PATENT
Attorney Docket No. 07385.0042-00000

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Request for Supplemental Examination of:	
U.S. Patent No. 6,346,532	Group Art Unit: *Not Yet Assigned*
Inventors: Tatsuya MARUYAMA et al.	Examiner: *Not Yet Assigned*
Issued: February 12, 2002	
For: AMIDE DERIVATIVES OR SALTS THEREOF	Confirmation No.: *Not Yet Assigned*

Commissioner for Patents
P.O. Box 1450
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Commissioner:

Request For Supplemental Examination
Of U.S. Patent No. 6,346,532

Astellas Pharma, Inc. (hereinafter "Astellas"), is the owner of the entire right, title and interest of U.S. Patent No. 6,346,532 ("the '532 patent"). The patent issued on national stage Application No. 09/529,096 ("the '096 application") based on PCT Application No. PCT/JP98/04671, filed October 15, 1998, claiming the benefit of Japanese Patent Application No. Hei 9-285778, filed October 17, 1997.

I. § 1.610(a)

The required fee of $16,860 is submitted herewith, which includes the $4,400.00 filing fee, the $12,100.00 reexamination fee, and a document size fee of $360.00. Astellas understands that if no reexamination is ordered, the $12,100.00 reexamination fee will be refunded. Please charge any additional required fees or apply any credits to Deposit Account No. 09-0619.

II. § 1.610(b)(1): Identification of the Number of the Patent for Which Supplemental Examination is Requested

Supplemental examination under 35 U.S.C. § 257 and 37 C.F.R. §§ 1.601-1.625 is requested for claims 1-14 of the '532 patent.

III. § 1.610(b)(2): A List of Items of Information that are Requested to be Considered, Reconsidered, or Corrected

The following is a list of the items of information that are requested to be considered:

1. U.S. Patent No. 6,346,532 ("the '532 patent")
2. Table of testing data for compounds including those disclosed in Examples 1-113 of U.S. Patent No. 6,346,532 ("Testing Data Table")[1];
3. Materials for Astellas R&D Meeting. Subcommittee on Development Theme Establishment, titled "YM178/Discontinuation of Development Theme for Diabetes Mellitus," dated October 27, 2003 ("R&D Meeting Materials);
4. YM178 in Type 2 Diabetes Mellitus 178-CL003 Study Report ("Study Report");
5. Yamanouchi BAN Compound Evaluation System ("R&D Flowchart") with English-language translation;
6. Yamanouchi Monthly Research Progress Report, dated April 26, 1995 ("Monthly Progress Report") with English-language translation;
7. Excerpts of the prosecution history of U.S. Patent Application No. 09/529,096, the U.S. National Stage of PCT/JP98/04671, filed October 15, 1998, that resulted in U.S. Patent No. 6,346,532 ("the Prosecution File History");

[1] The Testing Data Table also contains data for three compounds that are not exemplified in the '532 patent: (a) BAN-371A (compound number 6), which is the free base equivalent of BAN-371 (compound number 5), which is exemplified in Example 041; (b) BAN-371B (compound number 7), which is the racemic equivalent of BAN-371; and (c) BAN-371C (compound number 8), which is the S-enantiomer equivalent of BAN-371.

8. Japanese Patent Application Kokai Publication No. H10-218861, "Novel Phenethanol Derivative or Salt Thereof," published August 18, 1998, and certified English-language translation thereof ("JP '861");

9. Blin, N. et al., "Structural and Conformational Features Determining Selective Signal Transduction in the β3-Adrenergic Receptor," Molecular Pharmacology, 44:1094-1104 (1993) ("Blin");

10. PCT Publication WO 94/18161, published 18 August 1994 ("WO '161");

11. Thornber, C.W., "Isosterism and Molecular Modification in Drug Design," Chem. Soc. Rev. 18:563-580 (1979) ("Thornber");

12. Declaration by Dr. Tetsuo Matsui under 37 C.F.R. § 1.132 ("Matsui Dec.").

IV. § 1.610(b)(3): A List Identifying Prior or Concurrent Post-Patent and Trademark Office Proceedings Involving the Patent for which Supplemental Examination is Being Requested

A request for a Certificate of Correction under 37 C.F.R. §§ 1.322 and 1.323 was filed on April 17, 2002. The resulting Certificate of Correction was granted on July 13, 2002.

An Application for Extension of Patent Term under 35 C.F.R. § 156 of the '532 Patent was filed on August 21, 2012. This application is currently pending.

There are no other prior or concurrent proceedings involving the '532 patent.

V. § 1.610(b)(4): An Identification of Each Claim of the Patent for Which Supplemental Examination is Requested

Supplemental examination is requested for each of the claims 1-14 of the '532 patent.

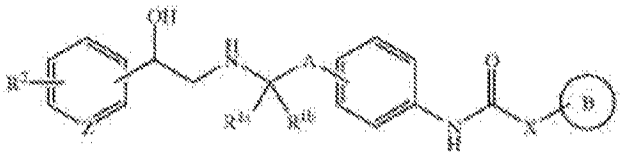
VI. § 1.610(b)(5): A Separate, Detailed Explanation of the Relevance and Manner of Applying Each Item of Information to Each Claim of the Patent for Which Supplemental Examination is Requested

A summary of the claimed subject matter and a detailed explanation of the relevance and manner of applying each item of information to each claim of the patent for which supplemental examination is requested is provided below.

A. Summary of Claimed Subject Matter

The '532 patent (Item of Information No.1) discloses and claims phenethanol amide derivatives represented by general formula (I) below, or salts thereof:

(I)



Ring "B" in formula (I) is a heteroaryl group, which may be unsubstituted or substituted and is optionally fused with a benzene ring. "X" may be a bond, or a lower alkylene or an alkenylene, both of which may be 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 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" may be a lower alkylene or a group represented by -lower alkylene-O—. R^{1a} and R^{1b} may be the same or different and each may be a hydrogen atom or a lower alkyl group. R^2 may be a hydrogen atom or a halogen atom. "Z" is a group represented by =CH—. (*See* claim 1.)

Claims 2-5 and 9 cover phenethanol derivative compounds represented by general formula (I), which are narrower in some respect compared to the compounds represented by general formula (I) as recited in claim 1.

Claim 6 recites the following nine species of phenethanol amide derivatives that fall within the scope of claim 1:

- (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-phenyl ethyl)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.

Claims 7, 8, and 10-12 recite compositions comprising at least one compound as claimed in claim 1-6.

Claim 13 recites a method for treating diabetes mellitus comprising administering to a patient an amount of a compound as claimed in claim 1.

Claim 14 recites a method for treating obesity comprising administering to a patient an amount of a compound as claimed in claim 1.

The '532 patent states that the compounds of the invention have selective stimulative action to human β_3-receptor, *i.e.*, they are β_3-adrenergic receptor-specific agonists. ('532 patent at col. 2, ll. 28-29, col. 12, ll. 9-11.) The '532 patent also states that it was known that β-adrenaline receptors are classified into β_1, β_2, and β_3 subtypes. ('532 patent at col. 1, ll. 44-47.) Moreover, the '532 patent explains that stimulation of the β_1-receptor causes an increase in heart rate, that stimulation of the β_2-receptor stimulates decomposition of glycogen in muscles, whereby synthesis of glycogen is inhibited, causing action such as muscular tremor, and that stimulation of the β_3-receptor shows anti-obesity and an anti-hyperglycemia action (such as decrease in triglyceride, decrease in cholesterol, and increase in HDL-cholesterol). ('532 patent, col. 1, ll. 46-54.)

The '532 patent states that, due to their selective stimulating action to β_3-receptors, the compounds of the invention are 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. ('532 patent, col. 2, ll. 31-37.) The '532 patent states that the selective human β_3-receptor stimulating action of the compounds of the invention was ascertained through β_1, β_2,

and β_3 testing. ('532 patent, col. 12, ll. 9-12.) Specifically, the patent teaches that the human β_3-receptor 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). ('532 patent, col. 11, ll. 56-63.)

The '532 patent specification concludes with 113 examples, each, with the exception of example 107, disclosing a different phenethanol derivative compound of the claimed invention. Example 41 discloses a compound having the chemical formula (R)-2-(2-aminothiazol-4-yl)-4'-[2-(2-hydroxy-2-phenylethyl)amino]-ethyl]acetanilide dihydrochloride, which is encompassed by claims 1-14 of the '532 patent. The compound of Example 41 is a dihydrochloride salt of a compound commonly known as mirabegron, which is an FDA-approved drug sold under the trademark, MYRBETRIQ™.

None of the current claims is limited to cover only Astellas' commercialized product, mirabegron. Should the Patent and Trademark Office order *ex parte* reexamination of the claims of the '532 patent in connection with this request for supplemental examination, Astellas intends to amend the claims of the '532 patent to cover only mirabegron and its salts.

B. Summary of Relevance to Claimed Subject Matter

1. The Testing Data Table (Item of Information No. 2), Matsui Dec. (Item of Information No. 12), R&D Meeting Materials (Item of Information No. 3) and Study Report (Item of Information No. 4)

As discussed above, the '532 patent states that the compounds of the invention are useful as therapeutic agents for treating diabetes mellitus. (*See, e.g.*, the '532

patent, col. 2, ll. 37-41; col. 9, ll. 62-63; Abstract.) However, the commercial embodiment of the claimed invention, mirabegron, is not approved for treating diabetes mellitus. Instead, MYRBETRIQ™ received FDA approval in June 2012 for the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency.

The Testing Data Table, discussed in more detail below, shows that the inventors conducted a series of *in vitro* and *in vivo* studies before October 15, 1998, the date on which the PCT application leading to the issuance of the '532 patent was filed. From the results of these preliminary studies mirabegron showed promise as an anti-diabetic medicine, and based upon the available information, the FDA approved commencement of Phase I clinical trials to determine appropriate dosages of mirabegron for Phase II clinical trials to assess efficacy for treating diabetes mellitus. (*See* Matsui Dec. ¶ 7; *see also* Testing Data Table, Compound BAN 371, Cols. 4-9.) Based on the results of the ensuing limited Phase IIa clinical trials, performed after the '532 patent issued, the then current assignee, Yamanouchi Pharmaceutical Co., Ltd. (hereinafter "Yamanouchi"),[2] decided that mirabegron did not demonstrate sufficient efficacy to be a commercially competitive drug for the treatment of diabetes mellitus, and so decided it would not pursue diabetes mellitus as an indicated use. (*See* Matsui Dec. ¶ 8; *see also, e.g.*, R&D Meeting Materials at p. 13 ("The results of the phase IIa study of [mirabegron] administered at a dose of 200 mg in the fed state could not confirm the efficacy of

[2] Yamanouchi Pharmaceutical Co., Ltd. is a predecessor company that through a merger with another pharmaceutical company formed Astellas, the current assignee.

[mirabegron] in terms of the primary end points (HbA_{1c} and fasting blood glucose level")).)

Despite the decision to discontinue the development of mirabegron for the treatment of diabetes mellitus, Yamanouchi conducted a detailed analysis of the results of the Phase IIa clinical study prior to the discontinuance of the project, which revealed that mirabegron did have some efficacy in certain patient subgroups. (*See* Matsui Dec. ¶ 9; *see also, e.g.*, the Study Report that states:

> Some efficacy was found only when HbA1c at baseline was above 7% (data from central laboratory; local data 7-8%); responses of HbA1c and FPG to [mirabegron] were mainly found for female patients.
>
> * * *
>
> Changes in HbA1c were mainly detected in young patients; in elderly no difference between [mirabegron] and placebo could be found, even when baseline HbA1c was taken into account.

(Study Report at p. 11, slides 21-22).)

Because the Phase IIa clinical trial results were not available until mid-2003, this information was not before the Patent and Trademark Office during prosecution of the '532 patent, which issued on February 12, 2002. Because no compound encompassed by claims 1-14 proved sufficiently efficacious to be considered commercially competitive for the treatment of diabetes mellitus, which was the principal utility described in the specification, this information may be considered to raise a substantial new question of patentability with respect to those claims, and in particular with respect to claim 13.

2. The Testing Data Table (Item of Information No. 2), Matsui Dec. (Item of Information No. 12), R&D Flowchart (Item of Information No. 5), Monthly Progress Report (Item of Information No. 6), and the Prosecution File History (Item of Information No. 7)

As confirmed by one of the inventors of the '532 patent, Dr. Matsui, the Testing Data Table was compiled from laboratory notebooks and other developmental materials generated by the inventors of the '532 patent. (Matsui Dec. ¶ 6.) The table presents certain testing data for all of the claimed compounds disclosed in Examples 1-106 and 108-113 of the '532 patent.[3] Column 1 of the Testing Data Table provides the internal Yamanouchi code (BAN) number for each of the compounds. Column 2 provides the example number from the '532 patent. Column 3 provides the chemical structure of the compound. Columns 4-6 provide the β-adrenergic receptor data for each compound as pD_2 values and IA% ("Intrinsic Activity" as compared to isoproterenol - numbers in parentheticals) using the CHO screening test. Column 7 provides ED_{30} data for several of the compounds based on hypoglycemic studies in KK mice. Column 8 provides β_3-adrenergic receptor data determined using the SK-N-MC screening test. Column 9 provides the test report dates for these data in columns 4-8. (Matsui Dec. ¶ 6.)

As discussed above, the '532 patent states that the compounds of the invention selectively stimulate the β_3 receptor. For example, column 2, lines 28-30, teach that the compounds of the invention "show a selective stimulating action to β_3-receptors, leading to accomplishment of the present invention." Similarly, column 2, line 37, states that the insulin secretion-promoting action and insulin sensitivity-potentiating action of the

[3] As mentioned above, the compound of Example 107 is not a phenethanol derivative and, therefore, is not covered by the claims of the '532 patent.

compounds of the invention are due to their "selective stimulating action to β_3-receptors." Likewise, column 9, lines 61-62, discuss the "selective β_3-receptor stimulating action" of the compounds of the invention. Further, column 10, lines 7-9, state that "[t]he β_3-receptor stimulating action of the compound of the present invention is selective to β_3-receptors in human being." In addition, column 10, lines 61-65, state that the compounds of the invention have "been ascertained to be selective to β_3-receptors . . . ."

The '532 patent states that β_3-receptor stimulating action for the compounds of the invention was ascertained by comparing the effects of the claimed compounds on the β_1, β_2, and β_3 receptor subtypes using cells expressing human-type receptors. (*See* col. 11, l. 56 to col. 12, l. 11; *see also* col. 10, ll. 61-65.) Specifically, stimulating activities of the compounds were investigated by incubating cells expressing each of the β-adrenergic receptor subtypes with the compounds of the invention and measuring production of cyclic adenosine monophosphate (cAMP), which is a byproduct of β-adrenergic receptor activation. (*Id.*)

As stated in the '532 patent, the intensity of action of each compound against the β_1, β_2, and β_3-receptors was compared by calculating the pD_2 value and the maximum value (IA% where the maximum reaction of 10^{-6}M isoproterenol, a non-selective β-agonist, was defined as 100%) from the resulting dose-reaction curve. (*See* the '532 patent at col. 11, l. 56 to col. 12, l. 11.)

a. Not All of the Claimed Compounds of Examples 1-106 and 108-113 of the '532 Patent Were Shown To Have Greater β_3 Receptor Activity Compared to Either β_1 or β_2 Receptor Activity

As can be seen in the Testing Data Table, cols. 4-6, the compounds of Examples 1-106 and 108-113 that fall within the scope of claim 1-14 of the '532 patent were tested using the CHO β_1, β_2, and β_3-receptor stimulation screening tests. Although all of the compounds tested showed some level of β_3-receptor agonist activity, depending on whether the IA% or pD_2 test results are used, a number of the claimed compounds exhibited β_3-receptor agonist activities that were not as high as the corresponding β_1- or β_2-receptor agonist activities. (Matsui Dec. ¶ 10; *see also* table below.) For example, although the compound of Example 1, designated BAN 404, covered by at least claims 1, 2, 6, 7, 8, 9, 10, 12, 13, and 14 of the '532 patent, showed β_3-receptor agonist activity greater than β_1-receptor agonist activity in both the IA% and pD_2 tests, it showed β_3-receptor agonist activity less than β_2-receptor agonist activity. (*Id.*; *see also* Testing Data Table, Compound BAN 404, cols. 4-6.) Because these initial CHO screening data provided in the Testing Data Table, which indicate that some of the compounds encompassed by claims 1-14 may not have β_3-receptor agonist activity selectivity over both the β_1- and β_2-receptors as taught in the '532 patent, were not before the Patent and Trademark Office during prosecution of the '532 patent, this information may be considered to raise a substantial new question of patentability with respect claims 1-14 of the '532 patent.

b. Not All of the Claimed Compounds of Examples 1-106 and 108-113 of the '532 Patent Met Yamanouchi's Internal Criteria For Further Development

As of time the '096 application was filed, and up to the time the '532 patent issued, Yamanouchi utilized certain internal screening criteria to determine whether a compound has sufficient β_3-receptor agonist activity and selectivity to warrant further evaluation for potential eventual submission as an anti-diabetic drug. (Matsui Dec ¶ 11.) As the R&D Flowchart shows, in general, before a candidate compound qualified for further evaluation, Yamanouchi's initial internal screen stated that a candidate compound should have an IA test result for β_3-receptor agonism of greater than 0.6 (or 60%) and a pD_2 value for the β_3-receptor of greater than 6.5, while at the same time having IA test results for β_1- and β_2-receptor agonism of less than 0.2 (or 20%). (*Id.*; *see also* R&D Flowchart.)

The following data, excerpted from the Testing Data Table, provide examples of the claimed compounds that did not meet Yamanouchi's initial β_3-receptor selectivity and/or activity criteria set forth in the R&D Flowchart:

Chart #	BAN #	Example #	Compound Covered By Claims	IA% β3 IA% β2 IA% β1	pD_2 β3 pD_2 β2 pD_2 β1
13	377	110	1,2,7,8,9,10,13,14	58.1 22.7 2.7	5.23 5.65 <4
19	390	105	1,2,7,8,9,10,13,14	24 28 17	6.3 5.9 5.3
21	395	88	1,2,7,8,9,10,13,14	18 50 20	5.9 4.2 <4.0
22	396	3	1,2,7,8,9,10,13,14	18 27 2	5.9 4.2 <4.0

Chart #	BAN #	Example #	Compound Covered By Claims	IA% β3 IA% β2 IA% β1	pD_2 β3 pD_2 β2 pD_2 β1
23	398	96	1,2,7,8,9,10,13,14	27 17 9	5.6 5.9 <4
29	404	1	1,2,6,7,8,9,10,12,13,14	10 25 0	5.1 5.4 <4
30	405	2	1,2,7,8,9,10,13,14	11 18 0	6.0 5.8 <4
32	407	11	1,2,3,4,7,8,9,10,13,14	40 37 3	6.4 6.4 <4
35	410	111	1,2,7,8,9,10,13,14	32 53 14	5.6 5.5 5.6
36	411	101	1,2,7,8,9,10,13,14	37 50 19	6.2 5.4 4.6
39	414	112	1,2,7,8,9,10,13,14	55 89 25	6.9 6.6 5.6
49	435	36	1,2,3,4,7,8,9,10,13,14	14 27 5	6.2 5.3 <4
50	440	37	1,2,3,4,7,8,9,10,13,14	27 19 6	<5.0 5.4 <4
53	447	8	1,2,7,8,9,10,13,14	41 35 23	6.3 5.2 6.6
55	455	18	1,2,7,8,9,10,13,14	49 31 69	5.8 5.9 4.4
61	478	113	1,2,7,8,9,10,13,14	52 49 14	5.8 6.4 4.9
109	548	15	1,2,3,4,5,7,8,9,10,11,13,14	68 36 74	7.1 5.4 5.1

Thus, there are 17 claimed compounds shown in the table above that did not satisfy Yamanouchi's internal criteria for further development based on either the pD_2 or IA% values. (Matsui Dec. ¶¶ 12-13.) This β_3-receptor selectivity and activity data, and Yamanouchi's internal criteria for evaluating it, were not before the Patent and Trademark Office during prosecution of the '532 patent. Because these examples do not satisfy Yamanouchi's internal β_3-receptor selectivity and/or activity criteria for some compounds that are within the scope of claims 1-14, they may be considered to raise a substantial new question of patentability with respect to claims 1-14 of the '532 patent.

c. The '532 Patent Did Not Correctly Identify the Assay Used to Determine β_3-Selectivity for the Claimed Compounds

As discussed above, the inventors determined β_3-stimulating action of the compounds of the invention by comparing the effects of the claimed compounds on the β_1, β_2, and β_3-receptor subtypes using cells expressing human-type receptors. According to the specification, an SK-N-MC cell system comprising human neuroblastoma cells permanently expressing the human β_1- and β_3-receptor was used to assess β_3 activity, and CHO cell systems comprising Chinese hamster ovary cells permanently expressing either the human β_1- or β_2-receptors were used to assess β_1 and β_2 activities. (*See* the '532 patent, col. 11, l. 56 to col. 12, l. 11.)

As shown by the information provided in column 9 of the Testing Data Table, however, none of the claimed compounds of Examples 1-106 and 108-113 in the '532 patent was tested for β_3-stimulating action using the SK-N-MC cell system until after the October 15, 1998, filing date of the international application that led to the '532 patent (*i.e.*, PCT/JP98/04671). (*See also* Matsui Dec. ¶ 15.) As reflected in the R&D Meeting

Materials, the inventors assessed the β_3-selectivity of mirabegron, and all of the claimed compounds disclosed in examples 1-106 and 108-113 of the '532 patent, using the CHO cell system. (*See* R&D Meeting Materials at p. 3; *see also* Matsui Dec. ¶ 15.) The CHO cell system used to assess the β_3-agonist activity of the claimed compounds disclosed in Examples 1-106 and 108-113 was essentially the same as the CHO cell system used by the inventors to assess the β_1- and β_2-agonist activity of those same compounds, except the CHO cells permanently expressed the human β_3-receptors only. (*See* Matsui Declaration at ¶ 16.)

The SK-N-MC cell system referred to in the specification was used by the inventors to evaluate potential anti-diabetic compounds that were synthesized before the compounds encompassed by the claims of the '532 patent, and it was considered competent as a basis for assessing the β_3-selectivity of those compounds. (Matsui Dec. ¶ 17.) A switch was made to the CHO cell system because the gene for the single human β_3-receptor became available and could be used to construct a CHO assay, whereas the cells in the SK-N-MC cell system also contained a β_1-receptor and required the use of a β_1-receptor blocker to mask any β_1 effects. (*Id.*; *see also* the '532 patent, col. 11, line 67 – col. 12, line 2.) The inventors obtained the gene for the β_3-receptor from a foreign patent office based upon a foreign patent filing. (Matsui Dec. ¶ 19.) They did not refer to the β_3-CHO cell system assay in the instant patent application because of a concern that using the β_3 gene in an experimental assay might be asserted to be an act of patent infringement in Japan. (*Id.*)

The Monthly Progress Report in which the inventors evaluated and compared the CHO β_3-test to the SK-N-MC β_3-test, before switching to the CHO β_3-test, states that

both cell systems, the SK-N-MC cell system and the CHO cell system, provide test results that have "significant correlation" with each other for assessing β_3-stimulating action. (Matsui Dec. ¶ 18; *see also* Monthly Progress Report, page 2.)

The fact that the specification did not correctly describe the test actually employed for assessing the β_3 agonist activity of the compounds encompassed by claims 1-14 may be considered to raise a substantial new question of patentability with respect to claims 1-14 of the '532 patent.

d. The Hypoglycemic Activity of the Claimed Compounds Compared to Prior Art Compounds

As stated in the '532 patent, the insulin sensitivity-potentiating action of the compounds of the invention was assessed using a hypoglycemic test in KK mice. (*See* the '532 patent at col. 11, ll. 1-31.)

The '532 patent explains that the compounds of the invention were administered to the mice for four days, and blood sugar levels were measured 15 to 18 hours after administration. (*Id.*) According to the patent, a dose at which the blood sugar level was lowered by 30% compared with that before administration of the drug was expressed as an ED_{30} value. (*Id.*) Lower ED_{30} values suggest stronger activity.

The '532 patent states that compounds of the invention significantly lowered the blood sugar level of KK mice as compared with blood levels before administration. ('532 patent at Col. 11, ll. 18-21.) At column 11, ll. 22-24, the '532 patent states "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." (Col. 11, ll. 22-24.) The '532 patent notes that certain prior art compounds were disclosed in International Publication

No. WO 95/29159, and states 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." (Col. 11, ll. 29-31.) With respect WO 95/29159, the '532 patent states that "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." (*Id.* at Col. 11, ll. 25-28.)

During prosecution of the '532 patent, in responding to a question raised by the Examiner about the enablement of the broad range of compounds claimed, reference was made to those statements in the specification: "[t]he 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 Prosecution File History (Item of Information No. 7), Amendment filed May 4, 2001, at p. 12; emphasis in original.)

Based on the information provided in column 7 of the Testing Data Table, however, several of the claimed compounds disclosed in Examples 1-106 and 108-113 in the '532 patent did not show ED_{30} values that are ten times greater than the prior art compounds disclosed in Examples 90 and 92 of WO 95/29159. Specifically the Testing Data Table shows that 21 compounds of the claimed invention for which ED_{30} data is listed have activities of >10 mg/kg, which is less than three times greater activity than the 30 mg/kg/day activities of the compounds disclosed in Examples 90 and 92 of WO 95/29159. Moreover, the Testing Data Table shows that other of the claimed compounds disclosed in Examples 1-106 and 108-113 have ED_{30} activities of between

3 and 10 mg/kg, which is also less than ten times greater activity than the prior art 30 mg/kg/day activity.

Only two compounds included in the Testing Data Table have ED_{30} values of less than 3.0 mg/kg/day: Compound No. 1 (BAN-358; Example 86) and Compound No. 3 (BAN-369A; Example 99). The following data excerpted from the Testing Data Table lists examples[4] of the claimed compounds that did not show an ED_{30} value for oral administration that was 3 mg/kg/day or less:

Chart #	BAN #	Example #	Compound Covered By Claims:	ED_{30} (mg/kg)
5	371	41	1,2,3,4,5,6,7,8,9,10,11,12,13,14	6.5
9	372	91	1,2,7,8,9,10,13,14	>10
10	374	94	1,2,7,8,9,10,13,14	>10
15	384	39	1,2,7,8,9,10,13,14	>10
33	408	90	1,2,7,8,9,10,13,14	>10
47	433	38	1,2,3,4,7,8,9,10,13,14	>10
49	435	36	1,2,3,4,7,8,9,10,13,14	>10
50	440	37	1,2,3,4,7,8,9,10,13,14	>10
63	484	25	1,2,7,8,9,10,13,14	10
71	501	56	1,2,7,8,9,10,13,14	>10
73	503	13	1,2,7,8,9,10,13,14	>10
78	508	71	1,2,7,8,9,10,13,14	>10
82	513	75	1,2,7,8,9,10,13,14	>10
83	514	77	1,2,7,8,9,10,13,14	>10
86	517	70	1,2,7,8,9,10,13,14	>10
87	521	64	1,2,7,8,9,10,13,14	>10
88	522	72	1,2,7,8,9,10,13,14	>10
89	523	64	1,2,7,8,9,10,13,14	>10
94	528	80	1,2,7,8,9,10,13,14	>10
95	529	73	1,2,7,8,9,10,13,14	>10
96	530	78	1,2,7,8,9,10,13,14	>10
97	531	76	1,2,7,8,9,10,13,14	>10
103	538	49	1,2,7,8,9,10,13,14	>10
107	544	28	1,2,7,8,9,10,13,14	10

[4] Testing Data Table shows other claimed compounds disclosed in examples 1-106 and 108-113 that are not listed in this table and that have ED_{30} activities of between 3 and 10 mg/kg.

112	552	33	1,2,6,7,8,9,10,12,13,14	9.5

Thus, while the statement in the specification is correct that "some" of the claimed compounds "were shown to have a potentiating action to insulin sensitivity *ten times* greater than those compounds disclosed in WO 95/29159," that was not the case for all of the claimed compounds. The ED_{30} KK mouse data for the compounds encompassed by claims 1-14 that do not meet the asserted criterion was not before the Patent and Trademark Office during prosecution of the '532 patent, and may be considered to raise a substantial new question of patentability with respect to claims 1-14 of the '532 patent.

3. JP 10-218861 (Item of Information No. 8)

JP 10-218861 ("JP '861") describes compounds said to have β_3-receptor stimulating action and said to be useful as active components of therapeutic agents for treating diabetes. (*See* JP '861 at Abstract.) JP '861 was cited during prosecution of the '532 patent against claims 1-8 of the '096 application in a rejection under 35 U.S.C. § 102(a). (*See* the Prosecution File History, non-final Office Action mailed in the '096 application on December 7, 2000, at p. 6.)

In lieu of presenting a substantive argument against the Section 102(a) rejection, a sworn translation of Japanese Application No. Hei 9-285778, filed October 17, 1997 (of which the '532 patent claims benefit under 35 U.S.C. § 119), was submitted to remove JP '861, which published on August 18, 1998, as prior art. (*See id.* at Amendment under 37 C.F.R. § 1.111 filed May 4, 2001, at pp. 13-14.) As a result, the Office withdrew the Section 102(a) rejection. (*See id.* at non-final Office Action mailed in the '096 application on June 19, 2001, at p. 3.)

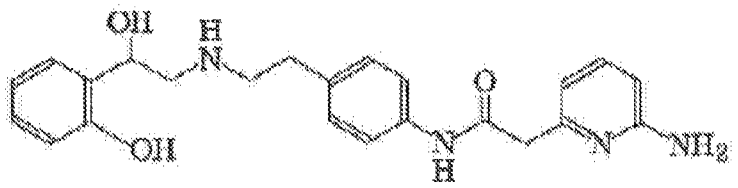
JP Hei 9-285778, however, may not provide sufficient written description support for the full scope of claims 1-5, 7-11, 13, and 14 of the '532 patent. Specifically, while JP Hei 9-285778 recites the same formulae as formula (I) in claim 1 of the '532 patent and formula (Ia) in claim 5 of the '532 patent, not all components of these formulae are described in the same manner in both documents. JP Hei 9-285778 states that B is "a nitrogen-containing heteroaryl group which may be substituted and may be fused with a benzene ring," while B in claims 1-5 of the '532 patent is "a heteroaryl group." Also, JP Hei 9-285778 states that A is "methylene, ethylene or a group represented by a formula $-CH_2-O-$," while A in claim 1 of the '532 patent is "lower alkylene or lower alkylene-O-."

Since claims 1-5, 7-11, 13, and 14 of the '532 patent may not be entitled to the October 17, 1997, priority date, JP '861 may be *prima facie* prior art under 35 U.S.C. § 102(a) and may raise a substantial new question of patentability with respect to those claims, at least for the reason it was cited during prosecution of the '532 patent.

4. JP 10-218861 in view of Blin (Item of Information No. 9)

JP '861 recites Compound 11 in Table 9:

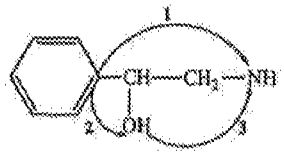
Compound 11



This Compound 11 differs from the compounds encompassed by claims 1-5, 7-11, 13, and 14 of the '532 patent only in that the terminal phenyl ring in Compound 11 has a hydroxyl substituent, whereas the corresponding terminal phenyl ring in the compounds encompassed by claims 1-5, 7-11, 13, and 14 of the '532 patent is not substituted with a hydroxyl group.

Blin, which was not of record during the prosecution of the '532 patent, discusses the structural-activity relationships of a large variety of compounds to determine the structural features responsible for the β_3 potency and selectivity of ligands. (*See* Blin at p. 1097.) Blin teaches that potent β_3 agonists may have the following minimal pharmacophore:

A



d1 (Å) = 3.83 ± 0.08
d2 (Å) = 2.47 ± 0.03
d3 (Å) = 3.07 ± 0.08

(*See id.* at pp. 1101-02.)

This minimal pharmacophore shares a similar portion of the skeleton, phenyl ring-CH(OH)-CH_2(NH), with Compound 11 of JP '861. However, the phenyl ring in the minimal pharmacophore of Blin is not substituted.

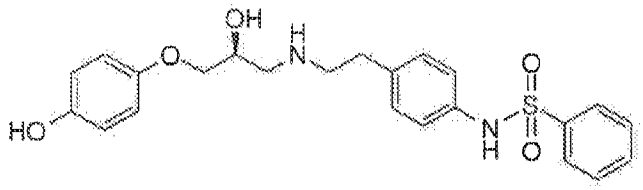
Blin, therefore, might be construed, *arguendo*, to teach that the terminal phenyl ring in Compound 11 of JP '861 need not be substituted with a hydroxyl group to retain its intended β_3-adrenergic receptor agonist activity. Accordingly, modification of

Compound 11 of JP '861 to replace the hydroxyl substituent on the terminal phenyl ring with hydrogen might be said to have been *prima facie* obvious in view of the teachings in Blin. Thus, as discussed above, since the hydroxyl substitution on the terminal phenyl ring in Compound 11 of JP '861 is the only difference between this compound and the compounds encompassed by claims 1-5, 7-11, 13, and 14 of the '532 patent, the combination of JP '861 and Blin may raise a substantial new question of patentability with respect to those claims.

5. WO 94/18161 (Item of Information No. 10) in view of Blin, Thornber (Item of Information No. 11), and JP 10-218861 (Item of Information No. 8)

WO 94/18161 ("WO '161"), which was not of record during prosecution of the '532 patent, describes a group of substituted sulfonamides that are said to be selective β_3-adrenergic receptor agonists having very little β_1 and β_2 adrenergic receptor activity that are expected to be useful in the treatment of Type II diabetes. (Abstract.) Among the specific compounds described in WO '161 is the following on page 32:

EXAMPLE 8 of WO '161

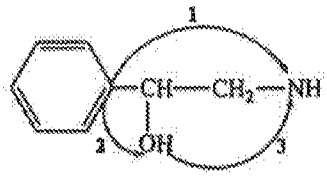


This compound differs from the compounds encompassed by claims 1-5, 7-11, 13, and 14 of the '532 patent in that it has, on the left hand side of the molecule, a hydroxyl-substituted phenyl ring-O-CH_2-CH(OH)-CH_2(NH), rather than a phenyl ring-CH_2-CH(OH)-CH_2(NH) without the hydroxyl substitution. Also, the compound of

Example 8 of WO '161 has, on the right hand side of the molecule, a --N(H)-S(O_2)-phenyl ring, while the compounds encompassed by claims 1-5, 7-11, 13, and 14 of the '532 patent have a –N(H)-C(O)-heteroaryl ring (optionally substituted).

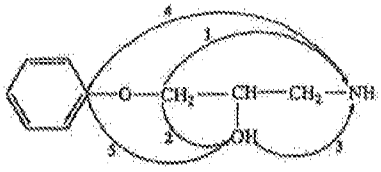
Blin, which is discussed above, discloses that potent β_3 agonists may have either of the following two minimal pharmacophores: phenyl ring-CH(OH)-CH_2(NH) and phenyl ring-O-CH_2-CH(OH)-CH_2(NH)

A



d1 (Å) = 3.83 ± 0.08
d2 (Å) = 2.47 ± 0.03
d3 (Å) = 3.07 ± 0.08

B



d1 (Å) = 3.64 ± 0.11
d2 (Å) = 2.40 ± 0.02
d3 (Å) = 2.95 ± 0.03
d4 (Å) = 5.35 ± 0.18
d5 (Å) = 4.31 ± 0.12

(*See* Blin, at pp. 1101-02.) Blin can also be said, *arguendo*, to teach that there is no need to include a hydroxyl substituent on the phenyl ring in these pharmacophores.

Thornber, which was not of record during prosecution of the '532 patent, discusses how bioisosterism techniques are used in the pharmaceutical arts to modify a lead compound and obtain compounds with similar properties. (*See* Thornber at p. 563 and 565.) Thornber teaches that bioisosteres are groups or molecules which have chemical and physical similarities that impart similar biological properties to a chemical compound. (*See* Thornber at p. 563.) Table 3 in Thornber provides a list of known bioisosteric replacements. For example, Table 3 teaches that a carbonyl group (--CO) may be replaced with a sulfoxide group (--SO_2).

As discussed above, JP '861 might be construed, *arguendo*, to teach that an optionally substituted heteroaryl group may be present at the right hand side of a phenethanol amide β_3-adrenergic receptor agonist.

Therefore, it arguably might have been considered *prima facie* obvious, based on the teachings of Blin, Thornber, and JP '861, to modify the compound disclosed in Example 8 of WO '161 to arrive at the claimed invention, by, for example:

(i) replacing the phenyl ring-O-CH_2-CH(OH)-CH_2(NH) component at the left hand side of the molecule with phenyl ring-CH(OH)-CH_2(NH) and omitting the hydroxyl substitution on the phenyl ring in view of the teachings in Blin;

(ii) replacing the –S(O_2)– group with the –C(O)– group in view of the teachings in Thornber; and

(iii) replacing the terminal phenyl ring at the right hand side of the molecule with a heteroaryl ring or a methylene-linked heteroaryl ring, where the heteroaryl ring may be substituted, in view of JP '861.

Moreover, based on the teachings of Blin, Thornber, and JP '861, there arguably might have been considered to be a reasonable expectation that these modifications could be made without adversely affecting the utility of the compound for treating diabetes. Thus, the combination of WO '161, Thornber, Blin, and JP '861 may raise a substantial new question of patentability with respect to claims 1-5, 7-11, 13, and 14 of the '532 patent.

VII. § 1.610(b)(6): A Copy of The Patent for Which Supplemental Examination is Requested and a Copy of any Disclaimer or Certificate Issued for the Patent

A copy of the '532 patent and a copy of a Certificate of Correction for the '532 patent are submitted herewith.

VIII. § 1.610(b)(7): A Copy Of Each Item Of Information Listed In Section II, Accompanied By A Written English Translation Of All Of The Necessary And Pertinent Parts Of Any Non-English Language Item Of Information

A copy of each item of information is submitted herewith.

IX. § 1.610(b)(8): A Summary of the Relevant Portions of any Submitted Document, Other than the Request, that is Over 50 Pages in Length

As the only submitted document over 50 pages in length is WO '161, a separate summary of the relevant portions of that document is provided as follows:

WO '161, published 18 August 1994, describes a group of substituted phenylsulphonamide compounds that are reported to be selective β_3 adrenergic receptor agonists with very little beta-1 and beta-2 adrenergic receptor activity. (Abstract.) The compounds are said to have very potent activity in the treatment of Type II diabetes and obesity. The scope of the compounds in WO '161 is described on pages 3-5, with several preferred compounds described on pages 5-7. Among the 219 examples described in WO '161 is Example 8 on page 32 of the specification that is referenced above on page 27 of this request.

X. § 1.610(b)(9): An Identification of the Owner(s) of the Entire Right, Title and Interest in the Patent Requested to be Examined, and a Submission By the Patent Owner in Compliance with § 3.73(c) Establishing the Entirety of the Ownership in the Patent Requested to be Examined

Astellas Pharma Inc. is the owner of the entire right, title and interest in the '532 patent by virtue of an assignment from the inventors to Yamanouchi Pharmaceutical Co., Ltd. recorded at reel 010808, starting at frame 0313, on April 17, 2000, and a change of name to Astellas Pharma Inc., recorded at reel 016784, starting at frame 0361, on November 16, 2005.

XI. Correspondence Address

Please send correspondence regarding this supplemental examination proceeding and any subsequent reexamination to the correspondence address associated with Customer No. 22852.

XII. Conclusion

Astellas respectfully requests supplemental examination of claims 1-14 of the '532 patent based on the **(no more than 12)** items of information submitted herewith, and that a supplemental examination certificate be issued.

Please grant any additional extensions of time required to enter the attached reply and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

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

Dated: November 21, 2013

By: Charles E. Van Horn

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Reg. No. 40,266
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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 Moritomo**; **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

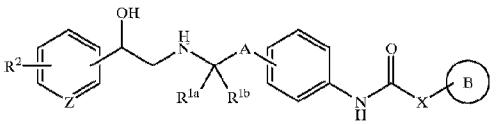
Konosu T. et al. "Triazole antif.", Chem.Pharm.Bull., 39/10, 2581–9, Oct. 1991.*

* 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 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.

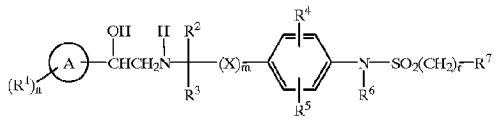
As to the therapy of diabetes mellitus, dietetic treatment, therapeutic exercise and remedy of obesity are mainly conducted in mild cases while, when the disease progresses, oral antidiabetic drugs (for example, insulin secretion promoters such as sulfonylurea compounds and insulin sensitivity potentiators 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.)

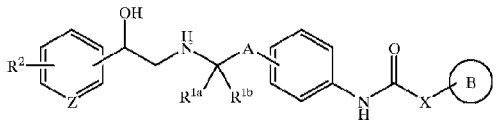
As such, there has been still a demand for creation of therapeutic agents for diabetes mellitus of a new type which have a highly clinical usefulness.

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.

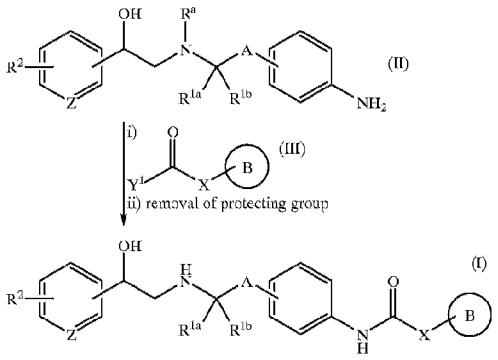
The compound (I) of the present invention has at least one asymmetric carbon atom and therefore, there are optical isomers such as (R)-compounds, (S)-compounds, etc., racemates, diastereomers, etc. The present invention includes all and each of isolated isomers and mixtures thereof. The present invention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

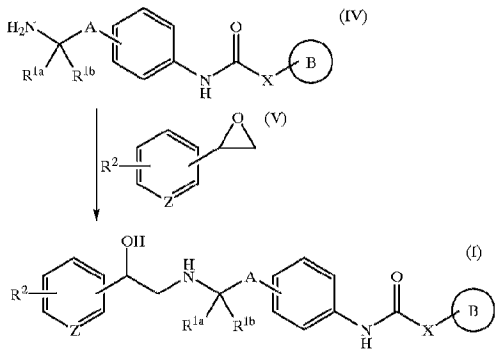
When Y^1 is halide, a method where the reaction is conducted in the above-mentioned inert solvent in the presence of a base may be applied.

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-anisole 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^{1a}, 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.

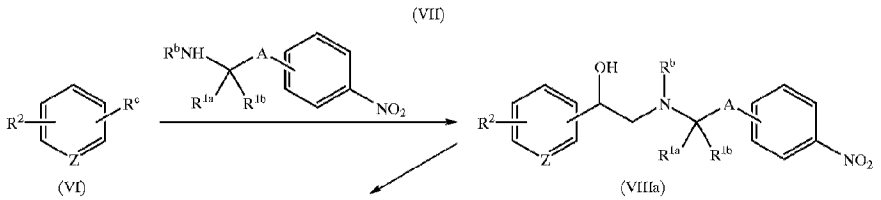
The amine compound (IV) and the compound (V) are reacted under heating or refluxing for 1 to 24 hours as they are or in an inert solvent, to give the compound (I) of the present invention.

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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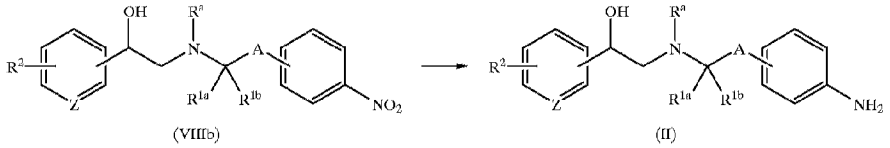


(VIIIb) (II)

(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.

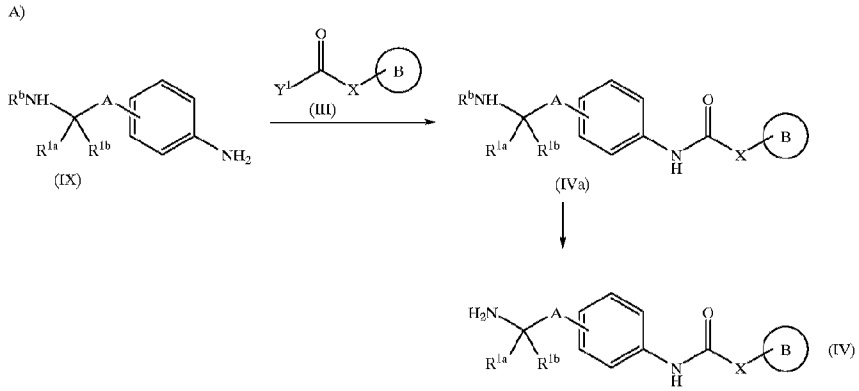
Step (b):

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)

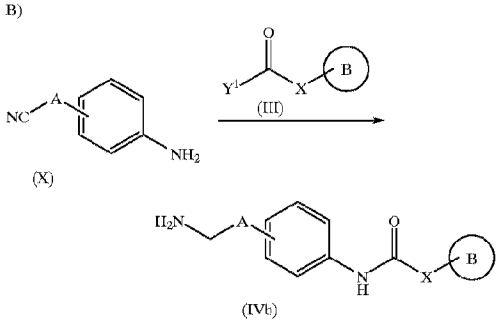


(IX) (III) (IVa) (IV)

(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.

B)



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*), 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 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)aminolethyl]-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-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.

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-Dichiorobenzyl)-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)aminolpropyl]-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: Nuclear magnetic 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, dt, 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), 4.52(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), 9.10–9.30(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), 5.01(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° 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), 9.11(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, c, 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(8H, 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, c, 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), 7.28–7.45(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)
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: 2.59–3.10(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° C., 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° 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), 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: 2.09–3.10(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), 8.92(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, 10.2 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: 2.88–3.22(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)

TABLE 2-continued

Ex.	DATA
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	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, c, 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), 5.53(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	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	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), 8.96(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, 10.6Hz), 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	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), 2.59–3.10(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(5H, 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), 7.65(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), 9.43(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)
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(5H,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	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.Hz), 5.33(2H, s), 6.80(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), 7.50–7.60(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(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	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), 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: 2.90–3.06(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° 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), 7.28–7.43(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° 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=8.8Hz), 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), 7.10–7.4112H, 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(12H, 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(12H, 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), 7.17–7.48(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)

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), 7.12–7.31(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° 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), 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)
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°0 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), 3.05–316(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° 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), 7.81–7.87(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)

TABLE 3

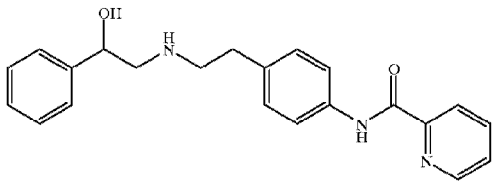
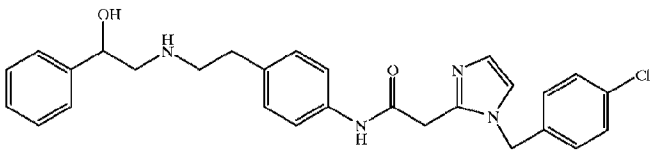
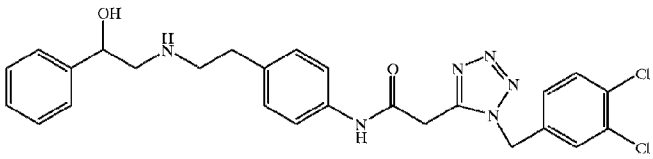
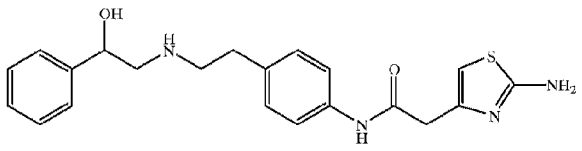
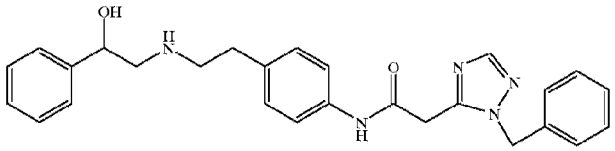
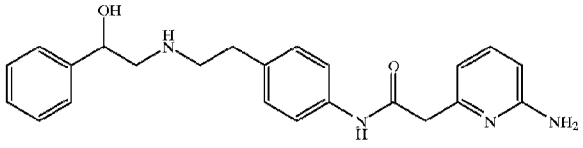
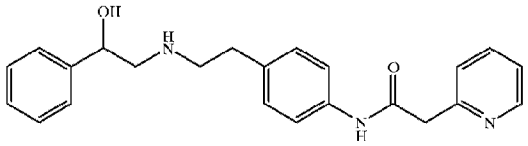
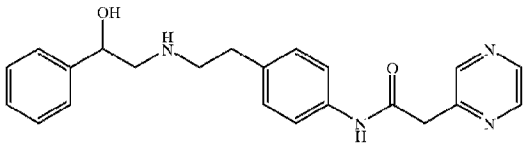
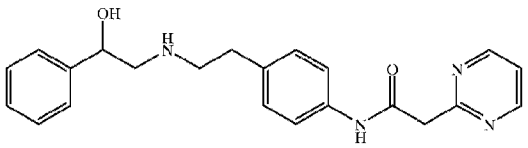
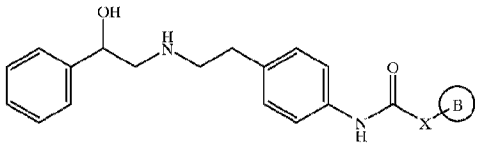
Ex.	Structure
1	
23	
33	

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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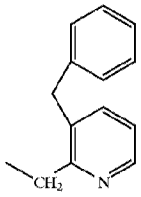
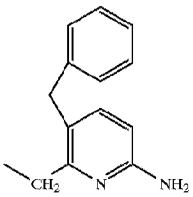
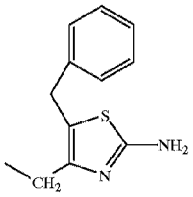
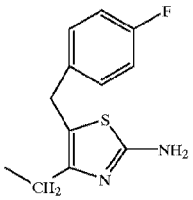
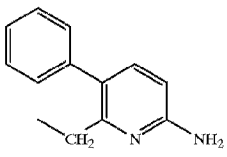
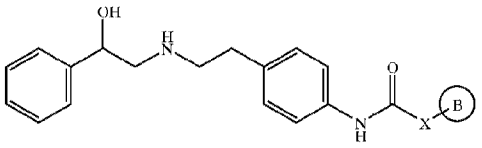
1	
2	
3	
4	
5	

TABLE 4-continued



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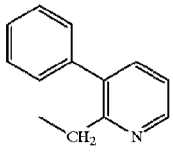
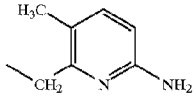
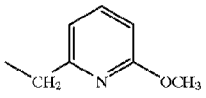
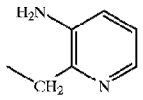
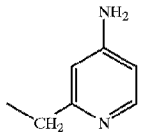
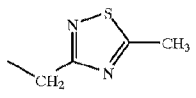
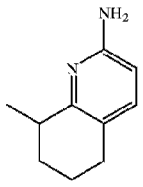
6	
7	
8	
9	
10	
11	
12	

TABLE 5

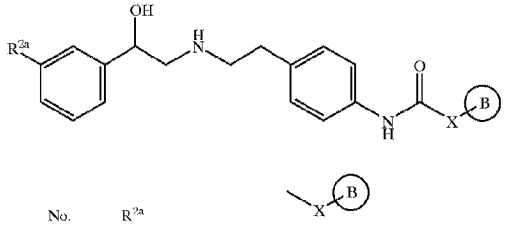
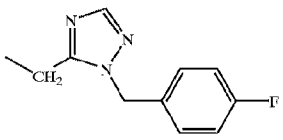
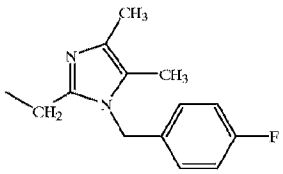
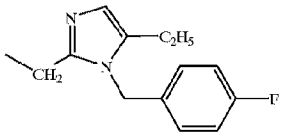
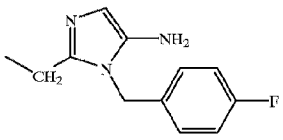
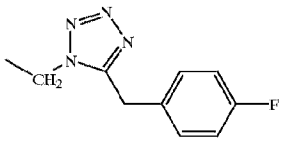
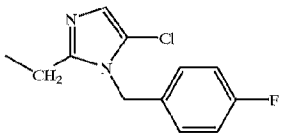
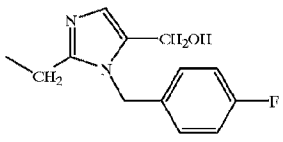
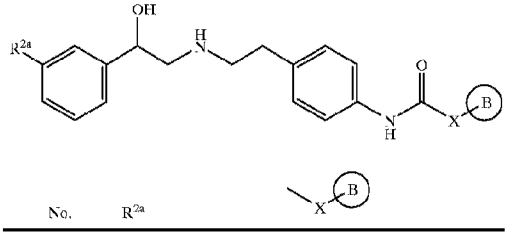
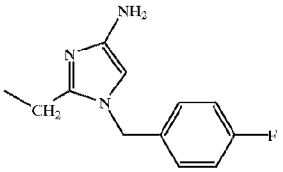
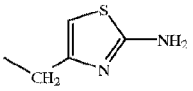
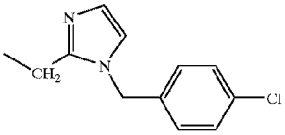
No.	R^{2a}	
13	H	
14	H	
15	H	
16	H	
17	H	
18	H	
19	H	

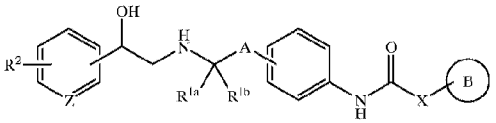
TABLE 5-continued

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 $—CH_2O—$.

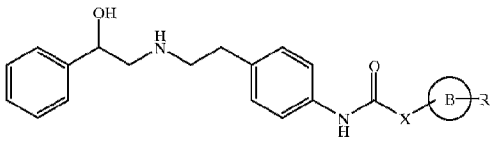
3. The compound of formula (I) or the salt thereof according to claim 2, wherein the ring B is a heteroaryl

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

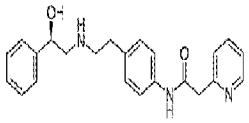
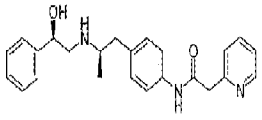
Thirtieth Day of July, 2002

Attest:

Attesting Officer

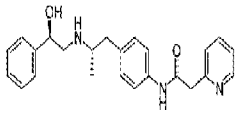
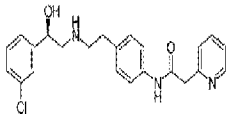
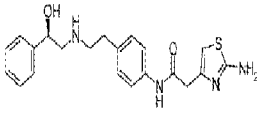
JAMES E. ROGAN
Director of the United States Patent and Trademark Office

Testing Data Table

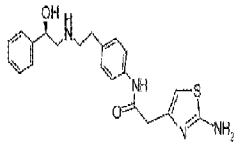
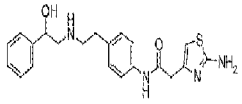
	1	2	3	4	5	6	7	8	9
No.	Compound	Ex.	Structure[1]	β3 pD2 (IA%)	β2 pD2 (IA%)	β1 pD2 (IA%)	KK Mice Hypoglycemic ED30[2]	β3 pD2 (IA%) SK-N-MC	Test Report Date
1	BAN-358	086		6.39 (67.3)	<4 (1.3)	<4 (5.6)	2.7	5.94 (88)	11/27/1996 [β1/ β 2/ β3] 06/25/1997 [KK Mice] 02/16/2000 [SK-N-MC]
2	BAN-369	098		6.7 (80)	6.3 (60)	6.2 (50)			01/29/1997 [β1/ β 2/ β3]

[1] The structures depicted provide the structures of the free base, not the salt forms that may have been synthesized by the patent examples.

[2] Unless a specific value is provided, ED_{30} (mg/kg) value is expressed as >10 (if the blood sugar level lowered is <30% at a dose of 10 mg/kg/day) or <10 (if the blood sugar level lowered is >30% at a dose of 10 mg/kg/day).

	1	2	3	4	5	6	7	8	9
No.	Compound	Ex.	Structure[1]	β3 pD2 (IA%)	β2 pD2 (IA%)	β1 pD2 (IA%)	KK Mice Hypoglycemic ED30[2]	β3 pD2 (IA%) SK-N-MC	Test Report Date
3	BAN-369A[3]	099		7 (60)	5.6 (10)	5.0 (30)	2.3		03/28/1997 [β1/β2/β3] 06/25/1997 [KK Mice]
4	BAN-370	106		6.25 (59)	4.54 (27.2)	5.4 (21.7)			11/27/1996 [β1/β2/β3]
5	BAN-371	041		7.40 (79.4)	4.95 (14.2)	4.63 (22.3)	6.5	6.54 (96)	11/27/1996 [β1/β2/β3] 08/27/1997 [KK Mice] 02/16/2000 [SK-N-MC]

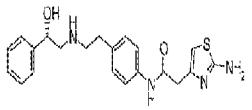
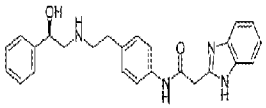
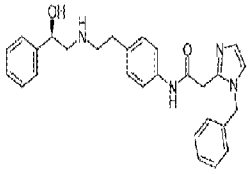
[3] A letter after a BAN number denotes an enantiomer of a compound having that BAN number. For example, BAN-369A is an enantiomer of BAN-369.

	1	2	3	4	5	6	7	8	9
No.	Compound	Ex.	Structure[1]	β3 pD2 (IA%)	β2 pD2 (IA%)	β1 pD2 (IA%)	KK Mice Hypoglycemic ED30[2]	β3 pD2 (IA%) SK-N-MC	Test Report Date
6	BAN-371A[4]	--		7.7 (0.8)	4.7 (0.1)	5.0 (0.0)	4.3	6.67 (87)	10/28/1998 [β1/ β 2/ β3] 04/28/1998 [KK Mice] 03/16/1999 [SK-N-MC]
7	BAN-371B[5]	--		7.2[6] (80)					07/01/2000 [β3]

[4] the free base equivalent of compound BAN-371, which is a HCl salt. Compound BAN-371A is not one of the synthesis examples in the patent specification.

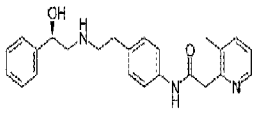
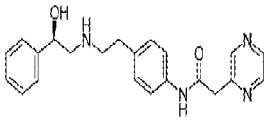
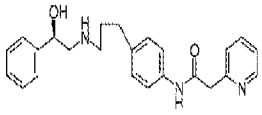
[5] the racemic equivalent of the R-enantiomer compound BAN-371. Compound BAN-371B is not one of the synthesis examples in the patent specification.

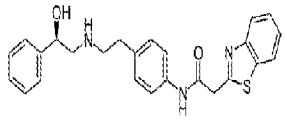
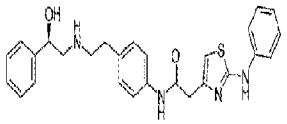
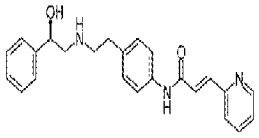
[6] calculated based on EC_{50} (nM) value of 60, using $pD_2 = -\log [EC_{50} (M)]$

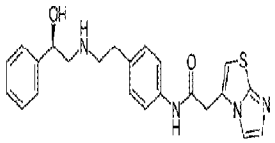
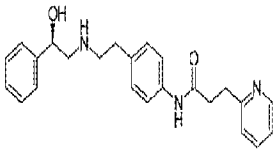
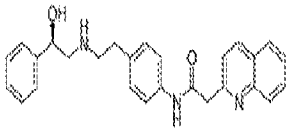
	1	2	3	4	5	6	7	8	9
No.	Compound	Ex.	Structure[1]	β3 pD2 (IA%)	β2 pD2 (IA%)	β1 pD2 (IA%)	KK Mice Hypoglycemic ED30[2]	β3 pD2 (IA%) SK-N-MC	Test Report Date
8	BAN-371C[7]	–		6.1[8] (50)					07/01/2000 [β3]
9	BAN-372	091		6.95 (51.2)	4.54 (28.8)	5.10 (13.7)	>10	6.43 (34)	11/27/1996 [β1/ β 2/ β3] 08/29/1997 [KK Mice] 02/23/2000 [SK-N-MC]
10	BAN-374	094		6.77 (74.7)	<4 (5.5)	5.43 (29.1)	> 10	6.34 (83)	11/27/1996 [β1/ β 2/ β3] 05/28/1997 [KK Mice] 02/23/2000 [SK-N-MC]

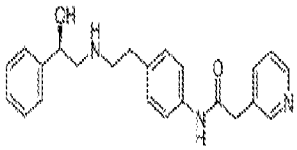
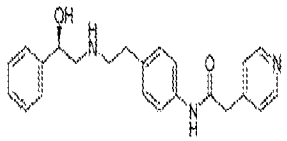
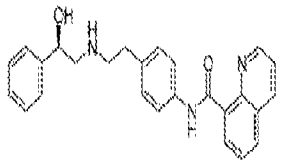
[7] the S-enatiomer compound equivalent of the R-enantiomer compound BAN-371. Compound BAN-371C is not one of the synthesis examples in the patent specification.

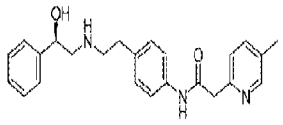
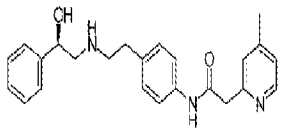
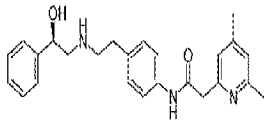
[8] calculated based on EC_{50} (nM) value of 790, using $pD_2 = -\log [EC_{50}(M)]$

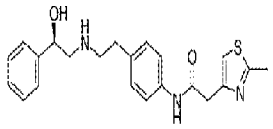
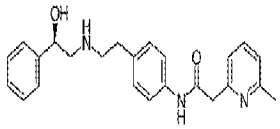
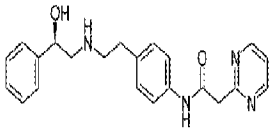
	1	2	3	4	5	6	7	8	9
No.	Compound	Ex.	Structure[1]	β3 pD2 (IA%)	β2 pD2 (IA%)	β1 pD2 (IA%)	KK Mice Hypoglycemic ED30[2]	β3 pD2 (IA%) SK-N-MC	Test Report Date
11	BAN-375	092		6.57 (61.7)	5.22 (12.6)	<4 (18.5)	< 10		11/27/1996 [β1/ β 2/ β3] 06/25/1997 [KK Mice]
12	BAN-376	093		6.70 (50.5)	5.04 (15.3)	5.05 (21.8)	<10	5.59 (82)	11/27/1996 [β1/ β 2/ β3] 01/10/1997 [KK Mice] 02/16/2000 [SK-N-MC]
13	BAN-377	110		5.23 (58.1)	5.65 (22.7)	<4 (2.7)			11/27/1996 [β1/ β 2/ β3]

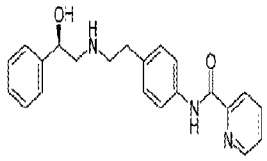
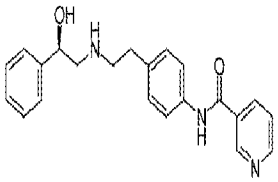
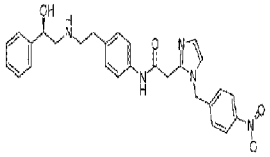
	1	2	3	4	5	6	7	8	9
No.	Compound	Ex.	Structure[1]	β3 pD2 (IA%)	β2 pD2 (IA%)	β1 pD2 (IA%)	KK Mice Hypoglycemic ED30[2]	β3 pD2 (IA%) SK-N-MC	Test Report Date
14	BAN-381	005		6.83 (33.5)	5.74 (15.5)	5.34 (27)		6.22 (34)	11/27/1996 [β1/β2/β3] 02/23/2000 [SK-N-MC]
15	BAN-384	039		6.57 (39.2)	<4 (0.4)	5.37 (22.4)	>10		11/27/1996 [β1/β2/β3] 03/06/1998 [KK Mice]
16	BAN-386	004		6.33 (26.8)	<4 (9)	6.07 (15.3)			11/27/1996 [β1/β2/β3]

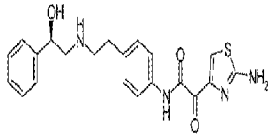
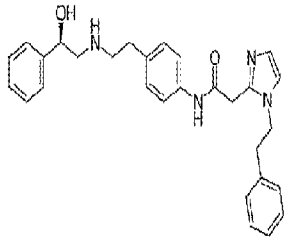
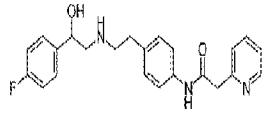
	1	2	3	4	5	6	7	8	9
No.	Compound	Ex.	Structure[1]	β3 pD2 (IA%)	β2 pD2 (IA%)	β1 pD2 (IA%)	KK Mice Hypoglycemic ED30[2]	β3 pD2 (IA%) SK-N-MC	Test Report Date
17	BAN-387	006		6.22 (53.5)	5.60 (22.3)	5.95 (36.7)		5.07 (60)	11/27/1996 [β1/β2/β3] 03/06/2000 [SK-N-MC]
18	BAN-388	089		6.30 (37.6)	5.91 (11.7)	5.44 (20.8)			11/27/1996 [β1/β2/β3]
19	BAN-390	105		6.3 (24)	5.9 (28)	5.3 (17)		6.06 (34)	02/26/1997 [β1/β2/β3] 02/16/2000 [SK-N-MC]

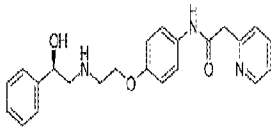
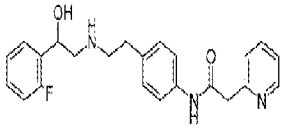
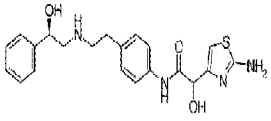
	1	2	3	4	5	6	7	8	9
No.	Compound	Ex.	Structure[1]	β3 pD2 (IA%)	β2 pD2 (IA%)	β1 pD2 (IA%)	KK Mice Hypoglycemic ED30[2]	β3 pD2 (IA%) SK-N-MC	Test Report Date
20	BAN-394	087		5.6 (26)	5.4 (19)	5.4 (12)		5.33 (58)	02/26/1997 [β1/ β 2/ β3] 02/16/2000 [SK-N-MC]
21	BAN-395	088		5.5 (18)	3.8 (50)	5.4 (20)		4.83 (68)	02/26/1997 [β1/ β 2/ β3] 02/16/2000 [SK-N-MC]
22	BAN-396	003		5.9 (18)	4.2 (27)	<4.0 (2)			02/26/1997 [β1/ β 2/ β3]

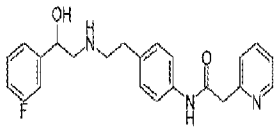
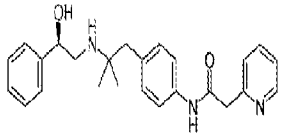
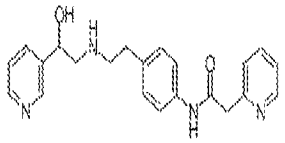
	1	2	3	4	5	6	7	8	9
No.	Compound	Ex.	Structure[1]	β3 pD2 (IA%)	β2 pD2 (IA%)	β1 pD2 (IA%)	KK Mice Hypoglycemic ED30[2]	β3 pD2 (IA%) SK-N-MC	Test Report Date
23	BAN-398	096		5.6 (27)	5.9 (17)	<4 (9)			02/26/1997 [β1/ β 2/ β3]
24	BAN-399	095		6.3 (54)	5.5 (17)	5.2 (18)			03/28/1997 [β1/ β 2/ β3]
25	BAN-400	109		5.9 (46)	5.1 (21)	<4 (8)			03/28/1997 [β1/ β 2/ β3]

	1	2	3	4	5	6	7	8	9
No.	Compound	Ex.	Structure[1]	β3 pD2 (IA%)	β2 pD2 (IA%)	β1 pD2 (IA%)	KK Mice Hypoglycemic ED30[2]	β3 pD2 (IA%) SK-N-MC	Test Report Date
26	BAN-401	007		6.5 (49)	5.4 (18)	<4 (1)	<10	5.89 (114)	03/28/1997 [β1/ β 2/ β3] 08/29/1997 [KK Mice] 02/16/2000 [SK-N-MC]
27	BAN-402	097		5.9 (53)	5.3 (34)	<4 (4)			03/28/1997 [β1/ β 2/ β3]
28	BAN-403	104		6.2 (31)	5.1 (12)	<4 (1)		4.93 (130)	03/28/1997 [β1/ β 2/ β3] 02/16/2000 [SK-N-MC]

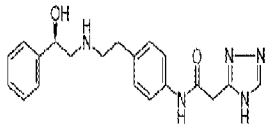
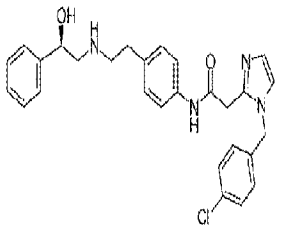
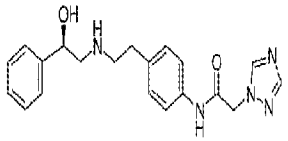
	1	2	3	4	5	6	7	8	9
No.	Compound	Ex.	Structure[1]	β3 pD2 (IA%)	β2 pD2 (IA%)	β1 pD2 (IA%)	KK Mice Hypoglycemic ED30[2]	β3 pD2 (IA%) SK-N-MC	Test Report Date
29	BAN-404	001		5.1 (10)	5.4 (25)	<4 (0)			03/28/1997 [β1/ β 2/ β3]
30	BAN-405	002		6.0 (11)	5.8 (18)	<4 (0)			03/28/1997 [β1/ β 2/ β3]
31	BAN-406	040		6.8 (63)	<4 (6)	<4 (2)	< 10		03/28/1997 [β1/ β 2/ β3] 05/28/1997 [KK Mice]

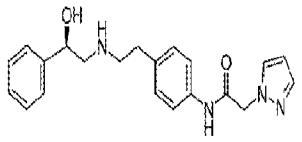
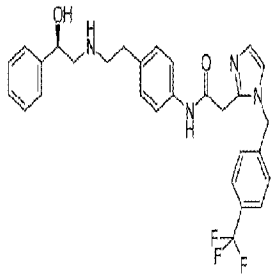
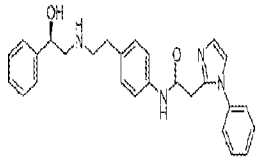
	1	2	3	4	5	6	7	8	9
No.	Compound	Ex.	Structure[1]	β3 pD2 (IA%)	β2 pD2 (IA%)	β1 pD2 (IA%)	KK Mice Hypoglycemic ED30[2]	β3 pD2 (IA%) SK-N-MC	Test Report Date
32	BAN-407	011		6.4 (40)	6.4 (37)	<4 (3)	<10		03/28/1997 [β1/ β 2/ β3] 09/06/2013 [KK Mice]
33	BAN-408	090		6.6 (50)	4 (29)	3.8 (24)	>10		03/28/1997 [β1/ β 2/ β3] 08/29/1997 [KK Mice]
34	BAN-409	103		6.4 (13)	5.5 (11)	<4 (6)			04/23/1997 [β1/ β 2/ β3]

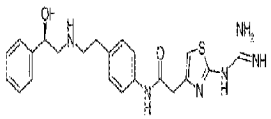
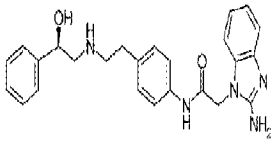
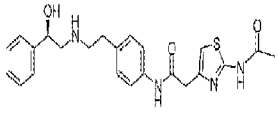
	1	2	3	4	5	6	7	8	9
No.	Compound	Ex.	Structure[1]	β3 pD2 (IA%)	β2 pD2 (IA%)	β1 pD2 (IA%)	KK Mice Hypoglycemic ED30[2]	β3 pD2 (IA%) SK-N-MC	Test Report Date
35	BAN-410	111		5.6 (32)	5.5 (53)	5.6 (14)			04/23/1997 [β1/ β 2/ β3]
36	BAN-411	101		6.2 (37)	5.4 (50)	4.6 (19)			04/23/1997 [β1/ β 2/ β3]
37	BAN-412	059		6.8 (51)	4.9 (44)	<4 (9)			04/23/1997 [β1/ β 2/ β3]

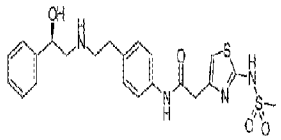
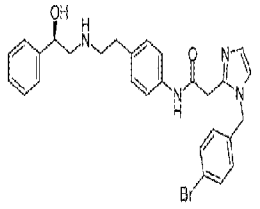
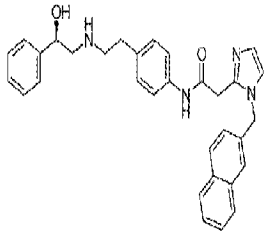
	1	2	3	4	5	6	7	8	9
No.	Compound	Ex.	Structure[1]	β3 pD2 (IA%)	β2 pD2 (IA%)	β1 pD2 (IA%)	KK Mice Hypoglycemic ED30[2]	β3 pD2 (IA%) SK-N-MC	Test Report Date
38	BAN-413	102		6.4 (43)	5.0 (42)	5.0 (13)			04/23/1997 [β1/ β 2/ β3]
39	BAN-414	112		6.9 (55)	6.6 (89)	5.6 (25)			04/23/1997 [β1/ β 2/ β3]
40	BAN-417[9]	107		5.69 (55.6)	5.14 (22.1)	<4 (3.5)			04/16/1997 [β1/ β 2] 03/26/1997 [β3]

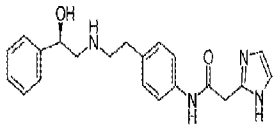
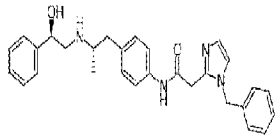
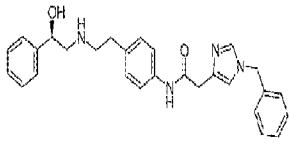
[9] Although this compound is exemplified as example 107 in the patent specification, compound BAN-417 is not covered by the claims.

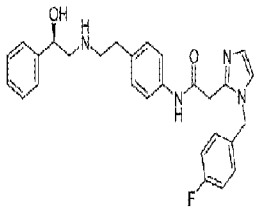
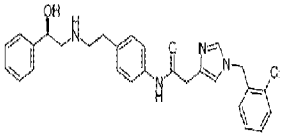
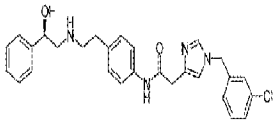
	1	2	3	4	5	6	7	8	9
No.	Compound	Ex.	Structure[1]	β3 pD2 (IA%)	β2 pD2 (IA%)	β1 pD2 (IA%)	KK Mice Hypoglycemic ED30[2]	β3 pD2 (IA%) SK-N-MC	Test Report Date
41	BAN-418	034		6.2 (37)	<4 (9)	<4 (2)		5.72 (85)	04/23/1997 [β1/ β 2/ β3] 02/16/2000 [SK-N-MC]
42	BAN-423	023		6.6 (66)	<4 (5)	5.5 (16)	< 10	(1)6.45 (102) (2)6.84 (78)	04/23/1997 [β1/ β 2/ β3] 08/27/1997 [KK Mice] (1)03/16/1999 [SK-N-MC] (2)02/23/2000 [SK-N-MC]
43	BAN-424	084		5.8 (38)	5.2 (22)	<4 (9)		5.08 (99)	04/23/1997 [β1/ β 2/ β3] 02/23/2000 [SK-N-MC]

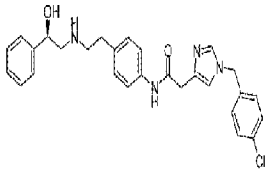
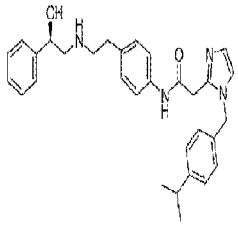
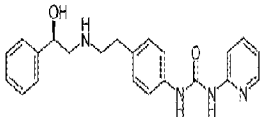
	1	2	3	4	5	6	7	8	9
No.	Compound	Ex.	Structure[1]	β3 pD2 (IA%)	β2 pD2 (IA%)	β1 pD2 (IA%)	KK Mice Hypoglycemic ED30[2]	β3 pD2 (IA%) SK-N-MC	Test Report Date
44	BAN-425	083		6.2 (54)	4.9 (11)	3.8 (34)		5.67 (76)	04/23/1997 [β1/β2/β3] 02/23/2000 [SK-N-MC]
45	BAN-428	026		6.7 (47)	<4 (4)	<4 (5)			04/23/1997 [β1/β2/β3]
46	BAN-429	051		6.2 (44)	<4 (8)	<4 (6)		5.80 (72)	04/23/1997 [β1/β2/β3] 02/23/2000 [SK-N-MC]

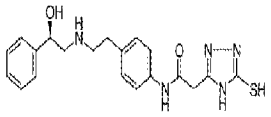
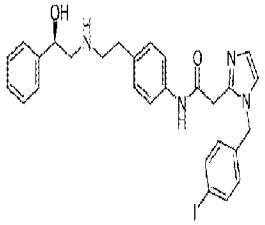
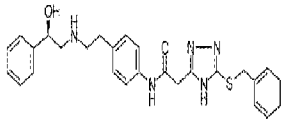
	1	2	3	4	5	6	7	8	9
No.	Compound	Ex.	Structure[1]	β3 pD2 (IA%)	β2 pD2 (IA%)	β1 pD2 (IA%)	KK Mice Hypoglycemic ED30[2]	β3 pD2 (IA%) SK-N-MC	Test Report Date
47	BAN-433	038		5.7 (33)	5 (21)	<4 (3)	>10		05/28/1997 [β1/ β 2/ β3] 03/06/1998 [KK Mice]
48	BAN-434	085		5.5 (66)	4.2 (55)	5.4 (16)			05/28/1997 [β1/ β 2/ β3]
49	BAN-435	036		6.2 (14)	5.3 (27)	<4 (5)	>10		05/28/1997 [β1/ β 2/ β3] 03/06/1998 [KK Mice]

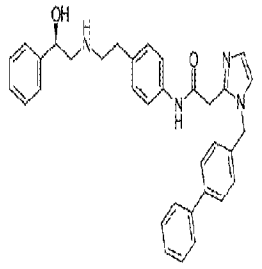
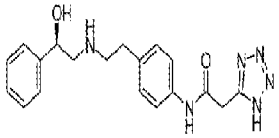
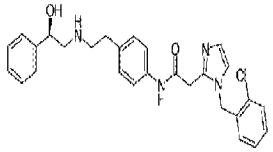
	1	2	3	4	5	6	7	8	9
No.	Compound	Ex.	Structure[1]	β3 pD2 (IA%)	β2 pD2 (IA%)	β1 pD2 (IA%)	KK Mice Hypoglycemic ED30[2]	β3 pD2 (IA%) SK-N-MC	Test Report Date
50	BAN-440	037		<5.0 (27)	5.4 (19)	<4 (6)	>10		05/28/1997 [β1/ β 2/ β3] 03/06/1998 [KK Mice]
51	BAN-443	024		6.3 (65)	6.1 (14)	5.8 (31)			06/25/1997 [β1/ β 2/ β3]
52	BAN-444	027		6.4 (48)	5.6 (17)	5.7 (25)			06/25/1997 [β1/ β 2/ β3]

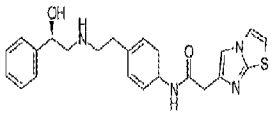
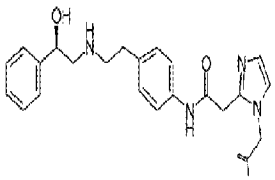
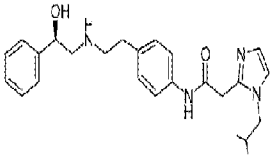
	1	2	3	4	5	6	7	8	9
No.	Compound	Ex.	Structure[1]	β3 pD2 (IA%)	β2 pD2 (IA%)	β1 pD2 (IA%)	KK Mice Hypoglycemic ED30[2]	β3 pD2 (IA%) SK-N-MC	Test Report Date
53	BAN-447	008		6.3 (41)	5.2 (35)	6.6 (23)	<10	5.68 (68)	06/25/1997 [β1/ β 2/ β3] 10/03/1997 [KK Mice] 02/16/2000 [SK-N-MC]
54	BAN-451	100		6.3 (67)	5.3 (34)	5.7 (42)			06/25/1997 [β1/ β 2/ β3]
55	BAN-455	018		5.8 (49)	5.9 (31)	4.4 (69)		5.96 (49)	06/25/1997 [β1/ β 2/ β3] 02/23/2000 [SK-N-MC]

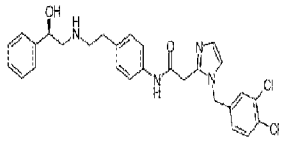
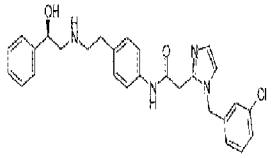
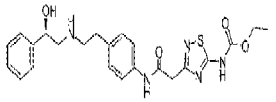
	1	2	3	4	5	6	7	8	9
No.	Compound	Ex.	Structure[1]	β3 pD2 (IA%)	β2 pD2 (IA%)	β1 pD2 (IA%)	KK Mice Hypoglycemic ED30[2]	β3 pD2 (IA%) SK-N-MC	Test Report Date
56	BAN-461	022		7.2 (79)	<4 (9)	5.7 (24)	<10	6.59 (117)	06/25/1997 [β1/ β 2/ β3] 08/27/1997 [KK Mice] 02/23/2000 [SK-N-MC]
57	BAN-465	019		6.0 (44)	<4 (23)	4.9 (17)			06/25/1997 [β1/ β 2/ β3]
58	BAN-466	020		6.2 (46)	4.5 (26)	5.1 (14)			06/25/1997 [β1/ β 2/ β3]

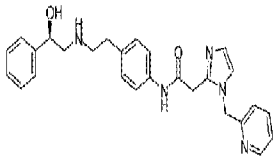
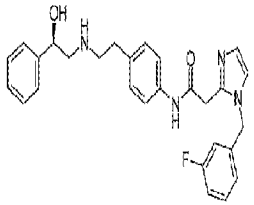
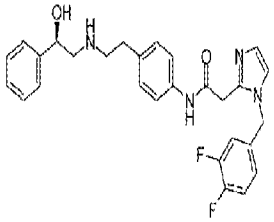
	1	2	3	4	5	6	7	8	9
No.	Compound	Ex.	Structure[1]	β3 pD2 (IA%)	β2 pD2 (IA%)	β1 pD2 (IA%)	KK Mice Hypoglycemic ED30[2]	β3 pD2 (IA%) SK-N-MC	Test Report Date
59	BAN-469	021		6.1 (71)	5.2 (16)	5.4 (12)			06/25/1997 [β1/ β 2/ β3]
60	BAN-473	052		6.5 (54)	<4 (7)	<4 (8)			06/25/1997 [β1/ β 2/ β3]
61	BAN-478	113		5.8 (52)	6.4 (49)	4.9 (14)			06/25/1997 [β1/ β 2/ β3]

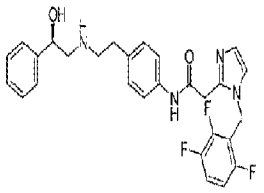
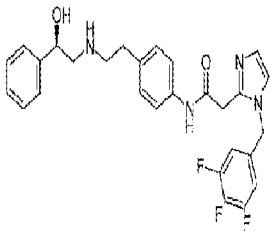
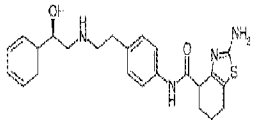
	1	2	3	4	5	6	7	8	9
No.	Compound	Ex.	Structure[1]	β3 pD2 (IA%)	β2 pD2 (IA%)	β1 pD2 (IA%)	KK Mice Hypoglycemic ED30[2]	β3 pD2 (IA%) SK-N-MC	Test Report Date
62	BAN-481	010		6.4 (44)	<4 (7)	4.5 (13)		4.94 (102)	07/30/1997 [β1/ β 2/ β3] 02/23/2000 [SK-N-MC]
63	BAN-484	025		6.9 (70)	<4 (4)	5.6 (13)	10		07/30/1997 [β1/ β 2/ β3] 08/27/1997 [KK Mice]
64	BAN-490	035		6.3 (59)	5.6 (14)	5.8 (21)		5.72 (116)	07/30/1997 [β1/ β 2/ β3] 02/23/2000 [SK-N-MC]

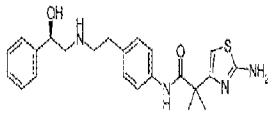
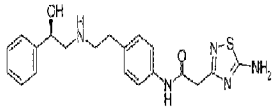
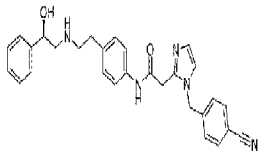
	1	2	3	4	5	6	7	8	9
No.	Compound	Ex.	Structure[1]	β3 pD2 (IA%)	β2 pD2 (IA%)	β1 pD2 (IA%)	KK Mice Hypoglycemic ED30[2]	β3 pD2 (IA%) SK-N-MC	Test Report Date
65	BAN-491	053		6.4 (56)	5.0 (9)	4.9 (13)			07/30/1997 [β1/ β 2/ β3]
66	BAN-493	009		6.4 (89)	<4 (8)	<4 (5)	<10	5.98 (79)	07/30/1997 [β1/ β 2/ β3] 08/27/1997 [KK Mice] 02/16/2000 [SK-N-MC]
67	BAN-494	054		6.6 (90)	<4 (8)	5.4 (38)			07/30/1997 [β1/ β 2/ β3]

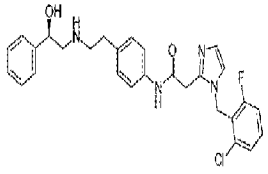
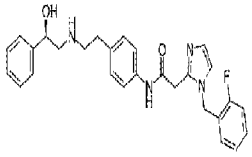
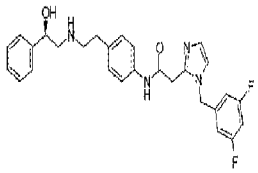
	1	2	3	4	5	6	7	8	9
No.	Compound	Ex.	Structure[1]	β3 pD2 (IA%)	β2 pD2 (IA%)	β1 pD2 (IA%)	KK Mice Hypoglycemic ED30[2]	β3 pD2 (IA%) SK-N-MC	Test Report Date
68	BAN-497	046		6.8 (55)	4.8 (13)	4.8 (18)		5.30 (74)	07/30/1997 [β1/ β 2/ β3] 03/06/2000 [SK-N-MC]
69	BAN-499	017		6.5 (70)	5.3 (16)	5.0 (47)			07/30/1997 [β1/ β 2/ β3]
70	BAN-500	061		6.6 (92)	<4 (7)	4.7 (36)			07/30/1997 [β1/ β 2/ β3]

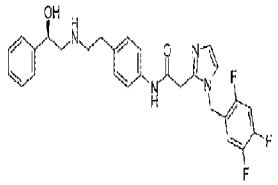
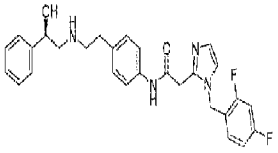
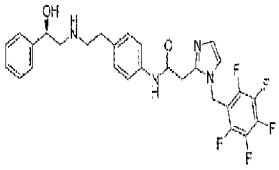
	1	2	3	4	5	6	7	8	9
No.	Compound	Ex.	Structure[1]	β3 pD2 (IA%)	β2 pD2 (IA%)	β1 pD2 (IA%)	KK Mice Hypoglycemic ED30[2]	β3 pD2 (IA%) SK-N-MC	Test Report Date
71	BAN-501	056		7.1 (88)	<4 (2)	5.9 (10)	>10		07/30/1997 [β1/ β 2/ β3] 08/27/1997 [KK Mice]
72	BAN-502	055		6.6 (70)	<4 (2)	5.6 (19)			07/30/1997 [β1/ β 2/ β3]
73	BAN-503	013		5.7 (45)	<4 (6)	4.1 (21)	>10		07/30/1997 [β1/ β 2/ β3] 03/06/1998 [KK Mice]

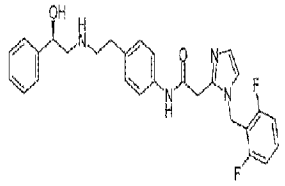
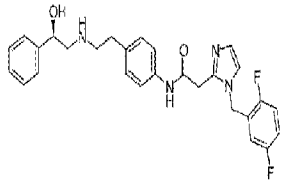
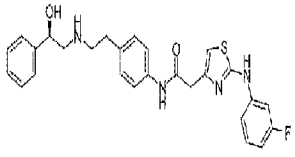
	1	2	3	4	5	6	7	8	9
No.	Compound	Ex.	Structure[1]	β3 pD2 (IA%)	β2 pD2 (IA%)	β1 pD2 (IA%)	KK Mice Hypoglycemic ED30[2]	β3 pD2 (IA%) SK-N-MC	Test Report Date
74	BAN-504	057		6.3 (51)	<4 (2)	<4 (10)			07/30/1997 [β1/ β 2/ β3]
75	BAN-505	063		7.0 (66)	<4 (3)	5.3 (29)			07/30/1997 [β1/ β 2/ β3]
76	BAN-506	068		7.3 (73)	<4 (1)	5.5 (21)	<10		08/27/1997 [β1/ β 2/ β3] 08/22/1997 [KK Mice]

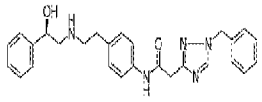
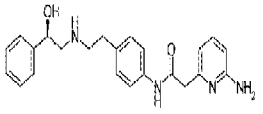
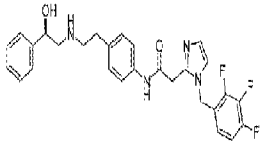
	1	2	3	4	5	6	7	8	9
No.	Compound	Ex.	Structure[1]	β3 pD2 (IA%)	β2 pD2 (IA%)	β1 pD2 (IA%)	KK Mice Hypoglycemic ED30[2]	β3 pD2 (IA%) SK-N-MC	Test Report Date
77	BAN-507	069		6.9 (62)	<4 (0)	5.4 (25)			08/27/1997 [β1/ β 2/ β3]
78	BAN-508	071		7.2 (59)	<4 (1)	5.7 (20)	>10		08/27/1997 [β1/ β 2/ β3] 09/30/1997 [KK Mice]
79	BAN-510	045		7.5 (58)	<4 (6)	<4 (6)	<10		08/27/1997 [β1/ β 2/ β3] 09/30/1997 [KK Mice]

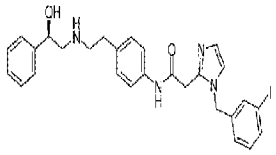
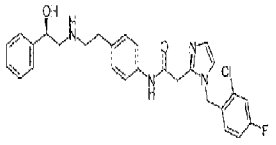
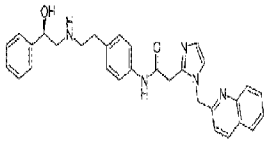
	1	2	3	4	5	6	7	8	9
No.	Compound	Ex.	Structure[1]	β3 pD2 (IA%)	β2 pD2 (IA%)	β1 pD2 (IA%)	KK Mice Hypoglycemic ED30[2]	β3 pD2 (IA%) SK-N-MC	Test Report Date
80	BAN-511	044		5.3 (44)	<4 (3)	<4 (7)			08/27/1997 [β1/ β 2/ β3]
81	BAN-512	012		7.4 (63)	<4 (5)	<4 (8)	<10	7.27 (78)	08/27/1997 [β1/ β 2/ β3] 09/30/1997 [KK Mice] 02/16/2000 [SK-N-MC]
82	BAN-513	075		7.0 (65)	<4 (7)	5.3 (12)	>10		08/27/1997 [β1/ β 2/ β3 & KK Mice]

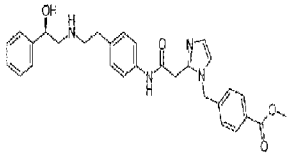
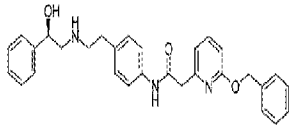
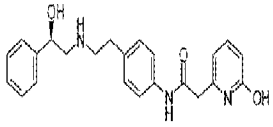
	1	2	3	4	5	6	7	8	9
No.	Compound	Ex.	Structure[1]	β3 pD2 (IA%)	β2 pD2 (IA%)	β1 pD2 (IA%)	KK Mice Hypoglycemic ED30[2]	β3 pD2 (IA%) SK-N-MC	Test Report Date
83	BAN-514	077		6.6 (76)	<4 (1)	5.1 (29)	>10		08/27/1997 [β1/β2/β3] 09/30/1997 [KK Mice]
84	BAN-515	062		6.9 (66)	<4 (0)	5.2 (21)	<10		08/27/1997 [β1/β2/β3 & KK Mice]
85	BAN-516	066		6.9 (63)	<4 (1)	5.4 (18)	<10		08/27/1997 [β1/β2/β3] 08/22/1997 [KK Mice]

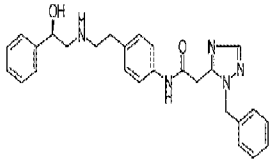
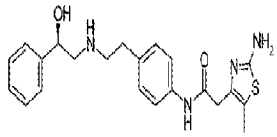
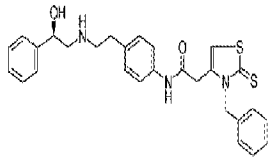
	1	2	3	4	5	6	7	8	9
No.	Compound	Ex.	Structure[1]	β3 pD2 (IA%)	β2 pD2 (IA%)	β1 pD2 (IA%)	KK Mice Hypoglycemic ED30[2]	β3 pD2 (IA%) SK-N-MC	Test Report Date
86	BAN-517	070		7.2 (51)	<4 (2)	5.0 (21)	>10		08/27/1997 [β1/β2/β3] 09/30/1997 [KK Mice]
87	BAN-521	064		7.1 (84)	<4 (1)	5.2 (18)	>10		08/27/1997 [β1/β2/β3 & KK Mice]
88	BAN-522	072		7.0 (69)	<4 (1)	5.3 (12)	>10		08/27/1997 [β1/β2/β3 & KK Mice]

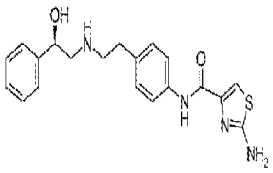
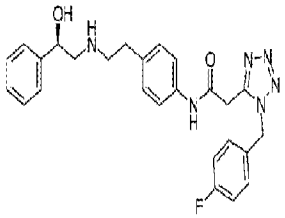
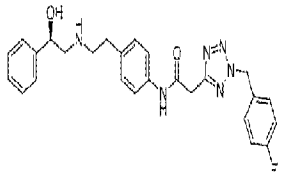
	1	2	3	4	5	6	7	8	9
No.	Compound	Ex.	Structure[1]	β3 pD2 (IA%)	β2 pD2 (IA%)	β1 pD2 (IA%)	KK Mice Hypoglycemic ED30[2]	β3 pD2 (IA%) SK-N-MC	Test Report Date
89	BAN-523	065		6.8 (77)	<4 (1)	4.9 (29)	>10		08/27/1997 [β1/β2/β3] 09/30/1997 [KK Mice]
90	BAN-524	067		7.1 (74)	<4 (7)	5.4 (19)	<10		08/27/1997 [β1/β2/β3 & KK Mice]
91	BAN-525	014		6.3 (63)	<4 (1)	5.5 (20)			08/27/1997 [β1/β2/β3]

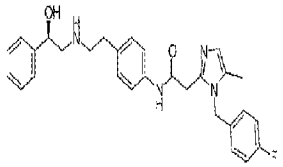
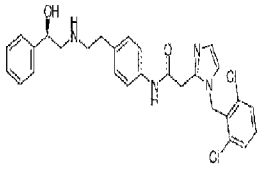
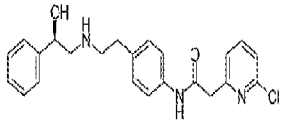
	1	2	3	4	5	6	7	8	9
No.	Compound	Ex.	Structure[1]	β3 pD2 (IA%)	β2 pD2 (IA%)	β1 pD2 (IA%)	KK Mice Hypoglycemic ED30[2]	β3 pD2 (IA%) SK-N-MC	Test Report Date
92	BAN-526	048		6.6 (62)	<4 (3)	5.0 (14)	<10	5.87 (79)	08/27/1997 [β1/ β 2/ β3] 09/30/1997 [KK Mice] 02/23/2000 [SK-N-MC]
93	BAN-527	058		7.0 (83)	<4 (2)	<4 (9)	<10	5.91 (97)	08/27/1997 [β1/ β 2/ β3] 09/30/1997 [KK Mice] 02/16/2000 [SK-N-MC]
94	BAN-528	080		7.2 (83)	<4 (0)	5.2 (26)	>10		08/27/1997 [β1/ β 2/ β3] 09/30/1997 [KK Mice]

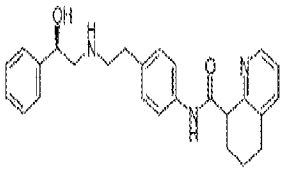
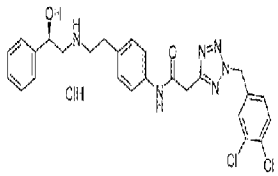
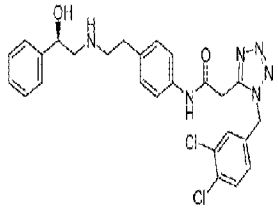
	1	2	3	4	5	6	7	8	9
No.	Compound	Ex.	Structure[1]	β3 pD2 (IA%)	β2 pD2 (IA%)	β1 pD2 (IA%)	KK Mice Hypoglycemic ED30[2]	β3 pD2 (IA%) SK-N-MC	Test Report Date
95	BAN-529	073		6.8 (74)	<4 (0)	4.8 (21)	>10		08/27/1997 [β1/ β 2/ β3] 09/30/1997 [KK Mice]
96	BAN-530	078		6.8 (74)	<4 (1)	5.0 (28)	>10		08/27/1997 [β1/ β 2/ β3] 09/30/1997 [KK Mice]
97	BAN-531	076		6.7 (61)	<4 (1)	<4 (8)	>10		08/27/1997 [β1/ β 2/ β3] 09/30/1997 [KK Mice]

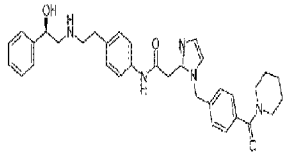
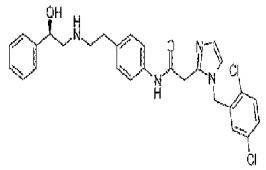
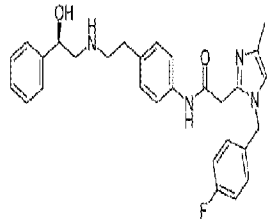
	1	2	3	4	5	6	7	8	9
No.	Compound	Ex.	Structure[1]	β3 pD2 (IA%)	β2 pD2 (IA%)	β1 pD2 (IA%)	KK Mice Hypoglycemic ED30[2]	β3 pD2 (IA%) SK-N-MC	Test Report Date
98	BAN-532	081		6.5 (76)	<4 (1)	<4 (8)			08/27/1997 [β1/ β 2/ β3]
99	BAN-533	016		5.4 (36)	<4 (1)	<4 (5)			08/27/1997 [β1/ β 2/ β3]
100	BAN-534	060		6.3 (40)	<4 (3)	5.3 (13)		5.88 (59)	08/27/1997 [β1/ β 2/ β3] 02/16/2000 [SK-N-MC]

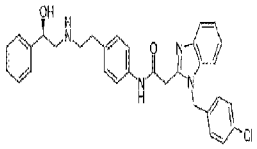
	1	2	3	4	5	6	7	8	9
No.	Compound	Ex.	Structure[1]	β3 pD2 (IA%)	β2 pD2 (IA%)	β1 pD2 (IA%)	KK Mice Hypoglycemic ED30[2]	β3 pD2 (IA%) SK-N-MC	Test Report Date
101	BAN-536	047		6.3 (91)	<4 (1)	4.8 (31)	<10	6.07 (105)	08/27/1997 [β1/β2/β3] 09/30/1997 [KK Mice] 02/23/2000 [SK-N-MC]
102	BAN-537	043		7.8 (76)	<4 (4)	<4 (6)	<10		09/30/1997 [β1/β2/β3 & KK Mice]
103	BAN-538	049		6.0 (67)	<4 (3)	5.9 (15)	>10		09/30/1997 [β1/β2/β3 & KK Mice]

	1	2	3	4	5	6	7	8	9
No.	Compound	Ex.	Structure[1]	β3 pD2 (IA%)	β2 pD2 (IA%)	β1 pD2 (IA%)	KK Mice Hypoglycemic ED30[2]	β3 pD2 (IA%) SK-N-MC	Test Report Date
104	BAN-539	042		5.5 (49)	<4 (1)	<4 (7)			09/30/1997 [β1/ β 2/ β3]
105	BAN-540	030		7.8 (80)	<4 (1)	4.9 (25)	<10	(1) 6.38 (197) (2) 5.91 (115)	09/30/1997 [β1/ β 2/ β3] 09/12/1997 [KK Mice] (1)02/23/2000 [SK-N-MC] (2)03/06/2000 [SK-N-MC]
106	BAN-541	032		6.8 (72)	<4 (1)	3.8 (35)		6.19 (90)	09/30/1997 [β1/ β 2/ β3] 02/23/2000 [SK-N-MC]

	1	2	3	4	5	6	7	8	9
No.	Compound	Ex.	Structure[1]	β3 pD2 (IA%)	β2 pD2 (IA%)	β1 pD2 (IA%)	KK Mice Hypoglycemic ED30[2]	β3 pD2 (IA%) SK-N-MC	Test Report Date
107	BAN-544	028		6.7 (71)	<4 (1)	5.3 (24)	10		09/30/1997 [β1/ β 2/ β3] 10/03/1997 [KK Mice]
108	BAN-545	074		7.2 (82)	5.1 (45)	4.9 (52)			09/30/1997 [β1/ β 2/ β3]
109	BAN-548	015		7.1 (68)	5.4 (39)	5.1 (74)		6.67 (108)	09/30/1997 [β1/ β 2/ β3] 02/16/2000 [SK-N-MC]

	1	2	3	4	5	6	7	8	9
No.	Compound	Ex.	Structure[1]	β3 pD2 (IA%)	β2 pD2 (IA%)	β1 pD2 (IA%)	KK Mice Hypoglycemic ED30[2]	β3 pD2 (IA%) SK-N-MC	Test Report Date
110	BAN-550	050		6.75 (58.4)	4.40 (29.4)	4.49 (16.9)			09/04-17/1997 [β1/ β 2/ β3]
111	BAN-551	031		6.9 (50)	5.7 (18)	5.7 (9)			09/30/1997 [β1/ β 2/ β3]
112	BAN-552	033		7.7 (78)	5.8 (12)	6.4 (22)	9.5		09/30/1997 [β1/ β 2/ β3] 11/04/1997 [KK Mice]

	1	2	3	4	5	6	7	8	9
No.	Compound	Ex.	Structure[1]	β3 pD2 (IA%)	β2 pD2 (IA%)	β1 pD2 (IA%)	KK Mice Hypoglycemic ED30[2]	β3 pD2 (IA%) SK-N-MC	Test Report Date
113	BAN-553	082		6.8 (69)	4.8 (14)	5.5 (25)	>10		09/30/1997 [β1/ β 2/ β3] 10/03/1997 [KK Mice]
114	BAN-554	079		6.9 (74)	5.0 (17)	5.1 (39)			09/30/1997 [β1/ β 2/ β3]
115	BAN-555	029		6.5 (55)	5.4 (30)	5.5 (22)			09/30/1997 [β1/ β 2/ β3]

	1	2	3	4	5	6	7	8	9
No.	Compound	Ex.	Structure[1]	β3 pD2 (IA%)	β2 pD2 (IA%)	β1 pD2 (IA%)	KK Mice Hypoglycemic ED30[2]	β3 pD2 (IA%) SK-N-MC	Test Report Date
116	BAN-556	108		6.2 (56)	5.3 (18)	5.0 (13)			09/30/1997 [β1/β2/β3]

Strictly Confidential

October 27, 2003

Materials for R&D Meeting

YM178/Discontinuation of Development Theme for Diabetes Mellitus

1 Overview of the Compound

(1) Research Experiment Code Number: BAN-371A

(2) YM Number: YM-179178

(3) Abbreviated Theme: 178

(4) Clinical Study Number: YM178

(5) Generic Name: Undetermined

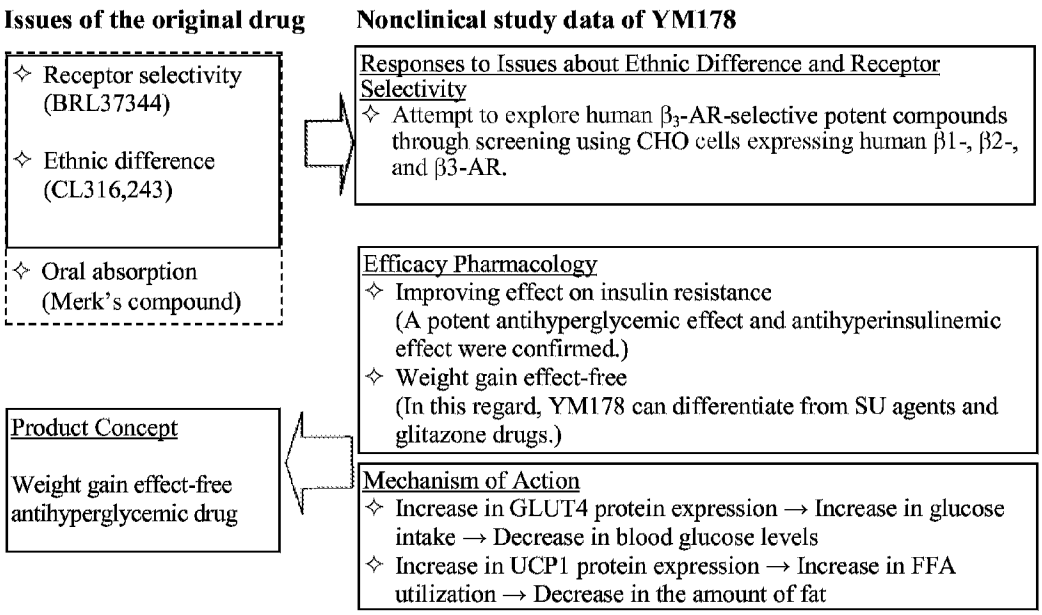
(6) Proprietary: Undetermined

(7) Drug Efficacy: Sympathetic β_3 receptor stimulant

(8) Indications: Type 2 diabetes mellitus

2 Background of R&D

1) YM178 Product Concept



2) Background of R&D

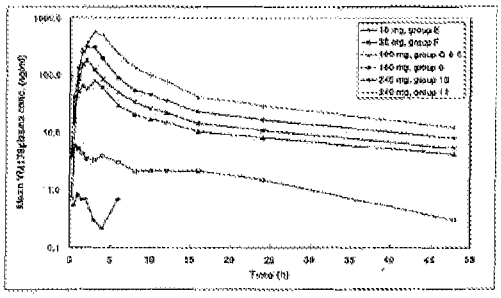
April, 1995	Research theme establishment
October, 1996	Synthesis of BAN-371
April, 1998	Selection of BAN-371 (free form) as an FT-FIM compound
March, 1999	Development subtheme establishment
January, 2000	Development theme establishment
June, 2000	Start of a phase I single-dose/food effect (-001) study
April, 2001	Start of a phase I consecutive-dose (-002) study
February, 2002	Start of phase IIa (-003/-004) studies
May, 2003	Completion of treatment in phase IIa studies
July, 2003	Revelation of an overview of the phase IIa study results

The antihyperglycemic effect of YM178 given at a dose of 200 mg in the fed state could not be confirmed.

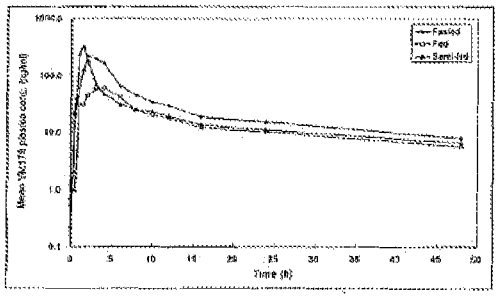
3 Clinical Study Data

1) Phase I Single-dose/food Effect (-001) Study

PK following a Single Dose



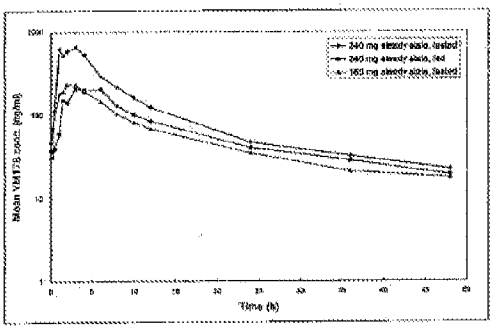
PK in the Food Effect Study



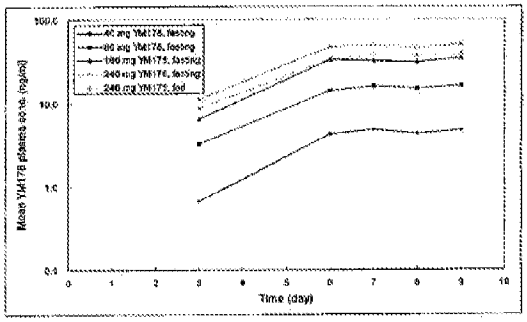
MTD for single-dose administration in the fasted state: 340 mg
Effect of food: Great

2) Phase I Consecutive-dose (-002) Study

Following 7-day Consecutive Doses



Plasma Trough Concentration-time Profile



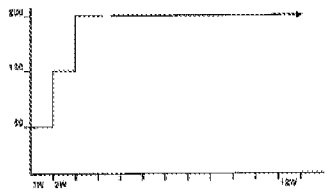
Steady state: Attained on day 4 of consecutive-dose treatment

C_{max} following administration of 240 mg in the fed state is almost comparable to that following administration of 160 mg in the fasted state.

Common AEs: Headache, tachycardia, and orthostatic hypotension

3) Phase IIa Studies

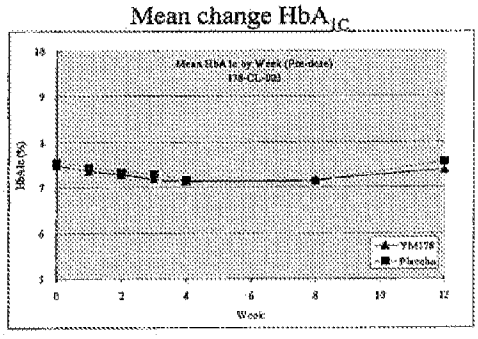
a. Overview of the Design



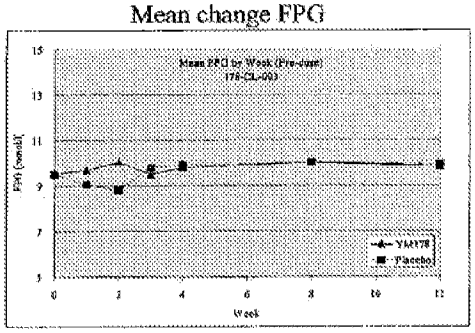
	Monotherapy (-003) Study	Combination Therapy (-004) Study
Objectives	1) To assess the efficacy of YM178 in patients with diabetes mellitus 2) To assess the safety and tolerability of YM178 3) To assess the PK of YM178	
Study patients	Patients with type 2 diabetes mellitus being treated with diet and exercise (pharmacotherapy-naïve)	Patients with type 2 diabetes mellitus being treated with metformin
Design	Placebo-controlled, dose-titration (60 mg → 130 mg → 200 mg), once-daily treatment after breakfast	
Total number of enrolled patients	60 patients (including 20 patients given placebo)	
Efficacy endpoints	• Primary: HbA_{1c} and FBG • Secondary: NEFA, C-peptide, triglyceride, etc.	
Safety endpoints	Adverse drug reactions (including assessment of hyperglycemic and hypoglycemic events), laboratory tests, vital signs, and ECG (including QTc assessment)	

b. Overview of Results/Monotherapy (-003) Study

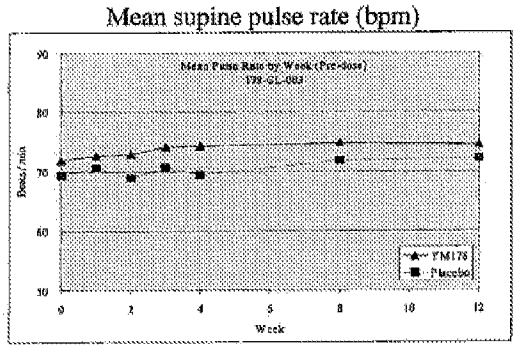
Mean change HbA_{1C}



Mean change FPG



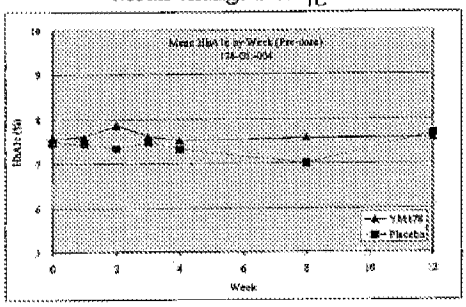
Mean supine pulse rate (bpm)



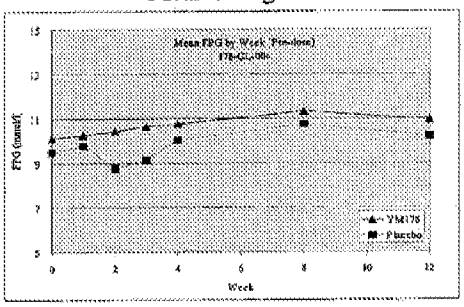
- Efficacy endpoints: No efficacy
- Pulse rate: Slightly elevated

c. Overview of Results/Combination Therapy (-004) Study

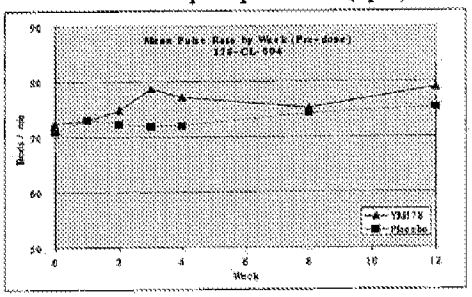
Mean change HbA_{1C}



Mean change FPG



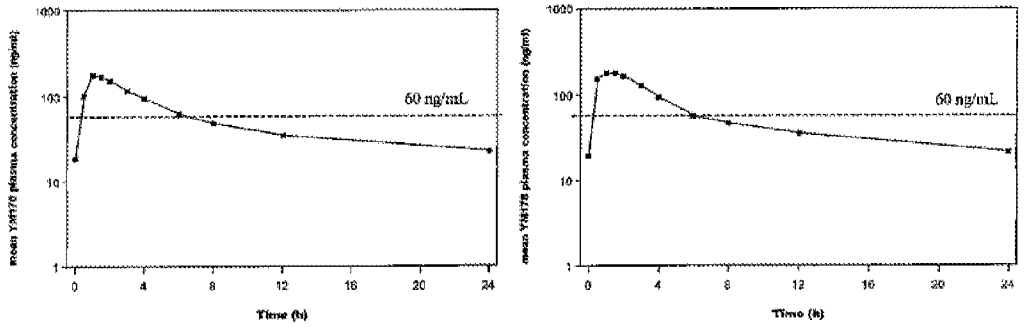
Mean supine pulse rate (bpm)



- Efficacy endpoints: No efficacy
- Pulse rate: Slightly elevated, compared with the monotherapy study results

d. Overview of Results/PK Results

Mean Blood Concentration Following Administration of YM178 at a Dose of 200 mg in Patients with Diabetes Mellitus in the Fed State



Monotherapy (-003) Study **Combination Therapy (-004) Study**

- The pharmacological data indicate that the target blood YM178 concentration is sustained for 6 to 7 hours.

e. Summary of Study Results

- Primary endpoints (HbA_{1c} and fasting blood glucose level)

When given at a dose of 200 mg in the fed state, the efficacy of YM178 for diabetes mellitus was not observed.

The stratified analysis and individual data analysis could also not confirm the efficacy of YM178.

- Secondary endpoints (NEFA, triglyceride, c-peptide, etc.)

The efficacy of YM178 could not be confirmed with any of the endpoints.

- Safety

Increases in heart rate by approximately 2 or 3 beats to 7 or 8 beats/min (bpm) were observed.

- PK

The obtained data covered estimated effective blood concentrations for an average of approximately 6 hours.

4) CYP2D6 (-005) Study

The effects of defective CYP2D6 were barely observed.

Coadministration of metoprolol with YM178 resulted in an approximately 2-fold increase in blood metoprolol concentrations. Coadministration with drugs metabolized by CYP2D6 may cause increased adverse events of coadministered drugs. Caution should therefore be needed.

5) Metformin/DDI (-006) Study Draft report: Scheduled in November

6) Mass Balance (-007) Study Draft report: Scheduled in mid-October

4 Reason for Proposing the Discontinuation of Development

The results of the two 178/phase IIa studies did not show the efficacy of YM178 for type 2 diabetes mellitus.

1) The results of the phase IIa study of YM178 administered at a dose of 200 mg in the fed state could not confirm the efficacy of YM178 in terms of the primary endpoints (HbA_{1c} and fasting blood glucose level).
2) Increases in heart rate were observed when YM178 was administered at a dose of 200 mg.

5 What was Gained from this Project (PJ)

- A proof-of-concept (POC) study was conducted to confirm the hypothesis formulated for diabetes mellitus/β_3 receptors, using YM178 in clinical settings; however, the results expected from preclinical study data could not be obtained.
- Prior to a phase IIa study of YM178, an agreement on goal settings and decision-making charts had been reached. We believe that this could lead to relatively smooth decision-making after the results became available.
- We would like to make good use of experiences gained from three regions through this PJ for future Y's PJs for diabetes mellitus (GTI, FIT, etc.).

6 Actual Costs for R&D

The actual cost for R&D development after development subtheme establishment was 3.06 billion Japanese yen.

		Indirect cost		Direct cost	Total of direct and indirect costs
		Person/ month	Thousand yen	Thousand yen	Thousand yen
Drug substance	Process Chemistry Laboratories	142	514,339	190,322	704,661
Drug product	Novel Pharmaceutical Laboratories	62	150,695	49,849	200,544
Toxicity	Safety Research Laboratories	58	140,237	327,889	468,126
Pharmacology	Pharmacology Laboratories	72	132,102	61,837	193,939
ADME	Drug Metabolism Laboratories	71	179,958	48,622	228,580
Others			8,622	31,008	31,008
Non-clinical study	Subtotal	405	1,125,953	709,527	1,835,480
Clinical study	YEU	-	-	1,069,498	1,069,498
	YPA	-	-	9,608	9,608
	Clinical Development Department	4	13,847	15	13,862
CTM manufacturers	YPCL	94	116,866	8,094	124,960
	YEU	-	-	11,411	11,411
Clinical study	Subtotal	97	130,713	1,098,626	1,229,339
Total		503	1,256,666	1,808,153	3,064,819

7 Conclusion

The development of YM178 for diabetes mellitus is discontinued.

YM178 in Type 2 Diabetes Mellitus
178-CL-003

A Subgroup Analysis

J. Pfeil (BMT)
E.M. van Gelderen (CPRD)

September 11, 2003

Disclaimer

Data presented are draft data to be subjected to QC-procedures
Differences from the final data cannot be excluded

Background

- No efficacy was shown by top line results from study 178-CL-003
- YEU-PT proposed subgroup analysis to identify responders and potential target patient population(s)
- Basic approach was to re-group patients and calculate mean change from baseline for the key parameters HbA1c and FPG, followed by adjustment of selection criteria (trial-and-error method)
- No formal statistics were performed

Definition of subgroups

- GPT proposed subgroups:
  - Males vs. females
  - High vs. low plasma concentration of YM178
  - High vs. low baseline HbA1c and FPG levels
  - High vs low BMI at baseline
  - High vs. low Waist-to-Hip ratio at baseline
  - High vs. Low age
  - High vs. low baseline insulin
  - High vs. low baseline triglyceride
  - High vs. low change in heart rate
  - Long vs. short history of type II diabetes (omitted, data not found in database, source data only)

178-CL-003, input data

- Input data consisted of the Full Analysis Set
- Individual plasma concentration versus time profiles of YM178 were used to identify non-treatment compliant patients;
  - Patients 104, 131 and 146 were excluded from analysis
- Extremes were excluded from analysis using the criteria:
  - change in HbA1c from baseline > +2% and/or..
  - change in FPG from baseline > +4 mmol/l
- Uneven patient distribution was avoided as much as possible
- FPG data were highly variable. Data were subjected to subgroup analysis but are only shown here if deemed usefull. In any case no trend could be discerned.

178-CL-003, Excluded patients

Patient Number	Treatment	Reason for Exclusion
104	YM178	Non-compliance
131	YM178	Non-compliance
146	YM178	Non-compliance
113	YM178	ΔFPG > +4 mmol/l
121	Placebo	ΔHbA1c> +2%
163	YM178	ΔFPG > +4 mmol/l
188	YM178	ΔHbA1c> +2%
192	YM178	ΔHbA1c> +2%

178-CL-003, Distribution of Responders

Responder ΔHbA1C < -0.1%	Placebo N (%)	YM178 N (%)
Yes	8 (44%)	21 (68%)
No	10 (56%)	10 (32%)
Total	18	31

Responder ΔFPG < -0.1mmol	Placebo N (%)	YM178 N (%)
Yes	8 (44%)	19 (61%)
No	10 (56%)	12 (39%)
Total	18	31

178-CL-003, HbA1c

Change in HbA1c (%) from baseline to end of treatment by baseline HbA1c

HbA1c(%)	Treatment	N	Mean (SD)	Min	Max
< 7	YM178	13	0.154 (0.62)	-0.8	1.1
	Placebo	8	-0.113 (0.76)	-1.2	0.8
(≥ 7)	YM178	18	-0.650 (1.10)	-2.4	2.0
	Placebo	10	-0.220 (0.94)	-1.8	1.0

- Despite placebo effect, YM178 reduced HbA1c when baseline levels were above 7%
- No differences between YM178 and placebo were found for FPG (data not shown).

178-CL-003, HbA1c

Change in HbA1c (%) from Baseline to End of Treatment by Gender

Gender	Treatment	N	Mean (SD)	Min	Max
Male	YM178	17	-0.106 (0.90)	-1.2	2.0
	Placebo	11	-0.355 (0.86)	-1.8	1.0
Female	YM178	14	-0.564 (1.09)	-2.4	1.4
	Placebo	7	0.114 (0.79)	-1.4	0.8

- No difference between YM178 and placebo in male patients.
- Reduction of HbA1c was found in female patients compared to placebo and male patients.

178-CL-003, FPG

Change in FPG (mmol/l) from Baseline to End of Treatment by Gender

Gender	Treatment	N	Mean (SD)	Min	Max
Male	YM178	17	0.312 (1.29)	-2.1	3.0
	Placebo	11	0.118 (1.94)	-4.3	3.0
Female	YM178	14	-0.664 (1.68)	-3.8	1.9
	Placebo	7	0.329 (1.38)	-2.0	2.1

- YM178 reduced FPG in female patients despite high variability.
- No difference between YM178 and placebo in male patients.

178-CL-003, HbA1c

Change in HbA1c (%) from baseline to end of treatment by Age

Age(y)	Treatment	N	Mean (SD)	Min	Max
Young (≤ 55)	YM178	21	-0.505 (1.06)	-2.4	2.0
	Placebo	14	-0.143 (0.86)	-1.8	1.0
Elderly (>55)	YM178	10	0.090 (0.77)	-1.2	1.1
	Placebo	4	-0.275 (0.90)	-1.4	0.7

- YM178 reduced HbA1c in young patients, but no changes were found in elderly
- In contrast, a small FPG reduction was found in elderly; for YM178 -0.490 mmol/l (n=10) vs placebo 0.675 mmol/l (n=4).

178-CL-003, HbA1c

Change in HbA1c (%) from baseline to end of treatment by Age (young) and baseline HbA1c

Age (y) / HbA1c (%)	Treatment	N	Mean (SD)	Min	Max
≤ 55 / < 7	YM178	8	-0.113 (0.61)	-0.8	1.0
	Placebo	6	-0.183 (0.80)	-1.2	0.8
≤ 55 / ≥ 7	YM178	13	-0.746 (1.22)	-2.4	2.0
	Placebo	8	-0.113 (0.95)	-1.8	1.0

- Reductions found with placebo and YM178. Biggest change at HbA1c above 7%
- No consistent changes in FPG in either category.

178-CL-003, HbA1c

Change in HbA1c (%) from baseline to end of treatment by Age (elderly) and baseline HbA1c

Age (y) / HbA1c (%)	Treatment	N	Mean (SD)	Min	Max
> 55 / < 7	YM178	5	0.580 (0.37)	0.1	1.1
	Placebo	2	0.100 (0.85)	-0.5	0.7
> 55 / ≥ 7	YM178	7	-0.400 (0.77)	-1.2	0.8
	Placebo	2	-0.650 (1.06)	-1.4	1.0

- No differences between YM178 and placebo treatment were found in either category. Note: subdivision is confounded by small groupsize
- Similarly, no differences for FPG between categories were found due to small group sizes.

178-CL-003, HbA1c

Change in HbA1c (%) from baseline to end of treatment by Age (young) and gender

Age (y) / Gender	Treatment	N	Mean (SD)	Min	Max
< 55 / male	YM178	11	-0.327 (1.00)	-1.2	2.0
	Placebo	10	-0.400 (0.89)	-1.8	1.0
< 55 / female	YM178	10	-0.700 (1.14)	-2.4	1.4
	Placebo	4	0.500 (0.22)	0.3	0.8

- Large placebo effects in males, biggest response to YM178 in young females
- Elderly data showed no clear gender differences due to small number of patients; group size ranged from 1 to 6 patients (data not shown).

178-CL-003, HbA1c

Change in HbA1c (%) from baseline to end of treatment by BMI

BMI (kg/m²)	Treatment	N	Mean (SD)	Min	Max
≤ 30	YM178	20	-0.135 (1.03)	-2.4	2.0
	Placebo	9	-0.122 (0.95)	-1.8	0.8
> 30	YM178	11	-0.636 (0.90)	-2.0	1.0
	Placebo	9	-0.222 (0.77)	-1.2	1.0

- Reductions were found in either category, largest response when BMI≥30 kg/m²
- Note: BMI by gender showed reductions in placebo and YM178 in males and females with high BMI; larger reductions in females compared to males despite small group sizes (data not shown).

Yamanouchi Europe B.V.
Clinical Pharmacology Research Department

Draft Data

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178-CL-003, FPG

Change in FPG (mmol/l) from baseline to end of treatment by BMI

BMI (kg/m²)	Treatment	N	Mean (SD)	Min	Max
≤ 30	YM178	20	-0.025 (1.78)	-3.8	3.0
	Placebo	9	-0.489 (1.74)	-4.3	1.6
> 30	YM178	11	-0.318 (0.99)	-2.1	1.6
	Placebo	9	0.889 (1.43)	-1.3	3.0

- FPG increased in placebo treated patients with high BMI, whereas small reductions were found with YM178

Yamanouchi Europe B.V.
Clinical Pharmacology Research Department

Draft Data

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178-CL-003, HbA1c

Change in HbA1c (%) from baseline to end of treatment by Waist-to-Hip Ratio

W/H ratio	Treatment	N	Mean (SD)	Min	Max
Low (≤ 0.9)	YM178	13	-0.715 (0.97)	-2.4	1.1
	Placebo	5	-0.340 (0.92)	-1.4	0.7
High (> 0.9)	YM178	18	-0.022 (0.94)	-1.2	2.0
	Placebo	9	-0.108 (0.84)	-1.8	1.0

- In contrast to BMI, large reductions were found when W/H ratio was low. This subgroup consisted entirely of female patients
- No differences between placebo and YM178 were found when the ratio at baseline was high.

178-CL-003, HbA1c

Change in HbA1c (%) from baseline to end of treatment by Insulin Level

Insulin (pmol/l)	Treatment	N	Mean (SD)	Min	Max
<50	YM178	13	-0.269 (0.95)	-1.2	2.0
	Placebo	4	-0.575 (1.20)	-1.8	0.5
50 -<100	YM178	14	-0.536 (0.98)	-2.4	1.1
	Placebo	9	-0.311 (0.70)	-1.2	0.7
≥100	YM178	4	0.325 (1.20)	-1.4	1.4
	Placebo	5	0.400 (0.59)	-0.5	1.0

- No clear differences between YM178 and placebo and no response in patients with high insulin levels (small groups!)
- Biggest response to YM178 found in young patients with insulin levels below 100 pmol/l (data not shown).

178-CL-003, HbA1c

Change in HbA1c (%) from baseline to end of treatment by Triglyceride Level

TG (nmol/l)	Treatment	N	Mean (SD)	Min	Max
High (>2)	YM178	11	-0.591 (1.08)	-2.4	1.4
	Placebo	9	-0.200 (0.94)	-1.8	1.0
Low (≤2)	YM178	20	-0.160 (0.94)	-2.4	1.1
	Placebo	9	-0.144 (0.78)	-1.4	0.7

- No clear differences between YM178 and placebo treatment. Slightly higher response at high baseline triglyceride levels
- No effect of YM178 on FPG was found for this subgroup (data not shown).

178-CL-003, HbA1c

Change in HbA1c (%) from baseline to end of treatment by Trough Level at visit 10*

C_{trough} (ng/ml)	Treatment	N	Mean (SD)	Min	Max
≥ 10	YM178	29	-0.369 (0.93)	-2.4	1.4
<10	YM178	2	0.500 (2.12)	-1.0	2.0
≥ 15	YM178	19	-0.463 (0.87)	-2.4	1.4
<15	YM178	12	-0.075 (1.18)	-2.0	2.0
≥ 20	YM178	12	-0.217 (0.99)	-2.4	1.1
<20	YM178	19	-0.374 (1.03)	-2.0	2.0

*If C_{trough} < 5 ng/ml at Visit 8 and/or 9 and/or 10 patient were excluded

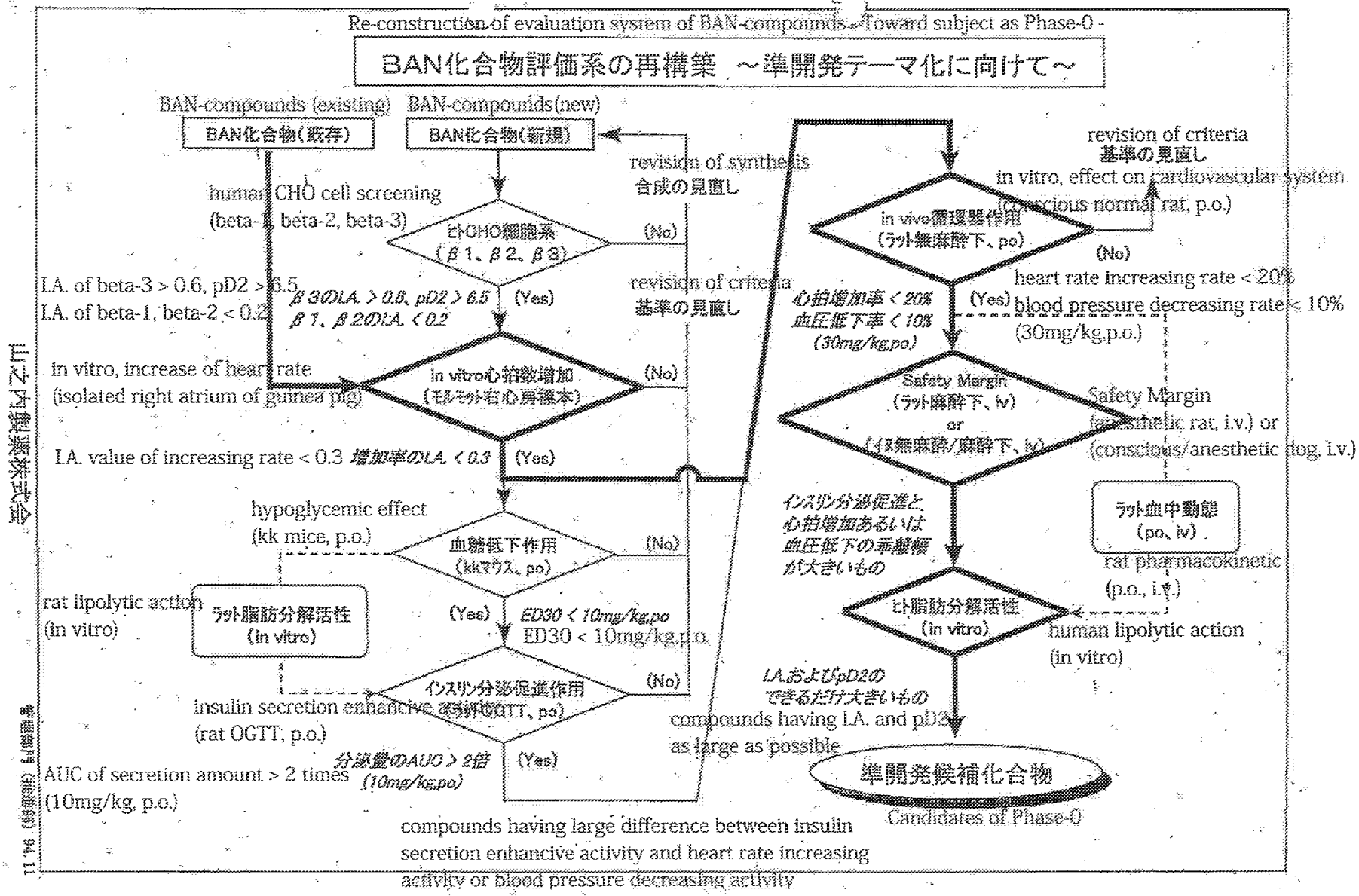
- A reduction of HbA1c was found with trough levels of YM178 above 10 ng/ml. The largest response was shown with levels of 15 ng/ml. Higher levels did not further increase the response to YM178.

178-CL-003, Summary

- For both HbA1c and FPG, ≥60% of the patients responded to YM178 whereas 44% responded to placebo
- Due to high intersubject variability of FPG no clear subgroup responding to YM178 could be defined on the basis of this parameter
- Mean changes in HbA1c from baseline to end of treatment were relatively small for all subgroups (≤0.75%) with high variability
- In view of the small numerical changes clinical relevance should be questioned
- Some efficacy was found only when HbA1c at baseline was above 7% (data from central laboratory; local data 7-8%); responses of HbA1c and FPG to YM178 were mainly found for female patients.

178-CL-003, Summary

- Changes in HbA1c were mainly detected in young patients; in elderly no differences between YM178 and placebo could be found, even when baseline HbA1c was taken into account
- The effect of age was most clear for female patients
- Larger responses in HbA1c and FPG were found in patients with high BMI, a finding not fully supported by the analysis of waist-to-hip ratio
- No clear effect of baseline insulin and triglyceride levels was shown, although patients with high insulin seem less responsive to YM178
- Steady state trough levels of YM178 above 15 ng/ml seem to be required to cause a pharmacodynamic response.



Status Report on Progress of Research	Date of Report	Department	Author of Report
	4 / 26 / 1995	Sugars Group Drug Development Research Lab III	Toshiyuki Takasu Tetsuo Matsui Jun Irie Masayuki Shibasaki
Theme Research on BAN Compounds No. 1		Dept. Head [seal] Fujikura	

<Summary>

1. Structuring of a human β3-CHO cell evaluation model
   1) Effects on activity of subculturing
   2) Correlation with SK-N-MC cell line

2. β3, β2, β3-receptor activity
   1) BAN compound screening results

3. Hypoglycemic effect (confirmation of main effect)
   1) BAN-90 insulin-releasing action (normal rat)
   2) kk-mouse hypoglycemia test

4. Future schedule

1. Structuring of a human β3-CHO cell evaluation line

1) Effects on activity of subculturing

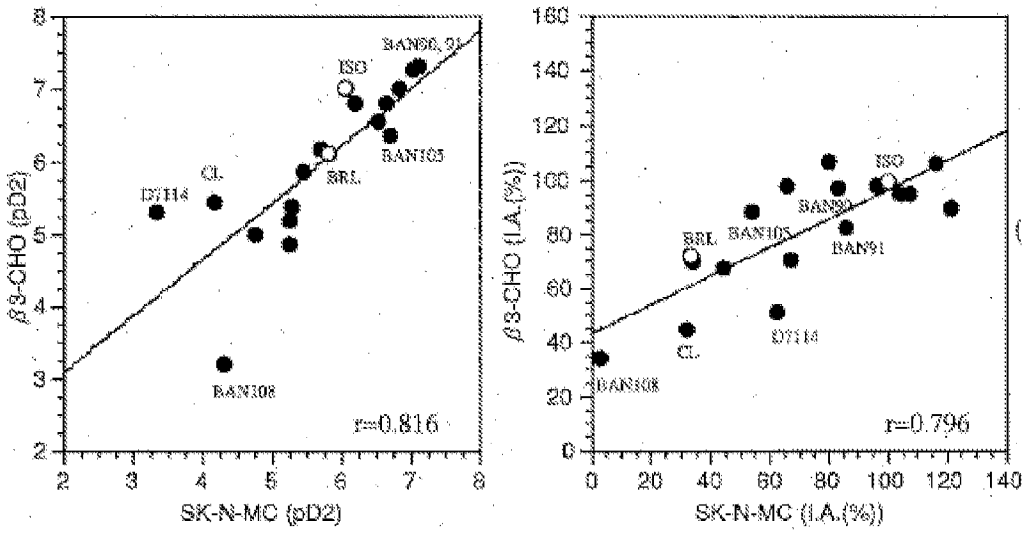
(Purpose) It is known that with expressing cells, activity is weakened by repeating cultivation. In this study, the effects on activity due to cultivation were studied by using cells supplied by an outsourcer as the originals (P-0), conducting cultivation, and with the third generation, P-6 to P-8, the pD2 value when ISO incited and maximum activity were indexed under the same conditions as β1- and β2-CHO cells (distributing 10^5 units/well in a 24-well plate, cultivating for 2 days, and then testing).

	pD2	Maximum Activity (pmol/ml)
P-6	7.36	124.0 ± 2.6
P-7	6.65	126.0 ± 2.9
P-8	6.97	121.4 ± 3.8
Average	6.99	123.8

- In this study, a slight variation was observed in the ISO pD2 value, but maximum activity was about the same value and stable.

2) Correlation between the SK-N-MC cell line and the β3-CHO cell line

- For the BAN compounds studied to date with both cell lines, the pD2 value and the intrinsic activity (I.A. (%)) of each were each plotted on a graph and the correlation was studied.



- The pD2 value and I.A. (%) for each compound was shown to have a significant correlation in the SK-N-MC cells and β3-CHO cells.

- Going forward, screening will be conducted of the BAN compounds switching to the β3-CHO cell line.

研究進行状況報告書	報告年月日	所属名	報告者名
	'95／4／26	第三創薬研究所 糖グループ	高須俊行 松井哲夫 入江　潤 柴崎雅之

テーマ

BAN化合物の研究

No. 1

所属長印

【概要】

1．ヒトβ3-CHO細胞評価系の構築
　1）継代による活性への影響
　2）SK-N-MC細胞系との相関性

2．β3, β2, β3-受容体活性
　1）BAN化合物スクリーニング結果

3．血糖低下作用（主作用の確認）
　1）BAN-90のインスリン分泌作用（正常ラット）
　2）kk-マウス血糖低下試験

4．今後の予定

1.ヒトβ3-CHO細胞評価系の構築

1)継代による活性への影響

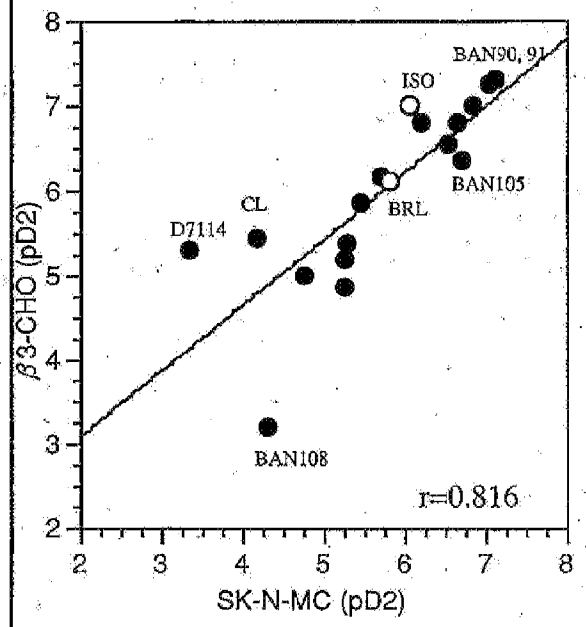
（目的）発現細胞の場合継代を繰り返すことにより活性が減弱することが知られている。今回、外注先より供給された細胞を初代(P-0)とし、継代を行ないP-6～P-8の3代について、β1-β2-CHO細胞と同じ条件（24wellプレートに10^5個／wellで蒔き2日間培養後、実験）で、ISO刺激時のpD2値ならびに最大活性を指標に、継代による活性への影響を検討した。

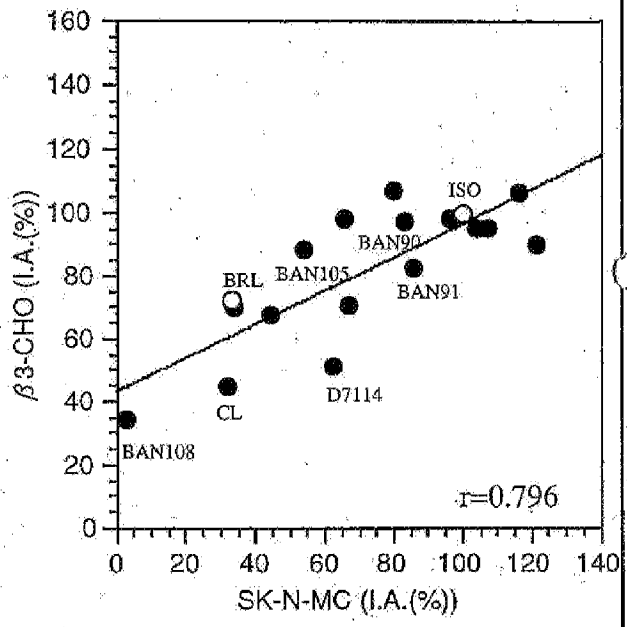
	pD2	最大活性 (pmol/ml)
P-6	7.36	124.0±2.6
P-7	6.65	126.0±2.9
P-8	6.97	121.4±3.8
平均	6.99	123.8

●今回の検討では、ISOのpD2値に若干の幅が見られたが、最大活性は、ほぼ同じ値を示し安定していた。

2)SK-N-MC細胞系とβ3-CHO細胞系の相関性

●これまでに両方の細胞系で検討したBAN化合物について、pD2値ならびに固有活性（I.A.(%)）を各々、グラフにプロットし相関性を検討した。





●各化合物のpD2値ならびにI.A.(%)は、SK-N-MC細胞とβ3-CHO細胞で有意な相関があることが示された。

●今後は、BAN化合物のスクリーニングをβ3-CHO細胞系に切り替えて行なう。

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	10,218,661	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).)

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 NBERHE 00000073 09529096
02 FC:186 180.00 OP

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INFORMATION DISCLOSURE CITATION
(Use several sheets if necessary)

OMB No. 0651-0011

Atty. Docket No.	2007-00	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

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

Filed: April 7, 2000

For: AMIDE DERIVATIVES OR SALTS THEREOF

Group Art Unit: 1624

Examiner: S. Patel

#8A
5/11/01
KM

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

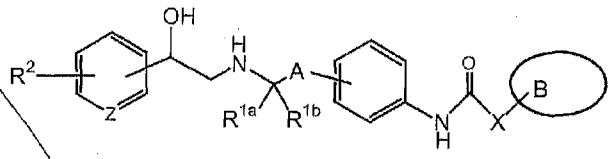
AMENDMENT UNDER 37 C.F.R. § 1.111

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:

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

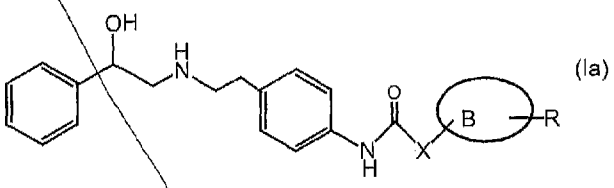
Z is a nitrogen atom or a group represented by =CH-;

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

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.

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

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

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.

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

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

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

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.

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

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.

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.

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.

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

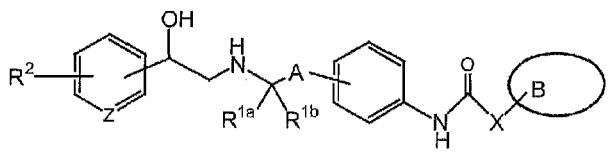
Enclosures:

- Appendix
- Verified Translation of Priority Document

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-;

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

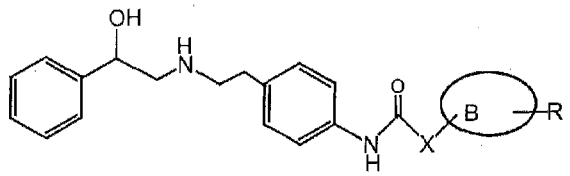
R^2[:] is a hydrogen atom or a halogen atom; and

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.

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 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,

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

Dated: May 4, 2001

By: David W. Hill
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CERTIFICATION OF TRANSLATION

I, John F. Bukacek, declare that:

1. I am a certified translator who is knowledgeable and fluent in both the Japanese and English languages.

2. The attached is an independent translation of Japanese Patent Application Kokai Publication No. H10-218861 ("Novel Phenethanol Derivative or Salt Thereof"), rendered to the best of my knowledge and ability.

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Chicago, Illinois 60660-5841

11 October 2013

(19) JAPANESE PATENT OFFICE (JP)
(12) Official Gazette for Kokai Patent Applications (A)
(11) Japanese Patent Application Kokai Publication No. H10-218861
(43) Kokai Publication Date: August 18, 1998

(51) Int. Cl.[6]	Ident. Symb.	F1	
C 07 D 213/56		C 07 D 213/56	
A 61 K 31/395		A 61 K 31/395	
31/415	ACN	31/415	ACN
31/42		31/42	
31/44		31/44	

Request for Examination: Not submitted
Number of Claims: 3 OL (Total of 20 pages in the original Japanese)

(21) Application Filing No. H09-21870
(22) Application Filing Date February 4, 1997

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Continued on the final page

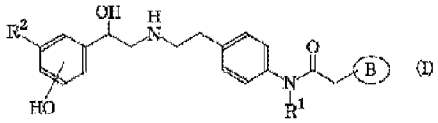
(54) **[Title of the Invention]** Novel Phenethanol Derivative or Salt Thereof

(57) **[Abstract]**

[Object] To create a therapeutic agent for the treatment of diabetes possessing both insulin secretion promoting effects and insulin sensitization enhancing effects, as well as selective stimulatory effects on β_3 receptors.

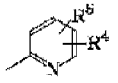
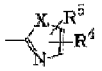
[Means] A novel phenethanol derivative or salt thereof represented by General Formula (I) below.

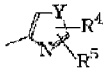
[Chemical Structure 1]



(I)

(Where the respective symbols have the meanings given below:

B ring: Group represented by the formula   Group represented by the formula

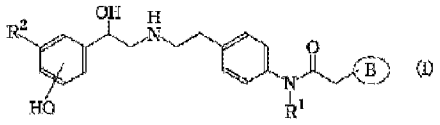
or a group represented by the fomula 

X, Y: An oxygen atom, a sulfur atom, or a group represented by NR^6
R^1: A hydrogen atom or a lower alkyl group
R^2: A hydrogen atom, lower alkyl group, a methylsulfonamide group, or a group represented by $-NHCOR^3$
R^3: A hydrogen atom, a lower alkyl group, a mono- or di-lower alkylamino group, an aryl group, or an aralkyl group
R^4, R^5: An identical or different hydrogen atom, a lower alkyl group, or an amino group
R^6: A hydrogen atom, a lower alkyl group, or an aralkyl group)

[Claims]

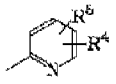
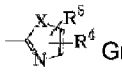
[Claim 1] A novel phenethanol derivative or salt thereof represented by General Formula (I) below.

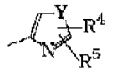
[Chemical Structure 1]



(Where the respective symbols have the meanings given below:

[Chemical Structure 2]

B ring: Group represented by the formula   Group represented by the formula

or a group represented by the fomula 

X, Y: An oxygen atom, a sulfur atom, or a group represented by NR^6
R^1: A hydrogen atom or a lower alkyl group
R^2: A hydrogen atom, lower alkyl group, a methylsulfonamide group, or a group represented by $-NHCOR^3$
R^3: A hydrogen atom, a lower alkyl group, a mono- or di-lower alkylamino group, an aryl group, or an aralkyl group
R^4, R^5: An identical or different hydrogen atom, a lower alkyl group, or an amino group
R^6: A hydrogen atom, a lower alkyl group, or an aralkyl group)

[Claim 2] A drug characterized in containing the phenethanol derivative or salt thereof according to claim 1.

[Claim 3] A therapeutic agent for diabetes characterized in having as its active constituent the phenethanol derivative or salt thereof according to claim 1.

[Detailed Description of the Invention]

[0001]

[Technical Field of the Invention] The present invention relates to a drug, and in particular, the present invention relates to a therapeutic agent for diabetes having as its active constituent a novel phenethanol derivative or salt thereof.

[0002]

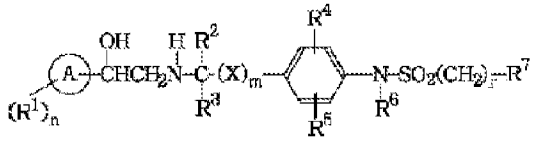
[Prior Art] Diabetes is a condition which is accompanied by a state of sustained hyperglycemia, and is reported to occur as a result of multiple environmental factors and hereditary factors. Insulin is the principal factor which regulates blood sugar, and it is known that high blood pressure results from a deficiency of insulin, or from an excess of factors which inhibit its action (e.g., a hereditary predisposition, lack of exercise, obesity, stress, and the like). There are two main types of diabetes: insulin-dependent diabetes mellitus (IDDM) which is caused by impaired pancreatic insulin secretory function due to an autoimmune condition, and non-insulin-dependent diabetes mellitus (NIDDM) which is caused by impaired pancreatic insulin secretory function due to pancreas exhaustion accompanying sustained elevated insulin secretion. Over 95% of Japanese diabetes patients are reported to have NIDMM, and an increase in the number of patients is a problem which accompanies changes which have occurred in lifestyle. Treatment of diabetes primarily involves dietary regimens, exercise regimens, reduction in obesity, and the like in mild cases, but if the condition progresses further, oral drugs for diabetes are administered (e.g., insulin release promoters such as sulfonylureas, and insulin sensitization enhancing agents which promote insulin sensitivity), and in more severe cases, insulin preparations are administered. However, there is a strong desire for a formulation of medications capable of a higher level of blood sugar control, and a strong desire to create therapeutic drugs for diabetes with greater efficacy and with a new mechanism.

[0003] U.S. Patent No. 4,396,627 and U.S. Patent No. 4,478,849 describe phenylethanolamine derivatives, and these compounds have been disclosed as being useful as anti-obesity drugs and anti-hyperglycemia drugs. The effects of these compounds are reported to be due to β_3 receptor stimulation. β_3 receptor stimulation is generally known to have anti-obesity effects and anti-hyperglycemia effects (e.g., triglyceride-lowering effects, cholesterol-lowering effects, and HDL cholesterol-raising effects). β-adrenalin receptors are classified into β_1, β_2, and β_3 sub-types. It is known that stimulation of β_1 receptors raises the heart rate, and stimulation of β_2 receptors inhibits glycogen synthesis by stimulating glycogenolysis in the muscles, which gives rise to muscle tremors. However, these early β_3 receptor agonists had a problem of side effects such as increased heart rate and muscle tremors, because their action was based on stimulating β_1 receptors and β_2 receptors. It has recently been found that species differences exist among β receptors, and it has been reported that even in the case of compounds found to have β_3 receptor selectivity in rodents such as rats, they were found to have effects based on stimulation of β_1 receptors and β_2 receptors in humans. Based on these findings, research is advancing in the area of compounds having selective stimulatory effects on β_3 receptors in humans, using human cells or cells which human receptors are expressed. For example, WO 95/29159 describes substituted sulfonamide derivatives shown in the general formula below. These are described as being

effective against obesity and hyperglycemia because they selectively stimulate β_3 receptors in humans. However, nothing has been specifically disclosed regarding insulin secretion promoting effects and insulin sensitization enhancing effects of these compounds.

[0004]

[Chemical Structure 3]



(For a description of the symbols, see the above-cited disclosure.)

[0005]

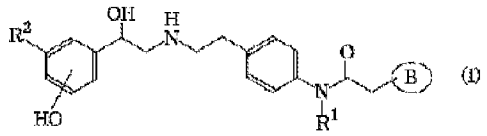
[Problems to Be Solved by the Invention] As mentioned above, there is a strong desire to create a new type of therapeutic agent for diabetes with even greater clinical efficacy.

[0006]

[Means for Solving These Problems] As a result of careful searching for compounds possessing both insulin secretion promoting effects and insulin sensitization enhancing effects, the present inventors found that novel phenethanol derivatives possess the dual activity of insulin secretion promoting effects and insulin sensitization enhancing effects, as well as selective stimulatory effects on β_3 receptors, thereby achieving the present invention. That is to say, the present invention relates to a phenethanol derivative or salt thereof shown in General Formula (I) below, which is useful in diabetes therapy, because it possesses insulin secretion promoting effects and insulin sensitization enhancing effects, as well as anti-obesity and anti-hyperlipidemia based on selective stimulatory effects on β_3 receptors. The present invention further relates to a drug which contains this phenethanol derivative, and in particular, the present invention relates to a therapeutic agent for diabetes having this phenethanol derivative as its active constituent.

[0007]

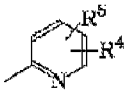
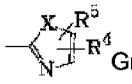
[Chemical Structure 4]

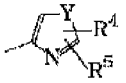


(Where the respective symbols have the meanings given below:

[0008]

[Chemical Structure 5]

B ring: Group represented by the formula   Group represented by the formula

Group represented by the formula 

X, Y: An oxygen atom, a sulfur atom, or a group represented by NR^6
R^1: A hydrogen atom or a lower alkyl group
R^2: A hydrogen atom, lower alkyl group, a methylsulfonamide group, or a group represented by $-NHCOR^3$
R^3: A hydrogen atom, a lower alkyl group, a mono- or di-lower alkylamino group, an aryl group, or an aralkyl group
R^4, R^5: An identical or different hydrogen atom, a lower alkyl group, or an amino group
R^6: A hydrogen atom, a lower alkyl group, or an aralkyl group)

[0009]

[Embodiments of the Invention] A further description of the compound of General Formula (I) is as follows. In the definition of the general formulae of this Specification, the term "lower" refers to a straight or branched carbon chain having 1-6 carbons, unless specified otherwise. "A lower alkyl group" is a straight or branched carbon chain having 1-6 carbon atoms, and specific examples include a methyl group, an ethyl group, a propyl group, an isopropyl group, a butyl group, an isobutyl group, a *sec*-butyl group, a *tert*-butyl group, a pentyl group, an isopentyl group, a neopentyl group, a *tert*-pentyl group, a 1-methylbutyl group, a 2-methylbutyl group, a 1,2-dimethylpropyl group, a hexyl group, an isohexyl group, a 1-methylpentyl group, a 2-methylpentyl group, a 3-methylpentyl group, a 1,1-dimethylbutyl group, a 1,2-dimethylbutyl group, a 2,2-dimethylbutyl group, a 1,3-dimethylbutyl group, a 2,3-dimethylbutyl group, a 3,3-dimethylbutyl group, a 1-ethylbutyl group, a 2-ethylbutyl group, a 1,1,2-trimethylpropyl group, a 1,2,2-trimethylpropyl group, a 1-ethyl-1-methylpropyl

group, a 1-ethyl-2-methyl propyl group, and the like. "Aryl group" refers to an aromatic hydrocarbon group, and preferably, an aryl group having 6-14 carbons, and specifically, a phenyl group, a tolyl group, a xylyl group, a biphenyl group, a naphthyl group, an indenyl group, a phenanthryl group, and the like. Of these, a phenyl group or a naphthyl group is particularly advantageous.

[0010]

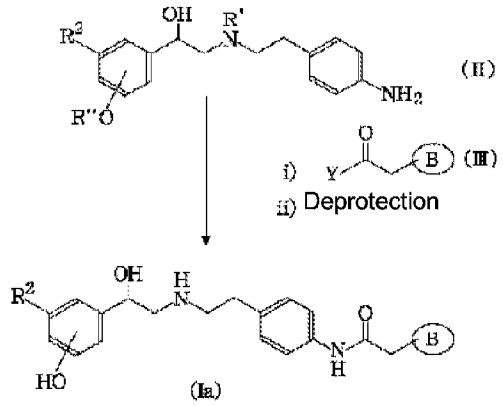
"An aralkyl group" is a lower alkyl group having an aryl group as a substituent group, and specific examples include a benzyl group, a methylbenzyl group, a methylphenethyl group, a dimethylbenzyl group, a dimethylphenethyl group, a benzhydryl group, a naphthylmethyl group, a naphthylethyl group, a an anthrylmethyl group, an anthrylethyl group, a triethyl group, a phenanthrylmethyl group, a phenanthrylethyl group, and the like. "A mono- or di-lower alkylamino group" refers to an amino group having 1 or 2 hydrogen atoms in an amino group substituted with an above-mentioned lower alkyl group, and specific examples include a methylamino group, an ethylamino group, a propylamino group, a dimethylamino group, a diethylamino group, a dipropylamino group, and the like. If Compound (I) of the present invention possesses 1 or more asymmetric carbon atoms, then (R)- and (S)- optical isomers, racemic isomers, and diastereomers are present. The present invention includes all of the isolates of these isomers or mixtures thereof. Moreover, the present invention also includes hydrates, ethanol solvates, and polymorphic crystal substances of Compound (I). Compound (I) of the present invention may form acids and salts. Examples of salts can include acid addition salts using inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or organic acids such as formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, citric acid, tartaric acid, carbonic acid, picric acid, methanesulfonic acid, ethanesulfonic acid, glutamic acid, and the like.

[0011] ***Processes of Preparation***

The compound of the present invention and salts thereof, can be prepared using a variety of methods of synthesis, utilizing characteristics based on its basic structure or based on the species of the substituent groups. Representative processes of preparation are described below.

First Process of Preparation

[Chemical Structure 6]



(Where R^2 and B ring have the same meanings as described above. R' is a protecting group of an amino group, R'' is a protecting group of a hydroxyl group, and Y is a leaving group such as a hydroxyl group, a lower alkoxy group, or a halide.)

The present process of preparation involves an amidation reaction of Compound (II) and Compound (III), and then removing the protecting groups, resulting in the synthesis of Compound (Ia) of the present invention. In the present process of preparation, amidation may be carried out using a conventional method. The solvent depends on Y in Compound (III), but is mainly an inert solvent or an alcohol-based (isopropanol) solvent. If Y is a hydroxyl group, a process can be implemented in which the reaction is carried out in the above inert solvent, in the presence of a condensing agent. Examples of condensing agents include *N,N'*-dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDCI), 1,1'-carbonyldiimidazole (CDI), diphenylphosphorylazide (DPPA), diethylphosphorylcyanide (DEPC), and the like. If Y is a lower alkoxy group, then the reaction may be implemented just as it is, or the reaction may be implemented in the above-mentioned inert solvent, and heated or heated to reflux. If Y is a halide, a process can be implemented in which the reaction is carried out in the above inert solvent, in the presence of a base.

[0012] Examples of inert solvents include dimethylformamide (DMF), dimethylacetamide, tetrachloroethane, dichloromethane, dichloroethane, chloroform, carbon tetrachloride, tetrahydrofuran, dioxane, dimethoxyethane, ethyl acetate, benzene, toluene, acetonitrile, dimethylsulfoxide, or mixtures thereof, and these can be suitably selected according to the various reaction conditions. Examples of bases include inorganic bases such as sodium hydroxide, potassium hydroxide, sodium carbonate, or potassium carbonate; and organic bases such as *N*-methylmorpholine, triethylamine, diisopropylethylamine, or pyridine, and the like. R'' refers to a protecting group of a hydroxyl group, and representative protecting groups of a hydroxyl group typically used by practitioners of the art include a methyl group,

an ethyl group, a propyl group, an isopropyl group, a *tert*-butyl group or other lower alkyl group, a lower alkoxy-lower alkyl group, a lower alkoxy-lower alkoxy-lower alkyl group, a benzyl group, or other arylmethyl group, a benzoyl group or lower alkanoyl group, or other acyl group, a trialkylsilyl group, and the like. R' refers to a protecting group of an amino group typically used by practitioners of the art, and representative examples include a formyl group, a an acetyl group, a propionyl group, a methoxyacetyl group, a methoxypropionyl group, a benzoyl group, a thienylacetyl group, a thiazolylacetyl group, a tetrazolylacetyl group, a thiazolyl glyoxyloyl group, a thienyl glyoxyloyl group, and other acyl group, a methoxycarbonyl group, an ethoxycarbonyl group, a *tert*-butoxycarbonyl group, or other lower alkoxycarbonyl group, a benzyloxycarbonyl group, a *p*-nitrobenzyl group, a benzhydryl group, a triethyl group, or other aralkyl group, a trimethylsilyl group, or other tri-lower alkylsilyl group, and the like.

[0013] In the present process of preparation, deprotection is accomplished by a conventional method. For example, removal of a protecting group of a hydroxyl group can be carried out as follows.

1) Catalytic reduction: This method can be carried out in ice or heated, and in the presence of a catalyst such as palladium-carbon, palladium hydroxide-carbon, Raney nickel, and the like.

2) Hydrolysis in the presence of an acid or a base: This method can be carried out by a conventional method of hydrolysis in the presence of a base such as sodium carbonate, sodium hydroxide, and the like, or an acid such as trifluoroacetic acid, hydrochloric acid, and the like.

3) Liquid ammonia reduction: This method can be carried out by adding a compound containing a protecting group of a hydroxyl group to liquid ammonia, then adding metallic sodium, and agitating.

4) Desilylation reaction: This method can be carried out by reacting a compound containing a protecting group of a hydroxyl group with an organic fluorine compound such as tetra-*n*-butylammonium fluoride or an inorganic fluorine compound such as sodium fluoride, potassium fluoride, hydrofluoric acid, in the inert solvent.

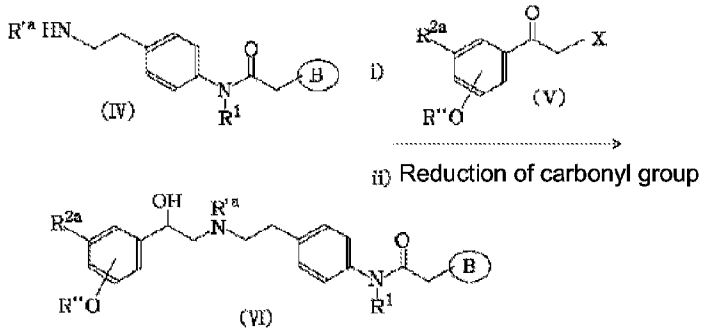
Removal of an R' protecting group of an amino group is readily carried out by i) Treatment with an acid such as formic acid, trifluoroacetic acid, a trifluoroacetic acid-anisole mixture, a hydrobromic acid-acetic acid mixture, a hydrochloric acid-dioxane mixture, and the like, when the protecting group is a benzhydryl group, *p*-methoxybenzyl group, trityl group, *tert*-butoxy carbonyl group, formyl group, and the like; ii) Catalytic reduction using palladium-carbon or palladium hydroxide-carbon when the protecting group is a benzyl group, a *p*-

nitrobenzyl group, a benzhydryl group, a trityl group, and the like; or iii) Treatment with water assisted by fluoride anions (tetra-*n*-butylammonium fluoride, sodium fluoride, potassium fluoride, hydrofluoric acid), and the like, when the protecting group is a tri-lower alkylsilyl group and the like.

[0014] ***Second Process of Preparation***

Step One

[Chemical Structure 7]



(Where R', B ring, and R'' have the same meanings as described above. R'^{a} is a hydrogen atom or an aralkyl-type protecting group. R^{2a} is a hydrogen atom, a lower alkyl group, a methylsulfonamide group, or a nitro group. X is a halogen atom.)

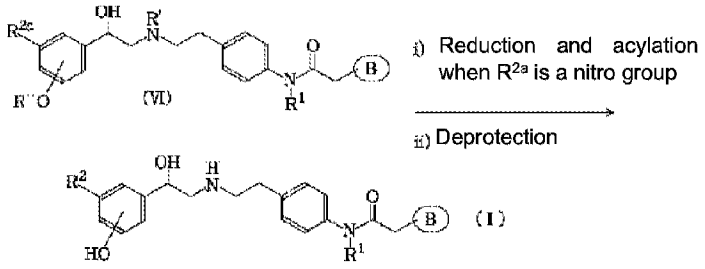
In this step, Compound (IV) and Compound (V) are reacted, then a reduction reaction is carried out to achieve carbonyl group reduction, resulting in Compound (VI).

i) The amine compound (IV) and Compound (V) are reacted just as they are, or in an inert solvent for 1-24 hours and heated or heated to reflux, and then ii) subjected to a reduction reaction to obtain Compound (VI). Examples of inert solvents include acetonitrile, tetrahydrofuran, 2-butanone, dimethylsulfoxide, or *N*-methylpyrrolidone. During the reaction of Compound (V) and amine compound (IV), a base such as sodium bicarbonate or diisopropylethylamine may be added. The reduction reaction may be carried out in the presence of a reducing agent, in an above-mentioned inert solvent or an alcohol-based solvent, and under agitation. Examples of reducing agents include sodium boron hydride, sodium boron cyanohydride, aluminum lithium hydride, and the like. Moreover, in this step, Compound (VI) may be produced by protecting the amino groups of amine compound (IV) for which the amino groups have not been protected (R' = H), after going through steps i) and ii), and Compound (VI) may be produced by carrying out i) and ii) after protecting the

amino groups of amine compound (IV) with an aralkyl-type protecting group.

[0015] ***Step Two***

[Chemical Structure 8]



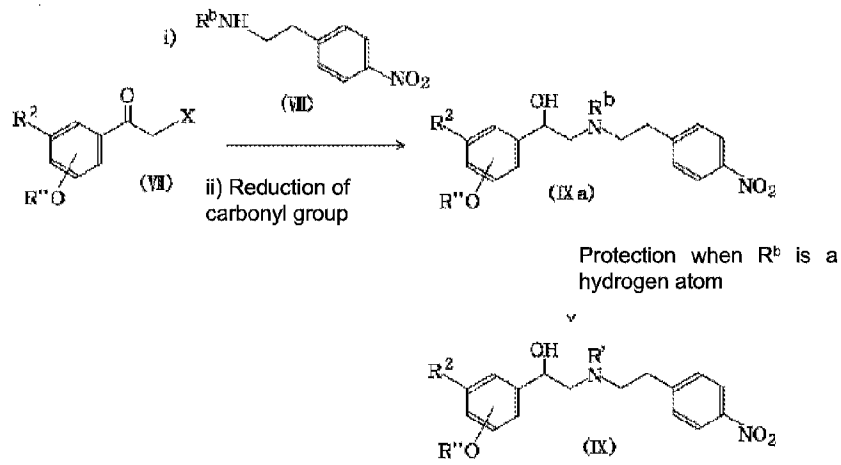
(Where R^1, R^2, R^{2a}, R', R'', and B ring have the same meanings as described above.)

In this step, when R^{2a} is a nitro group, it is reduced to an amino group, then acylation is carried out, and the protecting group is removed, resulting in Compound (I). If R^{2a} is a hydrogen atom, a lower alkyl group, or a methylsulfonamide group, the protecting group is removed without any further treatment, making it possible to obtain Compound (I). Reduction of the R^{2a} nitro group can be carried out by a conventional process such as metallic reduction using iron, zinc, and the like. Acylation of the amino group can be carried out by a conventional method involving an amidation reaction with a carbonic acid compound. This can be readily carried out using a reactive derivative of carbonic acid such as an acid anhydride, an acid hydride, an active ester, and the like. Deprotection can be carried out in the same manner as in the First Process of Preparation above. In the above process of preparation, undesirable byproducts can be removed to purify the product by means of recrystallization, pulverization, centrifugal thin-layer chromatography, silica gel flash chromatography such as described by W.C. Still *et al.* in *H. Org. Chem.*, 43, 2923 (1978), medium pressure liquid chromatography, or HPLC. A compound produced with HPLC can be isolated as a corresponding salt. The starting materials used in the above process of preparation can be readily produced by a process known to practitioners of the art. Following is a representative example thereof.

[0016] ***Process for Producing Starting Compound (II)***

Step One

[Chemical Structure 9]

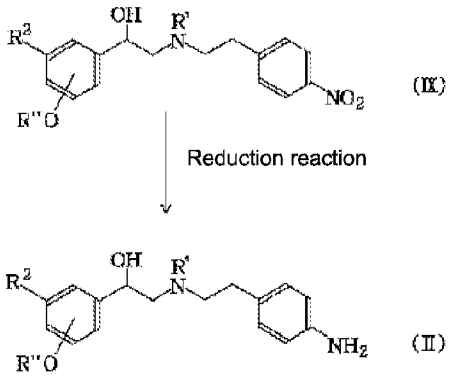


(Where R^2, R', and R'' have the same meanings as described above. R^b is a hydrogen atom or an aralkyl-type protecting group of an amino group.)

In this step, Compound (VII) and Compound (VIII) are reacted to synthesize Compound (IX). Examples of the aralkyl-type protecting group of an amino group include a benzyl group, a *p*-nitrobenzyl group, a benzhydryl group, and the like. This process can be carried out in the same manner as the Second Process of Preparation, and reaction conditions such as the reaction temperature, the solvent, and the like, are identical. If R^b is a hydrogen atom, amino group protection can be accomplished by a conventional method, using a di-*tert*-butyldicarbonate ester.

[0017] ***Step Two***

[Chemical Structure 10]

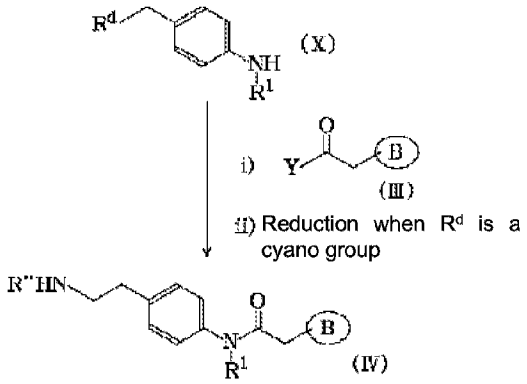


(Where R^2, R', and R'' have the same meanings as described above.)

In this step, Compound (IX) undergoes a reduction reaction to synthesize Compound (II). The reduction reaction can be carried out by metallic reduction or catalytic reduction. Under some reaction conditions, R' is a hydrogen atom, but re-protection can be carried out by a conventional method.

[0018] ***Process for Producing Starting Compound (IV)***

[Chemical Structure 11]



(Where R^1, R'', Y, and B ring have the same meanings as described above. R^d is a cyano group or a protected aminomethyl group.)

In this step, amidation is carried out by reacting Compound (X) and Compound (III). The reaction can be carried out in the same manner as in the First Process of Preparation above. If R^d is a cyano group, the reduction reaction may be carried out again, to obtain Compound (IV) by implementing protection, as desired. Reduction can be carried out by a conventional method such as catalytic reduction or reduction with cobalt chloride and sodium boron hydride. Accordingly, the resulting Compound (I) of the present invention is isolated and purified as a free compound, a salt thereof produced by a conventional salification process, a hydrate, a solvate of ethanol and the like, or a polymorphic crystal. Isolation/purification may be carried out an ordinary chemical operation such as extraction, concentration, distillation, crystallization, filtration, recrystallization, various types of chromatography, and the like. The various isomers can be isolated by a conventional method using the physiochemical differences among the various isomers. For example, racemic compounds can be converted to stereochemically pure isomers by an ordinary racemic resolution method (e.g., optical resolution achieved by forming a diastereomer salt with an ordinary optically

active acid such as tartaric acid). Also, a mixture of diastereomers can be separated by a conventional method such as fractional crystallization or chromatography. In addition, an optically active compound can be produced by using a suitable optically active starting material.

[0019]

[Advantageous Effects of the Invention] The phenethanol derivative or salt thereof shown in General Formula (I) is useful as a therapeutic agent for diabetes, because it possesses both insulin secretion promoting effects and insulin sensitization enhancing effects, and also possesses selective stimulatory effects on β_3 receptors. It is expected that the compound of the present invention will be useful in treating diabetes, because of its insulin secretion promoting effects and insulin sensitization enhancing effects, as has been confirmed in glucose tolerance tests and blood glucose-lowering tests in insulin-resistant model animals, which are described later. The mechanism of onset of action of the insulin secretion promoting effects and the insulin sensitization enhancing effects of the present invention is thought to possibly involve participation of the stimulatory effects on β_3 receptors, but other mechanisms are possible, and the details regarding them have yet to be elucidated. The stimulatory effects on β_3 receptors exhibited by the compound of the present invention are selective for β_3 receptors in humans. It is known that stimulation of β_3 receptors stimulates lipolysis (the breakdown of the trigycerides in adipose tissue into glycerols and free fatty acids), thereby promoting the elimination of fatty mass). Therefore, the compound of the present invention possesses anti-obesity effects and anti-hyperlipidemia effects (e.g., triglyceride-lowering effects, cholesterol-lowering effects, HDL cholesterol-raising effects, and the like) due to its stimulatory effects on β_3 receptors, and is useful as a preventive/therapeutic agent for obesity and hyperlipidemia. These conditions are known to exacerbating factors in diabetes, and amelioration of these conditions is also useful in preventing and treating diabetes.

[0020] The compound of the present invention is also useful in the prevention and treatment of other conditions for which it can serve to ameliorate symptoms by mitigation of the symptoms of obesity and hyperlipidemia. Examples of such conditions include ischemic heart disease such as arteriosclerosis, myocardial infarction, angina pectoris, and cerebral infarction such as arteriosclerosis, or aneurism. In addition, the selective stimulatory effects on β_3 receptors is also useful in the prevention and treatment of several conditions suggested as being ameliorated by the stimulation of β_3 receptors. Examples of these conditions are given below. It has been suggested that β_3 receptors mediate the motility of non-relaxing smooth muscle contraction, and it is thought that the selective stimulation of β_3 receptors, and the selective stimulation of β_3 receptors is thought to assist physiological control of intestinal motility, without concomitant cardiovascular effects. Thus, there is a possibility that the

compound of the present invention can be useful in treating conditions arising from disorders in intestinal motility, such as various gastrointestinal disorders such as irritable bowel syndrome. It is also useful in treating peptic ulcers, esophagitis, gastritis and duodenitis (including disorders induced by *H. pylori*), enterelcosis, inflammatory intestinal disorders, ulcerative colitis, Crohn's disease, and proctitis), and gastrointestinal ulcers. Moreover, β_3 receptors have been shown to affect the inhibition of release of neuropeptides of a variety of sensory fibers in the lungs. Sensory fibers plan an important role in neurogenic inflammation of the respiratory tract, including the lungs. Thus, a β_3-specific pharmacological agent of the present invention is useful in treating neurogenic inflammations such as asthma, and moreover, has few effects on the cardiopulmonary system. β_3 adrenalin receptors are able to produce selective antidepression effects by stimulating β_3 receptors in the brain, and it is therefore possible that the compound of the present invention may be useful as an antidepressant. Effects on the compound of the present invention on β receptors has been shown to be β_3 receptor-selective in experiments using human cells, and few or no side effects caused by other β_3 receptors have been observed.

[0021] The advantageous effects of the compound of the present invention have been confirmed with the following tests.

1. Blood glucose-lowering tests in kk mice (insulin resistance model: Obesity, hyperglycemia

Using male kk mice (blood glucose level 200 mg/dL or higher), blood glucose levels were measured after feeding, and the mice were randomly divided into groups. The test drug was dosed by forced oral administration or subcutaneously once a day for 4 days, and the blood glucose level 15-18 hours after the final dosing was compared with the blood glucose level prior to dosing (n=6). Blood was drawn from the caudal vein of the mice, using a glass capillary tube (after being treated with heparin), and after deproteinization, the glucose level (mg/dL) in the supernatant was determined by colorimetry with glucose oxidase. The compound of the present invention significantly reduced blood glucose levels in comparison to levels prior to administration of the test drug, whether administered orally or subcutaneously. These results show that the compound of the present invention possesses good insulin sensitization enhancing effects.

[0022]

2. Glucose tolerance tests in healthy rats

Using 7-week-old SD rats, after fasting a whole day and night, the rats were randomly divided into groups, and an oral glucose tolerance test (OGTT) was conducted (n=4). The

test compound was administered orally or subcutaneously 30 minutes prior to administering glucose (oral dose 2 g/kg). The rats were anesthetized with pentobarbital (65 mg/kg) , and blood was drawn from the abdominal vena cava, using a glass syringe treated with heparin. After deproteinization, the glucose level (mg/dL) in the supernatant was determined by colorimetry with glucose oxidase. The blood insulin level was determined by measuring plasma insulin (ng/mL) using radioimmunoassay (RIA). There was observed to be a significant increase in blood insulin levels in groups dosed either orally or subcutaneously with the compound of the present invention, as compared to untreated groups. In addition, increases in blood glucose levels were significantly suppressed after administering glucose. These results show the compound of the present invention has favorable insulin secretion promoting effects as well as hyperglycemia inhibiting effects.

[0023]

3. Human β_3, β_2, and β_1 receptor stimulation tests

Human β_3 agonism was studied using a SK-N-MC cell line (permanent human β_3 and β_1 receptors were expressed in the purchased cells), and human β_2, β_1 receptor agonism was studied using a CHO cell line (human β_2, β_1 receptors were forcibly expressed in the purchased cells). The stimulatory activity of the compound (10^{-10} to 10^{-4} M) was studied by culturing the cells on a 24-well plate at 10^5 cells/well, and with the cells in a subconfluent state after 2 days, cyclic AMP (cAMP) production activity was used as the index. Human β_3 agonism was studied in the presence of a β_1 receptor blocker (CGP20712A, 10^{-6} M). The cAMP production (pmol/mL) in the cells was measured by RIA using I-cAMP. The potency of effect of the various compounds was computed using the pD2 values from the dose-response curve and the maximum activity (I.A. (%), the maximum reaction of isoproterenol 10^{-6} M is set at 100%), and the results were compared. The compound of the present invention was found to have selective stimulatory effects on human β_3 receptors. Pharmaceutical compositions having one or more species of the compound of the present invention or salt thereof as the active constituent were prepared using an ordinary pharmaceutically acceptable carrier. The pharmaceutical composition according to the present invention can be administered orally, or in a non-orally dosed form, including an injection, suppository, transdermal, inhalant, or vesical injection. The dose is suitably determined with consideration given to the age and gender of the person receiving the dose, but is typically 0.01 mg/kg to 100 mg/kg per day in the case of oral administration to adults, and is administered once a day or divided into 2-4 times. Depending on the condition, if administered intravenously, the typical dose ranges from 0.001 mg/kg to 10 mg/kg per time for an adult, and dosing can be performed once or several times per day. The carrier for the preparation can be a solid ore liquid non-toxic pharmaceutical substance.

[0024] A solid composition for oral administration of the present invention can be in the form of a tablet, a pill, a capsule, a powder, or granules. In such a solid composition, one or more active substances, is mixed with at least one inert diluent, such as lactose, mannitol, D-glucose, hydroxypropyl cellulose, microcrystalline cellulose, starch, polyvinyl pyrrolidone, agar, pectin, magnesium aluminum metasilicate, and magnesium aluminate. The composition may also contain additives other than the inert diluent, such as a lubricating agent such as magnesium stearate, a disintegrator such as fibrous calcium glycolate, a stabilizer such as lactose, and a solubilizer such as glutamic acid or aspartic acid. As needed, tablets or pills may have a sugar coating such as cane sugar, gelatin, hydroxypropyl cellulose, hydroxypropyl methylcellulose, or a film to aid digestion in the stomach or the intestines. Liquid compositions for oral administration contain pharmaceutically acceptable emulsions, solutions, suspensions, syrups, elixirs, and the like, as well as commonly used inert diluents such as purified water and ethanol. In addition to inert diluents, this composition may also contain an adjuvant such as a lubricating agent or a suspension, or a sweetener, flavoring, fragrance, or antiseptic. Injections for non-oral administration contain an antiseptic aqueous or non-aqueous solution, suspension, or emulsion. An aqueous solution or suspension may contain distilled water and physiological saline for injection, for example. Examples of non-aqueous solutions and suspensions include propylene glycol, polyethylene glycol, cocoa butter, olive oil, sesame oil, or other vegetable oil, an alcohol such as ethanol, or gum Arabic, Polysorbate 80 (trade name), and the like. Such a composition may also contain an adjuvant such as an isotonizer, antiseptic, lubricating agent, emulsifier, dispersant, stabilizer (e.g., lactose), and solubilizer (e.g., glutamic acid, aspartic acid). These may be sterilized by passing through a bacterial retentive filter, adding a bacteriocide, or by irradiating. These can be used to produce a sterile solid composition, or they can be dissolved in sterile water or in a sterile solution for injection prior to use.

[0025]

[Examples] The present invention is described in further detail below on the basis of examples. The compound of the present invention is not limited to the compounds recited in the examples below, and may contain the compound shown in General Formula (I) above, a salt thereof, a hydrate thereof, a geometrical or optical isomer thereof, or a polymorphic crystal. The case where the starting material used in the present invention is novel is described in the Reference Examples.

[0026] ***Reference Example 1***

8.48 g of *N*-benzyl-2-(4-nitrophenyl)ethylamine, 5.2 g of diisopropylethylamine, 12 g of 4′-benzyloxyphenacyl bromide, and 200 mL of 2-butanone were sequentially added, and the reaction mixture was heated to reflux for 1 hour. After distilling off the solvent under

reduced pressure, the residue was diluted with ethyl acetate, washed sequentially with a saturated sodium hydrogencarbonate aqueous solution and saturated salt water, then the organic layer was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The resulting residue was dissolved in 100 mL of methanol and a small quantity of tetrahydrofuran. To this reaction solution was added 2 g of sodium boron hydride, in ice. After agitating the reaction solution for 1 hour at room temperature, the solvent was distilled off under reduced pressure. After adding water and ethyl acetate to the residue, the organic layer was washed with a saturated sodium hydrogencarbonate aqueous solution. After drying the organic layer with anhydrous magnesium sulfate, the solvent was distilled off under reduced pressure. The resulting residue was purified with silica gel column chromatography (eluent: hexane/ethyl acetate = 3/1), resulting in 15.2 g of 2-[*N*-benzyl-*N*-[2-(4-nitrophenyl)ethyl]amino]-1-(4-benzyloxyphenyl)ethanol.

[0027] ***Reference Example 2***

40 mL of 2 N HCl and 8.6 g of iron powder were added to a 250 mL methanol solution of 14.8 g of 2-[*N*-benzyl-*N*-[2-(4-nitrophenyl)ethyl]amino]-1-(4-benzyloxyphenyl)ethanol. The reaction solution was heated to reflux for 2 hours, after which the insoluble matter was filtered off with celite. After concentrating the filtrate under reduced pressure, a 1 N sodium hydroxide aqueous solution and chloroform were added, and the insoluble matter was again filtered off with celite. After drying the organic layer with anhydrous magnesium sulfate, the solvent was distilled off under reduced pressure. The resulting residue was purified with silica gel column chromatography (eluent: hexane/ethyl acetate = 2/1), resulting in 11.7 g of 2-[*N*-benzyl-*N*-[2-(4-aminophenyl)ethyl]amino]-1-(4-benzyloxyphenyl)ethanol.

[0028] ***Reference Example 3***

510 mg of 2-[*N*-benzyl-*N*-[2-(4-aminophenyl)ethyl]amino]-1-(4-benzyloxyphenyl)ethanol and a 10 mL xylene solution of 315 mg of 2-(3-methylpyridine-2-yl)ethyl acetate was heated to reflux for 13 hours. The solvent was distilled off under reduced pressure, and the residue was purified with silica gel column chromatography (eluent: chloroform/methanol = 100/1), resulting in 256 mg of 4′-[2-[*N*-benzyl-*N*-[2-(4-benzyloxyphenyl)-2-hydroxyethyl] amino]ethyl]-2-(3-methylpyridine-2-yl)anilide acetate.

[0029] ***Reference Example 4***

4′-[2-[*N*-benzyl-*N*-[2-(4-benzyloxyphenyl)-2-hydroxyethyl] amino]ethyl]-2-(4-methyl pyridine-2-yl)anilide acetate was synthesized according to the same process as in Reference Example 3.

[0030] ***Reference Example 5***

4′-[2-[*N*-benzyl-*N*-[2-(4-benzyloxyphenyl)-2-hydroxyethyl]amino]ethyl]-2-(3-methyl pyridine-6-yl)anilide acetate was synthesized according to the same process as in Reference Example 3.

[0031] ***Reference Example 6***

4′-[2-[*N*-benzyl-*N*-[2-(4-benzyloxyphenyl)-2-hydroxyethyl]amino]ethyl]-2-(2-methyl pyridine-6-yl)anilide acetate was synthesized according to the same process as in Reference Example 3.

[0032] ***Reference Example 7***

5.12 g of 2-(2-pyridyl)methyl acetate and a 50 mL xylene solution of 5.14 g of 4-aminophenylacetonitrile was heated to reflux for 24 hours. The solvent was distilled off under reduced pressure, and the resulting crude crystals were washed with diethylether to produce 5.65 g of 4′-cyanomethyl-2-(2-pyridyl)anilide acetate.

[0033] ***Reference Example 8***

4′-cyanomethyl-2-(2,4-dimethylpyridine-6-yl)anilide acetate was synthesized according to the same process as in Reference Example 7.

[0034] ***Reference Example 9***

20 mL of Raney nickel and concentrated ammonia water were added to a 50 mL tetrahydrofuran solution of 5.12 g of 4′-cyanomethyl-2-(2-pyridyl)anilide acetate. The reaction solution was agitated for 3 hours in a hydrogen environment at normal pressure at room temperature. After removing the insoluble matter with celite, the solvent was distilled off under reduced pressure. To the resulting residue were added 50 mL of toluene and 2.1 mL of benzaldehyde. This reaction mixture was heated to reflux for 3 hours while dehydrating with a Dienstag apparatus. After distilling off the solvent under reduced pressure, 1.0 g of sodium boron hydride was added in ice to a 50 mL methanol solution of the resulting residue. After agitating the reaction solution for 1 hour at room temperature, the solvent was distilled off under reduced pressure. Chloroform and a saturated sodium hydrogencarbonate aqueous solution were added to the residue, and the organic layer was dried with anhydrous magnesium sulfate. After that, the solvent was distilled off under reduced pressure. The resulting residue was purified with silica gel column chromatography (eluent: chloroform/methanol = 50/1), resulting in 4.63 g of 4′-(2-benzylaminoethyl)-2-(2-

pyridyl)anilide acetate.

[0035] ***Reference Example 10***

4′-(2-benzylaminoethyl)-2-(2-pyridyl)anilide acetate was synthesized according to the same process as in Reference Example 9.

[0036] ***Reference Example 11***

A reaction mixture of 338 mg of 4′-(2-benzylaminoethyl)-2-(2-pyridyl)anilide acetate, 299 mg of 4′-benzyloxyphenacylbromide, and 0.175 mL of diisopropylethylamine suspended in 20 mL of 2-butanone was heated to reflux for 3 hours. The insoluble matter was filtered off, and the filtrate was concentrated under reduced pressure. 120 mg of sodium boron hydride was added in ice to a 10 mL methanol solution of the resulting residue. After agitating the reaction solution for 1 hour at room temperature, the solvent was distilled off under reduced pressure. Chloroform and a saturated sodium hydrogencarbonate aqueous solution were added to the residue, and after drying the organic layer with anhydrous magnesium sulfate, the solvent was distilled off under reduced pressure. The residue was purified with silica gel column chromatography (eluent: chloroform/methanol = 100/1), resulting in 283 mg of 4′-[2-*N*-benzyl-*N*-[2-(4-benzyloxyphenyl)-2-hydroxy ethyl] amino]ethyl]-2-(2-pyridyl)anilide acetate.

[0037] ***Reference Example 12***

4′-[2-*N*-benzyl-*N*-[2-(4-benzyloxyphenyl)-2-hydroxyethyl]amino)ethyl]-2-(2,4-dimethyl pyridine-6-yl)anilide acetate was synthesized according to the same process as in Reference Example 11.

[0038] ***Reference Example 13***

4′-[2-*N*-benzyl-*N*-[2-(3-benzyloxyphenyl)-2-hydroxyethyl] amino]ethyl]-2-(2-pyridyl)anilide acetate was synthesized according to the same process as in Reference Example 11.

[0039] ***Reference Example 14***

4′-[2-*N*-benzyl-*N*-[2-(2-benzyloxyphenyl)-2-hydroxyethyl] amino]ethyl]-2-(2-pyridyl)anilide acetate was synthesized according to the same process as in Reference Example 11.

[0040] ***Reference Example 15***

50 mL of tetrahydrofuran and 15 mL of dimethylformamide were sequentially added to 5.14

g of 4-methylaminophenylacetonitrile, 12.1 g of 2-pyridylacetate hydrochloride, 10.5 g of (3-dimethylaminopropyl)carbodiimide hydrochloride, and 7.62 g of 1-hydroxybenzotriazole. After agitating the reaction solution for 2.5 hours at room temperature, the solvent was distilled off under reduced pressure. After diluting the residue with ethyl acetate, the organic layer was washed with a saturated sodium hydrogencarbonate aqueous solution, and dried with anhydrous magnesium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified with silica gel column chromatography (eluent: chloroform/methanol = 100/1 → 20/1), resulting in 6.07 g of 4′-cyanomethyl-*N*-methyl-2-(2-pyridyl)anilide acetate.

[0041] ***Reference Example 16***

4′-(2-benzylaminoethyl)-*N*-methyl-2-(2-pyridyl)anilide acetate was synthesized according to the same process as in Reference Example 9.

[0042] ***Reference Example 17***

4′-[2-*N*-benzyl-*N*-[2-(4-benzyloxyphenyl)-2-hydroxyethyl] amino]ethyl]-*N*′-methyl-2-(2-pyridyl)anilide acetate was synthesized according to the same process as in Reference Example 11.

[0043] ***Reference Example 18***

1.28 g of phenyltrimethylammonium tribromide was added to a 20 mL tetrahydrofuran solution of 1.03 g of *N*-(5-acetyl-2-benzyloxyphenyl)methanesulfonamide. After agitating the reaction solution for 0.75 hour at room temperature, the insoluble matter was filtered off. The filtrate was concentrated under reduced pressure, and the resulting crude crystals were crystallized using chloroform-hexane. To a mixture of the resulting crystals and 1.11 g of 4′-(2-benzylaminoethyl)-2-(2-pyridyl)anilide acetate were sequentially added 20 mL of 2-butanol and 0.56 mL of diisopropylethylamine. The reaction mixture was heated to reflux for 1 hour, and the insoluble matter was filtered off. The filtrate was concentrated under reduced pressure, and 160 mg of sodium boron hydride was added in ice to a 20 mL solution of the resulting residue. After agitating the reaction solution for 0.5 hour at room temperature, another 470 mg of sodium boron hydride was added to the reaction solution. After agitating the reaction solution for 0.5 hour at room temperature, the solvent was distilled off under reduced pressure. Ethyl acetate and a saturated sodium hydrogencarbonate aqueous solution were added to the residue, and after drying the organic layer with anhydrous magnesium sulfate, the solvent was distilled off under reduced pressure. The residue was purified with silica gel column chromatography (eluent: chloroform/methanol = 100/1), resulting in 920 mg of 4′-[2-*N*-benzyl-*N*-[2-(4-benzyloxy-3-methanesulfonylaminophenyl)-2-hydroxyethyl]

amino]ethyl]-2-(2-pyridyl)anilide acetate.

[0044] ***Reference Example 19***

4′-[2-*N*-benzyl-*N*-[2-(4-benzyloxy-3-nitrophenyl)-2-hydroxyethyl]amino]ethyl]-2-(2-pyridyl) anilide acetate was synthesized according to the same process as in Reference Example 11.

[0045] ***Reference Example 20***

4′-[2-*N*-benzyl-*N*-[2-(3-amino-4-benzyloxyphenyl)-2-hydroxyethyl]amino]ethyl]-2-(2-pyridyl) anilide acetate was synthesized according to the same process as in Reference Example 2.

[0046] ***Reference Example 21***

To a 10 mL chloroform solution of 670 mg of 4′-[2-*N*-benzyl-*N*-[2-(3-amino-4-benzyloxyphenyl)-2-hydroxyethyl]amino]ethyl]-2-(2-pyridyl)anilide acetate was added 1.0 mL of a formic acid-anhydrous acetic anhydride mixture (3:5), and this was agitated for 7 hours at room temperature. The solvent was distilled off under reduced pressure, and 15 mL of methanol, 1.0 mL of water, and 490 mg of sodium carbonate was added to the residue, and agitated for 1.5 hour at room temperature. The insoluble matter was filtered off, the solvent was concentrated under reduced pressure, and water and chloroform were added to the resulting residue. After washing the organic layer with saturated salt water, it was dried with anhydrous magnesium sulfate. The residue was purified with silica gel column chromatography (eluent: chloroform/methanol = 50/1), resulting in 590 mg of 4′-[2-*N*-benzyl-*N*-[2-(4-benzyloxy-3-formamidephenyl)-2-hydroxyethyl]amino]ethyl]-2-(2-pyridyl) anilide acetate.

[0047] ***Reference Example 22***

20 mL of acetic anhydride was added to 640 mg of 4′-[2-*N*-benzyl-*N*-[2-(3-amino-4-benzyloxyphenyl)-2-hydroxyethyl]amino]ethyl]-2-(2-pyridyl)anilide acetate, and the mixture was agitated for 2 hours at room temperature. The solvent was distilled off under reduced pressure, 30 mL of methanol and 5 mL of 1 N sodium hydroxide aqueous solution were added to the residue, and then agitated for 1.5 hour at room temperature. The solvent was distilled off under reduced pressure, water and ethyl acetate were added to the residue, and after washing the organic layer sequentially with water and saturated salt water, it was dried with anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified with silica gel column chromatography (eluent: chloroform/methanol = 50/1), resulting in 570 mg of 4′-[2-*N*-[2-(3-acetamide-4-benzyl

oxyphenyl)-2-hydroxyethyl]-*N*-benzylamino]ethyl]-2-(2-pyridyl)anilide acetate.

[0048] ***Reference Example 23***

2-[*N*-benzyl-*N*-[2-(4-nitrophenyl)ethyl]amino]-1-(2-benzyloxyphenyl) ethanol was synthesized according to the same process as in Reference Example 1.

[0049] ***Reference Example 24***

2-[*N*-benzyl-*N*-[2-(4-aminophenyl)ethyl]amino]-1-(2-benzyloxyphenyl) ethanol was synthesized according to the same process as in Reference Example 2.

[0050] ***Reference Example 25***

4′-2-[*N*-benzyl-*N*-[2-(2-benzyloxyphenyl)-2-hydroxyethyl]amino]ethyl-2-(1-benzylimidazole-2-yl)anilide acetate was synthesized according to the same process as in Reference Example 3.

[0051] ***Reference Example 26***

7.5 g of 4′-benzyloxyphenacylbromide was added to 100 mL of an acetonitrile solution of 8.2 g of 2-(4-nitrophenyl)ethylamine at room temperature. After agitating the reaction solution for 0.5 hour at room temperature, the resulting insoluble matter was filtered off, and a suitable amount of solvent distilled off under reduced pressure without heating. To the concentrated reaction solution was added 50 mL of methanol and 2.5 g of sodium boron hydride in ice, and this was agitated for 1 hour at room temperature. The solvent was distilled off under reduced pressure, and the residue was dissolved in chloroform and a saturated sodium hydrogencarbonate aqueous solution. The organic layer was dried with anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified with silica gel column chromatography (eluent: chloroform/methanol = 20/1), resulting in 4.36 g of 1-(4-benzyloxyphenyl)-2-[[2-(4-nitrophenyl)ethyl]amino]ethanol.

[0052] ***Reference Example 27***

A 100 mL tetrahydrofuran solution of 4.29 g of 1-(4-benzyloxyphenyl)-2-[[2-(4-nitrophenyl)ethyl]amino]ethanol and 2.39 g of di-*t*-butyl bicarbonate ester was heated to reflux for 2 hours. The solvent was distilled of under reduced pressure, and to a 150 mL solution of the resulting residue was added 1.1 g of 10% palladium-carbon, and agitated for 5 hours at room temperature in a hydrogen environment under normal pressure. After

removing the insoluble matter with celite, the filtrate was concentrated under reduced pressure to yield 3.53 g of *N*-[2-(4-aminophenyl)ethyl]-*N*-[2-hydroxy-2-(4-hydroxy phenyl)ethyl] carbamate *t*-butyl ester.

[0053] ***Reference Example 28***

320 mg of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride and 240 mg of 1-hydroxybenzotriazole were added to a 15 mL dimethylformamide solution of 513 mg of *N*-[2-(4-aminophenyl)ethyl]-*N*-[2-hydroxy-2-(4-hydroxyphenyl)ethyl] carbamate *t*-butyl ester and 243 mg 2-(2-aminothiazole-4-yl) acetate, and agitated for 14 hours at room temperature. The solvent was distilled off under reduced pressure, water and ethyl acetate were added to the residue, and the organic layer was washed with saturated salt water. After drying the organic layer with anhydrous magnesium sulfate, the solvent was distilled off under reduced pressure. The resulting residue was purified with silica gel column chromatography (eluent: chloroform/methanol = 30/1), resulting in 570 mg of *N*-[2-[4-[2-(2-aminothiazole-4-yl) ace amide]phenyl]ethyl]-*N*-[2-hydroxy-2-(4-hydroxyphentyl)ethyl] carbamate *t*-butylester.

[0054] ***Example 1***

135 mg of palladium-carbon was added to a 10 mL methanol solution of 253 mg of 4′-[2-[*N*-benzyl-*N*-[2-(4-benzyloxyphenyl)-2-hydroxyethyl] amino]ethyl]-2-(3-methylpyridine-2-yl)anilide acetate. The reaction solution was agitated for 2 hours in a hydrogen environment under normal pressure. After filtering off the insoluble matter with celite, the filtrate was concentrated under reduced pressure. A 0.1 mL 4 N hydrogenchloride-ethyl acetate solution was added to a methanol solution of the resulting residue, and the solvent was distilled off under reduced pressure. After crystallizing the residue with methanol-ethanol-diethyl ether, the crude crystals were recrystallized with methanol-ethanol, yielding 112 mg of 4′-[2-[[2-hydroxy-2-(4-hydroxyphenyl)ethyl]amino]ethyl-2-(4-methylpyridine-2-yl) anilide acetate hydrochloride.

[0055] ***Example 2***

4′-[2-[[2-hydroxy-2-(4-hydroxyphenyl)ethyl]amino]ethyl-2-(3-methylpyridine-6-yl) anilide acetate hydrochloride was synthesized according to the same process as in Example 1.

[0056] ***Example 3***

4′-[2-[[2-hydroxy-2-(4-hydroxyphenyl)ethyl]amino]ethyl-2-(2-pyridyl) anilide acetate hydrochloride was synthesized according to the same process as in Example 1.

[0057] ***Example 4***

4′-[2-[[2-hydroxy-2-(4-hydroxyphenyl)ethyl]amino]ethyl-2-(2,4-dimethylpyridine-6-yl) anilide acetate hydrochloride was synthesized according to the same process as in Example 1.

[0058] ***Example 5***

120 mg of 10% palladium-carbon was added to a 10 mL methanol solution of 236 mg of 4′-[2-[*N*-benzyl-*N*-[2-(4-benzyloxyphenyl)-2-hydroxyethyl] amino]ethyl]-2-(3-methylpyridine-2-yl)anilide acetate. The reaction solution was agitated for 4 hours in a hydrogen environment at normal pressure. After filtering off the insoluble matter using celite, the filtrate was concentrated under reduced pressure. 0.1 mL of 4 N hydrogen chloride-ethyl acetate solution was added to a methanol solution of the resulting residue, and the solvent was distilled off under reduced pressure. The residue was purified with silica gel column chromatography (eluent: chloroform/methanol = 5/1), resulting in 121 mg of 4′-[2-[[2-hydroxy-2-(4-hydroxyphenyl)ethyl]amino]ethyl-2-(3-methylpyridine-2-yl) anilide acetate hydrochloride.

[0059] ***Example 6***

4′-[2-[[2-hydroxy-2-(4-hydroxyphenyl)ethyl]amino]ethyl-2-(2-methylpyridine-6-yl) anilide acetate hydrochloride was synthesized according to the same process as in Example 5.

[0060] ***Example 7***

4′-[2-[[2-hydroxy-2-(3-hydroxyphenyl)ethyl]amino]ethyl-2-(2-pyridyl) anilide acetate hydrochloride was synthesized according to the same process as in Example 5.

[0061] ***Example 8***

4′-[2-[[2-hydroxy-2-(2-hydroxyphenyl)ethyl]amino]ethyl-2-(2-pyridyl) anilide acetate hydrochloride was synthesized according to the same process as in Example 5.

[0062] ***Example 9***

A 0.5 fumaric acid salt of 2-(1-benzylimidazole-2-yl)-4′-[2-[[2-hydroxy-2-(2-hydroxyphenyl)ethyl]amino]ethyl-2-(2-pyridyl) anilide acetate was synthesized according to the same process as in Example 5.

[0063] ***Example 10***

A fumaric acid salt of 4′-[2-[[2-hydroxy-2-(4-hydroxyphenyl)ethyl]amino]ethyl-*N*-methyl-2-(2-pyridyl) anilide acetate was synthesized according to the same process as in Example 5.

[0064] ***Example 11***

10 mL of a trifluoroacetic acid solution of 490 mg of *N*-[2-[4-[2-(2-aminothiazole-4-yl) acetamide]phenyl]ethyl]-*N*-[2-hydroxy-2-(4-hydroxyphentyl)ethyl] carbamate *t*-butylester was agitated for 30 minutes at room temperature. The solvent was distilled off under reduced pressure, 20 mL of tetrahydrofuran and 30 mL of a 4 N HCl-dioxane solution were added to the residue, and this was agitated for 1.5 hour at room temperature. The solvent was distilled off under reduced pressure, and the resulting residue was purified with reverse-phase column chromatography (eluent: water/methanol = 2/1), resulting in 340 mg of 2-(2-aminothiazole-4-yl)-4′[2—[[2-hydroxy-2-(2-hydroxyphenyl)ethyl]amino]ethyl] anilide acetate 0.5 hydrochloride, 1.5 trifluoroacetate salt.

[0065] ***Example 12***

4′-[2-[[2-hydroxy-2-(4-hydroxy-3-methanesulfonamidephenyl)ethyl]amino]ethyl]-2-(2-pyridyl)anilide acetate hydrochloride was synthesized according to the same process as in Example 1.

[0066] ***Example 13***

4′-[2-[[2-(3-formamide-4-hydroxyphenyl-2-hydroxyethyl)]amino]ethyl]-2-(2-pyridyl)anilide acetate hydrochloride was synthesized according to the same process as in Example 1.

[0067] ***Example 14***

4′-[2-[[2-(3-formamide-4-hydroxyphenyl-2-hydroxyethyl)]amino]ethyl]-2-(2-pyridyl)anilide acetate hydrochloride was synthesized according to the same process as in Example 1.

[0068] The physiochemical properties of the compounds of the Reference Examples are given in TABLES 1-4. The physiochemical properties compounds of the Examples are given in TABLES 5-6. The structural formulas for the compounds of the Examples are given in TABLE 7. The symbols given in the tables are explained as follows:

Rex. No.: Reference Example No.
Ex. No.: Example No.

sal.: Salt
DATA: Physiochemical properties
MS (m/z): Mass spectrometry values (m/z)
NMR: Nuclear magnetic resonance spectra (TMS internal standard)
Mp: Melting point
OH-pos: Hydroxyl group substitution position in phenyl group

[0069]

[TABLE 1]

Rex. No.	D A T A
1	MS (m/z) : 481 [(M H) +] NMR ($CDCl_3$) δ : 2.60 – 2.98 (6H, m), 3.50 – 3.60 (2H, m), 3.94 (1H, d, J – 13.2Hz), 4.02 (1H, dd, J = 10.0, 4.0Hz), 5.05 (2H, s), 6.92 – 6.97 (2H, m), 7.18 – 7.45 (14H, m), 8.07 – 8.13 (2H, m)
2	MS (m/z) : 453 [(M + H) +] NMR ($CDCl_3$) δ : 2.54 – 2.91 (6H, m), 3.40 – 3.80 (3H, m), 3.95 (1H, d, J = 14.0Hz), 4.58 (1H, dd, J = 9.6, 4.0Hz), 5.04 (2H, s), 6.59 – 6.64 (2H, m), 6.89 6.97 (4H, m), 7.18 7.44 (12H, m)
3	MS (m/z) : 586 [(M + H) +] NMR ($CDCl_3$) δ : 2.40 (3H, s), 2.55 – 2.98 (6H, m), 3.50 – 3.60 (2H, m), 3.87 (2H, s), 3.94 (1H, d, J = 13.2Hz), 4.62 (1H, dd, J = 10.0, 4.0Hz), 5.05 (2H, s), 6.92 – 6.97 (2H, m), 7.18 – 7.45 (18H, m), 8.40 – 8.50 (1H, m), 9.65 (1H, brs)
4	MS (m/z) : 586 [(M + H) +] NMR ($CDCl_3$) δ : 2.35 (3H, s), 2.55 – 2.99 (6H, m), 3.55 (1H, d, J = 13.6Hz), 3.71 (1H, brs), 3.80 (2H, s), 3.94 (1H, d, J = 13.6Hz), 4.57 (1H, dd, J = 9.6, 4.0Hz), 5.04 (2H, s), 6.92 – 6.97 (2H, m), 7.09 – 7.07 (2H, m), 7.12 (1H, s), 7.18 – 7.46 (15H, m), 8.46 (1H, d, J = 4.8Hz), 9.76 (1H, brs)
5	MS (m/z) : 586 [(M + H) +] NMR ($CDCl_3$) δ : 2.33 (3H, s), 2.55 – 3.00 (6H, m), 3.55 (1H, d, J = 13.6Hz), 3.80 (2H, s), 3.93 (1H, d, J = 13.2Hz), 4.57 (1H, dd, J = 9.6, 4.0Hz), 5.09 (2H, s), 6.90 – 7.50 (20H, m), 8.42 (1H, d, J = 2.0Hz), 9.71 (1H, brs)
6	MS (m/z) : 586 [(M + H) +] NMR ($CDCl_3$) δ : 2.56 3.00 (9H, m), 3.56 (1H, d, J = 13.6Hz), 3.72 (1H, brs), 3.81 (2H, s), 3.95 (1H, d, J = 14.0Hz), 4.58 (1H, dd, J = 9.6, 4.0Hz), 5.04 (2H, s), 6.90 – 6.94 (2H, m), 7.05 – 7.11 (4H, m), 7.19 – 7.48 (14H, m), 7.57 (1H, t, J = 8.0Hz), 10.20 (1H, brs)
7	MS (m/z) : 252 [(M + H) +] NMR ($CDCl_3$) δ : 3.70 (2H, s), 3.88 (2H, s), 7.23 – 7.32 (4H, m), 7.56 – 7.61 (2H, m), 7.71 (1H, dt, J = 1.6, 7.6Hz), 8.68 (1H, d, J = 4.4Hz), 10.04 (1H, brs)

[0070] **[TABLE 2]**

Rex. No.	D A T A
8	MS (m/z) : 280 [(M + H) +] NMR ($CDCl_3$) δ : 2.31 (3H, s), 2.59 (3H, s), 3.71 (2H, s), 3.77 (2H, s), 6.91 (1H, s), 6.98 (1H, s), 7.24 – 7.28 (2H, m), 7.55 – 7.60 (2H, m), 10.60 (1H, brs)
9	MS (m/z) : 346 [(M – H) –] NMR ($CDCl_3$) δ : 2.75 – 2.81 (2H, m), 2.83 – 2.89 (2H, m), 3.78 (2H, s), 3.86 (2H, s), 7.11 – 7.16 (2H, m), 7.20 – 7.33 (7H, m), 7.44 – 7.48 (2H, m), 7.69 (1H, dt, J = 2.0, 8.0Hz), 8.61 (1H, d, J = 5.2Hz), 9.72 (1H, brs)
10	MS (m/z) : 374 [(M + H) +] NMR ($CDCl_3$) δ : 2.30 (3H, s), 2.57 (3H, s), 2.75 – 2.82 (2H, m), 2.84 – 2.90 (2H, m), 3.76 (2H, s), 3.78 (2H, s), 6.91 (2H, s), 7.11 – 7.16 (2H, m), 7.20 – 7.33 (6H, m), 7.44 – 7.49 (2H, m), 10.27 (1H, brs)
11	MS (m/z) : 572 [(M + H) +] NMR ($CDCl_3$) δ : 2.54 – 2.94 (6H, m), 3.56 (1H, d, J = 13.6Hz), 3.86 (2H, s), 3.95 (1H, d, J = 13.6Hz), 4.57 (1H, dd, J = 10.0, 4.0Hz), 5.04 (2H, s), 6.90 – 6.94 (2H, m), 7.04 – 7.08 (2H, m), 7.18 – 7.48 (16H, m), 7.69 (1H, dt, J = 2.0, 8.0Hz), 8.62 (1H, d, J = 4.8Hz), 9.72 (1H, brs)
12	MS (m/z) : 598 [(M – H) –] NMR ($CDCl_3$) δ : 2.30 (3H, s), 2.50 – 3.00 (9H, m), 3.56 (1H, d, J = 13.7Hz), 3.60 – 3.80 (3H, m), 3.94 (1H, d, J = 13.2Hz), 5.04 (2H, s), 6.80 – 7.60 (20H, m), 10.25 (1H, brs)
13	MS (m/z) : 572 [(M + H) +] NMR ($CDCl_3$) δ : 2.56 – 2.90 (6H, m), 3.56 (1H, d, J = 13.6Hz), 3.86 (2H, s), 3.97 (1H, d, J = 13.6Hz), 4.60 (1H, dd, J = 2.0, 8.0Hz), 5.04 (2H, s), 6.83 – 6.90 (2H, m), 6.95 – 6.98 (1H, m), 7.03 – 7.08 (2H, m), 7.18 – 7.48 (15H, m), 7.69 (1H, dt, J = 8.0, 2.0Hz), 8.60 – 8.63 (1H, m), 9.72 (1H, brs)
14	MS (m/z) : 572 [(M + 1) +] NMR ($CDCl_3$) δ : 2.47 – 2.90 (6H, m), 3.49 (1H, d, J = 13.6Hz), 5.01 – 5.11 (3H, m), 6.89 (1H, d, J = 7.2Hz), 6.96 – 6.99 (3H, m), 7.18 – 7.52 (16H, m), 7.69 (1H, dt, J = 8.0Hz, J = 2.0Hz), 8.60 – 8.64 (1H, m), 9.68 (1H, s)

[0071] **[TABLE 3]**

Rex. No.	D A T A
15	MS (m/z) : 266 [(M − H) +] NMR ($CDCl_3$) δ : 3.67 (2H, brs), 3.77 (2H, s), 7.10 − 7.28 (4H, m), 7.33 − 7.39 (2H, m), 7.53 − 7.55 (1H, m), 8.43 (1H, brd, J = 3.6Hz)
16	MS (m/z) : 360 [(M − H) +] NMR ($CDCl_3$) δ : 2.80 − 2.94 (6H, m), 3.29 (3H, s), 3.67 (2H, S), 3.82 (2H, s), 7.08 − 7.34 (11H, m), 7.53 − 7.58 (1H, m), 8.46 (1H, d, J = 4.4Hz)
17	MS (m/z) : 586 [(M − H) +] NMR ($CDCl_3$) δ : 2.58 − 2.98 (6H, m), 3.29 (3H, s), 3.54 − 3.68 (3H, m), 3.96 (1H, d, J = 13.6Hz), 4.56 − 4.64 (1H, m), 5.05 (2H, s), 6.90 − 6.96 (2H, m), 7.06 − 7.44 (18H, m), 7.53 − 7.58 (1H, m), 8.47 (1H, d, J = 4.4Hz)
18	MS (m/z) : 665 [(M − H) +] NMR ($CDCl_3$) δ : 2.50 − 2.91 (9H, m), 3.55 (1H, d, J = 13.6Hz), 3.85 (2H, s), 3.94 (1H, d, J = 13.6Hz), 4.56 (1H, dd, J = 10.0, 3.6Hz), 5.08 (2H, s), 6.83 (1H, brs), 6.94 (1H, d, J = 8.4Hz), 7.04 − 7.12 (3H, m), 7.22 − 7.48 (15H, m), 7.69 (1H, dt, J = 2.0, 8.0Hz), 8.58 − 8.63 (1H, m), 9.70 (1H, brs)
19	MS (m/z) : 617 [(M − H) +] NMR ($CDCl_3$) δ : 2.48 − 2.54 (1H, m), 2.64 − 2.94 (5H, m), 3.57 (1H, d, J = 13.2Hz), 3.75 (1H, brs), 3.86 (2H, s), 3.92 (1H, d, J = 13.2Hz), 4.53 (1H, dd, J = 10.8Hz, J = 3.6Hz), 5.21 (2H, s), 7.03 − 7.08 (3H, m), 7.23 − 7.48 (15H, m), 7.67 − 7.75 (2H, m), 8.60 − 8.64 (1H, m), 9.75 (1H, s)
20	MS (m/z) : 587 [(M H) +] NMR ($CDCl_3$) δ : 2.59 − 2.88 (6H, m), 3.55 (1H, d, J = 13.2Hz), 3.67 (1H, brs), 3.81 (2H, brs), 3.86 (2H, s), 3.94 (1H, d, J = 13.2Hz), 4.49 − 4.52 (1H, m), 5.05 (2H, s), 5.59 − 6.79 (3H, m), 7.05 − 7.07 (2H, m), 7.23 − 7.46 (14H, m), 7.67 − 7.71 (1H, m), 8.61 − 8.62 (1H, m), 9.71 (1H, brs)
21	MS (m/z) : 515 [(M − H) +] NMR ($CDCl_3$) δ : 2.53 − 2.88 (6H, m), 3.55 (1H, d, J = 13.6Hz), 3.75 (1H, brs), 3.86 (2H, s), 5.94 (1H, d, J = 13.6Hz), 4.59 − 4.62 (1H, m), 5.08 − 5.08 (2H, m), 6.89 − 7.22 (5H, m), 7.23 − 7.48 (14H, m), 7.67 7.71 (1H, m), 7.78 8.72 (3H, m), 9.68 9.73 (1H, m)

[0072] **[TABLE 4]**

Rex. No.	D A T A
22	MS (m/z) : 629 [(M + H) +] NMR ($CDCl_3$) δ : 2.14 (3H, s), 2.58 – 2.87 (6H, m), 3.54 (1H, d, J = 13.2Hz), 3.74 (1H, brs), 3.86 (2H, s), 3.94 (1H, d, J = 13.2Hz), 4.56 – 4.64 (1H, m), 5.10 (2H, s), 6.90 (1H, d, J = 8.4Hz), 7.02 – 7.07 (3H, m), 7.22 – 7.46 (12H, m), 7.65 – 7.77 (2H, m), 8.28 – 8.32 (1H, m), 8.60 – 8.65 (1H, m), 9.69 (1H,s)
23	MS (m/z) : 483 [(M + H) +] NMR ($CDCl_3$) δ : 2.50 – 2.95 (6H, m), 3.50 (1H, d, J = 13.6Hz), 3.85 (1H, d, J = 13.2Hz), 5.00 – 5.14 (3H, m), 6.92 – 7.53 (16H, m), 8.03 – 8.08 (2H, m)
24	MS (m/z) : 453 [(M + H) +] NMR ($CDCl_3$) δ : 2.46 – 2.92 (6H, m), 3.40 – 3.80 (3H, m), 3.87 (1H, d, J = 13.6Hz), 5.00 – 5.15 (3H, m), 6.55 – 6.61 (2H, m), 6.82 – 6.91 (3H, m), 6.95 – 7.01 (1H, m), 7.17 – 7.43 (11H, m), 7.49 – 7.53 (1H, m)
25	MS (m/z) : 651 [(M + H) +] NMR ($CDCl_3$) δ : 2.46 – 2.92 (6H, m), 3.50 (1H, d, J = 13.6Hz), 3.62 (1H, brs), 3.72 (2H, s), 3.87 (1H, d, J = 13.6Hz), 6.00 – 6.16 (6H, m), 6.87 – 7.54 (25H, m), 10.23 (1H, brs)
26	MS (m/z) : 393 [(M + H) +] NMR ($CDCl_3$) δ : 2.73 (1H, dd, J = 8.8, 12.4Hz), 2.84 – 3.33 (5H, m), 4.64 (1H, dd, J = 3.6, 8.8Hz), 5.05 (2H, s), 6.93 – 6.98 (2H, m), 7.23 – 7.46 (9H, m), 8.13 – 8.17 (2H, m)
27	MS (m/z) : 371 [(M – H) –] NMR ($CDCl_3$) δ : 1.46 (9H, s), 2.55 – 2.72 (2H, m), 3.15 – 3.53 (4H, m), 4.72 – 4.83 (1H, m), 6.58 – 6.63 (2H, m), 6.73 – 6.79 (2H, m), 6.85 – 6.97 (2H, m), 7.13 – 7.19 (2H, m)
28	MS (m/z) : 513 [(M + H) +] NMR (DMSO – d_6) δ : 1.35 (9H, s), 2.58 – 2.70 (2H, m), 3.14 – 3.35 (4H, m), 3.44 (2H, s), 4.59 (1H, brs), 5.15 – 5.25 (1H, m), 6.29 (1H, s), 6.69 (2H, d, J = 8.0Hz), 6.89 (2H, m), 7.05 – 7.12 (4H, m), 7.49 (2H, d, J = 8.0Hz), 8.31 (1H, s), 9.23 (1H, s), 9.99 (1H, s)

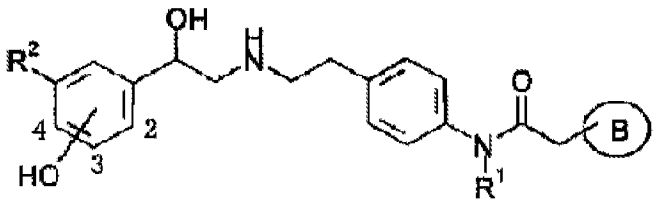
[0073] **[TABLE 5]**

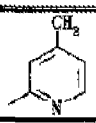
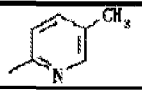
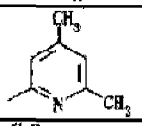
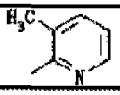
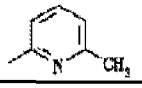
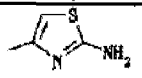
Ex. No.	D A T A
1	mp : 224 – 226℃ NMR (DMSO – d_6) δ : 2.31 (3H, s), 2.85 – 3.18 (6H, m), 3.78 (2H, s), 4.79 – 4.86 (1H, m), 6.00 (1H, d, J = 4.0Hz), 6.74 – 6.79 (2H, m), 7.08 – 7.12 (1H, m), 7.14 – 7.23 (5H, m), 7.54 – 7.61 (2H, m), 8.31 – 8.37 (1H, m), 9.47 (1H, brs), 10.28 (1H, brs)
2	mp : 215 – 216℃ NMR (DMSO – d_6) δ : 2.27 (3H, s), 2.85 – 3.18 (6H, m), 3.78 (2H, s), 4.79 – 4.87 (1H, m), 5.99 (1H, d, J = 3.2Hz), 6.74 – 6.79 (2H, m), 7.14 – 7.20 (5H, m), 7.28 (1H, d, J – 8.0Hz), 7.53 – 7.60 (3H, m), 8.31 – 8.34 (1H, m), 9.47 (1H, brs), 10.27 (1H, brs)
3	mp : 211 – 212℃ NMR (DMSO – d_6) δ : 2.84 – 3.20 (6H, m), 3.84 (2H, s), 4.77 – 4.86 (1H, m), 6.00 (1H, d, J = 3.2 Hz), 6.74 – 6.79 (2H, m), 7.14 – 7.20 (4H, m), 7.24 – 7.30 (1H, m), 7.39 (1H, d, J = 8.0Hz), 7.56 – 7.60 (2H, m), 7.76 (1H, dt, J = 2.0, 8.0Hz), 8.47 – 8.51 (1H, m), 8.71 (1H, brs), 8.91 (1H, brs), 9.46 (1H, brs), 10.29 (1H, brs)
4	mp : 194 – 196℃ NMR (DMSO – d_6) δ : 2.26 (3H, s), 2.39 (3H, s), 2.86 – 3.18 (6H, m), 3.74 (2H, s), 4.81 – 4.90 (1H, m), 6.00 (1H, d, J = 3.6Hz), 6.74 – 6.80 (2H, m), 6.96 (1H, s), 7.01 (1H, s), 7.09 – 7.20 (4H, m), 7.55 – 7.61 (2H, m), 9.49 (1H, brs), 10.33 (1H, brs)
5	MS (m/z) : 406 [(M + H) $^+$] NMR (DMSO – d_6) δ : 2.31 (3H, s), 2.84 – 3.16 (6H, m), 3.87 (2H, s), 4.79 (1H, d, J = 8.0Hz), 5.92 (1H, brs), 6.73 – 6.79 (2H, m), 7.13 – 7.21 (5H, m), 7.53 – 7.60 (3H, m), 8.27 – 8.33 (1H, m), 9.44 (1H, brs), 10.23 (1H, brs)
6	MS (m/z) : 406 [(M + H) $^+$] NMR (DMSO – d_6) δ : 2.44 (3H, s), 2.80 – 3.10 (6H, m), 3.78 (2H, s), 4.70 – 4.76 (1H, m), 5.81 (1H, brs), 6.72 – 6.77 (2H, m), 7.10 – 7.20 (5H, m), 7.53 – 7.66 (4H, m), 9.44 (1H, brs), 10.24 (1H, brs)
7	MS (m/z) : 392 [(M + H) $^+$] NMR (DMSO – d_6) δ : 2.84 – 3.03 (3H, m), 3.06 – 3.20 (3H, m), 3.84 (2H, s), 4.81 – 4.89 (1H, m), 6.12 (1H, d, J = 3.6Hz), 6.70 (1H, dd, J – 2.0, 8.0Hz), 6.76 – 6.83 (2H, m), 7.13 – 7.20 (3H, m), 7.24 – 7.30 (1H, m), 7.39 (1H, d, J = 8.0Hz), 7.56 – 7.60 (2H, m), 7.76 (1H, dt, J = 1.6, 7.2Hz), 8.47 – 8.52 (1H, m), 8.72 (1H, brs), 8.92 (1H, brs), 9.49 (1H, brs), 10.28 (1H, brs)

[0074] **[TABLE 6]**

Ex. No.	D A T A
8	MS (m/z) : 392 [(M + H) +] NMR (DMSO – d_6) δ : 2.78 – 2.91 (3H, m), 2.97 – 3.06 (3H, m), 3.33 (1H, brs), 3.84 (2H, s), 5.05 – 5.11 (1H, m), 6.79 – 6.82 (2H, m), 7.09 (1H, dt, J = 8.0Hz, J = 1.6Hz), 7.17 (2H, d, J = 8.0Hz), 7.25 – 7.40 (3H, m), 7.56 (2H, d, J = 8.4Hz), 7.75 (1H, dt, J = 8.0Hz, J = 2.4Hz), 8.49 – 8.50 (1H, m), 10.28 (1H, s)
9	MS (m/z) : 471 [(M + H) +] NMR (DMSO – d_6) δ : 2.84 – 3.00 (3H, m), 3.07 – 3.18 (3H, m), 3.79 (2H, s), 5.15 – 5.20 (1H, m), 5.25 (2H, s), 6.69 (1.2H, s), 6.80 – 6.87 (3H, m), 7.08 – 7.40 (10H, m), 7.50 – 7.57 (2H, m), 10.38 (1H, brs)
10	MS (m/z) : 406 [(M + H) +] NMR (DMSO – d_6) δ : 2.70 – 3.20 (9H, m), 3.57 (2H, brs), 4.70 – 4.80 (1H, m), 6.52 (2H, s), 6.70 – 6.75 (2H, m), 7.15 – 7.90 (8H, m), 7.60 – 7.70 (1H, m), 8.85 – 8.95 (1H, m)
11	MS (m/z) : 413 [(M + H) +] NMR (DMSO – d_6) δ : 2.85 – 3.17 (6H, m), 3.62 (2H, s), 4.79 – 4.81 (1H, m), 6.00 (1H, brs), 6.55 (1H, s), 6.77 (2H, d, J = 8.4Hz), 7.15 – 7.20 (4H, m), 7.55 (2H, d, J = 8.8Hz), 7.55 (1H, brs), 8.67 (1H, brs), 8.67 (1H, brs), 8.79 (1H, brs), 9.75 (1H, brs), 10.21 (1H, brs)
12	mp : 191 – 192℃ NMR (DMSO – d_6) δ : 2.84 – 3.01 (6H, m), 3.05 – 3.17 (3H, m), 3.84 (2H, s), 4.78 – 4.88 (1H, m), 6.05 (1H, brs), 6.92 (1H, d, J = 8.0 Hz), 7.06 (1H, dd, J = 2.0, 8.4Hz), 7.14 – 7.29 (4H, m), 7.39 (1H, d, J = 8.0Hz), 7.54 – 7.60 (2H, m), 7.75 (1H, dt, J = 2.0, 8.0Hz), 8.47 – 8.51 (1H, m), 10.30 (1H, brs)
13	mp : 217 – 219℃ NMR (DMSO – d_6) δ : 2.80 – 3.00 (3H, m), 3.00 – 3.20 (3H, m), 4.02 (2H, s), 4.83 (1H, d, J = 8.0Hz), 6.05 (1H, brs), 6.88 – 6.95 (2H, m), 7.14 – 7.20 (2H, m), 7.51 – 7.65 (4H, m), 8.05 (1H, t, J = 7.2Hz), 8.14 – 8.29 (2H, m), 8.64 (1H, d, J = 4.8Hz), 8.74 (1H, brs), 9.04 (1H, brs), 9.61 (1H, s), 10.12 (1H, s), 10.47 (1H, s)
14	mp : 216 – 222℃ NMR (DMSO – d_6) δ : 2.10 (3H, s), 2.87 – 3.02 (3H, m), 3.02 – 3.20 (3H, m), 3.93 (2H, s), 4.76 – 4.83 (1H, m), 6.06 (1H, d, J = 3.6Hz), 6.86 (1H, d, J = 8.4Hz), 6.94 – 6.96 (1H, m), 7.17 (2H, d, J = 8.8Hz), 7.26 – 7.29 (1H, m), 7.39 (1H, d, J = 8.0Hz), 7.67 (2H, d, J = 8.8Hz), 7.76 (1H, dt, J = 8.0Hz, J = 4.0Hz), 7.81 – 7.84 (1H, m), 8.50 (1H, d, J = 4.0Hz), 8.66 (1H, brs), 8.79 (1H, brs), 9.31 (1H, s), 9.86 (1H, s), 10.26 (1H, s)

[0075] **[TABLE 7]**



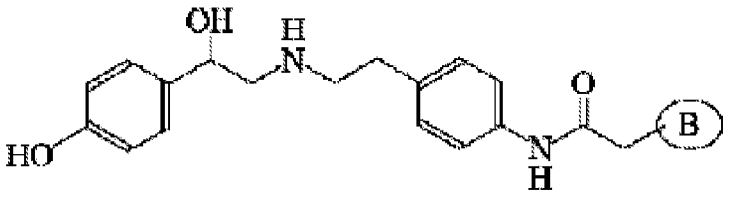
Ex. No.	OH-pos	-R ^{1}	-R ^{2}	B ring	salt
1	4	-H	-H		HCl
2	4	-H	-H		HCl
3	4	-H	-H		HCl
4	4	-H	-H		HCl
5	4	-H	-H		HCl
6	4	-H	-H		HCl
7	3	-H	-H		HCl
8	2	-H	-H		HCl
9	2	-H	-H		0.5 fumalate
10	4	-CH$_3$	-H		fumalate
11	4	-H	-H		1.5TFA 0.5HCl
12	4	-H	-NHSO$_2$CH$_3$		HCl
13	4	-H	-NHCHO		HCl
14	4	-H	-NHCOCH$_3$		HCl

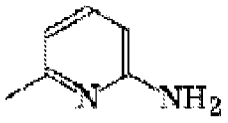
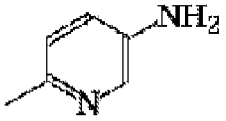
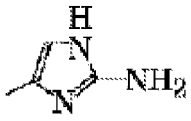
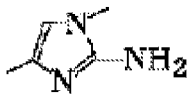
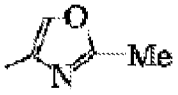
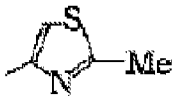
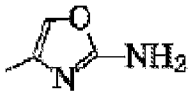
The compounds having the chemical structures shown in TABLES 8-9 can be easily prepared in almost the same manner as the processes given in the Examples or in the Processes of Preparation, or by utilizing a slightly modified process obvious to a practitioner the art. A variety of tautomers, geometrical isomers, and optical isomers may be present in the compounds given in TABLES 8-9, but the compound of the present invention includes various isomeric isolates or mixtures thereof.

[0076]

[TABLE 8]

[Chemical Structure 12]

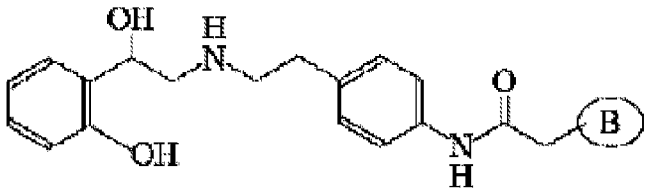


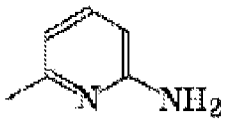
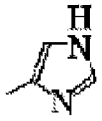
No.	B	No.	B
1		6	
2		7	
3		8	
4		9	
5		10	

[0077]

[TABLE 9]

[Chemical Structure 13]



No.	B	No.	B
11		14	
12		15	
13		16	

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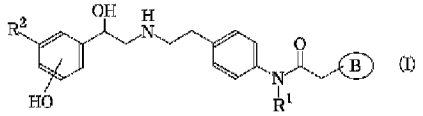
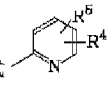
(54)【発明の名称】　新規なフェネタノール誘導体又はその塩

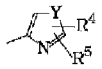
(57)【要約】
【課題】　インスリン分泌促進作用とインスリン感受性増強作用を併せ持ち，さらに選択的なβ_3受容体刺激作用を有する，糖尿病の治療剤の創製。
【解決手段】下記一般式（Ｉ）で示されるフェネタノール誘導体又はその塩。
【化１】



（Ⅰ）

（上記式中の記号は，それぞれ以下の意味を有する。

B環：式  で示される基，式  で示される基，

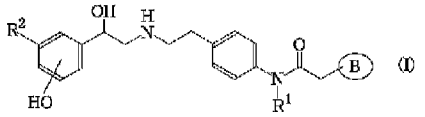
又は式  で示される基，

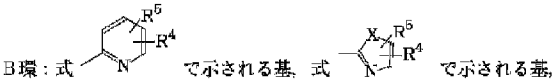
Ｘ，Ｙ：酸素原子，硫黄原子又は式ＮＲ[6]で示される基，
Ｒ[1]：水素原子又は低級アルキル基，
Ｒ[2]：水素原子，低級アルキル基，メチルスルホナミド基又は式－ＮＨＣＯＲ[3]で示される基，
Ｒ[3]：水素原子，低級アルキル基，モノ－若しくはジ－低級アルキルアミノ基，アリール基又はアラルキル基，
Ｒ[4]，Ｒ[5]：同一又は異なって水素原子，低級アルキル基又はアミノ基，
Ｒ[6]：水素原子，低級アルキル基又はアラルキル基）

【特許請求の範囲】

【請求項１】　下記一般式（Ｉ）で示されるフェネタノール誘導体又はその塩。

【化１】

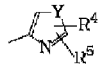




（上記式中の記号は，それぞれ以下の意味を有する。

【化２】

B環：式 で示される基，式 で示される基，

又は式  で示される基，

Ｘ，Ｙ：酸素原子，硫黄原子又は式ＮＲ^{6}で示される基，

Ｒ^1：水素原子又は低級アルキル基，

Ｒ^2：水素原子，低級アルキル基，メチルスルホナミド基又は式－ＮＨＣＯＲ^{3}で示される基，

Ｒ^3：水素原子，低級アルキル基，モノ－若しくはジ－低級アルキルアミノ基，アリール基又はアラルキル基，

Ｒ^4，Ｒ^5：同一又は異なって水素原子，低級アルキル基又はアミノ基，

Ｒ^6：水素原子，低級アルキル基又はアラルキル基）

【請求項２】　請求項１に記載のフェネタノール誘導体又はその塩を含有することを特徴とする医薬。

【請求項３】　請求項１に記載のフェネタノール誘導体又はその塩を有効成分とすることを特徴とする糖尿病治療剤。

【発明の詳細な説明】

【０００１】

【発明の属する技術分野】本発明は，医薬，特に新規なフェネタノール誘導体又はその塩及びそれらを有効成分とする糖尿病治療剤に関する。

【０００２】

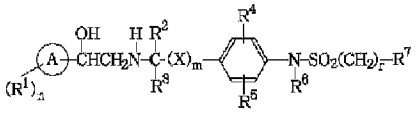
【従来の技術】糖尿病は，持続的高血糖状態を伴う疾患であり，多くの環境因子と遺伝的因子とが作用した結果生じるといわれている。血糖の主要な調整因子はインスリンであり，高血糖はインスリン欠乏あるいはその作用を阻害する諸因子（例えば，遺伝的素因，運動不足，肥満，ストレス等）が過剰となって生じることが知られている。糖尿病には主として２つの種類があり，自己免疫疾患による膵インスリン分泌機能の低下によって生じるインスリン依存性糖尿病（ＩＤＤＭ）と持続的な高インスリン分泌に伴う膵疲弊による膵インスリン分泌機能の低下が原因であるインスリン非依存性糖尿病（ＮＩＤＤＭ）とに分けられる。日本人の糖尿病患者の９５％以上はＮＩＤＤＭといわれており，生活様式の変化に伴い患者数の増加が問題となっている。糖尿病の治療は，軽症においては食事療法，運動療法及び肥満の改善等が主として行われ，更に進行すると，経口糖尿病薬（例えば，スルホニルウレア剤等のインスリン分泌促進剤，インスリンの感受性を増強するインスリン感受性増強剤等）の投与が行われ，更に重症の場合はインスリン製剤の投与が行われている。しかしながら，より高度な血糖管理が可能な薬剤の創製が切望されており，新たなメカニズムを有する有用性の高い糖尿病治療薬の開発が望まれている。

【０００３】一方，米国特許４，３９６，６２７号及び同４，４７８，８４９号には，フェニルエタノールアミン誘導体が記載されており，これらの化合物は抗肥満薬，抗高血糖症薬として有用であることが開示されている。これらの化合物の作用は，β_3受容体刺激作用によると報告されている。β_3受容体刺激作用としては，一般に抗肥満作用，抗高脂血作用（例えば，トリグリセライド低下作用，コレステロール低下作用，ＨＤＬコレステロール上昇作用等）が知られている。ここでβ－アドレナリン受容体はβ_1，β_2，β_3のサブタイプに分類され，β_1受容体の刺激は心拍数の増加を引き起こし，β_2受容体の刺激は筋肉中でのグリコーゲンの分解を刺激しこれによってグリコーゲンの合成を阻害し，筋肉振戦等の作用を生じることが知られている。しかしながら，これらの初期のβ_3受容体作動薬は，心拍数の増加や筋肉振戦等のβ_1受容体及びβ_2受容体刺激に基づく作用をも有しており，副作用の点で問題があった。又，最近β受容体には種差が存在することが確認され，従来ラット等の齧歯類にてβ_3受容体選択性が確認された化合物であっても，ヒトにおいてはβ_1及びβ_2受容体刺激作用に基づく作用が確認されたことが報告されている。このような点から，最近はヒトの細胞あるいはヒトの受容体を発現させた細胞を用いて，ヒトにおいてβ_3受容体選択的な刺激作用を有する化合物の研究が進められている。例えば，ＷＯ９５／２９１５９公報には，下記一般式で示される置換スルホンアミド誘導体が記載され，ヒトにお

いてβ_3受容体に選択的に刺激作用を有することより，肥満症，高血糖症等に有用であることが記載されている。しかしながら，これらの化合物のインスリン分泌促進作用並びにインスリン感受性増強作用については具体的に開示がない。

【０００４】

【化３】



（式中の記号は，上記公報参照。）

【０００５】

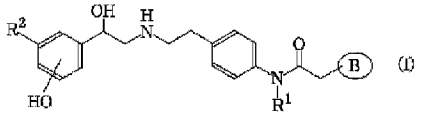
【発明が解決しようとする課題】前述のように，いまなお，臨床的に有用性の高い新しいタイプの糖尿病治療剤の創製が切望されている。

【０００６】

【課題を解決するための手段】本発明者等は，インスリン分泌促進作用とインスリン感受性増強作用を併せ持つ化合物を鋭意探索したところ，新規なフェネタノール誘導体が良好なインスリン分泌促進作用とインスリン感受性増強作用の両作用，さらには選択的なβ_3受容体刺激作用を有することを見いだし本発明を完成した。すなわち，本発明はインスリン分泌促進作用とインスリン感受性増強作用を併せ持ち，さらに選択的β_3受容体刺激作用に基づく抗肥満作用及び抗高脂血症作用をも併せ持つことから，糖尿病の治療に有用な，下記一般式（Ｉ）で示されるフェネタノール誘導体又はその塩に関する。また，当該フェネタノール誘導体を含有する医薬，殊に，当該フェネタノール誘導体を有効成分とする糖尿病治療剤に関する。

【０００７】

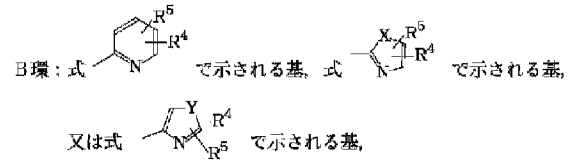
【化４】



（上記式中の記号は，それぞれ以下の意味を有する。

【０００８】

【化５】



Ｘ，Ｙ：酸素原子，硫黄原子又は式NR^6で示される基，

R^1：水素原子又は低級アルキル基，

R^2：水素原子，低級アルキル基，メチルスルホナミド基又は式$-NHCOR^3$で示される基，

R^3：水素原子，低級アルキル基，モノ－若しくはジ－低級アルキルアミノ基，アリール基又はアラルキル基，

R^4，R^5：同一又は異なって水素原子，低級アルキル基又はアミノ基，

R^6：水素原子，低級アルキル基又はアラルキル基）

【０００９】

【発明の実施の形態】一般式（Ｉ）の化合物をさらに説明すると，次の通りである。本明細書の一般式の定義において，「低級」なる用語は，特に断らない限り，炭素数が１乃至６個の直鎖状又は分岐状の炭素鎖を意味する。「低級アルキル基」とは，炭素数が１～６個の直鎖又は分岐のアルキル基であり，具体的には，例えばメチル基，エチル基，プロピル基，イソプロピル基，ブチル基，イソブチル基，ｓｅｃ－ブチル基，ｔｅｒｔ－ブチル基，ペンチル基，イソペンチル基，ネオペンチル基，ｔｅｒｔ－ペンチル基，１－メチルブチル基，２－メチルブチル基，１，２－ジメチルプロピル基，ヘキシル基，イソヘキシル基，１－メチルペンチル基，２－メチルペンチル基，３－メチルペンチル基，１，１－ジメチルブチル基，１，２－ジメチルブチル基，２，２－ジメチルブチル基，１，３－ジメチルブチル基，２，３－ジメチルブチル基，３，３－ジメチルブチル基，１－エチルブチル基，２－エチルブチル基，１，１，２－トリメチルプロピル基，１，２，２－トリメチルプロピル基，１－エチル－１－メチルプロピル基，１－エチル－２－メチルプロピル基等が挙げられる。「アリール基」は，芳香族炭化水素基を意味し，炭素数６乃至１４個のアリール基が好ましく，具体的には，フェニル基，トリル基，キシリル基，ビフェニル基，ナフチル基，インデニル基，アントリル基，フェナントリル基等が挙げられる。これらのうちフェニル基又はナフチル基が特に好ましい。

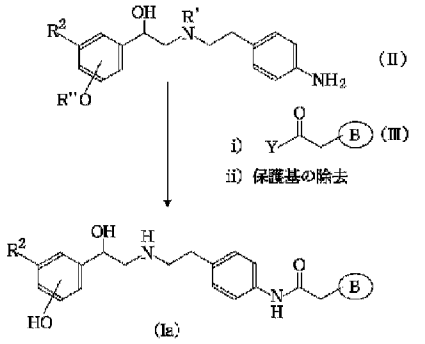
【００１０】「アラルキル基」とはアリール基を置換基として有している低級アルキル基であり具体的には，ベンジル基，フェネチル基，メチルベンジル基，メチルフェネチル基，ジメチルベンジル基，ジメチルフェネチル基，ベンズヒドリル基，ナフチルメチル基，ナフチルエチル基，アントリルメチル基，アントリルエチル基，トリチル基，フェナントリルメチル基，フェナントリルエチル基等が挙げられ，好ましくはベンジル基である。「モノ－若しくはジ－低級アルキルアミノ基」とは，ア

ミノ基中の水素原子１乃至２個が上記低級アルキル基で置換されたアミノ基を意味し，具体的には，例えば，メチルアミノ基，エチルアミノ基，プロピルアミノ基，ジメチルアミノ基，ジエチルアミノ基，ジプロピルアミノ基等が挙げられる。本発明化合物（Ｉ）は，１個乃至複数個の不斉炭素原子を有する場合があり，これに基づく（Ｒ）体，（Ｓ）体等の光学異性体，ラセミ体，ジアステレオマー等が存在する。本発明は，これらの異性体の分離されたものあるいは混合物を全て包含する。さらに，本発明には化合物（Ｉ）の水和物，エタノール等の溶媒和物や結晶多形の物質も包含される。本発明化合物（Ｉ）は酸と塩を形成する場合がある。かかる塩としては塩酸，臭化水素酸，ヨウ化水素酸，硫酸，硝酸，リン酸等の鉱酸や，ギ酸，酢酸，プロピオン酸，シュウ酸，マロン酸，コハク酸，フマール酸，マレイン酸，乳酸，リンゴ酸，クエン酸，酒石酸，炭酸，ピクリン酸，メタンスルホン酸，エタンスルホン酸，グルタミン酸等の有機酸との酸付加塩を挙げることができる。

【００１１】（製造法）本発明化合物及びその塩は，その基本骨格あるいは置換基の種類に基づく特徴を利用し，種々の合成法を適用して製造することができる。以下にその代表的な製造法について説明する。

第一製法

【化６】



（式中，R^2，Ｂ環は前記の意味を示す。Ｒ’はアミノ基の保護基を，Ｒ’’は水酸基の保護基を，Ｙは水酸基，低級アルコキシ基又はハロゲン化物のような脱離基を示す。）

本製法は化合物（ＩＩ）と化合物（ＩＩＩ）とをアミド化反応させ，次に保護基を除去して本発明化合物（Ｉａ）を合成する製法である。本製法のアミド化は常法により行うことができる。溶媒は化合物（ＩＩＩ）のＹによって異なるが，おもに不活性溶媒又はアルコール系（イソプロパノール）の溶媒が適用できる。ここで，Ｙが水酸基である場合は上記溶媒中，縮合剤の存在下で反応させる方法が適用できる。縮合剤としては，Ｎ，Ｎ’－ジシクロヘキシルカルボジイミド（ＤＣＣ），１－エチル－３－（３－ジメチルアミノプロピル）カルボジイミド（ＥＤＣＩ），１，１’－カルボニルジイミダゾール（ＣＤＩ），ジフェニルホスホリルアジド（ＤＰＰＡ）やジエチルホスホリルシアニド（ＤＥＰＣ）等が挙げられる。Ｙが低級アルコキシ基である場合はそのままで，又は前記不活性溶媒中，加熱下乃至加熱還流下で反応させる方法が適用できる。Ｙがハロゲン化物である場合は前記不活性溶媒中，塩基存在下で反応させる方法が適用できる。

【００１２】前記不活性溶媒としては，例えばジメチルホルムアミド（ＤＭＦ），ジメチルアセトアミド，テトラクロロエタン，ジクロロメタン，ジクロロエタン，クロロホルム，四塩化炭素，テトラヒドロフラン，ジオキサン，ジメトキシエタン，酢酸エチル，ベンゼン，トルエン，キシレン，アセトニトリル，ジメチルスルホキシド等やこれらの混合溶媒が挙げられるが，種々の反応条件に応じて適宜選択される。塩基としては水酸化ナトリウム，水酸化カリウム，炭酸ナトリウム又は炭酸カリウム等の無機塩基，Ｎ－メチルモルホリン，トリエチルアミン，ジイソプロピルエチルアミン又はピリジン等の有機塩基が挙げられる。Ｒ’’の水酸基の保護基として当業者が通常使用する水酸基の保護基を意味し代表的なものとしては，メチル基，エチル基，プロピル基，イソプロピル基，ｔｅｒｔ－ブチル基等の低級アルキル基，低級アルコキシ低級アルキル基，低級アルコキシ低級アルコキシ低級アルキル基，ベンジル基等のアリールメチル基，ベンゾイル基若しくは低級アルカノイル基等のアシル基，トリアルキルシリル基等が挙げられる。Ｒ’のアミノ基の保護基は当業者が通常使用するアミノ基の保護基を意味し，代表的なものとしてはホルミル基，アセチル基，プロピオニル基，メトキシアセチル基，メトキシプロピオニル基，ベンゾイル基，チエニルアセチル基，チアゾリルアセチル基，テトラゾリルアセチル基，チアゾリルグリオキシロイル基，チエニルグリオキシロイル基等のアシル基，メトキシカルボニル基，エトキシカルボニル基，ｔｅｒｔ－ブトキシカルボニル基等の低級アルコキシカルボニル基，ベンジルオキシカルボニル基，ｐ－ニトロベンジルオキシカルボニル基等のアラルキルオキシカルボニル基，メタンスルホニル基，エタンスルホニル基等の低級アルカンスルホニル基，ベンジル基，ｐ－ニトロベンジル基，ベンズヒドリル基，トリチル基等のアラルキル基，トリメチルシリル基等のトリ低級アルキルシリル基等が挙げられる。

【００１３】本製法における保護基の除去は常法に従えばよく，例えば，水酸基の保護基の除去は，以下のように行うことができる。

１）接触還元：本方法は，パラジウム－炭素，水酸化パラジウム－炭素，又はラネーニッケル等の触媒存在下，氷冷下乃至加温下で行うことができる。

２）酸あるいは塩基存在下での加水分解：本方法は炭酸ナトリウム，水酸化ナトリウム等の塩基，又はトリフルオロ酢酸，塩酸等の酸の存在下で加水分解する常法が適

用でき，氷冷下乃至１００℃の温度条件下で実施するのが好適である。

３）液安還元：本方法は水酸基の保護基を有する化合物を液体アンモニア中に加え，次いで金属ナトリウムを添加し，撹拌することにより行うことができる。

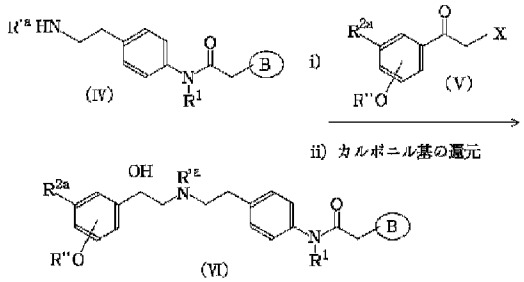
４）脱シリル化反応：本方法は，水酸基の保護基を有する化合物を前記不活性溶媒中，テトラｎ－ブチルアンモニウムフルオリド等の有機フッ素化合物あるいはフッ化ナトリウム，フッ化カリウム，フッ化水素酸等の無機フッ素化合物と反応させることにより行うことができる。

Ｒ’のアミノ基の保護基の除去は，ｉ）ベンズヒドリル基，ｐ－メトキシベンジル基，トリチル基，ｔｅｒｔ－ブトキシカルボニル基，ホルミル基等の保護基であるときは，ギ酸，トリフルオロ酢酸，トリフルオロ酢酸－アニソール混液，臭化水素酸－酢酸混液，塩酸－ジオキサン混液等の酸で処理する方法，ｉｉ）ベンジル基，ｐ－ニトロベンジル基，ベンズヒドリル基，トリチル基等であるときは，パラジウム－炭素又は水酸化パラジウム－炭素を用いる接触還元方法，ｉｉｉ）保護基がトリ低級アルキルシリル基等であるときは，水で処理する方法，フッ素化物アニオン（テトラｎ－ブチルアンモニウムフルオリド，フッ化ナトリウム，フッ化カリウム，フッ化水素酸）等により容易に除去される。

【００１４】第二製法

第一工程

【化７】



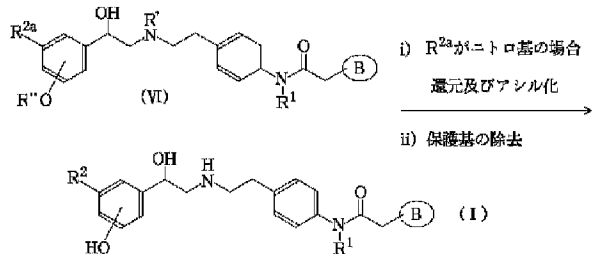
（式中，Ｒ’，Ｂ環，Ｒ’’は前記の意味を示す。Ｒ’ａは水素原子又はアラルキル系の保護基を示す。Ｒ２ａは水素原子，低級アルキル基，メチルスルホナミド基又はニトロ基を，Ｘはハロゲン原子をそれぞれ意味する。）

本工程は化合物（ＩＶ）と化合物（Ｖ）を反応させ，更に還元反応に付してカルボニル基を還元して化合物（ＶＩ）を得る工程である。

ｉ）アミン化合物（ＩＶ）及び化合物（Ｖ）をそのまま，あるいは不活性溶媒中で，ｉ）加熱下乃至加熱還流下，１～２４時間反応させ，さらにｉｉ）還元反応に付して化合物（ＶＩ）を得ることができる。不活性溶媒は例えばアセトニトリル，テトラヒドロフラン，２－ブタノン，ジメチルスルホキシド又はＮ－メチルピロリドンが挙げられる。また，化合物（Ｖ）とアミン化合物（ＩＶ）の反応の際，重炭酸ナトリウム又はジイソプロピルエチルアミンのような塩基を反応混合物に添加してもよい。還元反応は，還元剤の存在下，前記不活性溶媒又はアルコール系の溶媒中，撹拌しながら行うことができる。還元剤としては，例えば水素化ホウ素ナトリウム，水素化シアノホウ素ナトリウム，水素化リチウムアルミニウム等が用いられる。更に本工程においてはアミン化合物（ＩＶ）のアミノ基が保護されていないもの（Ｒ’＝Ｈ）をそのまま，ｉ），ｉｉ）の工程を経てからのち，アミノ基を保護し，化合物（ＶＩ）を製造してもよく，また，アミン化合物（ＩＶ）のアミノ基をアラルキル系保護基で保護した後にｉ），ｉｉ）の工程を経て化合物（ＶＩ）を製造してもよい。

【００１５】第二工程

【化８】



（式中，Ｒ１，Ｒ２，Ｒ２ａ，Ｒ’，Ｒ’’，Ｂ環は前記の意味を示す。）

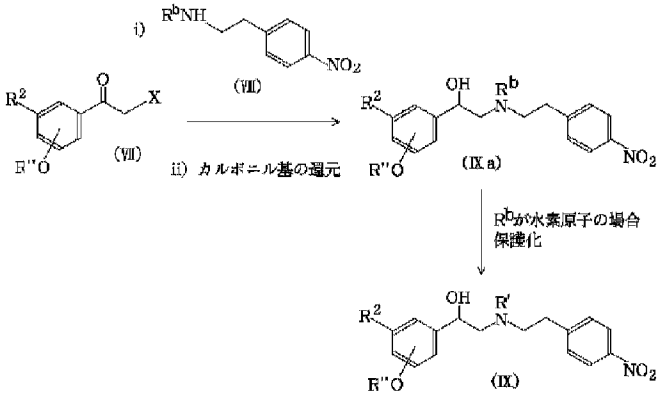
本工程はＲ２ａがニトロ基の場合はアミノ基に還元し，更にアシル化を行い，保護基を除去して化合物（Ｉ）を得る工程である。Ｒ２ａが水素原子，低級アルキル基又はメチルスルホナミド基である場合は，そのまま保護基を除

去して化合物（Ｉ）を得ることができる。R^{2a}のニトロ基の還元は鉄，亜鉛等を用いる金属還元等により常法で行うことができる。また，アミノ基のアシル化は，常法によりカルボン酸化合物とのアミド化反応により行われ，例えば酸無水物，酸ハライド，活性エステル等のカルボン酸の反応性誘導体を用いて容易に行うことができる。保護基の除去は，前記第一製法と同様に行うことができる。尚，上記製法において，再結晶化，粉砕，分取薄層クロマトグラフィー，Ｗ．Ｃ．Ｓｔｉｌｌら，Ｊ．Ｏｒｇ．Ｃｈｅｍ．４３，２９２３（１９７８）に記載されているようなシリカゲルフラッシュクロマトグラフィー，中圧液体クロマトグラフィー及びＨＰＬＣにより，望ましくない副生成物質を除き生成物質を精製することもできる。ＨＰＬＣで生成される化合物は，対応する塩として単離することができる。前記製法で用いる原料化合物は当業者に公知の方法で容易に製造することができる。以下にその代表的な製造法を示す。

【００１６】（原料化合物（ＩＩ）の製法）

第一工程

【化９】

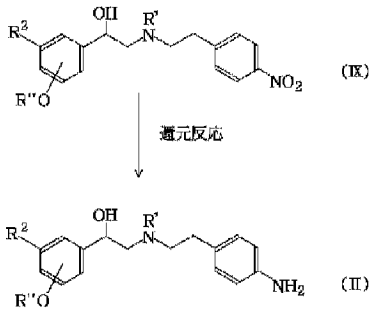


（式中，R^2，Ｒ’，Ｒ’’は前記の意味を示す。R^bは水素原子又はアラルキル系のアミノ基の保護基を示す。）

本工程は化合物（ＶＩＩ）と化合物（ＶＩＩＩ）とを反応させることにより，化合物（ＩＸ）を合成する工程である。ここで，本工程のアラルキル系のアミノ基の保護基としては，ベンジル基，ｐ－ニトロベンジル基，ベンズヒドリル基等が挙げられる。本工程は前記第二製法第一工程と同様にして行うことができ，反応温度，溶媒等の反応条件についても同様である。また，R^bが水素原子の場合は，ジｔｅｒｔ－ブチルジ炭酸エステル等を用いて，常法によりアミノ基の保護化を行うことができる。

【００１７】第二工程

【化１０】

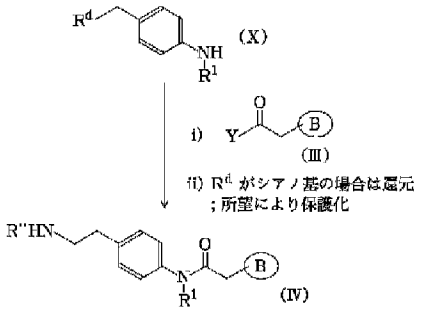


（式中，R^2，Ｒ’，Ｒ’’は前記の意味を示す。）

本工程は化合物（ＩＸ）を還元反応させることにより化合物（ＩＩ）を合成する工程である。還元反応は金属還元あるいは接触還元等により行うことができる。還元条件によってはＲ’が水素原子となる場合があるが，常法により再度保護化を行うことができる。

【００１８】（原料化合物（ＩＶ）の製法）

【化１１】



（式中，R^1，Ｒ’’，Ｙ及びＢ環は前記の意味を示す。R^dはシアノ基又は保護されたアミノメチル基を意味する。）

本工程は化合物（Ｘ）と化合物（ＩＩＩ）とを反応させ，アミド化する工程である。反応は，前記第一製法と同様にして行うことができる。尚，R^dがシアノ基である場合は，更に還元反応を行い，所望により保護化を行って化合物（ＩＶ）を得ることができる。還元は常法の接触還元又は塩化コバルト及び水素化ホウ素ナトリウム等で還元する方法を適用できる。このようにして製造さ

れた本発明化合物（Ｉ）は，遊離化合物，常法による造塩処理を施したその塩，水和物，エタノール等の各種溶媒和物，あるいは結晶多形等として単離・精製される。単離・精製は抽出，濃縮，留去，結晶化，沪過，再結晶，各種クロマトグラフィー等の通常の化学操作を適用して行われる。各種の異性体は異性体間の物理化学的な差を利用して常法により単離できる。例えば，ラセミ化合物は一般的なラセミ分割法により（例えば，一般的な光学活性酸（酒石酸等）とのジアステレオマー塩に導き，光学分割する方法等）立体化学的に純粋な異性体に導くことができる。又，ジアステレオマーの混合物は常法，例えば分別結晶化又はクロマトグラフィー等により分離できる。また，光学活性な化合物は適当な光学活性な原料を用いることにより製造することもできる。

【００１９】

【発明の効果】本発明の一般式（Ｉ）で示されるフェネタノール誘導体又はその塩は，インスリン分泌促進作用とインスリン感受性増強作用を併せ持ち，さらに選択的なβ_3受容体刺激作用を有することより，糖尿病の治療剤として有用である。本発明化合物は，後記耐糖能試験及びインスリン抵抗性モデル動物における血糖低下試験において確認されたように，良好なインスリン分泌促進作用とインスリン感受性増強作用を併せ持ち，糖尿病においてその有用性が期待されるものである。本発明化合物のインスリン分泌促進作用及びインスリン感受性増強作用発現のメカニズムは，β_3受容体刺激作用が関与している可能性も考えられるが，その他のメカニズムによるものである可能性も有り，その詳細は未解明である。本発明化合物のβ_3受容体刺激作用は，ヒトにおいてβ_3受容体に選択的である。β_3受容体の刺激は脂肪分解（脂肪組織トリグリセライドのグリセロールと遊離脂肪酸とへの分解）を刺激し，これによって脂肪塊の消失を促進することが知られている。従って本発明化合物は，β_3受容体刺激による抗肥満作用，抗高脂血作用（例えば，トリグリセライド低下作用，コレステロール低下作用，ＨＤＬコレステロール上昇作用等）を有し，肥満症，高脂血症（例えば高トリグリセライド血症，高コレステロール血症，低ＨＤＬ血症等）の予防・治療剤として有用である。これらの疾患は，糖尿病における増悪因子であることが知られており，これらの疾患の改善は糖尿病の予防・治療にも有用である。

【００２０】また，本発明化合物は，肥満症，高脂血症の症状を低減することにより症状の改善の図れるその他の疾患，例えば，動脈硬化症，心筋梗塞，狭心症等の虚血性心疾患，脳梗塞等の脳動脈硬化症あるいは動脈瘤等の予防・治療剤としても有用である。さらに，本発明化合物の選択的β_3受容体刺激作用は，β_3受容体の刺激により改善することが提唱されているいくつかの疾患の予防・治療にも有用である。これらの疾患の例を以下に示す。β_3受容体は非括約筋性平滑筋収縮の運動性を媒介することが提唱されており，選択的β_3受容体刺激作用は心臓血管作用を伴うことなく腸運動性の薬理的制御を助けると考えられることより，腸運動の異常により生じる疾患，例えば，過敏性腸症候群のような種々の胃腸疾患の治療に有用である可能性を有する。また，消化性潰瘍，食道炎，胃炎及び十二指腸炎（Ｈ．ｐｙｌｏｒｉにより誘発されるものを含む），腸潰瘍（炎症性腸疾患，潰瘍性結腸炎，クローン病及び直腸炎）及び胃腸潰瘍の治療に有用である。さらにβ_3受容体は，肺におけるある種の感覚繊維の神経ペプチドの放出の阻害に作用を及ぼすことが示されている。感覚神経は咳を含めた気道の神経原性炎症に重要な役割を演じるので，本発明の特異的β_3作動薬は喘息のような神経原性炎症の治療に有用であってしかも心肺系への作用が少ない。β_3アドレナリン受容体はさらに脳におけるβ_3受容体の刺激により選択的抗鬱作用を生じ得るので，従って本発明の化合物は抗鬱薬として有用である可能性を有する。本発明化合物のβ受容体に対する作用はヒトの細胞を用いた実験によって，β_3受容体選択的であることを確認しており，他のβ_3受容体刺激に起因する副作用は低いか若しくは有しないものである。

【００２１】本発明化合物の効果は以下の試験により確認された。

１．ｋｋマウス（インスリン抵抗性モデル：肥満，高血糖）における血糖低下試験

雄性ｋｋマウス（血糖値２００ｍｇ／ｄｌ以上）を用いて，摂食下で血糖値を測定後，無作為に群分けした。被験薬物は１日１回，４日間，強制経口投与若しくは皮下投与し，最終投与後１５～１８時間後の血糖値を投与前値と比較した（ｎ＝６）。血糖値はマウスの尾静脈より，ガラス毛細管（ヘパリン処理済み）を用いて採血し，除タンパク処理後，上清中のグルコース量（ｍｇ／ｄｌ）をグルコースオキシターゼ法により比色定量した。本発明化合物は経口投与，皮下投与のいずれにおいても，比験薬物投与前に比して有意に血糖値を低下させた。この結果より，本発明化合物が良好なインスリン感受性増強作用を有することが示された。

【００２２】２．正常ラットにおける耐糖能試験

７週齢の雄性ＳＤ系ラットを用いて，一昼夜絶食後，無作為に群分けし，oralglucose tolerance test（ＯＧＴＴ）を行った（ｎ＝４）。被験化合物は，グルコース（２ｇ／ｋｇを経口投与）の投与３０分前に経口投与あるいは皮下投与した。血糖値はラットをペントバルビタール（６５ｍｇ／ｋｇ）麻酔下で，ヘパリン処理したガラスシリンジを用いて腹大静脈より採血し，除タンパク処理後，上清中のグルコース量（ｍｇ／ｄｌ）をグルコースオキシターゼ法により比色定量した。血中インスリン値は，血漿中のインスリン量（ｎｇ／ｍｌ）を Radio imu noassay（ＲＩＡ）法により定量した。本発明化合物を経口投与あるいは皮下投与した群においては，薬剤

未処理群に比して血中インスリン値の有意な増加が観察された。また，グルコース投与後の血糖値の上昇も有意に抑制された。これらの結果より，本発明化合物は良好なインスリン分泌促進作用を有し，また，良好な高血糖抑制作用を有することが示された。

【００２３】３．ヒトβ_3，β_2及びβ_1－受容体刺激試験

ヒトβ_3－刺激作用はＳＫ－Ｎ－ＭＣ細胞系（permanent　にヒトβ_3及びヒトβ_1受容体を発現した細胞を購入）を用い，ヒトβ_2，β_1－刺激作用はＣＨＯ細胞系（ヒトβ_2，β_1受容体をそれぞれ強制発現させた細胞を購入）を用いて検討した。化合物（10^{-10}～10^{-4}Ｍ）の刺激作用は，各細胞を２４ｗｅｌｌプレート上に10^5個／ｗｅｌｌで培養し，２日後　subconfluent　な状態で，cyclic　ＡＭＰ（ｃＡＭＰ）の産生活性を指標に検討した。尚ヒトβ_3－刺激作用は，β_1－受容体遮断薬（ＣＧＰ２０７１２Ａ，10^{-6}Ｍ）存在下で検討した。各細胞中のｃＡＭＰ産生量（ｐｍｏｌ／ｍｌ）は，^{125}Ｉ－ｃＡＭＰを用いてＲＩＡ法により測定した。各化合物の作用強度は，得られた用量反応曲線からｐＤ２値及び最大活性（Ｉ．Ａ．（％），イソプロテレノール10^{-6}Ｍの最大反応を１００％とする）を算出し比較した。本発明化合物は，ヒトβ_3受容体に対して選択的に刺激作用を有することが確認された。本発明化合物又はその塩の一種又は二種以上を有効成分として含有する医薬組成物は，通常の製薬学的に許容される担体を用いて調製される。本発明における医薬組成物の投与は経口投与又は注射剤，座剤，経皮剤，吸入剤若しくは膀胱注入等による非経口投与のいずれの形態であってもよい。投与量は症状，投与対象の年齢，性別等を考慮して個々の場合に応じて適宜決定されるが，通常経口投与の場合成人１日当たり０．０１ｍｇ／ｋｇ乃至１００ｍｇ／ｋｇ程度であり，これを１回で，あるいは２～４回に分けて投与する。また，症状によって静脈投与される場合は，通常成人１回当たり，０．００１ｍｇ／ｋｇ乃至１０ｍｇ／ｋｇの範囲で１日に１回乃至複数回投与される。製剤用の担体としては固体又は液体状の非毒性医薬用物質が挙げられる。

【００２４】本発明による経口投与のための固体組成物としては，錠剤，丸剤，カプセル剤，散剤，顆粒剤等が用いられる。このような固体組成物においては，ひとつ又はそれ以上の活性物質が，少なくともひとつの不活性な希釈剤，例えば乳糖，マンニトール，ブドウ糖，ヒドロキシプロピルセルロース，微結晶セルロース，デンプン，ポリビニルピロリドン，寒天，ペクチン，メタケイ酸アルミン酸マグネシウム，アルミン酸マグネシウムと混合される。組成物は，常法に従って，不活性な希釈剤以外の添加剤，例えばステアリン酸マグネシウムのような潤滑剤や繊維素グリコール酸カルシウムのような崩壊剤，ラクトースのような安定化剤，グルタミン酸又はアスパラギン酸のような溶解補助剤を含有していてもよい。錠剤又は丸剤は必要によりショ糖，ゼラチン，ヒドロキシプロピルセルロース，ヒドロキシプロピルメチルセルロースフタレート等の糖衣又は胃溶性若しくは腸溶性物質のフィルムで被膜してもよい。経口投与のための液体組成物は，薬剤的に許容される乳濁剤，溶液剤，懸濁剤，シロップ剤，エリキシル剤等を含み，一般的に用いられる不活性な希釈剤，例えば精製水，エタノールを含む。この組成物は不活性な希釈剤以外に湿潤剤，懸濁剤のような補助剤，甘味剤，風味剤，芳香剤，防腐剤を含有していてもよい。非経口投与のための注射剤としては，無菌の水性又は非水性の溶液剤，懸濁剤，乳濁剤を包含する。水性の溶液剤，懸濁剤としては，例えば注射剤用蒸留水及び生理食塩水が含まれる。非水溶性の溶液剤，懸濁剤としては，例えばプロピレングリコール，ポリエチレングリコール，カカオバター，オリーブ油，ゴマ油のような植物油，エタノールのようなアルコール類，アラビアゴム，ポリソルベート８０（商品名）等がある。このような組成物は，さらに等張化剤，防腐剤，湿潤剤，乳化剤，分散剤，安定化剤（例えば，ラクトース），溶解補助剤（例えば，グルタミン酸，アスパラギン酸）のような補助剤を含んでもよい。これらは例えばバクテリア保管フィルターを通す沪過，殺菌剤の配合又は照射によって無菌化される。これらはまた無菌の固体組成物を製造し，使用前に無菌水又は無菌の注射用溶媒に溶解して使用することもできる。

【００２５】

【実施例】以下，実施例に基づき本発明をさらに詳細に説明する。本発明化合物は，下記実施例に記載の化合物に限定されるものではなく，また，前記一般式（Ｉ）に示される化合物，その塩，その水和物，その幾何並びに光学異性体，結晶多形の全てを包含するものである。さらに，本発明で使用される原料が新規な場合を，参考例として説明する。

【００２６】参考例１

Ｎ－ベンジル－２－（４－ニトロフェニル）エチルアミン８．４８ｇ，ジイソプロピルエチルアミン５．２ｇ，４’－ベンジルオキシフェナシルブロミド１２ｇ，２－ブタノン２００ｍｌを順次加え，反応混合物を１時間加熱還流した。溶媒を減圧下留去した後，残渣を酢酸エチルで希釈し飽和炭酸水素ナトリウム水溶液，飽和食塩水で順次洗浄後，有機層を無水硫酸マグネシウムで乾燥し，溶媒を減圧下留去した。得られた残渣をメタノール１００ｍｌと少量のテトラヒドロフランにて溶解した。この反応溶液に氷冷下，水素化ホウ素ナトリウム２ｇを加えた。反応溶液を室温にて１時間攪拌した後，溶媒を減圧下留去した。残渣に水，酢酸エチルを加えた後，有機層を飽和炭酸水素ナトリウム水溶液で洗浄した。有機層を無水硫酸マグネシウムで乾燥後，溶媒を減圧下留去した。得られた残渣をシリカゲルカラムクロマトグラフ

ィー（溶出液；ヘキサン／酢酸エチル＝３／１）にて精製することにより，２－［Ｎ－ベンジル－Ｎ－［２－（４－ニトロフェニル）エチル］アミノ］－１－（４－ベンジルオキシフェニル）エタノール１５．２ｇを得た。

【００２７】参考例２

２－［Ｎ－ベンジル－Ｎ－［２－（４－ニトロフェニル）エチル］アミノ］－１－（４－ベンジルオキシフェニル）エタノール１４．８ｇのメタノール２５０ｍｌ溶液に２Ｎ塩酸４０ｍｌ，鉄粉８．６ｇを加えた。反応混合物を２時間加熱還流した後，不溶物をセライトを用いて沪去した。沪液を減圧下濃縮した後，残渣に１Ｎ水酸化ナトリウム水溶液及びクロロホルムを加えた後，再び不溶物をセライトを用いて沪去した。有機層を無水硫酸マグネシウムで乾燥した後，溶媒を減圧下留去した。得られた残渣をシリカゲルカラムクロマトグラフィー（溶出液；ヘキサン／酢酸エチル＝２／１）にて精製することにより，２－［Ｎ－ベンジル－Ｎ－［２－（４－アミノフェニル）エチル］アミノ］－１－（４－ベンジルオキシフェニル）エタノール１１．７ｇを得た。

【００２８】参考例３

２－［Ｎ－ベンジル－Ｎ－［２－（４－アミノフェニル）エチル］アミノ］－１－（４－ベンジルオキシフェニル）エタノール５１０ｍｇ及び２－（３－メチルピリジン－２－イル）酢酸エチル３１５ｍｇのキシレン１０ｍｌ溶液を１３時間加熱還流した。溶媒を減圧下留去し，残渣をシリカゲルカラムクロマトグラフィー（溶出液；クロロホルム／メタノール＝１００／１）にて精製することにより，４’－［２－［Ｎ－ベンジル－Ｎ－［２－（４－ベンジルオキシフェニル）－２－ヒドロキシエチル］アミノ］エチル］－２－（３－メチルピリジン－２－イル）酢酸アニリド２５６ｍｇを得た。

【００２９】参考例４

４’－［２－［Ｎ－ベンジル－Ｎ－［２－（４－ベンジルオキシフェニル）－２－ヒドロキシエチル］アミノ］エチル］－２－（４－メチルピリジン－２－イル）酢酸アニリドを参考例３と同様の方法にて合成した。

【００３０】参考例５

４’－［２－［Ｎ－ベンジル－Ｎ－［２－（４－ベンジルオキシフェニル）－２－ヒドロキシエチル」アミノ」エチル］－２－（３－メチルピリジン－６－イル）酢酸アニリドを参考例３と同様の方法にて合成した。

【００３１】参考例６

４’－［２－［Ｎ－ベンジル－Ｎ－［２－（４－ベンジルオキシフェニル）－２－ヒドロキシエチル］アミノ］エチル］－２－（２－メチルピリジン－６－イル）酢酸アニリドを参考例３と同様の方法にて合成した。

【００３２】参考例７

２－（２－ピリジル）酢酸メチル５．１２ｇ及び４－アミノフェニルアセトニトリル５．１４ｇのキシレン５０ｍｌ溶液を２４時間加熱還流した。溶媒を減圧下留去し，得られた粗結晶をジエチルエーテルにて洗浄することにより，４’－シアノメチル－２－（２－ピリジル）酢酸アニリド５．６５ｇを得た。

【００３３】参考例８

４’－シアノメチル－２－（２，４－ジメチルピリジン－６－イル）酢酸アニリドを参考例７と同様の方法にて合成した。

【００３４】参考例９

４’－シアノメチル－２－（２－ピリジル）酢酸アニリド５．１２ｇのテトラヒドロフラン５０ｍｌ，エタノール４０ｍｌ溶液にラネーニッケル及び濃アンモニア水２０ｍｌを加えた。反応溶液を常圧水素雰囲気下，室温にて３時間撹拌した。不溶物をセライトを用いて除去した後，溶媒を減圧下留去した。得られた残渣にトルエン５０ｍｌ及びベンズアルデヒド２．１ｍｌを加えた。この反応混合物をディーンスターク装置により水を除去しながら３時間加熱還流した。溶媒を減圧下留去した後，得られた残渣のメタノール５０ｍｌ溶液に氷冷下水素化ホウ素ナトリウム１．０ｇを加えた。反応液を室温にて１時間撹拌した後，溶媒を減圧下留去した。残渣にクロロホルム，飽和炭酸水素ナトリウム水溶液を加え，有機層を無水硫酸マグネシウムで乾燥後，溶媒を減圧下留去した。得られた残渣をシリカゲルカラムクロマトグラフィー（溶出液；クロロホルム／メタノール＝５０／１）で精製することにより，４’－（２－ベンジルアミノエチル）－２－（２－ピリジル）酢酸アニリド４．６３ｇを得た。

【００３５】参考例１０

４’－（２－ベンジルアミノエチル）－２－（２，４－ジメチルピリジン－６－イル）酢酸アニリドを参考例９と同様の方法にて合成した。

【００３６】参考例１１

４’－（２－ベンジルアミノエチル）－２－（２－ピリジル）酢酸アニリド３３８ｍｇ，４’－ベンジルオキシフェナシルブロミド２９９ｍｇ，ジイソプロピルエチルアミン０．１７５ｍｌを２－ブタノン２０ｍｌに懸濁させた反応混合物を３時間加熱還流した。不溶物を沪去し，沪液を減圧下濃縮した。得られた残渣のメタノール１０ｍｌ溶液に氷冷下水素化ホウ素ナトリウム１２０ｍｇを加えた。反応溶液を室温にて１時間撹拌した後，溶媒を減圧下留去した。残渣にクロロホルム，飽和炭酸水素ナトリウム水溶液を加え，有機層を無水硫酸マグネシウムで乾燥後，溶媒を減圧下留去した。残渣をシリカゲルカラムクロマトグラフィー（溶出液；クロロホルム／メタノール＝１００／１）で精製することにより，４’－［２－［Ｎ－ベンジル－Ｎ－［２－（４－ベンジルオキシフェニル）－２－ヒドロキシエチル］アミノ］エチル］－２－（２－ピリジル）酢酸アニリド２８３ｍｇを得た。

【００３７】参考例１２
４’－［２－［Ｎ－ベンジル－Ｎ－［２－（４－ベンジルオキシフェニル）－２－ヒドロキシエチル］アミノ］エチル］－２－（２，４－ジメチルピリジン－６－イル）酢酸アニリドを参考例１１と同様の方法にて合成した。
【００３８】参考例１３
４’－［２－［Ｎ－ベンジル－Ｎ－［２－（３－ベンジルオキシフェニル）－２－ヒドロキシエチル］アミノ］エチル］－２－（２－ピリジル）酢酸アニリドを参考例１１と同様の方法にて合成した。
【００３９】参考例１４
４’－［２－［Ｎ－ベンジル－Ｎ－［２－（２－ベンジルオキシフェニル）－２－ヒドロキシエチル］アミノ］エチル］フェニル］－２－（２－ピリジル）酢酸アニリドを参考例１１と同様の方法にて合成した。
【００４０】参考例１５
４－メチルアミノフェニルアセトニトリル５．１４ｇ，２－ピリジル酢酸塩酸塩１２．１ｇ，１－エチル－３－（３－ジメチルアミノプロピル）カルボジイミド塩酸塩１０．５ｇ，１－ヒドロキシベンゾトリアゾール７．６２ｇにテトラヒドロフラン５０ｍｌ，ジメチルホルムアミド１５ｍｌを順次加えた。反応溶液を室温にて２．５時間撹拌した後，溶媒を減圧下留去した。残渣を酢酸エチルで希釈した後，有機層を飽和炭酸水素ナトリウム水溶液で洗浄し，無水硫酸マグネシウムで乾燥した。溶媒を減圧下留去することにより得られた残渣をシリカゲルカラムクロマトグラフィー（溶出液；クロロホルム／メタノール＝１００／１→２０／１））にて精製し，４’－シアノメチル－Ｎ－メチル－２－（２－ピリジル）酢酸アニリド６．０７ｇを得た。
【００４１】参考例１６
４’－（２－ベンジルアミノエチル）－Ｎ－メチル－２－（２－ピリジル）酢酸アニリドを参考例９と同様の方法にて合成した。
【００４２】参考例１７
４’－［２－［Ｎ－ベンジル－Ｎ－［２－（４－ベンジルオキシフェニル）－２－ヒドロキシエチル］アミノ］エチル］－Ｎ’－メチル－２－（２－ピリジル）酢酸アニリドを参考例１１と同様の方法にて合成した。
【００４３】参考例１８
Ｎ－（５－アセチル－２－ベンジルオキシフェニル）メタンスルホンアミド１．０３ｇのテトラヒドロフラン２０ｍｌ溶液にフェニルトリメチルアンモニウムトリブロミド１．２８ｇを加えた。反応溶液を室温にて０．７５時間撹拌した後，不溶物を沪去した。沪液を減圧下濃縮し，得られた粗結晶をクロロホルム－ヘキサンより結晶化した。得られた結晶及び４’－（２－ベンジルアミノエチル）－２－（２－ピリジル）酢酸アニリド１．１１ｇの混合物に２－ブタノン２０ｍｌ，ジイソプロピルエチルアミン０．５６ｍｌを順次加えた。反応混合物を１時間加熱還流し，不溶物を沪去した。沪液を減圧下濃縮し，得られた残渣のメタノール２０ｍｌ溶液に氷冷下，水素化ホウ素ナトリウム１６０ｍｇを加えた。反応溶液を室温下０．５時間撹拌した後，反応溶液に再び水素化ホウ素ナトリウム４７０ｍｇを加えた。反応溶液を室温にて０．５時間撹拌した後，溶媒を減圧下留去した。残渣に酢酸エチル，飽和炭酸水素ナトリウム水溶液を加え，有機層を無水硫酸マグネシウムで乾燥後，溶媒を減圧下留去した。残渣をシリカゲルカラムクロマトグラフィー（溶出液；クロロホルム／メタノール＝１００／１）で精製することにより，４’－［２－［Ｎ－ベンジル－Ｎ－［２－（４－ベンジルオキシ－３－メタンスルホニルアミノフェニル）－２－ヒドロキシエチル］アミノ］エチル］－２－（２－ピリジル）酢酸アニリド９２０ｍｇを得た。
【００４４】参考例１９
４’－［２－［Ｎ－ベンジル－Ｎ－［２－（４－ベンジルオキシ－３－ニトロフェニル）－２－ヒドロキシエチル］アミノ］エチル］－２－（２－ピリジル）酢酸アニリドを参考例１１と同様の方法にて合成した。
【００４５】参考例２０
４’－［２－［Ｎ－ベンジル－Ｎ－［２－（３－アミノ－４－ベンジルオキシフェニル）－２－ヒドロキシエチル］アミノ］エチル］－２－（２－ピリジル）酢酸アニリドを参考例２と同様の方法にて合成した。
【００４６】参考例２１
４’－［２－［Ｎ－ベンジル－Ｎ－［２－（３－アミノ－４－ベンジルオキシフェニル）－２－ヒドロキシエチル］アミノ］エチル］－２－（２－ピリジル）酢酸アニリド６７０ｍｇのクロロホルム１０ｍｌの溶液にギ酸－無水酢酸混合物（３：５）１．０ｍｌを加え，室温で７時間撹拌した。溶媒を減圧留去し，残渣にメタノール１５ｍｌと水１．０ｍｌと炭酸ナトリウム４９０ｍｇを加え，室温で１．５時間撹拌した。不溶物を沪去し，溶媒を減圧濃縮して得られた残渣に水，クロロホルムを加え，有機層を飽和食塩水で洗浄した後，無水硫酸マグネシウムで乾燥した。溶媒を減圧下留去し，残渣をシリカゲルカラムクロマトグラフィー（溶出液；クロロホルム／メタノール＝５０／１）で精製して４’－［２－［Ｎ－ベンジル－Ｎ－［２－（４－ベンジルオキシ－３－ホルムアミドフェニル）－２－ヒドロキシエチル］アミノ］エチル］－２－（２－ピリジル）酢酸アニリド５９０ｍｇを得た。
【００４７】参考例２２
４’－［２－［Ｎ－ベンジル－Ｎ－［２－（３－アミノ－４－ベンジルオキシフェニル）－２－ヒドロキシエチル］アミノ］エチル］－２－（２－ピリジル）酢酸アニリド６４０ｍｇに無水酢酸２０ｍｌを加え，混合物を室温で２時間撹拌した。溶媒を減圧留去し，残渣にメタノ

ール３０ｍｌと１Ｎ水酸化ナトリウム水溶液５ｍｌを加え，室温で１．５時間撹拌した。溶媒を減圧下留去し，残渣に水，酢酸エチルを加え，有機層を水，飽和食塩水で順次洗浄した後，無水硫酸マグネシウムで乾燥した。溶媒を減圧下留去し，残渣をシリカゲルカラムクロマトグラフィー（溶出液；クロロホルム／メタノール＝５０／１）で精製して４’－｛２－［Ｎ－［２－（３－アセタミド－４－ベンジルオキシフェニル）－２－ヒドロキシエチル］－Ｎ－ベンジルアミノ］エチル］－２－（２－ピリジル）酢酸アニリド５７０ｍｇを得た。

【００４８】参考例２３

２－［Ｎ－ベンジル－Ｎ－［２－（４－ニトロフェニル）エチル］アミノ］－１－（２－ベンジルオキシフェニル）エタノールを参考例１と同様の方法で合成した。

【００４９】参考例２４

２－［Ｎ－ベンジル－Ｎ－［２－（４－アミノフェニル）エチル］アミノ］－１－（２－ベンジルオキシフェニル）エタノールを参考例２と同様の方法にて合成した。

【００５０】参考例２５

４’－［２－［Ｎ－ベンジル－Ｎ－［２－（２－ベンジルオキシフェニル）－２－ヒドロキシエチル］アミノ］エチル］－２－（１－ベンジルイミダゾール－２－イル）酢酸アニリドを参考例３と同様の方法にて合成した。

【００５１】参考例２６

２－（４－ニトロフェニル）エチルアミン８．２ｇのアセトニトリル１００ｍｌ溶液に室温にて４’－ベンジルオキシフェナシルブロミド７．５ｇを加えた。反応溶液を室温にて０．５時間撹拌した後，生じた不溶物を沪別し，溶媒の適当量を減圧下にて加熱することなく留去した。濃縮された反応溶液にメタノール５０ｍｌ及び水素化ホウ素ナトリウム２．５ｇを氷冷下加え，室温にて１時間撹拌した。溶媒を減圧下留去し，残渣をクロロホルム及び飽和炭酸水素ナトリウム水溶液に溶解し，有機層を無水硫酸マグネシウムで乾燥した。溶媒を減圧下留去し，得られた残渣をシリカゲルカラムクロマトグラフィー（溶出液；クロロホルム／メタノール－２０／１）で精製することにより，１－（４－ベンジルオキシフェニル）－２－［［２－（４－ニトロフェニル）エチル］アミノ］エタノール４．３６ｇを得た。

【００５２】参考例２７

１－（４－ベンジルオキシフェニル）－２－［［２－（４－ニトロフェニル）エチル］アミノ］エタノール４．２９ｇ，ジ－ｔ－ブチルジ炭酸エステル２．３９ｇのテトラヒドロフラン１００ｍｌ溶液を２時間加熱還流した。溶媒を減圧下留去し得られた残渣のメタノール１５０ｍｌ溶液に１０％パラジウム－炭素１．１ｇを加え，常圧水素雰囲気下，室温にて５時間撹拌した。不溶物をセライトを用いて除去した後，沪液を減圧下濃縮することにより，Ｎ－［２－（４－アミノフェニル）エチル］－Ｎ－［２－（４－ヒドロキシ－２－（４－ヒドロキシフェニル）エチル］カルバミン酸　ｔ－ブチルエステル３．５３ｇを得た。

【００５３】参考例２８

Ｎ－［２－（４－アミノフェニル）エチル］－Ｎ－［２－ヒドロキシ－２－（４－ヒドロキシフェニル）エチル］カルバミン酸　ｔ－ブチルエステル５１３ｍｇと２－（２－アミノチアゾール４－イル）酢酸２４３ｍｇのジメチルホルムアミド溶液１５ｍｌに１－エチル－３－（３－ジメチルアミノプロピル）カルボジイミド塩酸塩３２０ｍｇと１－ヒドロキシベンゾトリアゾール２４０ｍｇを加え，室温で１４時間撹拌した。溶媒を減圧留去し，残渣に水，酢酸エチルを加え，有機層を飽和食塩水で洗浄した。有機層を無水硫酸マグネシウムで乾燥した後，溶媒を減圧留去して得た残渣をシリカゲルカラムクロマトグラフィー（溶出液；クロロホルム／メタノール＝３０／１）で精製してＮ－［２－［４－［２－（２－アミノチアゾール－４－イル）アセタミド］フェニル］エチル］－Ｎ－［２－ヒドロキシ－２－（４－ヒドロキシフェニル）エチル］カルバミン酸　ｔ－ブチルエステル５７０ｍｇを得た。

【００５４】実施例１

４’－［２－［Ｎ－ベンジル－Ｎ－［２－（４－ベンジルオキシフェニル）－２－ヒドロキシエチル］アミノ］エチル］－２－（４－メチルピリジン－２－イル）酢酸アニリド２５３ｍｇのメタノール１０ｍｌ溶液に１０％パラジウム－炭素１３５ｍｇを加えた。反応溶液を常圧水素雰囲気下２時間撹拌した。不溶物をセライトを用いて沪去した後，沪液を減圧濃縮した。得られた残渣のメタノール溶液に４Ｎ塩化水素－酢酸エチル溶液０．１ｍｌを加え，溶媒を減圧下留去した。残渣をメタノール－エタノール－ジエチルエーテルで結晶化した後，粗結晶をメタノール－エタノールで再結晶することにより４’－［２－［［２－ヒドロキシ－２－（４－ヒドロキシフェニル）エチル］アミノ］エチル］－２－（４－メチルピリジン－２－イル）酢酸アニリド　塩酸塩１１２ｍｇを得た。

【００５５】実施例２

４’－［２－［［２－ヒドロキシ－２－（４－ヒドロキシフェニル）エチル］アミノ］エチル］－２－（３－メチルピリジン－６－イル）酢酸アニリド　塩酸塩を実施例１と同様の方法にて合成した。

【００５６】実施例３

４’－［２－［［２－ヒドロキシ－２－（４－ヒドロキシフェニル）エチル］アミノ］エチル］－２－（２－ピリジル）酢酸アニリド　塩酸塩を実施例１と同様の方法にて合成した。

【００５７】実施例４

４’－［２－［［２－ヒドロキシ－２－（４－ヒドロキ

シフェニル）エチル］アミノ］エチル］－２－（２，４－ジメチルピリジン－６－イル）酢酸アニリド塩酸塩を実施例１と同様の方法にて合成した。

【００５８】実施例５

４’－［２－［Ｎ－ベンジル－Ｎ－［２－（４－ベンジルオキシフェニル）－２－ヒドロキシエチル］アミノ］エチル］－２－（３－メチルピリジン－２－イル）酢酸アニリド２３６ｍｇのメタノール１０ｍｌ溶液に１０％パラジウム－炭素１２０ｍｇを加えた。反応溶液を常圧水素雰囲気下４時間撹拌した。不溶物をセライトを用いて沪去した後，沪液を減圧濃縮した。得られた残渣のメタノール溶液に４Ｎ塩化水素－酢酸エチル溶液０．１ｍｌを加え，溶媒を減圧下留去した。残渣をシリカゲルカラムクロマトグラフィー（溶出液；クロロホルム／メタノール＝５／１）にて精製することにより，４’－［２－［［２－ヒドロキシ－２－（４－ヒドロキシフェニル）エチル］アミノ］エチル］－２－（３－メチルピリジン－２－イル）酢酸アニリド　塩酸塩１２１ｍｇを得た。

【００５９】実施例６

４’－［２－［［２－ヒドロキシ－２－（４－ヒドロキシフェニル）エチル］アミノ］エチル］－２－（２－メチルピリジン－６－イル）酢酸アニリド　塩酸塩を実施例５と同様の方法にて合成した。

【００６０】実施例７

４’－［２－［［２－ヒドロキシ－２－（３－ヒドロキシフェニル）エチル］アミノ］エチル］－２－（２－ピリジル）酢酸アニリド　塩酸塩を実施例５と同様の方法にて合成した。

【００６１】実施例８

４’－［２－［［２－ヒドロキシ－２－（２－ヒドロキシフェニル）エチル］アミノ］エチル］－２－（２－ピリジル）酢酸アニリド　塩酸塩を実施例５と同様の方法にて合成した。

【００６２】実施例９

２－（１－ベンジルイミダゾール－２－イル）－４’－［２－［［２－ヒドロキシ－２－（２－ヒドロキシフェニル）エチル］アミノ］エチル］酢酸アニリド０．５フマル酸塩を実施例５と同様の方法にて合成した。

【００６３】実施例１０

４’－［２－［［２－ヒドロキシ－２－（４－ヒドロキシフェニル）エチル］アミノ］エチル］－Ｎ－メチル－２－（２－ピリジル）酢酸アニリド　フマル酸塩を実施例５と同様の方法にて合成した。

【００６４】実施例１１

Ｎ－［２－［４－［２－（２－アミノチアゾール－４－イル）アセタミド］フェニル］エチル］－Ｎ－［２－ヒドロキシ－２－（４－ヒドロキシフェニル）エチル］カルバミン酸　ｔ－ブチルエステル４９０ｍｇのトリフルオロ酢酸溶液２０ｍｌを室温で３０分間撹拌した。溶媒を減圧下留去し，残渣にテトラヒドロフラン２０ｍｌ，４Ｎ塩酸－ジオキサン溶液３０ｍｌを加え，室温で１．５時間撹拌した。溶媒を減圧下留去して得られた残渣を逆相カラムクロマトグラフィー（溶出液；水／メタノール－２／１）で精製して，２－（２－アミノチアゾール－４－イル）－４’－［２－［［２－ヒドロキシ－２－（２－ヒドロキシフェニル）エチル］アミノ］エチル］酢酸アニリド　０．５塩酸塩　１．５トリフルオロ酢酸塩３４０ｍｇを得た。

【００６５】実施例１２

４’－［２－［［２－ヒドロキシ－２－（４－ヒドロキシ－３－メタンスルホナミドフェニル）エチル］アミノ］エチル］－２－（２－ピリジル）酢酸アニリド　塩酸塩を実施例１と同様の方法にて合成した。

【００６６】実施例１３

４’－［２－［［２－（３－ホルムアミド－４－ヒドロキシフェニル）－２－ヒドロキシエチル］アミノ］エチル］－２－（２－ピリジル）酢酸アニリド　塩酸塩を実施例１と同様の方法にて合成した。

【００６７】実施例１４

４’－［２－［［２－（３－アセタミド－４－ヒドロキシフェニル）－２－ヒドロキシエチル］アミノ］エチル］－２－（２－ピリジル）酢酸アニリド　塩酸塩を実施例１と同様の方法にて合成した。

【００６８】以下，表１～４に参考例化合物の物理化学的性状を，表５～６に実施例化合物の物理化学的性状を並びに表７に実施例化合物の構造式をそれぞれ示す。表中の記号は以下の意味を表す。

Ｒｅｘ．Ｎｏ．：参考例番号

Ｅｘ．Ｎｏ．：実施例番号

ｓａｌ．：塩

ＤＡＴＡ：物理化学的性状

ＭＳ（ｍ／ｚ）：質量分析値（ｍ／ｚ）

ＮＭＲ：核磁気共鳴スペクトル（ＴＭＳ内部標準）

ｍｐ：融点

ＯＨ－ｐｏｓ：フェニル基における水酸基の置換位置

【００６９】

【表１】

Rex. No.	D A T A
1	MS (m/z) : 481 [(M　H) +] NMR ($CDCl_3$) δ : 2.00－2.98 (6H, m), 3.50－3.60 (2H, m), 3.94 (1H, d, J－13.2Hz), 4.62 (1H, dd, J = 10.0, 4.0Hz), 5.05 (2H, s), 6.92－6.97 (2H, m), 7.18－7.45 (14H, m), 8.07－8.13 (2H, m)
2	MS (m/z) : 453 [(M＋H) +] NMR ($CDCl_3$) δ : 2.54－2.91 (6H, m), 3.40－3.80 (3H, m), 3.95 (1H, d, J＝14.0Hz), 4.58 (1H, dd, J = 9.6, 4.0Hz), 5.04 (2H, s), 6.59－6.64 (2H, m), 6.89　6.97 (4H, m), 7.18　7.44 (12H, m)
3	MS (m/z) : 586 [(M＋H) +] NMR ($CDCl_3$) δ : 2.40 (3H, s), 2.55－2.98 (6H, m), 3.50－3.60 (2H, m), 3.87 (2H, s), 3.94 (1H, d, J＝13.2Hz), 4.62 (1H, dd, J＝10.0, 4.0Hz), 5.05 (2H, s), 6.92－6.97 (2H, m), 7.18－7.45 (18H, m), 8.40－8.50 (1H, m), 9.65 (1H, brs)
4	MS (m/z) : 586 [(M＋H) +] NMR ($CDCl_3$) δ : 2.35 (3H, s), 2.55－2.99 (6H, m), 3.55 (1H, d, J＝13.6Hz), 3.71 (1H, brs), 3.80 (2H, s), 3.94 (1H, d, J＝13.6Hz), 4.57 (1H, dd, J＝9.6, 4.0Hz), 5.04 (2H, s), 6.92－6.97 (2H, m), 7.08－7.07 (2H, m), 7.12 (1H, s), 7.18－7.46 (15H, m), 8.48 (1H, d, J＝4.8Hz), 9.76 (1H, brs)
5	MS (m/z) : 586 [(M＋H) +] NMR ($CDCl_3$) δ : 2.33 (3H, s), 2.55－3.00 (6H, m), 3.55 (1H, d, J＝13.6Hz), 3.80 (2H, s), 3.93 (1H, d, J＝13.2Hz), 4.57 (1H, dd, J＝9.8, 4.0Hz), 5.03 (2H, s), 6.90－7.50 (20H, m), 8.42 (1H, d, J＝2.0Hz), 9.71 (1H, brs)
6	MS (m/z) : 586 [(M＋H) +] NMR ($CDCl_3$) δ : 2.56　3.00 (9H, m), 3.56 (1H, d, J＝13.6Hz), 3.72 (1H, brs), 3.81 (2H, s), 3.95 (1H, d, J＝14.0Hz), 4.58 (1H, dd, J＝9.8, 4.0Hz), 5.04 (2H, s), 6.90－6.94 (2H, m), 7.05－7.11 (4H, m), 7.19－7.48 (14H, m), 7.57 (1H, t, J＝8.0Hz), 10.20 (1H, brs)
7	MS (m/z) : 252 [(M＋H) +] NMR ($CDCl_3$) δ : 3.70 (2H, s), 3.88 (2H, s), 7.23－7.32 (4H, m), 7.56－7.81 (2H, m), 7.71 (1H, dt, J＝1.6, 7.8Hz), 8.68 (1H, d, J＝4.4Hz), 10.04 (1H, brs)

【００７０】　　【表２】

Rex. No.	D A T A
8	MS (m/z) : 280 [(M + H) −] NMR ($CDCl_3$) δ : 2.31 (3H, s), 2.59 (3H, s), 3.71 (2H, s), 3.77 (2H, s), 6.91 (1H, s), 6.98 (1H, s), 7.24 − 7.28 (2H, m), 7.66 − 7.80 (2H, m), 10.60 (1H, brs)
9	MS (m/z) : 346 [(M − H) −] NMR ($CDCl_3$) δ : 2.75 − 2.81 (2H, m), 2.83 − 2.89 (2H, m), 3.76 (2H, s), 3.86 (2H, s), 7.11 − 7.16 (2H, m), 7.20 − 7.33 (7H, m), 7.44 − 7.48 (2H, m), 7.69 (1H, dt, J = 2.0, 8.0Hz), 8.61 (1H, d, J = 5.2Hz), 9.72 (1H, brs)
10	MS (m/z) : 374 [(M + H) −] NMR ($CDCl_3$) δ : 2.30 (3H, s), 2.57 (3H, s), 2.75 − 2.82 (2H, m), 2.84 − 2.90 (2H, m), 3.76 (2H, s), 3.78 (2H, s), 6.91 (2H, s), 7.11 − 7.16 (2H, m), 7.20 − 7.33 (5H, m), 7.44 − 7.49 (2H, m), 10.27 (1H, brs)
11	MS (m/z) : 572 [(M + H) −] NMR ($CDCl_3$) δ : 2.54 − 2.94 (6H, m), 3.50 (1H, d, J − 13.6Hz), 3.86 (2H, s), 3.95 (1H, d, J − 13.6Hz), 4.57 (1H, dd, J − 10.0, 4.0Hz), 5.04 (2H, s), 6.90 − 6.94 (2H, m), 7.04 − 7.08 (2H, m), 7.18 − 7.48 (16H, m), 7.69 (1H, dt, J = 2.0, 8.0Hz), 8.62 (1H, d, J = 4.8Hz), 9.72 (1H, brs)
12	MS (m/z) : 598 [(M − H) −] NMR ($CDCl_3$) δ : 2.30 (3H, s), 2.50 − 3.00 (9H, m), 3.56 (1H, d, J = 13.7Hz), 3.80 − 3.80 (3H, m), 3.94 (1H, d, J = 13.2Hz), 5.04 (2H, s), 6.80 − 7.60 (20H, m), 10.25 (1H, brs)
13	MS (m/z) : 572 [(M + H) −] NMR ($CDCl_3$) δ : 2.56 − 2.90 (6H, m), 3.56 (1H, d, J − 13.6Hz), 3.86 (2H, s), 3.97 (1H, d, J − 13.6Hz), 4.60 (1H, dd, J − 2.0, 8.0Hz), 5.04 (2H, s), 6.83 − 6.90 (2H, m), 6.95 − 6.98 (1H, m), 7.08 − 7.08 (2H, m), 7.18 − 7.48 (15H, m), 7.69 (1H, dt, J = 8.0, 2.0Hz), 8.60 − 8.63 (1H, m), 9.72 (1H, brs)
14	MS (m/z) : 572 [(M + 1) +] NMR ($CDCl_3$) δ : 2.47 − 2.90 (6H, m), 3.49 (1H, d, J = 13.6Hz), 5.01 − 5.11 (3H, m), 6.89 (1H, d, J = 7.2Hz), 6.96 − 6.99 (3H, m), 7.18 − 7.52 (16H, m), 7.89 (1H, dt, J = 8.0Hz, J = 2.0Hz), 8.60 − 8.64 (1H, m), 9.88 (1H, s)

【００７１】　　【表３】

Rex. No.	D A T A
15	MS (m/z) : 286 [(M－Et) ＋] NMR ($CDCl_3$) δ : 3.67 (2H, brs), 3.77 (2H, s), 7.10－7.29 (4H, m), 7.33－7.39 (2H, m), 7.53－7.55 (1H, m), 8.43 (1H, brd, J = 3.6Hz)
16	MS (m/z) : 360 [(M－Et) ＋] NMR ($CDCl_3$) δ : 2.80－2.94 (6H, m), 3.29 (3H, s), 3.67 (2H, S), 3.82 (2H, s), 7.08－7.34 (11H, m), 7.53－7.58 (1H, m), 8.46 (1H, d, J = 4.4Hz)
17	MS (m/z) : 536 [(M－Et) ＋] NMR ($CDCl_3$) δ : 2.58－2.98 (6H, m), 3.29 (3H, s), 3.54－3.68 (3H, m), 3.96 (1H, d, J = 13.6Hz), 4.56－4.64 (1H, m), 5.05 (2H, s), 6.90－6.96 (2H, m), 7.05－7.44 (18H, m), 7.53－7.58 (1H, m), 8.47 (1H, d, J = 4.4Hz)
18	MS (m/z) : 665 [(M－Et) ＋] NMR ($CDCl_3$) δ : 2.50－2.91 (9H, m), 3.55 (1H, d, J = 13.6Hz), 3.85 (2H, s), 3.94 (1H, d, J = 13.6Hz), 4.56 (1H, dd, J = 10.0, 3.6Hz), 5.06 (2H, s), 6.83 (1H, brs), 6.94 (1H, d, J = 8.4Hz), 7.04－7.12 (3H, m), 7.22－7.48 (15H, m), 7.69 (1H, dt, J = 2.0, 8.0Hz), 8.58－8.63 (1H, m), 9.70 (1H, brs)
19	MS (m/z) : 617 [(M－Et) ＋] NMR ($CDCl_3$) δ : 2.48－2.54 (1H, m), 2.84－2.94 (5H, m), 3.57 (1H, d, J = 13.2Hz), 3.75 (1H, brs), 3.86 (2H, s), 3.92 (1H, d, J = 13.2Hz), 4.53 (1H, dd, J = 10.8Hz, J = 3.6Hz), 5.21 (2H, s), 7.03－7.08 (3H, m), 7.23－7.48 (15H, m), 7.67－7.75 (2H, m), 8.60－8.64 (1H, m), 9.75 (1H, s)
20	MS (m/z) : 587 [(M　Et) ＋] NMR ($CDCl_3$) δ : 2.59－2.88 (6H, m), 3.55 (1H, d, J = 13.2Hz), 3.67 (1H, brs), 3.81 (2H, brs), 3.86 (2H, s), 3.94 (1H, d, J = 13.2Hz), 4.49－4.52 (1H, m), 5.05 (2H, s), 6.59－6.73 (3H, m), 7.05－7.07 (2H, m), 7.23－7.46 (14H, m), 7.67－7.71 (1H, m), 8.61－8.62 (1H, m), 9.71 (1H, brs)
2_	MS (m/z) : 815 [(M－Et) ＋] NMR ($CDCl_3$) δ : 2.53－2.88 (6H, m), 3.55 (1H, d, J = 13.6Hz), 3.75 (1H, brs), 3.86 (2H, s), 3.94 (1H, d, J = 13.6Hz), 4.59－4.62 (1H, m), 5.06－5.08 (2H, m), 6.89－7.22 (5H, m), 7.23－7.48 (14H, m), 7.67　7.71 (1H, m), 7.78　8.72 (3H, m), 9.68　9.73 (1H, m)

【0072】　　【表4】

Rex. No.	D A T A
22	MS (m/z) : 629 [(M－H) +] NMR ($CDCl_3$) δ : 2.14 (3H, s), 2.58－2.87 (6H, m), 3.54 (1H, d, J＝13.2Hz), 3.74 (1H, brs), 3.86 (2H, s), 3.94 (1H, d, J＝13.2Hz), 4.56－4.64 (1H, m), 5.10 (2H, s), 6.90 (1H, d, J＝8.4Hz), 7.02　7.07 (3H, m), 7.22　7.46 (12H, m), 7.55　7.77 (2H, m), 8.28－8.32 (1H, m), 8.60－8.65 (1H, m), 9.69 (1H,s)
23	MS (m/z) : 483 [(M－H) +] NMR ($CDCl_3$) δ : 2.50－2.95 (6H, m), 3.50 (1H, d, J＝13.6Hz), 3.85 (1H, d, J＝13.2Hz), 5.00－5.14 (3H, m), 6.92－7.53 (16H, m), 8.03－8.08 (2H, m)
24	MS (m/z) : 453 [(M－H) +] NMR ($CDCl_3$) δ : 2.46－2.92 (6H, m), 3.40－3.80 (3H, m), 3.87 (1H, d, J－13.6Hz), 5.00－5.15 (3H, m), 6.55－6.61 (2H, m), 6.82－6.91 (3H, m), 6.95－7.01 (1H, m), 7.17－7.43 (11H, m), 7.49－7.53 (1H, m)
25	MS (m/z) : 651 [(M－H) +] NMR ($CDCl_3$) δ : 2.46－2.92 (6H, m), 3.50 (1H, d, J＝13.6Hz), 3.62 (1H, brs), 3.72 (2H, s), 3.87 (1H, d, J＝13.6Hz), 5.00　5.16 (6H, m), 6.87－7.54 (25H, m), 10.23 (1H, brs)
26	MS (m/z) : 393 [(M－H) +] NMR ($CDCl_3$) δ : 2.73 (1H, dd, J＝8.8, 12.4Hz), 2.84－3.33 (5H, m), 4.64 (1H, dd, J＝3.6, 8.8Hz), 5.05 (2H, s), 6.93－6.98 (2H, m), 7.23－7.45 (9H, m), 8.13－8.17 (2H, m)
27	MS (m/z) : 371 [(M　H) －] NMR ($CDCl_3$) δ : 1.46 (9H, s), 2.55－2.72 (2H, m), 3.15－3.53 (4H, m), 4.72－4.83 (1H, m), 6.58－6.63 (2H, m), 6.73－6.79 (2H, m), 6.85－6.97 (2H, m), 7.13－7.19 (2H, m)
28	MS (m/z) : 513 [(M－H) +] NMR ($DMSO－d_6$) δ : 1.35 (9H, s), 2.58－2.70 (2H, m), 3.14－3.35 (4H, m), 3.44 (2H, s), 4.59 (1H, brs), 5.15－5.25 (1H, m), 6.29 (1H, s), 6.69 (2H, d, J＝8.0Hz), 6.89 (2H, m), 7.05－7.12 (4E, m), 7.49 (2H, d, J＝8.0Hz), 8.31 (1H, s), 9.23 (1H, s), 9.99 (1H, s)

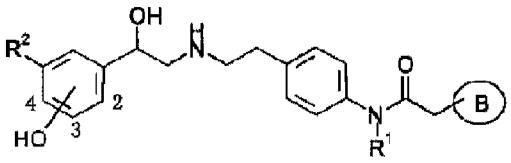
【0073】　　【表5】

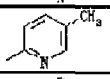
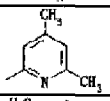
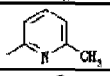
Ex. No.	D A T A
1	mp：224－226℃ NMR (DMSO－d_6) δ：2.31 (3H, s), 2.85－3.18 (6H, m), 3.78 (2H, s), 4.79－4.85 (1H, m), 6.00 (1H, d, J＝4.0Hz), 6.74　6.79 (2H, m), 7.08　7.12 (1H, m), 7.14－7.23 (5H, m), 7.54－7.61 (2H, m), 8.31－8.37 (1H, m), 9.47 (1H, brs), 10.28 (1H, brs)
2	mp：215－216℃ NMR (DMSO－d_6) δ：2.27 (3H, s), 2.85－3.18 (6H, m), 3.78 (2H, s), 4.79－4.87 (1H, m), 5.99 (1H, d, J＝3.2Hz), 6.74－6.79 (2H, m), 7.14－7.20 (5H, m), 7.28 (1H, d, J－8.0Hz), 7.53－7.60 (3H, m), 8.31－8.34 (1H, m), 9.47 (1H, brs), 10.27 (1H, brs)
3	mp：211－212℃ NMR (DMSO－d_6) δ：2.84－3.20 (6H, m), 3.84 (2H, s), 4.77－4.86 (1H, m), 6.00 (1H, d, J－3.2 Hz), 6.74－6.79 (2H, m), 7.14－7.20 (4H, m), 7.24－7.30 (1H, m), 7.39 (1H, d, J＝8.0Hz), 7.55－7.60 (2H, m), 7.76 (1H, dt, J＝2.0, 8.0Hz), 8.47－8.51 (1H, m), 8.71 (1H, brs), 8.91 (1H, brs), 9.46 (1H, brs), 10.28 (1H, brs)
4	mp：194－196℃ NMR (DMSO　d_6) δ：2.26 (3H, s), 2.39 (3H, s), 2.86－3.18 (6H, m), 3.74 (2H, s), 4.81－4.90 (1H, m), 6.00 (1H, d, J＝3.6Hz), 6.74－6.80 (2H, m), 6.96 (1H, s), 7.01 (1H, s), 7.09－7.20 (4H, m), 7.55－7.61 (2H, m), 9.49 (1H, brs), 10.33 (1H, brs)
5	MS (m／z)：406 [(M＋H) $^+$] NMR (DMSO－d_6) δ：2.31 (3H, s), 2.84－3.16 (6H, m), 3.87 (2H, s), 4.79 (1H, d, J＝8.0Hz), 5.92 (1H, brs), 6.73－6.79 (2H, m), 7.13－7.21 (5H, m), 7.53－7.60 (3H, m), 8.27－8.33 (1H, m), 9.44 (1H, brs), 10.23 (1H, brs)
6	MS (m／z)：406 [(M＋H) $^+$] NMR (DMSO－d_6) δ：2.44 (3H, s), 2.80－3.10 (6H, m), 3.78 (2H, s), 4.70－4.75 (1H, m), 5.81 (1H, brs), 6.72－6.77 (2H, m), 7.10－7.20 (5H, m), 7.53－7.66 (4H, m), 9.44 (1H, brs), 10.24 (1H, brs)
7	MS (m／z)：392 [(M＋H) $^+$] NMR (DMSO－d_6) δ：2.84－3.03 (3H, m), 3.08－3.20 (3H, m), 3.84 (2H, s), 4.81－4.89 (1H, m), 6.12 (1H, d, J＝3.6Hz), 6.70 (1H, dd, J－2.0, 8.0Hz), 6.76－6.83 (2H, m), 7.13－7.20 (3H, m), 7.24－7.30 (1H, m), 7.39 (1H, d, J＝8.0Hz), 7.56－7.60 (2H, m), 7.76 (1H, dt, J＝1.8, 7.2Hz), 8.47－8.52 (1H, m), 8.72 (1H, brs), 8.92 (1H, brs), 9.49 (1H, brs), 10.28 (1H, brs)

【0074】　　【表6】

Ex. No.	D A T A
8	MS (m/z) : 362 [(M－H) +] NMR (DMSO－d_6) δ : 2.78 – 2.91 (3H, m), 2.97 – 3.06 (3H, m), 3.33 (1H, brs), 3.84 (2H, s), 5.05 – 5.11 (1H, m), 6.79 – 6.82 (2H, m), 7.09 (1H, dt, J = 8.0Hz, J = 1.3Hz), 7.17 (2H, d, J = 8.0Hz), 7.25 – 7.40 (2H, m), 7.56 (2H, d, J = 8.4Hz), 7.76 (1H, dt, J = 8.0Hz, J = 2.4Hz), 8.49 – 8.50 (1H, m), 10.28 (1H, s)
9	MS (m/z) : 471 [(M－H) +] NMR (DMSO－d_6) δ : 2.84 – 3.00 (3H, m), 3.07 – 3.18 (3H, m), 3.79 (2H, s), 5.15 – 5.20 (1H, m), 6.25 (2H, s), 6.69 (1.2H, s), 6.80 – 6.87 (2H, m), 7.08 – 7.40 (10H, m), 7.50 – 7.57 (2H, m), 10.38 (1H, brs)
10	MS (m/z) : 406 [(M－H) +] NMR (DMSO－d_6) δ : 2.70 – 3.20 (3H, m), 3.57 (2H, brs), 4.70 – 4.80 (1H, m), 6.52 (2H, s), 6.70 – 6.75 (2H, m), 7.15 – 7.90 (8H, m), 7.60 – 7.70 (1H, m), 8.85 – 8.95 (1H, m)
11	MS (m/z) : 413 [(M－H) +] NMR (DMSO－d_6) δ : 2.85 – 3.17 (3H, m), 3.62 (2H, s), 4.79 – 4.81 (1H, m), 6.00 (1H, brs), 6.55 (1H, s), 6.77 (2H, d, J = 8.4Hz), 7.15 – 7.20 (4H, m), 7.55 (2H, d, J = 8.8Hz), 7.55 (1H, brs), 8.07 (1H, brs), 8.07 (1H, brs), 8.79 (1H, brs), 8.75 (1H, brs), 10.21 (1H, brs)
12	mp : 191 – 192℃ NMR (DMSO－d_6) δ : 2.84 – 3.01 (3H, m), 3.05 – 3.17 (3H, m), 3.84 (2H, s), 4.78 – 4.88 (1H, m), 6.05 (1H, brs), 6.92 (1H, d, J = 8.0 Hz), 7.06 (1H, dd, J = 2.0, 8.4Hz), 7.14 – 7.29 (4H, m), 7.39 (1H, d, J = 8.0Hz), 7.54 – 7.80 (2H, m), 7.75 (1H, dt, J = 2.0, 8.0Hz), 8.47 – 8.51 (1H, m), 10.30 (1H, brs)
13	mp : 217 – 219℃ NMR (DMSO－d_6) δ : 2.80 – 3.00 (3H, m), 3.00 – 3.20 (3H, m), 4.02 (2H, s), 4.83 (1H, d, J = 8.0Hz), 6.05 (1H, brs), 6.88 – 6.95 (2H, m), 7.14 – 7.20 (2H, m), 7.51 – 7.65 (4H, m), 8.05 (1H, t, J = 7.2Hz), 8.14 – 8.29 (2H, m), 8.64 (1H, d, J = 4.8Hz), 8.74 (1H, brs), 9.04 (1H, brs), 9.61 (1H, s), 10.12 (1H, s), 10.47 (1H, s)
14	mp : 216 – 222℃ NMR (DMSO－d_6) δ : 2.10 (3H, s), 2.87 – 3.02 (3H, m), 3.02 – 3.20 (3H, m), 3.83 (2H, s), 4.75 – 4.83 (1H, m), 6.06 (1H, d, J = 3.6Hz), 6.86 (1H, d, J = 8.4Hz), 6.94 – 6.96 (1H, m), 7.17 (2H, d, J = 8.8Hz), 7.26 – 7.29 (1H, m), 7.39 (1H, d, J = 8.0Hz), 7.57 (2H, d, J = 8.8Hz), 7.76 (1H, dt, J = 8.0Hz, J = 4.0Hz), 7.81 – 7.84 (1H, m), 8.50 (1H, d, J = 4.0Hz), 8.66 (1H, brs), 8.79 (1H, brs), 9.31 (1H, s), 9.86 (1H, s), 10.26 (1H, s)

【0075】　　【表7】



Ex. No.	OH-pos	-R ^{1}	-R ^{2}	B環	salt
1	4	-H	-H		HCl
2	4	-H	-H		HCl
3	4	-H	-H		HCl
4	4	-H	-H		HCl
5	4	-H	-H		HCl
6	4	-H	-H		HCl
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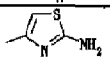
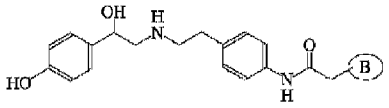
8	2	-H	-H		HCl
9	2	-H	-H		0.5 fumalate
10	4	-CH$_3$	-H		fumalate
11	4	-H	-H		1.5TFA 0.5HCl
12	4	-H	-NHSO$_2$CH$_3$		HCl
13	4	-H	-NHCHO		HCl
14	4	-H	-NHCOCH$_3$		HCl

また，表８～９に化学構造式を掲記する化合物は，前記実施例若しくは製造法に記載の方法とほぼ同様にして，又はそれらに当業者に自明の若干の変法を適用して，容易に製造することができる。尚，表８～９に掲記した化合物につき，各種，互変，幾何，光学異性体が存在する場合があるが，本発明化合物には前記各異性体の単離されたもの，又はその混合物が含まれる。

【００７６】

【表８】

【化１２】



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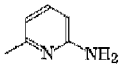
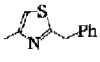
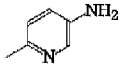
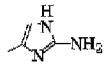
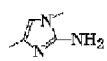
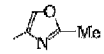
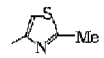
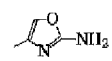
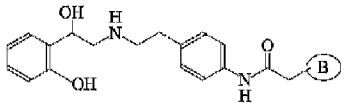
1		6	
2		7	
3		8	
4		9	
5		10	

【００７７】

【化１３】

【表９】



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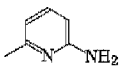
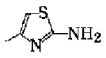
11		14	
12		15	
13		16	

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Ｃ０７Ｄ 233/64	１０６	Ｃ０７Ｄ 233/64	１０６
233/88		233/88	
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277/30		277/30	

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Structural and Conformational Features Determining Selective Signal Transduction in the β3-Adrenergic Receptor

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SUMMARY

With respect to the β1- and β2-adrenergic receptors (ARs), the β3-AR induces specific physiological effects in a few target tissues and exhibits atypical pharmacological properties that distinguish it unambiguously from its counterparts. Therefore, the β3-AR represents a suitable model to study the molecular mechanism responsible for receptor subtype selectivity and specificity. Potent β3-AR ligands newly characterized in Chinese hamster ovary cells expressing the β3-AR were also evaluated in Chinese hamster ovary cells expressing β1- and β2-ARs and were classified into three groups according to their pharmacological properties. Among the β1/β2/β3 agonists BRL 37344 and LY 79771 exhibit β3 selectivity in stimulating adenylyl cyclase; among the β1/β2 antagonists displaying β3 agonistic effects ICI 201651 exhibits β3-AR binding selectivity, whereas among the β1/β2/β3 antagonist class bupranolol is the most efficient (but not selective) β3-AR antagonist. The structures of these ligands were simulated and compared using computer-generated molecular modeling. Structure-activity relationship analysis indicates that potent or selective β3-AR compounds, in addition to possessing a pharmacophore common to all β-AR ligands, contain a long and bulky alkylamine substituent moiety, which is able to adopt and exchange extended and stacked conformations. Computerized three-dimensional models of the β1-, β2-, and β3-AR binding sites show that more bulky amino acid side chains point inside the groove of the β1 and β2 sites, compared with the β3 site, in a region implicated in signal processing. The long alkylamine chain of compounds behaving as β1/β2 antagonists and β3 agonists may thus adopt either a stacked conformation in the encumbered β1- and β2-AR sites, leading to antagonistic effects, or an extended conformation in the less encumbered β3 site, thus interacting with specific residues implicated in signal transduction.

Sympathetic stimulation via humoral (adrenergic) and neuronal (noradrenergic) pathways induces a number of physiological effects, such as modulation of heart rate, vascular tonus, bronchospasm, and glucose and lipid metabolism. Lands *et al.* (1) first subdivided the β-AR-mediated effects into β1 and β2, on the basis of the rank order of potency of epinephrine and norepinephrine in different tissues. Since this classification, many clinically active drugs, mimicking or blocking the effects of natural hormones, have been syntheaized and shown to discriminate between β1- and β2-AR-mediated effects.

In the following years, however, a number of novel compounds revealed atypical β-AR properties in various tissues. BRL 37344 was thus characterized as a potent thermogenic and lipolytic β-AR agonist in rat adipose tissue (2) and SR 58611A as an atypical β-AR agonist mediating relaxation in precontracted guinea pig ileum (3). Several β1/β2 antagonists displayed atypically low binding affinities in these tissues as well as low potencies in inhibiting responses mediated by these novel compounds, thus suggesting the existence of a novel β-AR pharmacological profile. However, partly because of its low

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ABBREVIATIONS: β-AR, β-adrenergic receptor; CHO, Chinese hamster ovary; CHO-β, Chinese hamster ovary cells expressing the β-adrenergic receptor; IA, intrinsic activity; ICYP, iodocyanopindolol; MD, molecular dynamics; RMS, root mean square index; TM, transmembrane domain; BRL 37344, (*RR,SS*)-(±)-4-(2′-[2-hydroxy-2-(3-chlorophenyl)ethylamino]propyl)phenoxyacetate sodium salt sesquihydrate; bucindolol, 2-[2-hydroxy-3-([2-(3-indolyl)-1,1-dimethylethyl]amino)propoxy]benzonitrile hydrochloride; bupranolol, 1-(2-chloro-5-methylphenoxy)-3-[(1,1-dimethylethyl)amino]-2-propanol; CGP 12177A, (±)-4-(3-*t*-butylamino-2-hydroxypropoxy)benzimidazol-2-one; CGP 20712A, (±)-[2-(3-carbamoyl-4-hydroxyphenoxy)ethylamino]-3-[4-(1-methyl-4-trifluoromethyl-2-imidazolyl)phenoxy]-2-propanolisopropylamino-2-propanol hydrochloride; cimaterol, 2-amino-5-(1-hydroxy-2-[(1-methylethyl)amino]ethyl)benzonitrile; clenbuterol, 4-amino-3,5-dichloro-α-[(1,1-dimethylethyl)amino]benzenemethanol; ICI 118551, D-(±)-1-(7-methylindan-4-yloxy)-3-isopropylaminobutan-2-ol; ICI 201651, (*R*)-4-(2-hydroxy-3-phenoxypropylaminoethoxy)-*N*-(2-methoxyethyl)phenoxyacetic acid; LY 79771, (*RS*)-(±)-4-(2′-[(2-hydroxy-3-phenylethyl)amino]butyl)benzyl alcohol; SM 11044, L-3-(3,4-dihydroxyphenyl)-*N*-[3-(4-fluorophenyl)propyl]serine pyrrolidine amide hydrobromide; SR 58611A, (*RS*)-*N*-[(2*S*)-7-ethoxycarbonylmethoxy-1,2,3,4-tetrahydronaphth-2-yl]-(2*R*)-2-(3-chlorophenyl)-2-hydroxyethanamine hydrochloride; PBS, phosphate-buffered saline; HEPES, 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid.

affinity for available β-AR radioligands and primarily because of the lack of suitable tools to study its expression among a population of conventional β-ARs, this atypical β-AR remained difficult to characterize unambiguously by a classical pharmacological approach, and some inconsistencies were described between drug affinities identified in binding studies and those measured in functional assays (4).

After the initial cloning of the β2- (5) and β1-ARs (6), a third gene, coding for a novel β-AR subtype (the β3-AR) sharing 51% and 46% identity with the human β1- and β2-AR amino acid sequences, respectively, was cloned from a human genomic library (7). The presence of human β3-AR mRNA transcripts has been demonstrated in human fat tissues as well as in gall bladder and colon biopsies (8), and evidence for a functional β3-AR in human fat cells has been recently shown by lipolysis stimulation studies (9). Functional β3-ARs, cloned from either human (7), mouse (10), or rat (11, 12) tissues, were characterized in transfected CHO cells, and their pharmacological pattern indicated that the β3-AR is closely related to the atypical β-AR in adipose tissues (13, 14). However, minor differences between the human and rodent β3-ARs as well as between atypical β-ARs from different tissues have led some authors to question whether these are actually the same pharmacological subtypes (11, 12, 15).

To settle this point, we performed a systematic pharmacological analysis in CHO-β3 (human) and CHO-β3 (mouse) using a large panel of β-AR ligands, and we showed (i) that both the human and the rodent β3-ARs display well defined pharmacological properties that distinguish them unambiguously from the β1- and β2-ARs, (ii) that the β3-AR is the prototype of the atypical β sites described in a few target tissues (adipose, gut, and cardiac tissues) where it induces specific physiological effects, and (iii) that some compounds (BRL 37344, bucindolol, bupranolol, CGP 12177A, cimaterol, ICI 201651, LY 79771, SR 58611A, and SM 11044) exhibit potent affinities or activities in CHO-β3.[1] These atypical and specific properties make the β3-AR a model receptor to study the molecular basis of subtype selectivity, using these new pharmacological tools.

In this study, we analyzed the selectivity of the subtype by evaluating pharmacological receptor binding and adenylyl cyclase activation properties of β-AR ligands in CHO cells expressing human β1-, β2-, or β3-ARs. Results led us to classify compounds into pharmacological classes, and the structure-activity relationship of these ligands was analyzed using MD simulations. Structural features of β3-efficient agonists and antagonists were examined to define a putative pharmacophore, as well as to provide new insights into the molecular mechanism responsible for the β3-AR potency and selectivity.

Materials and Methods

Chemicals. Bucindolol and nadolol were provided by Bristol-Myers Squibb (Princeton, NJ). CGP 12177A, CGP 20712A, alprenolol, and oxprenolol were gifts from Ciba-Geigy Corporation (Basel, Switzerland). ICI 118551 and ICI 201651 were obtained from Imperial Chemical Industries (Macclesfield, England). Cimaterol and LY 79771 were donated by American Cyanamid (Pearl River, NY) and Lilly Research Labs (Indianapolis, IN), respectively. Clenbuterol was obtained from Roussel Uclaf (Romainville, France). Pindolol and cyanopindolol were provided by Sandoz (Basel, Switzerland). (±)- and (−)-Bupranolol were gifts from Schwarz Pharma (Monheim, Germany). BRL 37344 was obtained from SmithKline Beecham Pharmaceuticals (Epsom, England). SM 11044 and SR 58611A were given by Sumitomo Pharmaceuticals (Osaka, Japan) and Sanofi-Midy (Milano, Italy), respectively. (−)-Isoproterenol and propranolol were purchased from Sigma Chemical Co. (St. Louis, MO).

Cell culture. Subclones of CHO cells stably transfected with human β1-, β2-, or β3-ARs were grown as described previously (7, 16).

Receptor binding assays. Preconfluent cells were harvested by treatment with Versen-EDTA (Seromed) and were washed with Hanks' balanced salt solution supplemented with 1 mM ascorbic acid and buffered with 20 mM HEPES to achieve a pH of 7.4. Aliquots of 10^5 cells were incubated with (−)-[3-^{125}I]ICYP (2000 Ci/mmol; Amersham, England) in the absence or presence of competitor, in a buffered 500-μl final volume with 0.1% (w/v) bovine serum albumin (Sigma) and 4 μM desipramine (Sigma). The reaction was performed for 45 min at 37°, with shaking, in the dark. After dilution with ice-cold PBS, pH 7.4, cells were immediately filtered and extensively washed over glass fiber disks (Whatman GF/C) that had been presoaked with 0.3% polyethyleneimine (Sigma). Radioactivity was measured in a LKB 1282 γ-radiation counter.

Saturation experiments were performed with ICYP concentrations ranging from 5 to 500 pM for the β1- and β2-ARs and from 50 to 5000 pM for the β3-AR. Nonspecific binding was determined in the presence of 2 μM (±)-propranolol for CHO-β1 and CHO-β2 or 100 μM (−)-isoproterenol for CHO-β3. Competition experiments were performed with ICYP concentrations of 50 pM for the β1 and β2 subtypes and 1 nM for the β3 subtype and various concentrations of competitor ranging from 1 pM to 100 μM. Ligand lipophilicity indexes (log $\frac{1}{f}$F) were calculated using the TSAR software (Oxford Molecular, Oxford, England).

Adenylyl cyclase binding assays. Because forskolin directly stimulates the catalytic subunit of adenylyl cyclase and displays greater efficacy and potency when its catalytic domain interacts with the α_s subunit of the G protein (17), forskolin binding experiments were performed with adherent transfected CHO-β in the absence or presence of β-AR ligands.

Preconfluent cells in six-well dishes (≈1.2 × 10^6 cells/well) were washed twice with 2 ml of ice-cold PBS, added to 1 ml of ice-cold Ham's F12 medium buffered with 20 mM HEPES, pH 7.4, and kept on ice for 30 min before the binding study. Cells were incubated at 4° for 1 hr, with slow shaking, in 500 μl of buffered [12-^{3}H]forskolin (20–35 Ci/mmol; New England Nuclear), in the absence or presence of nontritiated forskolin or β-AR ligands. Cells were then washed three times with 2 ml of PBS and dissolved in 1 ml of 1 N NaOH for 30 min at 37° before the homogenate was counted in a LKB-Wallac 1410 scintillation counter.

Cholera toxin ADP-ribosylates G_s, irreversibly blocking its GTPase activity and maintaining the stability of the α_s-cyclase complex in a way that is independent of receptor occupancy. Cells were treated with cholera toxin (2 μg/ml in culture medium; Sigma) for 5 hr at 37° before measurement of forskolin binding at 4°, a temperature that allows stabilization of the transient complex but probably leads to underestimation of the maximal complex association at 37°.

Adenylyl cyclase stimulation assays. CHO-β1, CHO-β2, and CHO-β3 were grown to preconfluence in six-well dishes (≈1.2 × 10^6 cells/well). After washing with 1 ml of Ham's F12 medium buffered with 20 mM HEPES, pH 7.4, and supplemented with 1 mM ascorbic acid and 1 mM 3-isobutylmethylxanthine (Sigma), cell monolayers were incubated for 30 min at 37° in 1 ml of buffer, in the absence (basal level, 5–25 pmol/10^6 cells) or in the presence of 10 μM (−)-isoproterenol (maximal stimulation mediated by β-AR, 170–400 pmol/10^6 cells), 25 μM forskolin (direct adenylyl cyclase stimulation, 420–850 pmol/10^6 cells), or 1 pM to 100 μM ligand. The reaction was stopped by one wash with 1 ml of PBS and immediate addition of 500 μl of 1 N NaOH. After a period of 20 min at 37°, dissolved cells were collected, buffered with

[1] N. Blin, C. Nahmias, M. F. Drumare, and A. D. Strosberg. The β3-adrenergic receptor: a single subtype responsible for atypical β-adrenergic receptor-mediated effects. Submitted for publication.

1 N acetic acid, and centrifuged at 3000 × g for 10 min at 4°. The total cAMP amount contained in an aliquot of supernatant was determined using the Amersham [^{3}H]cAMP assay or [^{125}I]-cAMP scintillation proximity assay.

For inhibition studies of adenylyl cyclase stimulation, cells were preincubated with the antagonist at 37° for 10 min before addition of a reference agonist [i.e., (−)-isoproterenol] at its K_{act} concentration (5 nM) and incubation for a subsequent 20-min period.

Data analyses. The data were expressed as the means ± standard errors of at least three independent experiments performed in duplicate, except for forskolin binding data, which resulted from two experiments only. Saturation experiments were computer analyzed with the EBDA program (Biosoft-Elsevier, Cambridge, UK) using the Scatchard plot representation. IC_{50} and EC_{50} parameters obtained from binding competition experiments or adenylyl cyclase activation or inhibition experiments were determined using a computerized, iterative, nonlinear, least squares curve-fitting program (Inplot 4.0, written by H. J. Motulsky, GraphPad Software, San Diego, CA). IC_{50} values measured in binding competition or cyclase antagonism experiments were corrected (K_i value) according to the method of Cheng and Prusoff. The IA of a compound was measured relative to the maximal cyclase stimulation obtained for (−)-isoproterenol. Ligands that possessed IA values of <0.90 were defined as partial agonists.

Molecular modeling. The conformations of the arylethanolamine-related compounds that were incorporated into the analysis were obtained using the BIOSYM molecular modeling software (BIOSYM Technologies, Inc., San Diego, CA) on a Silicon Graphics workstation.

Initial structures were built using the Insight II Builder module, which directly produced coarse three-dimensional starting structures. To mimic ionization at neutral pH, an *sp*3+ hybridization was assigned to the amine of the main alkyl chain, increasing the molecular electrostatic total charge by +1.

Energy minimization and MD simulations were performed with the Insight II Discover module, using the consistent valence force field. All calculations were performed for *in vacuo* conditions, using in the description of the coulombic interaction a distance-dependent dielectric constant fixed to 3.5 to avoid formation of intramolecular salt bridges.

The first step of modeling consisted of minimizing the structure previously constructed, to find a local energy minimum on the potential energy hypersurface of the molecule. Calculations were performed according to several algorithms commonly used in molecular mechanics minimization for choosing descent directions, namely steepest descent, conjugate gradient, and Newton-Raphson methods.

The second step of the conformational sampling procedure consisted of recording MD trajectories. By solving the equations of motion for a system of atoms, MD has an advantage in that it is not restricted to harmonic motion about a single minima but allows molecules to cross energy barriers and explore other stable conformations. Molecular conformers were sampled during a 1-nsec MD trajectory at 300°K. A time step of 5 fsec was used, and the system was equilibrated for 1 psec. A conformation was stored each 5 psec, so that 200 conformations were recorded by the end of the MD simulation.

All molecular conformations were compared using the Analysis module of Insight II. Conformational similarities were evaluated by calculating the RMS of deviation between heavy atoms for each possible pair of these 200 structures and by plotting the associated cluster graph. A threshold value of 4 Å was selected to plot the RMS evolution, so that numerous boxlike areas appeared along the diagonal, representing group of structures whose small RMS deviations (<1 Å) and closeness in time suggested that they may belong to the same conformational family. Conformational representatives extracted from each family were compared for each compound, as well as between different ligands, using a superimposition procedure.

Results and Discussion

Selectivity of β-AR Ligands in CHO-β1, CHO-β2, and CHO-β3

Although β-AR overexpression has been reported to affect adenylyl cyclase sensitivity (18–20), it offers the opportunity to thoroughly characterize receptors such as the β3-AR, for which high affinity radiolabeled antagonists have not been developed thus far. The human β1-, β2-, and β3-ARs overexpressed in CHO cells displayed selectivity profiles for catecholamines and reference β-AR ligands that were consistent with those described in tissues characterized by prevailing β1-, β2-, and β3-AR populations (16). The presence of six additional carboxyl-terminal residues in the sequence of the human β3-AR, resulting from splicing of an intron in the corresponding gene, has been reported (21, 22), but a recent pharmacological comparison failed to detect any difference between the 408- and 602-residue forms of this receptor (23).

Because the apparent affinity of agonists at ICYP binding sites may be influenced by varying degrees of internalization, we verified that the lipophilicity indices (log *P*) of the β1- and β2-AR agonists tested in CHO-β were higher than that of the ICYP radioligand. For the β3-AR, no bias in measurement of K_i values is expected, because this receptor subtype does not become sequestered (23).

Because differences in the level of receptor expressed in each CHO-β subclone [190,271 ± 16,796 sites/cell in CHO-β1 (human), 74,885 ± 22,461 sites/cell in CHO-β2 (human), and 108,785 ± 5,988 sites/cell in CHO-β3 (human)] and differences in receptor subtype coupling might interfere with the measurement of cyclase stimulation potency, the stoichiometry of receptor-G_s-adenylyl cyclase interactions was assessed in CHO-β1, CHO-β2, and CHO-β3. Because isoproterenol-stimulated forskolin binding measurements revealed approximately the same number of forskolin binding sites in the three types of cells as well as after cholera toxin stimulation (Fig. 1), it appeared that all of the cholera toxin-sensitive G protein coupled-adenylyl cyclase existing in CHO-β was stimulated by isoproterenol. Moreover, it appeared that coupling efficiency of the three β-AR subtypes should not bias the adenylyl cyclase stimulation potency measurements, thus allowing comparison of the β selectivity of ligands based on K_{act} values.

The selectivity of β-AR ligands exhibiting interesting pharmacological properties at the β3 site[1] was evaluated in CHO-β1, CHO-β2, and CHO-β3 and led to the classification of the compounds into three groups, i.e., agonists at the three β sites,

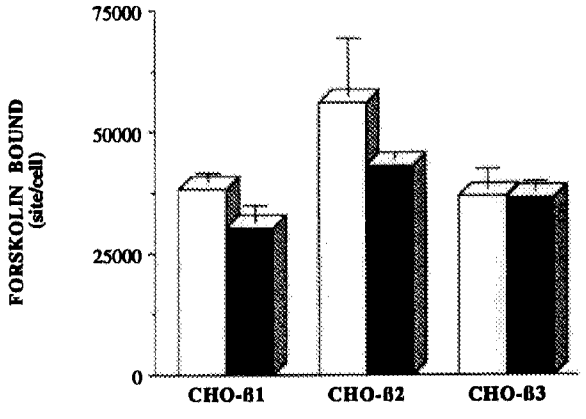


Fig. 1. Measurement of the rate of coupling in CHO-β1, CHO-β2, and CHO-β3. Forskolin binding was evaluated in intact CHO-β1, CHO-β2, and CHO-β3 preincubated (■) or not (□) with 2 μg/ml cholera toxin for 5 hr at 37° and incubated with 100 μM isoproterenol for 1 hr at 4°. Values are the mean ± standard error of two separate experiments performed in duplicate.

β1/β2 antagonists displaying β3 agonistic properties, and antagonists for the β1-, β2-, and β3-ARs (Table 1).

β1/β2/β3 agonists. The β3-AR was characterized by its potency for a class of arylethanolamine agonists that were initially found to be potent and selective activators of lipolysis and thermogenesis at the atypical β-ARs described in white and brown adipose tissues (Table 1). BRL 37344, the most representative compound of this class (2, 24), was a full agonist in CHO-β1 and CHO-β3, with partial agonistic effects (IA = 0.8) in CHO-β2, and exhibited a 10-fold β3-AR selectivity, relative to the β1- and β2-ARs. LY 79771, an activator of the metabolic rate in dogs (25), stimulated adenylyl cyclase with 5- and 17-fold greater potency in CHO-β3 than in CHO-β1 and CHO-β2, respectively. Thus, atypical β-AR compounds, which are potent in inducing thermogenesis in brown adipose tissue and in increasing the rates of cellular metabolism such as lipolysis in white adipose tissue, appeared to be β3-selective ligands.

SR 58611A and SM 11044, which were relaxant agents in the precontracted rat colon (3) and guinea pig ileum (26), respectively, were "rather β2/β3-selective" agonists in CHO-β. SR 58611A, the potent and most selective compound of the phenylethanolaminotetraline class, induced rat colon relaxation with an EC_{50} of 3.5 nM (3), compared with a K_{act} of 25 nM in stimulating CHO-β3 adenylyl cyclase. The SM 11044 functional selectivity order in guinea pig tissues, i.e., ileum relaxation (atypical β-AR) > trachea or lung relaxation (β2-AR) > atrium rate increase (β1-AR), was consistent with the selectivity of this drug in CHO-β1, CHO-β2, and CHO-β3. Although possessing rather low affinities at the β3 site (K_i range of 1–6 μM), these compounds were efficient enough (K_{act} values between 10 and 100 nM) to induce β3-AR-mediated functional relaxation in smooth muscle tissues.

Cimaterol and clenbuterol, reported to induce protein accretion and to increase skeletal muscle mass *in vivo* (25), were "rather β1/β2-selective" agonists in CHO-β. In addition, cimaterol exhibited high efficiency in stimulating the cyclase in CHO-β3, in agreement with its ability to potently activate lipolysis in rat white adipose tissue (25).

β1/β2 antagonists/β3 agonists. Among the β1/β2 antagonists displaying β3 agonistic properties, some exhibited high binding affinities and agonistic potencies in CHO-β3 (Table 1). Bucindolol, described as a high affinity nonselective β-AR antagonist (27), displayed the same binding affinities for β1- and β2-ARs expressed in CHO cells (K_i values of 0.2 nM and 0.1 nM, respectively) and possessed full and potent (K_{act} = 7 nM) β3 agonistic effects. ICI 201651, the *in vivo* metabolized form of ICI D7114 that is able to selectively stimulate brown adipose tissue activity (28), was a weak antagonist at the β1- and β2-AR sites (K_i values of 0.55 μM and 2.86 μM, respectively) but a potent full agonist in CHO-β3 (K_{act} = 20 nM). ICI 201651 was the most important compound of this class, exhibiting a β3 selectivity in binding affinities.

CGP 12177A, oxprenolol, pindolol, and alprenolol were 10–100-fold less potent in stimulating the β3-AR than were the previously mentioned full agonists and, except for alprenolol, demonstrated partial agonistic effects. Pindolol maintained its cyclase stimulation potency when a cyano group was added to the indol function of the molecule (K_{act} value of 153 nM, compared with 174 nM) but displayed an IA that increased from 0.55 to 0.82. These compounds bound to the β1- and β2-ARs with 10–100-fold higher affinities than those measured in CHO-β3.

Nadolol and propranolol were β1/β2 antagonists exhibiting weak (K_{act} values in the micromolar range) and partial agonistic effects in CHO-β3. In agreement with these results, Bond and Clarke (29) reported a biphasic effect for nadolol and propranolol in antagonizing the isoproterenol-induced relaxation of precontracted guinea pig ileum strips.

β1/β2/β3 antagonists. The third category of ligands included antagonists such as the β1-selective CGP 20712A, the β2-selective ICI 118551, and bupranolol (Table 1).

Kaumann (30) earlier reported that heart atypical β agonistic effects were antagonized by 1 μM bupranolol but not propranolol. Although (−)-bupranolol appeared to be the best antagonist available to characterize the β3-AR (K_i value of 50 nM), its receptor binding order of selectivity in CHO-β was β2-AR > β1-AR > β3-AR.

The selectivity profiles for these antagonists were CGP 20712A = bupranolol > ICI 118551 in CHO-β1, bupranolol ≥ ICI 118551 > CGP 20712A in CHO-β2, and bupranolol > ICI 118551 > CGP 20712A in CHO-β3.

Taken together, our data show that β3-selective agonists (BRL 37344 and LY 79771), β3-selective (ICI 201651) and β3-potent (bucindolol and CGP 12177A) agonists that exhibit β1/β2 antagonistic properties, a β3-potent antagonist (bupranolol), and β1- and β2-selective antagonists (CGP 20712A and ICI 118551, respectively) are useful tools that can help to distinguish β3-AR-mediated physiological effects from those mediated by conventional β1- and β2-ARs. To date, only [^{125}I] ICYP and [^{3}H]CGP 12177A have allowed direct characterization of tissue β3-ARs (13). In addition, radiolabeling of ICI 201651, which exhibited binding selectivity towards the β3 site, should provide a new pharmacological tool for the characterization of the β3-AR in tissues. More selective compounds for the β3-AR, however, remain to be found, and analysis of the structure-activity relationships for this large variety of compounds should help in determining the structural features responsible for the β3 potency and selectivity of ligands.

Structural Features of β3-AR Ligands

Fine specificity of the ligand recognition mechanism for G protein-coupled receptors. Norepinephrine stimulated adenylyl cyclase in CHO-β3 with a 1600-fold higher potency, relative to dopamine, which is its metabolic precursor and is specific for dopaminergic receptors (7). Although these compounds are structurally related, β-hydroxylation of the alkylamine chain appears to be important for ligand-receptor recognition. Indeed, this modification creates an asymmetrical center, leading to isomerization of the molecule, and this polar β-hydroxyl group may interact with an electrophilic center and form a hydrogen bond with an amino acid side chain inside the receptor groove.

Similarly, α- and β-ARs were distinguished upon the basis of the potency order of isoproterenol, relative to norepinephrine and epinephrine, three catecholaminergic structures that are closely related. Indeed, isoproterenol differs from (nor)-epinephrine by a (di)methyl substitution, which increases steric bulk and lipophilicity at the end of the alkylamine chain, and the substitution of a methyl group on the protonated amine moiety of norepinephrine corresponds, in thermodynamic calculations, to a loss of 6–7 kcal (31). These modifications seem

TABLE 1

Comparison of the pharmacological properties of human β1-, β2-, and β3-AR expressed in CHO cells

Binding competition assays were carried out with intact cells for 45 min at 37° in the presence of [^{125}I]ICYP, as described in Materials and Methods. Adenylyl cyclase stimulation assays were performed with intact cells preincubated or not with 5 nM isoproterenol for 10 min and incubated with drugs for 30 min at 37°. Concentration-response curves were fitted using least squares regression analysis, and binding competition (K_i) and adenylyl cyclase stimulation (K_{act}) constants were deduced. IA was calculated for each drug relative to isoproterenol-induced maximal cAMP accumulation. Values are means ± standard errors of at least three independent experiments performed in duplicate. Ligands were classified as β1/β2/β3 agonists (more β3-selective, more β2/β3-selective, or more β1/β2-selective agonists), β1/β2 antagonists/β3 agonists, or β1/β2/β3 antagonists. All data were obtained using similar experimental conditions.

	Human β1-AR			Human β2-AR			Human β3-AR		
	Binding K_i	Adenylyl cyclase stimulation		Binding K_i	Adenylyl cyclase stimulation		Binding K_i	Adenylyl cyclase stimulation	
		K_{act}	IA		K_{act}	IA		K_{act}	IA
	nM	nM		nM	nM		nM	nM	
β1/β2/β3 agonists									
BRL 37344	1,750 ± 310	112 ± 28	1.30 ± 0.11	1,120 ± 380	177 ± 47	0.80 ± 0.04	287 ± 92	15 ± 3	1.11 ± 0.12
LY 79771		86 ± 8	1.42 ± 0.30		325 ± 121	0.22 ± 0.03	555 ± 71	18 ± 3	1.06 ± 0.04
SR 58611A	38,500 ± 13,400	12,000 ± 600	0.96 ± 0.07	187 ± 26	36 ± 19	0.87 ± 0.07	6,640 ± 960	25 ± 5	1.23 ± 0.23
SM 11044	18,100 ± 1,700	190 ± 20	1.50 ± 0.21	4,100 ± 200	62 ± 6	1.03 ± 0.08	1,300 ± 200	84 ± 10	0.98 ± 0.10
Cimaterol		0.64 ± 0.15	1.20 ± 0.06		0.57 ± 0.002	0.98 ± 0.03	4,700 ± 1,710	17 ± 3	1.15 ± 0.08
Clenbuterol	190 ± 30			60 ± 9	1.0 ± 0.2	0.91 ± 0.02	1,100 ± 200	1,050 ± 130	0.72 ± 0.07
β1/β2 antagonists/β3 agonists									
Bucindolol	0.20 ± 0.04	Antagonist		0.10 ± 0.03	Antagonist		23 ± 10	7.0 ± 1.2	1.01 ± 0.10
ICI 201651	549 ± 200	Antagonist		2,860 ± 750	Antagonist		85 ± 12	20 ± 9	1.14 ± 0.14
CGP 12177A	0.9 ± 0.1	Antagonist		4 ± 2	Antagonist		88 ± 22	139 ± 44[a]	0.68 ± 0.02[a]
Oxprenolol	5.4 ± 1.3	Antagonist		1.5 ± 0.4	Antagonist		70 ± 10[b]	77 ± 13[b]	0.53 ± 0.07[b]
Pindolol	3.4 ± 0.7	Antagonist		2.3 ± 0.9	Antagonist		11 ± 2[b]	153 ± 12[b]	0.55 ± 0.05[b]
Cyanopindolol		Angatonist			Antagonist			174 ± 58	0.82 ± 0.04
Alprenolol	8.8 ± 0.2	Antagonist		1.5 ± 0.3	Antagonist		110 ± 30	219 ± 46	0.97 ± 0.07
Nadolol	40 ± 6	Antagonist		14 ± 5	Antagonist		636 ± 72	1,120 ± 350	0.80 ± 0.05
Propranolol	6.3 ± 1.0	Antagonist		0.7 ± 0.3	Antagonist		145 ± 8	1,490 ± 550	0.51 ± 0.12
β1/β2/β3 antagonists									
(−)-Bupranolol	1.7 ± 0.3	Antagonist		0.4 ± 0.1	Antagonist		50 ± 14	Antagonist	
(±)-Bupranolol	2.4 ± 0.5	Antagonist		0.5 ± 0.1	Antagonist		106 ± 8	Antagonist	
ICI 118551	120 ± 3[c]	Antagonist		1.2 ± 0.2[c]	Antagonist		257 ± 34[b]	Antagonist	
CGP 20712A	1.5 ± 0.2[c]	Antagonist		1,800 ± 400[c]	Antagonist		2,300 ± 450[b]	Antagonist	

[a] Results reported by Nahmias *et al.* (10), with IA expressed relative to isoproterenol.
[b] Data reported by Emorine *et al.* (7), with IA expressed relative to norepinephrine maximal cyclase stimulation.
[c] Data reported by Tate *et al.* (16).

to be crucial for the ligand-receptor recognition mechanism leading to subtype selectivity, and Lewell (32) suggested that residue Val^{117} in the β-AR sequence, replaced by the less hydrophobic amino acid cysteine in the α-AR sequence, could be mainly responsible for the β versus α subtype specificity.

Structural characteristics of the three pharmacological classes of β-AR ligands. Catecholamines are small molecules with an approximately 10-carbon skeleton. One part of the molecule consists of a catechol group equivalent to a reactive *ortho*-hydroquinone function (a potential hydrogen bond donor), and the other part is a positively charged β-hydroxylalkylamine chain ending in apolar alkyl substitutions. The aromatic ring, the β-hydroxyl group, the charged amine, and the alkyl substitutions are structural requirements common to all of the β-AR compounds evaluated in CHO-β1, CHO-β2, and CHO-β3 (Table 1).

Cimaterol and clenbuterol (Fig. 2A), which were rather β1/β2-selective compounds, possess a structure close to that of isoproterenol, except that both hydroxyl groups of the phenyl moiety are substituted by less polar but equally reactive amine functions, or an inductor-donor chlorine atom and an electrophilic cyano group, which favor delocalization of benzenic π-electrons and may increase hydrophilicity. Large structural modifications of the hydroxylalkylamine chain occur for the rather β2/β3-selective compounds like SR 58611A and SM 11044 (Fig. 2A); the skeleton becomes longer and possesses two asymmetrical centers and one additional aromatic ring substituted with electronegative or nucleophilic atoms, so that steric bulk as well as aromaticity might be strengthened. The rather β3-selective agonists BRL 37344 and LY 79771 share similar features (Fig. 2A), except that these molecules possess an alkylamine chain that appears less ramified and more flexible than those of SR 58611A and SM 11044.

Among β1/β2 antagonists exhibiting β3 agonistic effects (Fig. 2B), alprenolol and oxprenolol have similar structures and, remarkably, behaved similarly towards each of the three receptor subtypes. CGP 12177A and nadolol on one hand, and pindolol and propranolol on the other hand, possess the same ethoxyhydroxylalkylamine chain but different polar substitutions on the cyclic moiety, which may account for the 10-fold difference in binding affinity measured with each type of CHO-β either between CGP 12177A and nadolol or between pindolol and propranolol.

Affinities of the antagonists at the β3 site appear to be inversely related to the number of carbons in the backbone as well as to the steric bulk of the aromatic moiety (Fig. 2C). The number of compounds tested in this class is, however, insufficient to deduce important structural characteristics for β1/β2/β3 antagonists. In a general way, Dixon *et al.* (33) concluded that the subtype selectivity of antagonists appears to arise from the subtype selectivity of the substituents on the aromatic ring and/or from the addition of differentially substituted aromatic moieties to an alkyl chain on the amine.

From this analysis, it seems that an obvious correlation exists between β-AR ligands of similar structural formula and pharmacological classes defined in CHO-β1, CHO-β2, and CHO-β3. However, ICI 118551 and pindolol, which share basic structural similarities, exhibit either antagonistic or agonistic effects in CHO-β3, emphasizing therefore the structural complexity of the ligand-receptor recognition mechanism responsible for binding and signal processing.

Structural requirements for β3-selective and -potent ligands. A global analysis of structures shows that β1/β2 antagonists (Fig. 2, B and C) display an obvious structural difference, compared with β1/β2 agonists (Fig. 2A), because a $O\text{-}CH_2$ spacer is inserted between the aryl group and the β-hydroxylalkylamine chain, extending the molecule and inducing a mesomer-donor effect that might strengthen the aromaticity on the ring. The ethoxy linking group inside the aryloxyhydroxylalkylamine chain thus introduces a structural modification important enough to alter the transduction of signal in CHO-β1 and CHO-β2. Some authors have addressed the question of modes of binding of arylhydroxylalkylamine and aryloxyhydroxylalkylamine ligands to β-ARs and invoked either the existence of distinct binding sites for the aromatic moieties of each ligand type (34) or large conformational flexibility of the ligands, involving energetically more or less favorable folded or extended conformations that all fit into a single binding site (35). In CHO-β3, the ethoxy function seems to play a minor role in ligand-induced receptor activation, because bucindolol and ICI 201651 are as potent agonists as are BRL 37344, LY 79771, and SR 58611A, which do not possess this additional group; these results are in line with the second hypothesis.

Common structural requirements characterize the selective or potent β3-AR ligands, i.e., a 18–20-carbon backbone length, an aromatic ring (substituted or not), and an (oxy)hydroxylalkylamine chain ending in an indol function or a phenyl carrying hydroxyl, ether, or acid functions, which increase steric bulk and moderate lipophilicity.

From this structural formula analysis, it appears that small conventional β-AR ligands may achieve increased interactions with the β-AR sites by hydrogen bonding of *meta*- and *para*-hydroxyl groups of the catechol, whereas binding of long and bulky β3-potent compounds may be stabilized by aryl-aryl or polar interactions between the phenyl-substituted part of the alkylamine moiety and residues in the site.

Moreover, small molecules such as catecholamines were more efficient in activating the β1- and β2-ARs than the β3-AR, whereas the long and bulky molecules, which should occupy the whole space available in the site groove, were more potent or selective in CHO-β3. This suggests that the β3 efficiency is determined by the long and bulky amine substituent moiety of the ligands, which may interact with helices positioned on the opposite side, relative to those implicated more specifically in ligand binding.

Structure-Activity Analysis by Molecular Modeling

To further explore structural features responsible for the pharmacological properties of ligands, we used the recently developed molecular modeling tools, which provide more realistic insight into molecules because their three-dimensional conformations are related to their physico-chemical properties. Because biomolecules exist as a set of active conformations in an equilibrium state depending upon system internal entropy and intermolecular collisions, the dynamic motions of β3-AR ligands were studied using MD simulations on minimized structures.

Ligands as a set of bioactive conformers in equilibrium. Analysis of conformations generated by MD simulations for the BRL 37344 and LY 79771 ligands showed that, within a family, conformations were mostly similar, even though some superimpositional discrepancies occured in the plane of the

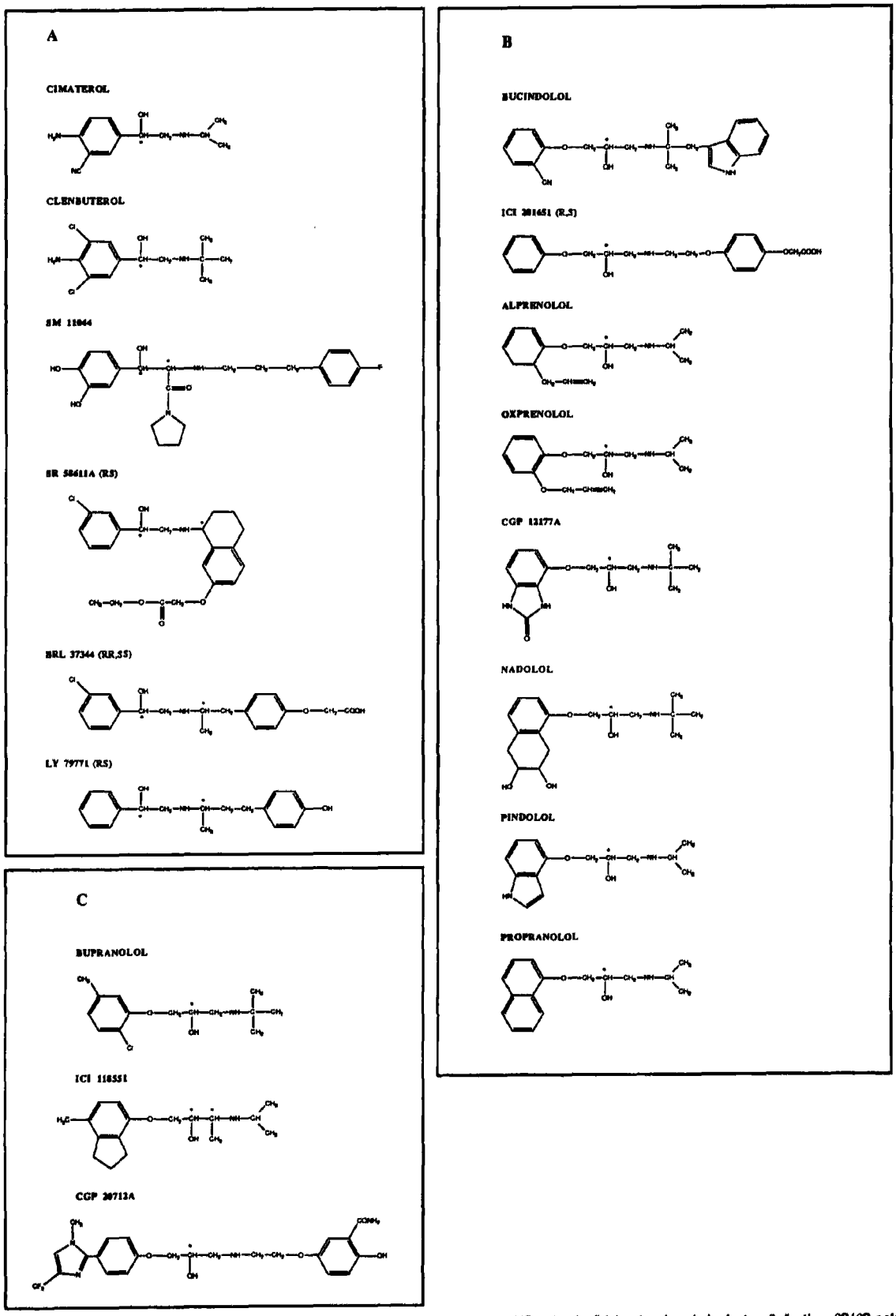


Fig. 2. Comparison of structural formulas for β-AR ligands that exhibited "rather β1/β2-selective" (cimaterol and clenbuterol), "rather β2/β3-selective" (SM 11044 and SR 58611A), or "rather β3-selective" (BRL 37344 and LY 79771) agonistic properties (A), β1/β2 antagonistic and β3 agonistic effects (B), or β1/β2/β3 antagonistic effects (C). Asterisks mark asymmetric carbons.

catechol moiety or at the end of the alkylamine chain, implying greater rotational ability for bonds implicated in these parts of the molecules. A detailed analysis of conformational families showed that the coexistence of two benzene rings within one structure led to the appearance of both extended and stacked conformations, with respective distances of 8.2–9.0 Å and 4.0–6.8 Å between the most remote carbon atoms (Fig. 3).

SR 58611A, in contrast to BRL 37344 and LY 79771, exhibited only stacked conformations (7–9 Å long), probably because of the constraint imposed by additional cyclization between the aromatic ring and the $NH(CH_3)$ group of the chain. To validate this hypothesis, we assayed the SR 58611A structure in a MD simulation over the same period but at higher temperature (600°K), to increase the kinetic energy of the system and to sample, therefore, a larger available conformational space. From this high thermal energy MD simulation, we indeed obtained an extended conformational family exhibiting a 16-Å distance between the most remote carbon atoms (Fig. 4).

For all molecules, the transition between extended and stacked conformations was mainly due to rotation around the C^{α}-C^{β} bond [C^{β}(OH)-C^{α}(NH)] of the hydroxylalkylamine chain. To analyze the possibility of transconformation between these two forms, we used a dynamics simulation forcing rotation of the dihedral angle (OH-C^{β}-C^{α}-NH) in 10° stepwise increments. BRL 37344 was able to move from an extended to a stacked conformation at an energy expense of 12 kcal/mol and in a time scale of 1 psec, consistent with binding kinetic equilibrium constants. Extended and stacked conformers may thus exchange, and it is possible that a ligand will sacrifice nearly 10 kcal/mol to adopt an optimal conformation, leading to the best fit into the receptor binding site.

Relationships between structural conformations and pharmacological properties. Of primary importance in a comparative molecular analysis is the definition of superimposition rules for the series of compounds under investigation. The potent β3 agonists were either β1/β2 agonists or β1/β2 antagonists, and in each case the compounds shared a similar portion of the skeleton, that is, aromatic carbon-CH(OH)-CH_2(NH) or aromatic carbon-O-CH_2-CH(OH)-CH_2(NH), respectively. Therefore, we used an automated superimposition procedure involving these consensual atoms, and the quality of the superimposition step was measured by the RMS deviation

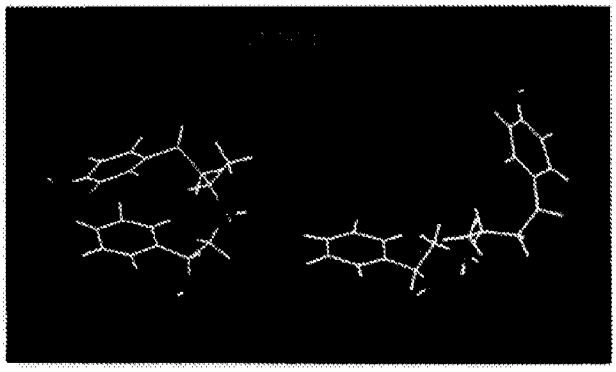


Fig. 3. Extended (*right*) and stacked (*left*) conformations of the potent β3 agonist LY 79771, obtained after a 300°K MD simulation step performed as described in Materials and Methods. The dot surface at van der Waals radius is depicted and shows the steric bulk of the conformers.

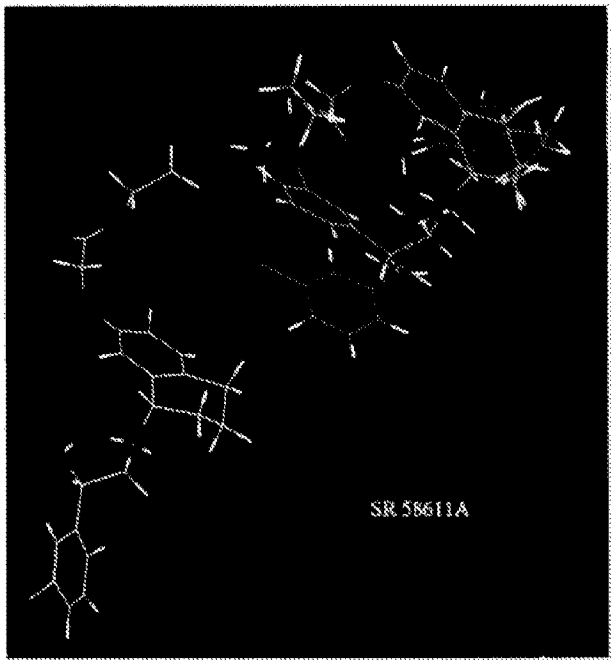


Fig. 4. Representation of the three conformational families obtained for the potent β3 agonist SR 58611A, using a 300°K (*purple* and *turquoise* folded conformations) or a 600°K (*orange* extended conformation) MD simulation step.

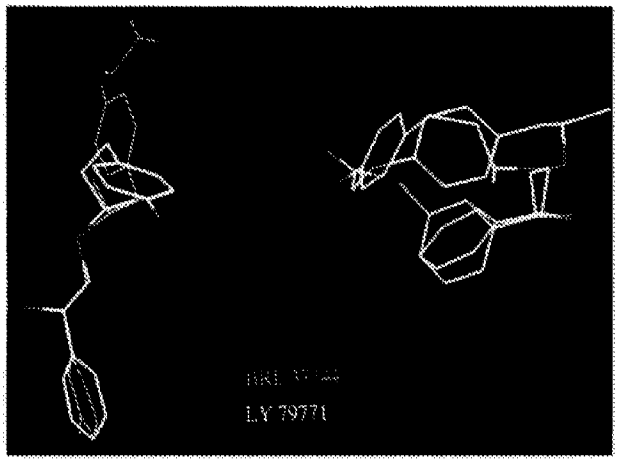


Fig. 5. Superimposition of representative extended and stacked conformers obtained by MD simulation procedures performed on the most selective β3-AR agonists, BRL 37344 and LY 79771.

in fitting.

Equally convincing steric fits (RMS between 0.08 and 0.21) were obtained for the extended and stacked conformations of BRL 37344 and LY 79771 (Fig. 5), as well as for the potent β3 agonists, which were either β1/β2 agonists (BRL 37344, LY 79771, SR 58611A, and cimaterol) or β1/β2 antagonists (bucindolol and ICI 201651) (Fig. 6).

The partial β3 agonists CGP 12177A and propranolol had conformations that overlapped well with each other (RMS between 0.28 and 0.62) but not with those of the full β3 agonists bucindolol and ICI 201651 (RMS between 0.88 and 0.97). An

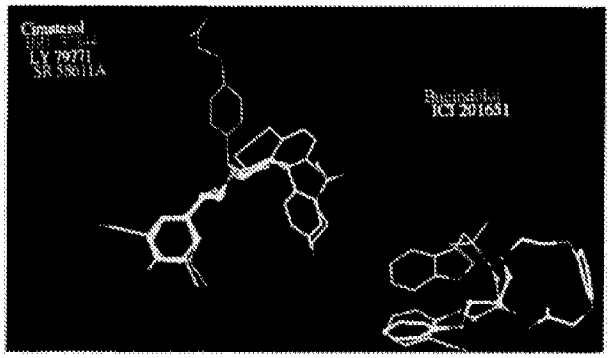


Fig. 6. Superimposition of MD simulation conformations obtained for the $\beta1/\beta2/\beta3$ agonists cimaterol, BRL 37344, LY 79771, and SR 58611A and for the $\beta1/\beta2$ antagonists/$\beta3$ agonists bucindolol and ICI 201651.

explanation could be that partial agonism may result from competitive occupancy of the receptor by energetically favorable (active) and unfavorable (inactive) conformers, with a 6–7-kcal enthalpic energy difference existing between the two forms of the ligand (31).

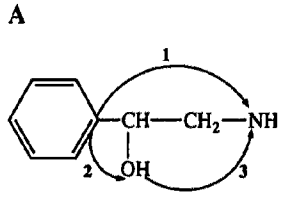
Common structural features appeared between bupranolol and ICI 118551 (RMS of 0.10), which exhibited interesting affinities at the $\beta3$ site but had mostly different conformations, compared with the weak $\beta3$ antagonist CGP 20712A (RMS approximatley 1.0) (data not shown).

To gain more insight into the relative orientations of conformers described above, we evaluated three-dimensional interatomic distances between involved atoms (Fig. 7). Coherent distances were measured for the totality of conformers, further supporting the sizeable role of atoms that were superimposed. On the basis of the hypothetical minimal pharmacophore model imposed during fitting, we thus obtained a mostly satisfactory representation of the manner in which ligands that induce similar pharmacological effects at the $\beta3$ site resemble each other at the three-dimensional level.

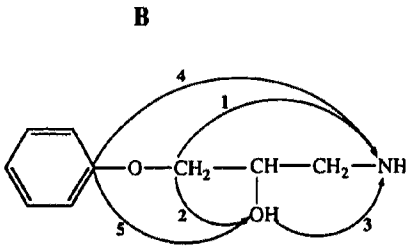
Although this model does not take into account the effect of environment on ligand conformation, the general picture that emerged from the present analysis could be used next to precisely assess the contribution of particular chemical functions in the interaction with the receptor. One may assume that β-AR ligands bind to the $\beta3$-AR in the same orientation because of their very similar steric and electrostatic properties, that is, (i) an aromatic group, which could stabilize aryl-aryl interactions, (ii) a β-hydroxyl or an ether function, which could establish a hydrogen bond, and (iii) a protonated amine, which should create an ionic bridge with a negatively charged carboxyl function inside the pocket site. All these atom groups and their relative orientations in space (depending on whether the ether function is present) constitute the pharmacophore for $\beta3$-AR agonists.

$\beta3$ Specificity of the Ligand-Receptor Interaction

Like the two other subtypes, the human $\beta3$-AR belongs to the family of surface membrane receptors that are structurally organized in seven hydrophobic α-helices connected by extra- and intracellular loops. Binding of ligands to β-ARs is governed by three important factors; (i) the ligand should fit sterically into the receptor groove, (ii) parts of the ligand and receptor with opposite electrostatic groups should closely complement



d1 (Å) = 3.83 ± 0.08
d2 (Å) = 2.47 ± 0.03
d3 (Å) = 3.07 ± 0.08



d1 (Å) = 3.64 ± 0.11
d2 (Å) = 2.40 ± 0.02
d3 (Å) = 2.95 ± 0.03
d4 (Å) = 5.35 ± 0.18
d5 (Å) = 4.31 ± 0.12

Fig. 7. Schematic representation of the $\beta3$-AR minimal pharmacophore. Three-dimensional distances (in Å) were measured between essential atoms of the different conformers obtained for $\beta3$-AR agonists. The means ± standard errors of interatomic distances between atoms joined by *arrows* are reported for 10 $\beta1/\beta2$ agonist conformers (A) and 12 $\beta1/\beta2$ antagonist conformers (B).

each other, and (iii) lipophilic regions should match, to induce optimal hydrophobic interactions.

In past years, site-directed mutagenesis (33, 34, 36, 37), chimeric receptor construction (38, 39), fluorescence binding probe analysis (40), and computer-aided three-dimensional model building (32, 35, 41, 42) have helped investigators understand the structure of the β-AR binding site. These studies all suggest that a number of highly conserved residues interact with the ligand in a 10–15-Å buried groove formed by the seven transmembrane α-helice bundle core, i.e., (i) the aromatic ring of the catechol moiety would be stacked between phenylalanine and tryptophan residues of helices 5 and 6, (ii) the *para*- and *meta*-hydroxyl groups of catechol may form hydrogen bonds with two serine residues, which are conserved as a pair in TM5 only for catecholaminergic receptors, (iii) a hydrogen bond between the β-hydroxyl group and a serine residue in TM4 could explain on one hand the extra stabilization upon binding of norepinephrine, compared with dopamine, and on the other hand the higher binding affinity of β-AR *R*-stereoisomers (32, 42), and (iv) the cationic amine might interact strongly with an aspartate amino acid side chain within a stabilizing hydrophobic cluster of phenylalanine and tryptophan residues in

TM3. All of these interactions were visualized using three-dimensional models of ligands and of β-ARs (43) and supported our assumptions concerning ligand atoms and their spatial arrangement forming the β-AR pharmacophore. The receptor binding site model also implies that large flexible chains can be substituted at the amine end of the ligand, because this part of the receptor corresponds to the receptor core cavity.

From the structural formula analysis of ligands, it appears that catecholamines and agonists that were rather β1/β2 selective possess a short backbone and a catechol group, which may stabilize the ligand in the receptor site by hydrogen bonding with the two serine residues of helix 5. For β3-potent agonists, however, the catechol is replaced by a benzene ring, and stabilization of the long alkylamine chain may be achieved by polar or aryl-aryl interactions between the bulky *N*-substituent and amino acid side chains pointing into the opposite side of the groove. Therefore, we suggest that β1/β2 agonists localize in a reduced space in the site formed by TM3, TM4, and TM5, whereas β3 agonists should establish additional interactions with amino acid side chains in TM7, TM1, and TM2. A three-dimensional view of the β2- and β3-AR sites showing the docking of β2- or β3-selective ligands confirms this difference in steric space occupation of the site (43). All of these findings are in agreement with molecular genetic analysis suggesting the involvement of multiple binding subsites that overlap (39), i.e., in the hamster β-AR sequence, Asp^{113} in TM3 seems to interact directly with the charged amine of β-AR ligands (36, 37) and to determine the physiological effect induced (34), whereas Asp^{79} in TM2 and Asn^{319} in TM7 appear to be selectively involved in agonist binding and signal transduction (36).

Study of ligand structures by three-dimensional molecular modeling showed that the long and flexible alkylamine chains of β3-potent agonists were able to exchange extended and stacked conformations. This mechanism of transconformation may underlie the ability of these ligands to induce agonistic effects specifically at the β3-AR site. Indeed, analysis of amino acids forming the three-dimensional β3-AR binding site and comparison with corresponding amino acids in the β1- and β2-AR sequences show some important differences, such as the substitution of glycine (β3) by alanine (β1) or phenylalanine (β2) in helix 1 and the replacement of adjacent alanine and leucine (β3) by phenylalanine and phenylalanine (β1) or leucine and leucine (β2) in helix 7. The presence of these bulky side chains pointing into the groove of β1- and β2-ARs renders this region of the site less accessible to molecules. In fact, it appears that receptor conformational changes induced by the binding of an agonist are triggered by specific amino acids in helices 1, 2, 3, and 7 (34, 36, 43). Furthermore, the presence of two additional proline residues in the β3-AR TM7 may play a direct role in message triggering, because this type of amino acid introduces noticeable kinks in helices, thus permitting complex conformational shifts and reorientations probably involved in signal transduction.

We suggest herein a mechanistic model in which the long alkylamine chains of β1/β2 antagonist/β3 agonist compounds adopt stacked conformations in the encumbered β1 and β2 sites that prevent access to the signal-processing region, whereas extended conformations, which could be adopted in the less encumbered β3 site, may induce agonistic effects. Only the evaluation of completely rigid compounds retaining the molecular determinants described above would definitively test our model.

This study led us to propose that the ligand conformational state plays a key role in the efficiency of the interaction and that the same compound is able to induce agonistic or antagonistic effects in different receptor subtypes depending on its conformational adaptation to amino acid side chains pointing into the groove. In addition, we suggest that variations in the affinity of structurally related ligands may result from micro-variations in the fitting of ligand and receptor conformations, a dynamic process leading to the existence of various interaction subsites.

In conclusion, this study has provided ligands to study the pharmacological characteristics and physiological implications of β3-ARs in tissues, as well as the specificity of the ligand-receptor interactions. Although these compounds are useful pharmacological tools, their potential clinical value remains limited by their lack of high selectivity. This analysis has helped to provide a theoretical framework for the design and development of new potent or selective β3-AR ligands by using computational methods such as quantitative structure-activity analysis. Additional enhancement in the quality of the designed compounds is expected from advances in methods that may precisely evaluate target molecules in terms of binding conformation, binding affinity, and ligand-induced changes in receptor conformation.

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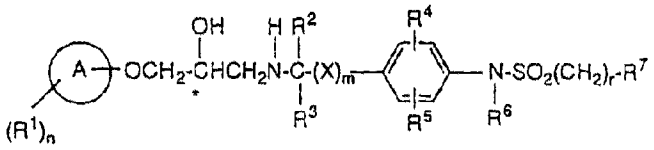

(I)

(57) **Abstract**

Substituted phenylsulphonamides having formula (I) where the variables are as defined in Claim 1; are selective beta-3 adrenergic receptor agonists with very little beta-1 and beta-2 adregenic receptor activity and as such the compounds are capable of increasing lipolysis and energy expenditure in cells. The compounds thus have very potent activity in the treatment of Type II diabetes and obesity. The compounds can also be used to reduce triglyceride levels and cholesterol levels or raise high density lipoprotein levels or to reduce gut motility. In addition, the compounds can be used to reduce neurogenic inflammation or as antidepressant agents. The compounds are prepared by coupling an aminoalkylphenylsulphonamide with an appropriately substituted alkyl epoxide. Compositions and methods for the use of the compounds in the treatment of diabetes and obesity and for the reduction of 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 PHENYL SULFONAMIDES AS SELECTIVE β_3 AGONISTS FOR THE TREATMENT OF DIABETES AND OBESITY

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of our copending application Serial Number 08/015689 filed February 9, 1993.

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 relaxtion (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 selectively, 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 selectively over the β_1 and β_2 activities, this selectively 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.

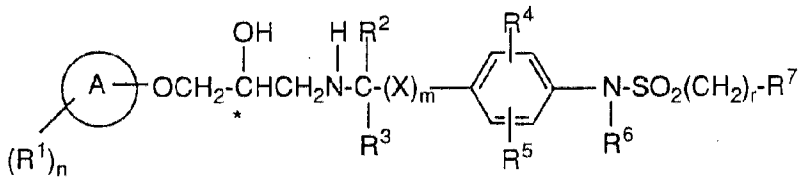
Recently, assays have been developed which more accurately predict the effects that can be expected in humans. These assays utilize cloned human β_3 receptors which have been expressed in Chinese hamster ovary cells. The agonist and antagonist effects of the various compounds on the cultivated cells 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 phenyl 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 phenylsulfonamides. 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 compounds of the instant invention are best realized in the following structural formula:



I

where

n is 0 to 7;

m is 0 or 1;

r is 0 to 3;

A is phenyl, naphthyl, a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur or nitrogen, a benzene ring fused to a C_3-C_8 cycloalkyl ring, a benzene ring fused to a 5 or 6-membered heterocyclic ring with from 1 to 3 heteroatoms selected from oxygen, sulfur or nitrogen or a 5 or 6-membered heterocyclic ring with from 1 to 3 heteroatoms selected from oxygen, sulfur or nitrogen fused to a 5 or 6-membered heterocyclic ring with from 1 to 3 heteroatoms selected from oxygen, sulfur or nitrogen;

R^1 is hydroxy, oxo, halogen, cyano, nitro, NR^8R^8, SR^8, trifluoromethyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_3-C_8 cycloalkyl, phenyl, SO_2R^9, NR^8COR^9, COR^9, $NR^8SO_2R^9$, $NR^8CO_2R^8$ or C_1-C_6 alkyl substituted by hydroxy, nitro, halogen, cyano, NR^8R^8, SR^8, trifluoromethyl, C_1-C_6 alkoxy, C_3-C_8 cycloalkyl, phenyl, NR^8COR^9, COR^9, SO_2R^9, $NR^8SO_2R^9$, $NR^8CO_2R^8$, or R^1 is a 5 or 6-membered heterocycle with from 1 to 3 heteroatoms selected from oxygen, sulfur or nitrogen;

R^2 and R^3 are independently hydrogen, C_1-C_6 alkyl or C_1-C_6 alkyl substituted by 1 to 3 of hydroxy, C_1-C_6 alkoxy, or halogen;

X is $-CH_2-$, $-CH_2-CH_2-$, $-CH=CH-$ or $-CH_2O-$;

R^4 and R^5 are independently hydrogen, C_1-C_6 alkyl, halogen, NHR_8, OR_8, SO_2R^9 or $NHSO_2R^9$;

R^6 is hydrogen or C_1-C_6 alkyl;

R^7 is C_1-C_6 alkyl, C_3-C_8 cycloalkyl, or B-$(R_1)_n$;

B is phenyl, naphthyl, a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur or nitrogen, a benzene ring fused to a C_3-C_8 cycloalkyl ring, a benzene ring fused to a 5 or 6-membered heterocyclic ring with from 1 to 3 heteroatoms selected from oxygen, sulfur or nitrogen or a 5 or 6-membered heterocyclic ring with from 1 to 3 heteroatoms selected from oxygen, sulfur or nitrogen fused to a 5 or 6-membered heterocyclic ring with from 1 to 3 heteroatoms selected from oxygen, sulfur or nitrogen;

R^8 is hydrogen, C_1-C_{10} alkyl, C_3-C_8 cycloalkyl, phenyl optionally substituted by 1 to 3 of halogen, C_1-C_6 alkyl or C_1-C_6 alkoxy, or C_1-C_{10} alkyl substituted by 1 to 3 of hydroxy, halogen, CO_2H, CO_2-C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_1-C_6 alkoxy, or phenyl optionally substituted by from 1 to 3 of halogen, C_1-C_6 alkyl or C_1-C_6 alkoxy;

R^9 is R^8, NHR^8 or NR^8R^8.

In the above structural formula and throughout the instant specification, 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.

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.

The preferred 5 and 6-membered heterocycles and fused heterocycles of A, B and R_1 are those heterocycles with from 1 to 4 heteroatoms independently selected from one of oxygen or sulfur or 1 to 4 nitrogen atoms.

The preferred values of A and B are phenyl, naphthyl or the foregoing preferred 5 and 6-membered heterocycles and fused heterocycles.

The more preferred values of A are phenyl, naphthyl, pyridyl, quinolinyl, pyrimidinyl, pyrrollyl, thienyl, imidazolyl, and thiazolyl.

The more preferred values of B are phenyl, naphthyl, quinolinyl, thienyl, benzimidazolyl, thiadiazolyl, benzothiadiazolyl, indolyl, indolinyl, benzodioxolyl, benzodioxanyl, benzothiophenyl, benzofuranyl, benzisoxazolyl, benzothiazolyl, tetrahydronaphthyl, dihydrobenzofuranyl, and tetrahydroquinolinyl.

Further preferred compounds of the instant invention are realized when in the above structural formula:

R^2 and R^3 are hydrogen or methyl;

X is $-CH_2-$

m is 1;

r is 0-2; and

R^4, R^5 and R^6 are hydrogen.

Still further preferred compounds of the instant invention are realized when in the above structural formula:

A is phenyl, quinolinyl, or a 6-membered heterocyclic ring with 1 or 2 nitrogen atoms;

B is	phenyl or quinolinyl;
R1 is	NH_2, hydroxy, halogen, cyano, trifluoromethyl, phenyl, NR^8COR^9, $NR^8CO_2R^8$, C1-C6 alkyl optionally substituted by hydroxy; and
r is	0 or 2.

Representative preferred antiobesity and antidiabetic compounds of the present invention include the following:

N-[4-[2-[[2-hydroxy-3-(4-hydroxyphenoxy)propyl]amino]ethyl]phenyl]-benzenesulfonamide
N-[4-[2-[[2-hydroxy-3-(4-hydroxyphenoxy)propyl]amino]ethyl]phenyl]-4-iodobenzenesulfonamide
N-[4-[2-[[2-hydroxy-3-(4-hydroxyphenoxy)propyl]amino]ethyl]phenyl]-2-naphthalenesulfonamide
N-[4-[2-[[2-hydroxy-3-(4-hydroxyphenoxy)propyl]amino]ethyl]phenyl]-4-(benzo-2,1,3-thiadiazole)sulfonamide
N-[4-[2-[[2-hydroxy-3-(4-hydroxyphenoxy)propyl]amino]ethyl]phenyl]-2-phenylethanesulfonamide
N-[4-[2-[[3-(4-fluorophenoxy)-2-hydroxypropyl]amino]ethyl]phenyl]-4-benzenesulfonamide
N-[4-[2-[[3-[(2-amino-5-pyridinyl)oxy]-2-hydroxypropyl]amino]ethyl]-phenyl]-2-naphthalenesulfonamide
N-[4-[2-[[2-hydroxy-3-(4-hydroxyphenoxy)propyl]amino]ethyl]phenyl]-3-quinolinesulfonamide
N-[4-[2-[[2-hydroxy-3-(4-hydroxyphenoxy)propyl]amino]ethyl]phenyl]-4-[(5-methoxycarbonyl)pentanoyl]amino]benzenesulfonamide
N-[4-[2-[[2-hydroxy-3-(4-hydroxyphenoxy)propyl]amino]ethyl]phenyl]-4-[(5-hydroxycarbonyl)pentanoyl]amino]benzenesulfonamide
N-[4-[2-[[2-hydroxy-3-(4-hydroxyphenoxy)propyl]amino]ethyl]phenyl]-4-(hexylaminocarbonylamino)benzenesulfonamide
N-[4-[2-[(2-hydroxy-3-phenoxypropyl)amino]ethyl]phenyl]-4-chlorobenzenesulfonamide

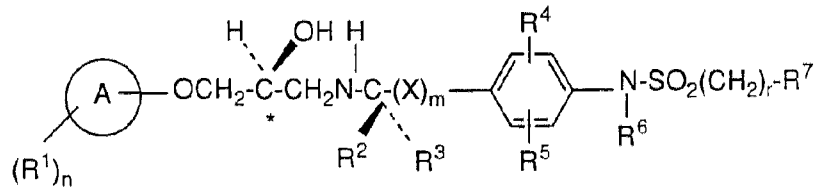
N-[4-[2-[[2-hydroxy-3-(3-cyanophenoxy)propyl]amino]ethyl]phenyl]-3-quinolinesulfonamide
N-[4-[2-[[3-(4-amino-3-cyanophenoxy)-2-hydroxypropyl]amino]ethyl]-phenyl]-3-quinolinesulfonamide
N-[4-[2-[[2-hydroxy-3-[(3-hydroxymethyl)phenoxy]propyl]amino]-ethyl]phenyl]-3-quinolinesulfonamide
N-[4-[2-[[2-hydroxy-3-(3-pyridyloxy)propyl]amino]ethyl]phenyl]-3-quinolinesulfonamide
N-[4-[2-[[2-hydroxy-3-(3-pyridyloxy)propyl]amino]ethyl]phenyl]-4-iodobenzenesulfonamide
N-[4-[2-[[3-[(2-amino-5-pyridinyl)oxy]-2-hydroxypropyl]amino]ethyl]-phenyl]-4-isopropylbenzenesulfonamide.

The compounds of the instant invention all have at least one asymmetric center as noted by the asterisk in structural Formulae I and Ia. 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 Ia, is more active and thus more preferred over the compound in which the hydroxy substituent is below the plane of the structure.

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 following stereospecific structure represents the preferred stereoisomers of the instant invention.

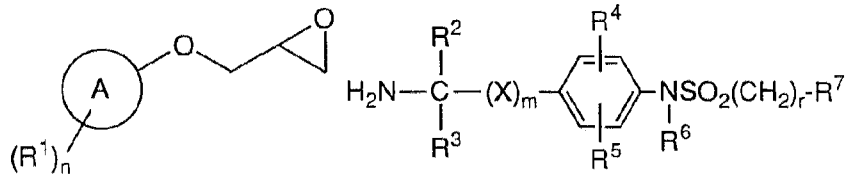


Ia

where the various substituents are as defined above.

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.

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.

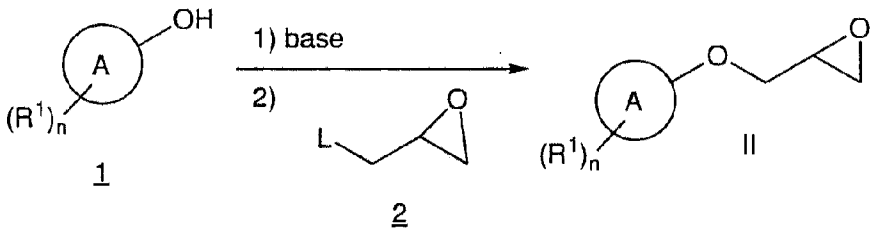


II III

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 can be conveniently prepared by a variety of methods familiar to those skilled in the art. One common route is illustrated in Scheme 1. Alcohol 1 is treated with base such as sodium hydride or potassium t-butoxide in a polar solvent such as anhydrous dimethylformamide. The resultant anion is alkylated with epoxide derivative 2, wherein "L" is a leaving group such as a sulfonate ester or a halide, for 0.5 to 24 hours at temperatures of 20-100°C to provide compound II. The epoxide derivative 2 is conveniently the commercially available, enantiomerically pure (2*S*) or (2*R*)-glycidyl 3-nitrobenzene sulfonate or (2*R*) or (2*S*)-glycidyl 4-toluenesulfonate, thus both the (*S*) and (*R*) enantiomers of epoxide II are readily available.

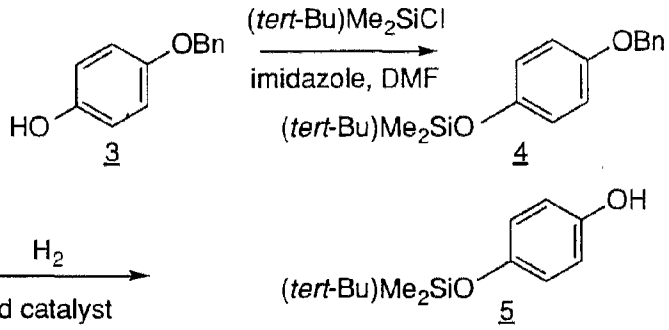
SCHEME 1



Many of the alcohols 1 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 alcohol 1 may need to be protected during the alkylation and 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. A useful method for protecting the preferred alchohol 1 wherein A $(R^1)_n$ is 4-hydroxy-phenyl as its *tert*-butyldimethylsilyl (TBS) derivative is illustrated in Scheme 2. Commercially available phenol 3 is treated with a silylating

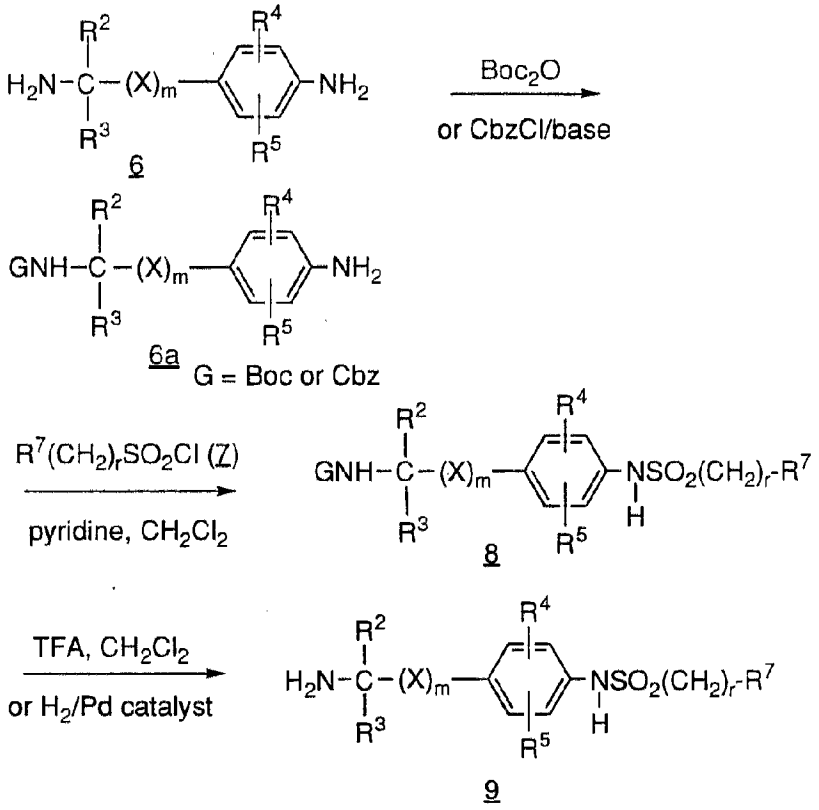
agent such as *tert*-butyldimethylsilyl chloride in the presence of a base such as imidazole in an aprotic solvent such as dimethylformamide. The benzyl group is then removed by catalytic hydrogenation to give the desired alcohol 5.

SCHEME 2



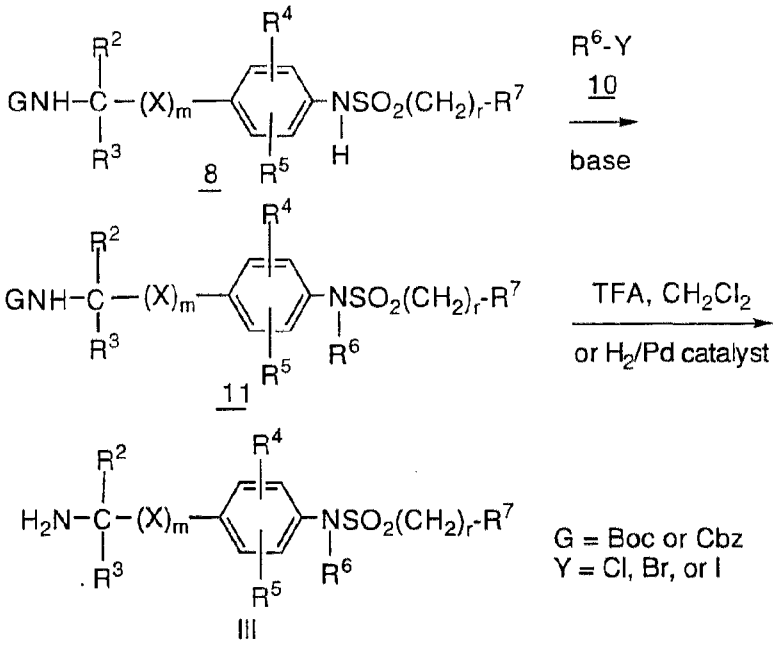
Compounds III can be conveniently prepared by a variety of methods familiar to those skilled in the art. A convenient route for their preparation when R^6 is hydrogen is illustrated in Scheme 3. Compound 6 is selectively protected as a suitable carbamate derivative 6a with, for example, di-*tert*-butyl 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 R6 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 III.

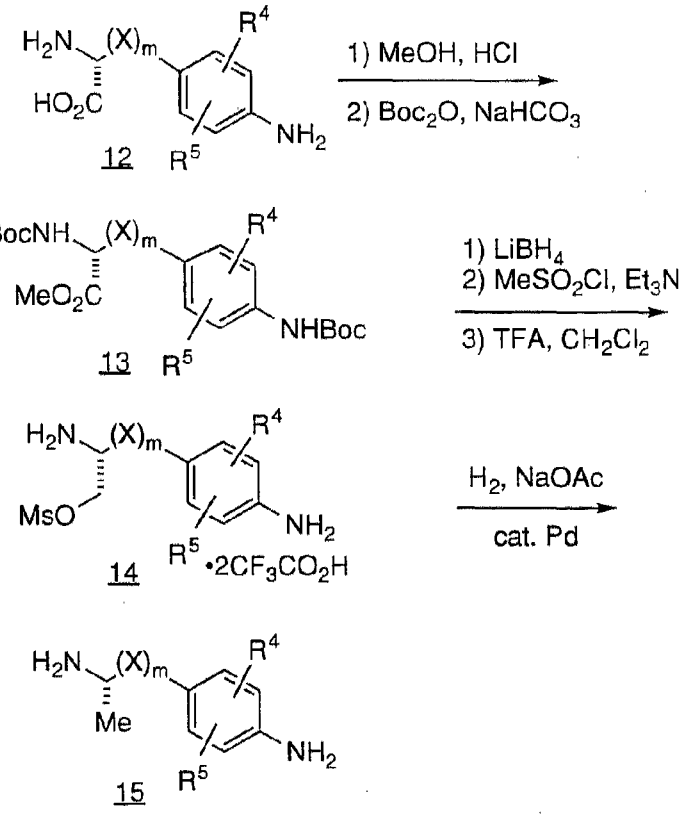
SCHEME 4



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 (1968). 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 cited therein). Alternatively, aromatic compounds may be treated with chlorosulfonic acid according to the procedure of Albert, et. al., J. Het. Chem. 15, 529 (1978), to provide the sulfonyl chlorides.

The diamines 6 are commercially available or readily prepared by methods described in the literature or known to those skilled in the art. Compound 6 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.

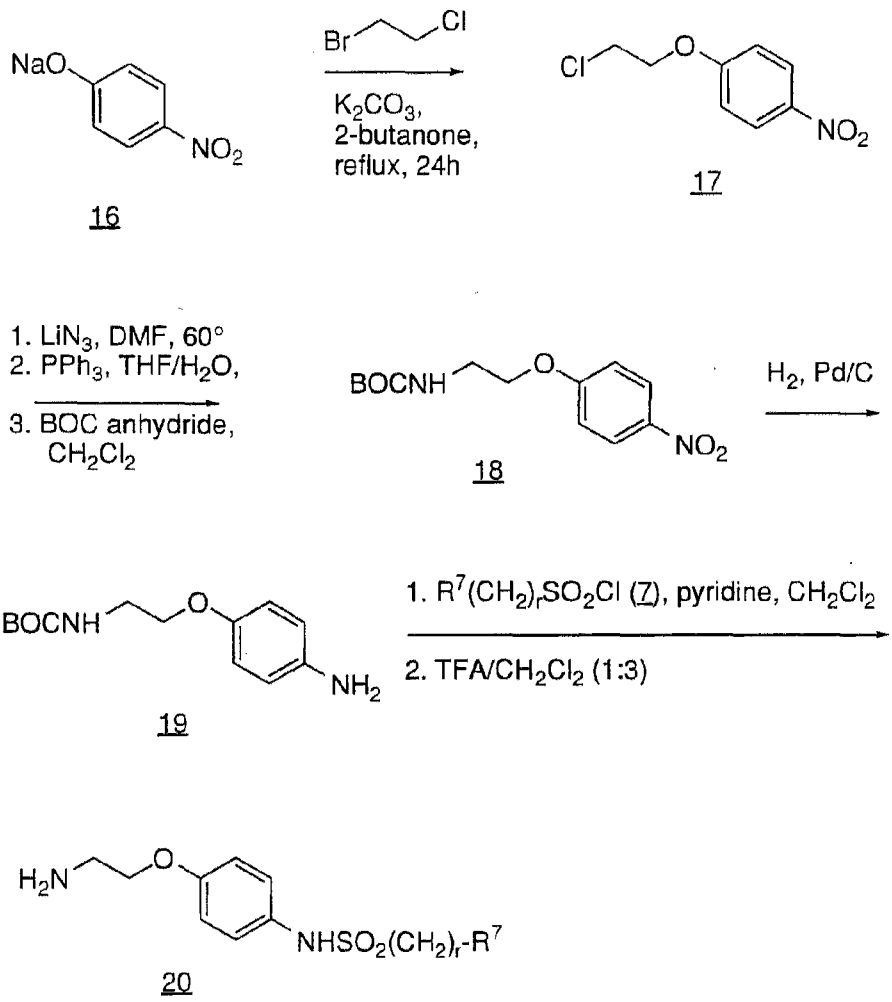
SCHEME 5



Diamines 6 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.

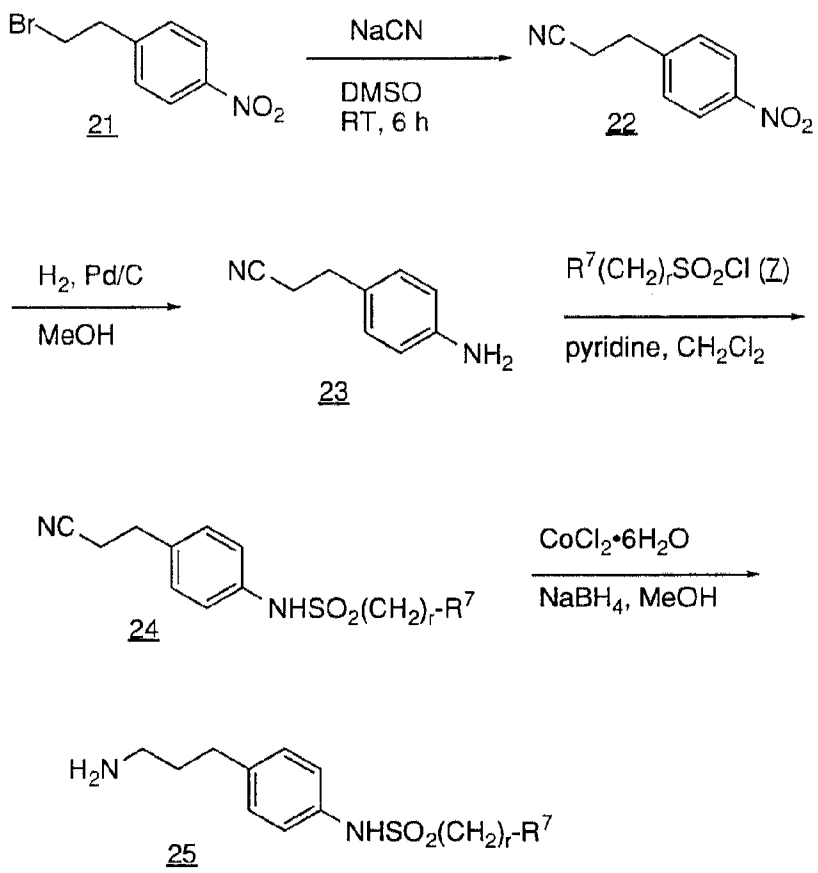
SCHEME 6



Alternatively, diamine 6 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 6 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

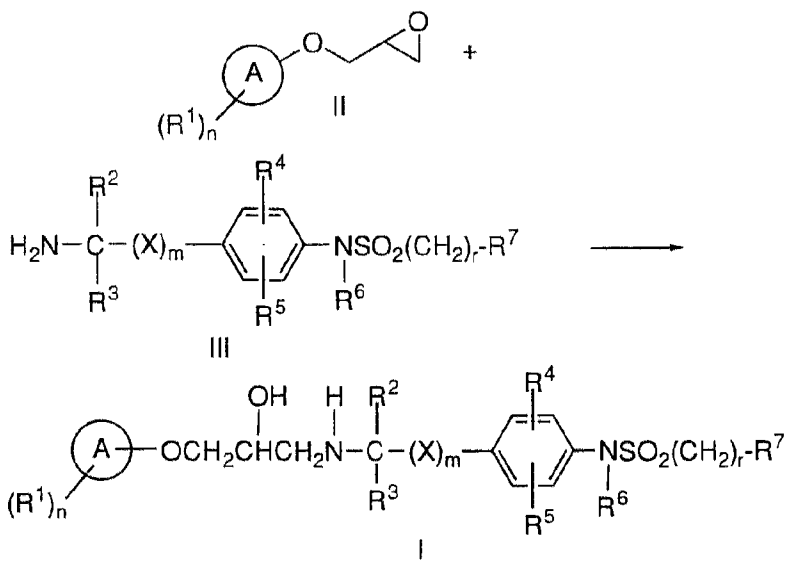


Alternatively, diamine 6 where X is $-CH_2CH_2-$ and m is 1 is available from intermediate 23 by reduction of the nitrile group with, for example, cobalt chloride and sodium borohydride. This diamine may then be modified as illustrated in Scheme 3.

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 diisopropylethylamine 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.

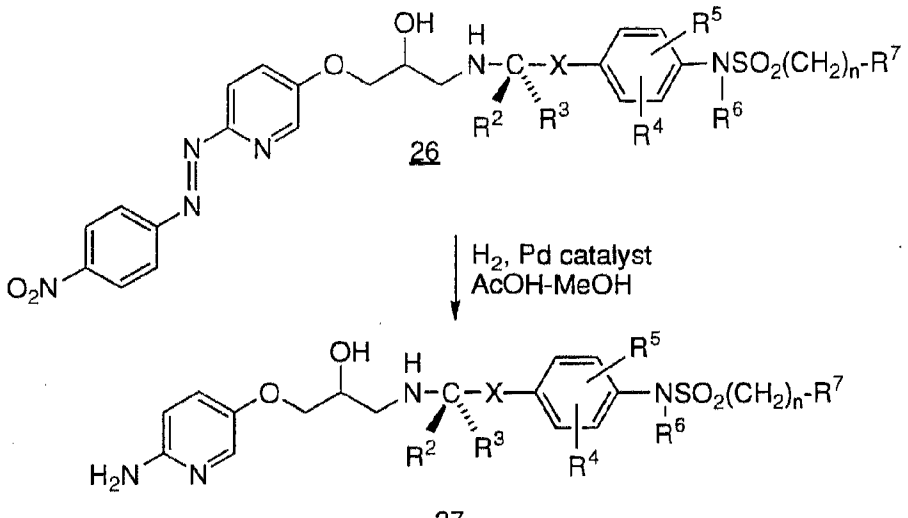
SCHEME 8



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 reduction, oxidation, alkylation, acylation, and hydrolysis reactions which are commonly known to those skilled in the art. One such example is illustrated in Scheme 9. Compound 26, which is prepared as outlined in the Scheme 8 from the corresponding epoxide, is subjected to catalytic

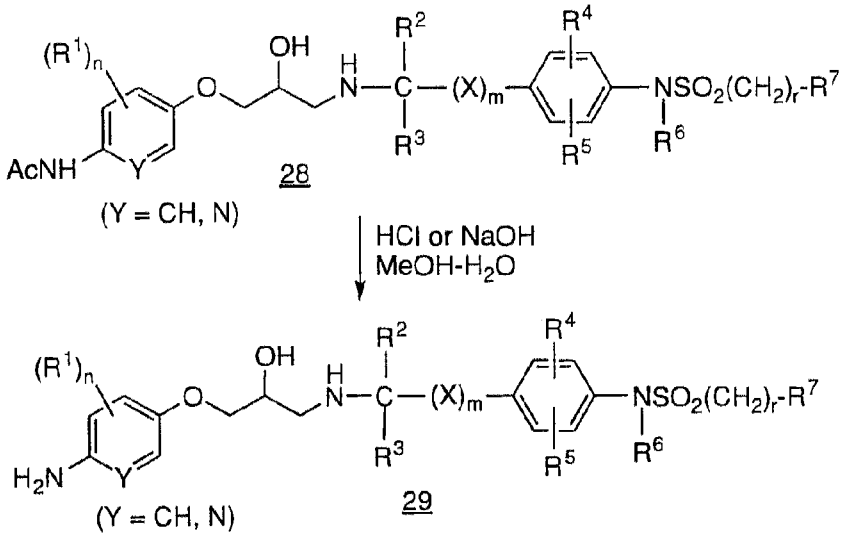
hydrogenation in a polar solvent such as 1:1 acetic acid/methanol to provide compound 27. Other examples of substituents on compound I which may be reduced to the corresponding amine by catalytic hydrogenation and methods commonly known to those skilled in the art include nitro groups, nitriles, and azides.

SCHEME 9



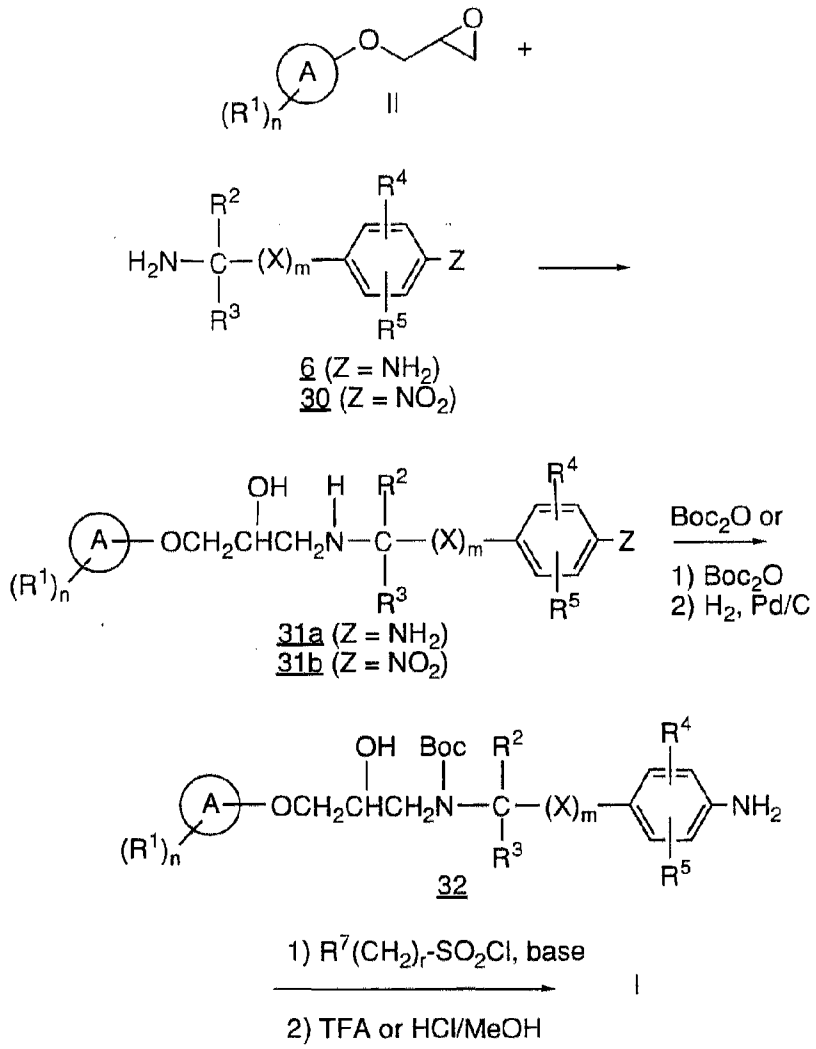
Scheme 10 illustrates an example of another such modification of the coupling product I. Acetamido derivative 28, which is prepared as outlined in the Scheme 8 from the corresponding epoxide, is subjected to hydrolysis in a protic solvent such as methanol/water with added acid or base such as hydrochloric acid or sodium hydroxide to provide the corresponding aniline derivative 29.

SCHEME 10



An alternate method for the synthesis of compound I is illustrated in Scheme 11. Epoxide II is coupled to amine 6 as described above for coupling intermediates II and III (Scheme 8) to give aniline derivative 31a. The secondary amine is selectively protected, for example, as a carbamate by treatment with di-*tert*-butyldicarbonate to provide carbamate 32. Alternatively, nitro amine 30 is used in the coupling reaction to provide 31b. Following protection as described above, the nitro group is reduced, for example, by catalytic hydrogenation, to provide intermediate 32. 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.

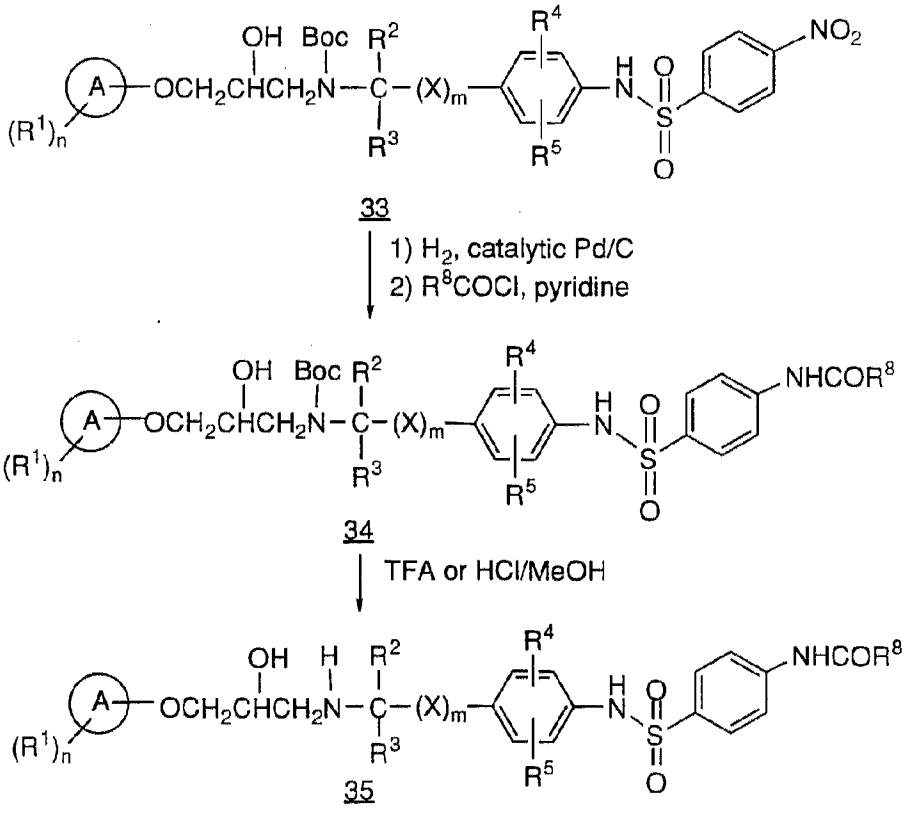
SCHEME 11



In some cases, sulfonamide I from the reaction sequence illustrated 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, as described above. In addition, manipulation of substituents on any of the intermediates in the reaction sequence illustrated in Scheme 11 may occur. An example of this is illustrated in

Scheme 12. N-Boc 4-nitrobenzenesulfonamide 33, which is prepared from intermediate 32 and 4-nitrobenzenesulfonyl chloride, is subjected to catalytic hydrogenation and the resultant aniline is acylated with, for example, an acid chloride in the presence of base to give N-Boc intermediate 34. Deprotection with acid such as trifluoroacetic acid or methanolic hydrogen chloride provides the desired sulfonamide 35.

SCHEME 12



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-linded 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, β3 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 β3 agonists may be useful in the treatment of neurogenetic inflammation , such as asthma, with minimal effects on the cardio-pulmonary system.

β3 adrenoreceptors are also able to produce selective antidepressant effects by stimulating the β3 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 adminastration, 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 adminastered 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 1 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 3.5 milligrams to about 140 milligrams, preferably from about 3.5 milligrams to about 5 milligrams. In the case of a 70 kg adult human, the total daily dose will generally be from about 7 milligrams to about 70 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 10 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 35 milligrams to about 1,400 milligrams, preferably from about 35 milligrams to about 50 milligrams. In the case of a 70 kg adult human, the total daily dose will generally be from about 70 milligrams to about 700 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.

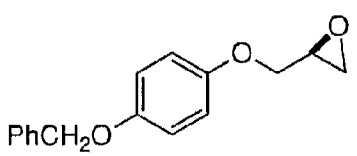
Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain, in addition to the active ingredient, sucrose as a sweetening agent, methyl and propylparabens as preservatives, 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 hydroxypropylcellulose. 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.

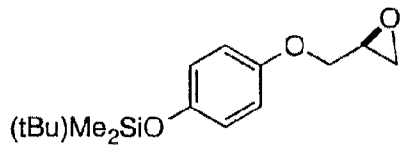
EXAMPLE 1



(S)-2-[[(4-Phenylmethoxy)phenoxy]methyl]oxirane

A solution of 1.54 g (7.72 mmol) of 4-benzyloxyphenol in 10 mL of dimethylformamide (DMF) was added dropwise via cannula to a mixture of 310 mg (7.72 mmol) of sodium hydride (60% dispersion in mineral oil). After the mixture was allowed to stir for 1 h, a solution of 2.00 g (7.72 mmol) of (2S)-glycidyl 3-nitrobenzene sulfonate in 10 mL of DMF was added via cannula. The reaction mixture was allowed to stir at room temperature for 4.5 h. It was diluted with ethyl acetate, washed with three portions of water, dried over magnesium sulfate, and concentrated. Purification by flash chromatography (silica gel, 20% ethyl acetate/hexane) gave 1.84 g (93%) of the title compound: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.41-7.28 (m, 5H), 6.90-6.80 (sym m, 4H), 4.99 (s, 2H), 4.14 (dd, 1H, J = 3.2, 11 Hz), 3.89 (dd, 1H, J = 5.6, 11 Hz), 3.29 (m, 1H), 2.86 (t, 1H, J = 5.1Hz), 2.71 (dd, 1H, J = 2.6, 5.1 Hz); EI MS *m/z* 256 (M), 165, 91.

EXAMPLE 2

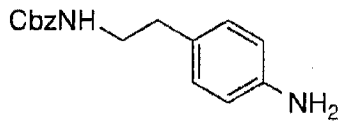


(S)-2-[[4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]phenoxy]methyl]-oxirane

A solution of 10.0 g (50.0 mmol) of 4-benzyloxyphenol, 9.04 g (60.0 mmol) of *tert*-butyldimethylsilyl chloride, and 4.42 g (65.0 mmol) of imidazole in dimethylforamide (DMF) was allowed to stir at ambient temperature overnight. The mixture was then diluted with ethyl acetate, washed sequentially with water, 1 M aqueous sodium bisulfate solution, 1 M aqueous sodium hydroxide solution, and brine, dried over magnesium sulfate, and concentrated to give a white solid. The unpurified compound was dissolved in 40 mL of ethyl acetate and allowed to stir over 20% palladium hydroxide on carbon under an atmosphere of hydrogen overnight. The reaction mixture was then filtered through a pad of Celite and concentrated. The resultant phenol

was dissolved in 40 mL of DMF and added dropwise over a 30-min period via cannula to a mixture of 2.60 g (65.0 mmol) of sodium hydride (60% dispersion in mineral oil) at 0°C. A 10-mL portion of DMF was added. After the mixture was allowed to stir at 0°C for 30 min, a solution of 14.3 g (55.0 mmol) of (2S)-glycidyl 3-nitrobenzene sulfonate in 40 mL of DMF was added dropwise over a 20-min period. After the reaction was judged to be complete by TLC analysis, it was quenched with water, diluted with ethyl acetate, washed sequentially with water, 1 M aqueous sodium hydroxide solution, and brine, dried over magnesium sulfate, and concentrated. Purification by flash chromatography (silica gel, 10% ethyl acetate/hexane) gave 5.04 g (36% overall yield) of the title compound: ^{1}H NMR (400 MHz, CD_3OD) δ 6.82 (d, 2H, J = 9.1 Hz), 6.74 (d, 2H, J = 9.1 Hz), 4.22 (dd, 1H, J = 2.6, 11.2 Hz), 3.79 (dd, 1H, J = 6.2, 11.2 Hz), 3.30 (m, 1H), 2.84 (t, 1H, J = 4.6 Hz), 2.71 (dd, 1H, J = 2.7, 5.0 Hz), 0.97 (s, 9H), 0.15 (s, 6H).

EXAMPLE 3

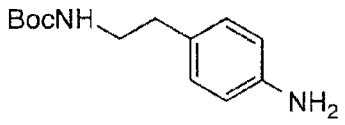


2-(4-Aminophenyl)ethylcarbamic acid phenylmethyl ester

A solution of 5.00 g (36.7 mmol) of 2-(4-aminophenyl)-ethylamine in 100 mL of chloroform was cooled to 0°C and 3.72 g (5.20 mL, 36.8 mmol) of triethylamine was added. A solution of 6.26 g (5.2 mL, 36.8 mmol) of benzyl chloroformate in 40 mL of chloroform was then added dropwise over a 30-min period. The reaction was allowed to stir at 0°C for 2 h. It was diluted with 100 mL of chloroform, washed with 100-mL portions of water and brine, dried over sodium sulfate and concentrated. The residue was dissolved in 50% ethyl acetate/hexane and stirred with 30 g of silica gel, filtered, and concentrated. Further purification by recrystallization from ethyl acetate/hexanes gave 4.82 g (49%) of the title compound as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) 7.33 (s, 5H), 6.94 (d, 2H, J = 8.2

Hz), 6.60 (d, 2H, J = 8.2 Hz), 5.07 (s, 2H), 4.84 (broad s, 1H), 3.55 (broad s, 2H), 3.37 (m, 2H), 2.67 (t, 2H, J = 6.9 Hz). FAB MS *m/z* 271 (M + 1).

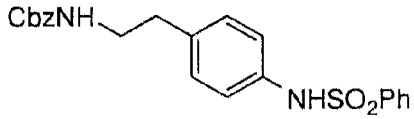
EXAMPLE 4



2-(4-Aminophenyl)ethylcarbamic acid 1,1-dimethylethyl ester

A solution of 817 mg (6.00 mmol) of 2-(4-aminophenyl)-ethylamine in 20 mL of tetrahydrofuran was treated with 1310 mg (6.00 mmol) of di-*tert*-butyl dicarbonate. After the reaction mixture was stirred at room temperature for 0.5 h, it was concentrated. Trituration from a solution of 5 mL of ether and 20 mL of hexane gave 1.04 g (73%) of the title compound as a pale yellow solid: ^{1}H NMR (400 MHz, CDCl3) 6.94 (d, 2H, J = 8.2 Hz), 6.59 (d, 2H, J = 8.2 Hz), 4.51 (broad s, 1H), 3.58 (broad s, 2H), 3.27 (m, 2H), 2.63 (t, 2H, J = 7.0 Hz), 1.38 (s, 9H). FAB MS *m/z* 237 (M + 1).

EXAMPLE 5

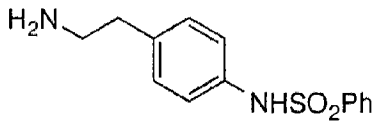


N-[4-[2-[(phenylmethoxycarbonyl)amino]ethyl]phenyl]benzenesulfonamide

A solution of 868 mg (3.22 mmol) of Cbz amine from Example 3 in 15 mL of dichloromethane was cooled to 0°C and treated with 0.286 mL (3.54 mmol) of pyridine followed by 569 mg (0.41 mL, 3.22 mmol) of benzenesulfonyl chloride. The reaction mixture was stirred at room temperature for 2 h and then partitioned between chloroform and water. The organic phase was washed sequentially with 5% aqueous hydrochloric acid and saturated aqueous sodium

bicarbonate, dried over magnesium sulfate, and concentrated. Purification by recrystallization from ethyl acetate/hexane gave 630 mg (48%) of the title compound as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) 7.72 (d, 2H, J = 7.2 Hz), 7.48 (m, 1H), 7.39 (m, 2H), 7.33 (m, 5H), 7.02 (d, 2H, J = 8.3 Hz), 6.95 (d, 2H, J = 8.3 Hz), 6.55 (s, 1H), 5.06 (s, 2H), 4.68 (broad s, 1H), 3.37 (m, 2H), 2.72 (t, 2H, J = 6.9 Hz). FAB MS *m/z* 411 (M + 1).

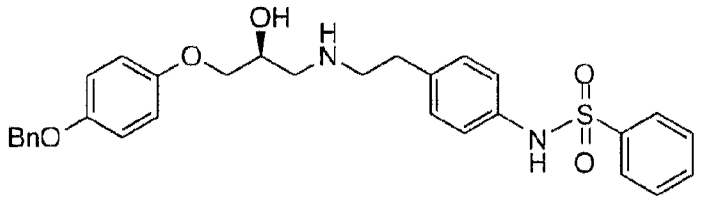
EXAMPLE 6



N-[4-(2-aminoethyl)phenyl]benzenesulfonamide

A solution of 600 mg (1.46 mmol) of Cbz amine from Example 5 in 18 mL of methanol was stirred over 20% palladium hydroxide on carbon under an atmosphere of hydrogen for 2.5 h. The reaction mixture was filtered through a Celite pad and concentrated to give 360 mg (89%) of a white solid: ^{1}H NMR (400 MHz, CD_3OD) δ 7.73 (d, 2H, J = 7.1 Hz), 7.52 (t, 1H, J = 7.4 Hz), 7.44 (t, 2H, J = 7.5 Hz), 7.04 (d, 2H, J = 8.7 Hz), 6.99 (d, 2H, J = 8.6 Hz), 2.82 (t, 2H, J = 7.3 Hz), 2.66 (t, 2H, J = 7.3 Hz).

EXAMPLE 7

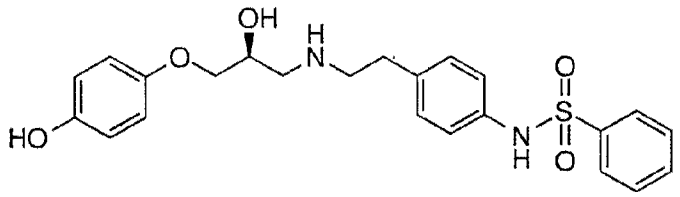


(S)-N-[4-[2-[[2-hydroxy-3-[(4-phenylmethoxy)phenoxy]propyl]amino]-ethyl]phenyl]benzenesulfonamide

A solution of 406 mg (1.47 mmol) of amine from Example 6 in 8 mL of anhydrous methanol was treated with 280 mg (1.10 mmol)

of epoxide from Example 1. The solution was heated at reflux under nitrogen overnight, then cooled to room temperature and concentrated. Purification by flash chromatography (silica gel, 5:4:1 ethyl acetate:hexane:10% methanolic ammonium hydroxide) gave 282 mg (48%) of the title compound: NMR (400 MHz, CD_3OD) δ 7.71 (d, 2H), 7.52 (m, 1H), 7.1-7.4 (7H), 7.06 (d, 2H), 7.00 (d, 2H), 6.75 (d, 2H), 6.70 (d, 2H), 5.02 (s, 2H), 3.99 (m, 1H), 3.82 (d, 2H), 2.6-2.9 (m, 6H).

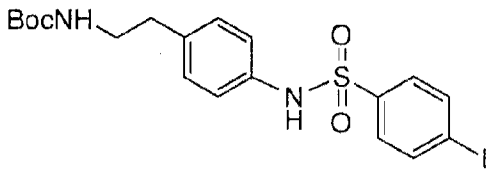
EXAMPLE 8



(S)-N-[4-[2-[[2-hydroxy-3-(4-hydroxyphenoxy)propyl]amino]ethyl]-phenyl]benzenesulfonamide

A solution of 282 mg (0.529 mmol) of benzyl ether from Example 7 in 5 mL of methanol and 5 mL of tetrahydrofuran was treated with 100 mg of 20% palladium hydroxide on carbon under an atmosphere of hydrogen for 2 h. It was then filtered and concentrated. Purification by flash chromatography (silica gel, 5:4:2 ethyl acetate:hexane:10% methanolic ammonium hydroxide) gave 141 mg (60%) of the title compound as a foam: ^1H NMR (400 MHz, CD_3OD) 7.71 (d, 2H, J = 7.1 Hz), 7.52 (m, 1H), 7.43 (m, 2H), 7.07 (d, 2H, J = 8.5 Hz), 6.99 (d, 2H, J = 8.5 Hz), 6.75 (d, 2H, J = 9.1), 6.68 (d, 2H, J = 9.1 Hz), 3.98 (m, 1H), 3.82 (d, 2H, J = 5.4 Hz), 2.6-2.9 (m, 6H). FAB MS *m/z* 443 (M + 1).

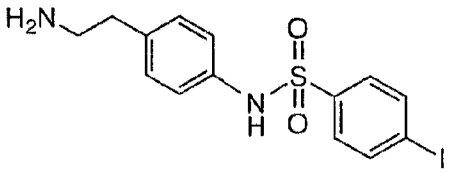
EXAMPLE 9



N-[4-[2-[[(1,1-dimethylethoxy)carbonyl]amino]ethyl]phenyl]-4-iodobenzenesulfonamide

In a manner analogous to that of Example 5, the title compound was prepared from the Boc amine in Example 2 and 4-iodobenzenesulfonyl chloride: ^{1}H NMR (400 MHz, CD_3OD) δ 7.86 (d, 2H), 7.46 (d, 2H), 7.07 (d, 2H), 6.99 (d, 2H), 3.27 (t, 2H), 2.76 (t, 2H), 1.38 (s, 9H).

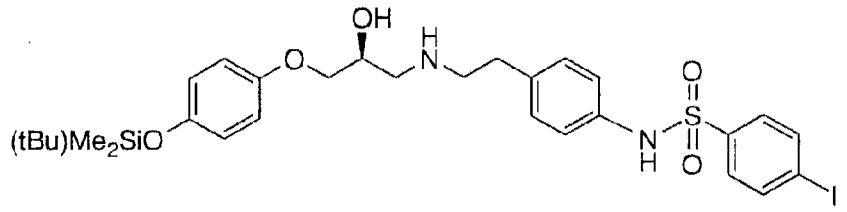
EXAMPLE 10



N-[4-(2-aminoethyl)phenyl]-4-iodobenzenesulfonamide

A solution of 1.80 g of Boc amine from Example 9 in 1:1 trifluoroacetic acid:dichloromethane was allowed to stand at room temperature for 15 min at which time TLC analysis indicated the reaction was complete. The solution was then concentrated. Purification by flash chromatography (silica gel, 15% of 10:1 methanol:concentrated ammonium hydroxide in dichloromethane) gave the title compound as a crystalline solid: ^{1}H NMR (200 MHz, CD_3OD) δ 7.80 (d, 2H), 7.46 (d, 2H), 7.06 (d, 2H), 6.98 (d, 2H), 2.81 (t, 2H), 2.65 (t, 2H).

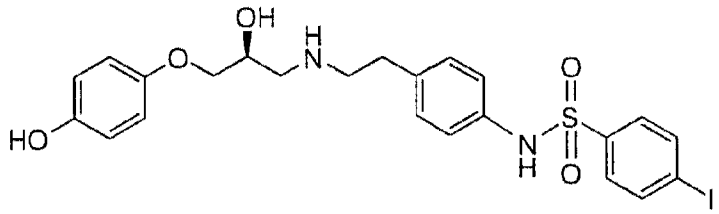
EXAMPLE 11



(S)-N-[4-[2-[[2-hydroxy-3-[[4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-phenoxy]propyl]amino]ethyl]phenyl]-4-iodo-benzenesulfonamide

In a manner analogous to that of Example 7, the title compound was prepared from the epoxide from Example 2 and the amine from Example 10: ^{1}H NMR (400MHz, CD_3OD) δ 7.82 (d, 2H, J = 8.6 Hz), 7.43 (d, 2H, 8.6 Hz), 7.10 (d, 2H, J = 8.5 Hz), 6.79 (d, 2H), 6.73 (d, 2H), 4.01 (m, 1H), 3.87 (d, 2H), 3.91-2.69 (m, 6H), 0.96 (s, 9H), 0.15 (s, 6H).

EXAMPLE 12

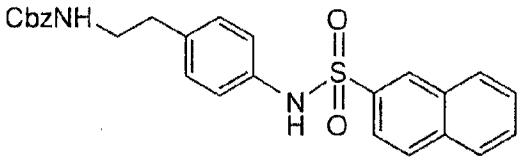


(S)-N-[4-[2-[[2-hydroxy-3-(4-hydroxyphenoxy)propyl]amino]ethyl]-phenyl]-4-iodobenzenesulfonamide

A 182-mg (0.266 mmol) sample of silyl ether from Example 11 was treated with 3% methanolic hydrogen chloride (prepared by adding 1 mL of acetyl chloride to 19 mL of methanol at 0°C). After the solution was allowed to stir at room temperature for 1h, it was concentrated. Purification by flash chromatography (silica gel, 10% of 10:1 methanol:concentrated ammonium hydroxide in dichloromethane) gave 106 mg (70%) of the title compound: ^{1}H NMR (400MHz, CD_3OD) δ 7.82 (d, 2H, J = 8.6 Hz), 7.43 (d, 2H, 8.6 Hz),

7.10 (d, 2H, J = 8.5 Hz), 6.99 (d, 2H, J = 8.5 Hz), 6.74 (d, 2H, J = 9.0 Hz), 6.68 (d, 2H, J = 9.0 Hz), 4.00 (m, 1H), 3.83 (d, 2H, J = 5.5 Hz), 3.34-2.67 (m, 6H); FAB MS *m/z* 569 (M + 1), 309, 154.

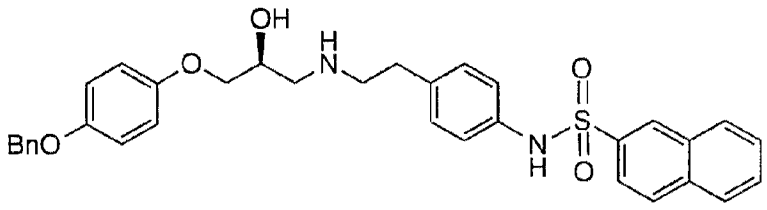
EXAMPLE 13



N-[4-[2-[(phenylmethoxycarbonyl)amino]ethyl]phenyl]-2-naphthalenesulfonamide

In a manner analogous to that of Example 5, the title compound was prepared from the Cbz amine from Example 3 and 2-naphthalenesulfonyl chloride: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.85 (m, 3H), 7.71 (dd, 1H, J = 1.8, 8.7 Hz), 7.61-7.52 (m, 2H), 7.34-7.28 (m, 5H), 6.99 (s, 4H), 6.77 (br s, 1H), 5.04 (s, 2H), 4.65 (br s, 1H), 3.33 (br q, 2H, J = 5.9 Hz), 2.68 (t, 2H, J = 7.0 Hz); FAB MS *m/z* 461 (M + 1), 270.

EXAMPLE 14

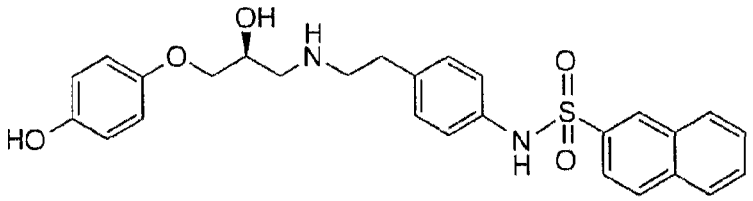


(S)-N-[4-[2-[[2-hydroxy-3-[(4-phenylmethoxy)phenoxy]propyl]amino]-ethyl]phenyl]-2-naphthalenesulfonamide

The Cbz amine from Example 13 was deprotected as described in Example 6. In a manner analogous to that of Example 7, the title compound was prepared from the resultant amine and the epoxide from Example 1: ^{1}H NMR (400 MHz, CD_3OD) δ 8.27 (s, 1H), 7.93-7.87 (m, 3H), 7.71 (dd, 1H, J = 1.9, 8.7 Hz), 7.62-7.54 (m, 2H),

7.39 (d, 2H, J = 7.2 Hz), 7.34 (t, 2H, J = 7.3 Hz), 7.27 (t, 1H, J = 7.1 Hz), 7.04 (d, 2H, J = 9.0 Hz), 7.01 (d, 2H, J = 9.0 Hz), 6.88 (d, 2H, J = 9.1 Hz), 6.79 (d, 2H, J = 9.1 Hz), 4.99 (s, 2H), 3.96 (m, 1H), 3.82 (d, 2H, J = 5.3 Hz), 2.80-2.63 (m, 6H); FAB MS *m/z* 583 (M + 1).

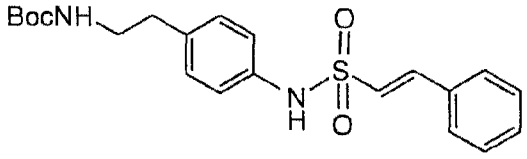
EXAMPLE 15



(S)-N-[4-[2-[[2-hydroxy-3-(4-hydroxyphenoxy)propyl]amino]ethyl]-phenyl]-2-naphthalenesulfonamide

In a manner analogous to that of Example 8, the title compound was prepared from the benzyl ether from Example 14: ^{1}H NMR (400 MHz, CD_3OD) δ 8.28 (s, 1H), 7.95-7.89 (m, 3H), 7.72 (dd, 1H, J = 1.9, 8.7 Hz), 7.62-7.57 (m, 2H), 7.07-7.01 (m, 4H), 6.73 (d, 2H, J = 9.0 Hz), 6.67 (d, 2H, J = 9.0 Hz), 3.97 (m, 1H), 3.81 (d, 2H, J = 5.2 Hz), 2.85-2.68 (m, 6H); FAB MS *m/z* 493 (M + 1).

EXAMPLE 16

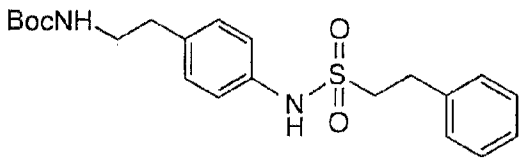


N-[4-[2-[[(1,1-dimethylethoxy)carbonyl]amino]ethyl]phenyl]-β-styrenesulfonamide

In a manner analogous to that of Example 5, the title compound was prepared from the Boc amine from Example 4 and β-styrenesulfonyl chloride: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, 1H, J = 15.4 Hz), 7.42-7.33 (m, 5H), 7.11 (s, 4H), 6.77 (d, 1H, J = 15.4 Hz),

6.56 (br s, 1H), 4.48 (br s, 1H), 4.10 (br m, 2H), 2.72 (t, 2H, J = 7.1 Hz), 1.39 (s, 9H).

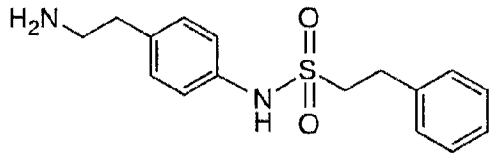
EXAMPLE 17



N-[4-[2-[[(1,1-dimethylethoxy)carbonyl]amino]ethyl]phenyl]-2-phenylethanesulfonamide

A solution of 204 mg (0.507 mmol) of Boc amine from Example 16 in methanol was stirred over 20% palladium hydroxide under an atmosphere of hydrogen overnight. The reaction mixture was then filtered and concentrated. Purification by flash chromatography (silica gel, 30% ethyl acetate/hexane) gave 168 mg (82%) of the title compound as a white solid: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.39-7.21 (m, 3H), 7.15-7.06 (m, 4H), 6.96 (d, 2H, J = 8.1 Hz), 6.25 (s, 1H), 4.49 (br s, 1H), 3.35-3.24 (m, 4H), 3.18-3.05 (m, 2H), 2.72 (t, 2H, J = 7.1 Hz), 1.40 (s, 9H).

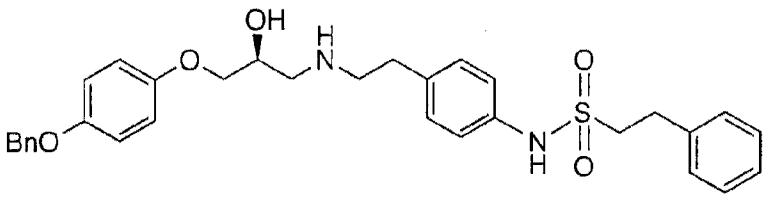
EXAMPLE 18



N-[4-(2-aminoethyl)phenyl]-2-phenylethanesulfonamide

In a manner analogous to that of Example 10, the title compound was prepared from the Boc amine from Example 17: ^{1}H NMR (400 MHz, CD_3OD) δ 7.25-7.12 (m, 7H), 7.11 (d, 2H, J = 6.8 Hz), 3.26 (m, 2H), 3.03 (m, 2H), 2.86 (t, 2H, J = 7.4 Hz), 2.72 (t, 2H, J = 7.4 Hz).

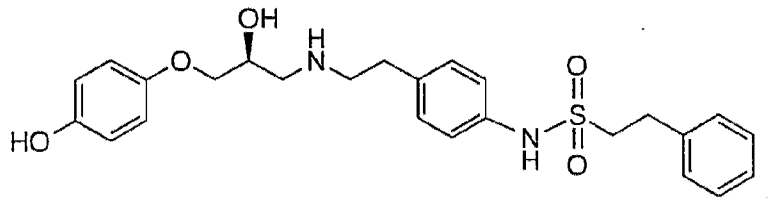
EXAMPLE 19



(S)-N-[4-[2-[[2-hydroxy-3-[(4-phenylmethoxy)phenoxy]propyl]amino]-ethyl]phenyl]-2-phenylethanesulfonamide

In a manner analogous to that of Example 7, the title compound was prepared from the amine from Example 18 and the epoxide from Example 1: ^{1}H NMR (400 MHz, CD_3OD) δ 7.40-7.09 (m, 14H), 6.88 (d, 2H, J = 9.2 Hz), 6.81 (d, 2H, J = 9.2 Hz), 4.00 (m, 1H), 3.85 (d, 2H, J = 5.3 Hz), 3.25 (m, 1H), 3.02 (m, 1H), 2.91-2.78 (m, 5H), 2.72 (dd, 1H, J = 8.1, 12.2 Hz); FAB MS *m/z* 561 (M + 1).

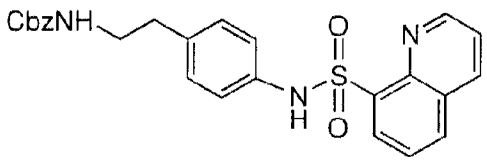
EXAMPLE 20



(S)-N-[4-[2-[[2-hydroxy-3-(4-hydroxyphenoxy)propyl]amino]ethyl]-phenyl]-2-phenylethanesulfonamide

In a manner analogous to that of Example 8, the title compound was prepared from the benzyl ether from Example 19: ^{1}H NMR (400 MHz, CD_3OD) δ 7.25-7.15 (m, 7H), 7.11 (d, 2H, J = 7.0 Hz), 6.75 (d, 2H, J = 9.1 Hz), 6.68 (d, 2H, J = 9.1 Hz), 4.05 (m, 1H), 3.89-3.83 (overlapping dd, 2H), 3.26 (m, 1H), 3.05-2.95 (m, 4H), 2.88-2.82 (m, 3H); FAB MS *m/z* 471 (M + 1).

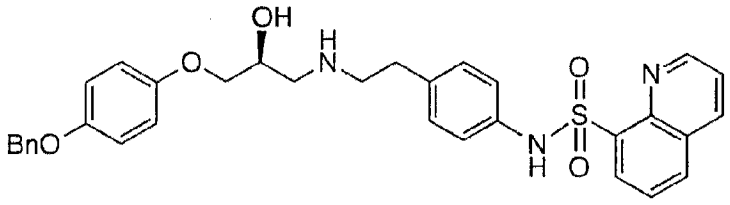
EXAMPLE 21



N-[4-[2-[(phenylmethoxycarbonyl)amino]ethyl]phenyl]-8-quinoline-sulfonamide

In a manner analogous to that of Example 5, the title compound was prepared from the Cbz amine from Example 3 and 8-quinolinesulfonyl chloride: ^{1}H NMR (400 MHz, d6-DMSO) 9.94 (s, 1H), 9.12 (m, 1H), 8.49 (dd, 1H), 8.31 (dd, 1H), 8.24 (dd, 1H), 7.70 (m, 2H), 7.2-7.4 (m, 4H), 6.94 (d, 2H), 6.88 (d, 2H), 4.94 (s, 2H), 3.04 (m, 2H), 2.48 (t, 2H). FAB MS *m/z* 462 (M + 1).

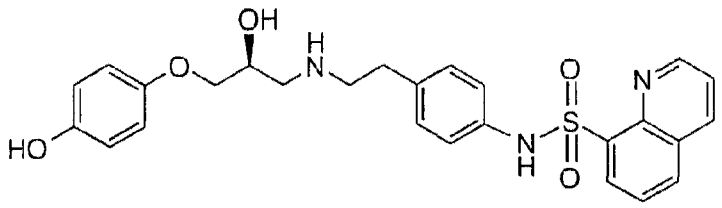
EXAMPLE 22



(S)-N-[4-[2-[[2-hydroxy-3-[(4-phenylmethoxy)phenoxy]propyl]amino]-ethyl]phenyl]-8-quinolinesulfonamide

The Cbz amine from Example 21 was deprotected as described in Example 6. In a manner analogous to that of Example 7, the title compound was prepared from the resultant amine and the epoxide from Example 1: ^{1}H NMR (400 MHz, CD_3OD) 9.12 (m, 1H), 8.49 (d, 1H), 8.31 (dd, 1H), 8.24 (dd, 1H), 7.3-7.5 (m, 7H), 7.07 (d, 2H, J = 8.5 Hz), 6.99 (d, 2H, J = 8.5 Hz), 6.75 (d, 2H, J = 9.1), 6.68 (d, 2H, J = 9.1 Hz), 5.04 (s, 2H), 3.98 (m, 1H), 3.82 (d, 2H, J = 5.4 Hz), 2.5-2.9 (m, 6H). FAB MS *m/z* 584 (M + 1).

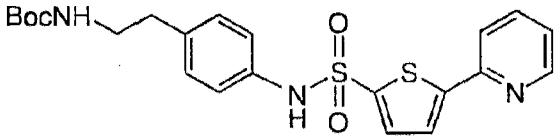
EXAMPLE 23



(S)-N-[4-[2-[[2-hydroxy-3-(4-hydroxyphenoxy)propyl]amino]ethyl]-phenyl]-8-quinolinesulfonamide

In a manner analogous to that of Example 8, the title compound was prepared from the benzyl ether from Example 22: ^{1}H NMR (400 MHz, CD_3OD) 9.95 (s, 1H), 9.12 (m, 1H), 8.48 (d, 1H, J = 6.9 Hz), 8.30 (d, 1H, J = 6.9 Hz), 8.24 (d, 1H, J = 7.0 Hz), 7.52 (m, 2H), 7.07 (d, 2H, J = 8.6 Hz), 6.99 (d, 2H, J = 8.6 Hz), 6.75 (d, 2H, J = 9.1 Hz), 6.68 (d, 2H, J = 9.1 Hz), 3.98 (m, 1H), 3.82 (d, 2H, J = 5.4 Hz), 3.34 (s, 1H), 2.6-2.9 (m, 6H). FAB MS *m/z* 494 (M + 1).

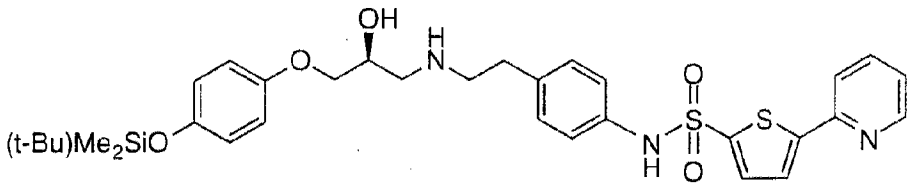
EXAMPLE 24



N-[4-[2-[[(1,1-dimethylethoxy)carbonyl]amino]ethyl]phenyl]-5-(pyridin-2-yl)-2-thiophenesulfonamide

In a manner analogous to that of Example 5, the title compound was prepared from the Boc amine from Example 4 and 5-(pyridin-2-yl)-2-thiophenesulfonyl chloride: ^{1}H NMR (400 MHz, CD_3OD) 8.48 (d, 1H, J = 5.2 Hz), 7.81 (m, 2H), 7.54 (d, 1H, J = 4.1 Hz), 7.41 (m, 1H), 7.30 (m, 1H), 7.11 (s, 4H), 3.18 (t, 2H, J = 7.1 Hz), 2.67 (t, 2H, J = 7.1 Hz), 1.38 (s, 9H). FAB MS *m/z* 460 (M + 1).

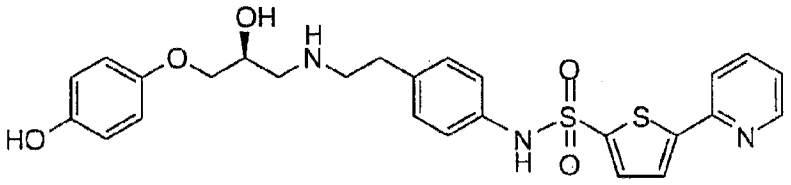
EXAMPLE 25



(S)-N-[4-[2-[[2-hydroxy-3-[[4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-phenoxy]propyl]amino]ethyl]phenyl]-5-(pyridin-2-yl)-2-thiophene]-sulfonamide

The Boc amine from Example 24 was deprotected as described in Example 10. In a manner analogous to that of Example 7, the title compound was prepared from the resultant amine and the epoxide from Example 2: ^{1}H NMR (400 MHz, CD_3OD) 8.48 (d, 1H, J = 5.1 Hz), 7.80 (m, 2H), 7.54 (d, 1H, J = 4.1 Hz), 7.39 (d, 1H, J = 4.1 Hz), 7.30 (m, 1H), 7.15 (d, 2H, J = 8.7 Hz), 7.10 (d, 2H, J = 8.8 Hz), 6.74 (d, 2H, J = 9.0 Hz), 6.67 (d, 2H, J = 9.0 Hz), 3.99 (m, 1H), 3.82 (d, 2H, J = 5.4 Hz), 2.7-2.9 (m, 6H), 1.01 (s, 9H), 0.15 (s, 6H).

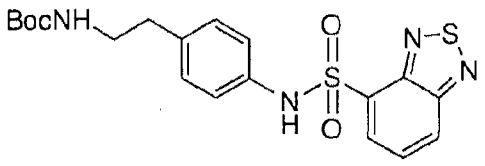
EXAMPLE 26



(S)-N-[4-[2-[[2-hydroxy-3-(4-hydroxyphenoxy)propyl]amino]ethyl]-phenyl]-5-[2-(pyridin-2-yl)thiophene]sulfonamide

In a manner analogous to that of Example 12, the title compound was prepared from the silyl ether from Example 25: ^{1}H NMR (400 MHz, CD_3OD) 8.48 (m, 1H), 7.80 (m, 2H), 7.54 (d, 1H, J = 4.0 Hz), 7.40 (d, 1H, J = 4.0 Hz), 7.29 (m, 1H), 7.13 (d, 2H, J = 8.8 Hz), 7.10 (d, 2H, J = 8.8 Hz), 6.74 (d, 2H, J = 9.1 Hz), 6.68 (d, 2H, J = 9.1 Hz), 3.99 (m, 1H), 3.83 (d, 2H, J = 5.4 Hz), 2.7-2.9 (m, 6H). FAB MS *m/z* 526 (M + 1).

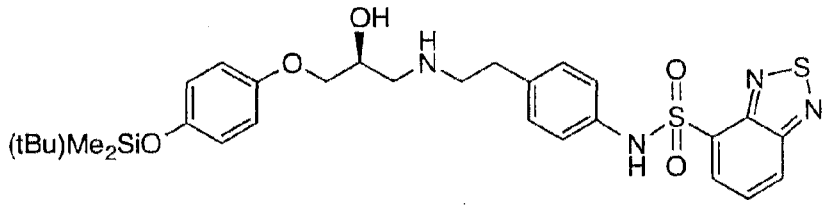
EXAMPLE 27



N-[4-[2-[[(1,1-dimethylethoxy)carbonyl]amino]ethyl]phenyl]-4-(benzo-2,1,3-thiadiazole)sulfonamide

In a manner analogous to that of Example 5, the title compound was prepared from the Boc amine from Example 4 and benzo-2,1,3-thiadiazole-4-sulfonyl chloride: ^{1}H NMR (400 MHz, $CDCl_3$) 8.23 (m, 2H), 7.71 (dd, 1H, J = 7.1, 8.7 Hz), 7.04 (m, 4H), 3.16 (m, 2H), 2.65 (t, 2H, J = 7.0 Hz), 1.37 (s, 9H). FAB MS *m/z* 435 (M + 1).

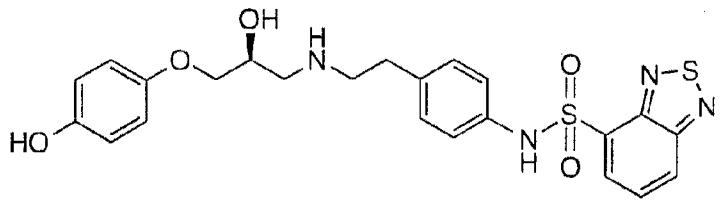
EXAMPLE 28



(S)-N-[4-[2-[[2-hydroxy-3-[[4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-phenoxy]propyl]amino]ethyl]phenyl]-4-(benzo-2,1,3-thiadiazole)-sulfonamide

The Boc amine from Example 27 was deprotected as described in Example 10. In a manner analogous to that of Example 7, the title compound was prepared from the resultant amine and the epoxide from Example 2: ^{1}H NMR (400 MHz, CD_3OD) 8.15 (m, 2H), 7.69 (dd, 1H, J = 7.2, 8.7 Hz), 6.97 (s, 4H), 6.73 (d, 2H, J = 9.1 Hz), 6.69 (d, 2H, J = 9.1 Hz), 4.88 (m, 1H), 3.80 (d, 2H, J = 5.1 Hz), 2.6-2.85 (m, 6H), 0.99 (s, 9H), 0.14 (s, 6H).

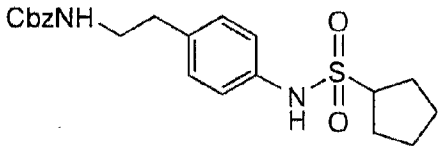
EXAMPLE 29



(S)-N-[4-[2-[[2-hydroxy-3-(4-hydroxyphenoxy)propyl]amino]ethyl]-phenyl]-4-(benzo-2,1,3-thiadiazole)sulfonamide

In a manner analogous to that of Example 12, the title compound was prepared from the silyl ether from Example 28: ^{1}H NMR (400 MHz, CD_3OD) 8.18 (m, 2H), 7.69 (dd, 1H, J = 7.1, 8.7 Hz), 6.97 (s, 4H), 6.73 (d, 2H, J = 9.1 Hz), 6.67 (d, 2H, J = 9.1 Hz), 4.89 (m, 1H), 3.80 (d, 2H, J = 5.0 Hz), 2.6-2.8 (m, 6H). FAB MS *m/z* 501 (M + 1), 309.

EXAMPLE 30

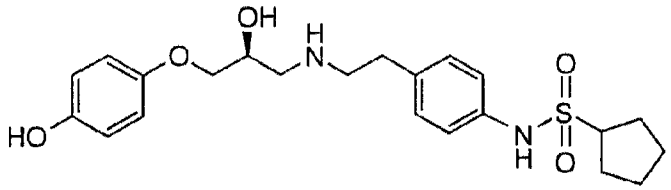


N-[4-[2-[(phenylmethoxycarbonyl)amino]ethyl]phenyl]cyclopentane-sulfonamide

Cyclopentanesulfonyl chloride was prepared according to the procedure of S. N. Bhattacharya, et. al., J. Chem. Soc. (C), 1265-1267 as follows. To a solution of 2.7 g (1.6 mL, 20 mmol) of sulfuryl chloride in 5 mL of hexane at 0°C was added a solution of 5 mL (10 mmol) of 2 M cyclopentylmagnesium chloride in ether over a 15-min period. The reaction mixture was allowed to warm to room temperature and stir overnight. The mixture was recooled to 0°C and a 5-mL portion of ether was added followed by a 10-mL portion of water. The layers were separated and the organic phase was washed with water, dried over sodium sulfate and concentrated to give 1.12

(70%) of cyclopentanesulfonyl chloride. This compound was used without further purification to prepare the title compound from the Cbz amine from Example 3 in a manner analogous to that of Example 5: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.30 (m, 5H), 7.13 (s, 4H), 6.44 (br s, 1H), 5.07 (s, 2H), 4.74 (br s, 1H), 3.50-3.39 (m, 3H), 2.76 (br t, 2H), 2.09-1.91 (m, 4H), 1.86-1.76 (m, 2H), 1.64-1.54 (m, 2H); FAB MS *m/z* 403 (M + 1).

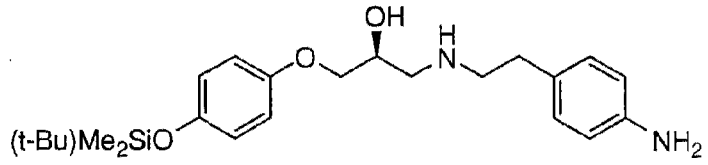
EXAMPLE 31



(S)-N-[4-[2-[[2-hydroxy-3-(4-hydroxyphenoxy)propyl]amino]ethyl]-phenyl]cyclopentanesulfonamide

Following the procedures outlined in Examples 6, 7, and 8, the title compound was prepared from the Cbz amine from Example 30: ^{1}H NMR (400 MHz, CD_3OD) δ 7.19 (s, 4H), 6.75 (d, 2H, J = 9.1 Hz), 6.68 (d, 2H, J = 9.0 Hz), 4.02 (m, 1H), 3.85 (d, 2H, J = 5.3 Hz), 3.49 (m, 1H), 2.95-2.73 (m, 6H), 2.03-1.86 (m, 4H), 1.79-1.71 (m, 2H), 1.64-1.53 (m, 2H); FAB MS *m/z* 435 (M + 1).

EXAMPLE 32

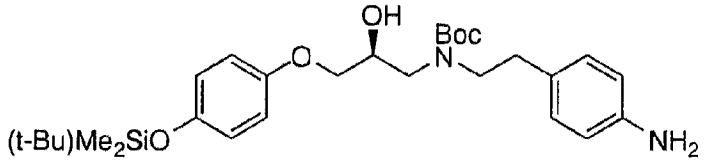


(S)-N-[2-[4-(aminophenyl)]ethyl]-2-hydroxy-3-[4-[[(1,1-Dimethylethyl)-dimethylsilyl]oxy]phenoxy]propylamine

In a manner analogous to that of Example 7, the title compound was prepared from the epoxide from Example 2 and 2-(4-

aminophenyl)ethylamine. Purification by flash chromatography (silica gel, 10% methanol:dichloromethane) gave the title compound: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (d, 2H), 6.72 (s, 4H), 6.61 (d, 2H), 3.98 (m, 1H), 3.87 (d, 2H), 3.55 (br s, 1H), 2.91-2.66 (m, 6H), 2.00 (br s, 3H), 0.93 (s, 9H), 0.14 (s, 6H).

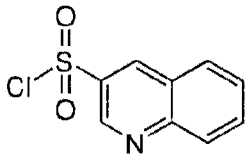
EXAMPLE 33



(S)-N-[2-[4-(aminophenyl)]ethyl]-2-hydroxy-3-[4-[[(1,1-Dimethylethyl)-dimethylsilyl]oxy]phenoxy]propylcarbamic acid 1,1-dimethylethyl ester

To a solution of 2.14 g (1.12 mmol) of amine from Example 32 in 50 mL of THF at 0°C was added a solution of di-*tert*-butyldicarbonate in 10 mL of THF. The reaction mixture was stirred at 0°C for 4.5 h, then concentrated. Purification by flash chromatography (silica gel, 40% ethyl acetate:hexanes) gave 2.23 g (84%) of the title compound as an oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00-6.90 (br m, 2H), 6.73 (s, 4H), 6.61 (d, 2H, J = 8.3 Hz), 4.06 (br m, 1H), 4.90-4.75 (br m, 2H), 3.44-3.28 (br m, 4H), 2.69 (m, 2H), 1.43 (s, 9H), 0.95 (s, 9H), 0.14 (s, 6H).

EXAMPLE 34

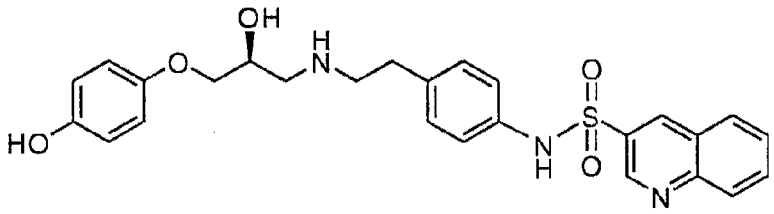


3-Quinolinesulfonyl chloride

A solution of *n*-butyllithium (20 mL of 2.5 *M* in hexanes, 50 mmol) in 250 mL of anhydrous ether was cooled in a dry ice-acetone bath and treated over a 10 min period with a solution of 3-

bromoquinoline (5.0 g, 24 mmol) in 50 mL of ether. The resulting slurry was stirred for 15 min at -78°C, and was then rapidly cannulated into a solution of sulfuryl chloride (7 mL, 100 mmol) in 500 mL anhydrous ether cooled to -78°C. The resulting orange slurry was stirred at -78°C for 30 min, and was then warmed to 0°C over 30 min and concentrated under reduced pressure to a thick semisolid yellow mass, which was partitioned between water and ethyl acetate. After addition of sodium bicarbonate, the aqueous layer was removed and extracted with an additional 50 mL of ethyl acetate. The combined organic extracts were dried over sodium sulfate and concentrated to a yellow oil. Flash chromatography (5%, then 25% EtOAc-hexanes eluant) afforded ca. 2 g of a yellow oil, which crystallized upon standing. Trituration with hexanes gave 250 mg of title compound as a white solid. NMR (400 MHz, d-6 DMSO) 9.42 (d, 1H, J = 2.0 Hz), 9.32 (s, 1H), 8.45 (d, 1H, J = 8.1 Hz), 8.28 (d, 1H, J = 8.8 Hz), 8.11 (apparent t, 1H), 7.94 (apparent t, 1H).

EXAMPLE 35

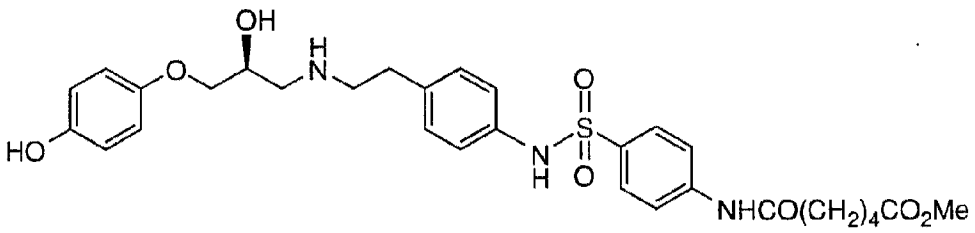


(S)-N-[4-[2-[[2-hydroxy-3-(4-hydroxyphenoxy)propyl]amino]ethyl]-phenyl]-3-quinolinesulfonamide

To a solution of the TBS-protected aniline from Example 33 (260 mg, 0.50 mmol) and pyridine (50 µL, 0.60 mmol) in 4 mL of methylene chloride was added 3-quinolinesulfonyl chloride (118 mg, 0.52 mmol). The red solution was stirred at room temperature for one hour and was concentrated under reduced pressure. The residue was dissolved in 2 mL of methanol, and approximately 5 mL of a 3% solution of HCl in methanol was added. After stirring at room temperature for 2 h, the solution was concentrated, and the residue was

dissolved in 5 mL of 10% methanolic ammonium hydroxide. After removal of solvent *in vacuo*, the residue was applied directly to a silica gel column. Elution with 5:4:1 EtOAc:hexanes:10% methanolic NH_4OH afforded 186 mg (0.38 mmol, 76% yield) of the title compound as an off-white solid. NMR (400 MHz, CD_3OD) 9.02 (d, 1H, J = 2.1 Hz), 8.67 (d, 1H, J = 2.1 Hz), 8.03 (d, 1H, J = 8.6 Hz), 7.97 (d, 1H, J = 7.9 Hz), 7.86 (apparent t, 1H), 7.66 (apparent t, 1H), 7.04 (two overlapping d, 4H), 6.72 (d, 2H, J = 9.1 Hz), 6.67 (d, 2H, J = 9.1 Hz), 3.98 (m, 1H), 3.81 (d, 2H, J = 5.4 Hz), 2.84 (m, 3H), 2.72 (m, 3H). FAB MS *m/z* 494 (M + 1).

EXAMPLE 36



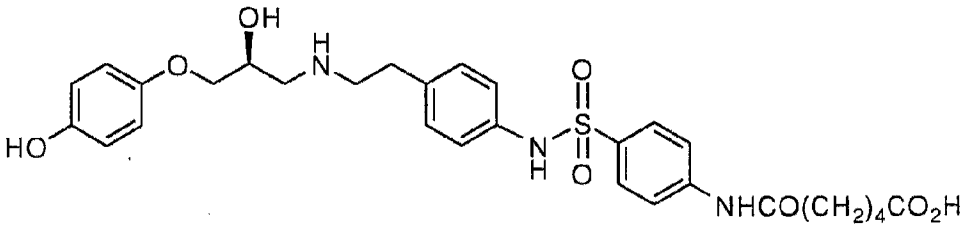
(S)-N-[4-[2-[[2-hydroxy-3-(4-hydroxyphenoxy)propyl]amino]ethyl]-phenyl]-4-[(5-methoxycarbonyl)pentanoyl]aminolbenzenesulfonamide

Pyridine 0.314 mL (3.88 mmol) and 4-nitrobenzene-sulfonyl chloride 454.3 mg (2.05 mmol) were added to a solution of BOC protected amine from Example 33 (1g, 1.94 mmol) in dichloromethane at 0°C. Stirring was continued for 2h, before diluting with EtOAc (40 ml), and washing with 3M hydrochloric acid (2 x 10ml), saturated sodium bicarbonate solution (2 x 10ml), and brine (20 ml). The solution was dried over anhydrous magnesium sulphate, concentrated, dissolved in methanol (20 ml), and treated with 20% palladium hydroxide on carbon 350 mg, under an atmosphere of hydrogen for 16h. The reaction was diluted with methanol (60 ml), filtered, concentrated, and purified by flash chromatography (silica gel, 2% methanol/ dichloromethane), to give the amine 888 mg (68%).

To amine, prepared above, 60.5 mg (0.09 mmol) and pyridine 0.016 mL (0.2 mmol) in dichloromethane (0.5 ml) at 0°C, was added a solution of monomethyl adipyl chloride (0.1 mmol, prepared from monomethyl adipate 0.015 mL (0.1 mmol), oxalyl chloride 0.050 mL (2M solution in dichloromethane, 0.1 mmol), and DMF (1 drop) in dichloromethane at 0°C for 30min). After 1h the reaction was diluted with dichloromethane (10 ml), work up as above and purification by flash chromatography, using the same solvent system as above, yielded the desired amide 67 mg. The material was dissolved in THF (1 ml) and treated with tetrabutylammonium fluoride 0.088 mL (1M in THF, 0.088 mmol). After stirring for 2h, the solution was diluted with EtOAc (10 ml), washed with water (10ml), back extracted with EtOAc (2 x5 ml), washed with brine (10ml), dried with anhydrous magnesium sulphate, concentrated and purified by flash chromatography (silica gel, 5% methanol/dichloromethane) to give the phenol 50 mg (70%).

A portion 11mg (0.0157 mmol) was treated with 1M hydrogen chloride in methanol (4.5 ml) at ambient temperature for 20 min, before concentration, and purification by preparative tlc (silica gel, 10% methanol (1% ammonium hydroxide)/dichloromethane) to give the title compound 5 mg (53%). ^{1}H NMR (CD_3OD) 7.66-7.62 (m, 4H), 7.08 (d, 2H, J=9.6 Hz), 7.01 (d, 2H, J=9.6 Hz), 6.74 (d, 2H, J=9.6Hz), 6.67(d, 2H, J=9.6Hz), 4.03 -3.97(m, 1H), 3.84-3.82 (m, 2H), 3.63 (s,3H), 2.90-2.70 (m, 6H), 2.38-2.33 (m, 4H), and 1.72-1.60 (m,4H).

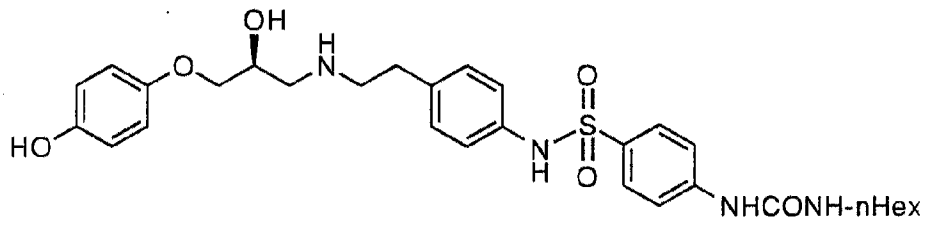
EXAMPLE 37



(S)-N-[4-[2-[[2-hydroxy-3-(4-hydroxyphenoxy)propyl]amino]ethyl]-phenyl]-4-[(5-hydroxycarbonyl)pentanoyl]amino]benzenesulfonamide

To the BOC protected phenolic methyl ester from Example 36 90 mg (0.129 mmol) in THF/ water (2ml, 1/1) was added lithium hydroxide monohydrate 27 mg (0.645 mmol), strirring was continued for 16h, before the mixture was neutralised with 3M hydrochloric acid, concentrated, and purified by mplc (35 water (0.1% TFA)/ 65 methanol) to give the acid 86 mg. A portion 22 mg (0.032 mmol) was treated with trifluoroacetic acid/ dichloromethane (1/1, 2 ml) at ambient temperature for 30min, before concentration, and purification by mplc (60 water (0.1% TFA)/ 40 methanol) to give the title compound 17 mg (90%). ^{1}H NMR (CD_3OD) 7.67 (m, 4H), 7.18-7.05 (m, 4H), 6.80-6.68 (m, 4H), 4.21-4.14 (m, 1H), 3.98-3.85 (m, 2H), 3.27-3.10 (m, 4H), 2.95-2.89 (m, 2H), 2.42-2.28 (m, 4H), and 1.73-1.60 (m, 4H).

EXAMPLE 38



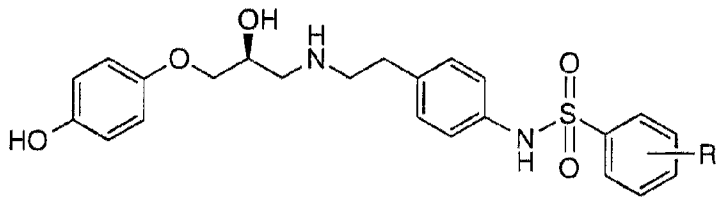
(S)-N-[4-[2-[[2-hydroxy-3-(4-hydroxyphenoxy)propyl]amino]ethyl]-phenyl]-4-(hexylaminocarbonylamino)benzenesulfonamide

To a suspension of 4-chlorosulphonylbenzene isocyanate 50 mg (0.23 mmol) at -40°C in chloroform (0.5 ml), was added hexylamine 0.23 ml (1M solution in chloroform, 0.23 mmol). Stirring was continued with warming to ambient temperature for 16h, then the mixture was cooled to 0°C and a solution of BOC protected amine from Example 33 (100 mg, 0.193 mmol) in dichloromethane (1 mL), containing pyridine 0.032 mL (0.4 mmol), was added. After 3h the solution was diluted with EtOAc (10 ml), washed with water (10ml), back extracted with EtOAc (2 x5 ml), washed with brine (10ml), dried

with anhydrous magnesium sulphate, concentrated, and purified by preparative tlc (silica gel, 2%methanol/ dichloromethane) to give the urea 80 mg. This was treated with 1M hydrogen chloride in methanol (4.5 ml) at ambient temperature for 20min, before concentration and purification by preparative tlc (silica gel, 15% methanol (1% ammonium hydroxide)/ dichloromethane) to give the title compound 53.6 mg (47%). ^{1}H NMR (CD_3OD) 7.58 (d, 2H, J = 8Hz), 7.42 (d, 2H, J = 8Hz), 7.09 (d, 2H, J = 8Hz), 7.01 (d, 2H, J = 8Hz), 6.78-6.65 (m, 4H), 4.06-4.00(m, 1H), 3.89-3.80 (m, 2H), 3.15 (t, 2H, J = 7.2Hz), 2.87-265 (m, 6H), 1.53-1.46 (m, 2H), 1.40-1.27 (m, 6H), 0.92-0.88 (m, 3H).

Following the procedures outlined for Examples 1-38, the compounds listed in Tables 1 and 2 were prepared.

TABLE 1



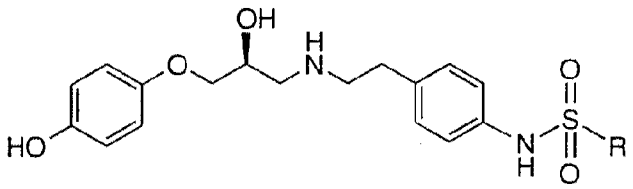
Example	R	Selected ^{1}H NMR (CD_3OD) Data
39	4-Me	2.34 (s, 3H)
40	4-OMe	3.79 (s, 3H)
41	4-Et	2.65 (q, 2H, J = 7.7 Hz), 1.19 (t, 3H, J = 7.7 Hz)
42	4-n-propyl	2.60 (t, 2H, J = 7.6 Hz), 1.60 (hex, 2H, J = 7.5 Hz), 0.89 (t, 3H, J = 7.4 Hz)
43	4-*tert*-butyl	1.29 (s, 9H)
44	2,4,6-trimethyl	2.24 (s, 3H), 2.54 (s, 6H)
45	4-isopropyl	1.21 (d, 6H, J = 6.8 Hz), 2.90 (quint, 1H, J = 6.9 Hz)
46	4-Cl	7.67 (d, 2H, J = 8.6 Hz), 7.45 (d, 2H, J = 8.5 Hz)
47	3,4-dichloro	7.82 (d, 1H, J = 2.0 Hz), 7.63-7.57 (m, 2H)
48	4-F	7.77-7.74 (m, 4H), 7.19 (t, 2H, J = 8.7 Hz)
49	4-CF_3	7.89 (d, 2H, J = 8.3 Hz), 7.77 (d, 2H, J = 8.3 Hz)
50	3,5-bistrifluoromethyl	8.18 (s, 2H), 8.15 (s, 1H)
51	2-Cl	7.99 (dd, 1H, J = 1.5, 8.7 Hz), 7.53-7.49 (m, 2H), 7.37 (m, 1H)
52	2-NO_2	7.85 (d, 1H, J = 7.9 Hz), 7.76 (d, 1H, J = 7.9 Hz), 7.69 (t, 1H, J = 7.7 Hz), 7.61 (t, 1H, J = 7.7 Hz)

53	3-NO_3	8.50 (t, J = 2.0 Hz), 8.37 (dt, 1H, J = 1.1, 8.2 Hz), 8.04 (dd, 1H, J = 1.6, 7.9 Hz), 7.71 (t, 1H, J = 8.0 Hz)
54	4-NO_2	8.30 (d, 2H, J = 8.9 Hz), 7.93 (d, 2H, J = 9.0 Hz)
55	2-F	7.79 (dt, 1H, J = 1.8, 7.8 Hz), 7.58 (m, 1H), 7.26-7.21 (m, 2H)
56	3-CF_3	7.98-7.95 (m, 2H), 7.86 (d, 1H, J = 7.9 Hz), 7.68 (t, 1H, J = 7.5 Hz)
57	3-Cl	7.70 (t, 1H, J = 1.9 Hz), 7.61 (dt, 1H, J = 1.3, 8.0 Hz), 7.54 (dq, 1H, J = 1.1, 8.0 Hz), 7.43 (t, 1H, J = 8.0 Hz)
58	3-Me	7.54 (br s, 1H), 7.50 (d, 1H, J = 8.2 Hz), 7.36-7.29 (m, 2H)
59	2,3,4,5,6-pentamethyl	2.52 (s, 6H), 2.23 (s, 3H), 2.18 (s, 6H)
60	4-Ph	7.78 (d, 2H), 7.70 (d, 2H), 7.60 (d, 2H), 7.43 (t , 2H), 7.37 (t , 3H)
61	2,5-dichloro	7.95 (s, 1H), 7.50 (s, 2H)
62	2,4-dichloro	7.94 (d, 1H, J = 8.5 Hz), 7.58 (s, 1H), 7.38 (d, 1H, J = 8.6 Hz)
63	2,3-dichloro	7.96 (d, 1H, J = 8.0 Hz), 7.70 (d, 1H, J = 8.0 Hz), 7.35 (t, 1H, J = 8.1 Hz)
64	4-CN	7.85 (d, 2H, J = 8.6 Hz), 7.81 (d, 2H, J = 8.7 Hz)
65	2-Cl, 3-F	7.81 (d, 1H, J = 6.8 Hz), 7.67-7.63 (m, 1H), 7.33 (t, 1H, J = 8.8 Hz)
66	3,4-dibromo	7.93 (s, 1H), 7.77 (d, 1H, J = 8.4 Hz), 7.52 (d, 1H, J = 8.5 Hz)

67	2,6-dichloro	7.45 (d, 2H, J = 7.7 Hz), 7.35 (t, 1H, J = 7.2 Hz)
68	3,5-dichloro	7.61 (s, 3H)
69	3,4-dimethoxy	3.82 (s, 3H), 3.74 (s, 3H)
70	2-CF_3	8.03 (d, 1H, J = 7.5 Hz, 7.89 (d, 1H, J = 7.5 Hz), 7.70-7.64 (m, 2H)
71	2,3,5,6-tetramethyl	7.14 (s, 1H), 2.49 (s, 6H), 2.22 (s, 6H)
72	4-Br	7.62 (d, 2H, J = 9.0 Hz), 7.59 (d, 2H, J = 9.0 Hz)
73	4-OH	7.55 (d, 1H, J = 8.8 Hz), 6.77 (overlapping d, 4H)
74	4-NHCOMe	2.12 (s, 3H)
75	4-NHCOEt	2.38 (q, 2H, J = 8Hz), 1.18 (t, 3H, J=8Hz)
76	4-NHCOCHMe2	2.63-2.57 (m, 1H), 1.27 (d, 6H, J=7.2Hz)
77	4-NHCO-nHex	2.35 (t, 2H, J = 8Hz), 1.70-1.62 (m, 2H), 1.38-1.27 (m, 6H), 0.91-0.88 (m, 3H)
78	4-NHCOCH2CO2Me	3.72 (s, 3H), 3.48 (s, 2H)
79	4-NHCOCH2CO2H	3.42 (s, 1H) enol form
80	4-NHCO(CH2)2CO2Me	3.66 (s, 3H), 2.68-2.65 (m, 4H)
81	4-NHCO(CH2)2CO2H	2.65 (s, 4H)
82	4-NHCO(CH2)3CO2Me	3.62 (s, 3H), 2.43-2.37 (m, 4H), 1.98-1.90 (m, 2H)
83	4-NHCO(CH2)3CO2H	2.45 (t, 2H, J = 8Hz), 2.37 (t, 2H, J = 8Hz), 1.98-1.90 (m, 2H)
84	4-NHCO(CH2)5CO2Et	4.07 (q, 2H, J=8Hz), 2.36 (t, 2H, J = 8Hz), 2.31 (t, 2H, J = 8Hz), 1.72-1.58 (m, 4H), 1.43-1.33 (m, 2H), 1.20 (t, 3H, J= 8Hz)

85	4-NHCO$(CH_2)_6CO_2Me$	3.61 (s, 3H), 2.36 (t, 2H, J =8 Hz), 2.30 (t, 2H, J = 8Hz), 1.70-1.55 (m, 4H), 1.40-1.30 (m, 4H)
86	4-NHCOPh	7.90 (d, 2H, J = 8Hz), 7.61-7.57 (m, 1H), 7.51-7.49 (m, 2H)
87	4-$NHCO_2Me$	3.72 (s, 3H)
88	4-$NHCO_2Et$	4.66 (q, 2H, J = 8Hz), 1.28 (t, 3H, J = 8Hz)
89	4-$NHCO_2CH_2Ph$	7.4-7.27 (m, 5H), 5.16 (s, 2H)
90	4-$NHCO_2CHMe_2$	4.97-4.88 (m, 1H), 1.28 (d, 6H, J = 7.2Hz)
91	4-$NHCO_2CH_2CO_2Me$	4.68 (s, 2H), 3.74 (s, 3H)
92	4-NHCONH-nPro	3.13 (t, 2H, J = 7.2Hz), 1.55-1.48 (m, 2H), 0.92 (t, 3H, J = 8Hz)
93	4-$NHCONHCHMe_2$	3.90-3.80 (m, 1H), 1.15 (d, 6H, J = 6.4Hz)
94	4-NHCONH-cHex	3.53 (m, 1H), 1.92-1.15 (m, 10H)
95	4-NHCONH-CH_2CO_2Me	3.95 (s, 2H), 3.72 (s, 3H)
96	3-NHCOEt	8.09 (s, 1H), 7.69 (d, 1H, J = 8 Hz), 7.34-7.43 (m, 2H), 2.37 (q, 2H, J = 8 Hz), 1.17 (t, 3H, J = 8 Hz)
97	3-NHCO-nPro	2.32 (t, 2H, J = 8Hz), 1.70 (m, 2H), 0.97 (t, 3H, J = 8 Hz)
98	3-NHCO$(CH_2)_4CO_2Me$	3.63 (s, 3H), 2.33-2.40 (m, 4H), 1.60-1.74 (m, 4H),
99	3-NHCO$(CH_2)_5CO_2Et$	4.09 (t, 2H, J = 8 Hz), 2.32 (m, 4H0, 1.67 (m, 4H), 1.38 (m, 2H), 1.21 (t, 3H)
100	3-NHCOPh	7.90 (s, 2H, J = 8 Hz), 7.57 (m, 1H), 7.45-7.52 (m, 2H)

TABLE 2

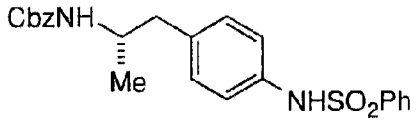


Example	R	Selected ^{1}H NMR (CD_3OD) Data
101	Me	2.89 (s, 3H)
102	Et	3.02 (q, 2H, J = 7.4 Hz), 1.27 (t, 3H, J = 7.4 Hz)
103	n-propyl	1.79 (hex, 2H, J = 7.7 Hz), 0.98 (t, 3H, J = 7.5 Hz)
104	n-butyl	1.89 (m, 2H), 1.38 (hex, 2H, 7.5 Hz), 0.88 (t, 3H, J = 7.3 Hz)
105	CH_2Ph	HBr salt: 7.32-7.24 (m, 7H), 4.37 (s, 2H)
106	$CH_2CH_2CH_2Ph$	7.24-7.10 (m, 9H), 2.07 (m, 2H)
107	naphth-1-yl	8.72 (d, 1H, J = 8.3 Hz), 8.14 (d, 1H, J = 7.3 Hz), 8.06 (d, 1H, J = 8.3 Hz), 7.95 (d, 1H, J = 7.5 Hz), 7.67 (t, 1H, J = 6.9 Hz), 7.59 (t, 1H, J = 8.0 Hz), 7.47 (t, 1H, J = 7.5 Hz)
108	thiophen-2-yl	7.68 (dd, 1H, J = 0.9, 4.4 Hz), 7.45 (d, 1H, J = 5.3 Hz), 7.04 (m, 1H)
109	pyridin-2-yl	8.63 (d, 1H, J = 5.7 Hz), 7.95 (m, 2H), 7.54 (m, 1H)
110	pyridin-3-yl	8.87 (d, 1H, J = 1.5 Hz), 8.74 (dd, 1H, J = 1.5, 5.1 Hz), 8.26 (m, 1H), 7.67 (dd, 1H, J = 5.1, 8.2 Hz)
111	2-methylthio-benzothiazol-5-yl	8.09 (d, 1H, J = 2.8 Hz), 7.95 (d, 1H, J = 8.4 Hz), 7.69 (dd, 1H, J = 2.8, 8.4 Hz), 2.79 (s, 3H)

112	quinolin-6-yl	8.95 (dd, 1H, J = 1.7, 4.3 Hz), 8.42 (d, 1H, J = 8.4 Hz), 8.37 (d, 1H, J = 2.0 Hz), 8.01 (dd, 1H, J = 2.0, 9.0 Hz), 7.61 (dd, 1H, J = 4.3, 8.4 Hz)
113	1,2,3,4-tetrahydro-quinolin-6-yl	7.71 (m, 1H), 7.46 (m, 1H), 7.19 (s, 1H), 3.50 (m, 2H), 2.80 (m, 1H), 2.13 (m, 2H), 1.97 (m, 1H)
114	indolin-5-yl	7.32 (m, 2H), 6.42 (d, 1H, J = 8.2 Hz), 3.52 (t, 2H, J = 8.7 Hz), 2.90 (t, 2H, J = 8.7 Hz)
115	1-acetylindolin-5-yl	8.09 (d, 1H, J = 8.6 Hz), 7.55 (m, 2H), 4.12 (t, 2H, J = 8.7 Hz), 3.16 (t, 2H, J = 8.7 Hz), 2.20 (s, 3H)
116	3-acetylindolin-5-yl	8.30 (overlapping s, 1H, and d, 1H, J = 8.4 Hz), 7.81 (d, 1H, J = 1.7 Hz), 7.57 (dd, 1H, J = 1.7, 8.4 Hz), 2.50 (s, 3H)
117	oxindol-5-yl	7.61 (m, 2H), 6.88 (d, 1H, J = 8.8 Hz), 3.34 (s, 2H)
118	indol-5-yl	8.00 (d, 1H, J = 1.7 Hz), 7.47 (dd, 1H, J = 1.7, 8.6 Hz), 7.40 (d, 1H, J = 8.6 Hz), 7.33 (d, 1H, J = 3.3 Hz), 6.52 (d, 1H, J = 3.3 Hz)
119	benzothiophen-5-yl	8.04 (d, 1H, J = 5.9 Hz), 7.97 (d, 1H, J = 5.9 Hz), 7.51 (d, 1H, J = 7.4 Hz), 7.37 (m, 2H)
120	benzothiophen-2-yl	7.86 (apparent t, 2H), 7.72 (s, 1H), 7.41 (m, 2H)
121	benzofuran-2-yl	7.64 (d, 1H, J = 7.8 Hz), 7.52 (d, 1H, J = 8.3 Hz), 7.43 (apparent dt, 1H, J = 1.3, 7.2 Hz), 7.30 (m, 2H)
122	5,6,7,8-tetrahydro-naphth-2-yl	7.40 (m, 2H), 7.11 (s, 1H), 2.76 (m, 4H), 1.73 (m, 4H)

123	1,3-benzodioxol-5-yl	7.29 (dd, 1H, J = 8, 2 Hz), 6.83 (d, 1H, J = 8 Hz), 6.01 (s, 2H)
124	1,4-benzodioxan-6-yl	7.19 (m, 2H), 6.85 (d, 1H, J = 8 Hz), 4.21 (m, 4H)
125	1,2-benzisoxazol-5-yl	7.8 (m, 2H), 6.95 (d, 1H, J = 8 Hz)
126	2,3-dihydrobenzofuran-5-yl	7.56 (s, 1H), 7.49 (dd, 1H, J = 8.5, 2Hz), 4.8 (t, 2H, J = 9 Hz), 3.19 (t, 2H, J = 9 Hz)

EXAMPLE 127



(S)-N-[4-[2-[(phenylmethoxycarbonyl)amino]propyl]phenyl]benzene-sulfonamide

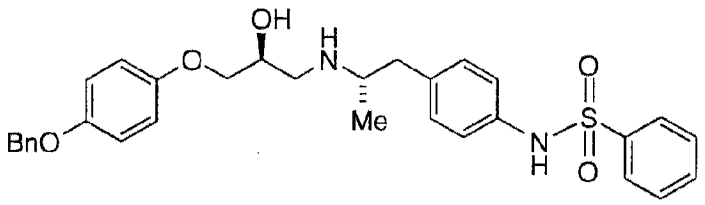
A slurry of 3.00 g (16.6 mmol) of 4-amino-D-phenylalanine hydrate in 100 mL of methanol was heated at relux while gaseous hydrogen chloride was bubbled into the flask. After a 2-h period, the reaction mixture was cooled to room temperature, flushed with nitrogen, and concentrated. The residue was dissolved in 120 mL of a mixture of 140 mL of tetrahydrofuran (THF) and 50 mL of water and treated with 9.15 g (49.8 mmol) of sodium bicarbonate portionwise over a 20-min period. A solution of 18 g of di-*tert*-butyl dicarbonate in remaining 70 mL of the THF-water mixture was added. The reaction mixture was allowed to stir at room temperature overnight and then was filtered and concentrated. The residue was partitioned between water and dichloromethane. The organic phase was dried over magnesium sulfate and concentrated. Purification by flash chromatography gave 5.17 g (79%) of the corresponding *N*-Boc methyl ester.

A 4.28-g (10.9 mmol) portion of the above compound was dissolved in 50 mL of THF and treated with 11 mL (22 mmol) of a 2 M lithium borohydride solution in THF. After the reaction mixture was allowed to stir overnight, it was quenched by the addition of 5 mL of

saturated aqueous ammonium chloride solution and concentrated. The residue was partitioned between water and ethyl acetate. The aqueous phase was extracted with ethyl acetate and the combined organic phases were dried over magnesium sulfate and concentrated. The resultant material was dissolved in 50 mL of dichloromethane, cooled to 0°C, and treated with 1.8 mL of triethylamine and 0.90 mL of methanesulfonyl chloride. After the reaction mixture was allowed to stir at 0°C for 1 h, it was washed sequentially with 5% aqueous hydrochloric acid and saturated aqueous sodium bicarbonate, dried over magnesium sulfate, and concentrated. The resultant semisolid was immediately dissolved in 150 mL of dichloromethane and treated with 30 mL of trifluoroacetic acid. After 1.5 h, the solution was concentrated. The residue was dissoved in 70 mL of ethanol and 5.0 g (49 mmol) of sodium acetate was added. The mixture was stirred over 1 g of 20% palladium hydroxide on carbon under hydrogen at 30 psi for 24 h. It was filtered through Celite and concentrated. Flash chromatography (4:1 dichloromethane: 10% concentrated ammonium hydroxide in methanol) to give 2.01 g of (2*S*)-1-(4-aminophenyl)propyl-2-amine.

A 451 mg (3.0 mmol) portion of the above compound was dissolved in 20 mL of chloroform and 2 mL of DMF and cooled to 0°C. Triethylamine (304 mg, 0.420 mL, 3.0 mmol) was added followed by 512 mg (0.428 mL, 3.0 mmol) of benzyl chloroformate, dropwise. The reaction mixture was allowed to stir at 0°C for 2 h and then allowed to warm to room temperature overnight. It was then partitioned between ethyl acetate and water. The organic phase was dried over magnesium sulfate and concentrated. Purification by flash chromatography (silica gel, 50% ethyl acetate/hexanes) gave 138 mg of the corresponding *N*-Cbz derivative. This compound was treated with benzenesulfonyl chloride according to the procedure described in Example 5 to give the title compound: ^{1}H NMR (400 MHz, $CDCl_3$) 7.70 (d, 2H, J = 7.5 Hz), 7.2-7.5 (m, 8H), 7.00 (d, 2H, J = 8.2 Hz), 6.93 (d, 2H, J = 8.2 Hz), 6.48 (s, 1H), 5.03 (s, 2H), 4.51 (m, 1H), 3.88 (m, 1H), 2.73 (m, 1H), 2.60 (dd, 1H, J = 6.8, 13.5 Hz), 1.55 (s, 1H), 1.04 (d, 3H, J = 6.7 Hz). FAB MS *m/z* 425 (M + 1).

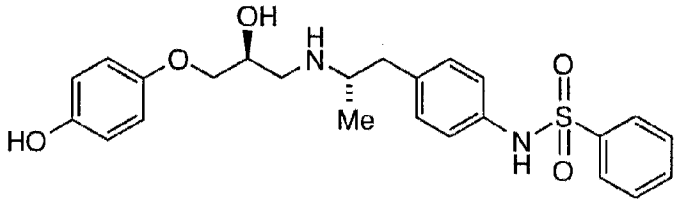
EXAMPLE 128



(S,S)-N-[4-[2-[[2-hydroxy-3-[(4-phenylmethoxy)phenoxy]propyl]-amino]propyl]phenyl]benzenesulfonamide

The Cbz amine from Example 127 was deprotected as described in Example 6. In a manner analogous to that of Example 7, the title compound was prepared from the resultant amine and the epoxide from Example 1: ^{1}H NMR (400 MHz, CD3OD) 7.70 (d, 2H, J = 7.1 Hz), 7.52 (m, 1H), 7.2-7.5 (m, 7H), 7.06 (d, 2H, J = 8.6 Hz), 7.00 (d, 2H, J = 8.6 Hz), 6.75 (d, 2H, J = 9.0), 6.68 (d, 2H, J = 9.0 Hz), 5.02 (s, 2H), 3.95 (m, 1H), 3.83 (d, 2H, J = 5.1 Hz), 2.85 (m, 2H), 2.67 (dd, 1H, J = 6.8, 13.2 Hz), 2.56 (m, 2H), 1.03 (d, 3H, J = 6.3 Hz). FAB MS *m/z* 547 (M + 1).

EXAMPLE 129

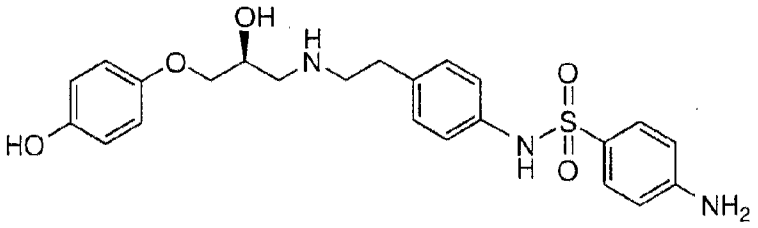


(S,S)-N-[4-[2-[[2-hydroxy-3-(4-hydroxyphenoxy)propyl]amino]-propyl]phenyl]benzenesulfonamide

In a manner analogous to that of Example 8, the title compound was prepared from the benzyl ether from Example 128: ^{1}H NMR (400 MHz, CD3OD) 7.71 (d, 2H, J = 7.2 Hz), 7.52 (m, 1H), 7.43 (m, 2H), 7.06 (d, 2H, J = 8.6 Hz), 7.00 (d, 2H, J = 8.6 Hz), 6.75 (d, 2H, J = 9.0), 6.68 (d, 2H, J = 9.0 Hz), 3.93 (m, 1H), 3.82 (d, 2H, J = 5.2

Hz), 2.88 (m, 2H), 2.66 (dd, 1H, J = 6.6, 13.2 Hz), 2.57 (m, 2H), 1.04 (d, 3H, J = 6.3 Hz). FAB MS *m/z* 457 (M + 1).

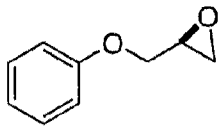
EXAMPLE 130



(S)-N-[4-[2-[[2-hydroxy-3-(4-hydroxyphenoxy)propyl]amino]ethyl]-phenyl]-4-aminobenzenesulfonamide

A solution of 67 mg (0.14 mmol) of nitro derivative from Example 54 in 5 mL of methanol was stirred over 20% palladium hydroxide on carbon under an atmosphere of hydrogen for 30 min. The reaction mixture was filtered and concentrated to give 36 mg (59%) of the title compound: ^{1}H NMR (400 MHz, CD_3OD) δ 7.39 (d, 2H, J = 8.8 Hz), 7.08 (d, 2H, J = 8.5 Hz), 7.00 (d, 2H, J = 8.5 Hz), 6.75 (d, 2H, J = 9.1 Hz), 6.68 (d, 2H, J = 9.0 Hz), 6.56 (d, 2H, J = 8.8 Hz), 4.04 (m, 1H), 3.89-3.82 (overlapping dd, 2H), 2.97-2.77 (m, 6H).

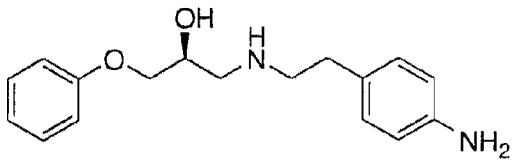
EXAMPLE 131



(S)-2-phenoxymethyloxirane

The title compound was prepared from phenol in a manner analogous to that of Example 1: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (t, 2H), 6.96 (t, 1H), 6.91 (d, 2H), 4.20 (dd, 1H), 3.96 (dd, 1H), 3.34 (m, 1H), 2.90 (t, 1H), 2.73 (dd, 1H).

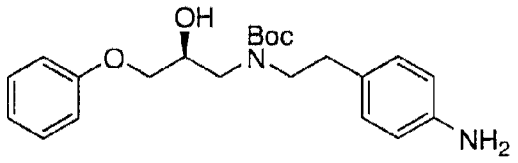
EXAMPLE 132



(S)-N-[2-[4-(aminophenyl)]ethyl]-2-hydroxy-3-phenoxypropylamine

In a manner analogous to that of Example 7, the title compound was prepared from the epoxide from Example 131 and 2-(4-aminophenyl)ethylamine: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (t, 2H, J = 8.0 Hz), 6.97 (d, 2H, J = 8.4 Hz), 6.93 (t, 1H, J = 7.4 Hz), 6.87 (d, 2H, J = 7.8 Hz), 6.61 (d, 2H, J = 8.4 Hz), 4.00 (m, 1H), 3.93 (d, 2H, J = 5.4 Hz), 3.57 (br s, 1H), 2.90-2.71 (m, 6H), 1.85 (br s, 3H).

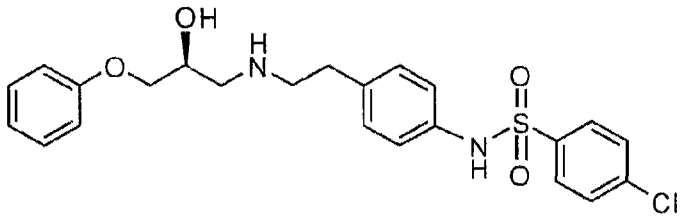
EXAMPLE 133



(S)-N-[2-[4-(aminophenyl)]ethyl]-2-hydroxy-3-phenoxypropylcarbamic acid 1,1-dimethylethyl ester

In a manner analogous to that of Example 33, the title compound was prepared from the amine from Example 132 and di-tert-butyldicarbonate: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (t, 2H, J = 8.0 Hz), 6-96-6.87 (m, 5H), 6.59 (d, 2H, J = 8.4 Hz), 4.10 (br m, 1H), 3.94 (br m, 1H), 3.84 (br m, 1H), 3.56 (br s, 1H), 3.45-3.20 (m, 4H), 2.78 (br m, 2H), 1.55 (br s, 3H), 1.43 (s, 9H).

EXAMPLE 134

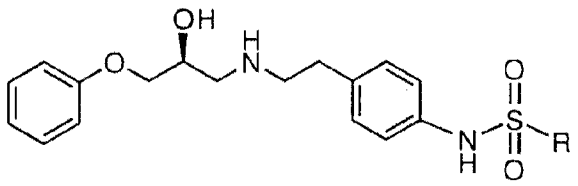


(S)-N-[4-[2-[(2-hydroxy-3-phenoxypropyl)amino]ethyl]-phenyl]-4-chlorobenzenesulfonamide

To a solution of the BOC-protected aniline from Example 133 (96 mg, 0.25 mmol) and pyridine (50 µL, 0.6 mmol) in 5 mL of methylene chloride was added 4-chlorobenzenesulfonyl chloride (57 mg, 0.27 mmol). The reaction mixture was stirred at room temperature under nitrogen atmosphere overnight. The red solution was concentrated under vacuum and the residue was purified by preparative thin layer chromatography on silica gel (eluant 2:3 ethyl acetate/hexanes) to give 133 mg (98%) of an off-white solid. This N-BOC sulfonamide (130 mg, 0.227 mmol) was dissolved in 3 mL of methylene chloride and 1 mL of trifluoroacetic acid was added. After stirring at room temperature for 1h, the solution was concentrated and the residue was purified by preparative thin layer chromatography on silica gel (eluant 10:90:1 methanol/methylene chloride/30% ammonium hydroxide) to give 130 mg (99%) of the title compound. ^{1}H NMR (400 MHz, CD_3OD) δ 7.71 (d, 2H, J = 9Hz), 7.47 (d, 2H, J = 9Hz), 7.27 (t, 2H, J = 9Hz), 7.16 (d, 2H, J = 8.5Hz), 7.07 (d, 2H, J = 8.5Hz), 6.94 (dd, 3H), 4.22 (m, 1H), 3.99 (m , 2H), 3.21 (m, 3H), 2.94 (m, 2H).

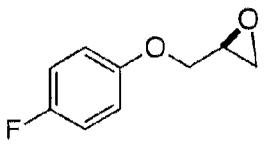
Following the procedures outlined for Examples 131-134, the compounds listed in Table 3 were prepared.

TABLE 3



Example	R	Selected ^{1}H NMR (CD_3OD) Data
135	Ph	7.72 (d, 2H, J = 7.1 Hz), 7.52 (t, 1H, J = 7.3 Hz), 7.44 (t, 2H, J = 7.5 Hz)
136	4-fluorophenyl	7.75 (dd, 2H, J = 5.1, 8.9 Hz), 7.17 (t, 2H, J = 8.8 Hz)
137	4-bromophenyl	7.62 (d, 2H, J = 9.1 Hz), 7.59 (d, 2H, J = 9.1 Hz)
138	2,3-dihydrobenzo-furan-5-yl	4.56 (t, 2H, J = 9Hz), 3.15 (t, 2H, J = 9 Hz)
139	1-acetylindolin-5-yl	8.08 (d, 1H, J = 8.7Hz), 7.52 (m, 2H), 4.09 (t, 2H, J = 8.7Hz), 3.13 (t, 2H, J = 8.7), 2.18 (s, 3H)
140	benzothiophen-2-yl	7.87 (apparent t, 2H, J = 8.1Hz), 7.75 (s, 1H), 7.42 (m, 2H)

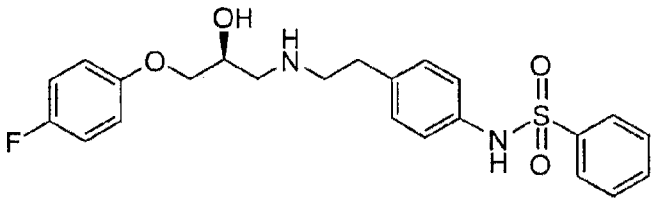
EXAMPLE 141



(S)-2-[(4-Fluorophenoxy)methyl]oxirane

The title compound was prepared from 4-fluorophenol in a manner analogous to that of Example 1: NMR (400 MHz, $CDCl_3$) 6.95 (m, 2H), 6.84 (m, 2H), 4.17 (dd, 1H, J = 3.0, 11.0 Hz), 3.88 (dd, 1H, J = 5.7, 11.0 Hz), 3.33 (m, 1H), 2.88 (m, 1H), 2.73 (dd, 1H, J = 2.6, 5.0 Hz).

EXAMPLE 142

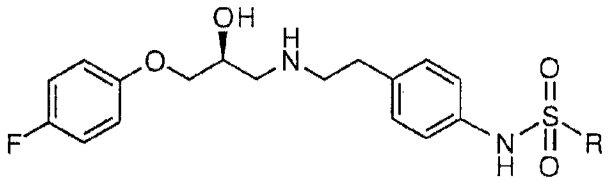


(S)-N-[4-[2-[[3-(4-fluorophenoxy)-2-hydroxypropyl]amino]ethyl]-phenyl]benzenesulfonamide

In a manner analogous to that of Example 7, the title compound was prepared from the amine from Example 6 and the epoxide from Example 141: ^1H NMR (300 MHz, CD_3OD): 2.93 (m, 2H), 3.1-3.28 (m, 4H), 3.96 (m, 2H), 4.2 (m, 1H), 6.9-7.16 (m, 8H), 7.5 (m, 3H), 7.74 (d, J = 7Hz, 1H); FAB-MS *m/z* 445 (M + 1).

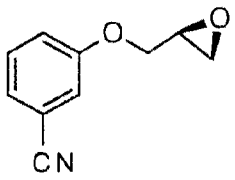
Following the procedures outlined for Examples 141-142, the compounds listed in Table 4 were prepared.

TABLE 4



Example	R	Selected ^{1}H NMR (CD_3OD) Data
143	4-methylphenyl	2.33 (s, 3H)
144	4-methoxyphenyl	7.63 (d, 2H, J = 9.0 Hz), 3.79 (s, 3H)
145	4-nitrophenyl	8.29 (d, 2H, J = 9.0 Hz), 7.91 (d, 2H, J = 9.0 Hz)
146	4-bromophenyl	7.62 (d, 2H, J = 9.1 Hz), 7.67 (d, 2H, J = 9.1 Hz)
147	4-iodophenyl	7.82 (d, 2H, J = 8.7 Hz), 7.43 (d, 2H, J = 8.7 Hz)
148	quinolin-3-yl	9.01 (d, 1H, J = 2.3 Hz), 8.71 (d, 1H, J = 2.0 Hz), 8.06 (d, 1H, J = 8.4 Hz), 8.02 (d, 1H, J = 8.4 Hz), 7.91 (apparent td, 1H), 7.71 (apparent t, 1H)
149	1,3-benzodioxol-5-yl	7.27 (dd, 1H, J = 7.2 Hz), 6.97 (d, 1H, J = 7 Hz)

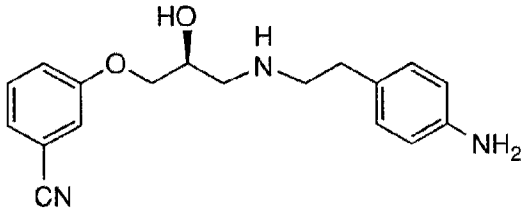
EXAMPLE 150



(S)-2-[[3-Cyanophenoxy]methyl]oxirane

The title compound was prepared from 3-cyanophenol in a manner analogous to that of Example 1: NMR (400 MHz, $CDCL_3$) δ 7.35 (t, 1H), 7.24 (d, 1H), 7.13 (m, 2H), 4.27 (dd, 1H, J = 2.7, 11.1Hz), 3.89 (dd, 1H, J = 6.0, 11.1 Hz), 3.33 (m, 1H), 2.90 (t, 1H), 2.75 (dd, 1H, J = 2.6, 4.8Hz).

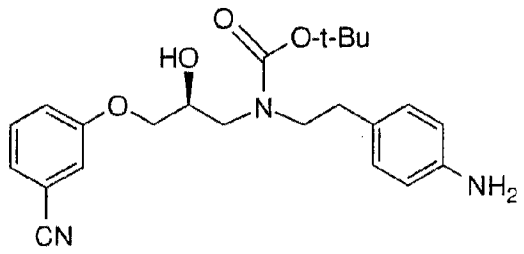
EXAMPLE 151



(S)-N-[4-[2-[[2-Hydroxy-3-(3-cyanophenoxy)propyl]amino]ethyl]-phenyl]amine

In a manner analogous to that of Example 7, the title compound was prepared from 2-(4-aminophenyl)ethylamine and the epoxide from Example 150: NMR (400 MHz, CD_3OD) δ 7.44 (t, 1H), 7.27 (m, 3H), 6.97 (d, 2H, J = 8.5Hz), 6.67 (d, 2H, J = 8.4Hz), 4.04 (m, 1H), 3.97 (m, 2H), 2.81 (m, 3H), 2.71 (m, 3H).

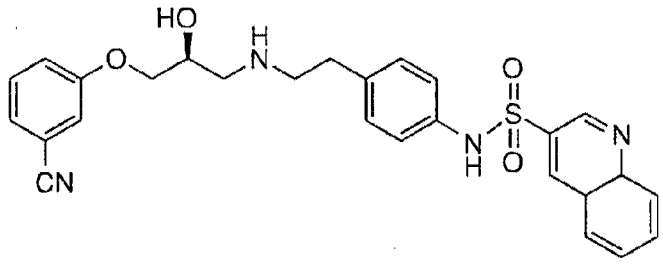
EXAMPLE 152



(S)-N-[2-[4-(Aminophenyl)]ethyl]-2-hydroxy-3-(3-cyanophenoxy)-propylcarbamic acid 1,1-dimethylethyl ester

In a manner analogous to that of Example 33, the title compound was prepared from the amine in the previous Example 151 and di-*tert*-butyldicarbonate: NMR (400 MHz, CD_3OD) δ 7.44 (t, 1H), 7.27 (m, 3H), 6.99 (d, 2H), 6.65 (d, 2H), 4.08 (m, 1H), 3.92 (m, 2H), 3.43 (m, 3H), 3.15 (m, 1H), 2.70 (t, 2H), 1.42 (s, 9H).

EXAMPLE 153

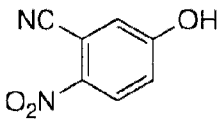


(S)-N-[4-[2-[[2-Hydroxy-3-(3-cyanophenoxy)propyl]amino]ethyl]-phenyl]-3-quinolinesulfonamide

In a manner analogous to that of Example 134, the title compound was prepared from the amine from Example 152 and 3-quinolinesulfonyl chloride from Example 34. The crude product treated with trifluoroacetic acid to remove Boc group: NMR (400 MHz, CD_3OD) δ 9.01 (d, 1H, J = 2.2Hz), 8.69 (d, 1H, J = 2.2Hz), 8.05 (dd, 2H), 7.90 (t, 2H), 7.70 (t, 1H), 7.42 (t, 1H), 7.26 (m, 3H), 7.06

(dd, 4H, J =8 .6, 21.6 Hz), 4.03 (m, 1H), 3.96 (m, 2H), 2.82 (m. 3H), 2.73 (m, 3H). FAB-MS *m/z* 503 (M+1).

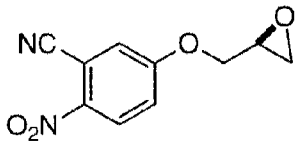
EXAMPLE 154



3-Cyano-4-nitrophenol

To a 0°C solution of 578 mg (2.28 mmol) 5-phenyl-methoxy-2-nitrobenzonitrile, prepared according to the procedure of E. Elslager, et. al., *J. Heterocyclic Chem.* **1972**, *9*, 759-773, in 5 mL of dichloromethane at 0°C was added 2.6 mL (2.62 mmol, 1.15 equiv) of a 1.0 M solution of boron tribromide in dichloromethane. After the reaction mixture was stirred for 3 h, it was diluted with ethyl acetate, washed sequentially with 1 N aqueous sodium hydrogen sulfate solution and saturated aqueous sodium chloride solution, dried over magnesium sulfate and concentrated to give 357 mg (96%) of the title compound which was used without further purification: ^{1}H NMR (400 MHz, CD_3OD) δ 8.17 (d, 1H, J = 9.2 Hz), 7.03 (d, 1H, J = 2.7 Hz), 6.92 (dd, 1H, J = 2.7, 9.3 Hz).

EXAMPLE 155

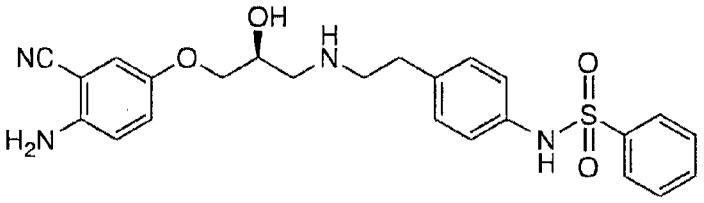


(S)-2-[(3-Cyano-4-nitrophenyl)methyl]oxirane

To a solution of 357 mg (2.18 mmol) of 3-cyano-4-nitrophenol from Example 154 in 5 mL of DMF at 0°C was added 91.0 mg (2.28 mmol) of sodium hydroxide as a 60% dispersion in oil. After the mixture was allowed to stir for 30 min, a solution of 513 mg (1.98 mmol) of (2S)-glycidyl 3-nitrobenzene sulfonate in 10 mL of DMF was

added via cannula. The reaction mixture was allowed to warm to room temperature and then heated at 55°C overnight. The reaction was cooled, quenched by the addition of saturated aqueous ammonium chloride solution, and poured into ethyl acetate. The organic phase was washed sequentially with two portions of water and one portion of saturated aqeous sodium chloride solution. The organic phase was dried over magnesium sulfate and concentrated. Purification by flash chromatography (silica, 40% ethyl acetate/hexanes) gave 287 mg (66%) of the title compound as a yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, 1H, J = 9.2 Hz), 7.36 (d, 1H, J = 2.8 Hz), 7.25 (dd, 1H, J = 2.8, 9.2 Hz), 4.47 (dd, 1H, J = 2.3, 11.3), 4.00 (dd, 1H, J = 6.2, 11.4 Hz), 3.37 (m, 1H), 2.95 (t, 1H, J = 4.3 Hz), 2.77 (dd, 1H, J = 2.6, 4.7 Hz).

EXAMPLE 156

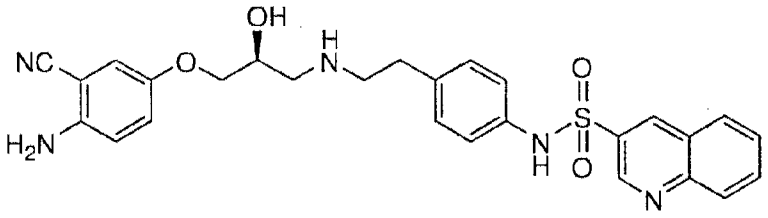


(S)-N-[4-[2-[[3-(4-Amino-3-cyanophenoxy)-2-hydroxypropyl]amino]-ethyl]phenyl]benzenesulfonamide

A solution of 75 mg (0.341 mmol) of the epoxide from Example 155 and 122 mg (0.443 mmol, 1.3 equiv) of amine from Example 6 were heated in methanol at reflux overnight. The mixture was concentrated. Purification by flash chromatography (silica, 5% methanol: dichloromethane) gave 48 mg (28%) of the resultant amino alcohol. This was dissoved in ethanol and treated with 10% palladium on carbon under an atmosphere of hydrogen for 6 h. The reaction mixture was filtered and concentrated. Purification by flash chromatography (silica, 5% 10:1 methanol: concentrated aqueous ammonium hydroxide in dichloromethane) gave 15 mg of the title compound: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, 2H, J = 7.2 Hz), 7.53 (t, 1H, J = 7.4 Hz), 7.44 (t, 2H, J = 7.6 Hz), 7.07 (d, 2H, J = 8.6

Hz), 7.01-6.98 (m, 3H), 6.90 (d, 1H, J = 2.8 Hz), 6.77 (d, 1H, J = 9.0 Hz).

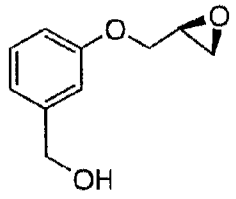
EXAMPLE 157



(S)-N-[4-[2-[[3-(4-Amino-3-cyanophenoxy)-2-hydroxypropyl]amino]-ethyl]-phenyl]-3-quinolinesulfonamide

In a manner analogous to that of Example 156, the title compound was prepared from the epoxide from Example 155 and N-[4-(2-aminoethyl)phenyl]-3-quinolinesulfonamide: ^{1}H NMR (400 MHz, CD_3OD) δ 9.01 (d, 1H, J = 2.3 Hz), 8.69 (d, 1H, J = 2.3 Hz), 8.06 (d, 1H, J = 8.5 Hz), 8.02 (d, 1H, J = 8.5 Hz), 7.90 (m, 1H), 7.70 (m, 1H), 7.11 (d, 2H), 7.04 (d, 2H), 6.98 (dd, 1H), 6.89 (d, 1H, J = 3.0 Hz), 6.76 (d, 1H, J = 9.0 Hz), 3.98 (m, 1H), 3.82 (d, 2H, J = 5.5 Hz), 2.91-2.71 (m, 6H).

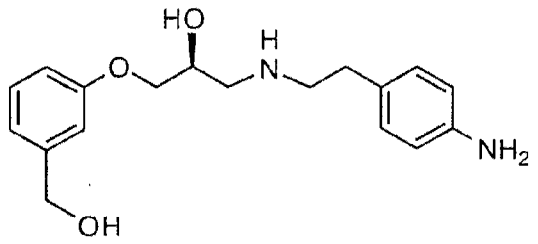
EXAMPLE 158



(S)-2-[[3-(Hydroxymethyl)phenoxy]methyl]oxirane

The title compound was prepared from 3-hydroxybenzyl alcohol in a manner analogous to that of Example 1: NMR (400 MHz, $CDCL_3$) δ 7.26 (m, 1H), 6.94 (m, 2H), 6.82 (d, 1H), 4.65 (s, 2H), 4.22 (dd, 1H, J = 3.2, 11.0 Hz), 3.95 (dd, 1H, J = 5.6, 10.7 Hz), 3.33 (m, 1H), 2.90 (t, 1H), 2.75 (m, 1H).

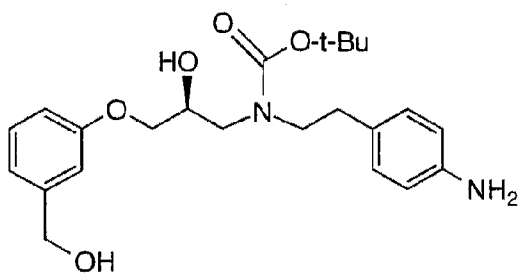
EXAMPLE 159



(S)-N-[4-[2-[[2-Hydroxy-3-[(3-hydroxymethyl)phenoxy]propyl]amino]-ethyl]phenyl]amine

In a manner analogous to that of Example 7, the title compound was prepared from 2-(4-aminophenyl)ethylamine and the epoxide from Example 158 above: NMR (400MHz, CD_3OD) δ 7.22 (t, 1H), 6.98 (d, 2H, J = 4.4Hz), 6.96 (d, 2H), 6.81 (d, 1H), 6.67 (d, 2H, J = 4.4 Hz), 4.56 (s, 2H), 4.08 (m, 1H), 3.92 (d, 2H, J = 5.4 Hz), 2.90 (m, 3H), 2.71 (m, 3H).

EXAMPLE 160

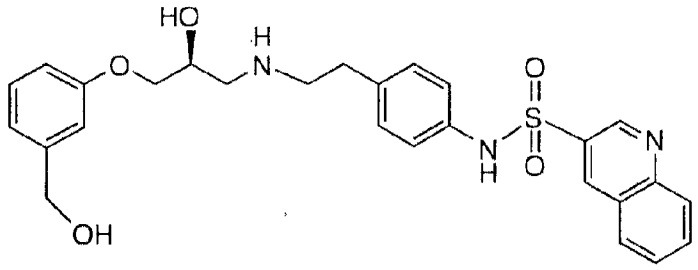


(S)-N-[2-[4-(Aminophenyl)]ethyl]-2-hydroxy-3-[(3-hydroxymethyl)-phenoxy]propylcarbamic acid 1,1-dimethylethyl ester

In a manner analogous to that of Example 33, the title compound was prepared from the amine from Example 159 and di-tert-butyldicarbonate: NMR (400MHz, CD_3OD) δ 7.21 (t, 1H), 7.09 (m, 1H), 6.92 (m, 3H), 6.81 (m, 1H), 6.66 (d, 2H), 4.57 (s, 2H), 4.07 (m,

1H), 3.89 (m, 2H), 3.43 (m, 2H), 3.20 (m, 2H), 2.69 (t, 2H), 1.40 (s, 9H).

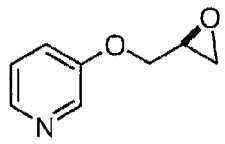
EXAMPLE 161



(S)-N-[4-[2-[[2-Hydroxy-3-[(3-hydroxymethyl)phenoxy]propyl]amino]-ethyl]phenyl]-3-quinolinesulfonamide

In a manner analogous to that of Example 134, the title compound was prepared from the amine from Example 160 and 3-quinolinesulfonyl chloride from Example 34. The crude product was treated with trifluoroacetic acid to remove the Boc group: NMR (400 MHz, CD_3OD) δ 9.01 (d, 1H, J = 2.3Hz), 8.68 (d, 1H, J = 2.3Hz), 8.04 (dd, 2H), 7.91 (t, 2H), 7.69 (t, 1H), 7.21 (t, 1H), 7.06 (q, 4H), 6.91 (mn, 2H), 6.79 (m, 1H), 4.55 (s, 2H), 4.03 (m, 1H), 3.91 (d, 2H, J = 6.6Hz), 2.87 (m, 3H), 2.78 (m, 3H). FAB-MS *m/z* 508 (M+1).

EXAMPLE 162

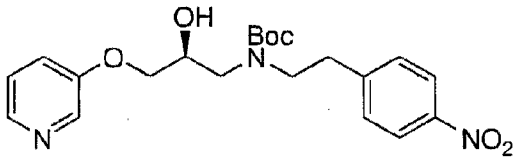


(S)-2-(3-pyridyloxymethyl)oxirane

To a solution of 11.9 g (0.125 mol) of 3-hydroxypyridine in 50 mL of DMSO at 15°C was added 120 mL (0.12 mol) of a 1.0 M solution of sodium hexamethyldisilylazide in THF. After the reaction mixture was allowed to stir for 5 min, 25.9 g (0.10 mol) of (2S)-glycidyl 3-nitrobenzene sulfonate was added in one portion. The

mixture was cooled with a room temperature water bath for 30 min. It was then quenched by the addition of 250 mL of water and extracted with three portions of ethyl acetate. The combined aqueous extracts were washed sequentially with water and brine, dried over sodium sulfate, treated with granular charcoal, filtered and concentrated to give 7.7 g (51%) of an orange oil which was used without further purification. An analytical sample was prepared by flash chromatography (silica gel, 80% ethyl acetate/hexane): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (m, 1H), 8.21 (m, 1H), 7.20-7.22 (m, 2H), 4.29 (dd, 1H, J = 1,6 Hz), 3.95 (m, 1H), 3.34 (m, 1H), 2.90 (t, 1H, J = 3Hz), 2.75 (m, 1H).

EXAMPLE 163

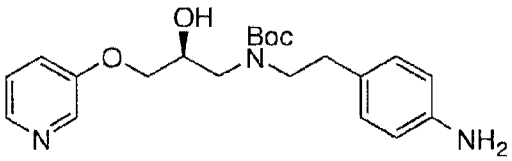


(S)-N-[2-[4-(nitrophenyl)]ethyl]-2-hydroxy-3-pyridinyloxypropyl-carbamic acid 1,1-dimethylethyl ester

A solution of 34.6 g (0.224 mol) of epoxide from Example 162 in 300 mL of anhydrous methanol was treated with 38 mL (0.275 mol) of triethylamine and 55.7 g (0.275 mol) of 4-nitrophenethylamine hydrochloride. The solution was heated at reflux for 10 h, then cooled to room temperature and concentrated. The resultant mixture was suspended in 500 mL of dichloromethane and treated with 115 g of di-*tert*-butyldicarbonate in three portions (90 g, 15 g, 10 g) over 4 h. The reaction mixture was stirred overnight. Dilute brine was added and the mixture was extracted three times with dichloromethane. The combined organic extracts were dried over sodium sulfate and concentrated. Purification by flash chromatography (silica gel, 50%, 75%, 100% ethyl acetate/hexane) gave 38.0 g of the title compound: ^{1}H NMR (400 MHz, CD_3OD) δ 8.23 (d, 1H, J = 4Hz), 8.12 (dd, 1H, J = 2.4Hz), 7.71(d, 2H, J = 8Hz), 7.52 (m, 1H), 7.40-7.48 (m, 3H), 7.35 (m, 1H),

7.09 (d, 2H, J = 10Hz), 7.00 (d, 2H, J = 10Hz), 3.95-4.08 (m, 3H), 2.69-2.90 (m, 6H).

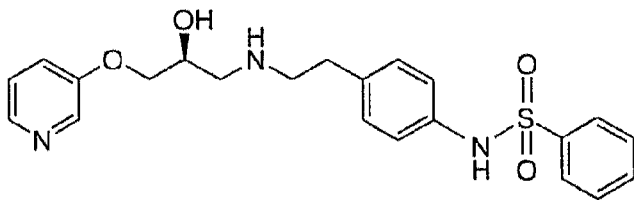
EXAMPLE 164



(S)-N-[2-[4-(Aminophenyl)]ethyl]-2-hydroxy-3-[(pyridin-3-yl)oxy]-propylcarbamic acid 1,1-dimethylethyl ester

A 37.8-g (0.09 mol) portion of the nitro compound from Example 163 was dissolved in 300 mL of ethyl acetate and hydrogenated over 7.1 g of 20 % palladium hydroxide on carbon overnight. The mixture was filtered and concentrated to give the title compound, which was used without further purification.

EXAMPLE 165

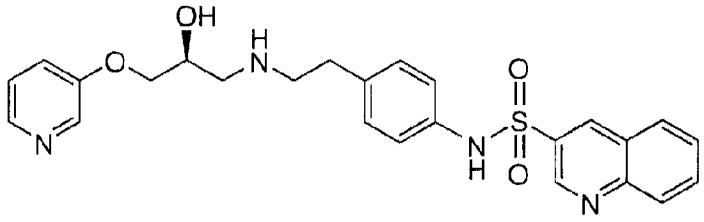


(S)-N-[4-[2-[[2-hydroxy-3-(3-pyridyloxy)propyl]amino]ethyl]-phenyl]benzenesulfonamide

In a manner analogous to that of Example 7, the title compound was prepared from the epoxide from Example 162 and N-[4-(2-aminoethyl)phenyl]benzenesulfonamide (Example 6). Purification by preparative thin layer chromatography on silica gel (eluant 90:10:2 methylen chloride/methanol/30% ammonium hydroxide) gave the title compound. ^{1}H NMR (400 MHz, CD_3OD) δ 8.23 (d, 1H, J = 4Hz), 8.12 (dd, 1H, J = 2.4Hz), 7.71(d, 2H, J = 8Hz), 7.52 (m, 1H), 7.40-7.48 (m,

3H), 7.35 (m, 1H), 7.09 (d, 2H, J = 10Hz), 7.00 (d, 2H, J = 10Hz), 3.95-4.08 (m, 3H), 2.69-2.90 (m, 6H).

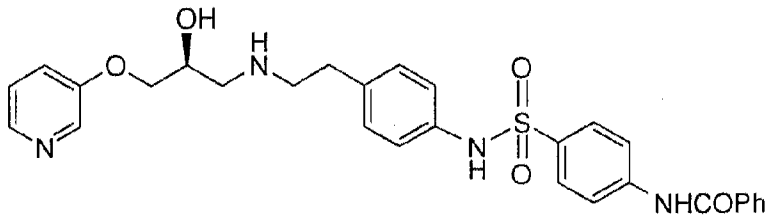
EXAMPLE 166



(S)-N-[4-[2-[[2-hydroxy-3-(3-pyridyloxy)propyl]amino]ethyl]-phenyl]-3-quinolinesulfonamide

To a solution of the aniline (1.0 g, 2.60 mmol) from Example 164 and pyridine (0.21 mL, 2.60 mmol) in 15 mL of methylene chloride was added 3-quinolinesulfonyl chloride (590 mg, 2.60 mmol) from Example 34. The pink solution was stirred at room temperature for 1.5 h and was concentrated under reduced pressure. The residue was dissolved in 20 mL of methanol, and approximately 8 mL of a 6N HCl was added. After warming at reflux for 18 h, the cooled solution was concentrated *in vacuo*, and the residue was dissolved in 10 mL of 10% methanolic ammonium hydroxide. After removal of solvent *in vacuo*, the residue was applied directly to a silica gel column. Elution with 9:1 CH_2Cl_2:10% methanolic NH_4OH afforded 0.84 g (1.78 mmol, 68% yield) of the title compound as an yellow solid. NMR (400 MHz, CD_3OD) 9.01 (d, 1H, J = 2.2 Hz), 8.75 (d, 1H, J = 2.2 Hz), 8.22 (d, 1H, J = 2.9 Hz), 8.12 (dd, 1H, J = 1.3, 4.7 Hz), 8.07 (d, 1H, J = 8.6 Hz), 8.04 (d, 1H, J = 8.6 Hz), 7.93 (apparent t, 1H), 7.72 (apparent t, 1H), 7.41 (m, 1H), 7.35 (dd, 1H, J = 4.7, 7.5 Hz). FAB MS *m/z* 479 (M + 1).

EXAMPLE 167



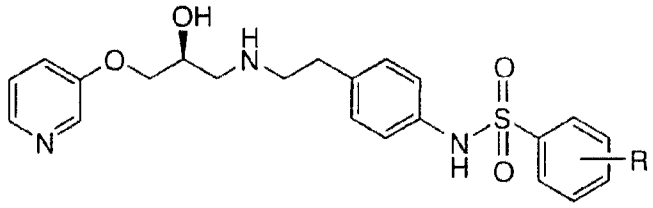
(S)-N-[4-[2-[[2-hydroxy-3-(3-pyridyloxy)propyl]amino]ethyl]-phenyl]-4-benzamidobenzenesulfonamide

To a solution of 1.00 g (2.58 mmol) of Boc aniline derivative from Example 164 and 0.25 mL (3.10 mmol, 1.2 equiv) of pyridine in dichloromethane at 0°C was added a solution of 572 mg (2.58 mmol) of 4-nitrobenzenesulfonyl chloride in 25 mL of dichloromethane via cannula. The reaction mixture was allowed to stir at 0°C for 1.5 h, then concentrated. Purification by flash chromatography (silica gel, ethyl acetate) gave 1.22 g (84%) of the resultant nitrobenzene sulfonamide. An 820-mg portion was dissolved in 15 mL of ethyl acetate and stirred over 20% palladium hydroxide on carbon under an atmosphere of hydrogen overnight. The reaction mixture was then filtered and concentrated. Purification by flash chromatography (silica, ethyl acetate) gave 636 mg (80%) of the corresponding 4-aminosulfonamide. A 203-mg (0.374 mmol) portion was dissolved in 4 mL of dichloromethane and treated with 36 mg (0.036 mL, 0.45 mmol) of pyridine and 58 mg (0.048 mL, 0.41 mmol) of benzoyl chloride. The reaction mixture was allowed to stir at 0°C for 45 min, and then 4 mL of trifluoroacetic acid was added. After 30 min, the reaction was concentrated. Purification by flash chromatography (silica, 7.5 % 10:1 methanol: concentrated aqueous ammonium hydroxide in dichloromethane) gave 144 mg (70%) of the title compound: ^{1}H NMR (400 MHz, CD_3OD) δ 8.21 (d, 1H, J = 2.9 Hz), 8.11 (dd, 1H, J = 1.3, 4.6 Hz), 7.90 (d, 2H, J = 7.0 Hz), 7.82 (d, 2H, J = 8.9 Hz), 7.69 (d, 2H, J = 8.9 Hz), 7.58 (t, 1H, J = 7.4 Hz), 7.49 (t, 2H, J = 7.4 Hz), 7.40 (ddd, 1H, J = 1.3, 2.9, 8.5 Hz), 7.34 (dd, 1H, J

= 4.5, 8.9 Hz), 7.10 (d, 2H, J = 8.5 Hz), 7.02 (d, 2H, J = 8.5 Hz), 4.06-3.95 (m, 3H), 2.86-2.69 (m, 6H).

Following the procedures outlined for Examples 162-167, the compounds listed in Tables 5 and 6 were prepared.

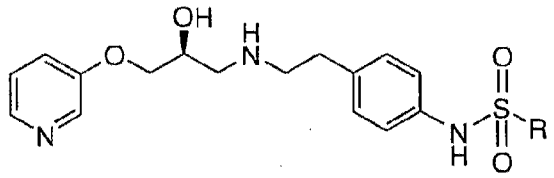
TABLE 5



Example	R	Selected ^{1}H NMR (CD_3OD) Data
168	4-Br	7.60 (s, 4H)
169	4-I	7.81 (d, 2H, J = 8.6 Hz), 7.44 (d, 2H, J = 8.6 Hz)
170	4-NO_2	8.27 (d, 2H, J = 7.0 Hz), 7.93 (d, 2H, J = 6.8 Hz)
171	4-NH_2	7.38 (d, 2H, J = 8.7 Hz), 6.56 (d, 1H, J = 8.7 Hz)
172	4-NHCOMe	7.65 (d, 2H, J = 9.2 Hz), 7.62 (d, 2H, J = 9.2 Hz), 2.10 (s, 3H)
173	4-$NHCO_2Et$	4.16 (q, 2H, J = 7.1 Hz), 1.27 (t, 3H, J = 7.1 Hz)
174	4-$NHCO_2CHMe_2$	4.08-3.96 (m, 4H), 1.26 (d, 6H, J = 6.2 Hz)
175	3-$NHCO(CH_2)_4CO_2Me$	3.63 (s, 3H), 2.33-2.40 (m, 4H), 1.60-1.73 (m, 4H)
176	4-$NHCO(CH_2)_4CO_2Me$	3.63 (s, 3H), 2.77 (q, 2H, J = 6.5 Hz), 2.36 (m, 2H), 1.66 (m, 4H)

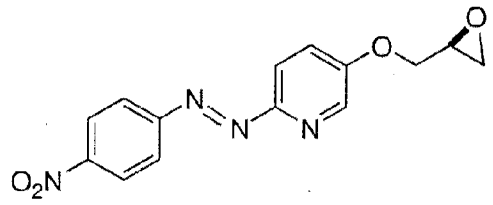
177	4-Propyl	7.61 (d, 2H, J = 8.4 Hz), 7.26 (d, 2H, J = 8.5 Hz), 2.60 (t, 2H, J = 7.7 Hz), 1.60 (hex, 2H, J = 7.5 Hz), 0.89 (t, 3H, J = 7.4 Hz)
178	4-OH	7.54 (d, 2H, J = 8.9 Hz), 6.76 (d, 2H, J = 8.9 Hz)
179	4-OMe	7.64 (d, 2H, J = 9.0 Hz), 6.95 (d, 2H, J = 9.0 Hz), 3.80 (s, 3H)

TABLE 6



Example	R	Selected ^{1}H NMR (CD_3OD) Data
180	CH_2CH_2Ph	7.25-7.15 (m, 7H), 3.26 (m, 2H), 3.03 (m, 2H)
181	2-methylthio-benzothiazol-5-yl	8.10 (d, 1H, J = 2.1 Hz), 7.94 (d, 1H, J = 8.1 Hz), 7.65 (dd, 1H, J = 2.1, 8.1 Hz), 2.81 (s, 3H)
182	1-acetylindolin-5-yl	8.09 (d, 1H), 7.53 (m, 2H), 4.13 (t, 2H, J = 8.8Hz), 3.17 (t, 2H, J = 8.7Hz), 2.20 (s, 3H)
183	benzofuran-2-yl	7.62 (d, 1H, J = 7.6Hz), 7.50 (d, 1H, J = 8.0 Hz), 7.38 (m, 1H), 7.24 (m, 2H)
184	benzothiophen-2-yl	7.88 (apparent t, 2H, J = 8.0Hz), 7.73 (s, 1H), 7.39 (m, 2H)

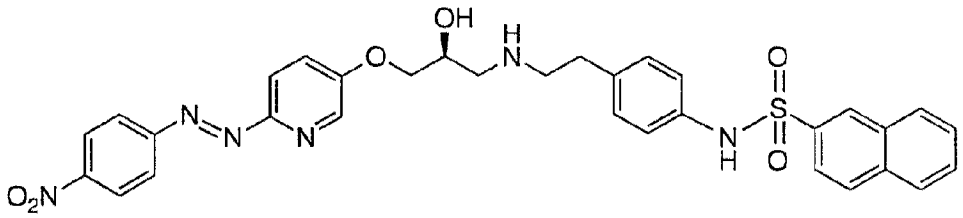
EXAMPLE 185



(S)-2-[[[2-(4-nitrobenzenazo)-5-pyridinyl]oxy]methyl]oxirane

The title compound was prepared from 5-hydroxy-2-(4-nitrobenzenazo)pyridine (J. A. Moore and F. J. Marascia, J. Amer. Chem. Soc., 81, 6049-6056 (1959)) in a manner analogous to that of Example 1: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 8.37 (d, 2H, J = 9.0 Hz), 8.11 (d, 2H, J = 9.0 Hz), 7.94 (d, 1H, J = 8.6 Hz), 7.45 (dd, 1H, J = 2.9, 8.8 Hz), 4.46 (dd, 1H, J = 2.5, 11 Hz), 4.06 (dd, 1H, J = 6.0, 11 Hz), 3.41 (m, 1H), 2.96 (t, 1H, J = 4.4 Hz), 2.80 (dd, 1H, J = 2.6, 4.6 Hz).

EXAMPLE 186

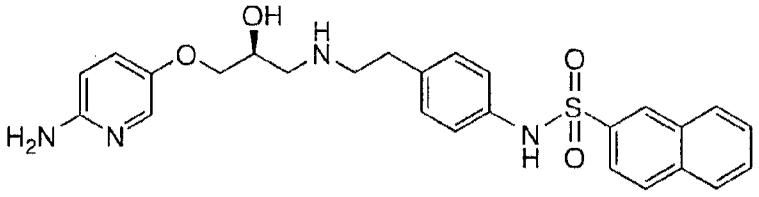


(S)-N-[4-[2-[[2-hydroxy-3-[[2-(4-nitrobenzenazo)-5-pyridinyl]oxy]-propyl]amino]ethyl]phenyl]-2-naphthalenesulfonamide

The Cbz amine from Example 13 was deprotected as described in Example 6. In a manner analogous to that of Example 7, the title compound was prepared from the resultant amine and the epoxide from Example 185: ^{1}H NMR (400 MHz, CD_3OD) δ 8.43 (d, 2H, J = 9.0 Hz), 8.38 (d, 1H, J = 2.9 Hz), 8.28 (d, 1H, J = 1.8 Hz), 8.13 (d, 2H, J = 9.0 Hz), 7.98 (d, 1H, J = 9.0 Hz), 7.93-7.88 (m, 3H), 7.72

(dd, 1H, J = 1.8, 8.7 Hz), 7.63-7.54 (m, 3H), 7.07 (d, 2H, J = 8.7 Hz), 7.03 (d, 2H, J = 8.7 Hz), 4.16-4.06 (m, 3H), 2.88-2.71 (m, 6H); FAB MS *m/z* 627 (M + 1).

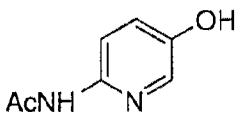
EXAMPLE 187



(S)-N-[4-[2-[[3-[(2-amino-5-pyridinyl)oxy]-2-hydroxypropyl]amino]-ethyl]phenyl]-2-naphthalenesulfonamide

A solution of 31.1 mg (0.0496 mmol) of the benzenazo derivative from Example 186 in 2 mL of acetic acid and 2 mL of methanol was stirred over 20% palladium hydroxide on carbon under an atmosphere of hydrogen for 1 h. It was then filtered and concentrated. Purification by flash chromatography (silica gel, 10% 10:1 methanol:concentrated ammonium hydroxide in dichloromethane) gave 19.0 mg (78%) of the title compound: ^{1}H NMR (400 MHz, CD_3OD) δ 8.27 (d, 1H, J = 1.8 Hz), 7.93-7.87 (m, 3H), 7.72 (dd, 1H, J = 1.8, 8.7 Hz), 7.62-7.54 (m, 3H), 7.17 (dd, 1H, J = 3.0, 9.0 Hz), 7.06-7.01 (overlapping d, 4H), 6.55 (d, 1H, J = 9.2 Hz), 3.95 (m, 1H), 3.86-3.79 (overlapping dd, 2H), 2.82-2.63 (m, 6H); FAB MS *m/z* 493 (M + 1).

EXAMPLE 188

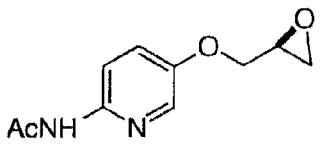


2-Acetamido-5-hydroxypyridine

A mixture of 1.72 g (10.4 mmol) of 2-acetamido-5-methoxypyridine, prepared according to the procedure of J.

Lombardino, *J. Med. Chem.* **1981**, *24*, 39-42, and 2.54 g (51.8 mmol) of sodium cyanide in 10 mL of DMSO was heated at 165°C under nitrogen for 48 h. The mixture was concentrated under vacuum to remove the DMSO. Purification by flash chromatography (silica, crude product transferred to column in methanol, then diluted with dichloromethane and eluted with 10% 10:1 methanol:concentrated aqueous ammonium hydroxide in dichloromethane) gave 0.881 g (56%) of the title compound as a brown solid: ^{1}H NMR (400 MHz, CD_3OD) δ 7.84-7.81 (overlapping d, 2H), 7.19 (dd, 1H, J = 2.9, 8.9 Hz), 2.12 (s, 3H).

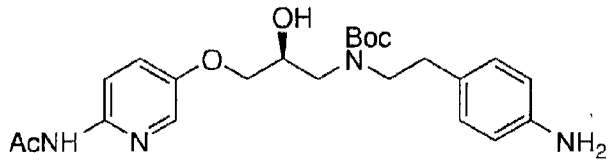
EXAMPLE 189



(S)-2-[(2-Acetamidopyridin-5-yl)methyl]oxirane

To a solution of 842 mg (5.53 mmol) of 2-acetamido-5-hydroxypyridine from Example 188 in 15 mL of DMF at 0°C was added 221 mg (5.53 mmol) of sodium hydroxide as a 60% dispersion in oil. After the mixture was allowed to stir for 30 min, 1.58 g (6.09 mmol, 1.1 equiv) of (2S)-glycidyl 3-nitrobenzene sulfonate was added. The reaction mixture was stirred at room temperature for 4 h, then partitioned between 400 mL of ethyl acetate and 100 mL of saturated aqeous sodium chloride solution. The aqueous layer was washed with 100 mL of ethyl acetate. The combined organic phases were dried over magnesium sulfate and concentrated under high vacuum to remove DMF. Purification by flash chromatography (silica, 80% ethyl acetate/hexane) gave 716 mg (62%) of the title compound as a crystalline solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, 1H, J = 9.1 Hz), 7.98 (br s, 1H), 7.95 (d, 1H, J = 2.9 Hz), 4.26 (dd, 1H, J = 2.9, 11.0 Hz), 3.92 (d, 1H, J = 5.8, 11.0 Hz), 3.33 (m, 1H), 2.90 (t, 1H, J = 4.5 Hz), 2.74 (dd, 1H, J = 2.6, 4.8 Hz), 2.16 (s, 3H).

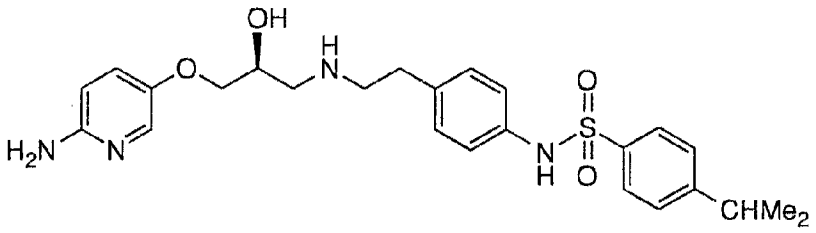
EXAMPLE 190



(S)-N-[2-[4-(Aminophenyl)]ethyl]-2-hydroxy-3-[(2-acetamidopyridin-5-yl)oxy]propylcarbamic acid 1,1-dimethylethyl ester

In a manner analogous to that of Examples 163 and 164, the title compound was prepared from the epoxide from Example 189: ^{1}H NMR (400 MHz, CD_3OD) δ 7.93-8.02 (m, 2H), 7.38 (d, 1H, J = 8Hz), 6.89-6.98 (m, 2H), 6.66 (d, 2H, 10 Hz), 4.06 (m, 1H), 3.89-4.00 (m, 2H), 3.38-3.50 (m, 3H), 3.14 (m, 1H), 2.70 (t, 2H,J = 8Hz), 2.13 (s, 3H), 1.41 (s, 9H).

EXAMPLE 191



(S)-N-[4-[2-[[3-[(2-amino-5-pyridinyl)oxy]-2-hydroxypropyl]amino]-ethyl]-phenyl]-4-isopropylbenzenesulfonamide

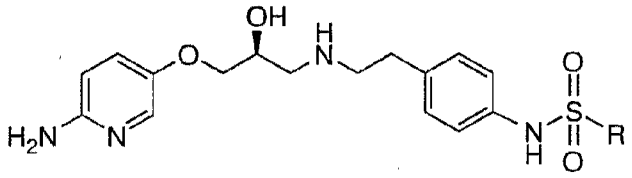
To a solution of the BOC-protected aniline from Example 190 (1.16 g, 2.6 mmol) and pyridine (300 μL, 3.64 mmol, 1.4 eq) in 45 mL of methylene chloride was added 4-isopropylbenzenesulfonyl chloride (577 mg, 2.6 mmol). The reaction mixture was stirred at room temperature under nitrogen atmosphere overnight. The pink solution was poured into brine (20 mL) and the organics were extacted with methylene chloride. The solution was washed with saturated ammonium chloride solution, water and brine and then dried over anhydrous magnesim sulfate. The solution was filtered and

concentrated under vacuum. Purification by flash column chromatography (silica gel, ethyl acetate) gave 1.54 g (94.5%) of the corresponding N-acetyl derivative: ^{1}H NMR (400 MHz, CD_3OD) δ 7.94-8.00 (m, 2H), 7.60-7.67 (m, 2H), 7,37 (d, 1H, J = 10 Hz), 7.31 (d, 2H, J = 10 Hz), 6.98-7.08 (m, 4H), 4.06 (m, 1H), 3.89-4.00 (m, 2H), 3.35-3.50 (m, 3H), 3.11 (m, 1H), 2.91 (m, 1H), 2.76 (t, 2H, J = 8 Hz), 2.13 (s, 3H), 1.38 (d, 9H), 1.20 (d, 6H, J = 8 Hz).

A solution of the N-acetyl derivative (1.54 g, 2.46 mmol) in 30 mL of methanol with 20 mL of 2 N hydrochloric acid was refluxed at 90°C for 20 h. The solvent was stripped under vacuum and the residue was purified by flash column chromatography (silica gel, 90:10:1 methylene chloride/methanol /30% ammonium hydroxide) to give 970 mg (83 %) of the titled compound. ^{1}H NMR (400 MHz, CD_3OD) δ 7.64 (d, 2H, J = 8 Hz), 7.60 (d, 1H, J = 2 Hz), 7.32 (d, 2H, J = 8 Hz), 7.19 (dd, 1H, J = 2,10 Hz), 7.08 (d, 2H, J = 8 Hz), 7.00 (d, 2H, J = 8 Hz), 6.56 (d, 1H, J = 10 Hz), 3.98 (m, 1H), 3.81-3.89 (m, 2H), 2.92 (hept, 1H, J = 8 Hz), 2.65-2.86 (m, 6H), 1.21 (d, 6H, J = 8 Hz).FAB-MS *m/e* 485 (M+1).

Following procedures outlined for Examples 185-191, the compounds listed in Table 7 were prepared.

TABLE 7

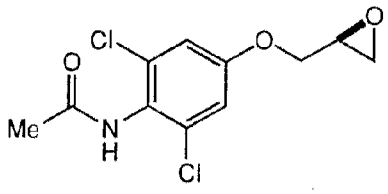


Example	R	Selected ^{1}H NMR (CD_3OD) Data
192	4-bromophenyl	7.61 (d, 2H, J = 9.3 Hz), 7.59 (d, 2H, J = 9.3 Hz)
193	4-iodophenyl	7.83 (d, 2H, J = 8.6 Hz), 7.43 (d, 2H, J = 8.6 Hz)

194	3,4-dichlorophenyl	7.61-7.58 (m, 3H)
195	4-methoxyphenyl	7.64 (d, 2H, J = 8.9 Hz), 6.94 (d, 2H, J = 8.9 Hz), 3.80 (s, 3H)
196	4-aminophenyl	7.38 (d, 2H, J = 8.9 Hz), 6.56 (d, 2H, J = 8.8 Hz)
197	4-phenylphenyl	7.78 (d, 2H, J = 8.6 Hz), 7.69 (d, 2H, J = 8.6 Hz), 7.62-7.59 (m, 3H), 7.43 (t, 2H, J = 7.4 Hz), 7.37 (t, 1H, J = 7.2 Hz)
198	4-CH_2CH_2Ph	7.26-7.14 (m, 8H), 3.27 (m, 2H), 3.03 (m, 2H)
199	naphth-1-yl	8.72 (d, 1H, J = 8.7 Hz), 8.14 (d, 1H, J = 7.3 Hz), 8.06 (d, 1H, J = 8.3 Hz), 7.95 (d, 1H, J = 8.7 Hz), 7.67 (dt, 1H, J = 1.5, 8.6 Hz), 7.61-7.57 (m, 2H), 7.47 (t, 1H, J = 7.8 Hz)
200	6-methoxynaphth-2-yl	8.20 (d, 1H, J = 1.8 Hz), 7.83 (d, 1H, J = 5.4 Hz), 7.81 (d, 1H, J = 5.4 Hz), 7.68 (dd, 1H, J = 1.1, 8.8 Hz), 7.60 (d, 1H, J = 2.6 Hz), 7.18 (m, 1H), 3.91 (s, 3H)
201	quinolin-3-yl	9.01 (d, 1H, J = 2.2 Hz), 8.74 (d, 1H, J = 2.2 Hz), 8.06 (m, 2H), 7.95 (apparent dt, 1H), 7.73 (apparent t, 1H)
202	1,3-benzodioxol-5-yl	7.77 (dd, 1H, J = 10.5, 3.5 Hz), 7.3 (dd, 1H, J = 9.5, 2 Hz), 7.14 (d, 1H, J = 2 Hz), 6.03 (s, 2H)
203	1,4-benzodioxan-6-yl	7.54 (s, 1H), 7.49 (d, 1H, J = 8 Hz), 4.25 (m, 5H)
204	2-methylthio-benzothiazol-5-yl	8.09 (s, 1H), 7.86 (d, 1H, J = 8.0 Hz), 7.63 (d, 1H, J = 8.0 Hz), 2.73 (s, 3H)

205	benzothiophen-2-yl	7.83 (t, 2H, J = 7.2), 7.71 (s, 1H), 7.40 (m, 2H)
206	1,2-benzisoxazol-5-yl	7.82-7.78 (m, 3H)

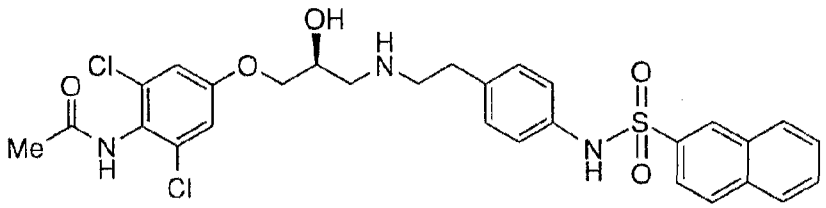
EXAMPLE 207



(S)-2-[(4-acetamido-3,5-dichlorophenoxy)methyl]oxirane

4-Acetamido-3,5-dichlorobenzenediazonium tetrafluoroborate was converted to the corresponding phenol according to the procedure of T. Cohen, et. al., J. Org. Chem., 42, 2053-2058 (1977). Thus, 22 g (94 mmol) of copper (II) nitrate was dissolved in 100 mL of water and 300 mg (0.94 mmol) of 4-acetamido-3,5-dichlorobenzenediazonium tetrafluoroborate was added. Copper (I) oxide (405 mg, 2.8 mmol) was added. The mixture was stirred for 35 min, then filtered through Celite, diluted with 1 N aqueous sodium bisulfate, and extracted with 4 portions of dichloromethane and 8 portions of ethyl acetate. The combined organic phases were dried over magnesium sulfate and concentrated. Purification by flash chromatography (silica, 50% ethyl acetate/hexanes) gave 72 mg (35%) of 4-acetamido-3,5-dichlorophenol. This compound was converted to the title compound in a manner analogous to that of Example 1: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (s, 2H), 4.21 (dd, 1H), 3.86 (dd, 1H), 3.32 (m, 1H), 2.91 (t, 1H), 2.73 (dd, 1H), 2.20 (s, 3H).

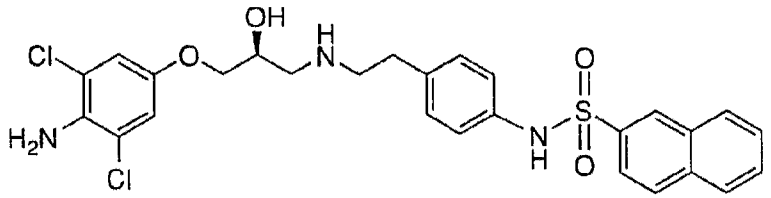
EXAMPLE 208



(S)-N-[4-[2-[[2-hydroxy-3-(4-acetamido-3,5-dichlorophenoxy)propyl]-amino]ethyl]phenyl]-2-naphthalenesulfonamide

The Cbz amine from Example 13 was deprotected as described in Example 6. In a manner analogous to that of Example 7, the title compound was prepared from the resultant amine and the epoxide from Example 207: ^{1}H NMR (400 MHz, CD_3OD) δ 8.28 (d, 1H, J = 1.7 Hz), 7.95-7.90 (m, 3H), 7.72 (dd, 1H, J = 1.9, 8.7 Hz), 7.63-7.57 (m, 2H), 7.09-7.02 (m, 6H), 4.02 (m, 1H), 3.97-3.88 (overlapping dd, 2H), 2.89-2.72 (m, 6H), 2.15 (s, 3H).

EXAMPLE 209

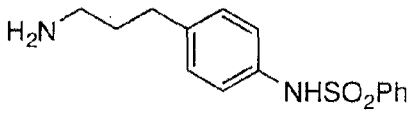


(S)-N-[4-[2-[[2-hydroxy-3-(4-amino-3,5-dichlorophenoxy)propyl]-amino]ethyl]phenyl]-2-naphthalenesulfonamide

A solution of 28 mg (0.016 mmol) of the acetamide from Example 208 in 5 mL of methanol and 0.24 mL of 2N aqueous hydrochloric acid was heated at reflux for 3 days. It was then cooled and concentrated. Purification by HPLC (ODS-3, 1:1 methanol:0.1% aqueous trifluoroacetic acid) gave 6.7 mg (13%) the title compound as its bis trifluoracetate salt: ^{1}H NMR (400 MHz, CD_3OD) δ 8.31 (d, 1H, J = 1.5 Hz), 7.96-7.90 (m, 3H), 7.75 (dd, 1H, J = 1.9, 8.7 Hz), 7.65-7.57 (m, 2H), 7.11 (s, 4H), 6.89 (s, 2H), 4.12 (m, 1H), 3.89 (dd, 1H, J =

5.0, 9.9 Hz), 3.85 (dd, 1H, J = 5.3, 9.9 Hz), 3.23-3.11 (m, 4 H0, 2.90-2.86 (m, 2H).

EXAMPLE 210



N-[4-(3-aminopropyl)phenyl]benzenesulfonamide

A mixture of 0.5g (2.17 mmol) 4-nitrophenethyl bromide and 0.134g (2.71 mmol) of sodium cyanide in dry DMSO was stirred at room temperature for 2 h. The resulting reaction mixture was diluted with water (50 mL) and extracted with methylene chloride twice. The combined organic layers were washed with water, brine, dried over magnesium sulfate and concentrated. The product was isolated by column chromatography on silica gel (15% ethyl acetate/85% Hexanes) to give 0.32 g (84 %) of the 4-nitrophenethyl nitrile.

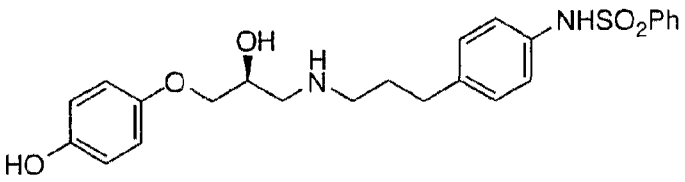
A 0.3 g-portion (1.7 mmol) of nitro compound in methanol was hydrogenated in the presence of 300 mg of 10% Pd/C until hydrogen uptake ceased. The reaction mixture was filtered and the solvent evaporated from the filtrate. The resultant amine (clean by ^1H NMR) was directly used in the next step without any purification.

To a stirred solution of 0.23 g (1.57 mmol) of the resultant amine in methylene chloride (10 mL) at room temperature was added 0.417 g (2.35 mmol) of benzenesulfonyl choride, followed by 0.25 g (3.14 mmol) of pyridine. After 6 h, the reaction mixture was concentrated and purified on silica (2% methanol/ 98 methylene chloride) to yield 0.32 g of the sulfonamide nitrile.

To a stirred mixture of 0.318 g (1.1 mmol) of sulfonamide nitrile and 0.53 g (2.22 mmol) of cobalt (II) chloride hexahydrate in methanol (10 mL) was added at room temperature in portions 0.42 g (11 mmol) of sodium borohydride (exothermic). The resulting reaction mixture (black) was stirred at room temperature for 5 h and acidified with 3N hydrochloric acid until the solution become clear. The reaction

mixture was concentrated and purified on silica (5% methanol/95 methylene chloride) to give 0.2 g of the amine. ^{1}H NMR (400 MHz, CD_3OD) 7.73 (dd, 2H), 7.54 m,1 H), 7.45 (m, 2H), 7.06-7.00 (AA', BB', 4H).

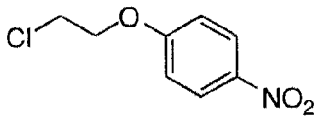
EXAMPLE 211



(S)-N-[4-[2-[[2-hydroxy-3-(4-hydroxyphenoxy)propyl]amino]propyl]-phenyllbenzenesulfonamide

Following the procedures outlined in Examples 7 and 12 the title compound is prepared from the amine from Example 210 and the epoxide from Example 2.

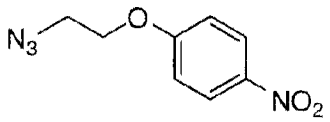
EXAMPLE 212



4-Nitrophenyl 2-chloroethyl ether

A solution of 1.611 g of 4-nitro sodium phenoxide (10 mmol), 2.15g (1.25 mL, 15.0 mmol) of 1-bromo-2-chloroethane, and 4.15 g (30.0 mmol) of potassium carbonate in 60 mL of methylethyl ketone was refluxed in an oil bath overnight under nitrogen atmosphere. The reaction was cooled and the solid was filtered off. The filterate was evaporated under vacuum and the residue was purified by flash column chromatography (silica gel, eluant 2:1 hexanes/ethyl acetate) to give 1.35 g (67%) of the title compound: ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.18 (d, 2H, J=9Hz), 6.95 (d, 2H, J=9Hz), 4.29 (t, 2H, J=6Hz), 3.82 (t, 2H, J=6Hz).

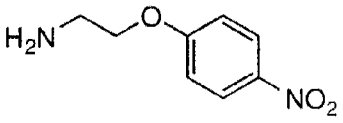
EXAMPLE 213



4-nitrophenyl 2-azidoethyl ether

A solution of 1.12 g (5.55 mmol) of 4-nitro 2-chloroethyl ether (Example 212) and lithium azide (544 mg, 11.1 mmol) in 3 mL of DMF was heated at 60°C in an oil bath overnight under nitrogen atmosphere. The reaction was poured into water and extracted with ethyl acetate. The organics were washed with water and brine and dried over anhydrous magnesium sulfate and concentrated to give 1.12 g (97%) of the product: ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.18 (d, 2H, *J*=9Hz), 6.96 (d, 2H, *J*=9Hz), 4.21 (t, 2H, *J*=5Hz), 3.63 (t, 2H, *J*=5Hz).

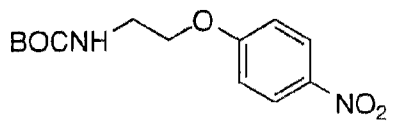
EXAMPLE 214



4-Nitrophenyl 2-aminoethyl ether

A solution of 4-nitro 2-aminoethyl ether (610 mg, 2.93 mmol) from Example 213 in 10 mL of THF/water (9:1) was treated with triphenyl phosphine (768 mg, 3.0 mmol) at ambient temperature. After stirring for 3 h, the solvent was removed under vacuum and the residue was purified by flash column chromatography on silica gel (eluant 1:9 methanol/methylene chloride) to give 480 mg (95%) of the title compound: ^{1}H NMR (200 MHz, CD_3OD) δ 8.18 (d, 2H, *J*=9Hz), 6.96 (d, 2H, *J*=9Hz), 4.13 (t, 2H, *J*=5.5Hz), 3.27 (t, 2H, *J*=5.5Hz).

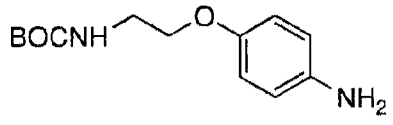
EXAMPLE 215



2-(4-Nitrophenoxy)ethylcarbamic acid 1,1-dimethylethyl ester

A solution of 480 mg (2.79 mmol) of amine from Example 214 in 20 mL of methylene chloride was treated with 610 mg (2.80 mmol) of di-tert-butyl dicarbonate. After stirring at room temperature for 40 min., the reaction mixture was concentrated and the resulting yellow solid was used for the next step without further purification: ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.15 (d, 2H, *J*=9Hz), 6.90 (d, 2H, *J*=9Hz), 4.94 (bs, 1H, N-H), 4.05 (bt, 2H, *J*=5.0Hz), 3.50 (q, 2H, *J*=5.0Hz).

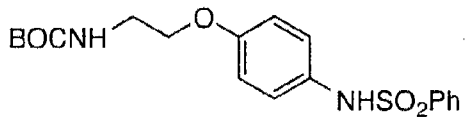
EXAMPLE 216



2-(4-Aminophenoxy)ethylcarbamic acid 1,1-dimethylethyl ester

A solution of 775 mg (2.75 mmol) of nitro compound from Example 215 in 20 mL of methanol with 10% palladium on carbon (150 mg) was introduced hydrogen via balloon at room temperature for 4 h. The catalyst was filtered off through Celite, and the filterate was concentrated under vacuum to give 690 mg of the title compound: ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.69 (d, 2H, *J*=8Hz), 6.58 (d, 2H, *J*=8Hz), 4.94 (bs, 1H, N-H), 3.89 (bt, 2H, *J*=5.0Hz), 3.40 (q, 2H, *J*=5.0Hz), 1.40 (s, 9H).

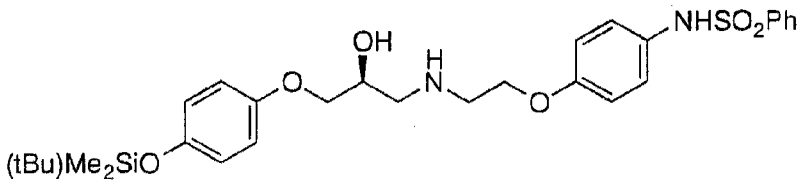
EXAMPLE 217



N-[4-[2-[[(1,1-dimethylethoxy)carbonyl]amino]ethoxy]phenyl]benzene-sulfonamide

To a solution of 314 mg(1.246 mmole) of t-BOC amine from Example 216 in 10 mL of methylene chloride was added pyridine (147 mg, 1.869 mmol, 1.5 eq) followed by benzenesulfonyl chloride (242 mg, 1.370 mmol, 1.1 eq) at room temperature. The reaction mixture was stirred at room temperature overnight and then partitioned between water and chloroform. The organic layer was separated and washed with 1N hydrochloric acid, water and brine and then dried over anhydrous sodium sulfate. The solution was filtered, concentrated and the residue was purified by flash column chromatography (eluant 2:1 hexanes/ethyl acetate) to give 248 mg (51%) of the product: ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.01 (d, 1H, *J*=8Hz), 7.67 (d, 2H, *J*=8Hz), 6.92 (d, 2H, *J*=9Hz), 6.72 (s, 1H, N-H), 6.70 (d, 2H, *J*=9Hz), 4.90 (bs, 1H, N-H), 3.89 (t, 2H, *J*=5.0Hz), 3.40 (q, 2H, *J*=5.0Hz), 1.40 (s, 9H).

EXAMPLE 218

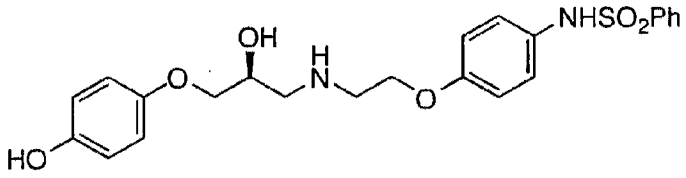


(S)-N-[4-[2-[[2-hydroxy-3-[[4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-phenoxy]propyl]amino]ethyloxy]phenyl]benzenesulfonamide

A solution of 248 mg (0.632 mmol) of t-BOC amine from Example 217 in 2 mL of methylene chloride was treated with 1 mL of trifluoroacetic acid for 0.5 h and the reaction mixture was concentrated

under vacuum to give the resultant amine (256 mg, 100%) as a trifluoroacetic acid salt. To a solution of this amine in 5 mL of dry methanol was added diisopropylethylamine (90 mg, .70 mmol) followed by the epoxide from example 2 (70 mg, .25 mmol, 0.4 equiv). The reaction was heated at reflux in an oil bath under nitrogen overnight and then cooled to room temperature and concentrated. Purification by preparative thin layer chromatography on silica (eluant 12:88 methanol/methylene chloride) gave 110 mg (77%) of the desired product as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (dd, 2H, *J*=8,1Hz), 7.39 (t, 1H, *J*=7.7Hz), 7.38 (t, 2H, *J*=7.7 Hz), 6.89 (d, 2H, *J*=9Hz), 6.70 (s, 4H), 6.69 (d, 2H, *J*=9Hz), 4.20 (m, 1H), 4.05 (m, 2H), 3.90 (m, 2H), 3.20-3.0 (m, 4H), 0.95 (s, 9H), 0.11 (s, 6H).

EXAMPLE 219

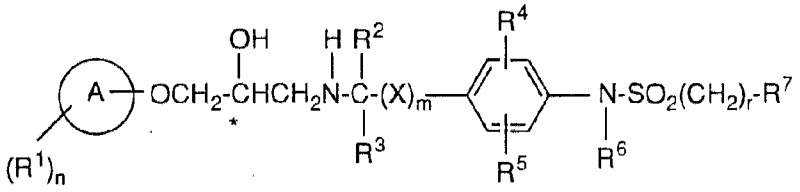


(S)-N-[4-[2-[[2-hydroxy-3-(4-hydroxyphenoxy)propyl]amino]ethoxy]-phenyl]benzenesulfonamide

In a manner analogous to that of Example 12, the title compound was prepared from the silyl ether from Example 218: ^{1}H NMR (200 MHz, CD_3OD) δ 7.68 (d, 2H,*J*=8Hz), 7.53 (t, 1H, *J*=8Hz), 7.43 (t, 2H, *J*=8 Hz), 7.0 (d, 2H, *J*=9Hz), 6.86 (d, 2H, *J*=9Hz), 6.79 (d, 2H, *J*=9Hz), 6.69 (d, 2H, *J*=9Hz), 4.21 (m, 1H), 3.92 (m, 2H), 3.50 (m, 2H), 3.40-3.20 (m, 4H), EI-MS: calculated for $C_{23}H_{26}N_2O_6S$ 458; found 459 (M+1).

WHAT IS CLAIMED IS:

1. A compound having the formula:



I

where

n is 0 to 7;

m is 0 or 1;

r is 0 to 3;

A is phenyl, naphthyl, a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur or nitrogen, a benzene ring fused to a C3-C8 cycloalkyl ring, a benzene ring fused to a 5 or 6-membered heterocyclic ring with from 1 to 3 heteroatoms selected from oxygen, sulfur or nitrogen or a 5 or 6-membered heterocyclic ring with from 1 to 3 heteroatoms selected from oxygen, sulfur or nitrogen fused to a 5 or 6-membered heterocyclic ring with from 1 to 3 heteroatoms selected from oxygen, sulfur or nitrogen;

R^1 is hydroxy, oxo, halogen, cyano, nitro, NR^8R^8, SR^8 trifluoromethyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_3-C_8 cycloalkyl, phenyl, SO_2R^9, $NHCOR^9$, COR^9, $NR^8SO_2R^8$, $NR^8CO_2R^8$, or C_1-C_6 alkyl substituted by hydroxy, nitro, halogen, cyano, NR^8R^8, SR^8, trifluoromethyl, C1-C6 alkoxy, C_3-C_8 cycloalkyl, phenyl, NR^8COR^9, COR^9, SO_2R^9, $NR^8SO_2R^9$, $NR^8CO_2R^8$, or R^1 is a 5 or 6-membered heterocycle with from 1 to 3 heteroatoms selected from oxygen, sulfur or nitrogen;

R^2 and R^3 are independently hydrogen, C_1-C_6 alkyl or C_1-C_6 alkyl substituted by 1 to 3 of hydroxy, C_1-C_6 alkoxy, or halogen;

X is $-CH_2-$, $-CH_2-CH_2-$, $-CH=CH-$ or $-CH_2O-$;

R^4 and R^5 are independently hydrogen, C_1-C_6 alkyl, halogen, NHR_8, OR_8, SO_2R_9 or $NHSO_2R^9$;

R^6 is hydrogen or C_1-C_6 alkyl;

R^7 is C_1-C_6 alkyl, C_3-C_8 cycloalkyl, or B-$(R_1)_n$;

B is phenyl, naphthyl, a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur or nitrogen, a benzene ring fused to a C_3-C_8 cycloalkyl ring, a benzene ring fused to a 5 or 6-membered heterocyclic ring with from 1 to 3 heteroatoms selected from oxygen, sulfur or nitrogen or a 5 or 6-membered heterocyclic ring with from 1 to 3 heteroatoms selected from oxygen, sulfur or nitrogen fused to a 5 or 6-membered heterocyclic ring with from 1 to 3 heteroatoms selected from oxygen, sulfur or nitrogen;

R^8 is hydrogen, C_1-C_{10} alkyl, C_3-C_8 cycloalkyl, phenyl optionally substituted by 1 to 3 of halogen, C_1-C_6 alkyl or C_1-C_6 alkoxy, or C_1-C_{10} alkyl substituted by 1 to 3 of hydroxy, halogen, CO_2H, CO_2-C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_1-C_6 alkoxy, or phenyl optionally substituted by from 1 to 3 of halogen, C_1-C_6 alkyl or C_1-C_6 alkoxy;

R^9 is R^8, NHR^8 or NR^8R^8.

2. A compound of Claim 1 wherein the 5 and 6-membered heterocycles and fused heterocycles of A, B and R_1 are those heterocycles with from 1 to 4 heteroatoms independently selected from one of oxygen or sulfur or 1 to 4 nitrogen atoms.

3. A compound of Claim 1 wherein A and B are independently phenyl, naphthyl, or a 5 or 6 membered heterocycle or fused heterocycle with from 1 to 4 heteroatoms independently selected from one of oxygen or sulfur or 1 to 4 nitrogen atoms.

4. A compound of Claim 3 wherein A is phenyl, naphthyl, pyridyl, quinolinyl, pyrimidinyl, pyrrollyl, thienyl, imidazolyl or thiazolyl.

5. A compound of Claim 3 wherein B is phenyl, naphthyl, quinolinyl, thienyl, benzimidazolyl, thiadiazolyl, benzothiadiazolyl, indolyl, indolinyl, benzodioxolyl, benzodioxanyl, benzothiophenyl, benzofuranyl, benzisoxazolyl, benzothiazolyl, tetrahydronaphthyl, dihydrobenzofuranyl, and tetrahydroquinolinyl.

6. A compound of Claim 3 wherein R^2 and R^3 are hydrogen or methyl; X is $-CH_2-$; m is 1; r is 0-2; and R^5 and R^6 are hydrogen.

7. A compound of Claim 3 wherein A is phenyl quinolinyl or a 6-membered heterocyclic ring with 1 or 2 nitrogen atoms;

B is phenyl or quinolinyl;

R^1 is NH_2, hydroxy, halogen, cyano, trifluoromethyl phenyl, NR^8COR^9, $NR^8CO_2R^8$, C_1-C_6 alkyl optionally substituted by hydroxy; and

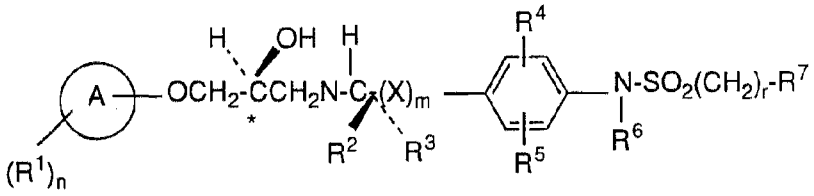
r is 0 or 2.

8. A compound of Claim 1 which is

N-[4-[2-[[2-hydroxy-3-(4-hydroxyphenoxy)propyl]amino]ethyl]phenyl]-benzenesulfonamide
N-[4-[2-[[2-hydroxy-3-(4-hydroxyphenoxy)propyl]amino]ethyl]phenyl]-4-iodobenzenesulfonamide
N-[4-[2-[[2-hydroxy-3(4-hydroxyphenoxy)propyl]amino]ethyl]phenyl]-2-naphthalenesulfonamide
N-[4-[2-[[2-hydroxy-3-(4-hydroxyphenoxy)propyl]amino]ethyl]phenyl]-4-(benzo-2,1,3-thiadiazole)sulfonamide
N-[4-[2-[[2-hydroxy-3-(4-hydroxyphenoxy)propyl]amino]ethyl]phenyl]-2-phenylethanesulfonamide
N-[4-[2-[[3-(4-fluorophenoxy)-2-hydroxypropyl]amino]ethyl]phenyl]-4-benzenesulfonamide
N-[4-[2-[[3-[(2-amino-5-pyridinyl)oxy]-2-hydroxypropyl]amino]ethyl]-phenyl]-2-naphthalenesulfonamide
N-[4-[2-[[2-hydroxy-3-(4-hydroxyphenoxy)propyl]amino]ethyl]phenyl]-3-quinolinesulfonamide
N-[4-[2-[[2-hydroxy-3-(4-hydroxyphenoxy)propyl]amino]ethyl]phenyl]-4-[(5-methoxycarbonyl)pentanoyl]amino]benzenesulfonamide
N-[4-[2-[[2-hydroxy-3-(4-hydroxyphenoxy)propyl]amino]ethyl]phenyl]-4-[(5-hydroxycarbonyl)pentanoyl]amino]benzenesulfonamide
N-[4-[2-[[2-hydroxy-3-(4-hydroxyphenoxy)propyl]amino]ethyl]phenyl]-4-(hexylaminocarbonylamino)benzenesulfonamide
N-[4-[2-[(2-hydroxy-3-phenoxypropyl)amino]ethyl]phenyl]-4-chlorobenzenesulfonamide
N-[4-[2-[[2-hydroxy-3-(3-cyanophenoxy)propyl]amino]ethyl]phenyl]-3-quinolinesulfonamide
N-[4-[2-[[3-(4-amino-3-cyanophenoxy)-2-hydroxypropyl]amino]ethyl]-phenyl]-3-quinolinesulfonamide
N-[4-[2-[[2-hydroxy-3-[(3-hydroxymethyl)phenoxy]propyl]amino]-ethyl]phenyl]-3-quinolinesulfonamide
N-[4-[2-[[2-hydroxy-3-(3-pyridyloxy)propyl]amino]ethyl]phenyl]-3-quinolinesulfonamide

N-[4-[2-[[2-hydroxy-3-(3-pyridyloxy)propyl]amino]ethyl]phenyl]-4-iodobenzenesulfonamide
N-[4-[2-[[3-[(2-amino-5-pyridinyl)oxy]-2-hydroxypropyl]amino]ethyl]-phenyl]-4-isopropylbenzenesulfonamide.

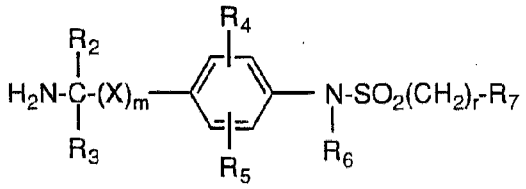
9. A compound of Claim 1 with the structural formula:



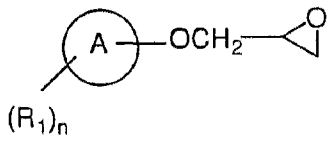
Ia

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 process for the preparation of a compound of Claim 1 which comprises treating a compound having the formula:



with a compound having the formula:



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.

11. A method for the treatment of diabetes which comprises administering to a diabetic patient an effective amount of a compound of Claim 1.

12. A method for the treatment of obesity which comprises administering to an obese patient an effective amount of a compound of Claim 1.

13. A method for lowering triglyceride levels and cholesterol levels of 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.

14. 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.

15. 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.

16. A method for reducing depression which comprises administering to a depressed patient an effective amount of a compound of Claim 1.

17. A method for treating gastrointestinal disorders which comprises administering to a patient with gastrointestinal disorders an effective amount of a compound of Claim 1.

18. 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

Int[illegible]nal Application No
PCT/US 94/00766

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07C311/21 C07C311/46 C07C311/47 C07D213/30 C07D213/38
C07D215/36 A61K31/18 A61K31/44 A61K31/47

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 5 C07C C07D

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	WO,A,90 00548 (SCHERING) 25 January 1990 see page 1 - page 4; examples I,II,III ---	1,10
X	JOURNAL OF MEDICINAL CHEMISTRY, vol. 33, no. 10 , October 1990 Washington, DC, US, pages 2883 - 2891 R. LIS, ET AL.: 'Synthesis of novel (aryloxy)propanolamines and related compounds posseing both class II and class III antiarrhythmic acitivity' * compounds 20,21,22 * ---	1,10
A	EP,A,0 328 251 (IMPERIAL CHEMICAL INDUSTRIES) 16 August 1989 see page 2 - page 3 & US-A-4 999 377 cited in the application --- -/--	1,12,18

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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"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

1

Date of the actual completion of the international search	Date of mailing of the international search report
28 April 1994	16. 05. 94

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	English, R

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 427 480 (IMPERIAL CHEMICAL INDUSTRIES) 15 May 1991 see page 2 & US-A-5 017 619 cited in the application	1,12,18
A	EP,A,0 091 749 (BEECHAM) 19 October 1983 see page 2 - page 3	1,12,18

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 94/00766

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9000548	25-01-90	US-A-	5051423	24-09-91
		CA-A-	1328105	29-03-94
		EP-A-	0358284	14-03-90
		JP-T-	3501617	11-04-91
EP-A-0328251	16-08-89	AU-B-	614809	12-09-91
		AU-B-	2843689	27-07-89
		CA-A-	1326025	11-01-94
		JP-A-	2001442	05-01-90
		US-A-	4999377	12-03-91
EP-A-0427480	15-05-91	DE-D-	69005984	24-02-94
		JP-A-	3193747	23-08-91
		US-A-	5187190	16-02-93
EP-A-0091749	19-10-83	JP-A-	58185554	29-10-83

Isosterism and Molecular Modification in Drug Design

By C. W. Thornber
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1 Introduction

The idea of isosterism goes back to Langmuir[1] in 1919. At that time the word isosterism was used to describe the similarity of molecules or ions which have the same number of atoms and valence electrons *e.g.* O^{2-}, F^-, Ne. Clearly only those isosteres with the same nett charge show similar chemical and physical properties. Grimm[2] enunciated his hydride displacement law to describe the similarity between groups which have the same number of valence electrons but different numbers of atoms. For example some similarities are present in the sequence: CH_3, NH_2, OH, Hal.

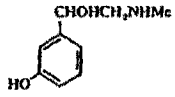
Grimm's hydride displacement law points out some similarities of size in groupings based on elements in the same row of the periodic table. Other similarities to be found in the periodic table are within the groups, where chemical reactivities are similar but with electronegativity decreasing as atomic weight increases and lipophilicity and polarizability increasing with the size of the atom. Other relationships exist in diagonal lines across the periodic table where atoms of similar electronegativity such as nitrogen and sulphur, oxygen and chlorine are found.

In trying to relate biological properties to the physical and chemical properties of atoms, groups, or molecules, many physical and chemical parameters may be involved and the simple relationships mentioned above are clearly inadequate for this purpose. Friedman[3] introduced the term 'bioisosterism' to describe the phenomenon in which compounds which are related in structure have similar or antagonistic properties. The use of the word isosterism has clearly outgrown its original meaning when used in medicinal chemistry and a loose flexible definition could be adopted such as: 'Bioisosteres are groups or molecules which have chemical and physical similarities producing broadly similar biological properties'.

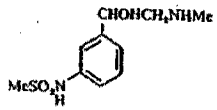
The term non-classical isosterism is also used interchangeably with bioisosterism, particularly in connection with isosteres which do not have the same number of atoms but do produce a similarity in some key parameter of importance in

[1] I. Langmuir, *J. Amer. Chem. Soc.*, 1919, 41, 868, 1543.
[2] H. G. Grimm, *Z. Elektrochem.*, 1925, 31, 474; 1928, 34, 430; 1934, 47, 53, 594.
[3] H. L. Friedman, 'Influence of Isosteric Replacements upon Biological Activity', National Academy of Sciences—National Research Council Publication No. 206, Washington D.C., 1951, p. 295.

that series. For example[4] the two β-adrenergic stimulants compounds (1) and (2) have similar activity.



(1) pK_a 9.6



(2) pK_a 9.1

The concept of bioisosterism has been described in reviews by Burger,[5a] Schatz,[5b] Foye,[6] Korolkovas,[7] Ariens,[8] and Hansch.[9] This present review collates and extends the earlier observations with more recent reports from the literature and suggests new techniques for exploiting the concept.

The 'classical' isosteres as defined by Burger[5] and Korolkovas[7] are given in Table 1.

Table 1

1) *Univalent atoms and groups*

	F	OH	NH_2	Me	Cl
		SH	PH_2		
		I	Bu^t		
		Br	Pr^i		

2) *Bivalent atoms and groups*

O	S	Se	CH_2	—N(H)—
CO_2R	COSR	$COCH_2R$	CONHR	

3) *Tervalent atoms and groups*

—N=	—CH=
—P=	—As=

4) *Quadrivalent atoms*

—C(—)(—)—	—Si(—)(—)—

5) *Ring equivalents*

—CH=CH—			S	e.g. benzene: thiophen
=C(H)—			=N—	e.g. benzene: pyridine
—O—	—S—	$—CH_2—$	—NH—	

[4] A. A. Larson and P. M. Lish, *Nature*, 1964, 203, 1283.
[5a] A. Burger in 'Medicinal Chemistry' 3rd Edn., ed. A. Burger, Wiley-Interscience, New York, 1970.
[5b] V. B. Schatz in 'Medicinal Chemistry' 2nd Edn., ed. A. Burger, Wiley-Interscience, New York, 1960.
[6] W. O. Foye, 'Principles of Medicinal Chemistry', Lea and Febiger, Philadelphia, 1970.
[7] A. Korolkovas, 'Essentials of Molecular Pharmacology: Background for Drug Design', Wiley, 1970.
[8] E. J. Ariens in 'Drug Design', ed. E. J. Ariens, Academic Press, New York, 1971, Vol. 1.
[9] C. Hansch, *Intra-Science Chem. Rep.*, 1974, 8, 17.

2 Bioisosterism in Molecular Modification

In the process of developing a lead compound, an antagonist to a known agonist, or an anti-metabolite from a known substrate, a large number of systematic molecular modifications will be made. The modern concept of bioisosterism can be an aid to the design of such modifications. In making a bioisosteric replacement the following parameters of the group being changed could be considered:

(*a*) *Size.*

(*b*) Shape (bond angles, hybridization).

(*c*) Electronic distribution (polarizability, inductive effects, charge, dipoles).

(*d*) Lipid solubility.

(*e*) Water solubility.

(*f*) pK_a.

(*g*) Chemical reactivity (including likelihood of metabolism).

(*h*) Hydrogen bonding capacity.

It is unlikely that any bioisosteric replacement will leave all these parameters undisturbed. The extent to which the replacement is useful will depend upon which of these parameters is important and which ones the bioisostere can best mimic.

The element of a molecule being modified may have one or more of the following roles.

(i) *Structural.* If the moiety has a structural role in holding other functionalities in a particular geometry, parameters such as size and bond angle will be important. The moiety may be buried deep in the molecule and have little contact with the external medium.

(ii) *Receptor interactions.* If the moiety to be replaced is concerned with a specific interaction with a receptor or enzyme its size, shape, electronic properties, pK_a, chemical reactivity, and hydrogen bonding will be the important parameters.

(iii) *Pharmacokinetics.* The moiety to be replaced may be necessary for the absorption, transport, and excretion of the compound. In this case lipophilicity, hydrophilicity, hydrogen bonding, and pK_a are likely to be important.

(iv) *Metabolism.* The moiety may be involved in blocking or aiding metabolism. In this case chemical reactivity will be an important parameter. For example chloro and methyl substituents on a benzene ring may be interchangeable for certain purposes but the toluene derivative can be metabolized to a benzoic acid and may therefore have a shorter half-life or unexpected side effects.

Usually one will not know which role(s) the various parts of the molecule play(s) in its action and this determination will be part of the structure–activity study. However, from the simple considerations listed above it is clear that:–

(A) A given molecular modification may allow some, but probably not all of the parameters (*a*)—(*h*) to be kept the same.

(B) Whether the same or a different biological activity results from the replacement will be governed by the role(s) which that moiety fulfils in the molecule and whether parameters affecting that role have been disturbed.

(C) From (A) and (B) it follows that what proves to be a good bioisosteric replacement in one series of compounds will not necessarily be useful in another.

Completely identical properties are rarely sought and will in any case be difficult if not impossible to achieve. What we are more likely to be seeking is a subtle change in the molecule which will leave some properties the same and some different in order to improve potency, selectivity, absorption, duration, and toxicity. Bioisosteric replacements allow molecular modifications, in which the number of variables changed are limited. Ariens[8] and Korolkovas[7] have tried to introduce the idea of partial bioisosteric groups as those which turn an agonist into an antagonist. Although their lists of groups may be suggestive to the drug designer, the idea is probably incorrect because of the statement (C) above. An 'antagonist' group in one molecule will only antagonize a similar 'agonist' group in another molecule if the agonist groups in both series are performing the same function. If an isosteric replacement results in a molecule which has some properties similar to the parent molecule but some important property has changed, it may be possible to compensate for this undesirable change by modifications elsewhere in the molecule. For example a molecular modification may reduce the lipid solubility of the molecule thereby affecting its absorption, transport, and apparent potency. Optimum activity may be regained by inserting lipophilic groups into the molecule at some sterically undemanding site. Consequently the best compounds in this parallel series of isosteres, such as for example furans and thiophens, are likely to have different substituent patterns.

3 The Mathematical Formulation

The arguments used above can be expressed in the mathematical form used by Hansch[10] for the case where a simple substituent is being varied, for example on a benzene ring. If the potency of a drug is a function of several parameters of the substituent then:

$$\log\frac{1}{c} = A(\pi) + B(\sigma) + C(E_s)$$

where Hansch's π value is used for the lipophilic character, Hammett's σ value for the electronic property, Taft's steric parameter to denote the size of the group and c is the concentration of drug required to achieve a given effect.

If such a relationship were found for a drug series in which the constants B and C were zero then the potency would be a function of π only. In this context groups would be bioisosteric if they have similar π values independent of their

[10] C. Hansch, *Accounts Chem. Res.*, 1969, 2, 232.

σ and E_s values. If however the three constants A, B, and C are all significant a much more limited range of equivalent groups will be available.

If a series of compounds has more than one property, as is usual, then more than one equation will be needed to describe the effects of changing the substituent:

$$\log\frac{1}{c} = A(\pi) + B(\sigma) + C(E_s)$$

Desired activity

$$\log\frac{1}{c} = D(\pi) + E(\sigma) + F(E_s)$$

Side effects

Clearly if $A = D$, $B = E$, and $C = F$, *etc.*, no selectivity can be found within this limited series. If however $C \ll F$ then for the desired activity E_s is not important and π and σ may be optimized while reducing the value of E_s, thereby reducing the side effects. This phenomenon of increasing selectivity by bioisosteric replacement relies upon the fact that some desirable properties in the molecule can be retained when unimportant parameters can be varied. An unimportant parameter for the biological activity desired *may* be a key parameter in the side effect.

Thus bioisosteric replacements are useful in searching for potency, selectivity, absorption, and duration. Following the Hansch treatment one could produce a modern definition of bioisosterism based upon measurable parameters such as π, σ, E_s, hydrogen bonding properties, pK_a, *etc.*, and Hansch[9] has used the term 'isolipophilic' for groups with the same π value.

Table 2 shows some functional groups with similar electron-withdrawing properties. If electronic effects alone influence the biological activity in a series of drugs then these groups would be equivalent. If, however, the lipophilicity and steric factors are important then absolute identity cannot be achieved.

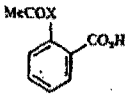
Table 2

Functional Group	σ_m	π	E_s
F	0.34	0.14	0.78
Cl	0.37	0.71	9.27
Br	0.39	0.86	0.08
I	0.35	1.12	−0.16
CF_3	0.43	0.88	−1.16
SCF_3	0.40	1.44	
COMe	0.31	−0.55	
CHO	0.36	−0.65	
CO_2Me	0.32	−0.01	
$CH{=}CH{-}NO_2$	0.32	0.11	

Extensive tables of σ, π, and E_s values are now available.[11] These can be used to gain a more quantitative idea of some aspects of isosterism using the better known functional groups.

4 Chemical Reactivity

Biological effects are generally produced by 'weak' interactions between the drug and the receptor but covalent bonding does occasionally play a part. A series of aspirin isosteres (3) was reported in 1975.[12] The nitrogen, sulphur, and carbon



(3) X = O, NH, S, or CH_2

isosteres were all totally inactive despite the classical purity of the replacements tried. Now that it is known that aspirin is an acetylating agent for prostaglandin synthetase this result is more readily understood.[13] The agents are widely different in their ability to act as acylating agents unless other substantial modifications are made in the molecules.

5 Non-classical Isosteres: Some Further Points

In considering bioisosterism in its widest sense it should be noted that similar effects in two functional groups need not imply atom upon atom overlap. Edwards[14] has pointed out that a common enzyme or receptor interaction involves hydrogen bonding to a carbonyl group. Strong hydrogen bonds may be formed to the carbonyl oxygen by hydrogen atoms within a cone having an angle of about 60° at its apex. Two molecules RXH and RAXH, where A is an additional atom, may be able to bind to the active site without identical positioning of the X or H. In addition the conformational mobility in both the drug and the receptor molecule will allow essentially similar binding of two drugs without the need to consider that the binding groups on the drugs are positioned in space in an identical manner.

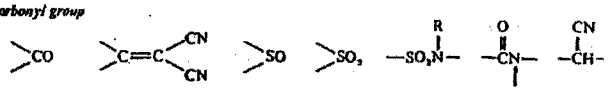
Examples of Non-classical Isosteres.—The list shown in Table 3 is drawn from earlier reviews[5–9] and from the examples given in Table 4 at the end of this

[11] Tables of substituent constants can be found in the following papers. C. Hansch, S. D. Rockwell, P. Y. C. Jow, A. Leo, and E. E. Steller, *J. Med. Chem.*, 1977, 20, 304; J. G. Topliss, *J. Med. Chem.*, 1972, 15, 1006, and 1977, 20, 463; C. Hansch, A. Leo, S. H. Unger, Ki Hwan Kim, D. Nikaitani, and E. J. Lien, *J. Med. Chem.*, 1973, 16, 1207.
[12] L. Thompkins and K. H. Lee, *J. Pharm. Sci.*, 1975, 64, 760.
[13] G. J. Roth, N. Stanford, and P. W. Majerus, *Proc. Nat. Acad. Sci. U.S.A.*, 1975, 72, 3073.
[14] P. N. Edwards, I.C.I. Pharmaceuticals Division, personal communication.

review. In addition a few proposals[15–17] which have not yet been realized in medicinal chemical work are included.

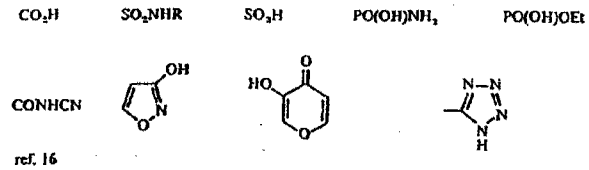
Table 3

Carbonyl group



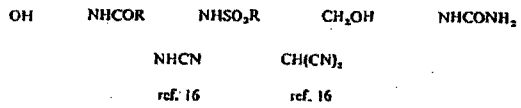
ref. 15

Carboxylic acid group



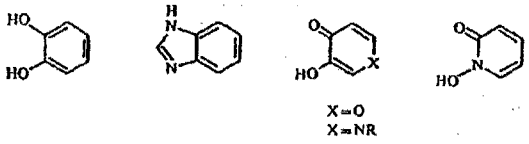
ref. 16

Hydroxy-group

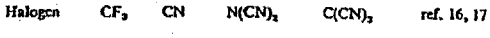


ref. 16 ref. 16

Catechol



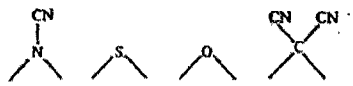
Halogen



[15] K. Wallenfels, K. Friedrich, J. Rieser, W. Ertel, and H. K. Thieme, *Angew. Chem. Internat. Edn.*, 1976, 15, 261.
[16] H. von Kohler, B. Eichler, and R. Salewski, *Z. anorg. Chem.*, 1970, 379, 183, also includes other possibilities in the sulphur and phosphorus and nitro acid series.
[17] K. von Wallenfels, *Chimia*, 1966, 20, 303.

Table 3 *continued*

Thioether



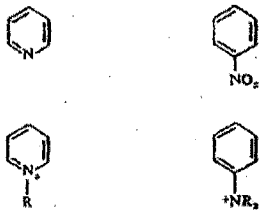
ref. 16

Thiourea

Azomethine

ref. 17

Pyridine



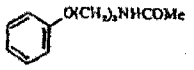
Spacer groups

In addition ring-opened forms of molecules may be considered to be isosteric with the corresponding ring-closed forms although the conformation of the *seco* form will be unlike the parent molecule. However, if in ring opening an atom is removed a conformation similar to the parent molecule may be possible.

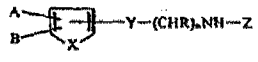
6 Substructure Searching and Bioisosterism

Although the classical Hansch approach is used largely for optimization within a series, molecular modifications based on bioisosterism principles can generate new series or even develop new leads if an agonist is used as the starting point for the design of an antagonist. One aid to this process is the use of a compound collection and computer techniques for doing substructure searches, *e.g.* the

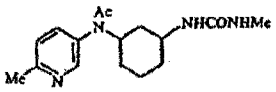
Crossbow suite of programmes.[18] For example suppose that random screening has turned up the lead (4). One may consider bioisosteric replacements for the ring, the oxygen, the polymethylene chain, or the amidic moiety, and design a substructure search for compounds of type (5). A vast number of permutations are possible and from these compounds may be available for tests which result in new leads which have properties worth exploiting, such as perhaps (6).



(4)



(5) X = CH=CH, CH=N, S, O, or NR
Y = O, S, SO, SO_2, Se, NCN, or NCOR
n = 2, 3, or 4
R = H or alkyl, including forming a ring
Z = COR, CO_2R, SOR, SO_2R, or CONHR
A = B = defined substituents

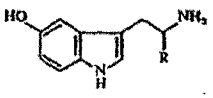


(6)

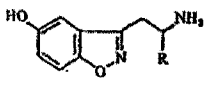
Examples.—The literature of medicinal chemistry is rich in examples of the use of the concept of bioisosterism and the reader is referred to the reviews mentioned[5–8] and the references quoted therein for examples reported before 1970. There follows a brief discussion of bioisosteres of some indole-amines which has some useful lessons, and Table 4 lists examples culled from the literature since 1970. Only the structures are given in this Table as an illustration of the kinds of change which have been useful. The reader is referred to the original papers for the full details of biological activity and selectivity. The list is not comprehensive but represents some uses of more novel non-classical types. Rudinger[19] has reviewed isosteric replacements in the field of peptide chemistry up to 1971 and some further discussions[20] have been published recently.

Indole-amines.—Campaigne[21] has studied and reviewed the work on bioisosteres of 5-hydroxytryptamine (7) and one or two details of the work are instructive. Whereas (8) was inactive as an agonist or antagonist on the rat uterus preparation, the corresponding tryptophan analogue (9) had weak activity as an enzyme inhibitor for 5-hydroxytryptamine decarboxylase.[22] This type of bioisostere

[18] E. E. Townsley and W. A. Warr, 'Chemical and Biological Data; An Integrated On-Line Approach' in 'Retrieval of Medicinal Chemical Information', ed. Howe, Milne, and Pennell (A. C. S. Symposium Series No. 84), American Chemical Society, Washington D.C.
[19] J. Rudinger, in ref. 8, Vol. II, Chapter 9.
[20] Further discussion of peptide backbone replacement is found in ref. 19 and W. Soudyn and L. van Wijngaarden, in 'Biological Activity and Chemical Structure', ed. J. A. Keverling Buisman, Elsevier, Holland, 1977; a peptide link isostere —CH_2—S— has been reported by J. A. Yankeelov, Kam-Fook Fok, and D. J. Carothers, *J. Org. Chem.*, 1978, 43, 1623.
[21] E. Campaigne, R. P. Maickel, and T. R. Bosin, Medicinal Chemistry, Specialist Contributions, 3rd International Symposium, 1972, Butterworths, 1973, p. 65.
[22] M. Pigini, M. Gianella, F. Gualtieri, C. Melchiorre, P. Bolle, and L. Angelucci, *European J. Med. Chem.*, 1975, 10, 29, 33.

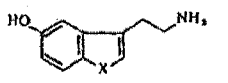


(7) R = H (5-hydroxytryptamine)
(10) R = CO_2H (5-hydroxytryptophan)



(8) R = H
(9) R = CO_2H

loses all affinity for the 5-hydroxytryptamine (5-HT) receptor but retains it in part for an enzyme system. Similarly, in the series of compounds 5-HT, (11), (12), and (13) activity has been measured against the rat fundic strip preparation and on the enzyme caeruloplasmin.[22] Whereas 5-HT is a substrate for the enzyme, compound (11) inhibited caeruloplasmin's oxidation of 5-HT and noradrenaline.



		Rat Fundic Strip	
	X	*Intrinsic activity*	PD_2
5-HT	NH	1	7.6
(11)	CH_2	0.96	5.6
(12)	O	0.84	4.6
(13)	S	1.08	6.1

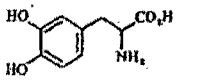
Compound (12) inhibits only 5-HT oxidation and compound (13) was inactive as a substrate or an antagonist. This would appear to demonstrate that for the enzyme system the imino grouping at the 1-position of the ring is essential.

On the rat fundic strip, however, all the analogues have full agonist activity though with reduced potency, demonstrating that the 5-HT receptor has a greater tolerance for loss of the imino nitrogen. These simple experiments demonstrate the role of bioisosteric replacements in exploring selectivity between different receptors and enzymes.

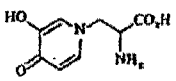
[22] B. C. Barrass, D. B. Goult, R. M. Finder, and M. Sheels, *Biochem. Pharmacol.*, 1973, 22, 2891.

Table 4 *Some recent examples of bioisosterism*

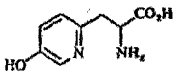
Dihydroxyphenylalanine analogues



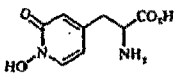
Dopa



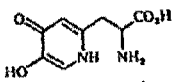
Mimosine ref. 24



ref. 25

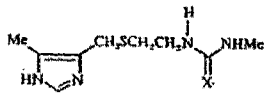


ref. 26

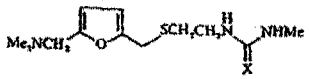


ref. 27

Histamine H-2 antagonists



X = S or NCN ref. 28

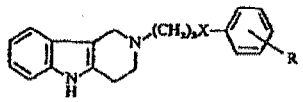


X = NCN or CHNO$_2$ ref. 29

[24] H. Haguchi, *Mol. Pharmacol.*, 1977, 13, 362.
[25] A natural product from *Streptomyces* species, S. Inoue, T. Shamura, T. Tsuruoka, Y. Ogawa, H. Watanabe, J. Yoshidea, and T. Ikuda, *Chem. and Pharm. Bull. (Japan)*, 1975, 23, 2669.
[26] Synthesized as a mimosine analogue, R. N. L. Harris and R. Teitei, *Austral. J. Chem.*, 1977, 30, 649.
[27] S. L. Norton and E. Sanders, *J. Med. Chem.*, 1967, 10, 961.
[28] R. W. Brimblecombe, W. A. M. Duncan, C. J. Durant, J. C. Emmett, C. R. Ganellin, and M. E. Parsons, *J. Int. Med. Res.* 1975, 3, 86. See also Sulphur–methylene isosterism in the development of metiamide, J. W. Black, G. J. Durant, J. C. Emmett, and C. R. Ganellin, *Nature*, 1974, 248, 65, and C. R. Ganellin, *J. Appl. Chem. Biotechnol.*, 1978, 28, 183.
[29] Allen and Hanbury, U.S.P. 4 128 658.

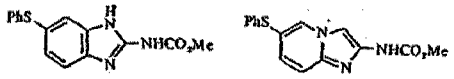
Table 4 *continued*

Neuroleptics

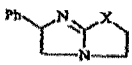


X = C(=O) or CH—CN ref. 30

Anthelmintics

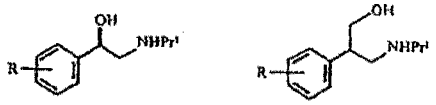


ref. 31



X = S or Se ref. 32

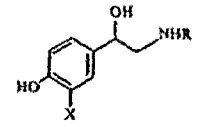
β-Adrenergic blockers



ref. 33

[30] Boehringer, Sohn C. H., U.S.P. 4 085 216.
[31] H. Fisher and M. Lusi, *J. Med. Chem.*, 1972, 15, 982; R. J. Bochis, R. A. Dybas, P. Eskola, P. Kulsa, B. O. Linn, A. Lusi, E. Mutzner, J. Milkowski, H. Mrozik, L. E. Olen, L. H. Peterson, R. L. Tolman, A. F. Wagner, F. S. Waksmunski, J. R. Egerton, and D. A. Ostcind, *J. Med. Chem.*, 1978, 21, 235.
[32] R. N. Hanson, R. N. Giese, M. A. Davis, and S. M. Costello, *J. Med. Chem*, 1978, 21, 496.
[33] T. Jen, J. S. Frazee, M. S. Schwartz, K. F. Erhard, C. Kaiser, D. F. Colella, and J. R. Wardell, *J. Med. Chem.*, 1977, 20, 1263.

β-Adrenergic stimulants

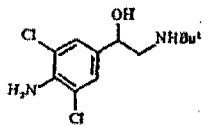


R = Me, X = OH Adrenaline

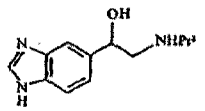
R = Bu^t, X = CH_2OH
Salbutamol ref. 34

R = Bu^t, X = $NHCONH_2$
Carbuterol ref. 35

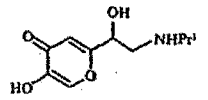
R = Pr^i, X = $NHSO_2Me$
Soterenol ref. 36



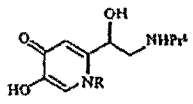
Clenbuterol ref. 37



ref. 38



ref. 39



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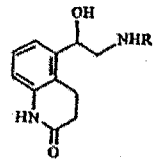

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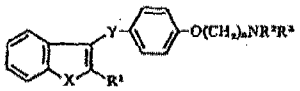
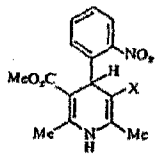
Table 4 *continued*

Vasodilators

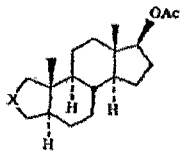


X = O or S, Y = SO_2 ref. 41
X = O, Y = CO ref. 42
X = S, Y = CO ref. 43



X = CO_2Me ref. 44
X = SO_2Me ref. 45

Androgens



X = S or NCN ref. 46

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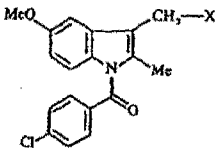
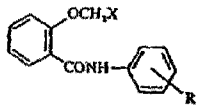
Anti-inflammatory



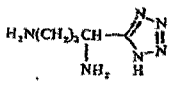
X =  ref. 47

X = CO_2H ref. 48



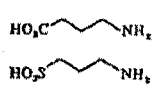
X = CO_2H or  ref. 49

Ornithine decarboxylase inhibitor



ref. 50

Gabergic agents



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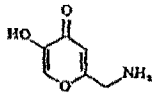

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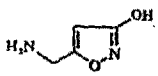

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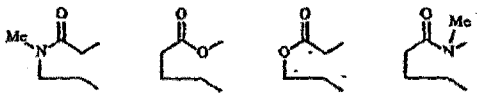
Table 4 *continued*

Prostaglandin ring systems



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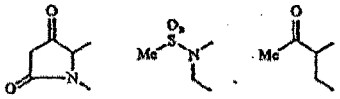

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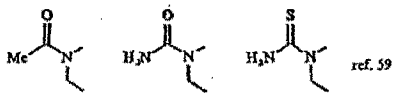

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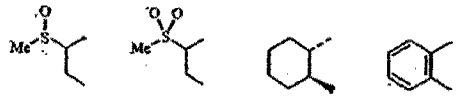

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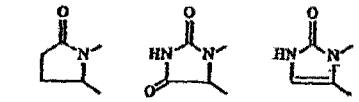
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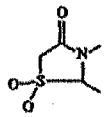
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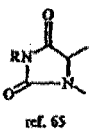
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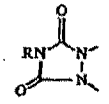
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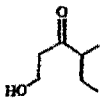
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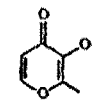
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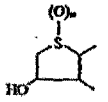
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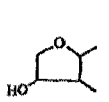
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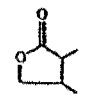
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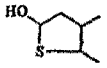
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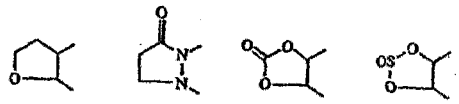
Table 4 *continued*

Prostaglandin ring system (continued)



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PATENT
Attorney Docket No. 07385.0042-00000

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Request for Supplemental Examination of:	
U.S. Patent No. 6,346,532	Group Art Unit: *Not Yet Assigned*
Inventors: Tatsuya MARUYAMA et al.	Examiner: *Not Yet Assigned*
Issued: February 12, 2002	
For: AMIDE DERIVATIVES OR SALTS THEREOF	Confirmation No.: *Not Yet Assigned*

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

DECLARATION UNDER 37 C.F.R. § 1.132

I, Tetsuo Matsui, do hereby make the following declaration:

1. I am one of the co-inventors of the subject matter described and claimed in U.S. Patent No. 6,346,532 ("the '532 patent").

A. Personal and Professional Background

2. I am a current employee of Astellas. I have been employed with Astellas and its predecessor company, Yamanouchi Pharmaceutical Co., Ltd. ("Yamanouchi"), for 20 years. During that period, my job titles have included Senior Research Fellow, and my responsibilities have included Theme Leader of Adrenergic beta-3 agonist for Type 2 diabetes (1993-2000), Sub-group Leader (2000-2002), Group Leader (2003-2005), and Research Manager (2005-2012) of the Metabolic Diseases Group or Diabetic Complications Group in the Pharmacology Research Laboratories. My current

job title is Senior Manager, and my current responsibilities include being in charge of Translational Science in the Research Management Group.

3. My educational background and my work experiences prior to Astellas include a Ph.D. from the Pharmacology Department of Toyama Medical & Pharmaceutical University (1990) and a position of Researcher of Aldose reductase inhibitors for diabetic complications at Sapporo Breweries LTD. (1990-1993). I am also a Japanese Pharmacological Society councilor (1992-).

4. I am one of the inventors of the '532 patent and am familiar with the work that led to the inventions claimed by the '532 patent.

B. Materials Reviewed and Considered

5. In connection with my work on this matter, I have reviewed and considered the following items of information:

1. U.S. Patent No. 6,346,532;

2. Table of testing data for compounds including those disclosed in Examples 1-113 of U.S. Patent No. 6,346,532 ("Testing Data Table");

3. Materials for Astellas R&D Meeting. Subcommittee on Development Theme Establishment, titled "YM178/Discontinuation of Development Theme for Diabetes Mellitus," dated October 27, 2003 ("R&D Meeting Materials");

4. YM178 in Type 2 Diabetes Mellitus 178-CL003 Study Report ("Study Report");

5. Yamanouchi BAN Compound Evaluation System ("R&D Flowchart");

6. Yamanouchi Monthly Research Progress Report, dated April 16, 1995 ("Monthly Progress Report");

C. The Testing Data Table for the Compounds Disclosed in Examples 1-113 of the '532 Patent

6. I have reviewed the Testing Data Table, and by reviewing the original laboratory notebooks and other internal documents, I am satisfied the information

provided in the Table is accurate for the compounds disclosed in Examples 1-113 of the '532 patent. Column 1 of the Testing Data Table provides the internal Yamanouchi code (BAN) number for each of the compounds. Column 2 provides the example number from the '532 patent. Column 3 provides the chemical structure of the compound. Columns 4-6 provide the β-adrenergic receptor data for each compound as pD_2 values and IA% ("Intrinsic Activity" as compared to isoproterenol - numbers in parentheticals) using the CHO screening test. Column 7 provides ED_{30} data for several of the compounds based on hypoglycemic studies in KK mice. Column 8 provides β_3-adrenergic receptor data determined using the SK-N-MC screening test. Column 9 provides the test report dates for these data in columns 4-8.

D. Efficacy of the Claimed Compounds to Treat Diabetes Mellitus

7. As is shown in the Testing Data Table, I and my co-inventors conducted a series of *in vitro* and *in vivo* studies before October 15, 1998, the date on which the PCT application leading to the issuance of the '532 patent was filed. From the results of these preliminary studies, we believed mirabegron (BAN-371, compound number 5) showed promise as an anti-diabetic medicine, and based upon the available information, the FDA approved commencement of Phase I clinical trials to determine appropriate dosages of mirabegron for Phase II clinical trials to assess efficacy for treating diabetes mellitus. (*See* Testing Data Table, Compound BAN 371, Cols. 4-9.)

8. Based on the results of the ensuing limited Phase IIa clinical trials, performed after the '532 patent issued, it was decided internally within Yamanouchi that mirabegron did not demonstrate sufficient efficacy for the treatment of diabetes mellitus to be a commercially competitive drug, and so we decided not to pursue diabetes

mellitus as an indicated use. (*See, e.g.*, R&D Meeting Materials at p. 13 ("The results of the phase IIa study of [mirabegron] administered at a dose of 200 mg in the fed state could not confirm the efficacy of [mirabegron] in terms of the primary end points (HbA_{1c} and fasting blood glucose level)").)

9. Despite our decision to discontinue the development of mirabegron for the treatment of diabetes mellitus, we conducted a detailed analysis of the results of the Phase IIa clinical study prior to the discontinuance of the project, which revealed that mirabegron did have some efficacy in certain patient subgroups. For example, the Study Report states:

> Some efficacy was found only when HbA1c at baseline was above 7% (data from central laboratory; local data 7-8%); responses of HbA1c and FPG to [mirabegron] were mainly found for female patients.
>
> * * *
>
> Changes in HbA1c were mainly detected in young patients; in elderly no difference between [mirabegron] and placebo could be found, even when baseline HbA1c was taken into account.

(Study Report at p. 11 (slides 21-22).)

E. Comparison of β_3-Activity to β_1 and β_2-Activities

10. As can be seen in the Testing Data Table, cols. 4-6, the compounds of Examples 1-113 of the '532 patent were tested using the CHO β_1, β_2, and β_3-receptor stimulation screening tests. Although all of the compounds tested showed some level of β_3-receptor agonist activity, depending on whether the IA% or pD_2 test results are used, a number of the claimed compounds exhibited β_3-receptor agonist activities that were not as high as the corresponding β_1- or β_2-receptor agonist activities. (*See* Testing Data Table, Cols. 4-6; *see also* table below.) For example, although the compound of Example 1, designated BAN 404, showed β_3-receptor agonist activity greater than β_1-

receptor agonist activity in both the IA% and pD_2 tests, it showed β_3-receptor agonist activity less than β_2-receptor agonist activity. (*See id.*, Compound BAN 404.)

F. **Yamanouchi's Internal β_3-receptor Screening Criteria**

11. As of time the '096 application was filed, and up to the time the '532 patent issued, we utilized certain internal screening criteria to determine whether a compound has sufficient β_3-receptor agonist activity and selectivity to warrant further evaluation for potential eventual submission as an anti-diabetic drug. As the R&D Flowchart shows, in general, before a candidate compound qualified for further evaluation, our initial internal screen stated that a candidate compound should have an IA test result for β_3-receptor agonism of greater than 0.6 (or 60%) and a pD_2 value for the β_3-receptor of greater than 6.5, while at the same time having IA test results for β_1- and β_2-receptor agonism of less than 0.2 (or 20%). (*See* R&D Flowchart.)

12. The following data, excerpted from the Testing Data Table, provide examples of the claimed compounds that did not meet our initial β_3-receptor selectivity and/or activity criteria set forth in the R&D Flowchart:

Chart #	**BAN #**	**Example #**	**Compound Covered By Claims**	**IA% β3 IA% β2 IA% β1**	**pD_2 β3 pD_2 β2 pD_2 β1**
13	377	110	1,2,7,8,9,10,13,14	58.1 22.7 2.7	5.23 5.65 <4
19	390	105	1,2,7,8,9,10,13,14	24 28 17	6.3 5.9 5.3
21	395	88	1,2,7,8,9,10,13,14	18 50 20	5.9 4.2 <4.0
22	396	3	1,2,7,8,9,10,13,14	18 27 2	5.9 4.2 <4.0

Chart #	BAN #	Example #	Compound Covered By Claims	IA% β3 IA% β2 IA% β1	pD_2 β3 pD_2 β2 pD_2 β1
23	398	96	1,2,7,8,9,10,13,14	27 17 9	5.6 5.9 <4
29	404	1	1,2,6,7,8,9,10,12,13,14	10 25 0	5.1 5.4 <4
30	405	2	1,2,7,8,9,10,13,14	11 18 0	6.0 5.8 <4
32	407	11	1,2,3,4,7,8,9,10,13,14	40 37 3	6.4 6.4 <4
35	410	111	1,2,7,8,9,10,13,14	32 53 14	5.6 5.5 5.6
36	411	101	1,2,7,8,9,10,13,14	37 50 19	6.2 5.4 4.6
39	414	112	1,2,7,8,9,10,13,14	55 89 25	6.9 6.6 5.6
49	435	36	1,2,3,4,7,8,9,10,13,14	14 27 5	6.2 5.3 <4
50	440	37	1,2,3,4,7,8,9,10,13,14	27 19 6	<5.0 5.4 <4
53	447	8	1,2,7,8,9,10,13,14	41 35 23	6.3 5.2 6.6
55	455	18	1,2,7,8,9,10,13,14	49 31 69	5.8 5.9 4.4
61	478	113	1,2,7,8,9,10,13,14	52 49 14	5.8 6.4 4.9
109	548	15	1,2,3,4,5,7,8,9,10,11,13,14	68 36 74	7.1 5.4 5.1

13. Thus, there are 17 claimed compounds shown in the table above that did not satisfy our internal criteria for further development based on either the pD_2 or IA% values.

G. Measurement of β_3-selectivity and the '532 Patent Disclosure

14. As discussed in the '532 patent, I and the other inventors determined the β_3-stimulating action of the compounds of the invention by comparing the effects of the claimed compounds on the β_1, β_2, and β_3-receptor subtypes using cells expressing human-type receptors. The '532 patent indicates that we utilized an SK-N-MC cell system comprising human neuroblastoma cells permanently expressing the human β_1- and β_3-receptor to assess β_3 activity, and CHO cell systems comprising Chinese hamster ovary cells permanently expressing either the human β_1- or β_2-receptors to assess β_1 and β_2 activities. (*See* the '532 patent, col. 11, line 56 to col. 12, line 11.) Stimulating activities of the compounds were investigated by incubating the cells with compounds of the invention and measuring production of cAMP. The effect of each compound was assessed by calculating the pD_2 value (the negative logarithmic value of the concentration at which half of the maximal response is induced by the compound) or the EC_{50} (the concentration at which half of the maximal response is induced by the compound), and intrinsic activity (IA%, where the maximum reaction of 10^{-6}M isoproterenol, a non-selective β-agonist, is defined as 100%). (*See Id.*)

15. However, as can be seen from the information provided in column 9 of the Testing Data Table, none of the compounds of Examples 1-113 in the '532 patent was tested for β_3-stimulating action using the SK-N-MC cell system until after the October 15, 1998, filing date of the international application that led to the '532 patent (*i.e.*,

PCT/JP98/04671). Instead, we assessed the β_3-selectivity of all of the compounds disclosed in examples 1-113 of the '532 patent, using the CHO cell system.

16. The CHO cell system used to assess the β_3-selectivity of the compounds disclosed in examples 1-113 was essentially the same as the CHO cell system we used to access the β_1- and β_2-selectivity of those same compounds, except the CHO cells permanently expressed the human β_3-receptors only.

17. We did use the SK-N-MC cell system to evaluate other potential anti-diabetic compounds that were synthesized before the compounds of Examples 1-113 of the '532 patent, and we did consider the SK-N-MC cell system competent as a basis for assessing the β_3-selectivity of those compounds. We made a switch to the CHO cell system because the gene for the single human β_3-receptor became available and could be used to construct a CHO assay, whereas the cells in the SK-N-MC cell system also contained a β_1-receptor and required the use of a β_1-receptor blocker to mask any β_1 effects. ('532 patent, col. 11, line 67 to col. 12, line 2.)

18. Before switching exclusively to the CHO β_3-test we compared the CHO β_3-cell test to the SK-N-MC cell test and concluded that the test results we obtained had significant correlation with each other for assessing β_3-stimulating action. (*See* Monthly Progress Report, page 2.)

19. We obtained the gene for the β_3-receptor from a foreign patent office based upon a foreign patent filing, and did not refer to the β_3-CHO cell system assay in the patent application that became the '532 patent because we were concerned that using that gene in an experimental assay might be asserted to be an act of patent infringement in Japan.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: 2013/11/21 By: Tetsuo Matsui

Tetsuo Matsui

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Bib Data Sheet

CONFIRMATION NO. 3506

SERIAL NUMBER	FILING OR 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
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AIA (First Inventor to File): YES

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APPLICANTS

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

This application is a SER of 09/529,096 04/07/2000 PAT 6346532
which is a 371 of PCT/JP98/04671 10/15/1998

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

Foreign Priority claimed	STATE OR COUNTRY	SHEETS DRAWING	TOTAL CLAIMS	INDEPENDENT CLAIMS
☐ yes ☐ no				
35 USC 119 (a-d) conditions met ☐ yes ☐ no ☐ Met after Allowance				
Verified and Acknowledged Examiner's Signature Initials				

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TITLE

AMIDE DERIVATIVES OR SALTS THEREOF

FILING FEE RECEIVED	FEES: Authority has been given in Paper No. _____ to charge/credit DEPOSIT ACCOUNT	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time)

0.00	No. _____ for following:	☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

Patent Assignment Abstract of Title

Total Assignments: 2

Application #: 09529096 **Filing Dt:** 04/07/2000 **Patent #:** 6346532 **Issue Dt:** 02/12/2002

PCT #: NONE **Publication #:** NONE **Pub Dt:**

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Title: AMIDE DERIVATIVES OR SALTS THEREOF

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OC000000066246552

Patent Number: 6346532 Control Number: 96/000,045 Date Mailed: 01/24/2014

NOTICE OF SUPPLEMENTAL EXAMINATION REQUEST FILING DATE

The patent owner is hereby notified that the filing date of the request for supplemental examination is 11/21/2013, the date that a request meeting all of the applicable requirements of 37 CFR §§ 1.605, 1.610, and 1.615 was received by the Office.

A supplemental examination certificate will issue within three months from the filing date of the request for supplemental examination. See 37 CFR 1.625.

This notice is being sent to the official correspondence address of record which, in a supplemental examination proceeding, is the official correspondence address of record in the patent file. See 37 CFR 1.33.

/RBELL/

Central Reexamination Unit
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
96/000,045	11/21/2013	6346532	07385.0042	3506

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EXAMINER
HUANG, EVELYN MEI

ART UNIT	PAPER NUMBER
3991	

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

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

REASONS FOR SUBSTANTIAL NEW QUESTION OF PATENTABILITY DETERMINATION

A supplemental examination request under 35 U.S.C. § 257 for claims 1-14 of US 6,346,532 was filed on 11/21/2013 and assigned Control No. 96/000,045.

US 6,346,532 is issued from US Application No. 09/529,096, which is a 371 of PCT/JP98/04671 filed on 10/15/1998, claiming the foreign priority date of 10/17/1997.

Item(s) of Information

The request includes only 12 items of information:

1. U.S. Patent No. 6,346,532 ("the '532 patent").

2. Table of testing data for compounds including those disclosed in Examples 1-113 of U.S. Patent No. 6,346,532 ("Testing Data Table").

3. Materials for Astellas R&D Meeting. Subcommittee on Development Theme Establishment, titled "YM178/Discontinuation of Development Theme for Diabetes Mellitus," dated October 27, 2003 ("R&D Meeting Materials").

4. YM178 in Type 2 Diabetes Mellitus 178-CL003 Study Report, dated September 11, 2003 ("Study Report").

5. Yamanouchi BAN Compound Evaluation System ("R&D Flowchart") with English-language translation.

6. Yamanouchi Monthly Research Progress Report, dated April 26, 1995 ("Monthly Progress Report") with English-language translation.

7. Excerpts of the prosecution history of U.S. Patent Application No. 09/529,096, the U.S. National Stage of PCT/JP98/04671, filed October 15, 1998, that resulted in U.S. Patent No. 6,346,532 ("the Prosecution File History").

8. Japanese Patent Application Kokai Publication No. H10-218861, "Novel Phenethanol Derivative or Salt Thereof," published August 18, 1998, and certified English-language translation thereof ("JP '861").

9. Blin, N. et al., "Structural and Conformational Features Determining Selective Signal Transduction in the β3-Adrenergic Receptor," Molecular Pharmacology, 44:1094-1104 (1993) ("Blin").

10. PCT Publication WO 94/18161, published 18 August 1994 ("WO '161").

11. Thornber, C.W., "Isosterism and Molecular Modification in Drug Design," Chem. Soc. Rev. 18:563-580 (1979) ("Thornber").

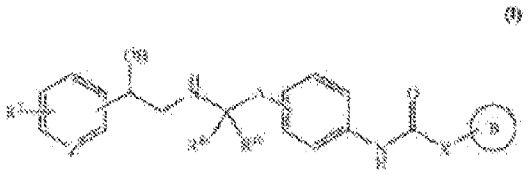
12. Declaration by Dr. Tetsuo Matsui under 37 C.F°R. § 1.132 ("Matsui Dec.").

Claims of US 6,346,532

There are 14 claims in the issued patent.

Claims 1-6 and 9 are drawn to a compound. Claims 7, 8 and 10-12 are drawn to a composition. Claims 13-14 are drawn to a method for treating diabetes mellitus and obesity respectively. Claim 1 is the only independent claim.

1. A compound of formula (I):



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

Ring B is a heteroaryl group, which may be 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 may be 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 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} and R^{lb} are the same or different and each may be a hydrogen atom or a lower alkyl group;

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

Z is a group represented by =CH- .

Items of Information NOT Raising a Substantial New Question of Patentability

1. **The Testing Data Table (Item 2), the Matsui Dec. (Item 12), R & D Meeting Materials (Item 3) and the Study Report (Item 4) as presented in the request (pages 7-9) do not raise a substantial new question of patentability affecting claims 1-14.**

Patent Owner (pages 7-9) submits that a substantial new question of patentability as to claims 1-14 is raised by the Testing Data Table (Item 2) the Matsui Dec. (Item 12), R & D Meeting Materials (Item 3) and the Study Report (Item 4), which show that no claimed compounds proved sufficiently efficacious to be considered commercially competitive for the treatment of diabetes mellitus, the principal utility disclosed in the specification.

The Testing Data Table shows the results of a series of *in vitro* and *in vivo* studies before October 15, 1998, the date on which the PCT application leading to the issuance of the '532 patent was filed. The results therein for mirabegron (Compound No. 5, BAN 371; Example 41) showed promise as an anti-diabetic medicine and was approved by the FDA for Phase I clinical trials to determine appropriate dosages for Phase II clinical trials to assess efficacy for treating diabetes mellitus (Matsui Dec. ¶ 7). The limited Phase IIa clinical trials were performed after the '532 patent issue date of 2/12/2002. As the results of the clinical trials, which was not available until mid-2003, show that mirabegron did not demonstrate sufficient efficacy to be a commercially competitive drug for the treatment of diabetes mellitus, the then current assignee, Yamanouchi Pharmaceutical Co., Ltd. ("Yamanouchi") decided not to pursue diabetes mellitus as an indicated use (Matsui Dec.¶8; R&D Meeting Materials, page 13). A detailed analysis of the results of the Phase IIa clinical study, however, revealed that mirabegron did have some efficacy in certain patient subgroups (Matsui Dec. ¶ 9; Study Report, page 11).

Since claims 1-6 and 9 are drawn to a compound of formula (I) or (Ia), claims 7-8 and 10-12 are directed to a composition thereof, and claim 14 is drawn to a method of treating

obesity, a reasonable examiner would not consider the above information of Items 2-4 and 12, particularly the 2003 results of the clinical trials for treating diabetes mellitus, important in deciding the patentability of the claims 1-12 and 14.

Claim 13 is drawn to a method of treating diabetes mellitus.

The information provided by Items 2-4 and 12 may have shown that mirabegron (the compound of Example 41) is not "sufficiently efficacious to be considered commercially competitive for the treatment of diabetes mellitus", but the claim or the specification does not recite the efficacy of the method or that the compound has to be "commercially competitive" for the treatment of diabetes mellitus. That Yamanouchi stopped pursuing diabetes mellitus as an indicated use for mirabegron because it is not "commercially competitive" for such treatment is not indicative or suggestive of no utility, as submitted by the Patent Owner. In fact, mirabegron was shown to have some efficacy in certain patient subgroups upon a more detailed analysis of the results of the Phase IIa clinical study (Matsui Dec. ¶ 9; Study Report at page 11). As such, a reasonable examiner would not consider the information provided by Items 2-4 and 12 important in deciding whether claim 13 is patentable.

Accordingly, Items 2-4 and 12 do not raise a substantial new question of patentability as to claims 1-14.

2. **The Testing Data Table (Item 2), Matsui Dec. (Item 12), R & D Meeting Materials (Item 3), R & D Flow Chart (Item 5), Monthly Progress Report (Item 6) and Prosecution File History (Item 7) as presented in the request (pages 10-20) do not raise a substantial new question of patentability affecting claims 1-14.**

a. Patent Owner (page 12) submits that a substantial new question of patentability as to claims 1-14 is raised by the Testing Data Table (Item 2) showing that not all of the claimed compounds of Examples 1-106 and 108-113 have selective β_3 receptor activity as taught by the '532 Patent, as discussed in the Matsui Dec. at ¶ 10 (Item 12).

The Testing Data Table shows that a number of the claimed compounds, such as compound BAN 404 (the compound of instant Example 1), exhibit lower β_3 receptor activity than β_2 and β_1 receptor activity (page 11; Matsui Dec. ¶ 10).

However, claims 1-6 and 9 are drawn to a compound of formula (I) or (Ia); claims 7-8 and 10-12 are directed to a composition thereof; claims 13-14 are drawn to a method of treating diabetes mellitus and a method of treating obesity respectively. These claims do not require that the compounds have greater β_3 receptor activity than β_2 and β_1 receptor activity. Even so, the Testing Data Table shows that most of the claimed compounds exhibit selective β_3 receptor activity, consistent with the disclosure of the specification. As such, a reasonable examiner would not consider the information provided by Items 2 and 12 important in deciding whether claims 1-14 are patentable.

> *b. Patent Owner (pages 13-15) submits that a substantial new question of patentability as to claims 1-14 is raised by the Testing Data Table (Item 2) showing that not all of the claimed compounds of Examples 1-106 and 108-113 met Yamanouchi's internal criteria for further development described in the R & D Flowchart (Item 5), as discussed in Matsui Dec. at ¶¶ 11-13 (Item 12).*

The R&D Flowchart shows that for further evaluation, a candidate compound should have an IA test result for β_3-receptor agonism of greater than 0.6 (or 60%) and a pD_2 value for the β_3-receptor of greater than 6.5, while at the same time having IA test results for β_1 and β_2 receptor agonism of less than 0.2 (or 20%). The Testing Data Table shows that 17 of the claimed compounds do not meet Yamanouchi's β_3 receptor selectivity and activity criteria (Matsui Dec. ¶¶11-13).

However, Yamanouchi's internal criteria for further development is not suggested or described in the specification or the claims. Importantly, claims 1-6 and 9 are drawn to a compound of formula (I) or (Ia); claims 7-8 and 10-12 are directed to a composition thereof; claims 13-14 are drawn to a method of treating diabetes mellitus and a method of treating obesity respectively. These claims do not require specific β_3 receptor selectivity or activity in accordance to Yamanouchi's internal criteria. Even so, the Testing Data Table shows that many of the

claimed compounds exhibit selective β_3 receptor activity and meet Yamanouchi's internal criteria for further development. As such, a reasonable examiner would not consider the information provided by Items 2, 5 and 12 important in deciding whether claims 1-14 are patentable.

> *c. Patent Owner (pages 15-17) submits that a substantial new question of patentability as to claims 1-14 is raised by the incorrect identification of the assay for determining the β_3 selectivity, as shown by the Testing Data Table (Item 2), R & D Meeting Materials (Item 3), the Monthly Progress Report (Item 6), and Matsui Dec. at ¶¶ 15-18 (Item 12).*

Patent Owner submits that the specification incorrectly describes the use of the SK-N-MC cell system (col. 11, line 56 to col. 12, line 11) instead of the CHO cell system for evaluating the β_3 activity of the inventive compounds. The Testing Data Table shows that the SK-N-MC cell system was used only after the October 15, 1998 filing date of the international application that led to the '532 patent (Matsui Dec. ¶15). At the time of the invention, the CHO cell system was used to assess the β_3 activity (R & D Meeting Materials, page 3; Matsui Dec. ¶¶15-17). The SK-N-MC cell system was actually used to evaluate other potential anti-diabetic compounds synthesized before the inventive compounds. A switch was made to the CHO cell system because the gene for the single human β_3 receptor became available and could be used to construct a CHO assay (Matsui Dec. ¶17). Both the SK-N-MC cell system and the CHO cell system provide test results that have "significant correlation" with each other for assessing β_3 receptor activity (Matsui Dec. ¶18; Monthly Progress Report, page 2).

However, claims 1-6 and 9 are drawn to a compound of formula (I) or (Ia); claims 7-8 and 10-12 are directed to a composition thereof; claims 13-14 are drawn to a method of treating diabetes mellitus and a method of treating obesity respectively. These claims do not recite β_3 receptor activity, or the particular cell system to be used for its assessment. As such, a reasonable examiner would not consider the information provided by Items 2, 3, 6 and 12 important in deciding whether claims 1-14 are patentable. This is especially so as the results with the use of the incorrectly identified SK-N-MC cell system correlates well with the results of the CHO cell system (Matsui Dec. ¶18; Monthly Progress Report, page 2).

d. Patent Owner (pages 17-20) submits that a substantial new question of patentability as to claims 1-14 is raised by the Testing Data Table (Item 2) showing that not all of the claimed compounds of Examples 1-106 and 108-113 have ED_{30} values ten times greater than the compounds of WO 95/29159, as described in the specification and argued by the Patent Owner during prosecution (The Prosecution File History, Item 7).

The specification (col. 11, lines 21-31) states that some of the inventive compounds exhibited a strong activity so that the ED_{30} value in the oral administration was 3 mg/kg/day or less, whereas the compound of Example 90 and Example 92 of WO 95/29159 had an ED_{30} value of 30 mg/kg/day. During prosecution, Patent Owner also argued that the inventive compounds have ED_{30} values ten times better than the prior art compounds (The Prosecution File History, 5/4/2001 amendment, page 12). The Testing Data Table shows that 21 claimed compounds of Examples 1-106 and 108-113 have ED_{30} values of >10 mg/kg/day, others have ED_{30} values between 3 to 10 mg/kg/day. Compounds No. 1 (BAN-358; Example 86) and Compound No. 3 (BAN-369A; Example 99) have ED_{30} values of 3 mg/kg/day or less.

However, claims 1-6 and 9 are drawn to a compound of formula (I) or (Ia); claims 7-8 and 10-12 are directed to a composition thereof; claims 13-14 are drawn to a method of treating diabetes mellitus and a method of treating obesity respectively. These claims do not recite ED_{30} value of 3 mg/kg/day or less. Even so, the Testing Data Table shows that "some" of the claimed compounds exhibit ED_{30} values of 3 mg/kg/day or less as stated in the specification. As such, a reasonable examiner would not consider the information provided by Items 2, and 7 important in deciding whether claims 1-14 are patentable.

Accordingly, Items 2-3, 5-7 and 12 do not raise a substantial new question of patentability as to claims 1-14.

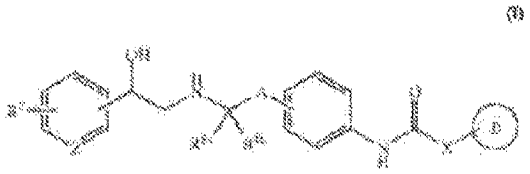
In summary, the above issues 1-2 set forth in the Request do not raise a substantial new question of patentability as to claims 1-14. These issues will not be considered in the reexamination proceeding based on this Supplemental Examination. The patentee is advised that

it may be desirable to consider filing a reissue application provided that the patentee believes one or more claims to be partially or wholly inoperative or invalid based upon these issues.

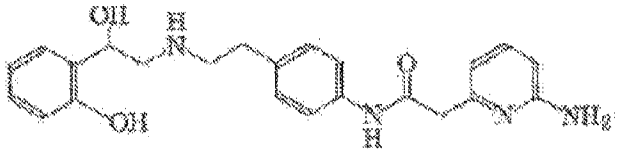
Items of Information Raising a Substantial New Question of Patentability

3. **JP '861 (Item No. 8) as presented in the request (pages 20-21) raises a substantial new question of patentability affecting claims 1-5, 7-11, 13 and 14.**

JP '861 (page 2) generically discloses a compound of the following formula (I):



Specific compounds are described in Tables 7-9. Compound 11 in Table 9 has the following formula:



The compound of formula (I) is useful as a therapeutic agent for diabetes. It possesses selective stimulatory effects on β_3 adrenergic receptor and thus has anti-obesity effects and anti-hyperlipidemia effects (page 14, [0019]).

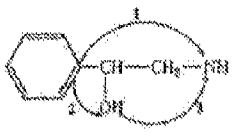
As such, a reasonable examiner would consider these teachings of JP '861 important in deciding whether claims 1-5, 7-11, 13 and 14 are patentable.

4. **JP '861 in combination with Blin (Items No. 8-9) as presented in the request (pages 21-23) raises a substantial new question of patentability affecting claims 1-5, 7-11, 13 and 14.**

JP '861 is as discussed above.

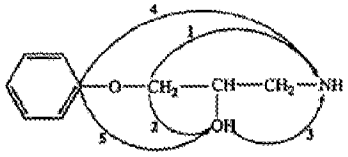
Blin studies the structural and conformational features determining selective signal transduction in the β_3 adrenergic receptor. Analysis of the structural-activity relationships of a large variety of compounds would determine the structural features responsible for the β_3 adrenergic receptor potency and selectivity of ligands (page 1097). Potent β_3 adrenergic receptor agonists may have one of the following minimal pharmacophores (page 1102, Fig. 7):

A



d1 (Å) = 3.83 ± 0.08
d2 (Å) = 2.47 ± 0.03
d3 (Å) = 3.07 ± 0.08

B

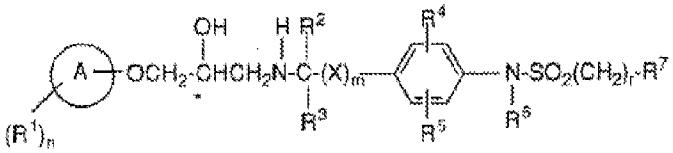


d1 (Å) = 3.64 ± 0.11
d2 (Å) = 2.40 ± 0.02
d3 (Å) = 2.95 ± 0.03
d4 (Å) = 5.35 ± 0.18
d5 (Å) = 4.31 ± 0.12

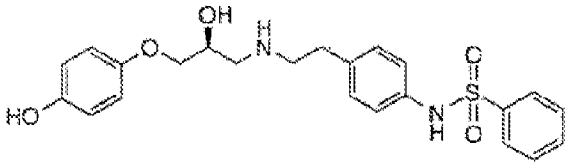
As such, a reasonable examiner would consider the teachings of JP '861 and Blin important in deciding whether claims 1-5, 7-11, 13 and 14 are patentable.

5. **WO '161 in combination with Blin, Thornber and JP '861(Items No. 8-11) as presented in the request (pages 23-26) raises a substantial new question of patentability affecting claims 1-5, 7-11, 13 and 14.**

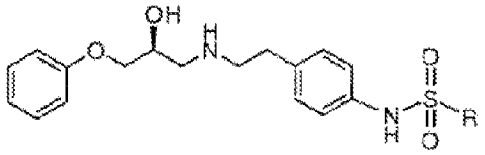
WO'161 (pages 3-4) generically discloses a compound of formula I



Specific compounds are described. The compound of Example 8 (page 32) has the following structure:



The compound of Example 135 (page 63, Table 3) has the following structure:



wherein R is phenyl.

The compounds of formula I are selective β_3 agonists useful for treatment of diabetes and obesity (page 1, Title; page 2, lines 23-26).

Thornber teaches that bioisosteres are groups or molecules which have chemical and physical similarities that impart similar biological properties to a chemical compound. They are often used in the pharmaceutical arts to modify a lead compound and obtain compounds with similar properties (pages 563 and 565). As shown in Table 3 (page 569), a carbonyl group (-CO-) may be replaced with the bioisosteric sulfoxide group (-SO_2-).

JP '861 and Blin are as discussed above.

As such, a reasonable examiner would consider the combined teachings of WO '161, Thornber, Blin and JP '861 important in deciding whether claims 1-5, 7-11, 13 and 14 are patentable.

In summary, the above issues 3-5 set forth in the Request raise a substantial new question of patentability as to claims 1-5, 7-11, 13 and 14. Accordingly, *ex parte* reexamination will be ordered pursuant to 35 U.S.C. 257.

/Evelyn Huang/
Patent Reexamination Specialist
CRU Art Unit 3991

Conferees:

/Padmashri Ponnaluri/
Patent Reexamination Specialist
CRU Art Unit 3991

/Deborah D Jones/
Supervisory Patent Examiner, Art Unit 3991

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
96/000,045	11/21/2013	6346532	07385.0042	3506

7590 01/31/2014

Fitzpatrick Cella Harper & Scinto
1290 Avenue of the Americas
New York, NY 10104-3800

EXAMINER	
HUANG, EVELYN MEI	
ART UNIT	PAPER NUMBER
3991	

MAIL DATE	DELIVERY MODE
01/31/2014	PAPER

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

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

(12) SUPPLEMENTAL EXAMINATION CERTIFICATE

United States Patent (10) **Number: US 6,346,532 F1**

Maruyama et al. (45) **Certificate Issued: Jan. 31, 2014**

Control No.: 96/000,045 **Filing Date: Nov. 21, 2013**

Primary Examiner: Evelyn Huang

A substantial new question of patentability affecting at least one claim of the patent is raised in the request for supplemental examination. See the Reasons for Substantial New Question of Patentability Determination in the file of this proceeding. Accordingly, ex parte reexamination will be ordered pursuant to 35 U.S.C. 257.

(56) **Items of Information**

U.S. PATENT DOCUMENTS

6,346,532	2/2002	Maruyama et al.

FOREIGN PATENT DOCUMENTS

JP	10-218861 A	8/1998
WO	94/18161 A1	8/1994

OTHER DOCUMENTS

Table of testing data for compounds including those described in Examples 1-113 of US 6,346,532, 40 pages.

Materials for Astellas R&D Meeting. Subcommittee on Development Theme Establishment, titled "YM178/Discontinuation of Development Theme for Diabetes Mellitus," 16 pages, dated October 27, 2003.

YM178 in Type 2 Diabetes Mellitus 178-CL-003 Study Report, 11 pages, dated September 11, 2003.

Yamanouchi BAN Compound Evaluation System with English translation, 1 page.

Yamanouchi Monthly Research Progress Report with English translation, 2 pages, dated April 26, 1995.

Excerpts of the prosecution history of U.S. Patent Application No. 09/529,096, the U.S. National Stage of PCT/JP98/04671, filed October 15, 1998, that resulted in U.S. Patent No. 6,346,532.

Blin et al., "Structural and Conformational Features Determining Selective Signal Transduction in the beta-3-Adrenergic Receptor," Molecular Pharmacology, 44:1094-1104 (1993).

Thornber, C. W., "Isosterism and Molecular Modification in Drug Design," Chem. Soc. Rev. 18:563-580 (1979).

Declaration by Dr. Tetsuo Matsui under 37 C.F.R 1.132, dated November 21, 2013.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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7590 03/06/2014

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EXAMINER
HUANG, EVELYN MEI

ART UNIT	PAPER NUMBER
3991	

MAIL DATE	DELIVERY MODE
03/06/2014	PAPER

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

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

Office Action in Ex Parte Reexamination	Control No. 96/000,045	Patent Under Reexamination 6346532	
	Examiner EVELYN HUANG	Art Unit 3991	AIA (First Inventor to File) Status No

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

a. ☐ Responsive to the communication(s) filed on _____ .
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

b. ☐ This action is made FINAL.

c. ☐ A statement under 37 CFR 1.530 has not been received from the patent owner.

A shortened statutory period for response to this action is set to expire *2* month(s) from the mailing date of this letter. Failure to respond within the period for response will result in termination of the proceeding and issuance of an *ex parte* reexamination certificate in accordance with this action. 37 CFR 1.550(d). **EXTENSIONS OF TIME ARE GOVERNED BY 37 CFR 1.550(c).** If the period for response specified above is less than thirty (30) days, a response within the statutory minimum of thirty (30) days will be considered timely.

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Information Disclosure Statement, PTO/SB/08.
3. ☐ Interview Summary, PTO-474.
4. ☐ _____.

Part II SUMMARY OF ACTION

1a. ☒ Claims *1-5,7-11,13 and 14* are subject to reexamination.
1b. ☒ Claims *6 and 12* are not subject to reexamination.
2. ☐ Claims _____ have been canceled in the present reexamination proceeding.
3. ☐ Claims _____ are patentable and/or confirmed.
4. ☒ Claims *1-5,7-11,13 and 14* are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ The drawings, filed on _____ are acceptable.
7. ☐ The proposed drawing correction, filed on _____ has been (7a) ☐ approved (7b) ☐ disapproved.
8. ☐ Acknowledgment is made of the priority claim under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the certified copies have
   1 ☐ been received.
   2 ☐ not been received.
   3 ☐ been filed in Application No. _____ .
   4 ☐ been filed in reexamination Control No. _____.
   5 ☐ been received by the International Bureau in PCT application No. _____.
   * See the attached detailed Office action for a list of the certified copies not received.
9. ☐ Since the proceeding appears to be in condition for issuance of an *ex parte* reexamination certificate 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.
10. ☐ Other: _____

cc: Requester (if third party requester)

The present application is being examined under the pre-AIA first to invent provisions.

Reexamination

1. This is a Non-Final Office Action in the ex parte reexamination proceeding of claims 1-5, 7-11, 13 and 14 of US 6,346,532 issued to Maruyama on 2/12/2002.

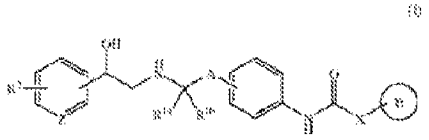
Claims of US 6,346,532

2. There are 14 claims in the issued patent. Claims 6 and 12 are not under reexamination as no substantial new question of patentability has been raised as to these claims.

Claims 1-5, 7-11 and 13-14 are under reexamination.

Claims 1-5 and 9 are drawn to a compound. Claims 7, 8 and 10-11 are drawn to a composition. Claims 13-14 are drawn to a method for treating diabetes mellitus and obesity respectively. Claims 1 and 5 are independent claims.

1. A compound of formula (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 may be 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 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-;

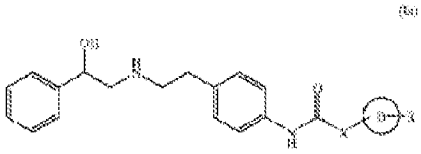
R^{1a} and R^{1b} are the same or different and each may be a hydrogen atom or a lower alkyl group;

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

Z is a group represented by =CH- ;

or a salt thereof

5. A compound of formula (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.

Priority

3. US 6,346,532 is issued from US Application No. 09/529,096, filed on 4/7/2000, which is a 371 of PCT/JP98/04671, filed on 10/15/1998, published as WO 99/20607 on 4/29/1999. It claimed the foreign priority of JP 9-285778, filed on 10/17/1997.

JP 9-285778 fails to provide adequate support for claims 1-5, 7-11 and 13-14. Particularly, in formula (I) of JP 9-285778, ring B is "a nitrogen-containing heteroaryl group", A is methylene, ethylene or $-CH_2O-$, and A is at a fixed position para to -NHCO-X-ring B. The instant claims 1 and 5, however, recite "a heteroaryl group" as ring B. Claim 1 further recites lower alkylene or -lower alkylene-O- as A, which position may vary with respect to -NHCO-X-ring B. Formula (I) of claim 1 and Formula (Ia) of claim 5 were described in PCT/JP98/04671

filed on 10/15/1998. Accordingly, the effective filing date for claims 1-5, 7-11 and 13-14 is 10/15/1998 rather than the 10/17/1997 filing date of JP 9-285778.

Cited References

4. Japanese Patent Application Kokai Publication No. H10-218861, "Novel Phenethanol Derivative or Salt Thereof," published August 18, 1998, and certified English-language translation thereof (**"JP '861"**).

Blin, N. et al., "Structural and Conformational Features Determining Selective Signal Transduction in the β3-Adrenergic Receptor," Molecular Pharmacology, 44:1094-1104 (1993) (**"Blin"**).

PCT Publication WO 94/18161, published 18 August 1994 (**"WO '161"**).

Thornber, C.W., "Isosterism and Molecular Modification in Drug Design," Chem. Soc. Rev. 18:563-580 (1979) (**"Thornber"**).

Claim Rejections - 35 USC § 103

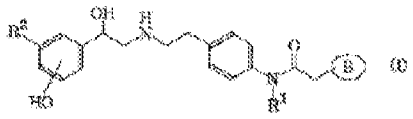
5. The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (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.

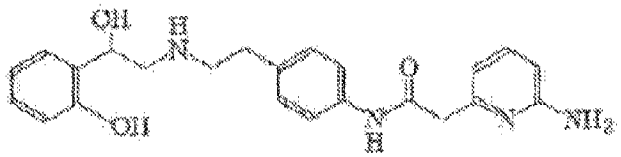
6. Claims 1-5, 7-11 and 13-14 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over JP '861 in view of Blin and WO '161.

JP '861, published on 8/18/1998, is available as prior art under 102(a).

JP '861 (page 2) discloses a compound of formula (I) that possesses selective stimulatory effects on β_3 adrenergic receptor and thus have anti-obesity effects and anti-hyperlipidemia effects. They are useful as therapeutic agents for treatment of diabetes (page 14, [0019]). The compound of formula (I) has the following structure:



Specific compounds of formula (I) are described in Tables 7-9. Compound 11 in Table 9 has the following structure:

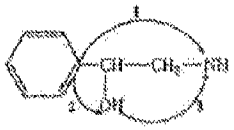


Compound 12 of Table 9 has the same structure as compound 11 except that its amino-pyridinyl (B ring) is replaced with amino-thiazolyl.

Compound 11 or compound 12 of JP '861 has a hydroxyl-substituted terminal phenyl, whereas the compound of claims 1-5 has an unsubstituted terminal phenyl.

However, Blin studies the structural-activity relationships of a large variety of compounds to determine the structural features responsible for the β_3 adrenergic receptor potency and selectivity of ligands (page 1097). Potent β_3 adrenergic receptor agonists have the following minimal pharmacophore (page 1102, Fig. 7) wherein the terminal phenyl is unsubstituted:

A



d1 (Å) = 3.83 ± 0.08
d2 (Å) = 2.47 ± 0.03
d3 (Å) = 3.97 ± 0.08

Blin thus teaches that the hydroxyl substitution on the terminal phenyl in the compound of JP '861 is not required for β_3 adrenergic receptor agonist activity. Indeed, WO '161 (page 3) discloses a structurally similar β_3 adrenergic receptor agonist compound, wherein the terminal phenyl may be unsubstituted (Table 3, Example 135) or substituted with hydroxyl (Example 8) or halogen (Example 142).

Accordingly, it would have been obvious to one of ordinary skill in the art to replace the hydroxyl-substituted phenyl of JP'861 with the unsubstituted phenyl to arrive at the compound of **claims 1-5**. In view of the teachings of JP'861, Blin and WO'161, there would have been a reasonable expectation of success in obtaining a compound with potent β_3 adrenergic receptor agonist activity.

> **Claims 7 and 11** recite a composition comprising a pharmaceutically acceptable carrier and a compound of formula (I) or the salt thereof as claimed in one of claims 1 through 4 (claim 7) and as claimed in claim 5 (claim 11).

JP '861 also discloses a pharmaceutical composition comprising the compound of formula I and a pharmaceutically acceptable carrier (page 16).

> **Claim 9** dependent from claim 1 further recites that the compound of formula I is an optical isomer, a hydrate, or a solvate of the compound of formula I. **Claim 10** recites that the compound of formula (I) of claim 1 in a composition is present as a polymorphic substance.

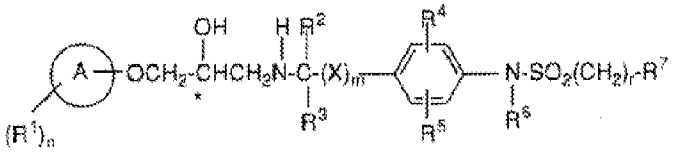
The compound of formula (I) described in JP '861 may be an optical isomer, a hydrate, a solvate of ethanol, or a polymorphic crystal (page 13).

Claims 13-14 are drawn to a method for treating diabetes mellitus and obesity respectively. Dependent **claim 8** further requires that the amount of the compound of formula I in the composition of claim 7 be effective for treating diabetes mellitus in a human or an animal.

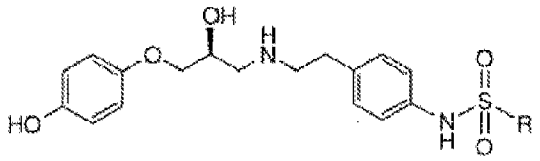
JP '861 further discloses that the compound of formula I is useful as a therapeutic agent for diabetes. It possesses selective stimulatory effects on β_3 adrenergic receptor and thus has anti-obesity effects and anti-hyperlipidemia effects (page 14, [0019]).

7. **Claims 1-5, 7-11 and 13-14 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over WO '161 in view of Blin, Thornber and JP '861.**

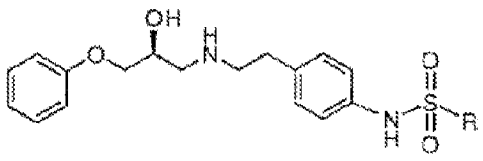
WO'161 (pages 3-4) generically discloses compounds of formula I that are selective β_3 agonists useful for treatment of diabetes and obesity (page 1, Title; page 2, lines 23-26).



Specific compounds with the following structure are described (page 55, Table 2):



wherein R is phenyl (page 32, Example 8), thiophenyl-2-yl (Example 108), pyridin-2-yl (Example 109) or pyridin-3-yl (Example 110). The compounds of Table 3 (page 63) have the following structure:

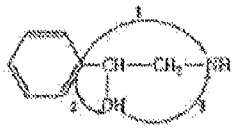


wherein R is phenyl (Example 135) or benzothiophen-2-yl (Example 140).

The compound of WO'161 has phenyl-OCH_2-CH(OH)-CH_2(NH)- instead of the instant phenyl-CH(OH)-CH_2(NH)-.

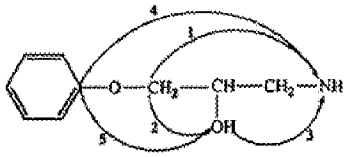
However, Blin studies the structural-activity relationships of a large variety of compounds to determine the structural features responsible for the β_3 adrenergic receptor potency and selectivity of ligands (page 1097). Potent β_3 adrenergic receptor agonists have one of the following minimal pharmacophores (page 1102, Fig. 7):

A



d1 (Å) = 3.83 ± 0.08
d2 (Å) = 2.47 ± 0.03
d3 (Å) = 3.07 ± 0.08

B



d1 (Å) = 3.64 ± 0.11
d2 (Å) = 2.40 ± 0.02
d3 (Å) = 2.95 ± 0.03
d4 (Å) = 5.35 ± 0.18
d5 (Å) = 4.31 ± 0.12

As such, phenyl-OCH_2-CH(OH)-CH_2(NH)- of WO '161 is an alternative to the instant phenyl-CH(OH)-CH_2(NH)-. Indeed, the β_3 adrenergic receptor agonist compound of JP '861 has the alternative phenyl-CH(OH)-CH_2(NH)- instead of the phenyl-OCH_2-CH(OH)-CH_2(NH)- of WO '161.

The compound of WO'161 has a -SO_2-heteroaryl instead of the instant -CO-heteroaryl.

However, Thornber teaches that sulfoxide group (-SO_2-) may be replaced by a carbonyl group (-CO-), which is a bioisostere of -SO_2- (page 569, Table 3). This is because bioisosteres are groups or molecules which have chemical and physical similarities that impart similar biological properties to a chemical compound. They are often used in the pharmaceutical arts to modify a lead compound and obtain compounds with similar properties (pages 563 and 565). . Indeed, the β_3 adrenergic receptor agonist compound of JP '861 has the bioisosteric -CO- instead of the -SO_2- of WO '161.

Accordingly, it would have been obvious to one of ordinary skill in the art to replace phenyl-OCH_2-CH(OH)-CH_2(NH)- of WO '161 with phenyl-CH(OH)-CH_2(NH)- and replace the -SO_2- with the bioisosteric -CO- to arrive at the compound of **claims 1-5**. There would have been a reasonable expectation of success in obtaining a potent β_3 adrenergic receptor agonist compound, especially in view of the combined teachings of the prior art.

> **Claims 7 and 11** recite a composition comprising a pharmaceutically acceptable carrier and a compound of formula (I) or the salt thereof as claimed in one of claims 1 through 4 (claim 7) and as claimed in claim 5 (claim 11).

WO '161 describes a pharmaceutical composition comprising the compound of formula I and an inert carrier (page 25; page 99, claim 18). JP '861 also discloses a pharmaceutical composition comprising the compound of formula I and a pharmaceutically acceptable carrier (page 16).

> **Claim 9** dependent from claim 1 further recites that the compound of formula I is an optical isomer, a hydrate, or a solvate of the compound of formula I. **Claim 10** recites that the compound of formula (I) of claim 1 in a composition is present as a polymorphic substance.

The compound of formula I of WO '161 contains at least one asymmetric center leading to formation of optical isomers (page 7, lines 14-22). The compound of formula I described in JP '861 may be an optical isomer, a hydrate, a solvate of ethanol, or a polymorphic crystal (page 13).

Claims 13-14 are drawn to a method for treating diabetes mellitus and obesity respectively. Dependent **claim 8** further requires that the amount of the compound of formula I in the composition of claim 7 be effective for treating diabetes mellitus in a human or an animal.

WO'161 (pages 3-4) discloses compounds of formula I that are selective β_3 agonists useful for treatment of diabetes and obesity (page 1, Title; page 2, lines 23-26; page 98, claims 11-12, 18). JP '861 further discloses that the compound of formula I is useful as a therapeutic agent for diabetes. It possesses selective stimulatory effects on β_3 adrenergic receptor and thus has anti-obesity effects and anti-hyperlipidemia effects (page 14, [0019]).

Conclusion

8. Claims 1-5, 7-11 and 13-14 are under reexamination.
Claims 6 and 12 are not reexamined.
Claims 1-5, 7-11 and 13-14 are rejected.

Future Amendment

9. Patent owner is notified that any proposed amendment to the specification and/or claims in this reexamination proceeding must comply with 37 CFR 1.530(d)-(j), must be formally presented pursuant to 37 CFR 1.52(a) and (b), and must contain any fees required by 37CFR 1.20(c).

In order to ensure full consideration of any amendments, affidavits or declarations, or other documents as evidence of patentability, such documents must be submitted in response to this Office action. Submissions after the next Office action, which is intended to be a FINAL ACTION, will be governed by the requirements of 37 CFR 1.116, which will be strictly enforced.

Ongoing Duty to Disclose

10. The patent owner is reminded of the continuing responsibility under 37 CFR 1.565(a) to apprise the Office of any litigation activity, or other prior or concurrent proceeding, involving Patent No. 6,346,532 throughout the course of this reexamination proceeding.

Future Correspondence

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Evelyn Huang whose telephone number is 571-272-0686. The examiner can normally be reached on Tuesday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Jones can be reached on 571-272-1535. The fax phone number for the organization where this application or proceeding is assigned is 571-273-9900.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

All correspondence relating to this ex parte reexamination proceeding should be directed:

By EFS: Registered users may submit via the electronic filing system EFS-Web at
https://efs.uspto.gov/efile/myportal/efs-registered

By Mail to: Mail Stop ex parte Reexam
Central Reexamination Unit
United States Patent & Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

By FAX to:	571-273-9900 Central Reexamination Unit
By Hand to:	Customer Service Window Randolph Building 401 Dulany St. Alexandria, VA 22314

/Evelyn Huang/
Patent Reexamination Specialist
CRU Art Unit 3991

Conferees: /Gary Kunz/
Patent Reexamination Specialist
CRU Art Unit 3991

/Deborah D Jones/
Supervisory Patent Examiner, Art Unit 3991

Notice of References Cited	Application/Control No. 96/000,045	Applicant(s)/Patent Under Reexamination 6346532	
	Examiner EVELYN HUANG	Art Unit 3991	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
*	N	JP 10-218861	08-1998	JP		
*	O	WO 94/18161	08-1994	WO		
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
*	U	Blin, N. et al., "Structural and Conformational Features Determining Selective Signal Transduction in the β3-Adrenergic Receptor," Molecular Pharmacology, 44:1094-1104 (1993).
*	V	Thornber, C.W., "Isosterism and Molecular Modification in Drug Design," Chem. Soc. Rev. 18:563-580 (1979).
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

UNITED STATES PATENT AND TRADEMARK OFFICE

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United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
96/000,045	11/21/2013	6346532	07385.0042	3506

7590 03/06/2014

Fitzpatrick Cella Harper & Scinto
1290 Avenue of the Americas
New York, NY 10104-3800

EXAMINER	
HUANG, EVELYN MEI	
ART UNIT	PAPER NUMBER
3991	

MAIL DATE	DELIVERY MODE
03/06/2014	PAPER

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

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

Ex Parte Reexamination Ordered Pursuant to 35 U.S.C. 257	Control No.	Patent Under Reexamination
	96/000,045	6346532
	Examiner	Art Unit
	EVELYN HUANG	3991

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

The supplemental examination proceeding filed on *21 November 2013* , concluded with the issuance of the supplemental examination certificate on *1/31/2014*. The certificate indicated that one or more items of information submitted as part of the request for supplemental examination raises a substantial new question of patentability. See the Reasons for Substantial New Question of Patentability Determination in the file of this proceeding.

Accordingly, *ex parte* reexamination of claim(s) *1-5,7-11,13 and 14* of U.S. Patent No. *6,346,532* is ordered. See 35 U.S.C. 257(b) and 37 CFR 1.625(b). This *ex parte* reexamination proceeding is hereby initiated by the mailing of this order. *Ex parte* reexamination under 35 U.S.C. 257 will be conducted in accordance with 37 CFR 1.530 through 1.570, which govern *ex parte* reexamination, subject to the exceptions enumerated in 37 CFR 1.625(d), and, in addition, to the exception that a patent owner's statement, including any amendment, under 37 CFR 1.530(a)-(c) may not be filed. For this reason, no amendment in an *ex parte* reexamination proceeding ordered under 35 U.S.C. 257 may be filed until after the mailing of a first Office action on the merits.

This reexamination proceeding has been assigned to the art unit listed above. All future correspondence should be directed to the assigned art unit and should be identified by the control number listed above, which is identical to the control number assigned to the now-concluded supplemental examination proceeding.

/Evelyn Huang/	/Gary Kunz/	/Deborah Jones/
Patent Reexamination Specialist	Patent Reexamination Specialist	SPRS, Art Unit 3991 CRU
Art Unit 3991	Art Unit 3991	

Applicant Initiated Interview Request Form

Application No.: 96/000,045 Examiner: Evelyn Huang
First Named Applicant: Tatsuya MARUYAMA Group Art Unit: 3991
Status of Application: First Action

Tentative Participants:

(1) Charles E. Van Horn (2) Jason Okun

(3) [Text] (4) [Text]

Proposed Date of Interview: 16 April 2014 **Proposed Time:** 2:00 p.m.

Type of Interview Requested:

- ☐ Telephonic
- ☒ Personal
- ☐ Video Conference

Exhibit to be Shown or Demonstrated?

- ☐ Yes
- ☐ No

If yes, provide brief description: [Text]

Issues to be Discussed

Issues (Rej., Obj. etc.)	Claims/Fig. #s	Prior Art	Discussed	Agreed	Not Agreed
1. § 103	[Text]	[Text]	☐	☐	☐
2. [Text]	[Text]	[Text]	☐	☐	☐
3. [Text]	[Text]	[Text]	☐	☐	☐
4. [Text]	[Text]	[Text]	☐	☐	☐

☐ Continuation Sheet Attached

Brief Description of Arguments to be Presented:
§ 103 Rejections: claims to be amended so they are supported in priority application - removing JP '861 as prior art on which, at least in part, all outstanding rejections are based.

An interview was conducted on the above-identified application on: _____

Note: This form should be completed by Applicant and submitted to the Examiner in advance of the interview (see MPEP § 713.01). This application will not be delayed from issue because of applicant's failure to file a statement of the substance of this interview (37 CFR § 1.133(b)) as soon as possible.

C E Van Horn

Charles E. Van Horn, Reg. No. 40,266 (202) 408-4000	Examiner/SPE Signature

Electronic Acknowledgement Receipt	
EFS ID:	18752556
Application Number:	96000045
International Application Number:	
Confirmation Number:	3506
Title of Invention:	AMIDE DERIVATIVES OR SALTS THEREOF
First Named Inventor/Applicant Name:	6346532
Correspondence Address:	Fitzpatrick Cella Harper & Scinto - 1290 Avenue of the Americas - New York NY 10104-3800 US - -
Filer:	Charles E. Van Horn/Charlene Woods
Filer Authorized By:	Charles E. Van Horn
Attorney Docket Number:	07385.0042
Receipt Date:	14-APR-2014
Filing Date:	21-NOV-2013
Time Stamp:	13:54:43
Application Type:	Supplemental Examination
Patent Number:	

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	Letter Requesting Interview with Examiner	Applicant_Initiated_Interview_Request_Form.pdf	83667 9db4f0b685c9accd4a4236acd4a28d4535a0781f	no	2

Warnings:	
Information:	
Total Files Size (in bytes):	83667

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

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

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

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

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
96/000,045	11/21/2013	6346532	07385.0042	3506

7590 04/22/2014

Fitzpatrick Cella Harper & Scinto
1290 Avenue of the Americas
New York, NY 10104-3800

EXAMINER	
HUANG, EVELYN MEI	
ART UNIT	PAPER NUMBER
3991	

MAIL DATE	DELIVERY MODE
04/22/2014	PAPER

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

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

Ex Parte Reexamination Interview Summary	Control No.	Patent Under Reexamination
	96/000,045	6346532
	Examiner	Art Unit
	EVELYN HUANG	3991

All participants (USPTO personnel, patent owner, patent owner's representative):

(1) *Evelyn Huang, Gary Kunz*	(3) *Charles Van Horn*
(2) *Padmashri Ponnaluri*	(4) *Jason Okun*

Date of Interview: *16 April 2014*

Type: a)☐ Telephonic b)☐ Video Conference
c)☒ Personal (copy given to: 1)☐ patent owner 2)☐ patent owner's representative)

Exhibit shown or demonstration conducted: d)☐ Yes e)☒ No.
If Yes, brief description: _____

Agreement with respect to the claims f)☐ was reached. g)☐ was not reached. h)☒ N/A.
Any other agreement(s) are set forth below under "Description of the general nature of what was agreed to…"

Claim(s) discussed: *all pending claims*.

Identification of prior art discussed: *JP '861*.

Description of the general nature of what was agreed to if an agreement was reached, or any other comments:
The discussion concerned amending the claims so that they have full support of the priority document filed on 10/17/1997, thereby removing JP '861 (published on 8/18/1998) as prior art.

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims patentable, if available, must be attached. Also, where no copy of the amendments that would render the claims patentable is available, a summary thereof must be attached.)

A FORMAL WRITTEN RESPONSE TO THE LAST OFFICE ACTION MUST INCLUDE PATENT OWNER'S STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. (See MPEP § 2281). IF A RESPONSE TO THE LAST OFFICE ACTION HAS ALREADY BEEN FILED, THEN PATENT OWNER IS GIVEN **ONE MONTH** FROM THIS INTERVIEW DATE TO PROVIDE THE MANDATORY STATEMENT OF THE SUBSTANCE OF THE INTERVIEW (37 CFR 1.560(b)). THE REQUIREMENT FOR PATENT OWNER'S STATEMENT CAN NOT BE WAIVED. **EXTENSIONS OF TIME ARE GOVERNED BY 37 CFR 1.550(c).**

/Evelyn Huang/ Patent Reexamination Specialist AU 3991	/Padmashri Ponnaluri/ Patent Reexamination Specialist AU 3991	/Gary Kunz/ Patent Reexamination Specialist AU 3991

cc: Requester (if third party requester)

Attorney Docket No. 07385.0042-00000

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Ex Parte Re-Examination of:	)	
	)	
U.S. Patent No.: 6,346,532	)	Group Art Unit: *3991*
	)	
Issued: February 12, 2002	)	Examiner: *Evelyn Huang*
	)	
Control No.: 96/000,045	)	Confirmation No.: *3506*
	)	
Filed: November 21, 2013	)	
	)	
Inventors: Tatsuya MARUYAMA et al.	)	
	)	
For: AMIDE DERIVATIVES OR SALTS THEREOF	)	

Mail Stop: Ex Parte Reexam
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT AND STATEMENT OF THE SUBSTANCE OF THE INTERVIEW

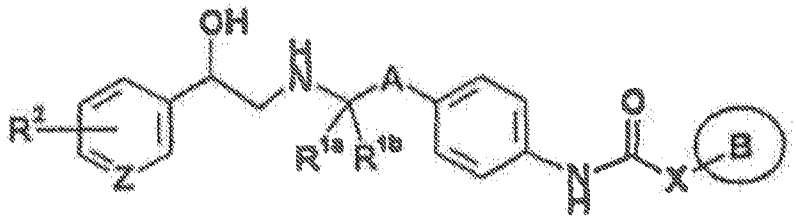
Sir:

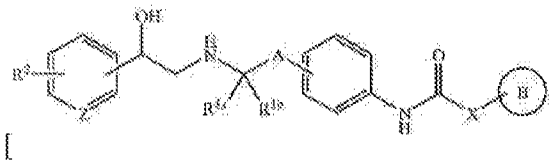
In response to the Office Action dated March 6, 2014, please amend the above-captioned patent as follows and consider the following remarks.

CLAIMS

Please amend the claims as follows.

1. (Amended) A compound of formula (I):





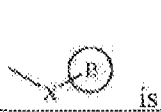
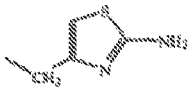
[ ](I)

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

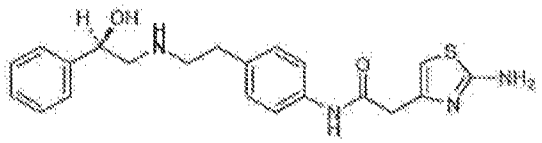
ring B is a nitrogen-containing heteroaryl group which is unsubstituted or substituted and is optionally fused with a benzene ring; X is [a bond, or] a lower alkylene or an alkenylene, both of which are unsubstituted or substituted with hydroxy or a lower alkyl group, or X is a carbonyl or a group represented 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 methylene, ethylene, [a lower alkylene] or a group represented by —CH_2O— [-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.

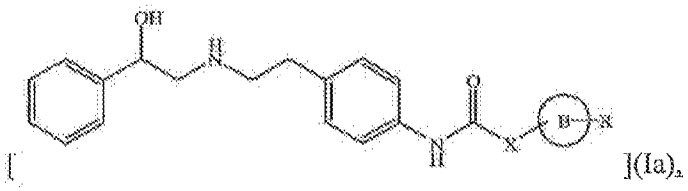
2. (Cancelled)

3. (Amended) The compound of formula (I) or the salt thereof according to claim 1 [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—, and di-lower alkyl-N— [, aryl-lower alkyl, halogeno aryl-lower alkyl, guanidino, lower alkyl-CO—NH, and lower alkyl-SO_2—NH—].

4. (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—] A is methylene, and  is 

5. (Amended) A compound of formula (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. (Cancelled)

8. (Cancelled)

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. (Amended) 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.

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.

15. (New) The compound according to claim 4 or the salt thereof, which is an optical isomer.

16. (New) The compound according to claim 4 or the salt thereof, which is a mixture of (R) and (S) optical isomers.

17. (New) The compound according to claim 16 or the salt thereof, which is a racemic mixture.

18. (New) A composition comprising at least one compound of formula (I) or the salt thereof as claimed in one of claims 1, 3, 4, and 15-17 in a pharmaceutically acceptable carrier.

19. (New) The composition as claimed in claim 18, 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.

STATEMENT OF THE SUBSTANCE OF THE INTERVIEW

Patent Owner and its attorneys, Charles E. Van Horn and Jason M. Okun, would like to thank Examiners Evelyn Huang, Gary Kunz, and Padmashri Ponnaluri for the courtesies extended during a personal interview conducted on April 16, 2014. During the interview, potential claim changes were discussed that would make all claims fully supported by priority Japanese Application No. 9-258778, thereby antedating JP 10-218861 (JP '861). It was agreed that if the claims were supported in the priority application, eliminating JP '861 as prior art, all prior art rejections of record would be withdrawn. The Examiners indicated that a new search would be conducted as required for any new or amended claims.

REMARKS

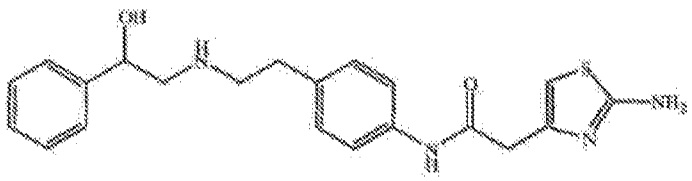
The claims are 1 and 3-6, and 9-19, with claims 1, 5, and 6 being in independent form.

Claim 1 has been amended to better reflect the subject matter disclosed in priority Japanese Application No. 9-258778 and to better define the intended invention. In particular, claim 1 has been amended to (i) specify that ring B is a nitrogen-containing heteroaryl group; (ii) specify that A is methylene, ethylene, or a group represented by —CH_2O—; (iii) specify the position of attachment of A on the phenylene ring with respect to —NHCO-X-ring B; and (iv) delete a bond from the list of options for X. Support for this amendment may be found, for example, in cancelled claim 2 and in the Examples, as well as in the priority application at paragraph [0007] and in the Examples.

Claim 2 has been cancelled without prejudice or disclaimer.

Claim 3 has been amended to reflect the cancellation of claim 2 and to shorten the list of substituents for ring B based on the list provided in the priority application at paragraph [0010].

Claim 4 has been amended to recite specifically the first structure shown at col. 39 (Table 3) of the specification:



The priority application supports this change, *inter alia*, in Example 41 and at paragraphs [0011] and [0026].

Claim 5 has been amended to recite specifically the structure of mirabegron, which is supported by Example 41 in both the instant specification and in the priority application, as well as by the recitation of the chemical name of this compound ((R)-2-(2-aminothiazol-4-yl)-4'-[2-(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide) in claim 6.

Claim 6 is not subject to reexamination.

Claims 7 and 8 have been cancelled without prejudice or disclaimer.

Claim 9 has not been changed. The priority application supports this claim, *inter alia*, at paragraphs [0011] and [0026].

Claim 10 has not been changed. The priority application supports this claim, *inter alia*, at paragraphs [0011], [0026], [0031][1] and [0032].

Claim 11 has been amended to reflect the changes made in claim 5. The priority application supports this claim, *inter alia*, at paragraphs [0031][2] and [0032].

Claim 12 is not subject to reexamination.

Claims 13 and 14 have not been changed. The priority application supports these claims, *inter alia*, at paragraph [0027].

Claims 15-19 have been added. Support for claims 15-17 may be found, *inter alia*, in claims 4 and 9 and in the paragraph at col. 4, ll. 8-15 of the specification, as well as in the priority application at paragraphs [0011] and [0026].

[1] Starting from the last paragraph on page 29 of the English language translation of the priority application filed March 7, 2001 during the original prosecution of U.S. Patent No. 6,346,532.
[2] Starting from the last paragraph on page 29 of the English language translation of the priority application filed March 7, 2001 during the original prosecution of U.S. Patent No. 6,346,532.

Claim 18 is a re-presentation of patent claim 7, which has been revised to reflect the cancellation of claim 2 and the addition of claims 15-17. The priority application supports claim 18, *inter alia*, at paragraphs [0031][3] and [0032].

Claim 19 is a re-presentation of patent claim 8, which has been revised to reflect the cancellation of claim 7 and to improve its form. The priority application supports claim 19, *inter alia*, at paragraph [0027].

No new matter has been added. Based on the above amendments and the following remarks, Patent Owner respectfully requests that the Examiner reconsider all outstanding rejections.

Claims 1-5, 7-11, 13, and 14 stand rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over JP 10-218861 (JP '861) in view of the Blin article (Blin) and WO 94/18161 (WO '161). These claims also stand rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over WO '161 in view of Blin, the Thornber article (Thornber), and JP '861. These rejections are respectfully traversed.

The Office Action alleges that the claims in the instant patent are entitled only to the international filing date of October 15, 1998, because these claims are not adequately supported by priority Japanese Application No. 9-258778. Therefore, since JP '861 was published on August 18, 1998, the Examiner cited this document as a reference under 35 U.S.C. § 102(a).

[3] Starting from the last paragraph on page 29 of the English language translation of the priority application filed March 7, 2001 during the original prosecution of U.S. Patent No. 6,346,532.

Patent Owner respectfully submits that the instant claims, as amended above, are adequately supported by the aforementioned priority application. In particular, the alleged discrepancies between the patent claims and the disclosure in the priority application mentioned in the Office Action at page 3 have all been addressed by the above amendment. Therefore, the present claims are entitled to the October 17, 1997 filing date of the priority Japanese application, which is before the October 15, 1998 publication date of JP '861. Accordingly, JP '861 is not prior art. Since all of the above rejections are based, at least in part, on JP '861, these rejections cannot be maintained for at least this reason alone, and should be withdrawn, as agreed during the personal interview conducted on April 16, 2014.

CONCLUSION

For at least the reasons stated above, claims 1, 3-5, 9-11, and 13-19, which are subject to reexamination, are patentable. Accordingly, Patent Owner respectfully requests reconsideration of the rejections and that the claims be confirmed and/or determined patentable. Should the Examiner believe anything further is desirable in order to place the claims in even better condition, the Examiner is invited to contact Patent Owner's undersigned representative.

It is believed that no fees are necessary in connection with this Amendment. However, in the event that the U.S. Patent and Trademark Office determines that fees are due, the Commissioner is hereby authorized to charge any such fees to the undersigned's Deposit Account No. 06 0916.

Respectfully submitted,

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

Dated: May 6, 2014

By: Charles E. Van Horn

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Title of Invention:	AMIDE DERIVATIVES OR SALTS THEREOF
First Named Inventor/Applicant Name:	6346532
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Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		Amendment_and_Statement_of_the_Substance_of_the_Interview.pdf	454503 ee27bd72d82ba2133cfe6ac4f14420960bca6ec6	yes	13

Multipart Description/PDF files in .zip description

Document Description	Start	End
Amendment/Req. Reconsideration-After Non-Final Reject	1	1
Claims	2	7
Applicant summary of interview with examiner	8	8
Applicant Arguments/Remarks Made in an Amendment	9	13

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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.

Litigation Search Report CRU 3999

Reexam Control No. 96/000,045

To: HUANG, Evelyn Location: Central Reexam Unit Art Unit: 3991 Date: 6/16/14 Case Serial Number: 96/000,045	From: Monica A. Graves Location: CRU 3999, MDW 4B31 Phone: (571) 272-7253 monica.graves@uspto.gov

Search Notes

Litigation search for U.S. Patent Number – **6,346,532**

No Litigation Found

(See Attached)

1) I performed a KeyCite Search in Westlaw, which retrieves all history on the patent including any litigation.

2) I performed a search on the patent in Lexis CourtLink for any open dockets or closed cases.

3) I performed a search in Lexis in the Federal Courts and Administrative Materials databases for any cases found.

4) I performed a search in Lexis in the IP Journal and Periodicals database for any articles on the patent.

5) I performed a search in Lexis in the news databases for any articles about the patent or any articles about litigation on this patent.

Westlaw

Date of Printing: Jun 16, 2014

KEYCITE

© US PAT 6346532 AMIDE DERIVATIVES OR SALTS THEREOF, Assignee: Yamanouchi Pharmaceutical Co., Ltd. (Feb 12, 2002)

History

Direct History

=> 1 **AMIDE DERIVATIVES OR SALTS THEREOF,** US PAT 6346532, 2002 WL 216985 (U.S. PTO Utility Feb 12, 2002)

Patent Family

2 NEW N-PHENYL HETEROAROMATIC CARBOXAMIDE BETA-3 RECEPTOR STIMULANTS, USED E.G. FOR TREATING DIABETES AND OBESITY, Derwent World Patents Legal 1999-302703

Assignments

3 Action: CHANGE OF NAME (SEE DOCUMENT FOR DETAILS). Number of Pages: 040, (DATE RECORDED: Nov 16, 2005)

4 ACTION: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS). NUMBER OF PAGES: 003, (DATE RECORDED: Apr 07, 2000)

Patent Status Files

.. Certificate of Correction, (OG DATE: Aug 20, 2002)

Prior Art (Coverage Begins 1976)

© 6 AMIDE DERIVATIVES AND MEDICINAL COMPOSITIONS THEREOF, US PAT 6177454Assignee: Yamanouchi Pharmaceutical Co., Ltd., (U.S. PTO Utility 2001)

© 7 AMIDE DERIVATIVES AND MEDICINAL COMPOSITIONS THEREOF, US PAT 6048884Assignee: Yamanouchi Pharmaceutical Co., Ltd., (U.S. PTO Utility 2000)

© 8 METHOD FOR DETECTING SETTING ERRORS OF CLEARANCE BETWEEN ROLLERS IN UNIVERSAL ROLLING MILL, AND METHOD FOR ROLLING H- SHAPED STEEL HAVING FAVORABLE FLANGE DIMENSIONS UTILIZING SAME DETECTING METHOD, US PAT 5553475Assignee: Kawasaki Steel Corporation, (U.S. PTO Utility 1996)

© 9 NEW QUATERNARY AMMONIUM COMPOUNDS, THEIR PREPARATION AND USE, US PAT 5223614Assignee: Boehringer Ingelheim GmbH, (U.S. PTO Utility 1993)

© 10 OXAZOLIDINEDIONE DERIVATIVES AND THEIR USE, US PAT 5614544Assignee: Takeda Chemical Industries, Ltd., (U.S. PTO Utility 1997)

C 11 SECONDARY AMINES, THEIR PREPARATION AND USE IN PHARMACEUTICAL COMPOSITIONS, US PAT 4478849Assignee: Beecham Group Limited, (U.S. PTO Utility 1984)

C 12 SECONDARY AMINES, THEIR PREPARATION AND USE IN PHARMACEUTICAL COMPOSITIONS, US PAT 4396627Assignee: Beecham Group Limited, (U.S. PTO Utility 1983)

C 13 SUBSTITUTED SULFONAMIDES AS SELECTIVE <<beta>>3 AGONISTS FOR THE TREATMENT OF DIABETES AND OBESITY, US PAT 5541197Assignee: Merck & Co., Inc., (U.S. PTO Utility 1996)

Search Result List							
Patent	Class	Subclass	Description	Court	Docket Number	Filed	Date Retrieved

Total number of results: 0

Search Title	Patent Search 6346532 6/16/2014
Patent Number	6346532
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529096 (09) 6346532 February 12, 2002

UNITED STATES PATENT AND TRADEMARK OFFICE GRANTED PATENT

6346532

Access PDF of Official Patent *
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February 12, 2002

Amide derivatives or salts thereof

INVENTOR: Maruyama, Tatsuya - Tsukuba, Japan (JP) ; Suzuki, Takayuki - Tsukuba, Japan (JP) ; Onda, Kenichi - Tsukuba, Japan (JP) ; Hayakawa, Masahiko - Tsukuba, Japan (JP) ; Moritomo, Hiroyuki - Tsukuba, Japan (JP) ; Kimizuka, Tetsuya - Tsukuba, Japan (JP) ; Matsui, Tetsuo - Tsukuba, Japan (JP)

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ASSIGNEE-PRE-ISSUE:
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ASSIGNEE-AFTER-ISSUE:
November 16, 2005 - CHANGE OF NAME (SEE DOCUMENT FOR DETAILS)., ASTELLAS PHARMA INC., 3-11 NIHONBASHI-HONCHO 2-CHOME, CHUO-KU, TOKYO, JAPAN ( ), Reel and Frame Number: 016784/0361

LEGAL-REP: Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P.

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July 15, 2009 - Payment of Maintenance Fee, 8th Year, Large Entity.
March 13, 2013 - Payment of Maintenance Fee, 12th Year, Large Entity.

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CL: 514, 544, 546, 548

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IPC-MAIN-CL: [8] C07C 233#07 (20060101) Advanced Inventive 20020810 (A F I B M RU)

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IPC-ADDL-CL: [7] C07D 239#02

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IPC-ADDL-CL: [8] A61K 031#16 (20060101) Advanced Inventive 20020810 (A L I B M RU)

IPC-ADDL-CL: [8] A61P 003#10 (20060101) Advanced Inventive 20020810 (A L I B M RU)

IPC-ADDL-CL: [8] C07C 229#38 (20060101) Advanced Inventive 20020810 (A L I B M RU)

IPC-ADDL-CL: [8] C07C 233#65 (20060101) Advanced Inventive 20020810 (A L I B M RU)

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IPC-ADDL-CL: [8] C07D 213#81 (20060101) Advanced Inventive 20051008 (A I R M EP)

IPC-ADDL-CL: [8] C07D 215#48 (20060101) Advanced Inventive 20051008 (A I R M EP)

IPC-ADDL-CL: [8] C07D 231#12 (20060101) Advanced Inventive 20051008 (A I R M EP)

IPC-ADDL-CL: [8] C07D 233#26 (20060101) Advanced Inventive 20051008 (A I R M EP)

IPC-ADDL-CL: [8] C07D 233#64 (20060101) Advanced Inventive 20060521 (A I R M EP)

IPC-ADDL-CL: [8] C07D 235#16 (20060101) Advanced Inventive 20051008 (A I R M EP)

IPC-ADDL-CL: [8] C07D 235#30 (20060101) Advanced Inventive 20051008 (A I R M EP)

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IPC-ADDL-CL: [8] C07D 277#40 (20060101) Advanced Inventive 20060521 (A I R M WO)

IPC-ADDL-CL: [8] C07D 277#82 (20060101) Advanced Inventive 20051008 (A I R M EP)

IPC-ADDL-CL: [8] C07D 401#04 (20060101) Advanced Inventive 20051008 (A I R M EP)

IPC-ADDL-CL: [8] C07D 513#04 (20060101) Advanced Inventive 20051008 (A I R M EP)

PRIM-EXMR: Raymond, Richard L.

ASST-EXMR: Patel, Sudhaker B.

REF-CITED:

5223614, June 29, 1993, Schromm et al., United States of America (US)
5541197, July 30, 1996, Fisher et al., United States of America (US)
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6177454, January 23, 2001, Maruyama et al., United States of America (US)
3743265, June 29, 1989, Federal Republic of Germany (DE)
10218861, August 18, 1998, Japan (JP)
9529159, November 2, 1995, World Intellectual Property Organization (WIPO) (WO)

NON-PATENT LITERATURE:
Konosu T. et al. "Triazole antif.", Chem.Pharm.Bull., 39/10, 2581-9, Oct. 1991.

CORE TERMS: brs, ethyl, amino, prime, acetanilide, compound, solvent, dihydrochloride, hydrochloride, residue, acid, evaporated, vacuo, receptor, hydrogen, atom, mixture, methanol, acetate, insulin, ensp, chromatography,]-4, stirred, purified, column, manufacturing, eluent, silica gel, chloroform

ENGLISH-ABST:

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 $\beta_{(3)}$ receptor.

NO-OF-CLAIMS: 14

EXMPL-CLAIM: 1

NO-OF-FIGURES: 0

NO-DRWNG-PP: 0

SUMMARY:

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 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 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 $\beta_{(3)}$-receptors. Incidentally, it has been known that β-adrenaline receptors are classified into $\beta_{(1)}$, $\beta_{(2)}$and $\beta_{(3)}$subtypes, that stimulation of $\beta_{(1)}$-receptor causes an increase in heart rate, that stimulation of $\beta_{(2)}$-receptor stimulates decomposition of glycogen in muscles, whereby synthesis of glycogen is inhibited, causing an action such as muscular tremor, and that stimulation of $\beta_{(3)}$-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 $\beta_{(3)}$-agonists also have actions caused by stimulation of $\beta_{(1)}$- and $\beta_{(2)}$-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 $\beta_{(3)}$-receptor selectivity in rodential animals such as rats show an action due to stimulating action to $\beta_{(1)}$- and $\beta_{(2)}$-receptors in human being. In view of the above, investigations for compounds having a stimulating action which is selective to $\beta_{(3)}$-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 $\beta_{(3)}$-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 $\beta_{(3)}$-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 $\beta_{(3)}$-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.

(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-anisole 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, $R^{(1a)}$, $R^{(1b)}$, $R^{(2)}$, 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)

(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)

(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 $\beta_{(3)}$-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 $\beta_{(3)}$-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 $\beta_{(3)}$-receptor stimulating action of the compound of the present invention is selective to $\beta_{(3)}$-receptors in human being. It has been known that the stimulation of $\beta_{(3)}$-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 $\beta_{(3)}$-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 $\beta_{(3)}$-receptor. Examples of those diseases are shown as follows.

It has been mentioned that the $\beta_{(3)}$-receptor mediates the motility of non-sphincteral smooth muscle contraction, and because it is believed that the selective $\beta_{(3)}$-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 $\beta_{(3)}$-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 $\beta_{(3)}$-agonist of the present invention is useful in the therapy of neurogenic inflammation and in addition, has little action to cariopulmonary system.

Moreover, the $\beta_{(3)}$-adrenaline receptor is capable of resulting in a selective antidepressant action due to stimulation of the $\beta_{(3)}$-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 $\beta_{(3)}$-receptors as a result of experiments using cells expressing human type receptors, and the adverse action caused by other $\beta_{(3)}$-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 $\beta_{(3)}$-, $\beta_{(2)}$- and $\beta_{(1)}$-receptors

Human $\beta_{(3)}$-stimulating action was investigated using an SK-N-MC cell system (cells in which human $\beta_{(3)}$-receptor and human $\beta_{(1)}$-receptor were permanently expressed were purchased) while human $\beta_{(2)}$- and $\beta_{(1)}$-stimulating actions were investigated using a CHO cell system (cells in which each of human $\beta_{(2)}$- and $\beta_{(1)}$-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 $\beta_{(3)}$-stimulating action was investigated in the presence of a $\beta_{(1)}$-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 $\beta_{(3)}$-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 solubilizers 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

DETDESC:

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)aminolethyl]-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-[l-(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-imidazoi-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 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.

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-[l-(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-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

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)aminolpropyl]-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

Search terms may have been found within the contents of this table. Please see the table in the original document.

Search terms may have been found within the contents of this table. Please see the table in the original document.

Search terms may have been found within the contents of this table. Please see the table in the original document.

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.

Search terms may have been found within the contents of this table. Please see the table in the original document.

Search terms may have been found within the contents of this table. Please see the table in the original document.

ENGLISH-CLAIMS:
Return to Top of Patent

What is claimed is:

1. A compound of formula (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 —$CH_{(2)}$O—.

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):

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 through4in 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.

LOAD-DATE: April 6, 2013

1. 79 FR 30622, Notices, DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS) Food and Drug Administration (FDA), [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, View PDF of Federal Register Print Version , Wednesday, May 28, 2014, ACTION: Notice., FEDERAL REGISTER Vol. 79, No. 102 FEDERAL REGISTER Vol. 79, No. 102

... 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 ...

Source: **Combined Source Set 3 - Intellectual Property Cases, Administrative Decisions & Regulations**
Terms: **6346532 or 6,346,532** (Suggest Terms for My Search)
View: Cite
Date/Time: Monday, June 16, 2014 - 10:37 AM EDT

1. Food and Drug Adminstration Documents and Publications, May 28, 2014, FOOD AND DRUG ADMINISTRATION - REGULATORY DOCUMENTS, 1071 words, Determination of Regulatory Review Period for Purposes of Patent Extension; MYRBETRIQ

   ... 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 ...

2. US Official News, May 28, 2014 Wednesday, 1087 words, Determination of Regulatory Review Period for Purposes of Patent Extension; MYRBETRIQ, Washington

   ... 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 ...

Source: **Combined Source Set 3 - English Language News (Most recent Two Years)**
Terms: **6346532 or 6,346,532** (Suggest Terms for My Search)
View: Cite
Date/Time: Monday, June 16, 2014 - 10:39 AM EDT

Attorney Docket No. 07385.0042-00000

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Ex Parte Re-Examination of:	)	
	)	
U.S. Patent No.: 6,346,532	)	Group Art Unit: *3991*
	)	
Issued: February 12, 2002	)	Examiner: *Evelyn Huang*
	)	
Control No.: 96/000,045	)	Confirmation No.: *3506*
	)	
Filed: November 21, 2013	)	
	)	
Inventors: Tatsuya MARUYAMA et al.	)	
	)	
For: AMIDE DERIVATIVES OR SALTS THEREOF	)	
	)	

Mail Stop: Ex Parte Reexam
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SUPPLEMENTAL AMENDMENT

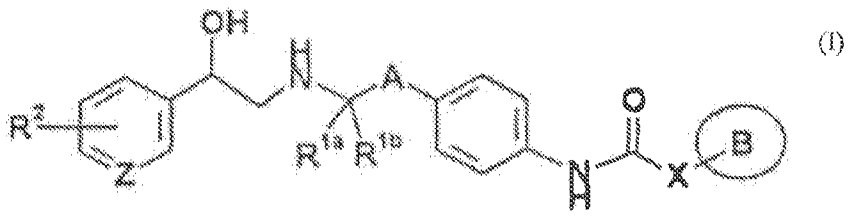
Sir:

In supplement to the response filed May 6, 2014, to the Office Action dated March 6, 2014, please amend the above-captioned patent as follows and consider the following remarks.

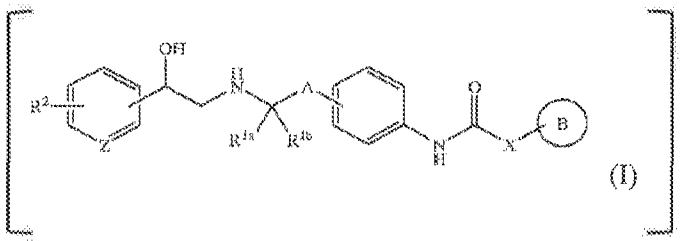
CLAIMS

Please amend the claims as follows.

1. (Amended) A compound of formula (I):



(I)



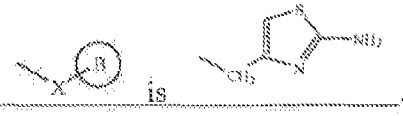
(I)

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

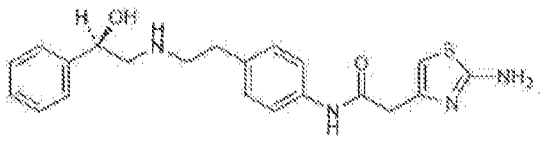
ring B is a nitrogen-containing heteroaryl group which is unsubstituted or substituted and is optionally fused with a benzene ring; X is [a bond, or] a lower alkylene or an alkenylene, both of which are unsubstituted or substituted with hydroxy or a lower alkyl group, or X is a carbonyl or a group represented 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 methylene, ethylene, [a lower alkylene] or a group represented by —CH_2O— [-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. (Cancelled)

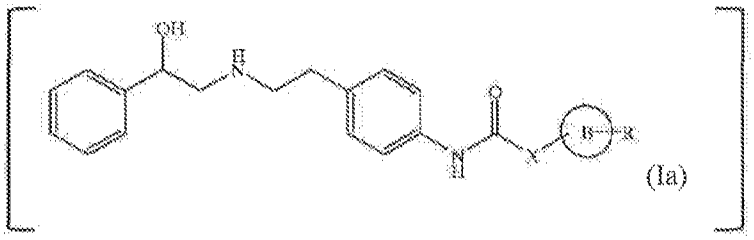
3. (Amended) The compound of formula (I) or the salt thereof according to claim 1 [claim 2], wherein the ring B is [a heteroaryl group which is] substituted with a substituent chosen from a halogen atom, lower alkyl, lower alkenyl, lower alkynyl, hydroxy, sulfanyl, halogeno lower alkyl, lower alkyl-O—, 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—, and di-lower alkyl-N— [, aryl-lower alkyl, halogeno aryl-lower alkyl, guanidino, lower alkyl-CO—NH, and lower alkyl-SO_2—NH—].

4. (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—] A is methylene, and  is .

5. (Amended) A compound of formula (Ia):



(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. (Cancelled)

8. (Cancelled)

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. (Amended) 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.

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.

15. (New) The compound according to claim 4 or the salt thereof, which is an optical isomer.

16. (Cancelled)

17. (Cancelled)

18. (New) 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.

19. (New) The composition as claimed in claim 18, 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.

REMARKS

Claims 1, 3-6, 9-15, and 18-19 remain pending.

Claims 16 and 17 have been cancelled without prejudice or disclaimer.

Pursuant to a telephone conference with Supervisory Examiner Jones regarding the clarity of the deletions to claims 1 and 5, this supplemental amendment is being filed to improve the clarity of those deletions.

Prompt and favorable reconsideration is respectfully requested.

It is believed that no fees are necessary in connection with this Amendment. However, in the event that the U.S. Patent and Trademark Office determines that fees are due, the Commissioner is hereby authorized to charge any such fees to the undersigned's Deposit Account No. 06 0916.

Respectfully submitted,

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

Dated: July 25, 2014

By: Charles E Van Horn

Charles E. Van Horn
Reg. No. 40,266
(202) 408-4000

Electronic Acknowledgement Receipt	
EFS ID:	19685597
Application Number:	96000045
International Application Number:	
Confirmation Number:	3506
Title of Invention:	AMIDE DERIVATIVES OR SALTS THEREOF
First Named Inventor/Applicant Name:	6346532
Correspondence Address:	Fitzpatrick Cella Harper & Scinto - 1290 Avenue of the Americas - New York NY 10104-3800 US - -
Filer:	Charles E. Van Horn/Charlene Woods
Filer Authorized By:	Charles E. Van Horn
Attorney Docket Number:	07385.0042
Receipt Date:	25-JUL-2014
Filing Date:	21-NOV-2013
Time Stamp:	14:07:31
Application Type:	Supplemental Examination
Patent Number:	

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		Supplemental_Amendment.pdf	247915 dc252acc920d467aaad3d00cd886cad18ca9e82	yes	7

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Supplemental Response or Supplemental Amendment	1	1
Claims	2	6
Applicant Arguments/Remarks Made in an Amendment	7	7

Warnings:

Information:

Total Files Size (in bytes):	247915

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

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

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

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

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
96/000,045	11/21/2013	6346532	07385.0042	3506

7590 07/31/2014

Fitzpatrick Cella Harper & Scinto
1290 Avenue of the Americas
New York, NY 10104-3800

EXAMINER
HUANG, EVELYN MEI

ART UNIT	PAPER NUMBER
3991	

MAIL DATE	DELIVERY MODE
07/31/2014	PAPER

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

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

Notice of Intent to Issue Ex Parte Reexamination Certificate	Control No.	Patent Under Reexamination	
	96/000,045	6346532	
	Examiner	Art Unit	AIA (First Inventor to File) Status
	EVELYN HUANG	3991	No

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

1. ☒ Prosecution on the merits is (or remains) closed in this *ex parte* reexamination proceeding. This proceeding is subject to reopening at the initiative of the Office or upon petition. *Cf.* 37 CFR 1.313(a). A Certificate will be issued in view of
   - (a) ☒ Patent owner's communication(s) filed: *25 July 2014*.
   - (b) ☐ Patent owner's failure to file an appropriate timely response to the Office action mailed: _____.
   - (c) ☐ Patent owner's failure to timely file an Appeal Brief (37 CFR 41.31).
   - (d) ☐ The decision on appeal by the ☐ Board of Patent Appeals and Interferences ☐ Court dated _____
   - (e) ☐ Other: _____.
2. The Reexamination Certificate will indicate the following:
   - (a) Change in the Specification: ☐ Yes ☒ No
   - (b) Change in the Drawing(s): ☐ Yes ☒ No
   - (c) Status of the Claim(s):
     - (1) Patent claim(s) confirmed: _____.
     - (2) Patent claim(s) amended (including dependent on amended claim(s)): *1,3-5,9-11,13 and 14*
     - (3) Patent claim(s) canceled: *2,7 and 8*.
     - (4) Newly presented claim(s) patentable: 15,18 and 19.
     - (5) Newly presented canceled claims: 16 and 17.
     - (6) Patent claim(s) ☐ previously ☐ currently disclaimed: _____
     - (7) Patent claim(s) not subject to reexamination: 6 and 12.
3. ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.
4. ☒ Note the attached statement of reasons for patentability and/or confirmation. Any comments considered necessary by patent owner regarding reasons for patentability and/or confirmation must be submitted promptly to avoid processing delays. Such submission(s) should be labeled: "Comments On Statement of Reasons for Patentability and/or Confirmation."
5. ☐ Note attached NOTICE OF REFERENCES CITED (PTO-892).
6. ☐ Note attached LIST OF REFERENCES CITED (PTO/SB/08 or PTO/SB/08 substitute).
7. ☐ The drawing correction request filed on _____ is: ☐ approved ☐ disapproved.
8. ☒ Acknowledgment is made of the priority claim under 35 U.S.C. § 119(a)-(d) or (f).
   a)☒ All b)☐ Some* c)☐ None of the certified copies have
   - ☐ been received.
   - ☐ not been received.
   - ☒ been filed in Application No. *09/529096*.
   - ☐ been filed in reexamination Control No. _____.
   - ☐ been received by the International Bureau in PCT Application No. _____.

   * Certified copies not received: _____.
9. ☐ Note attached Examiner's Amendment.
10. ☐ Note attached Interview Summary (PTO-474).
11. ☐ Other: _____.

All correspondence relating to this reexamination proceeding should be directed to the **Central Reexamination Unit** at the mail, FAX, or hand-carry addresses given at the end of this Office action.

EVELYN HUANG
Primary Examiner
Art Unit: 3991

cc: Requester (if third party requester)

Claims 1-14 are in the issued patent. Claims 6 and 12 are not under reexamination.

By the amendment filed on 5/6/2014, claims 2, 7 and 8 are canceled, claims 1, 3-5 and 11 are amended, and new claims 15-19 are added.

By the supplemental amendment filed on 7/25/2014, claims 16-17 are canceled.

Claims 1, 3-5, 11, 13-14 and new claims 15, 18-19 are pending. These claims are determined to be patentable for the following reasons.

STATEMENT OF REASONS FOR PATENTABILITY AND/OR CONFIRMATION

The 103(a) rejection for claims 1-5, 7-11 and 13-14 over JP'861, Blin and WO'161 and the 103(a) rejection for claims 1-5, 7-11 and 13-14 over WO '161, Blin, Thornber and JP'861 are withdrawn upon reconsideration in view of the amendments filed on 5/6/2014 and 7/25/2014. Particularly, the claims have been amended to delete the claimed subject matter not described in the priority document JP-9-285778, filed on 10/17/1997. The claims as amended are entitled to the priority date of 10/17/1997. As such, JP'861, published on 8/18/1998, is no longer available as prior art under 102(a), thereby obviating the 103(a) rejections. Accordingly, claims 1, 3-5, 9-11, 13-14, and new claims 15, 18-19 dependent therefrom, are patentable over the prior art of record.

Any comments considered necessary by PATENT OWNER regarding the above statement must be submitted promptly to avoid processing delays. Such submission by the patent owner should be labeled: "Comments on Statement of Reasons for Patentability and/or Confirmation" and will be placed in the reexamination file.

/Evelyn Huang/
Patent Reexamination Specialist
CRU Art Unit 3991

/Padmashri Ponnaluri/
Patent Reexamination Specialist
CRU Art Unit 3991

/Deborah D Jones/
Supervisory Patent Examiner, Art Unit 3991

Reexamination	Application/Control No.	Applicant(s)/Patent Under Reexamination
	96000045	6346532
	Certificate Date	Certificate Number
		C1

Requester Correspondence Address: ☒ **Patent Owner** ☐ **Third Party**

Fitzpatrick Celia Harper & Scinto
1290 Avenue of the Americas
New York, NY 10104-3800

LITIGATION REVIEW ☒	/EH/ (examiner initials)	07/28/2014 (date)
Case Name		Director Initials
none		

COPENDING OFFICE PROCEEDINGS	
TYPE OF PROCEEDING	**NUMBER**
1. none	

	/EVELYN HUANG/ Primary Examiner. Art Unit 3991

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

BIB DATA SHEET

CONFIRMATION NO. 3506

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
96/000,045	11/21/2013 RULE	514	3991	07385.0042

APPLICANTS

INVENTORS

6346532, Residence Not Provided;
ASTELLAS PHARMA INC., TOKYO, JAPAN;
PATENT OWNER, NEW YORK, NY;

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

This application is a SER of 09/529,096 04/07/2000 PAT 6346532
which is a 371 of PCT/JP98/04671 10/15/1998

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

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

Foreign Priority claimed ☑ Yes ☐ No 35 USC 119(a-d) conditions met ☑ Yes ☐ No Verified and Acknowledged /EVELYN MEI HUANG/ Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS

ADDRESS

Fitzpatrick Cella Harper & Scinto
1290 Avenue of the Americas
New York, NY 10104-3800

TITLE

AMIDE DERIVATIVES OR SALTS THEREOF

FILING FEE RECEIVED		
0.00	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	96000045	6346532
	Examiner	Art Unit
	EVELYN HUANG	3991

CPC						
Symbol					Type	Version
C07D		215	/	48	I	2013-01-01
C07D		277	/	82	I	2013-01-01
C07D		233	/	26	I	2013-01-01
C07D		235	/	30	I	2013-01-01
C07D		213	/	81	I	2013-01-01
C07D		401	/	04	I	2013-01-01
C07D		241	/	12	I	2013-01-01
C07D		277	/	36	I	2013-01-01
C07D		513	/	04	I	2013-01-01
C07D		231	/	12	I	2013-01-01
C07D		213	/	30	F	2013-01-01
C07D		257	/	04	I	2013-01-01
C07D		239	/	26	I	2013-01-01
C07D		213	/	56	I	2013-01-01
			/			

CPC Combination Sets							
Symbol					Type	Set	Ranking	Version
			/					
			/					

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	12	
/EVELYN HUANG/ Primary Examiner.Art Unit 3991	7/28/2014	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	96000045	6346532
	Examiner	Art Unit
	EVELYN HUANG	3991

US ORIGINAL CLASSIFICATION					
CLASS		SUBCLASS			
514		252.1			
CROSS REFERENCE(S)					
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)				
514	256				
544	330	332			
546	1	152			
548	186	190	214	252	260

INTERNATIONAL CLASSIFICATION										
CLAIMED					NON-CLAIMED					
A	6	1	K	31 / 495 (2006.01.01)						
A	6	1	K	31 / 505 (2006.01.01)						
C	0	7	D	239 / 02 (2006.01.01)						
C	0	7	D	213 / 00 (2006.01.01)						
C	0	7	D	249 / 00 (2006.01.01)						

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	12	
/EVELYN HUANG/ Primary Examiner.Art Unit 3991	7/28/2014	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	96000045	6346532
	Examiner	Art Unit
	EVELYN HUANG	3991

☒ Claims renumbered in the same order as presented by applicant	☐ CPA	☐ T.D.	☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original

NONE (Assistant Examiner)	(Date)	Total Claims Allowed: 12	
/EVELYN HUANG/ Primary Examiner.Art Unit 3991 (Primary Examiner)	7/28/2014 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure none

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	96000045	6346532
	Examiner	Art Unit
	EVELYN HUANG	3991

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
review prosecution history of the patented file	1/24/2014	
litigation search	6/16/2014	

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

	/EVELYN HUANG/ Primary Examiner. Art Unit 3991

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
96/000,045	11/21/2013	6346532	07385.0042	3506

7590 08/06/2014

Fitzpatrick Cella Harper & Scinto
1290 Avenue of the Americas
New York, NY 10104-3800

EXAMINER	
HUANG, EVELYN MEI	
ART UNIT	PAPER NUMBER
3991	

MAIL DATE	DELIVERY MODE
08/06/2014	PAPER

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

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

UNITED STATES DEPARTMENT OF COMMERCE
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Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450

APPLICATION NO./ CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR / PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.
96/000,045	21 November, 2013	6346532	07385.0042

Fitzpatrick Cella Harper & Scinto
1290 Avenue of the Americas
New York, NY 10104-3800

EXAMINER	
EVELYN HUANG	
ART UNIT	PAPER
3991	20140801

DATE MAILED:

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

Commissioner for Patents

NOTICE:

In order to make the Items of Information in this concluded supplemental examination proceeding more easily viewable to the public, this Office action places the Items of Information on a "Notice of References Cited." Because a "Notice of Intent to Issue Ex Parte Reexamination Certificate" has already been mailed by the Office and unless expressly set forth otherwise by the Office, no additional response by patent owner is required.

For inquiries regarding this Notice, please contact Supervisory Patent Reexamination Specialist Andrew J. Fischer at (571) 272-6779. In his absence, please contact Supervisory Patent Reexamination Specialist Stephen Stein at (572) 272-1544.

/EVELYN HUANG/
Patent Reexamination Specialist
CRU Art Unit 3991

PTO-90C (Rev.04-03)

Notice of References Cited	Application/Control No. Declaratio	Applicant(s)/Patent Under Reexamination 6346532	
	Examiner EVELYN HUANG	Art Unit 3991	Page 1 of 3

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-6,346,532	02-2002	Maruyama et al.	514/252.1
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
*	N	JP-10218861 A	08-1998	JP		
*	O	WO 94/18161 A1	08-1994	WO		
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
*	U	Table of testing data for compounds including those described in Examples 1-113 of US 6,346,532, 40 pages.
*	V	Materials for Astellas R&D Meeting. Subco~runittee on Development Theme Establishment, titled "YM 178/Discontinuation of Development Theme for Diabetes Mellitus," 16 pages, dated October 27, 2003.
*	W	YM178 in Type 2 Diabetes Mellitus 178-CL-003 Study Report, 11 pages, dated September 11, 2003.
*	X	Yamanouchi BAN Compound Evaluation System with English translation, 1 page.

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Notice of References Cited	Application/Control No. 96/000,045	Applicant(s)/Patent Under Reexamination 6346532	
	Examiner EVELYN HUANG	Art Unit 3991	Page 2 of 3

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
*	U	Yamanouchi Monthly Research Progress Report with English translation, 2 pages, dated April 26, 1995.
*	V	Excerpts of the prosecution history of U.S. Patent Application No. 09/529,096, the U.S. National Stage of PCT/JP98/04671, filed October 15, 1998, that resulted in U.S. Patent No. 6,346,532.
*	W	Blin et al., "Structural and Conformational Features Determining Selective Signal Transduction in the beta-3-Adrenergic Receptor," Molecular Pharmacology, 44:1094-1104 (1993).
*	X	Thornber, C. W., "Isosterism and Molecular Modification in Drug Design," Chem. Soc. Rev. 18:563-580 (1979).

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Notice of References Cited	Application/Control No. 96/000,045	Applicant(s)/Patent Under Reexamination 6346532	
	Examiner EVELYN HUANG	Art Unit 3991	Page 3 of 3

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
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	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
*	U	Declaration by Dr. Tetsuo Matsui under 37 C.F.R 1.132, dated November 21, 2013.
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

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.

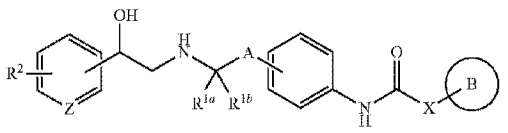
(56) **References Cited**

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.

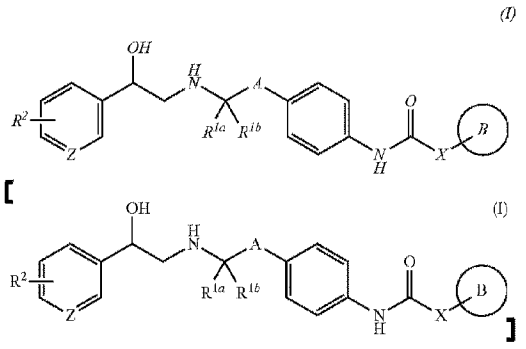
Claims **1**, **3-5** and **11** are determined to be patentable as amended.

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):



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—*;

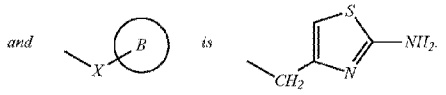
R^{1a}, R^{1b} are the same or different and each is a hydrogen atom or a lower alkyl group;

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

Z is a group represented by =CH—; or a salt thereof.

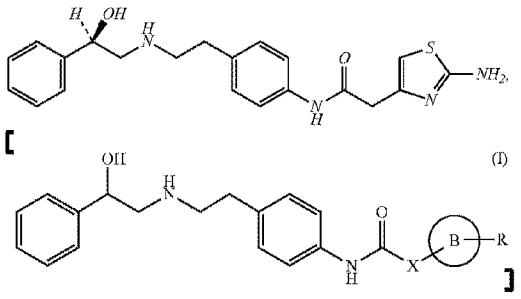
3. The compound of formula (I) or the salt thereof according to [claim **2**] *claim 1*, wherein the ring B is [a heteroaryl group which is] substituted with a substituent chosen from a halogen atom, lower alkyl, lower alkenyl, lower alkynyl, hydroxy, sulfanyl, halogeno lower alkyl, lower alkyl-O—, lower 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)



[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.

* * * * *

02213.003400. PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Ex Parte Re-Examination of:	)	
	:	Examiner: Evelyn Mei Huang
U.S. Patent No. 6,346,532	)	
	:	
Control No.: 96/000,045	)	Art Unit 3991
	:	
Inventors: TATSUYA MARUYAMA ET AL.	)	Conf. No.: 3506
	:	
Filed: November 21, 2013	)	
	:	
For: AMIDE DERIVATIVES OR SALTS THEREOF	)	
	:	
Reexamination Certificate Issued: February 24, 2015	)	May 13, 2016

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

CERTIFICATE OF CORRECTION
UNDER RULE 322

Sir:

It is respectfully requested that a Certificate of Correction be issued by the Patent and Trademark Office due to errors which appear in the printed *Ex Parte* Reexamination Certificate as a result of Patent and Trademark Office mistakes. A Certificate of Correction form (Form PTO/SB/44) is attached.

Patentees note that they previously provided the attached Form PTO/SB/44 to the Certificates of Correction Branch via facsimile for entry into the official record at the request of

the Certificates of Correction Branch. However, to date, that paper does not appear to have been placed in the file and considered.

Patentees' undersigned attorney may be reached in our New York office by telephone at (212) 218-2100. Correspondence should be directed to our address given below.

Respectfully submitted,

/Jason M. Okun/
Jason M. Okun
Attorney for Patentees
Registration No. 48,512

FITZPATRICK, CELLA, HARPER & SCINTO
1290 Avenue of the Americas
New York, New York 10104-3800
Facsimile: (212) 218-2200

UNITED STATES PATENT AND TRADEMARK OFFICE

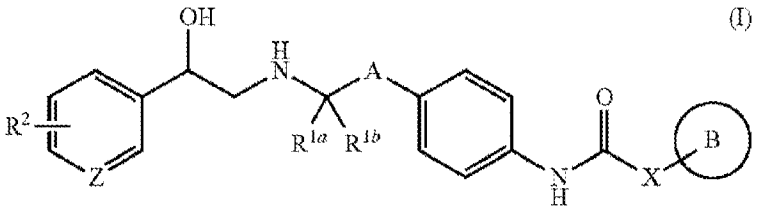
CERTIFICATE OF CORRECTION

PATENT NO. : U.S. 6,346,532 C1
DATED : February 24, 2015
INVENTOR(S) : TATSUYA 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 1:

Line 40, "[

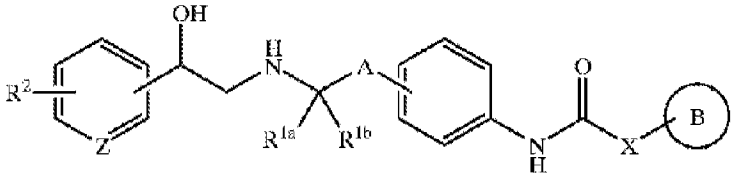


(I)

]"

should read --[

(I)



]--

Line 46, "unsubstituted substituted" should read --unsubstituted or substituted--.

MAILING ADDRESS OF SENDER:
FITZPATRICK, CELLA, HARPER & SCINTO
1290 Avenue of the Americas
New York, New York 10104-3800
(212) 218-2100 - Telephone
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PATENT NO.: US 6,346,532 C1

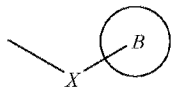
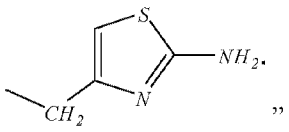
UNITED STATES PATENT AND TRADEMARK OFFICE

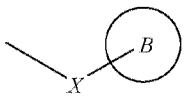
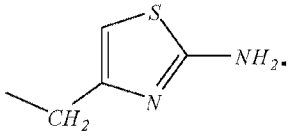
CERTIFICATE OF CORRECTION

PATENT NO. : U.S. 6,346,532 C1
DATED : February 24, 2015
INVENTOR(S) : TATSUYA 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 2:

Line 20, " *and*  *is*  "

should read --  *is*  --.

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PATENT NO.: US 6,346,532 C1

Form PTO/SB/44 (09-07)

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Electronic Acknowledgement Receipt	
EFS ID:	25770978
Application Number:	96000045
International Application Number:	
Confirmation Number:	3506
Title of Invention:	AMIDE DERIVATIVES OR SALTS THEREOF
First Named Inventor/Applicant Name:	6346532
Correspondence Address:	Fitzpatrick Cella Harper & Scinto - 1290 Avenue of the Americas - New York NY 10104-3800 US - -
Filer:	Jason M. Okun
Filer Authorized By:	
Attorney Docket Number:	07385.0042
Receipt Date:	13-MAY-2016
Filing Date:	21-NOV-2013
Time Stamp:	12:19:03
Application Type:	Supplemental Examination
Patent Number:	

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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request for Certificate of Correction	CertificateofCorrectionExParteReexamination02213003400.pdf	184331 8cd738a53c634b5a60cfcbc64abdc9fd6736e7bb	no	4

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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

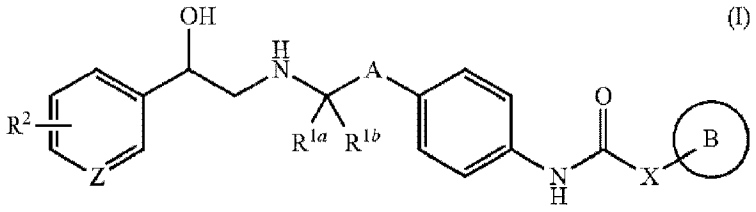
CERTIFICATE OF CORRECTION

PATENT NO. : 6,346,532 C1
APPLICATION NO. : 96/000045
DATED : February 24, 2015
INVENTOR(S) : Tatsuya 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:

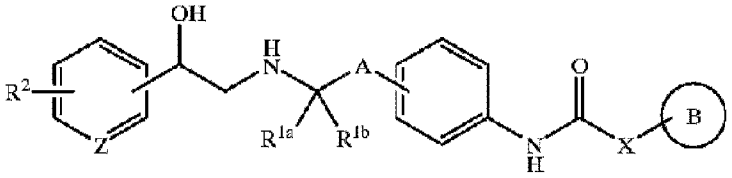
COLUMN 1:

Line 40, "[(I)]"



should read

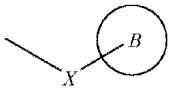
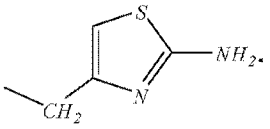
(I)



--[ ]--.

Line 46, "unsubstituted substituted" should read --unsubstituted or substituted--.

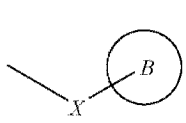
COLUMN 2:

Line 20, " and  is  ".

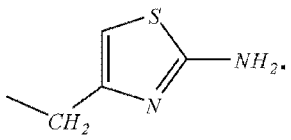
Signed and Sealed this
Fifth Day of July, 2016

Michelle K. Lee

Michelle K. Lee
Director of the United States Patent and Trademark Office



is



should read --

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