Dizziness	2.7	2.6
Sinusitis	2.7	1.5
Influenza	2.6	3.4
Arthralgia	2.1	2.0
Cystitis	2.1	2.3

In Study 4, in patients treated with Myrbetriq 50 mg once daily, adverse reactions leading to discontinuation reported by more than 2 patients and at a rate greater than active control included: constipation (0.9%), headache (0.6%), dizziness (0.5%), hypertension (0.5%), dry eyes (0.4%), nausea (0.4%), vision blurred (0.4%), and urinary tract infection (0.4%). Serious adverse events reported by at least 2 patients and exceeding active control included cerebrovascular accident (0.4%) and osteoarthritis (0.2%). Serum ALT/AST increased from baseline by greater than 10-fold in 2 patients (0.3%) taking Myrbetriq 50 mg, and these markers subsequently returned to baseline while both patients continued Myrbetriq.

In Study 4, serious adverse events of neoplasm were reported by 0.1%, 1.3%, and 0.5% of patients treated with Myrbetriq 50 mg, Myrbetriq 100 mg and active control once daily, respectively. Neoplasms reported by 2 patients treated with Myrbetriq 100 mg included breast cancer, lung neoplasm malignant and prostate cancer.

In a separate clinical study in Japan, a single case was reported as Stevens-Johnson syndrome with increased serum ALT, AST and bilirubin in a patient taking Myrbetriq 100 mg as well as an herbal medication (Kyufu Gold).

6.2 Postmarketing Experience

Because these spontaneously reported events are from the worldwide postmarketing experience, from a population of uncertain size, the frequency of events and the role of mirabegron in their causation cannot be reliably determined. The following events have been reported in association with mirabegron use in worldwide postmarketing experience:

Urologic: urinary retention *[see Warnings and Precautions (5.2)]*

7 DRUG INTERACTIONS

Drug interaction studies were conducted to investigate the effect of co-administered drugs on the pharmacokinetics of mirabegron and the effect of mirabegron on the pharmacokinetics of co-administered drugs (e.g., ketoconazole, rifampin, solifenacin, tamsulosin, and oral contraceptives) *[see Clinical Pharmacology (12.3)]*. No dose adjustment is recommended when these drugs are co-administered with mirabegron.

The following are drug interactions for which monitoring is recommended:

7.1 Drugs Metabolized by CYP2D6

Since mirabegron is a moderate CYP2D6 inhibitor, the systemic exposure of drugs metabolized by CYP2D6 enzyme such as metoprolol and desipramine is increased when co-administered with mirabegron. Therefore, appropriate monitoring and dose adjustment may be necessary when Myrbetriq is co-administered with these drugs, especially with narrow therapeutic index CYP2D6 substrates, such as thioridazine, flecainide, and propafenone *[see Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)]*.

7.2 Digoxin

When given in combination, mirabegron increased mean digoxin C_{max} from 1.01 to 1.3 ng/mL (29%) and AUC from 16.7 to 19.3 ng.h/mL (27%). Therefore, for patients who are initiating a combination of mirabegron and digoxin, the lowest dose for digoxin should initially be considered. Serum digoxin concentrations should be monitored and used for titration of the digoxin dose to obtain the desired clinical effect *[see Clinical Pharmacology (12.3)]*.

7.3 Warfarin

The mean C_{max} of S- and R-warfarin was increased by approximately 4% and AUC by approximately 9% when administered as a single dose of 25 mg after multiple doses of 100 mg mirabegron. Following a single dose administration of 25 mg warfarin, mirabegron had no effect on the warfarin pharmacodynamic endpoints such as International Normalized Ratio (INR) and prothrombin time. However, the effect of mirabegron on multiple doses of warfarin and on warfarin pharmacodynamic end points such as INR and prothrombin time has not been fully investigated *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C
There are no adequate and well-controlled studies using Myrbetriq in pregnant women. Myrbetriq should be used during pregnancy only if the potential benefit to the patient outweighs the risk to the patient and fetus. Women who become pregnant during Myrbetriq treatment are encouraged to contact their physician.

Risk Summary
Based on animal data, mirabegron is predicted to have a low probability of increasing the risk of adverse developmental outcomes above background risk. Reversible adverse developmental findings consisting of delayed ossification and wavy ribs in rats and decreased fetal body weights in rabbits occurred at exposures greater than or equal to 22 and 14 times, respectively, the maximal recommended human dose (MRHD). At maternally toxic exposures decreased fetal weights were observed in rats and rabbits, and fetal death, dilated aorta, and cardiomegaly were reported in rabbits.

Animal Data
In the rat embryo/fetal developmental toxicity study, pregnant rats received daily oral doses of mirabegron at 0, 10, 30, 100, or 300 mg/kg from implantation to closure of the fetal hard palate (7^{th} to 17^{th} day of gestation). Maternal systemic exposures were approximately 0, 1, 6, 22, or 96 times greater than exposures in women treated at the MRHD of 50 mg based on AUC. No embryo/fetal toxicities were observed in rats exposed up to 6 times the human systemic exposure at the MRHD of 50 mg. At systemic exposures equal to or greater than 22 times the human systemic exposure at the MRHD, delayed ossification and wavy ribs were observed in fetuses at an increased incidence. These findings were reversible.

In the rabbit embryo/fetal developmental toxicity study, pregnant rabbits received daily oral doses of mirabegron at 0, 3, 10, or 30 mg/kg from implantation to closure of the fetal hard palate (6^{th} to 20^{th} day of gestation). Maternal systemic exposures were 0, 1, 14, or 36 times that in women treated at the MRHD of 50 mg based on AUC. The embryo/fetal No Adverse Effect Level (NOAEL) was similar to the exposure in women at the MRHD and was established in this species based on reduced fetal body weight observed at systemic exposures that were 14-fold higher than the human systemic exposure at MRHD. At higher doses, where systemic exposures were 36-fold higher than the human exposure at MRHD, maternal body weight gain and food consumption were reduced, one of 17 pregnant rabbits died, the incidence of fetal death increased, and fetal findings of dilated aorta and cardiomegaly were reported.

The effects of mirabegron on prenatal and postnatal development was assessed in pregnant rats dosed at 0, 10, 30, or 100 mg/kg/day from the seventh day of gestation until 20 days after birth. Maternal systemic exposures were 0, 1, 6, and 22 times the exposure in women at the MRHD based on AUC. Rat pups exposed to mirabegron in utero and through 21 days of lactation had no discernable adverse effects at maternal systemic exposures 6 times the MRHD. A slight but statistically significant decrease in the survival of pups was observed 4 days after birth at exposures 22 times the MRHD (92.7% survival) compared to the control group (98.8%), however, there was no effect on survival of pups 21 days after birth. Absolute body weight of pups was not affected on the day of birth. However, at the 30 mg/kg dose (22-fold higher systemic exposure than humans at MHRD) body weight gain of pups was reduced 5% to 13% from postnatal day 4 to 7 but not throughout the remainder of the lactation period. In utero and lactational exposure did not affect behavior or fertility of offspring at exposures up to 22 times the MRHD.

8.3 Nursing Mothers

It is not known whether Myrbetriq is excreted in human milk. Mirabegron was found in the milk of rats at concentrations twice the maternal plasma level. Mirabegron was found in the lungs, liver, and kidneys of nursing pups. No studies have been conducted to assess the impact of Myrbetriq on milk production in humans, its presence in human breast milk, or its effects on the breast-fed child. Because Myrbetriq is predicted to be excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of Myrbetriq in pediatric patients have not been established.

8.5 Geriatric Use

No dose adjustment is necessary for the elderly. The pharmacokinetics of Myrbetriq is not significantly influenced by age *[see Clinical Pharmacology (12.3)]*. Of 5648 patients who received Myrbetriq in the phase 2 and 3 studies, 2029 (35.9%) were 65 years of age or older, and 557 (9.9%) were 75 years of age or older. No overall differences in safety or effectiveness were observed between patients younger than 65 years of age and those 65 years of age or older in these studies.

8.6 Renal Impairment

Myrbetriq has not been studied in patients with end stage renal disease (CL_{cr} <15 mL/min or eGFR <15 mL/min/1.73 m^2 or patients requiring hemodialysis), and, therefore is not recommended for use in these patient populations.

In patients with severe renal impairment (CL_{cr} 15 to 29 mL/min or eGFR 15 to 29 mL/min/1.73 m^2), the daily dose of Myrbetriq should not exceed 25 mg. No dose adjustment is necessary in patients with mild or moderate renal impairment (CL_{cr} 30 to 89 mL/min or eGFR 30 to 89 mL/min/1.73 m^2) *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

Myrbetriq has not been studied in patients with severe hepatic impairment (Child-Pugh Class C), and therefore is not recommended for use in this patient population.

In patients with moderate hepatic impairment (Child-Pugh Class B), the daily dose of Myrbetriq should not exceed 25 mg. No dose adjustment is necessary in patients with mild hepatic impairment (Child-Pugh Class A) *[see Clinical Pharmacology (12.3)]*.

8.8 Gender

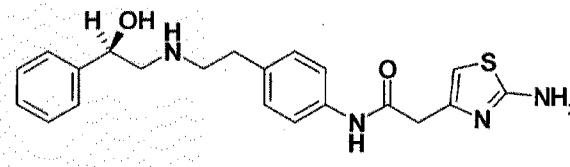
No dose adjustment is necessary based on gender. When corrected for differences in body weight, the Myrbetriq systemic exposure is 20% to 30% higher in females compared to males.

10 OVERDOSAGE

Mirabegron has been administered to healthy volunteers at single doses up to 400 mg. At this dose, adverse events reported included palpitations (1 of 6 subjects) and increased pulse rate exceeding 100 bpm (3 of 6 subjects). Multiple doses of mirabegron up to 300 mg daily for 10 days showed increases in pulse rate and systolic blood pressure when administered to healthy volunteers. Treatment for overdosage should be symptomatic and supportive. In the event of overdosage, pulse rate, blood pressure and ECG monitoring is recommended.

11 DESCRIPTION

Mirabegron is a beta-3 adrenergic agonist. The chemical name is 2-(2-aminothiazol-4-yl)-N-[4-(2-{[(2R)-2-hydroxy-2-phenylethyl]amino}ethyl)phenyl]acetamide having an empirical formula of $C_{21}H_{24}N_4O_2S$ and a molecular weight of 396.51. The structural formula of mirabegron is:



Mirabegron is a white powder. It is practically insoluble in water (0.082 mg/mL). It is soluble in methanol and dimethyl sulfoxide.

Each Myrbetriq extended release tablet, for oral administration contains either 25 mg or 50 mg of mirabegron and the following inactive ingredients: polyethylene oxide, polyethylene glycol, hydroxypropyl cellulose, butylated hydroxytoluene, magnesium stearate, hypromellose, yellow ferric oxide, and red ferric oxide (25 mg tablet only).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Mirabegron is an agonist of the human beta-3 adrenergic receptor (AR) as demonstrated by in vitro laboratory experiments using the cloned human beta-3 AR. Mirabegron relaxes the detrusor smooth muscle during the storage phase of the urinary bladder fill-void cycle by activation of beta-3 AR which increases bladder capacity. Although mirabegron showed very low intrinsic activity for cloned human beta-1 AR and beta-2 AR, results in humans indicate that beta-1 AR stimulation occurred at a mirabegron dose of 200 mg.

12.2 Pharmacodynamics

Urodynamics

The effects of Myrbetriq on maximum urinary flow rate and detrusor pressure at maximum flow rate were assessed in a urodynamic study consisting of 200 male patients with lower urinary tract symptoms (LUTS) and BOO. Administration of Myrbetriq once daily for 12 weeks did not adversely affect the mean maximum flow rate or mean detrusor pressure at maximum flow rate in this study. Nonetheless, Myrbetriq should be administered with caution to patients with clinically significant BOO *[see Warnings and Precautions (5.2)]*.

Cardiac Electrophysiology

The effect of multiple doses of Myrbetriq 50 mg, 100 mg and 200 mg once daily on QTc interval was evaluated in a randomized, placebo- and active- controlled (moxifloxacin 400 mg) four-treatment-arm parallel crossover study in 352 healthy subjects. In a study with demonstrated ability to detect small effects, the upper bound of the one-sided 95% confidence interval for the largest placebo adjusted, baseline-corrected QTc based on individual correction method (QTcI) was below 10 msec. For the 50 mg Myrbetriq dose group (the maximum approved dosage), the mean difference from placebo on QTcI interval at 4-5 hours post-dose was 3.7 msec (upper bound of the 95% CI 5.1 msec).

For the Myrbetriq 100 mg and 200 mg doses groups (dosages greater than the maximum approved dose and resulting in substantial multiples of the anticipated maximum blood levels at 50 mg), the mean differences from placebo in QTcI interval at 4-5 hours post-dose were 6.1 msec (upper bound of the 95% CI 7.6 msec) and 8.1 msec (upper bound of the 95% CI 9.8 msec), respectively. At the Myrbetriq 200 mg dose, in females, the mean effect was 10.4 msec (upper bound of the 95% CI 13.4 msec).

In this thorough QT study, Myrbetriq increased heart rate on ECG in a dose dependent manner. Maximum mean increases from baseline in heart rate for the 50 mg, 100 mg, and 200 mg dose groups compared to placebo were 6.7 beats per minutes (bpm), 11 bpm, and 17 bpm, respectively. In the clinical efficacy and safety studies, the change from baseline in mean pulse rate for Myrbetriq 50 mg was approximately 1 bpm. In this thorough QT study, Myrbetriq also increased blood pressure in a dose dependent manner (see *Effects on Blood Pressure*).

Effects on Blood Pressure

In a study of 352 healthy subjects assessing the effect of multiple daily doses of 50 mg, 100 mg, and 200 mg of Myrbetriq for 10 days on the QTc interval, the maximum mean increase in supine SBP/DBP at the maximum recommended dose of 50 mg was approximately 4.0/1.6 mmHg greater than placebo. The 24-hour average increases in SBP compared to placebo were 3.0, 5.5, and 9.7 mmHg at Myrbetriq doses of 50 mg, 100 mg and 200 mg, respectively. Increases in DBP were also dose-dependent, but were smaller than SBP.

In another study in 96 healthy subjects to assess the impact of age on pharmacokinetics of multiple daily doses of 50 mg, 100 mg, 200 mg, and 300 mg of Myrbetriq for 10 days, SBP also increased in a dose-dependent manner. The mean maximum increases in SBP were approximately 2.5, 4.5, 5.5 and 6.5 mmHg for Myrbetriq exposures associated with doses of 50 mg, 100 mg, 200 mg and 300 mg, respectively.

In three, 12-week, double-blind, placebo-controlled, safety and efficacy studies (Studies 1, 2 and 3) in OAB patients receiving Myrbetriq 25 mg, 50 mg, or 100 mg once daily, mean increases in SBP/DBP compared to placebo of approximately 0.5 - 1 mmHg were observed. Morning SBP increased by at least 15 mmHg from baseline in 5.3%, 5.1%, and 6.7% of placebo, Myrbetriq 25 mg and Myrbetriq 50 mg patients, respectively. Morning DBP increased by at least 10 mmHg in 4.6%, 4.1% and 6.6% of placebo, Myrbetriq 25 mg, and Myrbetriq 50 mg patients, respectively. Both SBP and DBP increases were reversible upon discontinuation of treatment.

Effect on Intraocular Pressure (IOP)

Myrbetriq 100 mg once daily did not increase IOP in healthy subjects after 56 days of treatment. In a phase 1 study assessing the effect of Myrbetriq on IOP using Goldmann applanation tonometry in 310 healthy subjects, a dose of Myrbetriq 100 mg was non-inferior to placebo for the primary endpoint of the treatment difference in mean change from baseline to day 56 in subject-average IOP; upper bound of the two-sided 95% CI of the treatment difference between Myrbetriq 100 mg and placebo was 0.3 mm Hg.

12.3 Pharmacokinetics

Absorption

After oral administration of mirabegron in healthy volunteers, mirabegron is absorbed to reach maximum plasma concentrations (C_{max}) at approximately 3.5 hours. The absolute bioavailability increases from 29% at a dose of 25 mg to 35% at a dose of 50 mg. Mean C_{max} and AUC increase more than dose proportionally. This relationship is more apparent at doses above 50 mg. In the overall population of males and females, a 2-fold increase in dose from 50 mg to 100 mg mirabegron increased C_{max} and AUC_{tau} by approximately 2.9- and 2.6-fold, respectively, whereas a 4-fold increase in dose from 50 to 200 mg mirabegron increased C_{max} and AUC_{tau} by approximately 8.4- and 6.5-fold. Steady state concentrations are achieved within 7 days of once daily dosing with mirabegron. After once daily administration, plasma exposure of mirabegron at steady state is approximately double that seen after a single dose.

Effect of Food

Co-administration of a 50 mg tablet with a high-fat meal reduced mirabegron C_{max} and AUC by 45% and 17%, respectively. A low-fat meal decreased mirabegron C_{max} and AUC by 75% and 51%, respectively. In the phase 3 studies, mirabegron was administered irrespective of food contents and intake (i.e., with or without food) and demonstrated both safety and efficacy. Therefore, mirabegron can be taken with or without food at the recommended dose [*see Dosage and Administration (2.1)*].

Distribution

Mirabegron is extensively distributed in the body. The volume of distribution at steady state (V_{ss}) is approximately 1670 L following intravenous administration. Mirabegron is bound (approximately 71%) to human plasma proteins, and shows moderate affinity for albumin and alpha-1 acid glycoprotein. Mirabegron distributes to erythrocytes. Based on *In vitro* study erythrocyte concentrations of ^{14}C-mirabegron were about 2-fold higher than in plasma.

Metabolism

Mirabegron is metabolized via multiple pathways involving dealkylation, oxidation, (direct) glucuronidation, and amide hydrolysis. Mirabegron is the major circulating component following a single dose of ^{14}C-mirabegron. Two major metabolites were observed in human plasma and are phase 2 glucuronides representing 16% and 11% of total exposure, respectively. These metabolites are not pharmacologically active toward beta-3 adrenergic receptor. Although *in vitro* studies suggest a role for CYP2D6 and CYP3A4 in the oxidative metabolism of mirabegron, *in vivo* results indicate that these isozymes play a limited role in the overall elimination. In healthy subjects who are genotypically poor metabolizers of CYP2D6, mean C_{max} and AUC_{tau} were approximately 16% and 17% higher than in extensive metabolizers of CYP2D6, respectively. *In vitro* and *ex vivo* studies have shown the involvement of butylcholinesterase, uridine diphospho-glucuronosyltransferases (UGT) and possibly alcohol dehydrogenase in the metabolism of mirabegron, in addition to CYP3A4 and CYP2D6.

Excretion

Total body clearance (CL_{tot}) from plasma is approximately 57 L/h following intravenous administration. The terminal elimination half-life ($t_{1/2}$) is approximately 50 hours. Renal clearance (CL_R) is approximately 13 L/h, which corresponds to nearly 25% of CL_{tot}. Renal elimination of mirabegron is primarily through active tubular secretion along with glomerular filtration. The urinary elimination of unchanged mirabegron is dose-dependent and ranges from approximately 6.0% after a daily dose of 25 mg to 12.2% after a daily dose of 100 mg. Following the administration of 160 mg ^{14}C-mirabegron solution to healthy volunteers, approximately 55% of the radioactivity dose was recovered in the urine and 34% in the feces. Approximately 25% of unchanged mirabegron was recovered in urine and 0% in feces.

Specific Populations

Geriatric Patients

The C_{max} and AUC of mirabegron following multiple oral doses in elderly volunteers (≥ 65 years) were similar to those in younger volunteers (18 to 45 years).

Pediatric Patients

The pharmacokinetics of mirabegron in pediatric patients have not been evaluated *[see Use in Specific Populations (8.4)]*.

Gender

The C_{max} and AUC of mirabegron were approximately 40% to 50% higher in females than in males. When corrected for differences in body weight, the mirabegron systemic exposure is 20% - 30% higher in females compared to males.

Race

The pharmacokinetics of mirabegron were comparable between Caucasians and African American Blacks. Cross studies comparison shows that the exposure in Japanese subjects is higher than that in North American subjects. However, when the C_{max} and AUC were normalized for dose and body weight, the difference is smaller.

Renal Impairment

Following single dose administration of 100 mg mirabegron in volunteers with mild renal impairment (eGFR 60 to 89 mL/min/1.73 m^2 as estimated by MDRD), mean mirabegron C_{max} and AUC were increased by 6% and 31% relative to volunteers with normal renal function. In volunteers with moderate renal impairment (eGFR 30 to 59 mL/min/1.73 m^2), C_{max} and AUC were increased by 23% and 66%, respectively. In patients with severe renal impairment (eGFR 15 to 29 mL/min/1.73 m^2), mean C_{max} and AUC values were 92% and 118% higher compared to healthy subjects with normal renal function. Mirabegron has not been studied in patients with End Stage Renal Disease-ESRD (CL_{cr} less than 15 mL/min or eGFR less than 15 mL/min/1.73 m^2 or patients requiring hemodialysis).

Hepatic Impairment

Following single dose administration of 100 mg mirabegron in volunteers with mild hepatic impairment (Child-Pugh Class A), mean mirabegron C_{max} and AUC were increased by 9% and 19% relative to volunteers with normal hepatic function. In volunteers with moderate hepatic impairment (Child-Pugh Class B), mean C_{max} and AUC values were 175% and 65% higher. Mirabegron has not been studied in patients with severe hepatic impairment (Child-Pugh Class C).

Drug Interaction Studies

In Vitro Studies

Effect of Other Drugs on Mirabegron

Mirabegron is transported and metabolized through multiple pathways. Mirabegron is a substrate for CYP3A4, CYP2D6, butyrylcholinesterase, UGT, the efflux transporter P-glycoprotein (P-gp) and the influx organic cation transporters (OCT) OCT1, OCT2, and OCT3. Sulfonylurea hypoglycemic agents glibenclamide (a CYP3A4 substrate), gliclazide (a CYP2C9 and CYP3A4 substrate) and tolbutamide (a CYP2C9 substrate) did not affect the *in vitro* metabolism of mirabegron.

Effect of Mirabegron on Other Drugs

Studies of mirabegron using human liver microsomes and recombinant human CYP enzymes showed that mirabegron is a moderate and time-dependent inhibitor of CYP2D6 and a weak inhibitor of CYP3A. Mirabegron is unlikely to inhibit the metabolism of co-administered drugs metabolized by the following cytochrome P450 enzymes: CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP2E1 because mirabegron did not inhibit the activity of these enzymes at clinically relevant concentrations. Mirabegron did not induce CYP1A2 or CYP3A. Mirabegron inhibited P-gp-mediated drug transport at high concentrations. Mirabegron is predicted not to cause clinically relevant inhibition of OCT-mediated drug transport. Mirabegron did not affect the metabolism of glibenclamide or tolbutamide.

In Vivo Studies

The effect of co-administered drugs on the pharmacokinetics of mirabegron and the effect of mirabegron on the pharmacokinetics of co-administered drugs was studied after single and multiple doses of mirabegron. Most drug-drug interactions (DDI) were studied using mirabegron 100 mg extended-release tablets. However, interaction studies of mirabegron with metoprolol and with metformin were studied using mirabegron 160 mg immediate release (IR) tablets.

The effect of ketoconazole, rifampicin, solifenacin, tamsulosin, and metformin on systemic mirabegron exposure is shown in Figure 1.

The effect of mirabegron on metoprolol, desipramine, combined oral contraceptive-COC (ethinyl estradiol-EE, levonorgestrel-LNG), solifenacin, digoxin, warfarin, tamsulosin, and metformin is shown in Figure 2.

In these studies, the largest increase in mirabegron systemic exposure was seen in the ketoconazole DDI study. As a potent CYP3A4 inhibitor, ketoconazole increased mirabegron C_{max} by 45% and mirabegron AUC by 80% after multiple dose administration of 400 mg of ketoconazole for 9 days prior to the administration of a single dose of 100 mg mirabegron in 23 male and females healthy subjects.

As a moderate CYP2D6 inhibitor, mirabegron increased the systemic exposure to metoprolol and desipramine:

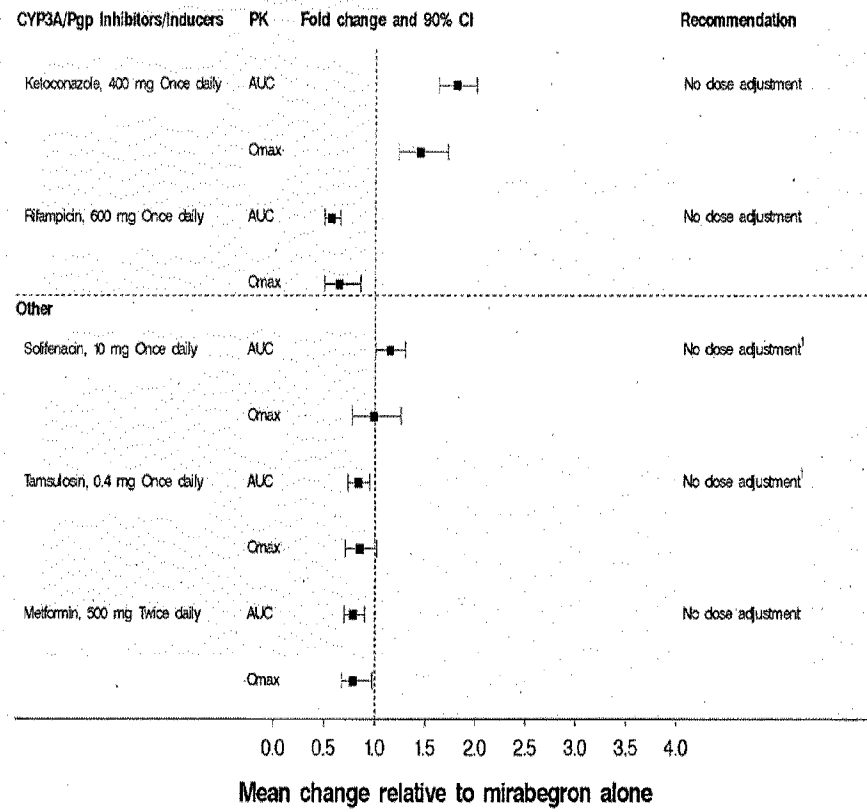
- Mirabegron increased the C_{max} of metoprolol by 90% and metoprolol AUC by 229% after multiple doses of 160 mg mirabegron IR tablets once daily for 5 days and a single dose of 100 mg metoprolol tablet in 12 healthy male subjects administered before and concomitantly with mirabegron.

- Mirabegron increased the C_{max} of desipramine by 79% and desipramine AUC by 241% after multiple dose administration of 100 mg mirabegron once daily for 18 days and a single dose of 50 mg desipramine before and concomitantly with mirabegron in 28 male and female healthy subjects.

Caution is advised if Myrbetriq is co-administered with CYP2D6 substrates such as metoprolol and desipramine, and especially narrow therapeutic index drugs, such as thioridazine, flecainide, and propafenone *[see Warnings and Precautions (5.3) and Drug Interactions (7.1)]*.

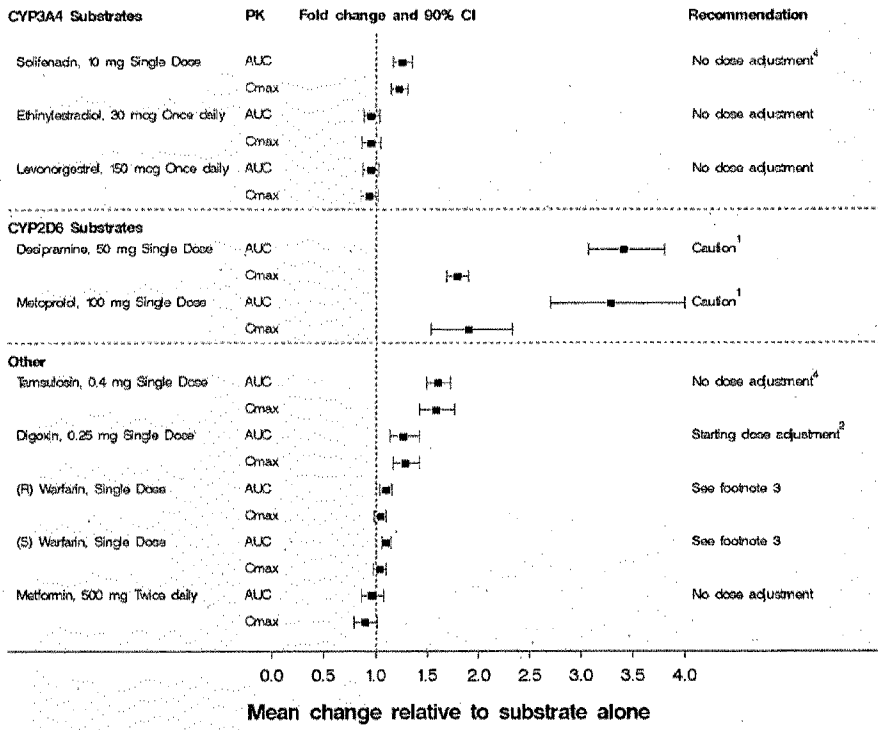
Figures 1 and 2 show the magnitude of these interactions on the pharmacokinetic parameters and the recommendations for dose adjustment, if any:

Figure 1: The Effect of Co-administered Drugs on Exposure of Myrbetriq and Dose Recommendation



(1) Although no dose adjustment is recommended with solifenacin or tamsulosin based on the lack of pharmacokinetic interaction, Myrbetriq should be administered with caution to patients taking antimuscarinic medications for the treatment of OAB and in patients with clinically significant BOO because of the risk of urinary retention *[see Warnings and Precautions (5.2)]*.

Figure 2: The Effect of Myrbetriq on Exposure of Co-administered Medication



(1) Since mirabegron is a moderate CYP2D6 inhibitor, the systemic exposure to CYP2D6 substrates such as metoprolol and desipramine is increased when co-administered with mirabegron. Therefore, appropriate monitoring and dose adjustment may be necessary, especially with narrow therapeutic index CYP2D6 substrates, such as thioridazine, flecainide, and propafenone *[see Warnings and Precautions (5.3) and Drug Interactions (7.1)]*.

(2) For patients who are initiating a combination of mirabegron and digoxin, the lowest dose for digoxin should initially be prescribed. Serum digoxin concentrations should be monitored and used for titration of the digoxin dose to obtain the desired clinical effect *[see Drug Interaction (7.2)]*.

(3) Warfarin was administered as a single 25 mg dose of the racemate (a mixture of R-warfarin and S-warfarin). Based on this single dose study, mirabegron had no effect on the warfarin pharmacodynamic endpoints such as INR and prothrombin time. However, the effect of mirabegron on multiple doses of warfarin and on warfarin pharmacodynamic end points such as INR and prothrombin time has not been fully investigated *[see Drug Interactions (7.3)]*.

(4) Although no dose adjustment is recommended with solifenacin or tamsulosin based on the lack of pharmacokinetic interaction, Myrbetriq should be administered with caution to patients taking antimuscarinic medications for the treatment of OAB and in BOO because of the risk of urinary retention *[see Warnings and Precautions (5.2)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity
Long-term carcinogenicity studies were conducted in rats and mice dosed orally with mirabegron for two years. Male rats were dosed at 0, 12.5, 25, or 50 mg/kg/day and female rats and both sexes of mice were dosed at 0, 25, 50, or 100 mg/kg/day. Mirabegron showed no carcinogenic potential at systemic exposures (AUC) 38 to 45-fold higher in rats and 21 to 38-fold higher in mice than the human systemic exposure at the 50 mg dose.

Mutagenesis
Mirabegron was not mutagenic in the Ames bacterial reverse mutation assay, did not induce chromosomal aberrations in human peripheral blood lymphocytes at concentrations that were not cytotoxic, and was not clastogenic in the rat micronucleus assay.

Impairment of Fertility
Fertility studies in rats showed that mirabegron had no effect on either male or female fertility at non-lethal doses up to 100 mg/kg/day. Systemic exposures (AUC) at 100 mg/kg in female rats was estimated to be 22 times the MRHD in women and 93 times the MRHD in men.

14 CLINICAL STUDIES

Myrbetriq was evaluated in three, 12-week, double-blind, randomized, placebo-controlled, parallel group, multicenter clinical trials in patients with overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency (Studies 1, 2, and 3). Entry criteria required that patients had symptoms of overactive bladder for at least 3 months duration, at least 8 micturitions per day, and at least 3 episodes of urgency with or without incontinence over a 3 day period. The majority of patients were Caucasian (94%) and female (72%) with a mean age of 59 years (range 18 – 95 years). The population included both naïve patients who had not received prior antimuscarinic pharmacotherapy for overactive bladder (48%) and those who had received prior antimuscarinic pharmacotherapy for OAB (52%).

In Study 1, patients were randomized to placebo, Myrbetriq 50 mg, Myrbetriq 100 mg, or an active control once daily. In Study 2, patients were randomized to placebo, Myrbetriq 50 mg or Myrbetriq 100 mg once daily. In Study 3, patients were randomized to placebo, Myrbetriq 25 mg or Myrbetriq 50 mg once daily.

The co-primary efficacy endpoints in all 3 trials were (1) change from baseline to end of treatment (Week 12) in mean number of incontinence episodes per 24 hours and (2) change from baseline to end of treatment (Week 12) in mean number of micturitions per 24 hours, based on a 3-day micturition diary. An important secondary endpoint was the change from baseline to end of treatment (Week 12) in mean volume voided per micturition.

Results for the co-primary endpoints and mean volume voided per micturition from Studies 1, 2, and 3 are shown in Table 3.

Table 3: Mean Baseline and Change from Baseline at Week 12‡ for Incontinence Episodes, Micturition Frequency, and Volume Voided per Micturition in Patients with Overactive Bladder in Studies 1, 2, and 3

Parameter	Study 1		Study 2		Study 3		
	Placebo	Myrbetriq 50 mg	Placebo	Myrbetriq 50 mg	Placebo	Myrbetriq 25 mg	Myrbetriq 50 mg
Number of Incontinence Episodes per 24 Hours^							
n	291	293	325	312	262	254	257
Baseline (mean)	2.67	2.83	3.03	2.77	2.43	2.65	2.51
Change from baseline (adjusted mean†)	-1.17	-1.57	-1.13	-1.47	-0.96	-1.36	-1.38
Difference from placebo (adjusted mean†)	--	-0.41	--	-0.34	--	-0.40	-0.42
95% Confidence Interval	--	(-0.72, -0.09)	--	(-0.66, -0.03)	--	(-0.74, -0.06)	(-0.76, -0.08)
p-value		0.003#		0.026#		0.005#	0.001#
Number of Micturitions per 24 Hours							
n	480	473	433	425	415	410	426
Baseline (mean)	11.71	11.65	11.51	11.80	11.48	11.68	11.66
Change from baseline (adjusted mean†)	-1.34	-1.93	-1.05	-1.66	-1.18	-1.65	-1.60
Difference from placebo (adjusted mean†)	--	-0.60	--	-0.61	--	-0.47	-0.42
95% Confidence Interval	--	(-0.90, -0.29)	--	(-0.98, -0.24)	--	(-0.82, -0.13)	(-0.76, -0.08)
p-value		<0.001#		0.001#		0.007#	0.015#
Volume Voided (mL) per Micturition							
n	480	472	433	424	415	410	426
Baseline (mean)	156.7	161.1	157.5	156.3	164.0	165.2	159.3
Change from baseline (adjusted mean†)	12.3	24.2	7.0	18.2	8.3	12.8	20.7
Difference from placebo (adjusted mean†)	--	11.9	--	11.1	--	4.6	12.4
95% Confidence Interval	--	(6.3, 17.4)	--	(4.4, 17.9)	--	(-1.6, 10.8)	(6.3, 18.6)
p-value		< 0.001#		0.001#		0.15	<0.001#

‡ Week 12 is last observation on treatment
† Least squares mean adjusted for baseline, gender, and geographical region
^For incontinence episodes per 24 hours, the analysis population is restricted to patients with at least 1 episode of incontinence at baseline.
#Statistically significantly superior compared to placebo at the 0.05 level with multiplicity adjustment

Myrbetriq 25 mg was effective in treating the symptoms of OAB within 8 weeks, and Myrbetriq 50 mg was effective in treating the symptoms of OAB within 4 weeks. Efficacy of both 25 mg and 50 mg doses of Myrbetriq was maintained through the 12-week treatment period.

Figures 3 through 8 show the co-primary endpoints, mean change from baseline (BL) over time in number of incontinence episodes per 24 hours and mean change from baseline over time in number of micturitions per 24 hours, in Studies 1, 2 and 3.

Figure 3. Mean (SE) Change from Baseline in Mean Number of Incontinence Episodes per 24 Hours –Study 1

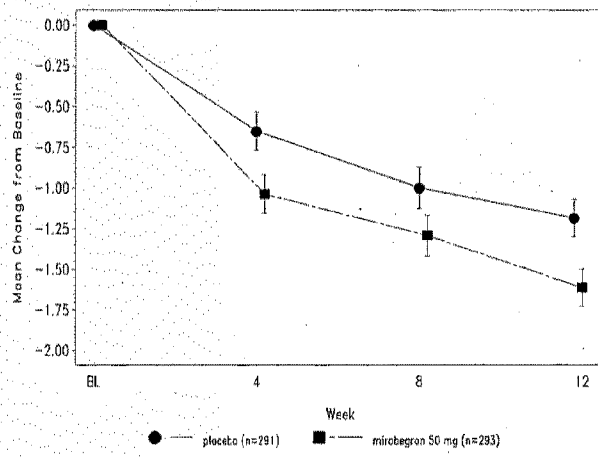


Figure 4. Mean (SE) Change from Baseline in Mean Number of Micturitions per 24 Hours - Study 1

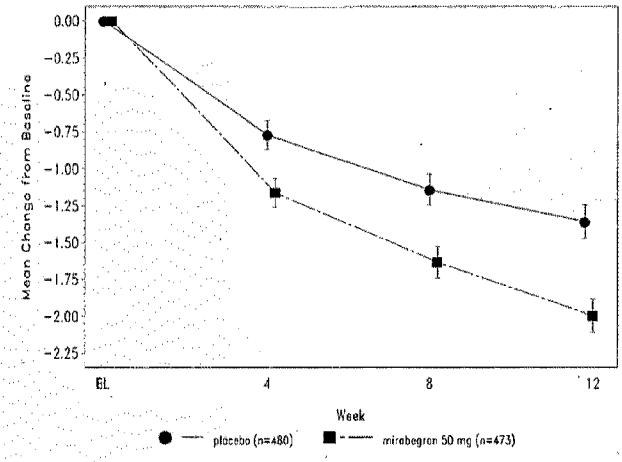


Figure 5. Mean (SE) Change from Baseline in Mean Number of Incontinence Episodes per 24 Hours - Study 2

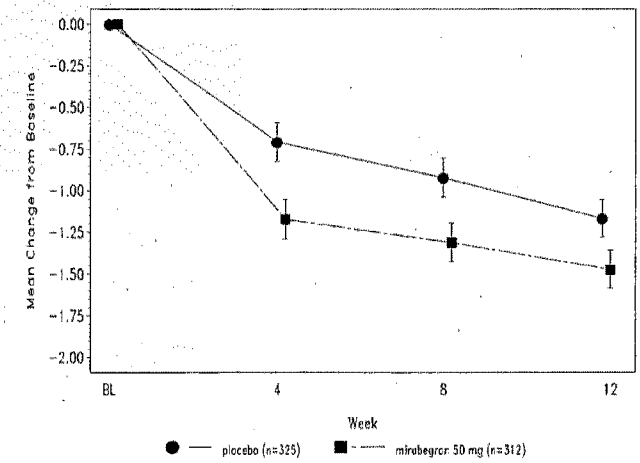


Figure 6. Mean (SE) Change from Baseline in Mean Number of Micturitions per 24 Hours - Study 2

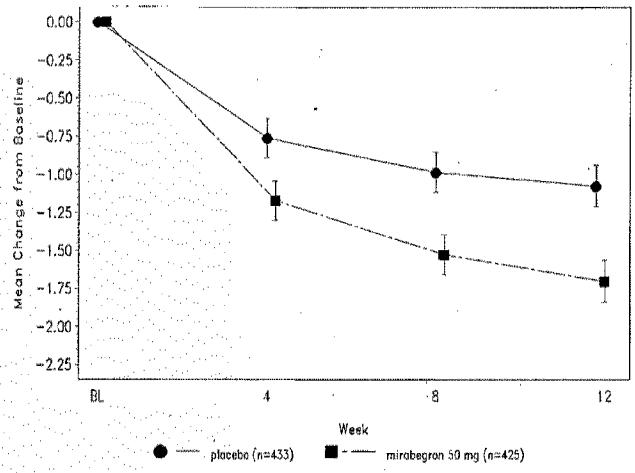


Figure 7. Mean (SE) Change from Baseline in Mean Number of Incontinence Episodes per 24 Hours - Study 3

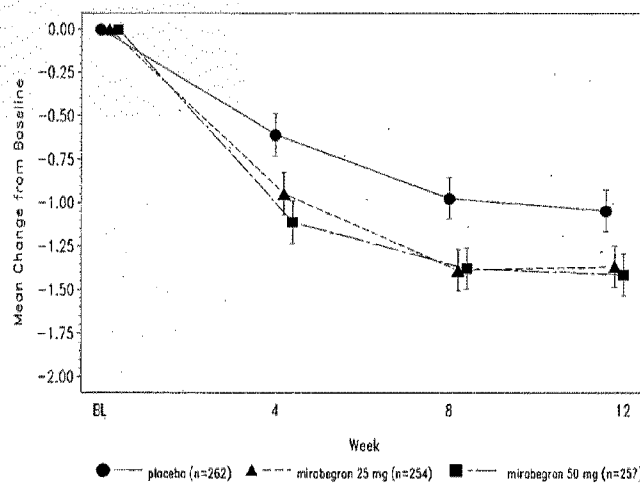
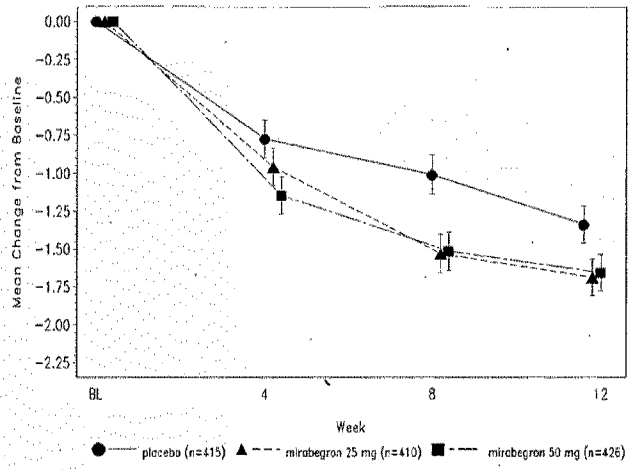


Figure 8. Mean (SE) Change from Baseline in Mean Number of Micturitions per 24 Hours - Study 3



16 HOW SUPPLIED/STORAGE AND HANDLING

Myrbetriq is supplied as oval, film coated extended-release tablets, available in bottles and blister units as follows

Strength	25 mg	50 mg
Color	brown	yellow
Debossed	logo, 325	logo, 355
Bottle of 30	NDC 0469-2601-30	NDC 0469-2602-30
Bottle of 90	NDC 0469-2601-90	NDC 0469-2602-90
Unit dose pack of 100	NDC 0469-2601-71	NDC 0469-2602-71

Store at 25°C (77°F) with excursions permitted from 15°C to 30°C (59°F to 86°F). {see USP controlled Room Temperature}

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information)

Inform patients that Myrbetriq may increase blood pressure. Periodic blood pressure determinations are recommended, especially in patients with hypertension. Myrbetriq has also been associated with infrequent urinary tract infections, rapid heart beat, rash, and pruritis. Inform patients that urinary retention has been reported when taking mirabegron in combination with antimuscarinic drugs used in the treatment of overactive bladder. Instruct patients to contact their physician if they experience these effects while taking Myrbetriq.

Patients should read the patient leaflet entitled "Patient Information" before starting therapy with Myrbetriq.

Patient Information

Myrbetriq (meer-BEH-trick)

(mirabegron)

extended-release tablets

Read the Patient Information that comes with Myrbetriq before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your medical condition or treatment.

What is Myrbetriq?

Myrbetriq is a prescription medicine for adults used to treat the following symptoms due to a condition called overactive bladder:

- Urge urinary incontinence: a strong need to urinate with leaking or wetting accidents
- Urgency: a strong need to urinate right away
- Frequency: urinating often

It is not known if Myrbetriq is safe and effective in children.

What should I tell my doctor before taking Myrbetriq?
Before you take Myrbetriq, tell your doctor if you:

- have liver problems
- have kidney problems
- have very high uncontrolled blood pressure
- have trouble emptying your bladder or you have a weak urine stream
- are pregnant or plan to become pregnant. It is not known if Myrbetriq
- will harm your unborn baby. Talk to your doctor if you are pregnant or plan to become pregnant.
- are breastfeeding or plan to breastfeed. It is not known if Myrbetriq passes into your breast milk. You and your doctor should decide if you will take Myrbetriq or breastfeed. You should not do both.

Tell your doctor about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements. Myrbetriq may affect the way other medicines work, and other medicines may affect how Myrbetriq works.

Tell your doctor if you take:
- thioridazine (Mellaril or Mellaril-S)
- flecainide (Tambocor)
- propafenone (Rythmol)
- digoxin (Lanoxin)

How should I take Myrbetriq?
- Take Myrbetriq exactly as your doctor tells you to take it.
- You should take 1 Myrbetriq tablet 1 time a day.
- You should take Myrbetriq with water and swallow the tablet whole.

- Do not crush or chew the tablet.
- You can take Myrbetriq with or without food.
- If you miss a dose of Myrbetriq, begin taking mirabegron again the next day. Do not take 2 doses of Myrbetriq the same day.
- If you take too much Myrbetriq, call your doctor or go to the nearest hospital emergency room right away.

What are the possible side effects of Myrbetriq?

Myrbetriq may cause serious side effects including:

- **increased blood pressure.** Myrbetriq may cause your blood pressure to increase or make your blood pressure worse if you have a history of high blood pressure. It is recommended that your doctor check your blood pressure while you are taking Myrbetriq.
- **inability to empty your bladder (urinary retention).** Myrbetriq may increase your chances of not being able to empty your bladder if you have bladder outlet obstruction or if you are taking other medicines to treat overactive bladder. Tell your doctor right away if you are unable to empty your bladder.

The most common side effects of Myrbetriq include:
- increased blood pressure
- common cold symptoms (nasopharyngitis)
- urinary tract infection
- headache

Tell your doctor if you have any side effect that bothers you or that does not go away or if you have hives, skin rash or itching while taking Myrbetriq.

These are not all the possible side effects of Myrbetriq. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Myrbetriq?

- Store Myrbetriq between 59°F to 86°F (15°C to 30°C). Keep the bottle closed.
- Safely throw away medicine that is out of date or no longer needed.

Keep Myrbetriq and all medicines out of the reach of children.

General information about the safe and effective use of Myrbetriq.

Medicines are sometimes prescribed for purposes other than those listed in Patient Information leaflet. Do not use Myrbetriq for a condition for which it was not prescribed. Do not give Myrbetriq to other people, even if they have the same symptoms you have. It may harm them.

This Patient Information leaflet summarizes the most important information about Myrbetriq. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about Myrbetriq that is written for health professionals.

For more information, go to www.Myrbetriq.com website or call 1-800- 727-7003.

What are the ingredients in Myrbetriq?

Active ingredient: mirabegron

Inactive ingredients: polyethylene oxide, polyethylene glycol, hydroxypropyl cellulose, butylated hydroxytoluene, magnesium stearate, hypromellose, yellow ferric oxide and red ferric oxide (25 mg Myrbetriq tablet only).

What is overactive bladder?
Overactive bladder occurs when you cannot control your bladder contractions. When these muscle contractions happen too often or cannot be controlled, you can get symptoms of overactive bladder, which are urinary frequency, urinary urgency, and urinary incontinence (leakage).

Rx Only

Manufactured by:
Astellas Pharma Technologies, Inc.
Norman, Oklahoma 73072

Marketed and Distributed by:
Astellas Pharma US, Inc.
Northbrook, Illinois 60062

Revised: June 2012
11G054-MIR

Appendix C

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202611

NDA APPROVAL

Astellas Pharma Global Development, Inc.
Attention: Judy Kannenberg, M.B.A., R.A.C.
Associate Director, Regulatory Affairs
Three Parkway North
Deerfield, IL 60015

Dear Dr. Kannenberg:

Please refer to your New Drug Application (NDA) dated August 26, 2011, received August 29, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Myrbetriq (mirabegron), 25 mg and 50 mg extended release tablets.

We acknowledge your amendments received September 12, October 11, 13, and 20, November 8 and 29, December 2, 8 (2), 9, 14, 16, 22, and 23, 2011; January 17, February 8, 9 (2) and 21, March 7 (2), 20, and 23, April 3, 11, 12, 17 and 18, May 4 (2), 9, 11(2), 16, 18, June 1, 5, 25, and 28 (2), 2012.

This new drug application provides for the use of Myrbetriq (mirabegron), 25 mg and 50 mg, for the treatment of overactive bladder.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert, Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your May 18, 2012, submission containing final printed carton and container labels.

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels submitted on as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 202611.**" Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to 4 years and 11 months because overactive bladder is not a condition in infants or young children who are not yet bladder trained and, therefore, necessary studies are not possible or highly impracticable.

We are deferring submission of your pediatric studies for ages 5 to 17 years and 11 months for this application because this product is ready for approval for use in adults and the pediatric study have not been completed.

Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. The required studies are listed below.

1898-1 Open label, multicenter single ascending dose study to evaluate pharmacokinetics, safety and tolerability of mirabegron modified release microgranule-based suspension in children from 5 to less than 18 years of age with neurogenic detrusor overactivity (NDO) or overactive bladder (OAB).

Final Protocol Submission:	January 2016
Study Completion:	September 2017
Final Report Submission:	September 2018

1898-2 Open label, baseline-controlled, multicenter, sequential dose titration study followed by a fixed dose observation period to evaluate pharmacokinetics, safety and efficacy of mirabegron modified release microgranule-based suspension in children from 5 to less than 18 years of age with NDO.

Final Protocol Submission:	January 2018
Study Completion:	June 2023
Final Report Submission:	June 2024

Submit the protocols to your IND 069416, with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess signals of serious risk related to: 1) observed increases in mean systolic and diastolic blood pressure and 2) increased reporting of new malignant events in the long-term clinical trial of Myrbetriq (mirabegron) at the 100 mg dose.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1898-3 A long-term observational study using electronic healthcare databases with appropriate linkages conducted in United States and European databases to evaluate the incidence of serious cardiovascular outcomes (both individual and composite outcomes) in patients administered Myrbetriq (mirabegron).

The timetable you submitted on June 27, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	March 2013
Assessment and Summary Report Submission:	March 2015
Interim Study Completion:	June 2017
Interim Analysis Report:	June 2018
Final Study Completion:	July 2018
Final Report Submission:	June 2019

1898-4 A long-term observational study in electronic healthcare databases with appropriate linkages to prospectively evaluate the incidence of new malignant events (excluding non-melanoma skin cancer) in patients using Myrbetriq (mirabegron).

The timetable you submitted on June 27, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	March 2013
Assessment and Summary Report Submission:	March 2015
Interim Study Completion:	June 2017
Interim Analysis Report:	June 2018
Final Study Completion:	July 2018
Final Report Submission:	June 2019

Submit the protocols to your IND 069416, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

We also request that you submit with your periodic adverse event reports an additional summary of postmarketing hepatic adverse reports for a period of 3 years following launch of Myrbetriq in the US.

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, please call Nenita Crisostomo, R.N., Regulatory Health Project Manager, at (301) 796-0875.

Sincerely,

{See appended electronic signature page}

Victoria Kusiak, M.D.
Deputy Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
Carton and Container Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

VICTORIA KUSIAK
06/28/2012

Reference ID: 3152173

Appendix D

US006346532B1

(12) **United States Patent**
Maruyama et al.

(10) **Patent No.: US 6,346,532 B1**
(45) **Date of Patent: Feb. 12, 2002**

(54) **AMIDE DERIVATIVES OR SALTS THEREOF**

(75) Inventors: **Tatsuya Maruyama**; **Takayuki Suzuki**; **Kenichi Onda**; **Masahiko Hayakawa**; **Hiroyuki Morittomo**; **Tetsuya Kimizuka**; **Tetsuo Matsui**, all of Tsukuba (JP)

(73) Assignee: **Yamanouchi Pharmaceutical Co., Ltd.**, Tokyo (JP)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/529,096**

(22) PCT Filed: **Oct. 15, 1998**

(86) PCT No.: **PCT/JP98/04671**

§ 371 Date: **Apr. 7, 2000**

§ 102(e) Date: **Apr. 7, 2000**

(87) PCT Pub. No.: **WO99/20607**

PCT Pub. Date: **Apr. 29, 1999**

(30) **Foreign Application Priority Data**

Oct. 17, 1997 (JP) 9-285778

(51) **Int. Cl.**[7] **A61K 31/495**; A61K 31/505; C07D 239/02; C07D 213/00; C07D 249/00

(52) **U.S. Cl.** **514/252.1**; 514/256; 544/330; 544/332; 546/1; 546/152; 548/190; 548/214; 548/186; 548/252; 548/260

(58) **Field of Search** 544/330, 332; 546/1, 152; 548/190, 214, 186, 252, 260; 514/252.1, 256

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,223,614	A *	6/1993	Schromm et al.	544/105
5,541,197	A *	7/1996	Fisher et al.	514/311
5,553,475	A	9/1996	Hayashi et al.	72/225
5,614,544	A	3/1997	Sohda et al.	514/376
6,048,884	A	4/2000	Maruyama et al.	514/370
6,177,454	B1	1/2001	Maruyama et al.	514/394

FOREIGN PATENT DOCUMENTS

DE	3743265	*	6/1989
JP	10218861	*	6/1989
WO	9529159	*	11/1995

OTHER PUBLICATIONS

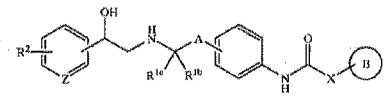
Konosu T. et al. "Triazole antif.", Chem.Pharm.Bull., 39/10, 2581-9, Oct. 1991.*

* cited by examiner

Primary Examiner—Richard L. Raymond
Assistant Examiner—Sudhaker B. Patel
(74) *Attorney, Agent, or Firm*—Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P.

(57) **ABSTRACT**

(I)



Amide derivatives represented by general formula (I) or salts thereof wherein each symbol has the following meaning: ring B: an optionally substituted heteroaryl optionally fused with a benzene ring; X: a bond, lower alkylene or lower alkenylene optionally substituted by hydroxy or lower alkyl, carbonyl, or a group represented by —NH— (when X is lower alkylene optionally substituted by lower alkyl which may be bonded to the hydrogen atom bonded to a constituent carbon atom of ring B to form lower alkylene to thereby form a ring); A: a lower alkylene or a group represented by -(lower alkylene)—O—; R^{1a} and R^{1b}: the same or different and each hydrogen or lower alkyl; R^2: hydrogen or halogeno; and Z: nitrogen or a group represented by =CH—. The compounds are useful as a diabetes remedy which not only functions to both accelerate the secretion of insulin and enhance insulin sensitivity but has an antiobestic action and an antihyperlipemic action based on its selective stimulative action on a β_3 receptor.

14 Claims, No Drawings

AMIDE DERIVATIVES OR SALTS THEREOF

TECHNICAL FIELD

The present invention relates to pharmaceuticals and, more particularly, it relates to novel amide derivatives or salts thereof and also to therapeutic agents for diabetes mellitus containing them as effective components.

BACKGROUND OF THE INVENTION

Diabetes mellitus is a disease accompanied by continuous hyperglycemic state and is said to be resulted by action of many environmental factors and genetic factors. The main controlling factor for blood sugar is insulin, and it has been known that hyperglycemia is resulted by deficiency of insulin or by excess of factors which inhibit its action (such as genetic cause, lack of exercise, obesity and stress).

Diabetes mellitus is classified into two main types. One is insulin-dependent diabetes mellitus (IDDM) caused by a lowering of insulin-secreting function of pancreas due to autoimmune diseases, and another is non-insulin-dependent diabetes mellitus (NIDDM), caused by a lowering of insulin-secreting function of pancrease due to pancreatic fatigue accompanied by continuous high insulin secretion. 95% or more of diabetic paticnts in Japan are said to suffer from NIDDM, and an increase in the patients due to a change in daily life style is becoming a problem.

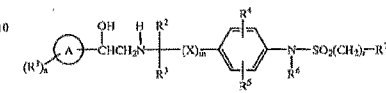
As to the therapy of diabetes mellitus, dietetic treatment, therapeutic exercise and remedy of obesity are mainly conducted in mild cases while, when the disease progresses, oral antidiabetic drugs (for example, insulin secretion promoters such as sulfonylurea compounds and insulin sensitivity potentiators which potentiate the sensitivity of insulin) are administered. In severe cases, an insulin preparation is administered. However, there has been a brisk demand for creation of the drugs whereby higher control for blood sugar is possible, and development of antidiabetic drugs having a new mechanism and having high usefulness has been demanded.

U.S. Pat. Nos. 4,396,627 and 4,478,849 describe phenylethanolamine derivatives and disclose that those compounds are useful as drugs for obesity and for hyperglycemia. Action of those compounds is reported to be due to a stimulating action to β_3-receptors. Incidentally, it has been known that β-adrenaline receptors are classified into β_1, β_2 and β_3 subtypes, that stimulation of β_1-receptor causes an increase in heart rate, that stimulation of β_2-receptor stimulates decomposition of glycogen in muscles, whereby synthesis of glycogen is inhibited, causing an action such as muscular tremor, and that stimulation of β_3-receptor shows an anti-obesity and an anti-hyperglycemia action (such as decrease in triglyceride, decrease in cholesterol and increase in HDL-cholesterol).

However, those β_3-agonists also have actions caused by stimulation of β_1- and β_2-receptors such as increase in heart rate and muscular tremor, and they have a problem in terms of side effects.

Recently, it was ascertained that β-receptors have differences to species, and it has been reported that even compounds having been confirmed to have a β_3-receptor selectivity in rodential animals such as rats show an action due to stimulating action to β_1- and β_2-receptors in human being. In view of the above, investigations for compounds having a stimulating action which is selective to β_3-receptor in human being have been conducted recently using human cells or cells where human receptors are expressed. For

example, WO 95/29159 describes substituted sulfonamide derivatives represented by the formula set forth below and discloses that due to their selective stimulating action to β_3-receptors in human being, they are useful against obesity, hyperglycemia, etc. However, this patent does not specifically disclose an insulin secretion promoting action and an insulin sensitivity potentiating action of those compounds.



(In the formula, the symbols should be referred to in the specification of this patent.)

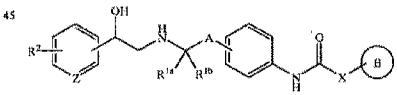
As such, there has been still a demand for creation of therapeutic agents for diabetes mellitus of a new type which have a highly clinical usefulness.

DISCLOSURE OF THE INVENTION

The present inventors have conducted an intensive investigation on compounds having both an insulin secretion promoting action and an insulin sensitivity potentiating action and found that novel amide derivatives show both a good insulin secretion promoting action and a good insulin sensitivity potentiating action and furthermore show a selective stimulating action to β_3-receptors, leading to accomplishment of the present invention.

That is, the present invention relates to an amide derivative represented by the general formula (I) set forth below or a salt thereof that is useful for the therapy of diabetes mellitus, having both an insulin secretion promoting action and an insulin sensitivity potentiating action and further having anti-obesity and anti-hyperlipemia actions due to a selective stimulating action to β_3-receptors. The present invention also relates to a pharmaceutical agent, particularly to a therapeutic agent for diabetes mellitus containing the amide derivative or the salt thereof as an effective ingredient.

(I)



(In the formula, each of the symbols means as follows:

ring B: a heteroaryl group which may be substituted and may be fused with a benzene ring;

X: a bond, lower alkylene or alkenylene which may be substituted with hydroxy or a lower alkyl group, carbonyl, or a group represented by —NH— (when X is a lower alkylene group which may be substituted with a lower alkyl group, the hydrogen atoms bonded to the carbon atom constituting the ring B may form a lower alkylene group together with the lower alkyl group so that a ring is formed);

A: lower alkylene or a group represented by -lower alkylene-O—;

R^{1a}, R^{1b}: they may be the same or different and each is a hydrogen atom or a lower alkyl group;

R^2: a hydrogen atom or a halogen atom; and

Z: a nitrogen atom or a group represented by =CH—.)

The compound of the general formula (I) is further illustrated as follows.

In the definitions used in the general formula in this specification, the term "lower" means a linear or branched hydrocarbon chain having from 1 to 6 carbon atoms unless otherwise specified.

Specific examples of the "lower alkyl group" are methyl, ethyl, and linear or branched propyl, butyl, pentyl and hexyl, preferably an alkyl having from 1 to 4 carbon atoms, and particularly preferably methyl, ethyl, propyl and isopropyl.

Examples of the "lower alkylene group" is a divalent group obtained by removing an arbitrary hydrogen atom(s) from the above "lower alkyl group", preferably an alkylene group having from 1 to 4 carbon atoms, and particularly preferably methylene, ethylene, propylene and butylene. Examples of the "lower alkenylene group" are vinylene, propenylene, butenylene, pentenylene and hexenylene groups.

The "heteroaryl group which may be fused with a benzene ring" in the "heteroaryl group which may be substituted and may be fused with a benzene ring" means a ring group where a benzene ring is fused with a heteroaryl group as mentioned later or a non-fused heteroaryl group.

Specific examples of the "ring group where the benzene ring is fused with a heteroaryl group" are fused-ring heteroaryl groups such as quinolyl, isoquinolyl, quinazolinyl, quinolidinyl, quinoxalinyl, cinnolinyl, benzimidazolyl, imidazopyridyl, benzofuranyl, benzoisoxazolyl, benzoxazolyl, benzothiazolyl, oxazolopyridyl, isothiazolopyridyl, benzothienyl, etc.; and oxo-added rings such as oxobenzofurayl, etc.

Examples of the "heteroaryl group" are monocyclic heteroaryl groups such as furyl, thienyl, pyrrolyl, imidazolyl, thiazolyl, pyrazolyl, isothiazolyl, isoxazolyl, pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, thiadiazolyl, triazolyl, tetrazolyl, etc.; and bicyclic heteroaryl groups such as naphthylidinyl, pyridopyrimidinyl, etc.

The substituent in the "heteroaryl group which may be substituted and may be fused with a benzene ring" may be any group which can be usually substituted in this ring group. Preferred examples are a halogen atom and lower alkyl, lower alkenyl, lower alkynyl, hydroxy, sulfanyl, halogeno lower alkyl, lower alkyl-O—, lower alkyl-S—, lower alkyl-O—CO—, carboxy, sulfonyl, sulfinyl, lower alkyl-SO—, lower alkyl-SO_2—, lower alkyl-CO—, lower alkyl-CO—O—, carbamoyl, lower alkyl-NH—CO—, di-lower alkyl-N—CO—, nitro, cyano, amino, guanidino, lower alkyl-CO—NH—, lower alkyl-SO_2—NH—, lower alkyl-NH—, di-lower alkyl-N—, —O-lower alkylene-O—, etc. These substituents may further be substituted with a substituent such as an aryl group, a heteroaryl group, a halogen atom, hydroxy, sulfanyl, halogeno lower alkyl, lower alkyl-O—, lower alkyl-S—, lower alkyl-O—CO—, carboxy, sulfonyl, sulfinyl, lower alkyl-SO—, lower alkyl-SO_2—, lower alkyl-CO—, lower alkyl-CO—O—, carbamoyl, lower alkyl-NH—CO—, di-lower alkyl-N—CO—, nitro, cyano, amino, guanidino, lower alkyl-CO—NH—, lower alkyl-SO_2—NH—, lower alkyl-NH—, di-lower alkyl-N—, etc. These substituents such as an aryl group, a heteroaryl group, etc. may further be substituted with a halogen atom, etc.

The "lower alkenyl group" is a linear or branched alkenyl group having 2 to 6 carbon atoms, and its specific examples are vinyl, propenyl, butenyl, pentenyl and hexenyl groups.

The "lower alkynyl group" is a linear or branched alkynyl group having 2 to 6 carbon atoms, and its specific examples are ethynyl, propynyl, butynyl, pentynyl and hexynyl.

The "halogen atom" means a fluorine atom, a chlorine atom, a bromine atom or an iodine atom, and the "halogeno lower alkyl group" means a group where an arbitrary hydrogen atom or atoms in the above-mentioned alkyl group is/are substituted with a halogen atom or atoms.

The case when X is a bond means that a carbon atom of the —CO— group is directly bonded to the ring B.

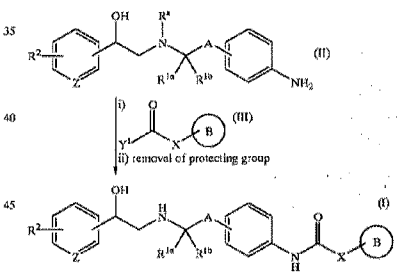
The compound (I) of the present invention has at least one asymmetric carbon atom and therefore, there are optical isomers such as (R)-compounds, (S)-compounds, etc., racemates, diastereomers, etc. The present invention includes all and each of isolated isomers and mixtures thereof. The present invention also includes hydrates, solvates (such as those with ethanol) and polymorphic substances of the compound (I).

The compound (I) of the present invention may form a salt with an acid. Examples of the salt are acid addition salts with mineral acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, phosphoric acid, etc.; and those with organic acids such as formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric aid, maleic acid, lactic acid, malic acid, citric acid, tartaric acid, carbonic acid, picric acid, methanesulfonic acid, ethanesulfonic acid, glutamic acid, etc.

Manufacturing Method

The compound of the present invention or the salt thereof may be manufactured by application of various synthetic methods utilizing the characteristics of its fundamental skeleton or type of the substituent. Representative manufacturing methods are illustrated as hereunder.

First Manufacturing Method



(In the formulae, R^{1a}, R^{1b}, R^2, A, B, X and Z have the same meanings as defined already; R^a is a protective group for amino; and Y^1 is a leaving group, and more specifically hydroxy, lower alkoxy or halide.)

In this method, the compound (II) and the compound (III) are subjected to amidation, and the protective group is then removed therefrom to synthesize the compound (I) of the present invention.

The amidation in this manufacturing method can be conducted by customary manners.

The solvent may vary depending upon Y^1 of the compound (III) and mostly, an inert solvent or an alcoholic solvent (such as isopropanol, etc.) may be applied.

When Y^1 is a hydroxy group, a method where the reaction is conducted in the above-mentioned solvent in the presence of a condensing agent may be applied. Examples of the condensing agent are N,N'-dicyclohexylcarbodiimide

(DCC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI), 1,1'-carbonyldiimidazole (CDI), diphenylphosphoryl azide (DPPA), diethylphosphoryl cyanide (DEPC), etc.

When Y^1 is lower alkoxy, a method where the reaction is conducted under heating or refluxing as it is or in the above-mentioned inert solvent may be applied.

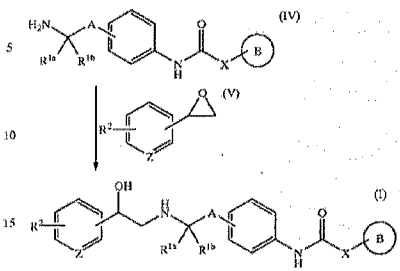
When Y^1 is halide, a method where the reaction is conducted in the above-mentioned inert solvent in the presence of a base may be applied.

Examples of the inert solvent are dimethylformamide (DMF), dimethylacetamide, tetrachloroethane, dichloromethane, dichloroethane, chloroform, carbon tetrachloride, tetrahydrofuran, dioxane, dimethoxyethane, ethyl acetate, benzene, toluene, xylene, acetonitrile, dimethyl sulfoxide, etc., and mixed solvents thereof, and they may be appropriately selected depending upon each reaction condition. Examples of the base are inorganic bases such as sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, etc.; and organic bases such as N-methylmorpholine, triethylamine, diisopropylethylamine, pyridine, etc.

The protective group of the amino represented by R^a means a protective group which is commonly used for amino by those skilled in the art, and its representative examples are acyl such as formyl, acetyl, propionyl, methoxyacetyl, methoxypropionyl, benzoyl, thienylacetyl, thiazolylacetyl, tetrazolylacetyl, thiazolylglyoxyloyl, thienylglyoxyloyl, etc.; lower alkoxycarbonyl such as methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl, etc.; aralkyloxy-carbonyl such as benzyloxycarbonyl, p-nitrobenzyloxycarbonyl, etc.; lower alkanesulfonyl such as methanesulfonyl, ethanesulfonyl, etc.; aralkyl such as benzyl, p-nitrobenzyl, benzhydryl, trityl, etc.; tri-(lower alkyl)silyl such as trimethylsilyl, etc.; and the like.

Removal of the protective group in this manufacturing method may be conducted by customary manners. For example, the protective group for amino represented by R^a may be easily removed, for example, by i) a method where in case that the protective group is benzhydryl, p-methoxybenzyl, trityl, tert-butoxycarbonyl, formyl, etc., treatment with an acid such as formic acid, trifluoroacetic acid, a trifluoroacetic acid-acisole mixed solution, a hydrobromic acid-acetic acid mixed solution, a hydrochloric acid-dioxane mixed solution, etc. is conducted; ii) a method where in case that the protective group is benzyl, p-nitrobenzyl, benzhydryl, trityl, etc., a catalytic reduction method using palladium-carbon or palladium hydroxide-carbon is conducted; and iii) a method where in case that the protective group is a tri-(lower alkyl) silyl or the like, treatment with water, fluoride anion (e.g., tetra-n-butylammonium fluoride, sodium fluoride, potassium fluoride, hydrofluoric acid), etc. is conducted.

Second Manufacturing Method



(In the formulae, R^{3a}, R^{1b}, R^2, A, B, X and Z have the same meanings as defined already.)

In this manufacturing method, the compound (IV) is reacted with the compound (V) to give the compound (I) of the present invention.

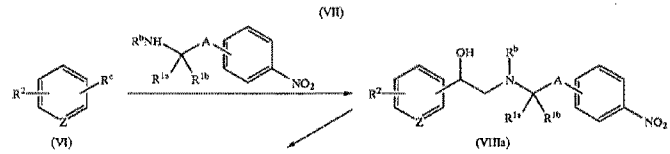
The amine compound (IV) and the compound (V) are reacted under heating or refluxing for 1 to 24 hours as they are or in an inert solvent, to give the compound (I) of the present invention.

Examples of the inert solvent are acetonitrile, tetrahydrofuran, 2-butanone, dimethyl sulfoxide and N-methylpyrrolidone. In the reaction, a base such as sodium bicarbonate, potassium carbonate or diisopropylethylamine may be added to the reaction mixture.

Incidentally, in the above manufacturing methods, it is possible to purify the resulting substance by removing undesired by-products by means of recrystallization, pulverization, preparative thin layer chromatography, silica gel flash chromatography (as described in W. C. Still, et al., *J. Org. Chem.*, 43, 2923 (1978)), medium-pressure liquid chromatography and HPLC. The compound produced through HPLC can be isolated as a corresponding salt.

The starting material used in the above-mentioned manufacturing methods may be easily manufactured by the methods which are known to those skilled in the art. One of the representative methods is shown as hereunder.

Manufacturing Method for the Starting Compound (II)



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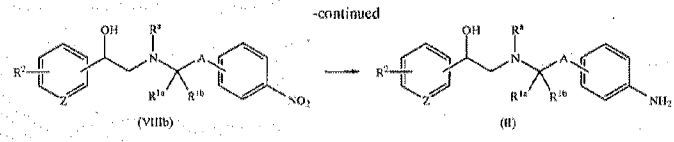


(VIIIb) (II)

(In the formulae, R^{1a}, R^{1b}, R^2, R^a, A and Z have the same meanings as defined already; R^b is a hydrogen atom or an aralkyl-based protective group for amino; and R^c is epoxy, 2-haloacetyl or 1-carboxymethan-1-ol.)

This manufacturing method is composed of from step (a) to step (c) in which the step (a) is a step where the compound (VI) is reacted with the compound (VII), followed by reduction reaction to give the compound (VIIIa) depending upon the type of R^c,; the step (b) is a step where protection is conducted when R^b of the compound (VIIIa) is a hydrogen atom; and the step (c) is a step where nitro is reduced to amino to give the compound (II).

Examples of the aralkyl-based protective group for amino used in this manufacturing method are benzyl, p-nitrobenzyl, benzhydryl, etc.

Step (a)

Illustration is made for the following three cases.

1) When R^c is epoxy, the compound (VI) may be reacted with the compound (VII) by the same manner as in the above-mentioned second manufacturing method. Reaction conditions such as reaction temperature, solvent, etc. are the same as well.

2) When R^c is 2-haloacetyl, the compound (VI) is reacted with the compound (VII) in the presence of a base, followed by reduction reaction to prepare the compound (VIIIa). The base is the same as that mentioned in the first manufacturing method. The reduction reaction may be conducted in the above-mentioned inert solvent or in a solvent of an alcohol type with stirring in the presence of a reducing agent. Examples of the reducing agent are sodium borohydride, sodium cyanoborohydride, lithium aluminum hydride, borane, etc.

3) When R^c is 1-carboxymethan-1-ol, the compound (VI) is reacted with the compound (VII) in the presence of a condensing agent, followed by reduction reaction in the same manner as in 2) to prepare the compound (VIIIa). The condensing agent is the same as that mentioned in the first manufacturing method.

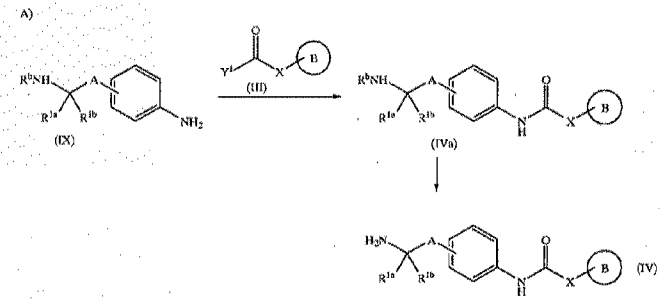
Step (b):

When R^b in the compound (VIIIa) is a hydrogen atom, the amino group is protected by customary manners using di-tert-butyl dicarbonate, etc., to prepare the compound (VIIIa).

Step (c):

A method for the reduction of nitro to amino may be conducted by customary manners such as metallic reduction using iron, zinc, etc. and catalytic reduction using a catalyst such as palladium-carbon, palladium hydroxide-carbon, Raney nickel, etc. R^a becomes a hydrogen atom depending upon the reduction conditions, but it may be protected again by customary manners.

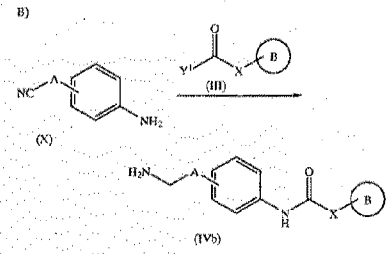
Manufacturing Method for Starting Compound (IV)



(IX) (III) (IVa) (IV)

(In the formulae, R^{1a}, R^{1b}, R^b, A, B, X and Y^1 have the same meanings as defined already.)

This reaction is a reaction where the compound (IX) and the compound (III) are subjected to amidation reaction to give a compound (IVa) and, when R^b is a protective group for amino, the protective group is removed to give a compound (IV). The amidation reaction can be conducted by the same manner as in the above-mentioned first manufacturing method, and the reaction conditions such as reaction temperature, solvent, etc. are the same as well.



This reaction is a reaction where the compound (X) and the compound (III) are subjected to amidation reaction and then to reduction reaction to give a compound (IVb). The amidation reaction can be conducted by the same manner as in the above-mentioned first manufacturing method, and the reaction conditions such as reaction temperature, solvent, etc. are the same as well. In the reduction reaction, the above-mentioned catalytic reduction, or a method where reduction is conducted using sodium borohydride in the presence of cobalt chloride, may be applied.

With regard to other compounds such as the compound (III), the compound (V), the compound (VI), and the compound (VII), those which are available in the market or are appropriately synthesized by known methods (such as N-alkylation reaction, cyclization reaction, hydrolysis reaction, etc.) from the commercially available compounds may be used.

The compound (I) of the present invention which is manufactured as such is isolated and purified as a free compound, a salt thereof obtained by means of salt formation by customary manners, a hydrate, a solvate with various solvents such as ethanol, etc., or polymorphic crystals, etc. The isolation and purification may be conducted by applying common chemical operations such as extraction, concentration, evaporation, crystallization, filtration, recrystallization, various chromatographic methods, etc.

Various isomers may be isolated by customary manners utilizing the physico-chemical differences between the isomers. For example, the racemate can be converted to stereochemically pure isomers by common racemic resolution (such as a method where the racemate is changed to diastereomer salts with usual optically active acid (for example, tartaric acid), followed by optical resolution, and the like). Incidentally, a mixture of diastereomers may be separated by customary method such as fractional crystallizaiton or chromatography, etc. In the case of an optically active compound, it may be manufactured starting from an appropriate optically active material.

Industrial Applicability

The phenethanol derivative of the present invention represented by the general formula (I) or the salt thereof has both an insulin secretion promoting action and an insulin sensitivity potentiating action and also has a selective β_3-receptor stimulating action, so that it is useful as a therapeutic agent for diabetes mellitus.

As confirmed by a glucose tolerance test and a hypoglycemic test in insulin-resisting model animals as described later, the compound of the present invention has both a good insulin secretion promoting action and a good insulin sensitivity potentiating action, so that its usefulness in diabetes mellitus is expected. Although the β_3-receptor stimulating action may have a possibility of participating in expression of the insulin secretion promoting action and the insulin sensitivity potentiating action, other mechanism might also possibly participate therein, and the details thereof have been still unknown yet. The β_3-receptor stimulating action of the compound of the present invention is selective to β_3-receptors in human being. It has been known that the stimulation of β_3-receptor stimulates decomposition of fat (decomposition of the fat tissue triglyceride into glycerol and free fatty acid), whereby a disappearance of fat mass is promoted. Therefore, the compound of the present invention has an anti-obesity action and an anti-hyperlipemia action (such as triglyceride lowering action, cholesterol lowering action and HDL cholesterol increasing action) and is useful as a preventive and therapeutic agent for obesity and hyperlipemia (such as hypertriglyceridemia, hypercholesterolemia and hypo-HDL-lipoproteinemia). Those diseases have been known as animus factors in diabetes mellitus, and amelioration of those diseases is useful for prevention and therapy of diabetes mellitus as well.

The compound of the present invention is also useful as a preventive and therapeutic agent for other diseases where the improvement of symptom can be achieved by reducing the symptoms of obesity and hyperlipemia such as ischemic coronary diseases such as arteriosclerosis, myocardial infarction, angina pectoris, etc. cerebral arteriosclerosis such as cerebral infarction, etc., or aneurysm, etc.

Further, the selective β_3-receptor stimulating action of the compound of the present invention is useful for prevention and therapy of s several diseases which have been reported to be improved by the stimulation of β_3-receptor. Examples of those diseases are shown as follows.

It has been mentioned that the β_3-receptor mediates the motility of non-sphincteral smooth muscle contraction, and because it is believed that the selective β_3-receptor stimulating action assists the pharmacological control of intestinal motility without being accompanied by cardiovascular action, the compound of the present invention has a possibility of being useful in therapy of the diseases caused by abnormal intestinal motility such as various gastrointestinal diseases including irritable colon syndrome. It is also useful as the therapy for peptic ulcer, esophagitis, gastritis and duodenitis (including that induced by *H. pylori*), enterekosis (such as inflammatory intestinal diseases, ulcerative colitis, clonal disease and proctitis).

It is further shown that the β_3-receptor affects the inhibition of release of neuropeptide of some sensory fibers in lung. The sensory nerve plays an important role in neurogenic inflammation of respiratory tract including cough, and therefore, the specific β_2-agonist of the present invention is useful in the therapy of neurogenic inflammation and in addition, has little action to cariopulmonary system.

Moreover, the β_3-adrenaline receptor is capable of resulting in a selective antidepressant action due to stimulation of the β_3-receptor in brain, and accordingly, the compound of the present invention has a possibility of being useful as an antidepressant.

The action of the compound of the present invention has been ascertained to be selective to β_3-receptors as a result of experiments using cells expressing human type receptors, and the adverse action caused by other β_3-receptor stimulation is low or none.

Effects of the compound of the present invention have been ascertained by the following tests.

1. Hypoglycemic Test in kk Mice (insulin-resisting model; Obesity and Hyperglycemia)

Male kk mice (blood sugar level: not lower than 200 mg/dl) were subjected to a measurement of blood sugar level under feeding and then randomly classified into groups. The drug to be tested was compulsorily administered orally or subcutaneously once daily for four days, and the blood sugar level after 15 to 18 hours from the final administration was compared with that before the administration (n=6). The blood was collected from a tail vein of the mice using a glass capillary (previously treated with heparin), the protein was removed therefrom, and the amount of glucose in the supernatant liquid (mg/dl) was measured by calorimetric determination by means of a glucose oxidase method. Further, a dose at which the blood sugar level was lowered by 30% as compared with that before the administration with the drug to be tested was expressed as an ED_{30} value.

As a result, the compound of the present invention significantly lowered the blood sugar level as compared with that before the administration with the drug to be tested in both cases of oral and subcutaneous administrations. In particular, some of the compounds of the present invention exhibited a strong activity so that the ED_{30} value in the oral administration was 3 mg/kg/day or less. On the other hand, in the above-referenced WO 95/29159, the compound of Example 90 had an ED_{30} value of 30 mg/kg/day or more, and the compound of Example 92 had an ED_{30} value of 30 mg/kg/day. From this fact, it has become clear that the compounds of the present invention have a superior potentiating action to insulin sensitivity as compared with those of the above-referenced WO 95/29159.

2. Glucose Tolerance Test in Normal Rats

Male rats of SD strain of seven weeks age were fasted for a whole day and night, then randomly classified into groups and subjected to an oral glucose tolerance test (OGTT) (n+4). The compound to be tested was administered orally or subcutaneously at 30 minutes before administration of glucose (2 g/kg by oral administration). The blood was collected from an abdominal aorta using a heparin-treated glass syringe from the rats which were anesthetized with pentobarbital (65 mg/kg), the protein was removed therefrom, and the amount of glucose in the supernatant liquid (mg/dl) was measured by colorimetric determination by means of a glucose oxidase method. The insulin value in blood was determined by measuring the amount of insulin in plasma (ng/ml) by means of radioimmunoassay (RIA).

As a result, in a group where the compound of the present invention was administered orally or subcutaneously, a significant increase in the insulin value in blood was observed as compared with the group to which no drug was given. An increase in the sugar blood level after administration of glucose was significantly inhibited as well. From those results, it is apparent that the compound of the present invention has a good insulin secretion promoting action and a good hyperglycemia inhibiting action.

3. Stimulating Test to Human β_3-, β_2- and β_1-receptors

Human β_3-stimulating action was investigated using an SK-N-MC cell system (cells in which human β_3-receptor and human β_1-receptor were permanently expressed were purchased) while human β_2- and β_1-stimulating actions were investigated using a CHO cell system (cells in which each of human β_2- and β_1-receptors was compulsorily expressed were purchased). Stimulating action of the compound (10^{-10} to 10^{-4} M) were investigated by incubating 10^5 cells/well of each of the cells on a 24-well plate and checking under a subconfluent state after two days using a producing activity of cyclic AMP (cAMP) as an index. Incidentally, the human β_3-stimulating action was investigated in the presence of a β_1-receptor blocker (CGP20712A, 10^{-6} M). Amount of production of cAMP in each cell (pmol/ml) was measured by an RIA method using ^{125}I-cAMP. Intensity of action of each compound was compared by calculating the pD2 value and the maximum activity (I.A. (%) where the maximum reaction of 10^{-6} M isoproterenol was defined as 100%) from the resulting dose-reaction curve.

As a result, it has been ascertained that the compound of the present invention has a selective stimulating action to human β_3-receptor.

A pharmaceutical composition containing one or more of the compound of the present invention or the salt thereof as an effective ingredient is prepared using common pharmaceutically acceptable vehicles. Administration of the pharmaceutical composition according to the present invention may be either by oral administration or by parenteral administration by, for example, injection, suppository, subcutaneous agent, inhaling agent or intracystic infusion.

The dose may be appropriately decided depending upon each particular case while taking into consideration symptom, age, sex, etc. of the patient but usually, is around 0.01 mg/kg to 100 mg/kg per day for adults in the case of oral administration, and that is administered at a time or by dividing into 2 to 4 times a day. When intravenous injection is conducted depending upon the symptom, the dose is usually around 0.001 mg/kg to 10 mg/kg per day for adults, and that is administered at a time or by dividing into two or more times a day.

With regard to a vehicle for the preparation, nontoxic solid or liquid substances for pharmaceuticals may be used.

Examples of the solid composition for use by means of oral administration according to the present invention are tablets, pills, capsules, diluted powder and granules. In such a solid composition, one or more active substances are mixed with at least one inert excipient such as lactose, mannitol, glucose, hydroxypropyl cellulose, microcrystalline cellulose, starch, polyvinylpyrrolidone, agar, pectin, magnesium metasilicate aluminate and magnesium aluminate. The composition may also contain additives other than the inert excipient such as lubricants such as magnesium stearate; disintegrants such as calcium cellulose glycolate; stabilizers such as lactose; and auxiliary solubilizers such as glutamic acid or aspartic acid by customary manners. Tablets and pills may, if necessary, be coated with sugar coat such as sucrose, gelatin, hydroxypropyl cellulose, hydroxypropylmethyl cellulose phthalate, etc., or with film of gastric or enteric coating substances.

The liquid composition for oral administration includes pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs and contains commonly used inert excipients such as purified water or ethanol. In addition to the inert excipient, the composition may further contain auxiliary agents such as moisturizing or suspending agents, sweeteners, tasting agents, aromatic agents and antiseptic agents. The injection for parenteral administration includes aseptic aqueous or non-aqueous solutions, suspensions and emulsions. The non-aqueous solutions and suspensions include, for example, distilled water for injection and a physiological saline solution. Examples of the solvent for non-aqueous solution and suspension are propylene glycol; polyethylene glycol; plant oils such as cacao butter, olive oil and sesame oil; alcohols such as ethanol; gum arabic; and Polysolvate 80 (trade name). Such a composition may further contain auxiliary agents such as isotonizing agents; antiseptic agents; moisturizing agents; emulsifiers; dispersing agents; stabilizers such as lactose; and auxiliary solubi-

lizers such as glutamic acid and aspartic acid). These may be sterilized, for example, by filtration passing through a bacteria-preserving filter or by compounding of or irradiation with a bactericide. These may also be used by manufacturing a sterile solid composition, followed by dissolving in sterile water or a sterile solvent for injection before use.

Best Mode for Carrying Out the Invention

The present invention is further illustrated by way of Examples as hereunder. Compounds of the present invention are not limited to those mentioned in the following Examples but cover all of the compounds represented by the above general formula (I), salts thereof, hydrates thereof, geometric and optical isomers thereof and polymorphic forms thereof. Incidentally, the case where the material which is used in the present invention is novel is illustrated by way of the following Referential Example.

REFERENTIAL EXAMPLE 1

To a mixed solution of ethyl acetate and a 1N aqueous solution of sodium hydroxide was added 25.2 g of 4-nitrophenyl ethylamine hydrochloride, and the mixture was vigorously stirred. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated. To the resulting residue were added 100 ml of 2-propanol and 15.0 g of (R)-styrene oxide successively, and the reaction mixture was heated to reflux for 12 hours. The solvent was evaporated in vacuo, and the residue was purified by silica gel column chromatography (eluent: chloroform/methanol=100/1→10/1) The resulting residue was again subjected to silica gel column chromatography (eluent: hexane/ethyl acetate/triethylamine=1/5/trace) to give 8.05 g of (R)-1-phenyl-2-[[2-(4-nitrophenyl) ethyl] amino]ethanol.

REFERENTIAL EXAMPLE 2

A solution of 8.02 g of (R)-1-phenyl-2-[[2-(4-nitrophenyl) ethyl]amino]ethanol and 6.30 g of di-tert-butyl dicarbonate in 80 ml of tetrahydrofuran was stirred for 12 hours at room temperature. The residue obtained by evaporation of the solvent was purified by silica gel column chromatography (eluent: hexane/ethyl acetate=3/1) to give 10.8 g of tert-butyl (R)-N-(2-hydroxy-2-phenylethyl)-N-[2-(4-nitro-phenyl) ethyl]carbamate.

REFERENTIAL EXAMPLE 3

To a solution of tert-butyl (R)-N-(2-hydroxy-2-phenylethyl)-N-[2-(4-nitrophenyl)ethyl]carbamate in 200 ml of ethanol was added 1.03 g of 10% palladium-carbon and the mixture was stirred for two hours at room temperature in a hydrogen atmosphere under atmospheric pressure. Insoluble matters were removed using Celite, and the filtrate was concentrated in vacuo to give 9.54 g of tert-butyl (R)-N-[2-(4-aminophenyl)-N-(2-hydroxy-2-phenylethyl) ethyl]-carbamate.

REFERENTIAL EXAMPLE 4

To a solution of 448 mg of tert-butyl (R)-N-[2-(4-aminophenyl)-N-(2-hydroxy-2-phenylethyl)ethyl] carbamate and 330 mg of triethylamine in 4 ml of chloroform was added 146 mg of 2-pyridinecarbonyl chloride. The reaction solution was stirred at room temperature for two hours, and the solvent was evaporated in vacuo. The residue was diluted with chloroform, and the organic layer was washed with a saturated aqueous solution of sodium hydrogen carbonate and dried over anhydrous magnesium sulfate. The residue obtained by evaporating the solvent in vacuo was purified by silica gel column chromatography (eluent: hexane/ethyl acetate=1/3) to give 321 mg of tert-butyl (R)-N-(2-hydroxy-2-phenylethyl)-N-[2-[4-[(2-pyridinecarbonyl)amino]phenyl]ethyl]carbamate.

REFERENTIAL EXAMPLE 5

To a solution of 377 mg of tert-butyl (R)-N-[2-(4-aminophenyl)-N-(2-hydroxy-2-phenylethyl)ethyl] carbamate in 10 ml of tetrahydrofuran were added 203 mg of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, 143 mg of 1-hydroxybenzotriazole and 202 mg of 8-quinolinecarboxylic acid successively. The reaction solution was stirred at room temperature for 18.5 hours, and the solvent was evaporated in vacuo. The residue was diluted with ethyl acetate, and the organic layer was washed with a saturated aqueous solution of sodium hydrogen carbonate and dried over anhydrous magnesium sulfate. The residue obtained by evaporation of the solvent was purified by silica gel column chromatography (eluent: hexane/ethyl acetate=2/1) to give 302 mg of tert-butyl (R)-N-(2-hydroxy-2-phenylethyl)-N-[2-[4-[(8-quinolinecarbonyl)amino] phenyl]ethyl]carbamate.

REFERENTIAL EXAMPLE 6

To a solution of 403 mg of tert-butyl (R)-N-(2-hydroxy-2-phenylethyl)-N-[2-[4-[(2-1H-imidazol-2-ylacetyl)amino] phenyl]ethyl]carbamate in 10 ml of acetonitrile were added 120 mg of potassium carbonate and 164 mg of 2-fluorobenzyl bromide successively at room temperature. The reaction solution was stirred at 50° C. for 12 hours. Insoluble matters were filtered off using Celite, and the solvent was evaporated. The resulting residue was purified by silica gel column chromatography to give 253 mg of tert-butyl (R)-N-[2-[4-[[2-[1-(2-fluorobenzyl)-1H-imidazol-2-yl]-acetyl]amino]phenyl]ethyl]-N-(2-hydroxy-2-phenylethyl)-carbamate.

REFERENTIAL EXAMPLE 7

To a solution of 13.4 g of (R)-2-[N-benzyl-N-[2-(4-nitrophenyl)ethyl]amino]-1-phenylethanol in 150 ml of methanol were added 8.6 g of iron powder and 40 ml of a 2N aqueous hydrochloric acid solution. The reaction mixture was heated to reflux for two hours, a 1N aqueous solution of sodium hydroxide was added thereto, and the insoluble matters thus produced were filtered off using Celite. The filtrate was concentrated in vacuo to remove the methanol. The resulting aqueous phase was extracted with chloroform, the organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated in vacuo. The resulting residue was purified by silica gel column chromatography (eluent: hexane/ethyl acetate=1/1) to give 11.45 g of (R)-2-[N-[2-(4-amino-phenyl)ethyl]-N-benzylamino]-1-phenylethanol.

REFERENTIAL EXAMPLE 8

To 502 mg of (R)-2-[N-[2-(4-aminophenyl)ethyl]-N-benzylamino]-1-phenylethanol were added 336 mg of ethyl 2-(3-methylpyridin-2-yl)acetate and 10 ml of xylene. The reaction mixture was refluxed for nine hours, and the solvent was evaporated in vacuo. The resulting residue was purified by silica gel column chromatography (eluent: hexane/ethyl acetate=1/3) to give 222 mg of (R)-4'-[2-[N-benzyl-N-(2-hydroxy-2-phenylethyl)amino]ethyl3-2-(3-methylpyridin-2-yl)acetanilide.

REFERENTIAL EXAMPLE 9

To a solution of 0.96 g of 2-fluoroacetophenone in 20 ml of tetrahydrofuran was added 2.65 g of benzyltrimethylammonium tribromide. The reaction mixture was stirred at room temperature for 30 minutes, insoluble matters were filtered off, and the solvent was concentrated in vacuo. The resulting residue was dissolved in 40 ml of 2-butanone, then 1.81 g of N-benzyl-4-nitrophenethylamine and 0.92 g of diisopropyl ethylamine were added, and the reaction mixture was heated to reflux for one hour. The solvent was evaporated in vacuo, ethyl acetate was added thereto, and the mixture was washed with water and a saturated saline solution successively. The organic layer was dried over anhydrous magnesium sulfate and evaporated in vacuo. The resulting residue was dissolved in 40 ml of methanol, 0.34 g of sodium borohydride was added thereto, and the reaction mixture was stirred at room temperature for one hour. The solvent was evaporated in vacuo, ethyl acetate was added, and the mixture was washed with water and a saturated saline solution successively. The organic layer was dried over anhydrous magnesium sulfate and evaporated in vacuo. The resulting residue was purified by silica gel column chromatography (eluent: chloroform) to give 1.95 g of 2-[N-benzyl-N-[2-(4-nitrophenyl)ethyl]amino]-1-(2-fluorophenyl)ethanol.

REFERENTIAL EXAMPLE 10

A reaction mixture of 5.12 g of methyl 2-pyridylacetate, 5.14 g of 4-aminobenzyl cyanide and 50 ml of xylene was heated to reflux for 24 hours. An appropriate amount of the solvent was evaporated, diethyl ether was added to the residue, and the resulting crystals were taken by filtration to give 5.65 g of 4'-cyanomethyl-2-(2-pyridyl)acetanilide.

REFERENTIAL EXAMPLE 11

To a solution of 640 mg of 4'-cyanomethyl-2-(4,6-dimethyl-2-pyridyl)acetanilide in 15 ml of tetrahydrofuran was added 15 ml of an ethanolic suspension of a Raney nickel, and concentrated aqueous ammonia was added to adjust the pH of the mixture to about 10. The mixture was stirred at room temperature for one hour in a hydrogen atmosphere under atmospheric pressure. The reaction mixture was filtered using Celite, and the solvent was evaporated in vacuo to give 640 mg of 4'-(2-aminomethyl)-2-(4,6-dimethyl-2-pyridyl)acetanilide.

REFERENTIAL EXAMPLE 12

To a solution of 630 mg of 4'-(2-aminomethyl)-2-(4,6-dimethyl-2-pyridyl)acetanilide in 20 ml of toluene was added 0.27 ml of benzaldehyde, and the mixture was heated to reflux for three hours using a Dean-Starke apparatus. The reaction mixture was filtered, and the solvent was evaporated in vacuo. A solution of the resulting residue in 30 ml of methanol was cooled at 0° C., 63 mg of sodium borohydride was added, and the mixture was stirred at 0° C. for one hour. About one-half of the solvent of the reaction mixture was evaporated in vacuo, water and ethyl acetate were added to the residue, the organic layer was washed with a saturated saline solution twice and dried over anhydrous magnesium sulfate and the solvent was evaporated in vacuo. To a solution of the resulting residue in 50 ml of isopropanol was added 0.26 ml of (R)-styrene oxide, and the mixture was heated to reflux for 12 hours. The solvent was evaporated in vacuo, and the resulting residue was purified by silica gel column chromatography (eluent: chloroform/methanol=100/3) to give 920 mg of (R)-4'-[2-[N-benzyl-N-(2-hydroxy-2-phenylethyl)-amino]ethyl]-2-(4,6-dimethyl-2-pyridyl)acetanilide.

EXAMPLE 1

A 4N hydrogen chloride-ethyl acetate solution (10 ml) was added to 10 ml of an ethanolic solution of 458 mg of tert-butyl (R)-N-(2-hydroxy-2-phenylethyl)-N-[2-[4-[(2-pyridinecarbonyl)amino]phenyl]ethyl]carbamate. The reaction solution was stirred at room temperature for three hours, and the solvent was then evaporated in vacuo. The obtained crude crystals were recrystallized from methanol-ethanol-ethyl acetate to give 289 mg of (R)-4'-[2-[(2-hydroxy-2-phenyl-ethyl)amino]ethyl]-2-pyridinecarboxanilide dihydrochloride.

The compounds of Examples 2 to 33 were prepared by the same manner as in Example 1.

EXAMPLE 2

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-3-pyridinecarboxanilide dihydrochloride

EXAMPLE 3

(R)-41-[2-[(2-Hydroxy-2-phenylethyl)aminoethyl]-8-quinolinecarboxanilide dihydrochloride

EXAMPLE 4

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-(E)-3-(2-pyridyl)acrylic anilide dihydrochloride

EXAMPLE 5

(R)-2-(Benzothiazol-2-yl)-4'-[2-[(2-hydroxy-2-phenyl-ethyl)amino]ethyl]acetanilide dihydrochloride

EXAMPLE 6

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(imidazo[2,1-b]thiazol-3-yl)acetanilide dihydrochloride

EXAMPLE 7

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(2-methylthiazol-4-yl)acetanilide hydrochloride

EXAMPLE 8

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(1H-imidazol-2-yl)acetanilide dihydrochloride

EXAMPLE 9

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(1H-tetrazol-5-yl)acetanilide hydrochloride

EXAMPLE 10

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(5-sulfanyl-1H-1,2,4-triazol-3-yl)acetanilide hydrochloride

EXAMPLE 11

(R)-2-(2-Aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenyl-ethyl)amino]ethyl]-2-oxoacetanilide dihydrochloride

EXAMPLE 12

(R)-2-(5-Amino-1,2,4-thiadiazol-3-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

EXAMPLE 13

(R)-2-(5-Ethoxycarbonylamino-1,2,4-thiadiazol-3-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl] acetanilide hydrochloride

EXAMPLE 14

(R)-2-[(2-(3-Fluorophenylamino) thiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

EXAMPLE 15

(R)-2-(2-Chloropyridin-6-yl)-4'-[2-[(2-hydroxy-2-phenyl-ethyl)amino]ethyl]acetanilide hydrochloride

EXAMPLE 16

(R)-2-(2-Benzyloxypyridin-6-yl)-4'-(2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide hydrochloride

EXAMPLE 17

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-[1-(2-methyl-3-propenyl)-1H-imidazol-2-yl) acetanilide dihydrochloride

EXAMPLE 18

(R)-2-(1-Benzyl-1H-imidazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

EXAMPLE 19

(R)-2-[1-(2-Chlorobenzyl)-1H-imidazol-4-yl]-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

EXAMPLE 20

(R)-2-[1-(3-Chlorobenzyl)-1H-imidazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

EXAMPLE 21

(R)-2-[1-(4-Chlorobenzyl)-1H-imidazol-4-yl]-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydro-chloride

EXAMPLE 22

(R)-2-[1-(4-Fluorobenzyl)-1H-imidazol-2-yl]-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

EXAMPLE 23

(R)-2-[1-(4-Chlorobenzyl)-1H-imidazol-2-yl]-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

EXAMPLE 24

(R)-2-[1-(4-Bromobenzyl)-1H-imidazol-2-yl]-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

EXAMPLE 25

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-[1-(4-iodobenzyl)-1H-imidazol-2-yl]acetanilide dihydrochloride

EXAMPLE 26

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-[1-(4-trifluoromethylbenzyl)-1H-imidazol-2-yl] acetanilide dihydrochloride

EXAMPLE 27

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-[1-(2-naphthyl)-1H-imidazol-2-yl]acetanilide dihydrochloride

EXAMPLE 28

(R)-2-[1-(4-Fluorobenzyl)-5-methyl-1H-imidazol-2-yl]-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl] acetanilide dihydrochloride

EXAMPLE 29

(R)-2-[1-(4-Fluorobenzyl)-4-methyl-1H-imidazol-2-yl]-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl] acetanilide dihydrochloride

EXAMPLE 30

(R)-2-[1-(4-Fluorobenzyl)-1H-tetrazol-5-yl]-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide hydrochloride

EXAMPLE 31

(R)-2-[2-(3,4-Dichlorobenzyl)-1H-tetrazol-5-yl]-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl] acetanilide hydrochloride

EXAMPLE 32

(R)-2-[2-(4-Fluorobenzyl)-1H-tetrazol-5-yl]-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide hydrochloride

EXAMPLE 33

(R)-2-[1-(3,4-Dichlorobenzyl)-1H-tetrazol-5-yl]-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl] acetanilide hydrochloride

EXAMPLE 34

To a solution of 175 mg of tert-butyl (R)-N-[2-[4-[2-(1H-1,2,4-triazol-3-yl)acetylaminolphenyl]ethyl]N-(2-hydroxy-2-phenylethyl) carbamate in 5 ml of methanol was added 4 ml of a solution of 4N hydrogen chloride in ethyl acetate. The mixture was stirred at room temperature for three hours, the solvent was filtered off, and the resulting powder was washed with ethanol. The resulting powder was dried to give 125 mg of (R)-4'-[2-[(2-hydroxy-2-phenylethyl)amino] ethyl]-2-(1H-1,2,4-triazol-3-yl)acetanilide dihydrochloride.

The compounds of Examples 35 to 40 were prepared by the same manner as in Example 34.

EXAMPLE 35

(R)-2-(5-Benzylsulfanyl-1H-1,2,4-triazol-3-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

EXAMPLE 36

(R)-2-(2-Acetamidothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide hydrochloride

EXAMPLE 37

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(2-methanesulfonamidothiazol-4-yl)acetanilide hydrochloride

EXAMPLE 38

(R)-2-(2-Guanidinothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

EXAMPLE 39

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)aminolethyl]-2-(2-phenylaminothiazol-4-yl)acetanilide hydrochloride

EXAMPLE 40

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-[1-(4-nitrobenzyl)-1H-imidazol-2-yl]acetanilide hydrochloride

EXAMPLE 41

To 690 mg of tert-butyl (R)-N-[2-[4-[2-(2-amino-thiazol-4-yl)acetamino]phenyl]ethyl]-N-[(2-hydroxy-2-phenyl) ethyl]carbamate were added 30 ml of methanol and 15 ml of a solution of 4N hydrogen chloride in ethyl acetate, and the mixture was stirred at room temperature for two hours. The solvent was evaporated in vacuo, and the residue was purified by a reverses phase column chromatography (eluent: water/methanol 2/1) to give 310 mg of (R)-2-(2-aminothiazol-4-yl)-4'-[2-(2-hydroxy-2-phenylethyl)amino]-ethyl]acetanilide dihydrochloride.

The compounds of Examples 42 to 57 were prepared by the same manner as in Example 41.

EXAMPLE 42

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-(2-amino-thiazol-4-yl)carboxanilide hydrochloride

EXAMPLE 43

(R)-2-(2-Amino-5-methylthiazol-4-yl)-4'-2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

EXAMPLE 44

(R)-2-(2-Aminothiazol-4-yl)-2-methyl-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]propionanilide hydrochloride

EXAMPLE 45

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-(2-amino-4,5,6,7-tetrahydrobenzothiazol-4-yl) carboxanilide dihydrochloride

EXAMPLE 46

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(imidazo[2,1-b]thiazol-6-yl)acetanilide hydrochloride

EXAMPLE 47

(R)-2-(2-Benzyl-1H-1,2,4-triazol-3-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide hydrochloride

EXAMPLE 48

(R)-2-(1-Benzyl-1H-1,2,4-triazol-3-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide hydrochloride

EXAMPLE 49

(R)-2-(3-Benzyl-2-thioxothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide hydrochloride

EXAMPLE 50

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-(5,6,7,8-tetrahydroquinolin-8-yl)carboxanilide dihydrochloride

EXAMPLE 51

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(1-phenyl-1H-imidazol-2-yl)acetanilide dihydrochloride

EXAMPLE 52

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-[(1-(4-isopropylbenzyl)-1H-imidazol-2-yl) acetanilide dihydrochloride

EXAMPLE 53

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-[(1-(4-phenylbenzyl)-1H-imidazol-2-yl)acetanilide dihydrochloride

EXAMPLE 54

(R)-2-[1-(2-Chlorobenzyl)-1H-imidazol-2-yl]-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

EXAMPLE 55

(R)-2-[1-(3-Chlorobenzyl)-1H-imidazol-2-yl]-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

EXAMPLE 56

(R)-2-[1-(3,4-Dichlorobenzyl)-1H-imidazol-2-yl]-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl] acetanilide dihydrochloride

EXAMPLE 57

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-[(1-(2-pyridyl)methyl-1H-imidazol-2-yl) acetanilide dihydrochloride

The compound of Example 58 was prepared by the same manner as in Example 1.

EXAMPLE 58

(R)-2-(2-aminopyridin-6-yl)-4'-[2-[(2-hydroxy-2-phenyl-ethyl)amino]ethyl]acetanilide dihydrochloride

EXAMPLE 59

To a solution of tert-butyl (R)-N-[2-[4-[[2-(2-amino-thiazol-4-yl)-2-oxoacetyl]amino]phenyl]ethyl]-N-(2-hydroxy-2-phenylethyl) carbamate in 30 ml of methanol was added 130 mg of sodium borohydride at room temperature. The reaction mixture was stirred at room temperature for three hours, and the solvent was evaporated in vacuo. The residue was dissolved in 5 ml of methanol, and to this reaction solution was added 10 ml of a solution of 4N hydrogen chloride-ethyl acetate. The reaction solution was stirred at room temperature for eight hours and the solvent was evaporated in vacuo. The residue was purified by silica gel column chromatography (eluent: chloroform/methanol=5/1). The resulting residue was purified by reversed phase column chromatography (eluent: water/methanol=2/1) to give 77 mg of (R)-2-(2-amino-thiazol-4-yl)-2-hydroxy-4'-[2-(2-hydroxy-2-phenylethyl)-amino]acetanilide hydrochloride

EXAMPLE 60

To 349 mg of tert-butyl (R)-N-[2-[4-[[2-(2-benzyl-oxypyridin-6-yl)acetyl]amino]phenyl]ethyl]-N-(2-hydroxy-2-phenylethyl) carbamate were added 478 mg of pentam-ethylbenzene and 5 ml of trifluoroacetic acid successively. The reaction solution was stirred at room temperature for four hours, and the solvent was evaporated in vacuo. To the residue were added water and potassium carbonate to make the solution basic, and the aqueous phase was extracted with a mixed solvent of chloroform and tetrahydrofuran. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated in vacuo. The residue was purified by silica gel column chromatography (eluent: chloroform/methanol=10/1→5/1). To an ethanolic solution of the resulting residue was added 100 μl of a 4N hydrogen chloride-ethyl acetate solution, and then the solvent was evaporated in vacuo. The resulting crude crystals were recrystallized from ethanol-ethyl acetate to give 65 mg of (R)-2-(2-benzyloxypyridin-6-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide hydrochloride.

The compounds of Examples 61 to 76, 83 and 85 were prepared by the same manner as in Example 1; and the compounds of Examples 77 to 82 were prepared by the same manner as in Example 41.

EXAMPLE 61

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)aminolethyl]-2-(2-methylpropyl-1H-imidazol-2-yl)acetanilide dihydrochloride

EXAMPLE 62

(R)-2-[1-(2-Fluorobenzyl)-1H-imidazol-2-yl]-4'-[2-(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

EXAMPLE 63

(R)-[1-(3-Fluorobenzyl)-1H-imidazol-2-yl]-4'-[2-(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

EXAMPLE 64

(R)-2-[1-(2,4-Difluorobenzyl)-1H-imidazol-2-yl]-4'-[2-(2-hydroxy-2-phenylethyl)amino]ethyl] acetanilide dihydrochloride

EXAMPLE 65

(R)-2-[1-(2,6-Difluorobenzyl)-1H-imidazol-2-yl]-4'-[2-(2-hydroxy-2-phenylethyl)amino]ethyl] acetanilide dihydrochloride

EXAMPLE 66

(R)-2-[1-(3,5-Difluorobenzyl)-1H-imidazol-2-yl]-4'-[2-(2-hydroxy-2-phenylethyl)amino]ethyl] acetanilide dihydrochloride

EXAMPLE 67

(R)-2-[1-(2,5-Difluorobenzyl)-1H-imidazol-2-yl])-4'-[2-(2-hydroxy-2-phenylethyl)amino]ethyl] acetanilide dihydrochloride

EXAMPLE 68

(R)-2-[1-(3,4-Difluorobenzyl)-1H-imidazol-2-yl3-4'-[2-(2-hydroxy-2-phenylethyl)amino]ethyl] acetanilide dihydrochloride

EXAMPLE 69

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-[1-(2,3,6-trifluorobenzyl)-1H-imidazol-2-yl] acetanilide dihydrochloride

EXAMPLE 70

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-[1-(2,4,5-trifluorobenzyl)-1H-imidazol-2-yl] acetanilide dihydrochloride

EXAMPLE 71

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-[1-(3,4,5-trifluorobenzyl)-1H-imidazol-2-yl] acetanilide dihydrochloride

EXAMPLE 72

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-[1-(2,3,4,5,6-pentafluorobenzyl)-1H-imidazol-2-yl]acetanilide dihydrochloride

EXAMPLE 73

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-[1-(3-iodobenzyl)-1H-imidazol-2-yl]acetanilide dihydrochloride

EXAMPLE 74

(R)-2-[1-(2,6-Dichlorobenzyl)-1H-imidazol-2-yl]-4'-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide hydrochloride

EXAMPLE 75

(R)-2-[1-(4-Cyanobenzyl)-1H-imidazol-2-yl]-4'-[2-(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

EXAMPLE 76

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-[1-(quinolin-2-yl)-1H-imidazol-2-yl]acetanilide trihydrochloride

EXAMPLE 77

(R)-2-[1-(2-Chloro-6-fluorobenzyl)-1H-imidazol-2-yl]-4'-[2-(2-hydroxy-2-phenylethyl)amino]ethyl] acetanilide

EXAMPLE 78

(R)-2-[1-(2-Chloro-4-fluorobenzyl)-1H-imidazol-2-yl]-4'-[2-(2-hydroxy-2-phenylethyl)amino]ethyl] acetanilide

EXAMPLE 79

(R)-2-[1-(2,5-Dichiorobenzyl)-1H-imidazol-2-yl]-4'-[2-(2-hydroxy-2-phenylethyl)amino]ethyl] acetanilide dihydrochloride

EXAMPLE 80

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-[1-(2,3,4-trifluorobenzyl)-1H-imidazol-2-yl] acetanilide dihydrochloride

EXAMPLE 81

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-[1-(4-methoxycarbonylbenzyl)-1H-imidazol-2-yl] acetanilide dihydrochloride

EXAMPLE 82

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-[1-[(piperidine-1-carbonyl)benzyl]-1H-imidazol-2-yl]acetanilide dihydrochloride

EXAMPLE 83

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(1-pyrazolyl)acetanilide hydrochloride

EXAMPLE 84

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(1,2,4-triazol-1-yl)acetanilide dihydrochloride

EXAMPLE 85

(R)-2-(2-Aminobenzimidazol-1-yl)-4'-[(2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

EXAMPLE 86

To a solution of 20.1 g of 4'-[2-[N-benzyl-N-(2-hydroxy-2-phenylethyl)amino]ethyl]-2-(2-pyridyl) acetanilide in 400

ml of methanol was added 5.96 g of 10% palladium-carbon. The reaction solution was stirred for six hours in a hydrogen atmosphere under atmospheric pressure. Insoluble matters were filtered off using Celite and the filtrate was concentrated in vacuo. To a methanolic solution of the resulting residue was added 10.8 ml of a 4N hydrogen chloride-ethyl acetate solution, and the solvent was evaporated in vacuo. The resulting crude crystals were recrystallized from methanol-ethanol to give (R)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]-2-(2-pyridyl)acetanilide hydrochloride.

The compounds of 87 to 90 were prepared by the same manner as in Example 86.

EXAMPLE 87

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(3-pyridyl)acetanilide hydrochloride

EXAMPLE 88

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(4-pyridyl)acetanilide hydrochloride

EXAMPLE 89

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-3-(2-pyridyl)propionanilide hydrochloride

EXAMPLE 90

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-[(1-phenylethyl)-1H-imidazol-2-yl]acetanilide dihydrochloride

EXAMPLE 91

(R)-2-(1H-Benzimidazol-2-yl)-4'-[4-[2-[N-benzyl-N-(2-hydroxy-2-phenylethyl)amino]ethyl]phenyl]acetanilide (240 mg) was dissolved in 30 ml of ethanol, then 170 mg of 10% palladium-carbon was added thereto and the mixture was stirred for nine hours in a hydrogen atmosphere under atmospheric pressure. The catalyst was filtered off, the solvent was evaporated in vacuo, and the residue was washed with ethanol-ethyl acetate to give 200 mg of (R)-2-(1H-benzimidazol-2-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]-ethyl]acetanilide.

The compounds of Examples 92 and 93 were prepared by the same manner as in Example 86.

EXAMPLE 92

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(3-methylpyridin-2-yl]acetanilide hydrochloride

EXAMPLE 93

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(2-pyrazinyl)acetanilide hydrochloride

EXAMPLE 94

(R)-4'-[4-[2-[N-Benzyl-N-(2-hydroxy-2-phenylethyl)-amino]ethyl]phenyl]-2-(1-benzyl-1H-imidazol-2-yl) acetanilide (350 mg) was dissolved in 20 ml of ethanol, then 130 mg of 10% palladium-carbon was added thereto, and the mixture was stirred for 17.5 hours in a hydrogen atmosphere under atmospheric pressure. The catalyst was filtered off, the solvent was evaporated in vacuo, and the residue was purified by silica gel column chromatography (eluent: chloroform/methanol/concentrated aqueous ammonia=200/10/1). The resulting oily substance was dissolved in methanol, and 280 μl of a 4N hydrogen chloride-ethyl acetate solution was added thereto. The mixture was filtered after adding active carbon was added thereto, and the solvent was evaporated in vacuo to give 200 mg of (R)-2-(1-benzyl-1H-imidazol-2-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride.

The compounds of Examples 95 and 97 were prepared by the same manner as in Example 91; the compounds of Examples 98 and 100 were prepared by the same manner as in Example 94; and the compounds of Examples 99 and 101 to 103 were prepared by the same manner as in Example 86.

EXAMPLE 95

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(4-methyl-2-pyridyl)acetanilide

EXAMPLE 96

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(5-methyl-2-pyridyl)acetanilide

EXAMPLE 97

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(6-methyl-2-pyridyl)acetanilide

EXAMPLE 98

4'-[(R)-2-[((R)-2-Hydroxy-2-phenylethyl)amino]propyl]-2-(2-pyridyl)acetanilide hydrochloride

EXAMPLE 99

4'-[(S)-2-[((R)-2-Hydroxy-2-phenylethyl)aminolpropyl]-2-(2-pyridyl)acetanilide hydrochloride

EXAMPLE 100

2-(1-Benzyl-1H-imidazol-2-yl)-4'-[(S)-2-[((R)-2-hydroxy-2-phenylethyl)amino]propyl]acetanilide hydrochloride

EXAMPLE 101

4'-[2-[[2-Hydroxy-2-(2-fluorophenyl)ethyl]amino]ethyl]-2-(2-pyridyl)acetanilide hydrochloride

EXAMPLE 102

4'-[2-[[2-Hydroxy-2-(3-fluorophenyl)ethyl]amino]ethyl]-2-(2-pyridyl)acetanilide hydrochloride

EXAMPLE 103

4'-[2-[[2-Hydroxy-2-(4-fluorophenyl)ethyl]amino]ethyl]-2-(2-pyridyl)acetanilide hydrochloride

EXAMPLE 104

To a solution of 805 mg of 4'-cyanomethyl-2-(2-pyrimidinyl)acetanilide in 30 ml of tetrahydrofuran were added 30 ml of an ethanolic solution of a Raney nickel and 3 ml of concentrated aqueous ammonia. The reaction solution was stirred for four hours in a hydrogen atmosphere under atmospheric pressure, then insoluble matters were filtered off using Celite, and the solvent was evaporated. To the resulting residue were added 10 ml of 2-propanol, 300 mg of (R)-styrene oxide and 2 ml of methanol successively. The reaction mixture was heated to reflux for ten hours, and the solvent was evaporated. The residue was purified by silica gel column chromatography (eluent: chloroform/methanol=10/1). To a methanolic solution of the resulting residue was added 150 μl of 4N hydrogen chloride-ethyl acetate solution, and the solvent was evaporated in vacuo. The resulting residue was crystallized from methanol-ethanol-ethyl acetate and then recrystallized from ethanol-diethyl ether to give 160 mg of (R)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]-2-(2-pyrimidinyl]acetanilide hydrochloride.

The compounds of Examples 105 to 108 were prepared by the same manner as in Example 104; and the compound of Example 109 was prepared by the same manner as in Example 91.

EXAMPLE 105

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(2-quinolyl)acetanilide hydrochloride

EXAMPLE 106

(R)-4'-[2-[[2-Hydroxy-2-(3-chlorophenyl)ethyl]amino]-ethyl]-2-(2-pyridyl)acetanilide hydrochloride

EXAMPLE 107

4'-[2-[[2-Hydroxy-2-(3-pyridyl)ethyl]amino]ethyl]-2-(2-pyridyl)acetanilide hydrochloride

EXAMPLE 108

(R)-2-[1-(4-Chlorobenzyl)-1H-benzimidazol-2-yl]-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

EXAMPLE 109

(R)-2-(4,6-Dimethyl-2-pyridyl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide

EXAMPLE 110

To 4'-(3-aminopropyl)-2-(2-pyridyl)acetanilide were added 10 ml of 2-propanol and 600 mg of (R)-styrene oxide successively. The reaction mixture was heated to reflux for four hours, and the solvent was evaporated. The residue was purified by silica gel column chromatography (eluent: chloroform/methanol=30/1Δ10/1). To a methanolic solution of the resulting residue was added 100 μl of a 4N hydrogen chloride-ethyl acetate solution, and the solvent was evaporated in vacuo. The resulting crude crystals were recrystallized from ethanol-diethyl ether to give 71 mg of (R)-4'-[3-[(2-hydroxy-2-phenylethyl)amino]propyl]-2-(2-pyridyl) acetanilide hydrochloride.

EXAMPLE 111

To a solution of 3.62 g of tert-butyl N-[2-[4-[[2-(2-pyridyl)acetyl]amino]phenoxy]ethyl]carbamate in 30 ml of methanol was added 50 ml of a 4N hydrochloride-ethyl acetate solution. After the reaction solution was stirred at room temperature for eight hours, the solvent was evaporated in vacuo. To the residue were added an aqueous solution of sodium hydrogen carbonate and potassium carbonate to adjust to pH about 12. The resulting aqueous phase was extracted with a mixed solvent of chloroform and tetrahydrofuran. The organic layer was dried over anhydrous magnesium sulfate and concentrated, the resulting residue was dissolved in 40 ml of methanol, and 1.02 g of (R)-styrene oxide was added thereto. After the reaction solution was heated to reflux for 26 hours, the solvent was evaporated in vacuo. The resulting residue was purified by silica gel column chromatography (eluent: chloroform/methanol=30/1→10/1) and dissolved in methanol, 0.59 ml of a 4N hydrogen chloride-ethyl acetate solution was added, and the solvent was evaporated in vacuo. The resulting crude crystals were recrystallized from methanol-ethanol to give 320 mg of (R)-4'-[2-[(2-hydroxy-2-phenylethyl)-amino]ethoxy]-2-(2-pyridyl)acetanilide hydrochloride

EXAMPLE 112

To a solution of 490 mg of tert-butyl N-[1,1-di-methyl-2-[4-[[2-(2-pyridyl)acetyl]amino]phenyl]ethyl]-carbamate in 10 ml of methanol was added 30 ml of a 4N hydrochloride-ethyl acetate solution. After the reaction solution was stirred at room temperature for eight hours, the solvent was evaporated in vacuo. To the residue were added an aqueous solution of sodium hydrogen carbonate and potassium carbonate to adjust to pH about 12. The resulting aqueous phase was extracted with a mixed solvent of chloroform and tetrahydrofuran. The organic layer was dried over anhydrous magnesium sulfate and concentrated, the resulting residue was dissolved in 2 ml of 2-propanol and 2 ml of methanol, and 120 mg of (R)-styrene oxide was added thereto. After the reaction solution was heated to reflux for 24 hours, the solvent was evaporated in vacuo. The resulting residue was purified by silica gel column chromatography (eluent: chloroform/methanol=30/1→15/1) and dissolved in methanol, 0.1 ml of a 4N hydrogen chloride-ethyl acetate solution was added, and the solvent was evaporated in vacuo. The resulting residue was purified by silica gel column chromatography (eluent: chloroform/methanol=5/1) and a reversed phase column chromatography (eluent: water/methanol=2/1→1/1) to give 35 mg of (R)-4'-[2,2-dimethyl-2-[(2-hydroxy-2-phenylethyl)amino]ethyl]-2-(2-pyridyl)acetanilide hydrochloride.

The compound of Example 113 was prepared by the same manner as in Example 1.

EXAMPLE 113

(R)-1-(4-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]phenyl]-3-(2-pyridyl)urea dihydrochloride

As hereunder, physical and chemical properties of the compounds of the Referential Examples are given in Tables 1 and those of the compounds of the Examples are given in Tables 2.

The symbols in the tables have the following meanings.

Rex.: Referential Example No.

Ex.: Example No.

DATA: Physico-chemical properties

NMR: Nucleomagnetic resonance spectrum (TMS internal standard; DMSO-d was used as a solvent unless otherwise specified)

mp: melting point

dec: decomposition

MS (m/z): mass spectrographic data (m/z)

Structure: structural formula

TABLE 1

Rex.	DATA
1	NMR ($CDCl_3$) δ: 2.75(1H, dd, J=12.4, 8.8Hz), 2.85–3.04 (5H, m), 4.70(1H, dd, J=8.8, 3.7Hz), 7.24–7.40(7H, m), 8.10–8.20 (2H, m)
2	NMR ($CDCl_3$) δ: 1.44(9H, s), 2.75–3.10(2H, m), 3.20–3.70 (4H, m), 4.93(1H, br), 7.25–7.40(7H, m), 8.14(2H, d, J=8.4Hz)
3	NMR ($CDCl_3$) δ: 1.47(9H, s), 2.55–2.80(2H, m), 3.20–3.40 (2H, m), 3.45–3.65(2H, m), 4.87(1H, m), 6.57–6.65(2H, m), 6.83–7.04(2H, m), 7.25–7.40(5H, m)
4	NMR ($CDCl_3$) δ: 1.47(9H, s), 2.62–2.93(2H, m), 3.14–3.58 (4H, m), 4.35(1H, brs), 4.90(1H, br), 7.06–7.40(7H, m), 7.45–7.50 (1H, m), 7.67–7.72(2H, m), 7.90(1H, d, J=2.0, 8.0Hz), 8.25–8.31 (1H, m), 8.58–8.63(1H, m), 9.98(1H, brs)
5	NMR ($CDCl_3$) δ: 1.49(9H, s), 2.64–2.90(2H, m), 3.16–3.60 (4H, m), 4.38(1H, brs), 4.91(1H, br), 7.10–7.42(7H, m), 7.55(1H, dd, J=8.0, 4.4Hz), 7.74(1H, t, J=8.0Hz), 7.77–7.84(2H, m), 8.01(1H, d, J=8.0, 1.2Hz), 8.34(1H, d, J=8.4, 1.6Hz), 8.96(1H, d, J=7.6, 1.6Hz), 9.02(1H, d, J=4.4, 2.0Hz), 13.61(1H, brs)
6	NMR ($CDCl_3$) δ: 1.47(9H, s), 2.60–2.80(2H, m), 3.15–3.55 (4H, m), 3.78(2H, s), 4.36(1H, brs), 4.82–4.94(1H, m), 5.18 (2H, s), 6.92–6.99(2H, m), 7.00–7.13(5H, m), 7.25–7.38 (6H, m), 7.42–7.48(2H, m), 10.34(1H, brs)
7	NMR ($CDCl_3$) δ: 2.56–2.94(6H, m), 3.40–3.65(2H, m), 3.80(1H, brs), 3.95(1H, d, 13.6Hz), 4.62(1H, dd, J=10.0, 3.2Hz), 6.57–6.66(2H, m), 6.87–6.98(2H, m), 7.20–7.37(10H, m)
8	NMR ($CDCl_3$) δ: 2.40(3H, s), 2.54–3.00(6H, m), 3.57(1H, d, J=13.6Hz), 3.88(2H, s), 3.95(1H, d, J=13.6Hz), 4.62(1H, dd, J=10.4, 3.6Hz), 7.00–7.75(16H, m), 8.44(1H, d, J=4.4Hz), 9.66(1H, brs)
9	NMR ($CDCl_3$) δ: 2.58–2.65(1H, m), 2.75–3.00(5H, m), 3.59(1H, d, J=13.2Hz), 3.95(1H, d, J=13.2Hz), 5.01(1H, dd, J=10.0, 3.2Hz), 6.97–7.03(1H, m), 7.12–7.35(9H, m), 7.48–7.56(1H, m), 8.04–8.13(2H, m)
10	NMR ($CDCl_3$) δ: 3.70(2H, s), 3.88(2H, s), 7.23–7.32 (4H, m), 7.54–7.62(2H, m), 7.71(1H, dt, J=7.6, 1.6Hz), 8.63(1H, d), 10.04(1H, brs)
11	NMR ($CDCl_3$) δ: 2.26(3H, s), 2.39(3H, s), 2.57(2H, t, J=7.2Hz), 2.72(2H, t, J=7.2Hz), 3.72(2H, s), 6.95(1H, s), 7.01(1H, s), 7.11(2H, d, J=8.8Hz), 7.51(2H, d, J=8.8Hz), 10.17(1H, s)
12	NMR δ: 2.32(3H, s), 2.41(3H, s), 2.90–3.19(6H, m), 3.75(2H, s), 4.01(2H, s), 4.89(1H, dt, J=7.6, 3.2Hz), 6.99–7.71(16H, m), 10.26(1H, s)

TABLE 2

Ex.	DATA
1	mp: 223–225° C., NMR δ: 2.95–3.28(6H, m), 4.98–5.07(1H, m), 7.23–7.44(6H, m), 7.65–7.75(1H, m), 7.88(2H, d, J=8.4Hz), 8.05–8.22(2H, m), 8.75(1H, d, J=4.4Hz), 8.97(1H, brs), 9.43(1H, brs), 10.65(1H, brs)
2	mp: 263–265° C., NMR δ: 2.92–3.10(3H, m), 3.13–3.27(3H, m), 5.00(1H, dd, J=10.8, 2.8Hz), 7.24–7.44(8H, m), 7.74–7.81(3H, m), 8.57(1H, d, J=8.0Hz), 8.81–8.96(2H, m), 9.20–9.30(2H, m), 10.71(1H, brs)
3	mp: 145–147° C., NMR δ: 2.94–3.10(3H, m), 3.14–3.30(3H, m), 4.97–5.05(1H, m), 7.27–7.46(7H, m), 7.77–7.90(4H, m), 8.30(1H, dd, J=8.4, 1.6Hz), 8.60–8.71(2H, m), 8.89(1H, brs), 9.40–9.30(2H, m), 13.12(1H, brs)
4	mp: 246–248° C. (dec), NMR δ: 2.92–3.09(3H, m), 3.11–3.26(3H, m), 5.03(1H, dd, J=10.4, 2.8Hz), 7.24(2H, d, J=8.4Hz), 7.29–7.47(6H, m), 7.56–7.75(4H, m), 7.85(1H, d, J=8.0Hz), 8.11(1H, t, J=7.6Hz), 8.73(1H, d, J=4.4Hz), 8.92 (1H, brs), 9.32(1H, brs), 10.69(1H, brs)
5	mp: 228–233° C. (dec), NMR δ: 2.88–3.09(3H, m), 3.10–3.24(3H, m), 4.30(2H, s), 4.93–5.01(1H, m), 6.19(1H, d, J=3.6Hz), 7.18–7.27(2H, m), 7.28–7.53(7H, m), 7.57–7.62(2H, m), 7.97(1H, d, J=7.6Hz), 8.08(1H, d, J=8.0Hz), 8.83(1H, brs), 9.31(1H, brs), 10.57(1H, brs)
6	mp: 161–162° C., NMR δ: 2.86–3.24(6H, m), 4.2492H, s), 4.97(1H, dd, J=9.6, 2.8Hz), 7.16–7.23(2H, m), 7.27–7.44 (5H, m), 7.55(1H, s), 7.61(2H, d, J=8.4Hz), 7.85(1H, s), 8.27(1H, d, J=2.4Hz), 8.97(1H, brs), 9.47(1H, brs), 10.94(1H, brs)
7	NMR δ: 2.70(3H, s), 2.86–3.27(6H, m), 3.85(2H, s), 5.00–5.05(1H, m), 7.18–7.60(10H, m), 10.43(1H, s)
8	mp: 203–207° C., NMR δ: 2.92–3.08(3H, m), 3.10–3.22(3H, m), 4.28(2H, s), 5.01(1H, d, J=7.8Hz), 6.21(1H, brs), 7.22(2H, d, J=8.3Hz), 7.25–7.63(4H, m), 8.93(1H, brs), 9.38(1H, brs), 10.86(1H, s)
9	mp: 259–261° C., NMR δ: 2.90–3.10(3H, m), 3.10–3.25(3H, m), 4.15(2H, s), 4.97(1H, d, J=10.8Hz), 6.20(1H, d, J=3.9Hz), 7.21(2H, 3, J=8.8Hz), 7.30–7.42(5H, m), 7.57(2H, d, J=8.8Hz), 8.85(1H, brs), 9.14(1H, brs), 10.58(1H, s)
10	mp: 210–213° C., NMR δ: 2.86–3.08(3H, m), 3.12–3.22(3H, m), 3.73(2H, s), 4.91–4.98(1H, m), 6.19(1H, d, J=3.9Hz), 7.21(2H, d, J=8.3Hz), 7.29–7.42(5H, m), 7.54(2H,d, J=8.3Hz), 8.78(1H, brs), 8.99(1H, brs), 10.35(1H, s), 13.21(1H, brs), 13.34(1H, brs)
11	mp: 205–210° C. (dec), NMR δ: 2.90–3.25(6H, m), 4.95–5.04(1H, m), 7.23–7.44(7H, m), 7.67–7.75(2H, m), 8.15(1H, s), 8.88(1H, brs), 9.25(1H, brs)
12	mp: 244–246° C., NMR δ: 2.90–3.08(3H, m), 3.10–3.20(3H, m), 3.67(2H, s), 5.00(1H, dd, J=24, 10.02Hz), 7.192H, d, J=8.3Hz), 7.28–7.42(5H, m), 7.57(2H, d, J=8.3Hz), 8.90(1H, s), 9.31(1H, s), 10.31(1H, s)
13	mp: 205–208° C., NMR δ: 1.27(3H, t, J=7.1Hz), 2.88–3.08(3H, m), 3.12–3.22(3H, m), 3.86(2H, s), 4.27(2H, q, J=7.1 Hz), 4.96(1H, d, J=8.3Hz), 6.20(1H, s), 7.19(2H, d, J=8.3Hz), 7.30–7.42(5H, m), 7.57(2H, d, J=8.3Hz), 8.81(1H, s), 9.10(1H, s), 10.33(1H, s), 12.53(1H, s)

TABLE 2-continued

Ex.	DATA
14	mp: 169–173° C., NMR δ: 2.88–3.22(6H, m), 3.66(2H, s), 4.98(1H, dd, J=2.9, 13.1Hz), 6.72(1H, s), 7.19(2H, d, J=8.3Hz), 7.23–7.42(8H, m), 7.59(2H, d, J=8.3Hz), 7.72–7.78(1H, m), 8.85(1H, s), 9.18(1H, brs), 10.24(1H, brs), 10.55 (1H, s)
15	mp: 248–251° C., NMR δ: 2.90–3.08(3H, m), 3.09–3.21(3H, m), 3.88(2H, s), 5.02(1H, dd, J=10.0, 2.4Hz), 6.20(1H, brs), 7.16–7.22(2H, m), 7.28–7.46(7H, m), 7.57–7.63(2H, m), 7.84(1H, t, J=7.2Hz), 8.95(1H, brs), 9.40(1H, brs), 10.48 (1H, brs)
16	mp: 237–238° C., NMR δ: 2.87–3.24(6H, m), 3.77(2H, s), 4.93–5.03(1H, m), 5.32(2H, s), 6.20(1H, d, J=4.0Hz), 6.73 (1H, d, J=8.0Hz), 6.99(1H, d, J=7.2Hz), 7.16–7.22(2H, m), 7.25–7.46(10H, m), 7.57–7.63(2H, s), 7.67(1H, dd, J=8.4, 7.2Hz), 8.87(1H, brs), 9.24(1H, brs), 10.30(1H, brs)
17	mp: 190–193° C., NMR δ: 1.68(3H, m), 2.90–3.10(3H, m), 3.10–3.30(3H, m), 4.32(2H, s), 4.67(1H, s), 4.83(2H, s), 4.94(1H, s), 4.99(1H, d, J=8.3Hz), 6.21(1H, brs), 7.21(2H, d, J=8.7Hz), 7.24–7.42(5H, m), 7.55(2H, d, J=8.8Hz), 7.66 (2H, d, J=1.9Hz), 7.71(1H, d, J=1.9Hz), 8.89(1H, brs), 9.30(1H, brs), 10.92(1H, s)
18	mp: 139–141° C., NMR δ: 3.01(3H, brs), 3.15(3H, brs), 3.92(2H, s), 5.05(1H, d, J=10.3Hz), 5.44(2H, s), 6.19(1H, brs), 7.19(2H, d, J=8.3Hz), 7.31–7.47(10H, m), 7.60(2H, d, J=8.3Hz), 7.66(1H, s), 9.05(1H, brs), 9.35(1H, s), 9.60(1H, brs), 10.76(1H, s)
19	mp: 140–143° C., NMR δ: 2.99–3.09(3H, m), 3.16(3H, brs), 3.95(2H, s), 5.06(1H, d, J=10.4Hz), 5.57(2H, s), 6.19(1H, brs), 7.19(2H, d, J=8.6Hz), 7.29–7.35(1H, m), 7.37–7.48(8H, m), 7.55–7.57(1H, m), 7.61(2H, d, J=8.6Hz), 9.09(1H, brs), 9.31(1H, d, J=1.5Hz), 9.65(1H, brs), 10.79(1H, s)
20	mp: 140–143° C., NMR δ: 3.01–3.09(3H, m), 3.16(3H, brs), 3.93(2H, s), 5.06(1H, d, J=10.3Hz), 5.47(2H, s), 6.15 (1H, brs), 7.19(2H, d, J=8.6Hz), 7.29–7.33(1H, m), 7.38–7.46(7H, m), 7.61(2H, d, J=8.6Hz), 7.63(1H, s), 7.70(1H, s), 9.08 (1H, brs), 9.38(1H, s), 9.63(1H, brs), 10.78(1H, s)
21	mp: 141–146° C., NMR δ: 2.96–3.14 (3H, m), 3.15(3H, brs), 3.91(2H, s), 5.04(1H, d, J=10.3Hz), 5.45(2H, s), 6.22 (1H, brs), 7.19(2H, d, J=8.6Hz), 7.29–7.42(6H, m), 7.50(3H, s), 7.59(2H, d, J=8.6Hz), 7.65(1H, s), .02(1H, brs), 9.32 (1H, d, J=1.5Hz), 9.55(1H, brs), 10.73(1H, s)
22	mp: 230–235° C., NMR δ: 2.89–3.10(3H, m), 3.10–3.25(3H, m), 4.47(2H, s), 5.01(1H, dd, J=10.3, 2.4Hz), 5.45(2H, s), 6.21(1H, brs), 7.16–7.22(4H, m), 7.28–7.53(7H, m), 7.54(2H, d, J=8.3Hz), 7.68(2H, dd, J=5.8, 1.9Hz), 8.94(1H, brs), 9.42(1H, brs), 10.98(1H, s)
23	mP: 203–209° C., NMR δ: 2.90–3.10(3H, m), 3.10–3.20(3H, m), 4.43–4.48(2H, m), 4.95–5.05(1H, m), 5.46(2H, s), 6.21(1H, brs), 7.20(2H, d, J=8.6Hz), 7.30–7.42(5H, m), 7.50–7.54(2H, m), 7.70(2H, s), 8.92(1H, brs), 9.39(1H, brs), 10.88–10.95(1H, m)
24	mp: 221–223° C., NMR δ: 2.90–3.08(3H, m), 3.10–3.22(3H,m), 4.04(2H, s), 4.97(1H, d, J=9.1Hz), 5.44(2H, s), 6.20 (1H, brs), 7.20(2H, d, J=8.1Hz), 7.30–7.41(9H, m), 7.49(2H, d, J=8.6Hz), 7.55(2H, d, J=8.6Hz), 8.83(1H, brs), 9.16 (1H, brs), 10.76(1H, s)
25	mp: 222–225° C., NMR δ: 2.60–3.05(3H, m), 3.10–3.20(3H, m), 4.43(2H, s), 5.01(1H, d, J=7.6Hz), 5.44(2H, s), 6.21 (1H, brs), 7.15–7.23(4H, m), 7.26–7.46(5H, m), 7.51(2H, d, J=8.8Hz), 7.65–7.72(4H, m), 8.94(1H, brs), 9.41(1H, brs), 10.93(1H, s), 14.72(1H, brs)
26	mp: 197–203° C., NMR δ: 2.80–3.10(3H, m), 3.10–3.25(3H, m), 4.44(2H, s), 4.99(1H, d, J=8.0Hz), 5.61(2H, s), 6.21 (1H, brs), 7.17(2H, d, J=8.6Hz), 7.30–7.42(5H, m), 7.48(2H, d, J=8.5Hz), 7.54(2H, d, J=8.0Hz), 7.70(2H, d, J=8.1Hz), 7.72–7.77(2H, m), 8.90(1H, brs), 9.34(1H, brs), 10.90(1H, s)
27	mp: 208–214° C., NMR δ: 2.90–3.10(3H, m), 3.10–3.22(3H, m), 4.44(2H, s), 4.97(1H, d, J=9.7Hz), 5.62(2H, s), 6.20 (1H, brs), 7.16(2H, d, J=8.0Hz), 7.30–7.55(10H, m), 7.70–7.94(6H, m), 8.82(1H, brs), 9.14(1H, brs), 10.76(1H, s)
28	mp: 219–223° C., NMR δ: 2.11(3H, s), 2.92–3.08(3H, m), 3.10–3.20(3H, m), 4.43(2H, s), 5.02(1H, dd, J=10.2, 2.4 Hz), 5.51(2H, s), 6.22(1H, brs), 7.14–7.34(7H, m), 7.36–7.42(4H, m), 7.48–7.53(3H, m), 8.95(1H, brs), 9.43(1H, brs), 10.94 (1H, s), 14.61(1H, brs)
29	mp: 204–207° C., NMR δ: 2.24(3H, s), 2.80–3.10(3H, m), 3.10–3.50(3H, m), 4.43(2H, s), 5.01(1H, dd, J=10.3, 2.5Hz), 5.39(2H, s), 6.21(1H, brs), 7.17–7.24(2H, m), 7.47(2H, dd, J=8.8, 5.4Hz), 7.552H, d, J=8.3Hz), 8.94(1H, brs), 9.40(1H, brs), 13.00(1H, s), 14.70(1H, brs)
30	mp: 225–228° C., NMR δ: 2.90–3.07(3H, m), 3.10–3.23(3H, m), 4.28(2H, s), 4.97(1H, d, J=10.3Hz), 5.68(2H, s), 6.20(1H, d, J=3.4Hz), 7.16–7.23(4H, m), 7.30–7.46(7H, m), 7.53(2H, d, J=8.8Hz), 8.82(1H, brs), 9.11(1H, brs), 10.63(1H, s)
31	mp: 232–235° C., NMR δ: 2.90–3.10(3H,m), 3.10–3.25(3H, m), 4.03(2H, s), 4.98(1H, d, J=10.3Hz), 5.97(2H, s), 6.20(1H, brs), 7.19(2H, d, J=8.3Hz), 7.29–7.42(6H, m), 7.55(2H, d, J=8.3Hz), 7.67–7.77(2H, m), 8.87(1H, brs), 9.22(1H, brs), 10.49(1H, s), 14.61(1H, brs)
32	mp: 233–235° C., NMR δ: 2.09–3.10(3H, m), 3.10–3.25(3H, m), 4.01(2H, s), 4.98(1H, d, J=10.3Hz), 5.91(2H, s), 6.19(1H, brs), 7.17–7.48(11H, m), 7.55(2H, d, J=8.3Hz), 8.85(1H, brs), 9.18(1H, brs), 10.47(1H, s)
33	mp: 240–242° C., NMR δ: 2.90–3.10(3H, m), 3.10–3.25(3H, m), 4.32(2H, s), 4.98(1H, dt, J=10.3, 3.4Hz), 5.72(2H, s), 6.20(1H, d, J=3.9Hz), 7.20(2H, d, J=8.3Hz), 7.30–7.40(6H, m), 7.51(2H, d, J=8.8Hz), 7.62(1H, d, J=8.3Hz), 7.67 (1H, d, J=2.0Hz), 8.86(1H, brs), 9.17(1H, brs), 10.67(1H, s)
34	mp: 221–224° C., NMR δ: 2.90–3.07(3H, m), 3.10–3.20(3H, m), 4.05(2H, s), 5.00(2H, dd, J=2.7, 10.2Hz), 7.21(2H, d, J=8.6Hz), 7.29–7.42(5H,m), 7.58(2H, d, J=8.6Hz), 8.83(1H, s), 8.93(1H, brs), 9.32(1H, brs), 10.62(1H, s)
35	mp: 222–224° C., NMR δ: 2.89–3.07(3H, m), 3.12–3.21(3H, m), 3.84(2H, s), 4.33(2H, s), 4.58(1H, dd, J=2.4, 10.2 Hz), 7.20(2H, d, J=8.3Hz), 7.22–7.42(10H, m), 7.58(2H, d, J=8.3Hz), 8.87(1H, brs), 9.22(1H, brs), 10.44(1H, s)
36	mp: 242–245° C., NMR δ: 2.11(3H, s), 2.99–3.06(3H, m), 3.09–3.21(3H, m), 3.68(2H, s), 5.00(1H, dd, J=2.1, 10.2Hz), 6.02(1H, brs), 6.98(1H, s), 7.18(2H, d, J=8.1Hz), 7.28–7.42(5H, m), 7.58(2H, d, J=8.1Hz), 8.89(1H, brs), 9.30(1H, brs), 10.25(1H, s), 12.10(1H, s)
37	mp: 252–256° C., NMR δ: 2.89(3H, s), 2.91–3.07(3H, m), 3.11–3.21(3H, m), 3.65(2H, s), 4.95–5.02(1H, m), 6.20 (1H, brs), 6.58(1H, s), 7.20(2H, d, J=8.6Hz), 7.28–7.42(5H, m), 7.57(2H, d, J=8.6Hz), 8.87(1H, brs), 9.24(1H, brs), 10.39 (1H, s), 12.56(1H, s)
38	mp: >230° C. (dec.), NMR δ: 2.68–3.22(6H,m), 3.73(2H, s), 3.65(2H, s), 5.00(1H, dd, J=2.0, 10.0Hz), 6.20(1H, brs), 7.12(1H, s), 7.18(2H, d, J=8.8Hz), 7.28–7.42(5H, m), 7.59(2H, d, J=8.8Hz). 8.39(4H, brs), 8.93(1H, brs), 9.32(1H, brs), 10.41(1H, s), 12.60(1H, s)
39	mp: 177–181° c., NMR δ: 2.90–3.10(3H, m), 3.10–3.25(3H, m), 3.67(2H, s), 5.00(1H, dd, J1=10.0, 2.0Hz), 6.68 (1H, s), 6.97(1H, t, J=7.2Hz), 7.19(2H, d, J=8.4Hz), 7.27–7.42(9H, m), 7.59(2H, d, J=8.0Hz), 8.90(1H, brs), 9.29(1H, brs), 10.29(1H, s), 10.54(1H, brs)
40	mp: 237–243° C., NMR δ: 2.90–3.06(3H, m), 3.06–3.20(3H, m), 4.45(2H, s), 5.01(1H, dd, J=7.8, 2.0Hz), 5.70(2H, s), 6.21(1H, brs), 7.14(2H, d, J=8.8Hz), 7.29–7.42(5H, m), 7.46(2H, d, J=8.8Hz), 7.54(2H, d, J=8.8Hz), 7.77(2H, dd, J=14.6, 2.0Hz), 8.13(2H, d, J=8.4Hz), 8.94(1H, brs), 9.41(1H, brs), 10.95(1H, s)

TABLE 2-continued

Ex.	DATA
41	mp: 151–159° C., NMR δ: 2.90–3.10(3H, m), 3.30–3.20(3H, m), 3.76(2H, s), 5.02(1H, dd, J=10.2, 2.7Hz), 6.70(1H, s), 7.20(2H, d, J=8.8Hz), 7.25–7.40(5H, m), 7.59(2H, d, J=8.8Hz), 8.96(1H, brs), 9.21(1H, brs), 9.43(1H, brs), 10.58 (1H, s)
42	mp: 205–209° C., NMR δ: 2.90–3.08(3H, m), 3.13–3.23(3H, m), 4.92–4.97(1H, m), 6.20(1H, brs), 7.19–7.42(10H, m), 7.71(2H, d, J=8.8Hz), 8.76(1H, brs), 8.92(1H, brs), 9.65(1H, s)
43	NMR δ: 2.20(3H, s), 2.90–3.07(3H, m), 3.10–3.20(3H, m), 3.74(2H, s), 5.00(1H, dd, J=2.5, 10.3Hz), 7.20(2H, d, J=8.8 Hz), 7.28–7.42(5H, m), 7.59(2H, d, J=8.8Hz), 8.91(1H, brs), 9.13(1H, brs), 9.33(1H, brs), 10.58(1H, s)
44	NMR δ: 1.48(6H, s), 2.86–3.22(6H,m), 4.90–4.96(1H, m), 6.19(1H, brs), 6.40(1H, brs), 7.17(2H, d, J=8.8Hz), 7.27–7.41(5H, m), 7.56(2H, d, J=8.8Hz), 8.74(1H, brs), 8.90(1H, brs), 9.53(1H, brs)
45	NMR δ: 1.68–2.12(4H,m), 2.43–2.59(2H, m), 2.91–3.07(3H, m), 3.11–3.20(3H, m), 3.76–3.81(1H, m), 5.00(1H, d, J= 2.5, 10.3Hz), 6.20(1H, brs), 7.19(2H, d, J=8.3Hz), 7.27–7.42(5H, m), 7.60(1H, d, J=8.3Hz), 8.90(1H, brs), 9.33(1H, brs), 10.43(1H, s)
46	NMR δ: 2.88–3.24(6H, m), 3.83(2H, s), 4.95–5.04(1H, m), 6.19(1H, brs), 7.16–7.22(2H, m), 7.26–7.45(6H, m), 7.55–7.63(2H, m), 7.87(1H, s), 8.04(1H, d, J=3.6Hz), 8.91(1H, brs), 9.32(1H, brs), 10.42(1H, brs)
47	MS (m/z): 456[(M+H)$^+$], NMR δ: 2.84–3.19(6H, m), 4.03(2H, s), 4.87–4.97(1H, m), 5.43(2H, s), 6.12(2H, s), 7.20 (2H, d, J=8.3Hz), 7.25–7.41(11H, m), 7.53(2H, d, J=8.3Hz), 7.90(1H, s), 10.38(1H, s)
48	NMR δ: 2.88–3.18(6H, m), 3.69(2H, s), 4.87–4.95(1H, m), 5.36(2H, s), 6.15–6.21(1H, m), 7.18(2H, d, J=8.3Hz), 7.27–7.41(11H, m), 7.54(2H, d, J=8.3Hz), 8.57(1H, s), 8.72(1H, brs), 8.82(1H, brs), 10.20(1H, s)
49	NMR δ: 2.88–3.07(3H, m), 3.11–3.21(3H, m), 3.67(2H, s), 4.93–4.99(1H, m), 5.52(2H, s), 6.20(1H, d, J=3.9Hz), 7.00 (1H, s), 7.13(2H, d, J=7.3Hz), 7.18(2H, d, J=8.3Hz), 7.24–7.42(8H, m), 7.49(2H, d, J=8.3Hz), 8.82(1H, brs), 9.11(1H, brs), 10.35(1H, s)
50	NMR δ: 1.76–1.87(2H, m), 2.18–2.26(2H, m), 2.80–3.22(8H, m), 4.39–4.47(1H, m), 4.95–5.07(3H, m), 7.15–7.22(2H, m), 7.27–7.43(5H, m), 7.54–7.63(2H, m), 7.74–7.82(1H, m), 8.27(1H, d, J=7.2Hz), 8.67(1H, d, J=4.8Hz), 8.97(1H, brs), 9.47(1H, brs), 10.74(1H, brs)
51	NMR δ: 2.90–3.10(3H, m), 3.10–3.20(3H, m), 4.18(2H, s), 4.96(1H, d, J=8.0Hz), 6.20(1H, brs), 7.18(2H, d, J=8.6Hz), 7.20–7.60(12H, m), 7.84(1H, s), 7.97(1H, s), 8.83(1H, brs), 9.17(1H, brs), 10.55(1H, s)
52	NMR δ: 1.14(6H, d, J=12.9Hz), 2.83(1H, sep, J=12.9Hz), 2.90–3.22(6H, m), 4.38(2H, s), 4.97(1H, d, J=4.1Hz), 5.39 (2H, s), 6.20(1H, brs), 7.07–7.42(10H, m), 7.52(2H, d, J=8.8Hz), 7.67(2H, d, J=3.9Hz), 8.84(1H, brs), 9.17(1H, brs), 10.76(1H, s)
53	NMR δ: 1.14(6H, d, J=12.9Hz), 2.83(1H, sep, J=12.9Hz), 2.90–3.22(6H,m), 4.38(2H, s), 4.97(1H, d, J=4.1Hz), 5.39 (2H, s), 6.20(1H, brs), 7.07–7.42(10H, m), 7.52(2H, d, J=8.8Hz), 7.67(2H, d, J=3.9Hz), 8.84(1H, brs), 9.17(1H, brs), 10.76(1H, s)
54	NMR δ: 2.95–3.02(3H, m), 3.15(3H, brs), 4.44(2H, s), 5.10(1H, dd, J=10.3, 2.5Hz), 5.58(2H, s), 6.21(1H, brs), 7.19 (2H, d, J=8.6Hz), 7.27–7.42(6H, m), 7.51(2H, d, J=8.6Hz), 7.58–7.60(1H, m), 7.69(1H, d, J=2.4Hz), 7.72(1H, d, J=2.0Hz), 7.75(1H, d, J=2.0Hz), 8.95(1H, brs), 9.44(1H, brs), 10.91(1H, s)
55	NMR δ: 2.94–3.04(3H, m), 3.15(3H, brs), 3.94(2H, s), 5.01(1H, d, J=10.3Hz), 5.31(2H, s), 6.21(1H, d, J=3.9Hz), 7.01 (1H, s), 7.17–7.41(12H, m), 7.54(2H, d, J=8.3Hz), 8.98(1H, brs), 9.35(1H, brs), 10.55(1H, s)
56	NMR δ: 2.95–3.05(3H, m), 3.15(3H, brs), 4.44(2H, s), 5.01(1H, dd, J=10.3, 2.5Hz), 5.51(2H, s), 6.20(1H, brs), 7.19 (3H, d, J=8.6Hz), 7.26–7.42(7H, m), 7.50–7.54(3H, m), 7.58(1H, d, J=2.0Hz), 7.73(1H, d, J=2.0Hz), 8.95(1H, brs), 9.43 (1H, brs), 10.98(1H, s)
57	NMR δ: 2.92–3.05(3H, m), 3.15(3H, brs), 4.43(2H, s), 5.01(1H, dd, J=10.2, 2.6Hz), 5.65(2H, s), 7.20(2H, d, J=8.4Hz), 7.29–7.48(5H, m), 7.50–7.53(3H, m), 7.70(1H, d, J=2.0Hz), 7.78(1H, d, J=2.0Hz), 7.85(1H, dt, J=8.0, 2.0Hz), 8.49 (1H, d, J=8.0Hz), 8.94(1H, brs), 9.42(1H, brs), 10.86(1H, s)
58	mp: 150–152° C., NMR δ: 2.88–3.07(3H, m), 3.08(3H, m), 3.95(2H, s), 5.00(1H, dd, J=2.8, 10.0Hz), 6.21(1H, s), 6.82(1H, d, J=7.6Hz), 6.91(1H, d, J=8.0Hz), 7.17–7.23(2H, m), 7.28–7.43(5H, m), 7.55–7.62(2H, m), 7.82–8.04(3H, m), 8.90(1H, brs), 9.33(1H, brs), 10.67(1H, brs), 14.07(1H, brs)
59	NMR δ: 2.90–3.25(6H, m), 4.95–5.04(1H, m), 5.20(1H, s), 6.22(1H, brs), 6.78(1H, s), 7.17–7.24(2H, m), 7.27–7.44 (5H, m), 7.67–7.75(2H, m), 8.50–9.10(3H, br), 9.45(1H, br), 10.22(1H, brs)
60	mp: 214–216° C., NMR δ: 2.86–3.24(6H, m), 3.65(2H, s), 4.98(1H, dd, J=2.8, 10.4Hz), 6.18(1H, d, J=6.8Hz), 6.28 (1H, d, J=8.8Hz), 7.16–7.22(2H, m), 7.28–7.45(6H,m), 7.53–7.59(2H, s), 8.85(1H, brs), 9.18(1H, brs), 10.36(1H, brs)
61	mp: 180–182° C., NMR δ: 0.87(6H, d, J=6.8Hz), 2.05–2.15(1H, m), 2.39–3.10(3H, m), 3.10–3.20(3H, m), 4.03(2H, d, J=7.8Hz), 4.41(2H, s), 5.01(1H, d, J=8.5Hz), 6.20(1H, brs), 7.21(2H, d, J=8.3Hz), 7.29–7.42(9H, m), 7.60(2H, d, J=8.8Hz), 7.69(1H, d, J=1.9Hz), 7.75(1H, d, J=2.0Hz)
62	mp: 226–228° C., NMR δ: 2.87–3.23(6H, m), 4.45(2H, s), 5.02(1H, dd, J=2.4, 10.0Hz), 5.55(2H, s), 6.21(1H, brs), 7.16–7.46(11H, m), 7.49–7.55(2H, m), 7.66(1H, d, J=2.0Hz), 7.71(1H, d, J=2.0Hz), 8.95(1H, brs), 9.44(1H, brs), 10.93 (1H, brs), 14.82(1H, brs)
63	mp: 224–225° C., NMR δ: 2.90–3.05(3H, m), 3.05–3.25(3H, m), 4.46(2H, s), 5.01(1H, d, J=8.0Hz), 5.50(2H, s), 6.21 (1H, brs), 7.14–7.50(11H, m), 7.54(2H, d, J=8.8Hz), 7.70–7.73(2H, m), 8.93(1H, brs), 9.39(1H, brs), 10.95(1H, s)
64	mp: 205–208° C., NMR δ: 2.90–3.06(3H, m), 3.10–3.21(3H, m), 4.41(2H, s), 4.99(1H, d, J=8.3Hz), 5.51(2H, s), 6.21 (1H, s), 7.06–7.12(1H, m), 7.20(2H,d, J=8.3Hz), 7.28–7.42(6H,m), 7.69(2H, dd, J=2.0, 8.3Hz), 8.87(1H, s), 9.26(1H, s), 10.81(1H, s)
65	mp: 211–216° C., NMR δ: 3.00(3H, brs), 3.15(3H, brs), 4.44(2H, s), 5.05(1H, dd, J=10.2, 1.9Hz), 5.58(2H, s), 6.22 (1H, brs), 7.14–7.22(4H, m), 7.29–7.32(1H, m), 7.37–7.42(4H, m), 7.47–7.54(3H, m), 7.55(1H, s), 7.69(1H, d, J=1.9Hz), 9.02(1H, brs), 9.55(1H, brs), 10.97(1H, s)
66	mp: 199–201° C., NMR δ: 2.87–3.23(6H, m), 4.45(2H, s), 4.95–5.04(1H, m), 5.51(2H, s), 6.20(1H, brs), 7.10–7.43 (10H, m), 7.49–7.55(2H, m), 7.71(1H, d, J=2.0Hz), 7.74(1H, d, J=2.0Hz), 8.89(1H, brs), 9.30(1H, brs), 10.90(1H, brs), 14.73(1H, brs)
67	mp: 131–135° C., NMR δ: 3.00(3H, brs), 3.16(3H, brs), 4.49(2H, s), 5.04(1H, d, J=10.0Hz), 5.56(2H, s), 6.23(1H, brs), 7.20(2H, d, J=8.2Hz), 7.23–7.34(4H, m), 7.37–7.42(4H,m), 7.53(2H, d, J=8.2Hz), 7.72(2H, s), 9.01(1H, brs), 9.54 (1H, brs), 11.00(1H, s)
68	mp: 217–219° C., NMR δ: 2.90–3.05(3H, m), 3.05–3.20(3H, m), 4.46(2H, s), 5.00(1H, d, J=8.0Hz), 5.47(2H, s), 6.21 (1H, brs), 7.20(2H, d, J=8.0Hz), 7.25–7.50(7H, m), 7.50–7.60(3H, m), 7.70(1H, d, J=1.9Hz), 7.71(1H, d, J=2.0Hz), 8.91(1H, brs), 9.33(1H, brs), 10.93(1H, s)
69	mp: 213–217° C., NMR δ: 2.90–3.05(3H,m), 3.05–3.20(3H,m), 4.42(2H, s), 5.02(1H, dd, J=10.2, 2.4Hz), 5.62(2H, s), 6.21(1H, brs), 7.20(2H, d, J=8.3Hz), 7.29–7.42(6H, m), 7.49(2H, d, J=8.3Hz), 7.51–7.60(1H, m), 7.68–7.73(2H, m), 8.95(1H, brs), 9.42(1H, brs), 10.89(1H, s)
70	mp: 212–213° C., NMR δ: 2.87–3.23(6H, m), 4.47(2H, s), 5.02(1H, dd, J=2.4, 10.0Hz), 5.53(2H, s), 6.21(1H, brs),

TABLE 2-continued

Ex.	DATA
	7.16–7.23(2H, m), 7.28–7.34(1H, m), 7.36–7.43(4H, m), 7.48–7.55(2H, m), 7.57–7.67(2H, m), 7.69–7.74(2H, m), 8.95 (1H, brs), 9.45(1H, brs), 10.95(1H, brs), 14.86(1H, brs)
71	mp: 209–213° C., NMR δ: 2.90–3.05(3H, m), 3.05–3.20(3H, m), 4.47(2H, s), 4.98–5.01(1H, m), 5.49(2H, s), 6.21 (1H, brs), 7.21(2H, d, J=8.3Hz), 7.28–7.34(1H, m), 7.36–7.44(6H,m), 7.53(2H, d, J=8.8Hz), 7.71(1H, d, J=1.9Hz), 7.74 (1H, d, J=1.9Hz), 8.91(1H, brs), 9.34(1H, brs), 10.97(1H, s)
72	mp: 190–193° C., NMR δ: 2.90–3.08(3H, m), 3.10–3.21(3H,m), 4.38(2H, s), 4.99(1H, dd, J=2.5, 10.2Hz), 5.69(2H, s), 6.20(1H, s), 7.21(2H, d, J=8.8Hz), 7.29–7.42(5H, m), 7.48(2H, d, J=8.3Hz), 7.70(1H, d, J=1.9Hz), 7.77(1H, s), 8.88 (1H, s), 9.27(1H, s), 10.84(1H, s)
73	mp: 233–234° C., NMR δ: 2.90–3.23(6H, m), 4.47(2H, s), 5.02(1H, dd, J=2.4, 10.0Hz), 5.44(2H, s), 6.21(1H, brs), 7.12–7.23(3H, m), 7.28–7.34(1H, m), 7.36–7.44(5H, m), 7.52–7.58(2H, m), 7.66–7.73(2H, m), 7.79–7.81(1H, m), 8.96 (1H, brs), 9.44(1H, brs), 10.96(1H, brs), 14.79(1H, brs)
74	mp: 180–183° C., NMR δ: 2.67–2.76(4H, m), 2.78–2.86(2H, m), 4.00(2H, s), 4.66(1H, dd, J=8.3, 3.9Hz), 5.39(2H, s), 5.42(1H, brs), 6.57(1H, d, J=0.9Hz), 6.78(1H, s), 7.03(2H, d, J=8.3Hz), 7.21–7.25(1H, m), 7.27–7.34(4H, m), 7.46–7.50(1H, m), 7.52(2H, d, J=8.3Hz), 7.56(1H, s), 7.58(1H, s), 8.32(1H, s), 10.32(1H, s)
75	mp: 210–215° C., NMR δ: 2.91–3.03(3H, m), 3.15(3H, brs), 4.44(2H, s), 5.01(1H, dd, J=10.4, 2.6Hz), 5.53(2H, s), 6.21(1H, brs), 7.18(2H, d, J=8.3Hz), 7.30–7.32(1H, m), 7.37–7.42(4H, m), 7.48(2H, d, J=7.49(2H, d, J=8.3Hz), 7.74(1H, d, J=2.0Hz), 7.75(1H, d, J=2.0Hz), 7.79(2H, d, J=8.3Hz), 8.94(1H, brs), 9.39(1H, brs), 10.93(1H, s)
76	mp: 162–165° C., NMR δ: 2.93–3.05(3H, m), 3.14(3H, brs), 4.47(2H, s), 5.03(1H, dd, J=10.3, 2.5Hz), 5.62(1H, brs), 5.89(2H, s), 7.12(2H, d, J=8.3Hz), 7.30–7.37(1H, m), 7.39–7.43(6H,m), 7.63(2H, d, J=8.8Hz), 7.69(1H, t, J=7.5Hz), 7.75(1H, d, J=1.9Hz), 7.83–7.86(2H, m), 7.97(1H, d, J=8.3Hz), 8.44(1H, d, J=8.3Hz), 8.99(1H, brs), 9.52(1H, brs), 10.84 (1H, s)
77	NMR δ: 2.64–2.74(4H, m), 2.77–2.82(2H, m), 3.93(2H, s), 4.63(1H, dd, J=7.8, 4.4Hz), 5.33(2H, s), 5.80(2H, d, J=6.3 Hz), 7.14(2H, d, J=8.8Hz), 7.20–7.24(1H, m), 7.28–7.35(5H, m), 7.43(1H, d, J=7.8Hz), 7.47–7.52(3H, m), 10.27(1H, s)
78	NMR δ: 2.63–2.72(4H, m), 2.75–2.81(2H, m), 3.79(2H, s), 4.62(1H, dd, J=7.8, 4.4Hz), 5.30(1H, brs), 5.33(2H, s), 6.68 (1H, d, J=1.0Hz), 6.91(1H, dd, J=8.8, 5.9Hz), 7.06(1H, d, J=1.0Hz), 7.12(2H, d, J=8.8Hz), 7.19–7.24(2H, m), 7.28–7.33(4H, m), 7.43(2H, d, J=8.3Hz), 7.49(1H, dd, J=8.3, 2.5Hz), 8.32(1H, s), 10.21(1H, s)
79	NMR δ: 2.88–3.08(3H, m), 3.10–3.22(3H, m), 4.40(2H, s), 4.97(1H, d, J=8.3Hz), 5.56(2H, s), 6.20(1H, s), 7.19(2H, d, J=8.3Hz), 7.24(1H, d, J=2.5Hz), 7.30–7.60(9H, m), 7.64(1H, d, J=2.0Hz), 7.72(1H, s), 8.83(1H, s), 9.14(1H, s), 10.71 (1H, s)
80	NMR δ: 2.90–3.08(3H, m), 3.10–3.22(3H, m), 4.44(2H, s), 5.02(1H, d, J=8.8Hz), 5.59(2H, s), 6.21(1H, s), 7.20(2H, d, J=8.0Hz), 7.24–7.42(7H, m), 7.50(2H, d, J=8.8Hz), 7.72(2H, d, J=6.8Hz), 8.94(1H, s), 9.42(1H, s), 10.93(1H, s)
81	NMR δ: 2.87–3.23(6H,m), 3.85(3H, s), 4.30(2H, s), 4.94–5.01(1H, m), 5.55(2H, s), 6.17–6.22(3H, br), 7.14–7.23(2H, m), 7.28–7.50(9H, m), 7.57–7.64(2H, m), 7.87–7.93(2H, m), 8.83(1H, brs), 9.10(1H, brs), 10.68(1H, brs), 14.86(1H, brs)
82	NMR δ: 1.30–1.64(6H, m), 2.88–3.22(8H,m), 3.43–3.65(2H, m), 4.39(2H, s), 4.97(1H, d, J=9.8Hz), 5.50(2H, s), 6.21 (1H, s), 7.20(2H, d, J=8.3Hz), 7.30–7.42(9H, m), 7.51(2H, d, J=8.7Hz), 7.71(2H, d, J=7.8Hz), 8.81(1H, s), 9.14(1H, s), 10.77(1H, s)
83	mp: 229–232° C., NMR δ: 2.90–3.00(3H, m), 3.10–3.18(3H, m), 5.00(1H, dd, J=2.8, 10.1Hz), 5.03(2H, s), 6.27(1H, t, J=2.0Hz), 7.20(2H, d, J=8.8Hz), 7.29–7.42(5H, m), 7.46(1H, d, J=2.4Hz), 7.58(2H, d, J=8.8Hz), 7.77(1H, d, J=2.0Hz), 8.91(1H, s), 9.32(1H, s), 10.53(1H, s)
84	mp: 237–240° C., NMR δ: 2.90–3.08(3H, m), 3.10–3.22(3H, m), 4.96(1H, dd, J=2.0, 10.0Hz), 5.15(2H, s), 7.21(2H, d, J=8.0Hz), 7.28–7.42(5H, m), 7.56(2H, d, J=8.4Hz), 8.03(1H, s), 8.61(1H, s), 8.82(1H,s), 9.09(1H, s), 10.57(1H, s)
85	mp: 244–248° C., NMR δ: 2.90–3.05(3H, m), 3.10–3.20(3H, m), 5.00(1H, d, J=7.6Hz), 5.20(2H, s), 6.20(1H, s), 7.20–7.50(11H, m), 7.59(2H, d, J=7.2Hz), 8.94(1H, s), 9.36(1H, s), 10.95(1H, s), 12.92(1H, s)
86	mp: 223–224° C., NMR δ: 2.86–3.22(6H, m), 3.49(2H, s), 4.93–5.03(1H, m), 6.20(1H, d, J=4.0Hz), 7.15–7.43(9H, m), 7.55–7.62(2H, m), 7.75(1H, dt, J=1.6, 8.0Hz), 8.45–8.53(1H, m), 8.06–9.50(2H, br), 10.35(1H, brs)
87	mp: 236–238° C., NMR δ: 2.86–3.23(6H, m), 3.72(2H, s), 4.91–5.02(1H, m), 6.20(1H, d, J=4.0Hz), 7.15–7.22(2H, m), 7.27–7.45(6H, m), 7.53–7.62(2H, m), 7.73–7.82(1H, m), 8.40–8.60(2H, m), 8.84(1H, brs), 9.16(1H, brs), 10.35–10.50 (1H, br)
88	mp: 195–198° C., NMR δ: 2.86–3.22(6H, m), 3.73(2H, s), 4.93–5.04(1H, m), 6.15–6.25(1H, br), 7.14–7.22(2H, m), 7.23–7.43(7H, m), 7.54–7.63(2H, m), 8.47–8.53(2H, m), 9.07(2H, brs), 10.50(1H, brs)
89	mp: 202–204° C., NMR δ: 2.71–2.81(2H, m), 2.88–3.24(8H, m), 3.49(2H, s), 4.93–5.05(1H, m), 6.20(1H, brd, J=3.2 Hz), 7.15–7.23(3H, m), 7.26–7.44(6H, m), 7.52–7.60(2H m), 7.69(1H, dt, J=1.6, 7.6Hz), 8.45–8.51(1H, m), 9.07(2H, brs), 10.07(1H, brs)
90	mp: 220–227° C., NMR δ: 2.80–3.20(8H, m), 4.31(2H, s), 4.42(2H, t, J=8.0Hz), 5.00(1H, d, J=1.0Hz), 6.21(1H, brs), 7.20–7.40(12H, m), 7.59(2H, d, J=8.6Hz), 7.65(2H, dd, J=12.9, 0.9Hz), 8.91(1H, brs), 9.34(1H, brs), 10.98(1H, s)
91	mp: 158–165° C., NMR δ: 2.51–2.78(6H, m), 3.96(2H, s), 4.59(1H, t, J=5.2Hz), 5.20(1H, brs), 7.13–7.32(9H, m), 7.50–7.53(4H, m), 10.33(1H, s), 12.37(1H, brs)
92	mp: 216–217° C., NMR δ: 2.31(3H, s), 2.86–3.24(6H, m), 3.89(2H, s), 4.92–5.07(1H, m), 6.20(1H,d, J=4.0Hz), 7.12–7.22(3H, m), 7.28–7.45(5H, m), 7.50–7.64(2H, m), 8.30(1H, d, J=4.4Hz), 8.60–9.50(2H, br), 10.32(1H, brs)
93	mp: 236–238° C., NMR δ: 2.86–3.24(6H, m), 3.95(2H, s), 4.91–5.01(1H, m), 5.44(2H, s), 6.19(1H, d, J=4.4Hz), 7.15–7.22(2H, m), 7.27–7.43(5H, m), 7.52–7.62(2H, m), 8.50–8.69(3H, m), 8.83(1H, br), 9.12(1H, brs), 10.41(1H, brs)
94	NMR δ: 2.90–3.10(3H, m), 3.10–3.20(3H, m), 4.38(2H, s), 4.98(1H, t, J=10.4Hz), 5.44(2H, s), 6.20(1H, d, J=3.2Hz), 7.20(2H, d, J=8.4Hz), 7.30–7.45(9H, m), 7.53(2H, d, J=8.81Hz), 7.64(2H, s), 8.85(1H, brs), 9.21(1H, brs), 10.79(1H, s)
95	NMR δ: 2.31(3H, s), 2.89–3.17(6H, m), 3.79(2H, s), 4.98(1H, dt, J=3.2, 10.4Hz), 7.10–7.41(2H, m), 10.32(1H, s)
96	NMR δ: 2.27(3H, s), 2.89–3.17(6H, m), 3.79(2H, s), 4.99(1H, dt, J=3.6, 10.0Hz), 7.17–7.59(2H, m), 10.31(1H, s)
97	NMR δ: 2.44(3H, s), 2.78–3.20(6H, m), 3.80(2H, s), 4.97(1H, dt, J=3.2, 10.4Hz), 7.12–7.66(2H, m), 10.33(1H, s)
98	NMR δ: 1.06(3H, d, J=6.4Hz), 2.50–2.65(2H, m), 2.90–3.15(3H, m), 3.83(2H, s), 4.80–4.94(1H, m), 7.10–7.18(2H, m), 7.23–7.45(7H, m), 7.52–7.60(2H, m), 7.71–7.80(1H, m), 8.41–8.52(1H, m), 10.25(1H, brs)
99	mp: 203–204° C., NMR δ: 1.13(3H, d, J=6.4Hz), 2.55–2.64(1H, m), 3.00–3.50(4H, m), 3.84(2H, s), 4.92–5.02(1H, m), 6.20(1H, d, J=4.0Hz), 7.13–7.20(2H, m), 7.24–7.46(7H, m), 7.54–7.60(2H, m), 7.73–7.80(1H, m), 8.51(1H, brs), 8.67 (1H, brs), 9.13(1H, brs), 10.31(1H, brs)
100	NMR δ: 1.06(3H, d, J=6.4Hz), 2.50–2.65(1H, m), 2.57–3.50(4H, m), 3.78(2H, s), 4.77–4.92(1H, m), 5.25(2H, s), 6.85 (1H, s), 7.10–7.55(15H, m), 10.33(1H, brs)
101	mp: 194–196° C., NMR δ: 2.88–3.25(6H, m), 3.89(2H, s), 5.20–5.26(1H, m), 6.30(1H, s), 7.37–7.48(7H, m), 7.54–7.60(3H, m), 7.81–7.88(1H, m), 8.54(1H, d, J=4.0Hz), 8.82(1H, s), 9.16(1H, s), 10.35(1H, s)

TABLE 2-continued

Ex.	DATA
102	mp: 214–215° C., NMR δ: 2.88–3.25(6H, m), 3.85(2H, s), 4.96–5.02(1H, m), 6.33(1H, d, J=3.8Hz), 7.12–7.21(6H, m), 7.39–7.48(2H, m), 7.58(2H, d, J=8.3Hz), 7.74–7.80(1H, m), 8.50(1H, s), 8.82(1H, s), 9.01(1H, s), 10.30(1H, s)
103	mp: 223–225° C., NMR δ: 2.88–3.06(3H, m), 3.10–3.20(3H, m), 3.84(2H, s), 4.94–5.01(1H, m), 5.24(1H, d, J=4.0Hz), 7.16–7.30(5H, m), 7.38–7.46(3H, m), 7.58(2H, d, J=8.8Hz), 7.76(1H, dt, J=1.6, 7.6Hz), 8.50(1H, d, J=8.8Hz), 8.83 (1H, s), 9.08(1H, s), 10.31(1H, s)
104	mp: 208–210° C., NMR δ: 2.88–3.24(6H, m), 3.99(2H, s), 4.90–5.10(1H, m), 6.20(1H, d, J=3.6Hz), 7.15–7.24(2H, m), 7.28–7.44(6H, m), 7.53–7.62(2H, m), 8.50–9.30(4H, m), 10.33(1H, brs)
105	mp: 234–235° C., NMR δ: 2.94–3.25(6H, m), 4.07(2H, s), 4.90–5.02(1H, m), 6.20(1H, d, J=4.0Hz), 7.16–7.23(2H, m), 7.27–7.44(5H,m), 7.53–7.65(4H, m), 7.71–7.78(1H, m), 7.94–8.00(2H, m), 8.33(1H, d, J=8.0Hz), 8.50–9.25(2H, m), 10.46(1H, brs)
106	mp: 221–222° C., NMR δ: 2.90–3.25(6H, m), 3.85(2H, s), 4.92–5.08(1H, m), 6.35(1H, d, J=3.6Hz), 7.14–7.23(2H, m), 7.23–7.31(1H, m), 7.33–7.50(5H, m), 7.54–7.64(2H, m), 7.76(1H, dt, J=1.6, 7.6Hz), 8.43–8.55(1H, m), 8.80–9.40 (2H, br), 10.36(1H, brs)
107	mp: 204–205°C., NMR δ: 2.85–3.28(6H, m), 3.85(2H, s), 5.02–5.14(1H, m), 6.37(1H, d, J=4.0Hz), 7.14–7.32(3H, m), 7.365–7.46(2H, m), 7.55–7.64(2H, m), 7.70–7.86(2H, m), 8.46–8.56(2H, m), 8.57–8.65(1H, m), 9.13(2H, brs), 10.37 (1H, brs)
108	NMR δ: 2.63–2.67(4H, m), 2.73–2.78(2H, m), 4.07(2H, s), 4.60(1H, dd, J=7.4, 4.9Hz), 5.24(1H, brs), 5.57(2H, s), 7.12–7.23(7H, m), 7.27–7.31(4H, m), 7.37(3H, d, J=8.3Hz), 7.46(2H, d, J=8.3Hz), 7.60–7.61(1H, m), 8.31(1H, s), 10.31 (1H, s)
109	NMR δ: 2.26(3H, s), 2.40(3H, s), 2.90–3.17(6H, m), 3.75(2H, s), 4.99(1H, dt, J=3.2, 6.8Hz), 6.97–7.60(11H, m), 10.35 (1H, s)
110	mp: 183–184° C., NMR δ: 1.85–2.05(2H, m), 2.53–2.65(2H, m), 2.83–3.03(3H, m), 3.05–3.16(1H, m), 3.88(2H, s), 4.95(1H, d, J=9.8Hz), 6.15(1H, brs), 7.10–7.18(2H, m), 7.22–7.43(7H, m), 7.50–7.60(2H, m), 7.75(1H, dt, J=1.6, 7.2Hz), 8.65–8.53(3H, m), 8.91(2H, brs), 10.29(1H, brs)
111	mp: 225–226° C., NMR δ: 3.02–3.14(1H, m), 3.18–3.46(3H, m), 3.84(2H, s), 4.22–4.35(2H, m), 4.98–5.08(1H, m), 6.21(1H, d, J=3.6Hz), 6.90–6.97(2H, m), 7.23–7.44(7H, m), 7.53–7.62(2H, m), 7.76(1H, dt, J=1.6, 7.2Hz), 8.45–8.54 (1H, m), 8.80–9.50(2H, br), 10.29(1H, brs)
112	NMR δ: 1.21(6H, s), 2.85–3.23(4H, m), 3.89(2H, s), 4.90–5.00(1H, m), 6.21(1H, brs), 7.11–7.19(2H, m), 7.28–7.50 (7H, m), 7.53–7.62(2H, m), 7.78–7.90(1H, m), 8.45–8.60(2H, m), 9.00–9.10(1H, br), 10.35(1H, brs)
113	mp: 132–133° C., NMR δ: 2.90–3.10(3H, m), 3.13–3.23(3H, m), 4.96(1H, dd, J=2.5, 10.2Hz), 7.06–7.11(1H, m), 7.21(2H, d, J=8.7Hz), 7.30–7.42(5H, m), 7.47–7.53(3H, m), 7.83–7.87(1H, m), 8.29(1H, d, J=4.9Hz), 8.78(1H, s), 9.00 (1H, s), 9.88(1H, s), 10.51(1H, s)

TABLE 3

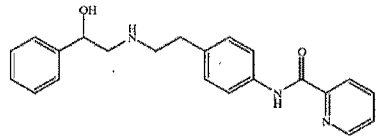
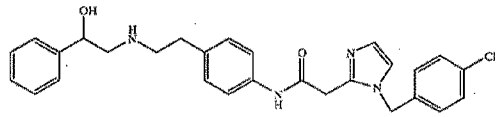
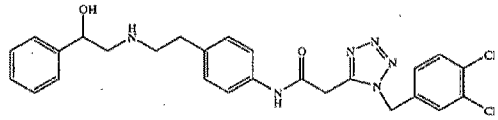
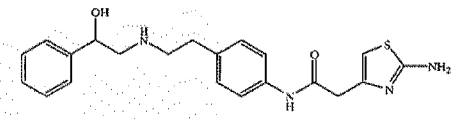
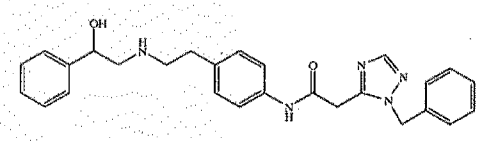
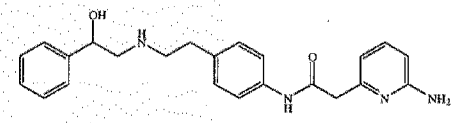
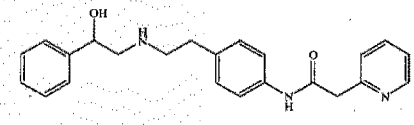
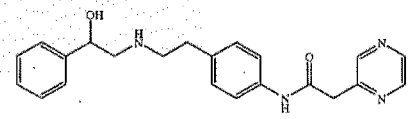
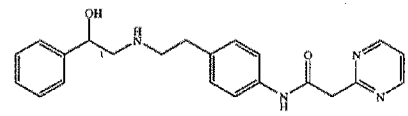
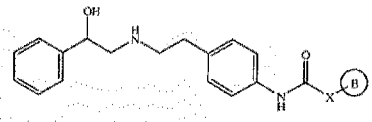
Ex.	Structure
1	
23	
33	

TABLE 3-continued

Ex.	Structure
41	
47	
58	
86	
93	
104	

The compounds shown in Tables 4 and 5 together with chemical structural formulae can be easily manufactured by almost the same method as mentioned in the above Examples or Manufacturing Methods or by the method to which some modifications known to the persons skilled in the art are applied. Incidentally, in some cases, there are tautomeric, geometric or optical isomers for the compounds mentioned in Tables 4 and 5, and the compounds of the present invention cover each of the isolated isomers of the above-mentioned ones or a mixture thereof.

TABLE 4



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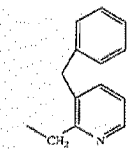
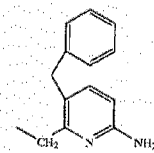
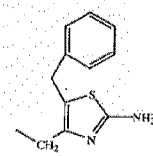
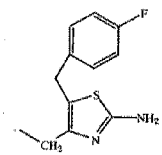
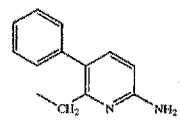
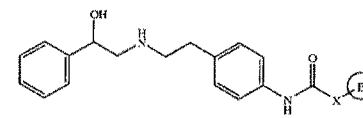
1	
2	
3	
4	
5	

TABLE 4-continued



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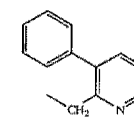
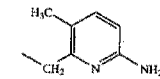
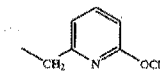
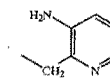
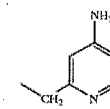
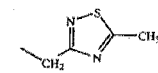
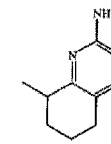
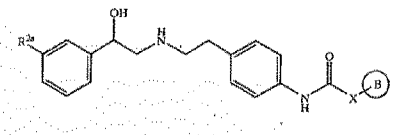
6	
7	
8	
9	
10	
11	
12	

TABLE 5



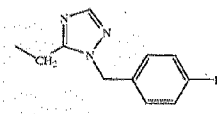
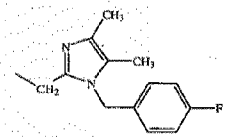
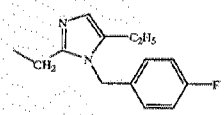
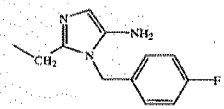
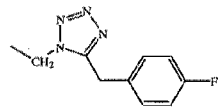
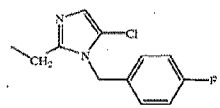
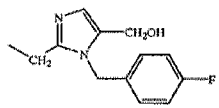
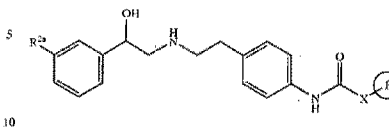
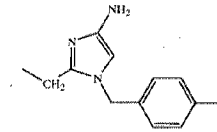
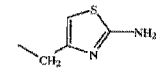
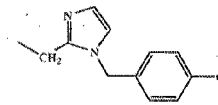
No.	R^{2a}	
13	H	
14	H	
15	H	
16	H	
17	H	
18	H	
19	H	

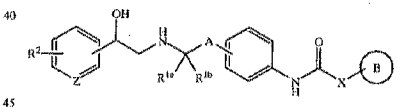
TABLE 5-continued



No.	R^{2a}	
20	H	
21	Cl	
22	Cl	

What is claimed is:

1. A compound of formula (I):



(I)

in the formula, each of the symbols means as follows:

ring B is a heteroaryl group which is unsubstituted or substituted and is optionally fused with a benzene ring;

X is a bond, or a lower alkylene or an alkenylene, both of which are unsubstituted or substituted with hydroxy or a lower alkyl group, or X is a carbonyl or a group represented by —NH—, and when X is a lower alkylene which is substituted with a lower alkyl group, a carbon atom of the ring B optionally bonds with the lower alkyl group so that a ring is formed;

A is a lower alkylene or a group represented by -lower alkylene-O—;

R^{1a}, R^{1b} are the same or different and each is a hydrogen atom or a lower alkyl group;

R^2 is a hydrogen atom or a halogen atom; and

Z is a group represented by =CH—; or a salt thereof.

2. The compound of formula (I) or the salt thereof according to claim 1, wherein A is methylene, ethylene, or a group represented by —CH_2O—.

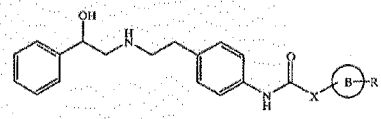
3. The compound of formula (I) or the salt thereof according to claim 2, wherein the ring B is a heteroaryl

group which is substituted with a substituent chosen from a-halogen atom, lower alkyl, lower alkenyl, lower alkynyl, hydroxy, sulfanyl, halogeno lower alkyl, lower alkyl-O—, lower alkyl-S—, lower alkyl-O—CO—, carboxy, sulfonyl, sulfinyl, lower alkyl-SO—, lower alkyl-SO_2—, lower alkyl-CO—, lower alkyl-CO—O—, carbamoyl, lower alkyl-NH—CO—, di-lower alkyl-N—CO—, nitro, cyano, amino, lower alkyl-NH—, di-lower alkyl-N—, aryl-lower alkyl, halogeno aryl-lower alkyl, guanidino, lower alkyl-CO—NH, and lower alkyl-SO_2—NH—.

4. The compound of formula (I) or the salt thereof according to claim 3, wherein R^2, R^{1a} and R^{1b} are each a hydrogen atom, and Z is =CH—.

5. A compound of formula (Ia):

(Ia)



in the formula, each of the symbols means as follows:

ring B is a heteroaryl group;

X is a bond or a lower alkylene group;

R is a hydrogen atom, a halogen atom, a lower alkyl group, amino group, an aryl lower alkyl group, or a halogeno aryl-lower alkyl group; or a salt thereof.

6. A compound:

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-pyridinecarboxyanilide,

(R)-2-[1-(4-chlorobenzyl)-1H-imidazol-2-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]-acetanilide, (R)-2-[1-(3,4-dichlorobenzyl)-1H-tetrazol-5-yl]-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide,

(R)-2-(2-aminothiazol-4-yl)-4'-[2-(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide,

(R)-2-(2-benzyl-1H-1,2,4-triazol-3-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)-amino]ethyl]acetanilide,

(R)-2-(2-aminopyridin-6-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide, (R)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]-2-(2-pyridyl) acetanilide,

(R)-4'-[2-[(2-hydroxy-2-phenylethyl)-amino]ethyl)-2-(2-pyrazinyl)acetanilide, (R)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl)-2-(2-pyrimidinyl)-acetanilide, or a salt of any of the foregoing.

7. A composition comprising at least one compound of formula (I) or the salt thereof as claimed in one of claims 1 through 4 in a pharmaceutically acceptable carrier.

8. The composition as claimed in claim 7, wherein the at least one compound of formula (I) or the salt thereof is present in an amount effective for the treating of diabetes mellitus in a human or animal patient in need of such treating.

9. The compound of formula (I) as claimed in claim 1, wherein the compound of formula (I) is an optical isomer, a hydrate, or a solvate of the compound of formula (I).

10. A composition comprising a compound of formula (I) as claimed in claim 1 in a pharmaceutically acceptable carrier, wherein the compound of formula (I) is present as a polymorphic substance.

11. A composition comprising at least one compound of formula (I) or the salt thereof as claimed in claim 5, in a pharmaceutically acceptable carrier.

12. A composition comprising at least one compound or the salt of any of the foregoing as claimed in claim 6, in a pharmaceutically acceptable carrier.

13. A method for treating diabetes mellitus in a human or animal patient in need of such treatment comprising administering to the patient an amount of a compound of formula (I) as claimed in claim 1, wherein the amount is an amount effective for such treatment.

14. A method for treating obesity in a human or animal patient in need of such treatment comprising administering to the patient an amount of a compound of formula (I) as claimed in claim 1, wherein the amount is an amount effective for such treatment.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,346,532 B1
DATED : February 12, 2002
INVENTOR(S) : T. Maruyama et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 16,
Lines 29-30, (Example 3) should read: -- (R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino] ethyl]-8-quinolinecarboxanilide dihydrochloride

Column 17,
Lines 40-41, (Example 16) should read:
-- (R)-2-(2-Benzyloxypyridin-6-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl] acetanilide hydrochloride --

Column 19,
Lines 58-60, (Example 39) should read: -- (R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino] ethyl]-2-(2-phenylaminothiazol-4-yl)acetanilide hydrochloride --

Column 23,
Lines 3-5, (Example 66) should read:
-- (R)-2-[1-(3,5-Difluorobenzyl)-1H-imidazol-2-yl]-4'-
[2-(2-hydroxy-2-phenylethyl)amino]ethyl] acetanilide dihydrochloride --

Column 26,
Lines 47-49, (Example 99) should read: -- 4'[(S)-2-[((R)-2-Hydroxy-2-phenylethyl) amino]propyl]-2-(2-pyridyl)acetanilide hydrochloride --

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,346,532 B1
DATED : February 12, 2002
INVENTOR(S) : T. Maruyama et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 28,
Line 2, change "30/1 Δ 10/1)." to -- 30/1 → 10/1). --.
Line 7, should read: -- [(2-hydroxy-2-phenylethyl)amino]propyl]-2-(2-pyridyl) --
Lines 62-63, (Example 113) should read: -- (R)-1-[4-[2-[(2-Hydroxy-2-phenylethyl) amino]ethyl] phenyl]-3-(2-pyridyl)urea dihydrochloride --

Column 45,
Line 4, should read: -- (R)-2-[1-(4-chlorobenzyl)-1H-imidazol-2-yl]-4'-[2-[(2- --

Signed and Sealed this

Thirtieth Day of July, 2002

Attest:

Attesting Officer

JAMES E. ROGAN
Director of the United States Patent and Trademark Office

Appendix E

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
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www.uspto.gov

Customer No 197 | ISTMT | DATE PRINTED 08/15/2012

CPA GLOBL LIMITED
2318 Mill Road 12th Floor
ALEXANDRIA VA 22314

MAINTENANCE FEE STATEMENT

According to the records of the U.S.Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed below. The "PYMT DATE" column indicates the payment date (i.e., the date the payment was filed).

The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
6,346,532	$900.00	$0.00	07/20/05	09/529,096	02/12/02	04/07/00	04	NO	07385.0007

PTOL-439 (Rev. 09/2006)

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Customer No 197 | ISTMT | DATE PRINTED 08/15/2012

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2318 Mill Road 12th Floor
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MAINTENANCE FEE STATEMENT

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Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
6,346,532	$2,480.00	$0.00	07/15/09	09/529,096	02/12/02	04/07/00	08	NO	ASTELLAS PHARMA INC

PTOL-439 (Rev. 09/2006)

Appendix F

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,346,532 B1
DATED : February 12, 2002
INVENTOR(S) : T. Maruyama et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 16,
Lines 29-30, (Example 3) should read: -- (R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino] ethyl]-8-quinolinecarboxanilide dihydrochloride

Column 17,
Lines 40-41, (Example 16) should read:
-- (R)-2-(2-Benzyloxypyridin-6-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl] acetanilide hydrochloride --

Column 19,
Lines 58-60, (Example 39) should read: -- (R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino] ethyl]-2-(2-phenylaminothiazol-4-yl)acetanilide hydrochloride --

Column 23,
Lines 3-5, (Example 66) should read:
-- (R)-2-[1-(3,5-Difluorobenzyl)-1H-imidazol-2-yl]-4'-
[2-(2-hydroxy-2-phenylethyl)amino]ethyl] acetanilide dihydrochloride --

Column 26,
Lines 47-49, (Example 99) should read: -- 4'[(S)-2-[((R)-2-Hydroxy-2-phenylethyl) amino]propyl]-2-(2-pyridyl)acetanilide hydrochloride --

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,346,532 B1
DATED : February 12, 2002
INVENTOR(S) : T. Maruyama et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 28,
Line 2, change "30/1 Δ 10/1)." to -- 30/1 ⟹ 10/1). --.
Line 7, should read: -- [(2-hydroxy-2-phenylethyl)amino]propyl]-2-(2-pyridyl) --
Lines 62-63, (Example 113) should read: -- (R)-1-[4-[2-[(2-Hydroxy-2-phenylethyl) amino]ethyl] phenyl]-3-(2-pyridyl)urea dihydrochloride --

Column 45,
Line 4, should read: -- (R)-2-[1-(4-chlorobenzyl)-1H-imidazol-2-yl]-4'-[2-[(2- --

Signed and Sealed this

Thirtieth Day of July, 2002

Attest:

Attesting Officer

JAMES E. ROGAN
Director of the United States Patent and Trademark Office

Appendix G

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 69,416

Astellas Pharma US, Inc.
Attention: Donald L. Raineri, Pharm.D.
Senior Director, Regulatory Affairs
Three Parkway North
Deerfield, IL 60015-2548

Dear Dr. Raineri:

We acknowledge receipt of your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned:	69,416
Sponsor:	Astellas Pharma US, Inc.
Name of Drug:	YM178
Date of Submission:	May 9, 2006
Date of Receipt:	May 10, 2006

Studies in humans may not be initiated until 30 days after the date of receipt shown above. If, on or before June 9, 2006, we identify deficiencies in the IND that require correction before human studies begin or that require restriction of human studies, we will notify you immediately that (1) clinical studies may not be initiated under this IND ("clinical hold") or that (2) certain restrictions apply to clinical studies under this IND ("partial clinical hold"). In the event of such notification, you must not initiate or you must restrict such studies until you have submitted information to correct the deficiencies, and we have notified you that the information you submitted is satisfactory.

It has not been our policy to object to a sponsor, upon receipt of this acknowledgement letter, either obtaining supplies of the investigational drug or shipping it to investigators listed in the IND. However, if the drug is shipped to investigators, they should be reminded that studies may not begin under the IND until 30 days after the IND receipt date or later if the IND is placed on clinical hold.

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations). Those responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]; (2) reporting any adverse experience associated with use of the drug that is both serious and unexpected in writing no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]; and (3) submitting annual progress reports [21 CFR 312.33].

As required by the Food and Drug Modernization Act and the Best Pharmaceuticals for Children Act, you are also responsible for registering certain clinical trials involving your drug product in the Clinical Trials Data Bank (http://clinicaltrials.gov & http://prsinfo.clinicaltrials.gov/). If your drug is intended for the treatment of a serious or life-threatening disease or condition and you are conducting clinical trials to test its effectiveness, then you must register these trials in the Data Bank. Although not required, we encourage you to register effectiveness trials for non-serious diseases or conditions as well as non-effectiveness trials for all diseases or conditions, whether or not they are serious or life-threatening. Additional information on registering your clinical trials, including the required and optional data elements and the FDA Draft Guidance for Industry, "Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions," is available at the Protocol Registration System (PRS) Information Site http://prsinfo.clinicaltrials.gov/.

Please cite the IND number listed above at the top of the first page of any communications concerning this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call Jean Makie, Sr. Regulatory Project Manager, at 301-796-0952.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph., M.P.A.
Chief, Project Management Staff
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Margaret Kober
5/18/2006 11:53:01 AM
Chief, Project Management Staff

Appendix H

Mirabegron (YM178) FDA Submission/Correspondence Index

SUBMISSION/ RECEIPT DATE	DESCRIPTION
05/09/06	Original IND Application
06/05/06	FDA Fax 30 day IND safety review complete with comments
06/07/06	General Correspondence: Response to FDA 30-day review comments for new protocol 178-CL-036
07/17/06	Protocol Amendment: Revised Protocol 178-CL-036 incorporating Amendments 1 and 2
07/28/06	General Correspondence –proposal to amend Protocol 178-CL-036
08/15/06	FDA IND chemistry review complete with comments
09/15/06	Information Amendment: Chemistry, Manufacturing and Controls
09/21/06	Protocol Amendment: New Protocol 178-CL-060 /Information Amendment: 50 mg tablet
04/05/07	General Correspondence – Request for Protocol Review (Core Protocol 178-CL-037)
04/26/07	FDA Fax requesting additional information on Protocol 178-CL-037
06/05/07	General Correspondence – Additional Information Requested for IRT-QT Review of Core Protocol 178-CL-037
06/12/07	Protocol Amendment: Protocol 178-CL-060 Amendment 1
08/02/07	Information Amendment: Pharmacology /Toxicology - Final Nonclinical Study Reports
08/07/07	Annual Report – Reporting Interval June 9, 2006 through June 8, 2007
08/17/07	General Correspondence: Request for End of Phase 2 Meeting
08/28/07	FDA IRT-QT Review comments on protocol 178-CL-037
09/21/07	General Correspondence: Additional Information Requested for Review of QT Protocol 178-CL-037
10/05/07	End of Phase 2 Briefing Document
10/09/07	FDA IRT-QT Review comments on protocol 178-CL-037
10/26/07	Protocol Amendment: New Protocol 178-CL-044
11/08/07	General Correspondence: Additional Information Requested for QT Protocol 178-CL-037
12/03/07	General Correspondence: Sponsor End of Phase 2 Meeting Minutes
12/11/07	FDA End of Phase 2 Meeting Minutes
12/21/07	Protocol Amendment: Request for Special Protocol Assessment (SPA) for Protocol 178-CL-047
12/21/07	Protocol Amendment: Request for Special Protocol Assessment (SPA) for Protocol 178-CL-046
01/29/08	Information Amendment: New Investigator's Brochure
01/31/08	Protocol Amendment: New Protocol 178-cl-037 and Information Amendment: CMC
02/05/08	FDA Comments on SPA review for protocols 178-CL-046 and -047

SUBMISSION/ RECEIPT DATE	DESCRIPTION
02/22/08	General Correspondence: Response to SPA comments: Clinical Protocols 178-cl-046 and -047
03/07/08	Protocol Amendment: New Protocols 178-CL-046, 178-CL-047 and 178-CL-049 with associated Amendments
04/25/08	Protocol Amendment: Protocol 178-cl-049 incorporating Amendments 1 and 2
06/16/08	Form FDA1572, Statement of Investigator, use in Norway
07/18/08	Information Amendment: Pharmacology/Pharmacokinetics/Toxicology Non-Clinical Reports
07/31/08	Protocol Amendment: New Protocols 178-CL-039, 178-CL-040, 178-CL-058 and 178-CL-059
08/07/08	IND Annual Report (June 9, 2007 - June 8, 2008)
08/26/08	Protocol Amendment: New Protocol 178-cl-038
09/02/08	FDA Denial of Alternate Statement of Investigator Form FDA 1572
09/18/08	Protocol Amendment: New Protocol 178-cl-070)
10/23/08	Protocol Amendment: Amendment 2 for protocols 178-CL-046, 178-CL-047 and Amendment 3 for Protocol 178-CL-049
10/31/08	Protocol Amendment: New Protocol 178-cl-068
11/20/08	Information Amendment: Investigator's Brochure edition 8.0
01/07/09	Transfer Letter to APGD
01/26/09	Information Amendment: CMC (IV Formulation)
01/26/09	Protocol Amendment: Amendment 1 for Protocol 178-cl-038
02/16/09	Information Amendment - CMC (25 mg Formulation)
02/18/09	Protocol Amendment: Withdrawal of Norway sites from IND
03/05/09	Request for Special Protocol Assessment: Amended Clinical Protocol 178 CL-047
03/05/09	Request for Special Protocol Assessment: Amended Clinical Protocol 178 CL-046
03/17/09	FDA Request for Patient Information in Protocol 178-CL-049
03/20/09	General Correspondence: Response to Protocol 178-CL-049 Patient Information Requested
04/01/09	General Correspondence - Protocol 178-CL-049 Patient Information Requested
04/07/09	New Protocol 178-CL-076, CMC Amendment
04/17/09	Protocol Amendment: New Protocol 178-CL-074
04/23/09	Protocol Amendment: Revised Protocol 178-CL-049 incorporating Amendments 4 and 5
04/30/09	Information Amendment: New Investigator's Brochure v8.0 Addendum dated March 2009
05/14/09	Protocol Amendment: Protocol 178-CL-038 Amendment 2
05/14/09	Protocol Amendment: New Protocol 178-CL-041

SUBMISSION/ RECEIPT DATE	DESCRIPTION
05/20/09	FDA Comments on Amended protocols 178-CL-046 and -047
06/18/09	Proprietary Name Request
07/22/09	Information Amendment: Clinical (Final Clinical Study Report 178-CL-060)
07/31/09	Information Amendment -pharmacology and toxicology reports
08/07/09	Annual Report – Reporting Interval June 9, 2008 through June 8, 2009
08/18/09	Protocol Amendment: New Protocols 178-CL-053, 178-CL-069, 178-CL-072
08/27/09	FDA Request for Patient Information in Protocol 178-CL-049
08/28/09	Response to Information Request
09/14/09	Response to Information Request (CRFs for 178-CL-046 and 148-CL-049)
09/25/09	Type C Meeting Request
10/05/09	FDA Request for Patient Information
10/06/09	FDA Comments on Protocols 178-CL-069 and -072
10/06/09	General Correspondence: Protocol 178-CL-047 and 178-CL-049 Patient Information Requested
10/19/09	Protocol Amendment: Request for IRT-QT Review of Protocol 178-CL-077
10/27/09	FDA Teleconference Regarding protocol 178-CL-053
11/05/09	Type C Meeting Briefing Document
11/10/09	Protocol Amendment - Protocol 178-CL-053 Amendment 1
11/10/09	General Correspondence - Protocol 178-CL-049 Patient Information Request
11/18/09	General Correspondence: Human Metabolites of Mirabegron
11/18/09	Information Amendment: Final Clinical Study Report Protocol 178-CL-036
12/02/09	FDA Request for Datasets for Study 178-CL-037
12/04/09	Information Amendment: Datasets for QT Study 178-CL-037
12/08/09	Information Amendment Clinical: Response to Comments for Protocol 178-CL-069 and 178-CL-072
12/10/09	FDA Request for Patient information
12/16/09	FDA Response to Proprietary Name Request
12/23/09	Submission of Sponsor Type C Meeting Minutes
01/05/09	FDA Meeting Minutes from Type C Meeting
01/08/09	FDA Meeting Minutes from October 27, 2009 Teleconference
01/15/10	Type B Meeting Request [CMC]
01/20/10	Information Amendment - Response to Information Request [178-CL-037 Dataset]
02/03/10	Type B Meeting Pre-NDA CMC Briefing Document
02/15/10	Request for Proprietary Name Review
03/17/10	FDA Meeting Minutes from Type B CMC meeting
03/23/10	Protocol Amendment - Protocol 178-CL-053 Amendment 2

SUBMISSION/ RECEIPT DATE	DESCRIPTION
03/30/10	Protocol Amendment: Protocol 178-cl-049 incorporating Amendments 1 - 7
04/19/10	FDA IRT-QT Review comments on protocol 178-CL-077
04/22/10	Information Amendment: Investigator's Brochure edition 9.0
04/27/10	Protocol Amendment: Protocol 178-CL-077 Amendment 1
05/13/10	Information Amendment Clinical: Final Clinical Study Report 178-CL-041
05/27/10	Information Amendment: Nonclinical
06/17/10	FDA Request for Medwatch Reports
06/24/10	Information Amendment - Response to Information Request
07/01/10	Response to Information Request
07/01/10	FDA Teleconference
07/21/10	Response to Information Request
07/22/10	FDA Teleconference
07/27/10	Protocol Amendment: New Protocol 178-CL-080
07/28/10	General Correspondence: Meeting Minutes - July 1, 2010 teleconference
08/03/10	Information Amendment: PharmTox
08/09/10	Annual Report – Reporting Interval June 9, 2009 through June 8, 2010
08/09/10	Response to Information Request
08/10/10	General Correspondence: Type B preNDA Meeting Request
08/18/10	Information Amendment - Response Additional Information - Protocol 178-CL-081 / Preclinical Assessment
08/19/10	General Correspondence: Meeting Minutes - July 22, 2010 teleconference
08/25/10	FDA Teleconference
09/16/10	Information Amendment - 178-CL-047 Clinical Study Report
09/22/10	Protocol Amendment - New Protocol 178-CL-081
09/28/10	Information Amendment - 178-CL-046 Clinical Study Report
10/01/10	PreNDA Briefing Document
10/13/10	General Correspondence: Meeting Minutes - August 25, 2010 teleconference
10/22/10	Information Amendment - Additional Information for Type B Pre-NDA Meeting
11/04/10	FDA Comments on Protocol 178-CL-081
11/11/10	Protocol Amendment - Protocol 178-CL-081 Amendment 1
11/19/10	General Correspondence - SponsorPre-NDA Meeting Minutes (November 2, 2010)
12/03/10	Protocol Amendment - Protocol 178-CL-081 Amendment 2 and SAP
12/09/10	FDA PreNDA Meeting Minutes
01/19/11	Proprietary Name Rebuttal
01/26/11	Amendment to Proprietary Name Review

SUBMISSION/ RECEIPT DATE	DESCRIPTION
02/01/11	Information Amendment - Clinical Study Reports 178-CL-038 and 178-CL-039
02/16/11	Information Amendment - Investigator's Brochure Edition 10
03/11/11	Electronic Submission Meeting Request
04/19/11	Information Amendment - 178-CL-049 Clinical Study Report
05/04/11	Information Amendment: PharmTox
05/17/11	Briefing Package for Type C Electronic Submission Meeting
06/24/11	Information Amendment: Toxicology
07/11/11	Sponsor Electronic Submission Meeting Minutes
07/19/11	FDA Response to Proprietary Name Request
07/21/11	FDA Meeting Minutes Electronic Submission Meeting
08/26/11	New Drug Application 202611 Submission
09/06/11	FDA NDA Acknowledgement Letter
09/09/11	FDA Request for Word version of Labeling text
09/12/11	FDA Request for FDA Form 3674
09/12/11	Information Amendment: Draft Labeling in Word format and FDA Form 3674
10/07/11	FDA Request for final versions Protocols 178-CL-046, -047, -074
10/11/11	Response to Information Request: -046 Protocol with Amendments
10/13/11	Request for Proprietary Name Review
10/20/11	FDA Request for updated labeling with Trade Name
10/19/11	Response to Information Request: Updated Draft Labeling to add tradename
11/03/11	FDA Request for Resized Datasets
11/03/11	FDA Request for statistical programming code
11/09/11	FDA Filing Communication Day 74 Letter
11/17/11	FDA Request for Clinical Patient Information
11/28/11	Response to Day 74 Letter (Updated Labeling)
12/01/11	Response to Day 74 Letter (ClinPharm)
12/01/11	Response to Day 74 Letter (Biostatistics)
12/07/11	Clinical Information Response
12/07/11	FDA Request for CMC samples and equipment
12/09/11	Clinical Information Response (Additional Patient Information)
12/13/11	FDA Request for Highlights of Clinical Pharmacology Form
12/13/11	Response to Information Request (Highlights of Clinical Pharmacology)
12/15/11	FDA Request for Carton and Container label changes
12/15/11	Amendment to Pending Application (Resized Datasets)
12/21/11	120 Day Safety Update (Updated CMC)
12/22/11	Amendment to Pending Application (Updated Vital Signs Analyses)
01/05/12	FDA CMC Request
01/13/12	Response to Information Request (CMC)
02/07/12	Response to Information Request (List of Investigators)
02/08/12	Request for Proprietary Name Review

SUBMISSION/ RECEIPT DATE	DESCRIPTION
02/08/12	FDA Mid-Cycle Review Comments and CVD Analysis
02/08/12	Response to Information Request (Updated draft carton and container labels)
02/14/12	Investigator's Brochure, Edition 11
02/17/12	Request for Comments and Advice (Proposed Analysis Plan)
02/29/12	FDA CMC Request
03/06/12	Response to Information Request (CMC Micro Testing)
03/07/12	Response to Information Request (CVD Analysis)
03/19/12	Response to Information Request (CMC Comparability Protocol)
03/23/12	Response to Information Request (10-yr CVD Risk Analysis)
04/03/12	Withdrawal of Request for Proprietary Name Review
04/10/12	Response to Information Request (CMC Cap Liners)
04/12/12	FDA Request for Pediatric Information
04/16/12	Proprietary name Review Request
04/17/12	Response to Information Request [Pediatric Administrative Information]
05/03/12	FDA Telecon: Post-marketing Commitments and Labeling comments
05/04/12	Response to Information Request (Pediatric Administrative Information-
05/04/12	Response to Information Request (Cardiovascular Protocol Outline)
05/09/12	Response to Information Request (Updated Package Insert)
05/10/11	FDA Labeling PMR/PMC Letter
05/11/12	Response to Information Request (Hepatotox PM Surveillance)
05/11/12	Response to Information Request (Updated draft carton and container labels)
05/16/12	Response to Information Request (Neoplasm Protocol Outline)
05/18/12	Response to Information Request (Updated draft carton and container labels)
06/01/12	Response to Information Request (Hepatotox PM Surveillance)
06/04/12	Astellas Change of Address
06/25/12	Response to Information Request (Postmarketing Requirements)
06/27/12	Response to Information Request (Revised Postmarketing Requirements)
06/28/12	Response to Information Request (Updated draft labeling text)
06/28/12	FDA NDA Approval Letter

PTO/SB/81A (12-06)
Approved for use through 11/30/2011. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT - POWER OF ATTORNEY OR REVOCATION OF POWER OF ATTORNEY WITH A NEW POWER OF ATTORNEY AND CHANGE OF CORRESPONDENCE ADDRESS

Patent Number	6,346,532 B1
Issue Date	February 12, 2002
First Named Inventor	Tatsuya Maruyama et al.
Title	AMIDE DERIVATIVES OR SALTS THEREOF
Attorney Docket Number	02213.003400

I hereby revoke all previous powers of attorney given in the above-identified patent.

☐ A Power of Attorney is submitted herewith.

OR

☒ I hereby appoint Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s) with respect to the patent identified above, and to transact all business in the United States Patent and Trademark Office connected therewith: 05514

OR

☐ I hereby appoint Practitioner(s) named below as my/our attorney(s) or agent(s) with respect to the patent identified above, and to transact all business in the United States Patent and Trademark Office connected therewith:

Practitioner(s) Name	Registration Number

Please recognize or change the correspondence address for the above-identified patent to:

☐ The address associated with the above-mentioned Customer Number.

OR

☒ The address associated with Customer Number: 05514

OR

☐ Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the:

☐ Inventor, having ownership of the patent.

OR

☒ Patent owner.

Statement under 37 CFR 3.73(b) (Form PTO/SB/96) submitted herewith or filed on _____

SIGNATURE of Inventor or Patent Owner

Signature		Date	9/20/2012
Name	Hiroshi MORITA	Telephone	+81-3-3244-3051
Title and Company	Vice President Intellectual Property - Astellas Pharma Inc.		

NOTE: Signatures of all the inventors or patent owners of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☒ *Total of 1 forms are submitted.

This collection of information is required by 37 CFR 1.31, 1.32 and 1.33. 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 1.11 and 1.14. This collection is estimated to take 3 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.

PTO/SB/96 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Tatsuya Maruyama et al.

Application No./Patent No.: 6,346,532 B1 Filed/Issue Date: February 12, 2002

Titled: AMIDE DERIVATIVES OR SALTS THEREOF

Astellas Pharma Inc. , a Corporation
(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.

states that it is:

1. [X] the assignee of the entire right, title, and interest in;

2. [ ] an assignee of less than the entire right, title, and interest in
(The extent (by percentage) of its ownership interest is _____ %); or

3. [ ] the assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made)

the patent application/patent identified above, by virtue of either:

A. [ ] An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy therefore is attached.

OR

B. [X] A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: Inventors To: Yamanouchi Pharmaceutical Co., Ltd.
The document was recorded in the United States Patent and Trademark Office at
Reel 010808, Frame 0313, or for which a copy thereof is attached.

2. From: Yamanouchi Pharmaceutical Co., Ltd. To: Astellas Pharma Inc.
The document was recorded in the United States Patent and Trademark Office at
Reel 016784, Frame 0361, or for which a copy thereof is attached.

3. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

[ ] Additional documents in the chain of title are listed on a supplemental sheet(s).

[ ] As required by 37 CFR 3.73(b)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (*i.e.*, a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

Signature 8/20/2012
Date

Hiroshi MORITA Vice President, Intellectual Property
Printed or Typed Name Title

Electronic Acknowledgement Receipt

EFS ID:	13808223
Application Number:	09529096
International Application Number:	
Confirmation Number:	2160
Title of Invention:	AMIDE DERIVATIVES OR SALTS THEREOF
First Named Inventor/Applicant Name:	TATSUYA MARUYAMA
Customer Number:	22852
Filer:	Jason M. Okun/DAVID NGUY
Filer Authorized By:	Jason M. Okun
Attorney Docket Number:	07385.0007
Receipt Date:	21-SEP-2012
Filing Date:	07-APR-2000
Time Stamp:	16:11:36
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	Power of Attorney	POA532patent.pdf	91900 b3f8316bc0f99c71df43fe513ce9d88f834c d81	no	1

Warnings:	
Information:	

2	Assignee showing of ownership per 37 CFR 3.73(b).	Statement532Patent.pdf	100827 e6517121400eaa889a0942fe537955ef3817ec88	no	1
Warnings:					
Information:					
			Total Files Size (in bytes):	192727	

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.

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	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
09/529,096	04/07/2000	TATSUYA MARUYAMA	02213.003400

CONFIRMATION NO. 2160

POA ACCEPTANCE LETTER

5514
FITZPATRICK CELLA HARPER & SCINTO
1290 Avenue of the Americas
NEW YORK, NY 10104-3800

OC000000056879857

Date Mailed: 10/02/2012

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 09/21/2012.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

/dtvernon/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

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	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
09/529,096	04/07/2000	TATSUYA MARUYAMA	07385.0007

CONFIRMATION NO. 2160

POWER OF ATTORNEY NOTICE

22852
FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER LLP
901 NEW YORK AVENUE, NW
WASHINGTON, DC 20001-4413

Date Mailed: 10/02/2012

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 09/21/2012.

- The Power of Attorney to you in this application has been revoked by the assignee who has intervened as provided by 37 CFR 3.71. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

/dtvernon/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Office of Regulatory Policy
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 51, Rm. 6222
Silver Spring, MD 20993-0002

MAR 13 2013

Attention: Beverly Friedman

The attached application for patent term extension of U.S. Patent No. 6,346,532 was filed on August 23, 2012, under 35 U.S.C. § 156. Please note that a patent term extension application for U.S. Patent No. 7,342,117 and U.S. Patent No. 7,750,029 for NDA 69,416 for the human drug product MYRBETRIQ ™ (mirabergron) was filed concurrently, pursuant to the provisions of 37 C.F.R. § 1.785.

The assistance of your Office is requested in confirming that the product identified in the application, MYRBETRIQ ™, has been subject to a regulatory review period within the meaning of 35 U.S.C. § 156(g) before its first commercial marketing or use and that the application for patent term extension was filed within the sixty-day period beginning on the date the product was approved. Since a determination has not been made whether the patent in question claims a product which has been subject to the Federal Food, Drug and Cosmetic Act, or a method of manufacturing or use of such a product, this communication is NOT to be considered as notice which may be made in the future pursuant to 35 U.S.C. § 156(d)(2)(A).

Our review of the application to date indicates that the subject patent would be eligible for extension of the patent term under 35 U.S.C. § 156.

Inquiries regarding this communication should be directed to Ali Salimi at (571) 272-0909 (telephone) or (571) 273-0909 (facsimile) or by e-mail at ali.salimi@uspto.gov.

Mary C. Till
Senior Legal Advisor
Office of Patent Legal Administration
Office of the Associate Commissioner
for Patent Examination Policy

cc: Jason M. Okun
Fitzpatrick, Cella, Harper & Scinto
1290 Avenue of Americas
New York, New York 10104-3800

Department of Health and Human Services | Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Building # 51, Room 6284
Silver Spring, MD 20993

JUL 10 2013

Re: Myrbetriq
Patent Nos. 6,346,532; 7,342,117; 7,750,029
Docket Nos. FDA-2013-E-0410;
FDA-2013-E-0411;
And FDA-2013-E-0412

The Honorable Teresa Stanek Rea
Acting Under Secretary of Commerce and
Acting Director of the United States Patent and Trademark Office
Mail Stop Hatch-Waxman PTE
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Acting Director Rea:

This is concerning the applications for patent term extension for U.S. Patent Nos. 6,346,532; 7,342,117; and 7,750,029, filed by Astellas Pharma Inc., under 35 U.S.C. 156. The human drug product claimed by the patents is Myrbetriq (mirabergron), which was assigned new drug application (NDA) No. 202611.

A review of the Food and Drug Administration's official records indicates that this product was subject to a regulatory review period before its commercial marketing or use, as required under 35 U.S.C. 156(a)(4). Our records also indicate that it represents the first permitted commercial marketing or use of the product, as defined under 35 U.S.C. 156(f)(1).

The NDA was approved on June 28, 2012, which makes the submission of the patent term extension application on August 23, 2012, timely within the meaning of 35 U.S.C. 156(d)(1).

Should you conclude that the subject patent is eligible for patent term extension, please advise us accordingly. As required by 35 U.S.C. 156(d)(2)(A) we will then determine the applicable regulatory review period, publish the determination in the *Federal Register*, and notify you of our determination.

Please let me know if we can be of further assistance.

Sincerely yours,

Carol Bennett

for Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

cc: Jason M. Okun
Fitzpatrick, Cella, Harper & Scinto
1290 Avenue of the Americas
New York, NY 10104-3800

02213.003400. PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re: U.S. Patent No. 6,346,532 B1

Issued: February 12, 2002

To: Tatsuya Maruyama, Takayuki Suzuki, Kenichi Onda, Masahiko Hayakawa, Hiroyuki Moritomo, Tetsuya Kimizuka, and Tetsuo Matsui

For: AMIDE DERIVATIVES OR SALTS THEREOF

Mail Stop Hatch-Waxman PTE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SUBMISSION UNDER 37 C.F.R. § 1.765

Sir:

In compliance with the duty of disclosure in patent term extension proceedings under 37 C.F.R. § 1.765, Applicant would like to advise the Office as follows:

- A Request for Supplemental Examination of the above-captioned U.S. Patent No. 6,346,532 B1 was filed on November 21, 2013. A Notice of Supplemental Examination Request Filing Date confirming that this Request satisfied all relevant requirements for supplemental examination was issued on January 24, 2014.
- The Supplemental Examination was assigned Control No. 96/000,045.
- A Supplemental Examination Certificate was issued on January 31, 2014, indicating that a substantial new question of patentability affecting at least one claim of the patent is raised by the aforementioned Request. Accordingly, an *ex-parte* reexamination will be ordered pursuant to 35 U.S.C. § 257.

Applicant's undersigned attorney may be reached in our New York Office by telephone at (212) 218-2100. All correspondence should continue to be directed to our address listed below.

Respectfully submitted,

/Jason M. Okun/
Jason M. Okun
Attorney for Applicant
Reg. No. 48,512

Date: February 27, 2014

FITZPATRICK, CELLA, HARPER & SCINTO
1290 Avenue of the Americas
New York, New York 10104-3800
Telephone: (212) 218-2100
Facsimile: (212) 218-2200

Electronic Acknowledgement Receipt

EFS ID:	18305367
Application Number:	09529096
International Application Number:	
Confirmation Number:	2160
Title of Invention:	AMIDE DERIVATIVES OR SALTS THEREOF
First Named Inventor/Applicant Name:	TATSUYA MARUYAMA
Customer Number:	5514
Filer:	Jason M. Okun/DAVID NGUY
Filer Authorized By:	Jason M. Okun
Attorney Docket Number:	02213.003400
Receipt Date:	27-FEB-2014
Filing Date:	07-APR-2000
Time Stamp:	12:25:06
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	Miscellaneous Incoming Letter	Rule765Submission02213003400.pdf	96902 ae4babc162d1f95fd71a6f1c204efbc7279a147	no	2
Warnings:					
Information:					

Total Files Size (in bytes):	96902

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.

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

APR - 2 2014

Office of Regulatory Policy
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 51, Rm. 6284
Silver Spring, MD 20993-0002

Attention: Beverly Friedman

Dear Ms. Axelrad:

Transmitted herewith is a copy of the application for patent term extension of U.S. Patent No. 6,346,532. The application was filed on August 23, 2012, under 35 U.S.C. § 156. Please note that patent term extension for U.S. Patent No. 7,750,029 and U.S. Patent No. 7,342,117 for NDA No. 202611 for the product MYRBETRIQ ® (mirabergron) was filed concurrently, pursuant to the provisions of 37 C.F.R. § 1.785.

The patent claims a product that was subject to regulatory review under the Federal Food, Drug and Cosmetic Act. Subject to final review, the subject patent is considered to be eligible for patent term extension. Thus, a determination by your office of the applicable regulatory review period is necessary. Accordingly, notice and a copy of the application are provided pursuant to 35 U.S.C. § 156(d)(2)(A).

Inquiries regarding this communication should be directed to Ali Salimi at (571) 272-0909 (telephone) or (571) 273-0909 (facsimile) or by e-mail at ali.salimi@uspto.gov.

Mary C. Till
Senior Legal Advisor
Office of Patent Legal Administration
Office of the Associate Commissioner
for Patent Examination Policy

cc: Jason M. Okun
Fitzpatrick, Cella, Harper & Scinto
1290 Avenue of Americas
New York, New York 10104-3800

RE: MYRBETRIQ ® (mirabergron)
Docket No. FDA-2013-E-0410

Department of Health and Human Services Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Building # 51, Room 6257
Silver Spring, MD 20993

Re: MYRBETRIQ
Patent Nos. 6,346,532; 7,342,117; 7,750,029
Docket Nos.: FDA-2013-E-0410; FDA-2013-E-0411; FDA-2013-E-0412

MAY 09 2014

Acting Under Secretary of Commerce and
Acting Director of the United States Patent and Trademark Office
Mail Stop Hatch-Waxman PTE
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Acting Director:

This is in regard to the applications for patent term extension for U.S. Patent Nos. 6,346,532; 7,342,117; and 7,750,029, filed by Astellas Pharma Inc., under 35 U.S.C. section 156 et seq. We have reviewed the dates contained in the applications and have determined the regulatory review period for MYRBETRIQ (mirabegron), the human drug product claimed by the patents.

The total length of the regulatory review period for MYRBETRIQ (mirabegron) is 2,213 days. Of this time, 1,908 days occurred during the testing phase and 305 days occurred during the approval phase. These periods of time were derived from the following dates:

1. The date an exemption under subsection 505(i) of the Federal Food, Drug, and Cosmetic Act involving this drug product became effective: June 9, 2006.

   The applicant claims May 10, 2006, as the date the investigational new drug application (IND) became effective. However, FDA records indicate that the IND effective date was June 9, 2006, which was 30 days after FDA receipt of the IND.

2. The date the application was initially submitted with respect to the human drug product under section 505 of the Federal Food, Drug, and Cosmetic Act: August 29, 2011.

   FDA has verified the applicant's claim that the new drug application (NDA) for MYRBETRIQ (NDA 202611) was submitted on August 29, 2011.

3. The date the application was approved: June 28, 2012.

   FDA has verified the applicant's claim that NDA 202611 was approved on June 28, 2012.

This determination of the regulatory review period by FDA does not take into account the effective date of the patent, nor does it exclude one-half of the testing phase as required by 35 U.S.C. section 156(c)(2).

Please let me know if we can be of further assistance.

Sincerely yours,

for Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

cc: Jason M. Okun
Fitzpatrick, Cella, Harper & Scinto
1290 Avenue of the Americas
New York, NY 10104-3800

Conjugate Vaccine). MENHIBRIX is a vaccine indicated for active immunization to prevent invasive disease caused by *Neisseria meningitides* serogroups C and Y and *Haemophilus influenzae* type b. Subsequent to this approval, the Patent and Trademark Office received patent term restoration applications for MENHIBRIX (U.S. Patent Nos. 5,693,326 and 5,955,079) from the Henry M. Jackson Foundation for the Advancement of Military Medicine, and the Patent and Trademark Office requested FDA's assistance in determining the patents' eligibility for patent term restoration. In a letter dated March 4, 2013, FDA advised the Patent and Trademark Office that this human biological product had undergone a regulatory review period and that the approval of MENHIBRIX represented the first permitted commercial marketing or use of the product. Thereafter, the Patent and Trademark Office requested that FDA determine the product's regulatory review period.

FDA has determined that the applicable regulatory review period for MENHIBRIX is 2,924 days. Of this time, 1,886 days occurred during the testing phase of the regulatory review period, while 1,038 days occurred during the approval phase. These periods of time were derived from the following dates:

1. *The date an exemption under section 505(i) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(i)) became effective:* June 14, 2004. The applicant claims June 12, 2004, as the date the investigational new drug application (IND) became effective. However, FDA records indicate that the IND effective date was June 14, 2004, which was 30 days after FDA receipt of the IND.

2. *The date the application was initially submitted with respect to the human biological product under section 351 of the Public Health Service Act (42 U.S.C. 262):* August 12, 2009. FDA has verified the applicant's claim that the biologics license application (BLA) for MENHIBRIX (BLA 125363) was initially submitted on August 12, 2009.

3. *The date the application was approved:* June 14, 2012. FDA has verified the applicant's claim that BLA 125363 was approved on June 14, 2012.

This determination of the regulatory review period establishes the maximum potential length of a patent extension. However, the Patent and Trademark Office applies several statutory limitations in its calculations of the actual period for patent extension. In its applications for patent extension, this applicant seeks 1,825 days of patent term extension.

Anyone with knowledge that any of the dates as published are incorrect may submit to the Division of Dockets Management (see **ADDRESSES**) either electronic or written comments and ask for a redetermination by July 28, 2014. Furthermore, any interested person may petition FDA for a determination regarding whether the applicant for extension acted with due diligence during the regulatory review period by November 24, 2014. To meet its burden, the petition must contain sufficient facts to merit an FDA investigation. (See H. Rept. 857, part 1, 98th Cong., 2d sess., pp. 41–42, 1984.) Petitions should be in the format specified in 21 CFR 10.30.

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) electronic or written comments and written or electronic petitions. It is only necessary to send one set of comments. Identify comments with the docket number found in brackets in the heading of this document. If you submit a written petition, two copies are required. A petition submitted electronically must be submitted to *http://www.regulations.gov*, Docket No. FDA–2013–S–0610. Comments and petitions that have not been made publicly available on *http://www.regulations.gov* may be viewed in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

Dated: May 21, 2014.

Leslie Kux,

Assistant Commissioner for Policy.

[FR Doc. 2014–12294 Filed 5–27–14; 8:45 am]

BILLING CODE 4160–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket Nos. FDA–2013–E–0410; FDA–2013–E–0411; FDA–2013–E–0412]

Determination of Regulatory Review Period for Purposes of Patent Extension; MYRBETRIQ

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) has determined the regulatory review period for MYRBETRIQ and is publishing this notice of that determination as required by law. FDA has made the determination because of the submission of applications to the Director of Patents and Trademarks, Department of Commerce, for the extension of a patent which claims that human drug product.

ADDRESSES: Submit electronic comments to *http://www.regulations.gov*. Submit written petitions (two copies are required) and written comments to the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit petitions electronically to *http://www.regulations.gov* at Docket No. FDA–2013–S–0610.

FOR FURTHER INFORMATION CONTACT: Beverly Friedman, Office of Management, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 6257, Silver Spring, MD 20993–0002, 301–796–7900.

SUPPLEMENTARY INFORMATION: The Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98–417) and the Generic Animal Drug and Patent Term Restoration Act (Pub. L. 100–670) generally provide that a patent may be extended for a period of up to 5 years so long as the patented item (human drug product, animal drug product, medical device, food additive, or color additive) was subject to regulatory review by FDA before the item was marketed. Under these acts, a product's regulatory review period forms the basis for determining the amount of extension an applicant may receive.

A regulatory review period consists of two periods of time: A testing phase and an approval phase. For human drug products, the testing phase begins when the exemption to permit the clinical investigations of the drug becomes effective and runs until the approval phase begins. The approval phase starts with the initial submission of an application to market the human drug product and continues until FDA grants permission to market the drug product. Although only a portion of a regulatory review period may count toward the actual amount of extension that the Director of Patents and Trademarks may award (for example, half the testing phase must be subtracted as well as any time that may have occurred before the patent was issued), FDA's determination of the length of a regulatory review period for a human drug product will include all of the testing phase and approval phase as specified in 35 U.S.C. 156(g)(1)(B).

FDA has approved for marketing the human drug product MYRBETRIQ (mirabegron). MYRBETRIQ is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary

frequency. Subsequent to this approval, the Patent and Trademark Office received patent term restoration applications for MYRBETRIQ (U.S. Patent Nos. 6,346,532; 7,342,117; 7,750,029) from Astellas Pharma Inc., and the Patent and Trademark Office requested FDA's assistance in determining the patents' eligibility for patent term restoration. In a letter dated July 10, 2013, FDA advised the Patent and Trademark Office that this human drug product had undergone a regulatory review period and that the approval of MYRBETRIQ represented the first permitted commercial marketing or use of the product. Thereafter, the Patent and Trademark Office requested that FDA determine the product's regulatory review period.

FDA has determined that the applicable regulatory review period for MYRBETRIQ is 2,213 days. Of this time, 1,908 days occurred during the testing phase of the regulatory review period, while 305 days occurred during the approval phase. These periods of time were derived from the following dates:

1. *The date an exemption under section 505(i) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 355(i)) became effective:* June 9, 2006. The applicant claims May 10, 2006, as the date the investigational new drug application (IND) became effective. However, FDA records indicate that the IND effective date was June 9, 2006, which was 30 days after FDA receipt of the IND.

2. *The date the application was initially submitted with respect to the human drug product under section 505(b) of the FD&C Act:* August 29, 2011. FDA has verified the applicant's claim that the new drug application (NDA) for MYRBETRIQ (NDA 202611) was submitted on August 29, 2011.

3. *The date the application was approved:* June 28, 2012. FDA has verified the applicant's claim that NDA 202611 was approved on June 28, 2012.

This determination of the regulatory review period establishes the maximum potential length of a patent extension. However, the Patent and Trademark Office applies several statutory limitations in its calculations of the actual period for patent extension. In its applications for patent extension, this applicant seeks 515, 938, or 1,259 days of patent term extension.

Anyone with knowledge that any of the dates as published are incorrect may submit to the Division of Dockets Management (see **ADDRESSES**) either electronic or written comments and ask for a redetermination by July 28, 2014. Furthermore, any interested person may petition FDA for a determination regarding whether the applicant for extension acted with due diligence during the regulatory review period by November 24, 2014. To meet its burden, the petition must contain sufficient facts to merit an FDA investigation. (See H. Rept. 857, part 1, 98th Cong., 2d sess., pp. 41–42, 1984.) Petitions should be in the format specified in 21 CFR 10.30.

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) electronic or written comments and written or electronic petitions. It is only necessary to send one set of comments. Identify comments with the docket number found in brackets in the heading of this document. If you submit a written petition, two copies are required. A petition submitted electronically must be submitted to *http://www.regulations.gov*, Docket No. FDA–2013–S–0610. Comments and petitions that have not been made publicly available on *http://www.regulations.gov* may be viewed in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

Dated: May 21, 2014.

Leslie Kux,

Assistant Commissioner for Policy.

[FR Doc. 2014–12292 Filed 5–27–14; 8:45 am]

BILLING CODE 4160–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2012–E–1246]

Determination of Regulatory Review Period for Purposes of Patent Extension; RESOLUTE INTEGRITY ZOTAROLIMUS–ELUTING CORONARY STENT SYSTEM

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) has determined the regulatory review period for RESOLUTE INTEGRITY ZOTAROLIMUS–ELUTING CORONARY STENT SYSTEM and is publishing this notice of that determination as required by law. FDA has made the determination because of the submission of an application to the Director of Patents and Trademarks, Department of Commerce, for the extension of a patent which claims that medical device.

ADDRESSES: Submit electronic comments to *http://www.regulations.gov*. Submit written petitions (two copies are required) and written comments to the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit petitions electronically to *http://www.regulations.gov* at Docket No. FDA–2013–S–0610.

FOR FURTHER INFORMATION CONTACT: Beverly Friedman, Office of Management, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 6257, Silver Spring, MD 20993–0002, 301–796–7900.

SUPPLEMENTARY INFORMATION: The Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98–417) and the Generic Animal Drug and Patent Term Restoration Act (Pub. L. 100–670) generally provide that a patent may be extended for a period of up to 5 years so long as the patented item (human drug product, animal drug product, medical device, food additive, or color additive) was subject to regulatory review by FDA before the item was marketed. Under these acts, a product's regulatory review period forms the basis for determining the amount of extension an applicant may receive.

A regulatory review period consists of two periods of time: A testing phase and an approval phase. For medical devices, the testing phase begins with a clinical investigation of the device and runs until the approval phase begins. The approval phase starts with the initial submission of an application to market the device and continues until permission to market the device is granted. Although only a portion of a regulatory review period may count toward the actual amount of extension that the Director of Patents and Trademarks may award (half the testing phase must be subtracted as well as any time that may have occurred before the patent was issued), FDA's determination of the length of a regulatory review period for a medical device will include all of the testing phase and approval phase as specified in 35 U.S.C. 156(g)(3)(B).

FDA has approved for marketing the medical device, RESOLUTE INTEGRITY ZOTAROLIMUS–ELUTING CORONARY STENT SYSTEM. RESOLUTE INTEGRITY ZOTAROLIMUS–ELUTING CORONARY STENT SYSTEM is indicated for improving coronary luminal diameters in patients, including those with diabetes mellitus, with symptomatic ischemic heart disease due to de novo lesions of length less than or equal to 27 millimeters (mm) in native

Department of Health and Human Services | Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Building #51, Room 5237
Silver Spring, MD 20993

Re: Myrbetriq
Patent Nos. 6,346,532; 7,342,117; 7,750,029
Docket Nos. FDA-2013-E-0410
FDA-2013-E-0411
FDA-2013-E-0412

JAN 2 1 2015

The Honorable Michelle K. Lee
Deputy Under Secretary of Commerce for Intellectual Property
Acting Director of the United States Patent and Trademark Office
Mail Stop Hatch-Waxman PTE
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Director Lee:

This is in regard to the patent term extension applications for U.S. Patent Nos. 6,346,532; 7,342,117; 7,750,029 filed by Astellas Pharma Inc., under 35 U.S.C. § 156. The patents claim Myrbetriq (mirabegron), which was assigned new drug application (NDA) 202-611.

In the May 28, 2014, issue of the Federal Register (79 Fed. Reg. 30622), the Food and Drug Administration published its determination of this product's regulatory review period, as required under 35 U.S.C. § 156(d)(2)(A). The notice provided that on or before November 24, 2014, 180 days after the publication of the determination, any interested person could file a petition with FDA under 35 U.S.C. § 156(d)(2)(B)(i) for a determination of whether the patent term extension applicant acted with due diligence during the regulatory review period.

The 180-day period for filing a due diligence petition pursuant to this notice has expired and FDA has received no such petition. Therefore, FDA considers the regulatory review period determination to be final.

Please let me know if we can provide further assistance.

Sincerely yours,

for Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

cc: Jason M. Okun
Fitzpatrick, Cella, Harper & Scinto
1290 Avenue of the Americas
New York, NY 10104-3800

02213.003400. PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re: U.S. Patent No. 6,346,532 B1

Issued: February 12, 2002

To: Tatsuya Maruyama, Takayuki Suzuki, Kenichi Onda, Masahiko Hayakawa, Hiroyuki Moritomo, Tetsuya Kimizuka, and Tetsuo Matsui

For: AMIDE DERIVATIVES OR SALTS THEREOF

Mail Stop Hatch-Waxman PTE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SUBMISSION UNDER 37 C.F.R. § 1.765

Sir:

In compliance with the duty of disclosure in patent term extension proceedings under 37 C.F.R. § 1.765, Applicant would like to advise the Office as follows:

- As a result of the *ex-parte* reexamination (Control No. 96/000,045) of the above-captioned U.S. Patent No. 6,346,532 B1 ordered pursuant to 35 U.S.C. § 257 in view of the Request for Supplemental Examination that was filed on November 21, 2013, Reexamination Certificate No. 6,346,532 C1 was issued on February 24, 2015. A copy of this Reexamination Certificate is provided herewith as set forth in 37 C.F.R. § 1.740(a)(8).[1]
- The Reexamination Certificate amends original patent claims 1, 3-5, and 11, cancels original claims 2, 7, and 8, and adds new claims 15-17.

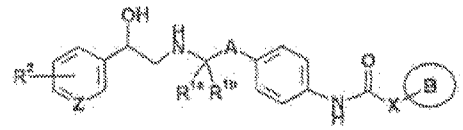
[1] A Certificate of Correction of this Reexamination Certificate was requested to correct several printing errors in claims 1 and 4.

- As a result of the Reexamination Certificate, claims 1, 3-6, 9-12, and 15-17 read on the approved product. Claims 13 and 14 read on a method of using the approved product.
- A manner in which at least one of the claims (claim 6) reads on the approved product has been demonstrated in the August 23, 2012 Application for Extension of Patent Term. Because claim 6 was not changed by the Reexamination Certificate, no additional showing in that regard is believed to be needed.
- A manner in which at least one of the claims (claim 13) reads on the approved product, taking into consideration the changes made by the Reexamination Certificate, is as follows:

Claim 13 reads as follows:

13. A method for treating diabetes mellitus in a human or animal patient in need of such treatment comprising administering to the patient an amount of a compound of formula (I) as claimed in claim 1, wherein the amount is an amount effective for such treatment.

Claim 13 reads on a method of using the approved product when, in the compound of formula (I):



R^2 is a hydrogen atom
R^{1a} is a hydrogen atom
R^{1b} is a hydrogen atom

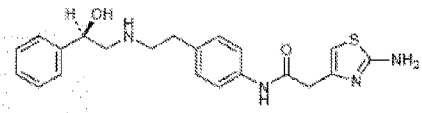
Z is =CH–

A is methylene

B is a nitrogen-containing heteroaryl group, which is substituted

X is a lower alkylene, which is unsubstituted.

Mirabegron:



- Therefore, Applicant believes that all requirements set forth in 37 C.F.R. § 1.740(a)(9), as well as the other requirements in 37 C.F.R. §§ 1.710 through 1.785, have been satisfied.

Applicant's undersigned attorney may be reached in our New York Office by telephone at (212) 218-2100. All correspondence should continue to be directed to our address listed below.

Respectfully submitted,

/Jason M. Okun/
Jason M. Okun
Attorney for Applicant
Reg. No. 48,512

Date: June 2, 2015

FITZPATRICK, CELLA, HARPER & SCINTO
1290 Avenue of the Americas
New York, New York 10104-3800
Telephone: (212) 218-2100
Facsimile: (212) 218-2200

US006346532C1

(12) EX PARTE REEXAMINATION CERTIFICATE (25th)

Ex Parte Reexamination Ordered under 35 U.S.C. 257

United States Patent
Maruyama et al.

(10) **Number: US 6,346,532 C1**
(45) **Certificate Issued: Feb. 24, 2015**

(54) **AMIDE DERIVATIVES OR SALTS THEREOF**

(75) Inventors: **Tatsuya Maruyama**, Tsukuba (JP); **Takayuki Suzuki**, Tsukuba (JP); **Kenichi Onda**, Tsukuba (JP); **Masahiko Hayakawa**, Tsukuba (JP); **Hiroyuki Moritomo**, Tsukuba (JP); **Tetsuya Kimizuka**, Tsukuba (JP); **Tetsuo Matsui**, Tsukuba (JP)

(73) Assignee: **Astellas Pharma Inc.**, Chuo-Ku, Tokyo (JP)

Supplemental Examination Request:
No. 96/000,045, Nov. 21, 2013

Reexamination Certificate for:

Patent No.:	**6,346,532**
Issued:	**Feb. 12, 2002**
Appl. No.:	**09/529,096**
PCT Filed:	**Oct. 15, 1998**
PCT No.:	**PCT/JP98/04671**
§ 371 (c)(1),	
(2), (4) Date:	**Apr. 7, 2000**
PCT Pub. No.:	**WO99/20607**
PCT Pub. Date:	**Apr. 29, 1999**

Certificate of Correction issued Jul. 13, 2002

(51) **Int. Cl.**

A61K 31/495	(2006.01)
A61K 31/505	(2006.01)
C07D 239/02	(2006.01)
C07D 213/00	(2006.01)
C07D 249/00	(2006.01)
C07D 215/48	(2006.01)
C07D 277/82	(2006.01)
C07D 233/26	(2006.01)
C07D 235/30	(2006.01)
C07D 213/81	(2006.01)
C07D 401/04	(2006.01)
C07D 241/12	(2006.01)
C07D 277/36	(2006.01)
C07D 513/04	(2006.01)
C07D 231/12	(2006.01)
C07D 213/30	(2006.01)
C07D 257/04	(2006.01)
C07D 239/26	(2006.01)
C07D 213/56	(2006.01)

(52) **U.S. Cl.**
CPC ***C07D 213/30*** (2013.01); ***C07D 215/48*** (2013.01); ***C07D 277/82*** (2013.01); ***C07D 233/26*** (2013.01); ***C07D 235/30*** (2013.01); ***C07D 213/81*** (2013.01); ***C07D 401/04*** (2013.01); ***C07D 241/12*** (2013.01); ***C07D 277/36*** (2013.01); ***C07D 513/04*** (2013.01); ***C07D 231/12*** (2013.01); ***C07D 257/04*** (2013.01); ***C07D 239/26*** (2013.01); ***C07D 213/56*** (2013.01)
USPC **514/252.1**; 514/256; 544/330; 544/332; 546/1; 546/152; 548/186; 548/190; 548/214; 548/252; 548/260

(58) **Field of Classification Search**
None
See application file for complete search history.

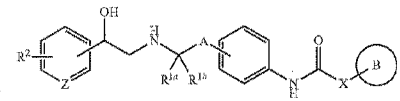
(56) **References Cited**

To view the complete listing of prior art documents cited during the supplemental examination proceeding and the resulting reexamination proceeding for Control Number 96/000,045, please refer to the USPTO's public Patent Application Information Retrieval (PAIR) system under the Display References tab.

Primary Examiner — Evelyn Huang

(57) **ABSTRACT**

(I)



Amide derivatives represented by general formula (I) or salts thereof wherein each symbol has the following meaning: ring B: an optionally substituted heteroaryl optionally fused with a benzene ring; X: a bond, lower alkylene or lower alkenylene optionally substituted by hydroxy or lower alkyl, carbonyl, or a group represented by —NH—(when X is lower alkylene optionally substituted by lower alkyl which may be bonded to the hydrogen atom bonded to a constituent carbon atom of ring B to form lower alkylene to thereby form a ring); A: a lower alkylene or a group represented by -(lower alkylene)—O—; R^{1a} and R^{1b}: the same or different and each hydrogen or lower alkyl; R^2: hydrogen or halogeno; and Z: nitrogen or a group represented by =CH—. The compounds are useful as a diabetes remedy which not only functions to both accelerate the secretion of insulin and enhance insulin sensitivity but has an antiobestic action and an antihyperlipemic action based on its selective stimulative action on a β_3 receptor.

EX PARTE REEXAMINATION CERTIFICATE ISSUED UNDER 35 U.S.C. 307

THE PATENT IS HEREBY AMENDED AS INDICATED BELOW.

Matter enclosed in heavy brackets [ ] appeared in the patent, but has been deleted and is no longer a part of the patent; matter printed in italics indicates additions made to the patent.

AS A RESULT OF REEXAMINATION, IT HAS BEEN DETERMINED THAT:

Claims **2**, **7** and **8** are cancelled.

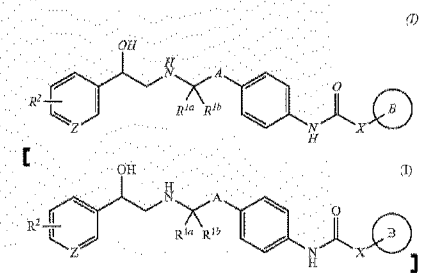
Claims **1**, **3-5** and **11** are determined to be patentable as amended.

Claims **9**, **10**, **13** and **14**, dependent on an amended claim, are determined to be patentable.

New claims **15-17** are added and determined to be patentable.

Claims **6** and **12** were not reexamined.

1. A compound of formula (I):



(I)

[

(I)

]

in the formula, each of the symbols means as follows:

ring B is a *nitrogen-containing* heteroaryl group which is unsubstituted substituted and is optionally fused with a benzene ring;

X is [a bond, or] a lower alkylene or an alkenylene, both of which are unsubstituted or substituted with hydroxy or a lower alkyl group, or X is a carbonyl or a group represented by —NH—, and when X is a lower alkylene which is substituted with a lower alkyl group, a carbon atom of the ring B optionally bonds with the lower alkyl group so that a ring is formed;

A is [a lower alkylene] *methylene, ethylene,* or a group represented by [-lower alkylene-O—] —CH_2O—;

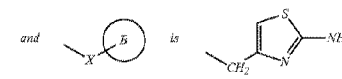
R^{1a}, R^{1b} are the same or different and each is a hydrogen atom or a lower alkyl group;

R^2 is a hydrogen atom or a halogen atom; and

Z is a group represented by =CH—; or a salt thereof.

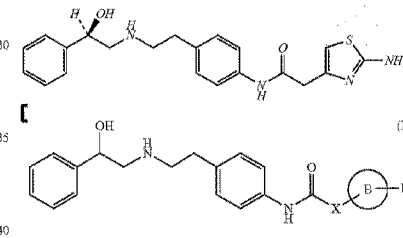
3. The compound of formula (I) or the salt thereof according to [claim **2**] *claim 1*, wherein the ring B is [a heteroaryl group which is] substituted with a substituent chosen from a halogen atom, lower alkyl, lower alkenyl, lower alkynyl, hydroxy, sulfanyl, halogeno lower alkyl, lower alkyl-O—, lower alkyl-S—, lower alkyl-O—CO—, carboxy, sulfonyl, sulfinyl, lower alkyl-SO—, lower alkyl-SO_2—, lower alkyl-CO—, lower alkyl-CO—O—, carbamoyl, lower alkyl-NH—CO—, di-lower alkyl-N—CO—, nitro, cyano, amino, lower alkyl-NH—, *and* di-lower alkyl-N—[, aryl-lower alkyl, halogeno aryl-lower alkyl, guanidino, lower alkyl-CO—NH, and lower alkyl-SO_2—NH—].

4. The compound of formula (I) or the salt thereof according to claim **3**, wherein R^2, R^{1a} and R^{1b} are each a hydrogen atom, [and Z is =CH—] *A is methylene, and*



5. A compound of formula (Ia):

(Ia)



[

(I)

]

[in the formula, each of the symbols means as follows:

ring B is a heteroaryl group;

X is a bond or a lower alkylene group;

R is a hydrogen atom, a halogen atom, a lower alkyl group, amino group, an aryl lower alkyl group, or a halogeno aryl-lower alkyl group;] or a salt thereof.

11. A composition comprising [at least one] *the* compound of formula [(I)] *(Ia)* or the salt thereof as claimed in claim **5**, in a pharmaceutically acceptable carrier.

15. The compound according to claim 4 or the salt thereof, which is an optical isomer.

16. A composition comprising at least one compound of formula (I) or the salt thereof as claimed in one of claims 1, 3, 4, and 15 in a pharmaceutically acceptable carrier.

17. The composition as claimed in claim 16, wherein the at least one compound of formula (I) or the salt thereof is present in an amount effective for treating diabetes mellitus in a human or animal patient in need of such treating.

* * * * *

Electronic Acknowledgement Receipt

EFS ID:	22505691
Application Number:	09529096
International Application Number:	
Confirmation Number:	2160
Title of Invention:	AMIDE DERIVATIVES OR SALTS THEREOF
First Named Inventor/Applicant Name:	TATSUYA MARUYAMA
Customer Number:	5514
Filer:	Jason M. Okun/DAVID NGUY
Filer Authorized By:	Jason M. Okun
Attorney Docket Number:	02213.003400
Receipt Date:	02-JUN-2015
Filing Date:	07-APR-2000
Time Stamp:	12:07:57
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	Miscellaneous Incoming Letter	SubmissionUnder37CFR176502213003400.pdf	164020 8b4d2082f203aa506be5e36a25c1d52ddb0441f69	no	3
Warnings:					
Information:					

2	Miscellaneous Incoming Letter	ReexaminationCertificate02213003400.PDF	127021 6437437746676d8fcfb2a18e411f240ec15a81e6e5	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	291041		

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.

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Jason M. Okun
Fitzpatrick, Cella, Harper & Scinto
1290 Avenue of Americas
New York, New York 10104-3800

In Re: Patent Term Extension
Application for
U.S. Patent No. 6,346,532

JAN 28 2016

NOTICE OF FINAL DETERMINATION AND REQUIREMENT FOR ELECTION

A determination has been made that U.S. Patent No. 6,346,532, claims of which cover a method of using the human drug product MYRBETRIQ ® (mirabegron), is eligible for patent term extension under 35 U.S.C. § 156. The period of extension has been determined to be 1,259 days.

A single request for reconsideration of this final determination as to the length of extension of the term of the patent may be made if filed within one month of the date of this notice. Extensions of time under 37 CFR § 1.136(a) are not applicable to this time period.

Applicant also has applied for patent term extension of U.S. Patent No. 7,342,117 and U.S. Patent No. RE44872 E based on the regulatory review period for MYRBETRIQ ® (mirabegron).

When patent term extension applications are filed for extension of the terms of different patents based upon the same regulatory review period for a product, the certificate of extension is issued to the patent having the earliest date of issuance, unless applicant elects a different patent. In the absence of an election by applicant within one month of the date of this notice, and in accordance with 37 CFR 1.785(b), the application for patent term extension in the above-identified patent U.S. Patent No. 7,342,117 and U.S. Patent No. RE44872 E will be denied. Accordingly, the application for patent term extension of the patent having the earlier date of issuance will be granted, i.e., a certificate of extension will be issued to U.S. Patent No 6,346,532. In the absence of a request for reconsideration, and if U.S. Patent No. 6,346,532 is elected, the Director will issue to the applicant a certificate of extension, under seal, for a period of 1,259 days in U.S. Patent No. 6,346,532.

The period of extension has been calculated using the Food and Drug Administration determination of the length of the regulatory review period published in the Federal Register of 79 Fed. Reg. 30622 (June 06, 2014). Under 35 U.S.C. § 156(c):

$$\text{Period of Extension} = \text{RRP} - \text{PGRRP} - \text{DD} - \tfrac{1}{2}(\text{TP} - \text{PGTP})^{1}$$

[1] Consistent with 35 U.S.C. § 156(c), "RRP" is the total number of days in the regulatory review period, "PGRRP" is the number of days of the RRP which were on and before the date on which the patent issued, "DD" is the number of days of the RRP that the applicant did not act

= 2,213 - 0 - 0 - ½ (1,908 - 0)
= 1,259 days (3.4 years)

Since the regulatory review period began June 09, 2006, after the patent issued (February 12, 2002), the entire regulatory review period has been considered in the above determination of the length of the extension period 35 U.S.C. § 156(c). No determination of a lack of due diligence under 35 U.S.C. § 156(c)(1) was made.

Neither the limitations of 35 U.S.C. § 156(g)(6) nor 35 U.S.C. § 156(c)(3) operate to reduce the period of extension determined above.

Upon issuance of the certificate of extension, the following information will be published in the Official Gazette:

U.S. Patent No.:	6,346,532
Granted:	February 12, 2002
Original Expiration Date[2]:	October 15, 2018
Applicant:	Maruyama, *et al.*
Owner of Record:	Yamanouchi Pharmaceutical Co., Ltd.,
Title:	Amide Derivatives Or Salts Thereof
Product Trade Name:	MYRBETRIQ ® (mirabegron)
Term Extended:	1,259 days
Expiration Date of Extension:	March 27, 2022

with due diligence, "TP" is the testing phase period described in paragraphs (1)(B)(i), (2)(B)(i), (3)(B)(i), (4)(B)(i), and (5)(B)(i) of subsection (g) of 35 U.S.C. § 156, and "PGTP" is the number of days of the TP which were on and before the date on which the patent issued, wherein half days are ignored for purposes of the subtraction of ½ (TP - PGTP).

[2]Subject to the provisions of 35 U.S.C. § 41(b).

Any correspondence from applicant with respect to this matter should be submitted via the USPTO's EFS Web system and should be addressed as follows:

By mail: Mail Stop Hatch-Waxman PTE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450.

Telephone inquiries related to this determination should be directed to Ali Salimi at (571) 272-0909.

Mary C. Till
Senior Legal Advisor
Office of Patent Legal Administration
Office of the Associate Commissioner
for Patent Examination Policy

cc: FDA, CDER, Office of Regulatory Policy
10903 New Hampshire Avenue,
Bldg. 51 Room 6250
Silver Spring MD 20993-0002

Attention: Beverly Friedman

RE: MYRBETRIQ ®
(mirabegron)
Docket No.: FDA-2013-E-0410

02213.003400.1 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re: U.S. Patent No. 6,346,532

Issued: February 12, 2002

To: Tatsuya Maruyama, Takayuki Suzuki, Kenichi Onda, Masahiko Hayakawa, Hiroyuki Moritomo, Tetsuya Kimizuka, and Tetsuo Matsui

For: AMIDE DERIVATIVES OR SALTS THEREOF

Mail Stop Hatch-Waxman PTE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO NOTICE OF FINAL DETERMINATION AND REQUIREMENT FOR ELECTION

Sir:

In response to the NOTICE OF FINAL DETERMINATION AND REQUIREMENT FOR ELECTION issued on January 8, 2016 in the above-captioned matter and in accordance with 37 C.F.R. § 1.785, Applicant hereby elects U.S. Patent No. 6,346,532 (the '532 patent), which claims both the approved product Myrbetriq™ (mirabegron) and a method of using this approved product. Accordingly, the Director is respectfully requested to issue to Applicant a certificate of extension, under seal, for the '532 patent.

Applicant's undersigned attorney may be reached in our New York Office by telephone at (212) 218-2100. All correspondence should continue to be directed to our address listed below.

Respectfully submitted,

/Jason M. Okun/
Jason M. Okun
Attorney for Applicant
Reg. No. 48,512

Date: January 27, 2016

FITZPATRICK, CELLA, HARPER & SCINTO
1290 Avenue of the Americas
New York, New York 10104-3800
Telephone: (212) 218-2100
Facsimile: (212) 218-2200

Electronic Acknowledgement Receipt

EFS ID:	24733828
Application Number:	09529096
International Application Number:	
Confirmation Number:	2160
Title of Invention:	AMIDE DERIVATIVES OR SALTS THEREOF
First Named Inventor/Applicant Name:	TATSUYA MARUYAMA
Customer Number:	5514
Filer:	Jason M. Okun/DAVID NGUY
Filer Authorized By:	Jason M. Okun
Attorney Docket Number:	02213.003400
Receipt Date:	27-JAN-2016
Filing Date:	07-APR-2000
Time Stamp:	14:55:30
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	Election in Response to Notice of Final Determination	RESPTONOTICEOFFINALDETERMINATIONANDREQFORELECTION02213003400-1.pdf	99582 a16c9c6cd2a2f4309d3dc1cdc59f7c4b43e973a	no	2

Warnings:	
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New Applications Under 35 U.S.C. 111

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

National Stage of an International Application under 35 U.S.C. 371

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

New International Application Filed with the USPTO as a Receiving Office

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

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
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1290 Avenue of Americas
New York, New York 10104-3800

In Re: Patent Term Extension
Application for
U.S. Patent No. 6,346,532

[redacted] F-6 2016

Dear Mr. Okun:

A certificate under 35 U.S.C. § 156 is enclosed extending the term of U.S. Patent No. 6,346,532 for a period of 1,259 days. While a courtesy copy of this letter is being forwarded to the Food and Drug Administration (FDA), you should directly correspond with the FDA regarding any required changes to the patent expiration dates set forth in the Patent and Exclusivity Data Appendix of the Orange Book (Approved Drug Products with Therapeutic Equivalence Evaluations) or in the Patent Information set forth in the Green Book (FDA Approved Animal Drug Products). Effective August 18, 2003, patent submissions for publication in the Orange Book and Docket *95S-0117 need to be submitted on form FDA-3542 which may be downloaded from FDA's Electronic Forms Download Website: http://www.fda.gov/opacom/morechoices/fdaforms/default.html (http://www.fda.gov/opacom/morechoices/fdaforms/FDA-3542.pdf).

Inquiries regarding this communication should be directed to Ali Salimi by telephone at (571) 272-0909, or by e-mail at ali.salimi@uspto.gov.

Mary C. Till
Senior Legal Advisor
Office of Patent Legal Administration
Office of the Associate Commissioner
for Patent Examination Policy

cc: Food & Drug Administration
CDER, Office of Regulatory Policy
10903 New Hampshire Avenue,
Bldg. 51 Room 6250
Silver Spring MD 20993-0002

Attention: Beverly Friedman

RE: MYRBETRIQ ®
(mirabegron)
Docket No.: FDA-2013-E-0410

UNITED STATES PATENT AND TRADEMARK OFFICE

(12) CERTIFICATE EXTENDING PATENT TERM
UNDER 35 U.S.C. § 156

(68)	PATENT NO.	:	6,346,532
(45)	ISSUED	:	February 12, 2002
(75)	INVENTOR	:	Tatsuya Maruyama, *et al.*
(73)	PATENT OWNER	:	Astellas Pharma Inc.
(95)	PRODUCT	:	MYRBETRIQ ® (mirabegron)

This is to certify that an application under 35 U.S.C. § 156 has been filed in the United States Patent and Trademark Office, requesting extension of the term of U.S. Patent No. 6,346,532 based upon the regulatory review of the product MYRBETRIQ ® (mirabegron) by the Food and Drug Administration. Since it appears that the requirements of the law have been met, this certificate extends the term of the patent for the period of

(94) 1,259 days

from October 15, 2018, the original expiration date of the patent, subject to the payment of maintenance fees as provided by law, with all rights pertaining thereto as provided by 35 U.S.C. § 156.

I have caused the seal of the United States Patent and Trademark Office to be affixed this 5th day of April 2016.

Michelle K. Lee

Michelle K. Lee
Under Secretary of Commerce for Intellectual Property and
Director of the United States Patent and Trademark Office