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DESCRIPTION

PHENYLAMINOALKYLCARBOXYLIC ACID DERIVATIVES AND
PHARMACEUTICAL COMPOSITIONS COMPRISING THE SAME

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Technical Field

The present invention relates to novel phenylaminoalkyl-carboxylic acid derivatives and pharmaceutically acceptable salts thereof which are useful as medicaments.

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Background Art

It is known that three subtypes of sympathomimetic β -adrenoceptor, which have been classified as β_1 , β_2 and β_3 , are present and that each receptor subtype is distributed in specified organs in living body and has specific functions.

For example, β_1 -adrenoceptor is mainly present in the heart and the stimulation of this receptor leads to increment of heart rate and cardiac contractility. β_2 -Adrenoceptor is mainly present in smooth muscle of blood vessels, the trachea and uterus. The stimulation of this receptor leads to vasodilation, bronchodilation and inhibition of uterine contraction. β_3 -Adrenoceptor is mainly present in adipocytes, the gallbladder and intestinal tract. It is known that β_3 -adrenoceptor is also present in the brain, liver, prostate and stomach. It has been reported that the stimulation of β_3 -adrenoceptor leads to increment of lipolysis, inhibition of intestinal tract motility, increment of glucose uptake, anti-depression and so on (Drugs of the Future, Vol.18, No.6, pp.529-

549 (1993); Molecular Brain Research, Vol.29, pp.369-375 (1995);
European Journal of Pharmacology, Vol.289, pp.223-228 (1995);
Pharmacology, Vol.51, pp.288-297 (1995)).

In addition, it has been recently reported that β_3 -
5 adrenoceptor is predominantly present in human bladder and that human
bladder is relaxed by a β_3 -adrenoceptor stimulant (The Japanese
Journal of Urology, Vol.88, No.2, p.183 (1997); NEUROUROLOGY AND
URODYNAMICS, Vol.16, No.5, pp.363-365 (1997)).

Many β_1 -adrenoceptor stimulants and β_2 -adrenoceptor
10 stimulants have been developed and are used for medicinal purposes
as cardiotonics, bronchodilators, preventive agents for threatened
abortion or premature labor, and so on.

On the one hand, it has been found that β_3 -adrenoceptor
stimulants are useful as agents for the prevention or treatment of
15 obesity, hyperglycemia, the diseases caused by intestinal
hypermotility, pollakiuria, urinary incontinence, depression, the
diseases caused by biliary calculi or hypermotility of biliary tract
and so on. Consequently, studies have been actively made to develop
agents for the prevention or treatment of such diseases, but any
20 β_3 -adrenoceptor stimulant has not been sold yet (Drugs of the Future,
Vol.18, No.6, pp.529-549(1993); European Journal of Pharmacology,
Vol.219, pp.193-201(1992) etc.).

Therefore, it has been desired to develop novel β_3 -
adrenoceptor stimulants having excellent β_3 -adrenoceptor
25 stimulating effects.

More preferably, it has been desired to develop novel and
higher selective β_3 -adrenoceptor stimulants having potent β_3 -

adrenoceptor stimulating effects in comparison with β_1 and/or β_2 -adrenoceptor stimulating effects and having attenuated side effects caused by β_1 and β_2 -adrenoceptor stimulating effects such as palpitation and tremor.

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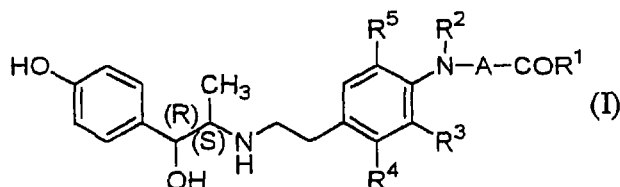
Disclosure of the Invention

The present inventors have studied extensively to solve the above objects. As a result, it was found that certain phenyl-aminoalkylcarboxylic acid derivatives have potent stimulating effects on β_3 -adrenoceptors, thereby forming the basis of the present invention.

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Accordingly, the present invention relates to a phenylaminoalkylcarboxylic acid derivative represented by the general formula:

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(wherein R^1 represents a hydroxy group, a lower alkoxy group, an aralkoxy group, an amino group, an alicyclic amino group or a mono or di(lower alkyl)amino group which may have a hydroxy group or a lower alkoxy group as a substituent; R^2 represents a hydrogen atom or a lower alkyl group; R^3 represents a hydrogen atom or a halogen atom; R^4 and R^5 are the same or different and each represents a hydrogen atom, a halogen atom or a lower alkyl group; A represents a lower alkylene group; the carbon atom marked with (R) represents a carbon

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atom in (*R*) configuration; and the carbon atom marked with (*S*) represents a carbon atom in (*S*) configuration) or a pharmaceutically acceptable salt thereof.

The present invention relates to a pharmaceutical composition
5 comprising the phenylaminoalkylcarboxylic acid derivative represented by the above general formula (I) or a pharmaceutically acceptable salt thereof.

The present invention relates to a β_3 -adrenoceptor stimulant comprising as the active ingredient the phenylaminoalkylcarboxylic
10 acid derivative represented by the above general formula (I) or a pharmaceutically acceptable salt thereof.

The present invention relates to an agent for the prevention or treatment of obesity, hyperglycemia, the diseases caused by intestinal hypermotility, pollakiuria, urinary incontinence,
15 depression, or the diseases caused by biliary calculi or hypermotility of biliary tract which comprises as the active ingredient the phenylaminoalkylcarboxylic acid derivative represented by the above general formula (I) or a pharmaceutically acceptable salt thereof.

20 The present invention relates to a method for the prevention or treatment of obesity, hyperglycemia, the diseases caused by intestinal hypermotility, pollakiuria, urinary incontinence, depression, or the diseases caused by biliary calculi or hypermotility of biliary tract which comprises administering a
25 therapeutically effective amount of the phenylaminoalkylcarboxylic acid derivative represented by the above general formula (I) or a pharmaceutically acceptable salt thereof.

The present invention relates to a use of the phenyl-aminoalkylcarboxylic acid derivative represented by the above general formula (I) or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for the prevention or treatment of obesity, hyperglycemia, the diseases caused by intestinal hypermotility, pollakiuria, urinary incontinence, depression, or the diseases caused by biliary calculi or hypermotility of biliary tract.

The present invention relates to a use of the phenyl-aminoalkylcarboxylic acid derivative represented by the above general formula (I) or a pharmaceutically acceptable salt thereof as an agent for the prevention or treatment of obesity, hyperglycemia, the diseases caused by intestinal hypermotility, pollakiuria, urinary incontinence, depression, or the diseases caused by biliary calculi or hypermotility of biliary tract.

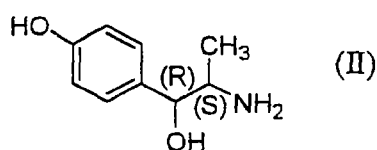
The present invention relates to a process for the manufacture of a pharmaceutical composition for the prevention or treatment of obesity, hyperglycemia, the diseases caused by intestinal hypermotility, pollakiuria, urinary incontinence, depression, or the diseases caused by biliary calculi or hypermotility of biliary tract, characterized in the use, as an essential constituent of said pharmaceutical composition, of the phenylaminoalkylcarboxylic acid derivative represented by the above general formula (I) or a pharmaceutically acceptable salt.

In the compounds represented by the above general formula (I) of the present invention, the term "lower alkoxy group" means a straight or branched alkoxy group having 1 to 6 carbon atoms such

as a methoxy group, an ethoxy group, a propoxy group, an isopropoxy group and a butoxy group; the term "aralkoxy group" means the above lower alkoxy group having an aryl group such as a phenyl group and a naphthyl group; the term "lower alkyl group" means a straight or
5 branched alkyl group having 1 to 6 carbon atoms such as a methyl group, an ethyl group, a propyl group, an isopropyl group and a butyl group; the term "alicyclic amino group" means an aliphatic cycloamino group which may have an oxygen atom in the ring chain such as a piperidino group, a morpholino group and a 1-pyrrolidinyl group; the term
10 "halogen atom" means a fluorine atom, a chlorine atom, a bromine atom or an iodine atom; and the term "lower alkylene group" means a straight alkylene group having 1 to 6 carbon atoms such as a methylene group, an ethylene group, a trimethylene group and a tetramethylene group.

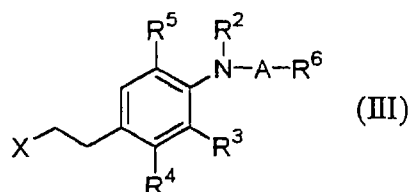
The compounds represented by the above general formula (I)
15 of the present invention can be prepared according to the following procedures.

For example, the compounds of the present invention can be prepared by allowing an amine compound represented by the formula:



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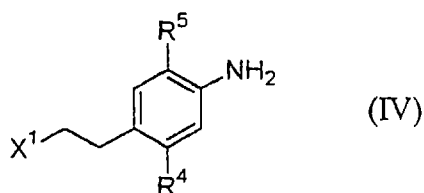
(wherein the carbon atom marked with (R) and the carbon atom marked with (S) have the same meanings as defined above) to react with an alkylating agent represented by the general formula:



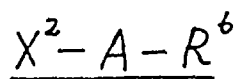
(wherein R^6 represents a protected carboxy group; X represents a leaving group; and R^2 , R^3 , R^4 , R^5 and A have the same meanings as defined above) in the presence or absence of a base such as *N,N*-diisopropylethylamine in an inert solvent such as *N,N*-dimethylformamide, removing the carboxy-protective group or subjecting the resulting compound to amidation using ammonia, a mono or di(lower alkyl)amine compound which may have a hydroxy group or a lower alkoxy group as a substituent, or an alicyclic amine compound in the usual way as occasion demands.

The amine compound represented by the above formula (II) which is used as a starting material in the above production process can be prepared by optical resolution of a commercially available enantiomeric mixture in the usual way or a method described in a literature (e.g., J. Med. Chem., Vol. 20, No. 7, pp.978-981(1977)).

The compounds represented by the above general formula (III) which are used as starting materials in the above production process can be prepared by subjecting an amine compound represented by the general formula:



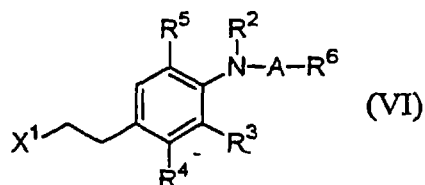
(wherein X^1 represents a hydroxy group, a chlorine atom or a bromine atom; and R^4 and R^5 have the same meanings as defined above) to *N*-alkylation using an alkylating agent represented by the general formula:



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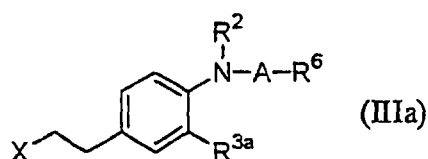
(V)

(wherein X^2 represents a chlorine atom, a bromine atom or an iodine atom; and R^6 and A have the same meanings as defined above) in the presence of a base such as potassium carbonate, subjecting the
 10 resulting compound to halogenation of the benzene ring and/or alkylation of the secondary amino group in the usual way as occasion demands to give a compound represented by the general formula:



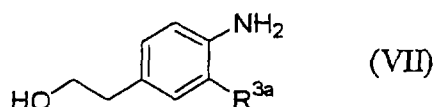
15 (wherein R^2 , R^3 , R^4 , R^5 , R^6 , A and X^1 have the same meanings as defined above), and, when X^1 is a hydroxy group, converting the hydroxy group to a leaving group in the usual way.

Of the compounds represented by the above general formula (III) which are used as starting materials in the above production process,
 20 compounds represented by the general formula:



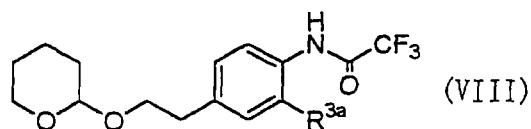
(wherein R^{3a} represents a halogen atom; and R^2 , R^6 , A and X have the same meanings as defined above) can be prepared by subjecting a phenethyl alcohol derivative represented by the general formula:

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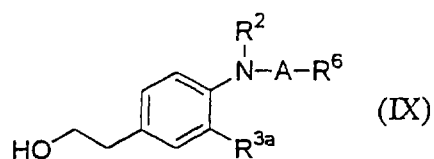
(wherein R^{3a} has the same meaning as defined above) to protection of the amino group and the hydroxy group by a trifluoroacetyl group and a tetrahydropyranyl group respectively in the usual way,

10 subjecting the resulting compound represented by the general formula:



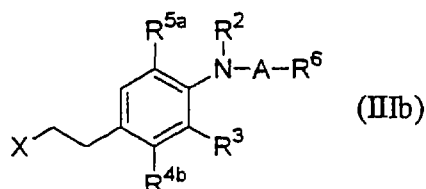
(wherein R^{3a} has the same meaning as defined above) to *N*-alkylation using the alkylating agent represented by the above general formula (V) in the presence of a base such as sodium hydride, removing the protective group of the amino group and the hydroxy group, subjecting the resulting compound to alkylation of the secondary amino group in the usual way as occasion demands to give a compound represented by the general formula:

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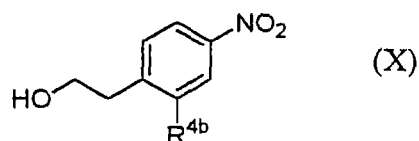


(wherein R^2 , R^{3a} , R^6 and A have the same meanings as defined above) and converting the hydroxy group to a leaving group in the usual way.

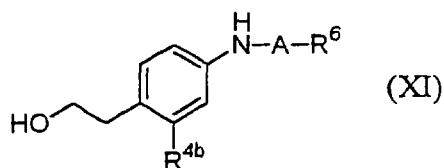
Of the compounds represented by the above general formula (III)
 5 which are used as starting materials in the above production process, compounds represented by the general formula:



(wherein R^{4b} represents a halogen atom; R^{5a} represents a hydrogen atom or a halogen atom; and R^2 , R^3 , R^6 , A and X have the same meanings as
 10 defined above) can be prepared by converting the hydroxy group of a phenethyl alcohol derivative represented by the general formula:



(wherein R^{4b} has the same meaning as defined above) to a leaving group
 15 in the usual way, reducing the nitro group to an amino group in the usual way, subjecting the resulting compound to N-alkylation using the alkylating agent represented by the above general formula (V) in the presence of a base such as potassium carbonate to give a compound represented by the general formula:



(wherein R^{4b} , R^6 , A and X have the same meanings as defined above) and subjecting the resulting compound to halogenation of the benzene ring and/or *N*-alkylation of the secondary amino group in the usual way as occasion demands.

The compounds represented by the above general formulae (IV), (V), (VII) and (X) which are used as starting materials in the above production process can be prepared from a commercially available reagent in the usual way or a method described in a literature (Org. Synth., III, pp.183-184(1955); J. Med. Chem., Vol.15, No.5, pp. 490-493(1972); a published Japanese Patent Application (KOKOKU) No. Sho 47-45747; J. Med. Chem., Vol.28, No.12, pp.1828-1832(1985); Helvetica Chimica Acta, Vol.64, pp.1688-1703(1981) etc.).

In the above production process, the term "protected carboxy group" means an ester group including a straight or branched alkoxy group having 1 to 6 carbon atoms such as a methoxycarbonyl group, an ethoxycarbonyl group, a propoxycarbonyl group and an isopropoxycarbonyl, and an amide group including an amino group which may have one or two alkyl groups having 1 to 6 carbon atoms (e.g., an amino group, a methylamino group, a dimethylamino group) and an alicyclic amino group (e.g., a piperidino group, a morpholino group); the term "leaving group" means a leaving group which is used generally in *N*-alkylation such as a *p*-toluenesulfonyloxy group, a

methanesulfonyloxy group, a chlorine atom, a bromine atom and an iodine atom.

The phenylaminoalkylcarboxylic acid derivatives represented by the above general formula (I) of the present invention can be converted their pharmaceutically acceptable salts in the usual way. Examples of such salts include acid addition salts formed with mineral acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid and phosphoric acid; acid addition salts formed with organic acids such as formic acid, acetic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, propionic acid, citric acid, succinic acid, tartaric acid, fumaric acid, butyric acid, oxalic acid, malonic acid, maleic acid, lactic acid, malic acid, carbonic acid, glutamic acid, aspartic acid; and inorganic base salts such as a sodium salt, a potassium salt and a calcium salt.

The compounds of the present invention obtained by the above production process can be isolated and purified by conventional separation means such as fractional recrystallization, purification using column chromatography and solvent extraction.

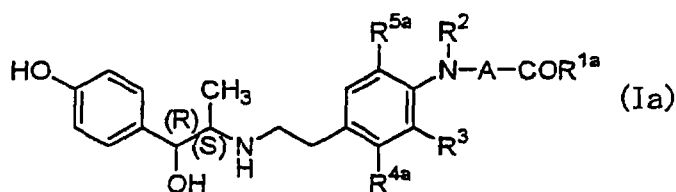
The compounds of the present invention include their solvates with pharmaceutically acceptable solvents such as water and ethanol.

The compounds represented by the above general formula (I) of the present invention and pharmaceutically acceptable salts thereof have excellent β_3 -adrenoceptor stimulating effects and are extremely useful as medicaments such as agents for the prevention or treatment of obesity, hyperglycemia, the diseases caused by intestinal hypermotility, pollakiuria, urinary incontinence,

depression, or the diseases caused by biliary calculi or hypermotility of biliary tract.

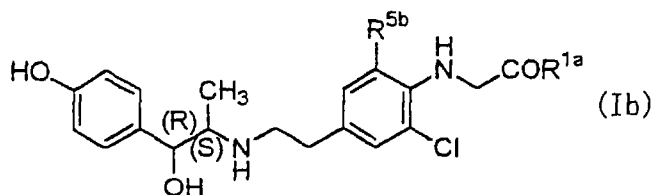
In the compounds represented by the above general formula (I) of the present invention, compounds wherein the substituent R^1 represents a hydroxy group or a lower alkoxy group are preferred and
 5 compounds wherein the substituents R^4 and R^5 independently represent a hydrogen atom or a halogen atom are preferred.

In the compounds represented by the above general formula (I) of the present invention, for example, compounds represented by the
 10 general formula:



(wherein R^{1a} represents a hydroxy group or a lower alkoxy group; R^{4a} and R^{5a} are the same or different and each represents a hydrogen atom or a halogen atom; and R^2 , R^3 , the carbon atom marked with (R) and
 15 the carbon atom marked with (S) have the same meanings as defined above) are preferred because these compounds have potent β_3 -adrenoceptor stimulating effects compared with β_1 and/or β_2 -adrenoceptor stimulating effects thereof and have attenuated side
 20 effects caused by β_1 and/or β_2 -adrenoceptor stimulating effects.

Specially, compounds represented by the general formula:



(wherein R^{5b} represents a hydrogen atom or a chlorine atom; and R^{1a}, the carbon atom marked with (R) and the carbon atom marked with (S) have the same meanings as defined above) are preferred.

5 When the phenylaminoalkylcarboxylic acid derivatives represented by the above general formula (I) and pharmaceutically acceptable salts thereof of the present invention are employed in the practical treatment, they are administered orally or parenterally as powders, granules, fine granules, tablets, capsules, injections,
10 solutions, ointments, suppositories and the like. These pharmaceutical compositions can be formulated in accordance with conventional methods using conventional pharmaceutical carriers, excipients and the like.

 The dosage is appropriately decided depending on the age, sex,
15 body weight, degree of symptoms of each patient to be treated, which is approximately within the range of from 1 to 1,000 mg per day per adult human in the case of oral administration and approximately within the range of from 0.01 to 100 mg per day per adult human in the case of parenteral administration, and the daily dose can be
20 divided into one to several doses per day.

Best Mode for Carrying Out the Invention

The present invention is further illustrated in more detail by way of the following Reference Examples, Examples and Test Examples.

The present invention is not limited thereto.

Reference Example 1

4-(2-Bromoethyl)aniline hydrobromide

- 5 To 4-aminophenethyl alcohol (25g) was added 48% hydrobromic acid (250ml), and the mixture was heated under reflux for 4 hours with stirring. After cooling, collection of the resulting precipitates by filtration gave 4-(2-bromoethyl)aniline hydrobromide (30.3g).
- 10 ¹H-NMR (DMSO-*d*₆) δ ppm: 3.15 (2H, t, *J*=7.0Hz), 3.74 (2H, t, *J*=7.0Hz), 7.25 (2H, d, *J*=8.0Hz), 7.38 (2H, d, *J*=8.0Hz), 9.70 (2H, br)

Reference Example 2

Ethyl *N*-[4-(2-bromoethyl)phenyl]aminoacetate

- 15 To a solution of 4-(2-bromoethyl)aniline hydrobromide (9.15g) in *N,N*-dimethylformamide (65ml) were added potassium carbonate (4.95g) and ethyl bromoacetate (3.97ml), and the mixture was stirred for 36 hours at room temperature. The reaction mixture was poured into ice-water, and collection of the resulting precipitates by
- 20 filtration gave ethyl *N*-[4-(2-bromoethyl)phenyl]aminoacetate (8.39g).
- ¹H-NMR (CDCl₃) δ ppm: 1.29 (3H, t, *J*=7.1Hz), 3.04 (2H, t, *J*=7.8Hz), 3.49 (2H, t, *J*=7.8Hz), 3.88 (2H, s), 4.15-4.35 (2H, m), 6.56 (2H, d, *J*=8.5Hz), 7.02 (2H, d, *J*=8.5Hz)

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Reference Example 3

2-[[4-(2-Bromoethyl)phenyl]amino]-*N,N*-dimethylacetamide

2-[[4-(2-Bromoethyl)phenyl]amino]-*N,N*-dimethylacetamide was prepared according to a similar manner to that described in Reference Example 2 using 2-bromo-*N,N*-dimethylacetamide.

¹H-NMR (CDCl₃) δ ppm: 2.95-3.10 (8H, m), 3.50 (2H, t, *J*=7.8Hz), 3.84
5 (2H, s), 4.87 (1H, br s), 6.58 (2H, d, *J*=8.5Hz), 7.03 (2H, d, *J*=8.5Hz)

Reference Example 4

Ethyl *N*-[4-(2-hydroxyethyl)phenyl]aminoacetate

To a solution of 4-aminophenethyl alcohol (25g) in *N,N*-
10 dimethylformamide (500ml) were added potassium carbonate (30g) and ethyl bromoacetate (24ml), and the mixture was stirred for 16 hours at room temperature. Diethylamine (38ml) was added to the reaction mixture, and the resulting mixture was stirred for 1 hour. The insoluble material was filtered off and the filtrate was concentrated
15 *in vacuo*. To the residue was added diethyl ether, and the resulting insoluble material was filtered off. The filtrate was washed with 10% aqueous citric acid solution, a saturated aqueous sodium bicarbonate solution and brine subsequently, and dried over anhydrous magnesium sulfate. Removal of the solvent *in vacuo* gave ethyl
20 *N*-[4-(2-hydroxyethyl)phenyl]aminoacetate (35.5g).

¹H-NMR (CDCl₃) δ ppm: 1.20-1.40 (4H, m), 2.76 (2H, t, *J*=6.5Hz),
3.75-3.85 (2H, m), 3.88 (2H, d, *J*=4.4Hz), 4.15-4.30 (3H, m), 6.58
(2H, d, *J*=8.3Hz), 7.05 (2H, d, *J*=8.3Hz)

25 Reference Example 5

Ethyl 4-[[4-(2-hydroxyethyl)phenyl]amino]butyrate

Ethyl 4-[[4-(2-hydroxyethyl)phenyl]amino]butyrate was

prepared according to a similar manner to that described in Reference Example 4 using ethyl 4-bromobutyrate.

¹H-NMR (CDCl₃) δppm: 1.25 (3H, t, J=7.1Hz), 1.46 (1H, br), 1.85-2.00 (2H, m), 2.42 (2H, t, J=7.2Hz), 2.75 (2H, t, J=6.5Hz), 3.16 (2H, t, J=6.9Hz), 3.65 (1H, br), 3.70-3.85 (2H, m), 4.14 (2H, q, J=7.1Hz), 6.57 (2H, d, J=8.4Hz), 7.03 (2H, d, J=8.4Hz)

Reference Example 6

Ethyl N-[2,6-dibromo-4-(2-bromoethyl)phenyl]aminoacetate

To a stirred solution of ethyl N-[4-(2-bromoethyl)-phenyl]aminoacetate (516mg) in acetonitrile (3.6ml) were added concentrated hydrochloric acid (150μl) and N-bromosuccinimide (641mg) under ice-cooling, and the mixture was stirred for 1 hour. Ethanol (3.6ml) was added to the reaction mixture, and the mixture was stirred for 30 minutes under ice-cooling. 0.4M Aqueous sodium thiosulfate solution (9.00ml) was added to the reaction mixture, and the mixture was stirred for 1 hour under ice-cooling. The reaction mixture was diluted with water and extracted with ethyl acetate. The extract was washed with brine and dried over anhydrous magnesium sulfate, and the solvent was removed *in vacuo*. Purification of the residue by medium pressure liquid column chromatography on silica gel (eluent: hexane/ethyl acetate = 6/1) gave ethyl N-[2,6-dibromo-4-(2-bromoethyl)phenyl]aminoacetate (842mg).

¹H-NMR (CDCl₃) δppm: 1.29 (3H, t, J=7.1Hz), 3.03 (2H, t, J=7.4Hz), 3.50 (2H, t, J=7.4Hz), 4.12 (2H, d, J=5.7Hz), 4.24 (2H, q, J=7.1Hz), 4.78 (1H, t, J=5.7Hz), 7.32 (2H, s)

Reference Example 7

Ethyl N-[2-bromo-4-(2-bromoethyl)phenyl]aminoacetate

Ethyl N-[2-bromo-4-(2-bromoethyl)phenyl]aminoacetate was prepared according to a similar manner to that described in Reference
5 Example 6 using 1 molar equivalent of both N-bromosuccinimide and 0.4M aqueous sodium thiosulfate solution to ethyl N-[4-(2-bromoethyl)phenyl]aminoacetate.

¹H-NMR (CDCl₃) δppm: 1.30 (3H, t, J=7.1Hz), 3.03 (2H, t, J=7.6Hz), 3.49 (2H, t, J=7.6Hz), 3.93 (2H, s), 4.26 (2H, q, J=7.1Hz), 4.90 (1H,
10 br s), 6.46 (1H, d, J=8.2Hz), 7.03 (1H, dd, J=8.2, 2.0Hz), 7.31 (1H, d, J=2.0Hz)

Reference Example 8

Ethyl N-[4-(2-bromoethyl)-2-iodophenyl]aminoacetate

15 To a stirred solution of ethyl N-[4-(2-bromoethyl)-phenyl]aminoacetate (580mg) in acetonitrile (4.05ml) were added concentrated hydrochloric acid (169μl) and N-iodosuccinimide (912mg) under ice-cooling, and the mixture was stirred for 1 hour. Ethanol (4.0ml) was added to the reaction mixture, and the mixture
20 was stirred for 45 minutes under ice-cooling. A solution of sodium thiosulfate (640mg) in water (20ml) was added to the reaction mixture, and the mixture was stirred for 1 hour under ice-cooling. The reaction mixture was diluted with water and extracted with ethyl acetate. The extract was washed with brine and dried over anhydrous
25 magnesium sulfate, and the solvent was removed in vacuo. Purification of the residue by medium pressure liquid column chromatography on silica gel (eluent: hexane/ethyl acetate = 9/1)

gave ethyl *N*-[4-(2-bromoethyl)-2-iodophenyl]aminoacetate (449mg).

¹H-NMR (CDCl₃) δ ppm: 1.31 (3H, t, *J*=7.1Hz), 3.01 (2H, t, *J*=7.6Hz),
3.48 (2H, t, *J*=7.6Hz), 3.92 (2H, d, *J*=5.3Hz), 4.26 (2H, q, *J*=7.1Hz),
4.75-4.85 (1H, m), 6.39 (1H, d, *J*=8.2Hz), 7.06 (1H, dd, *J*=8.2, 1.9Hz),
5 7.54 (1H, d, *J*=1.9Hz)

Reference Example 9

2-[[4-(2-Bromoethyl)-2,6-dichlorophenyl]amino]-*N,N*-dimethyl- acetamide

10 To a stirred solution of 2-[[4-(2-bromoethyl)phenyl]-
amino]-*N,N*-dimethylacetamide (1.13g) in acetonitrile (11.3ml) were
added concentrated hydrochloric acid (331μl) and *N*-chloro-
succinimide (1.06g) under ice-cooling, and the mixture was stirred
for 1 hour. A solution of sodium thiosulfate (1.26g) in water (20ml)
15 was added to the reaction mixture, and the resulting mixture was
stirred for 30 minutes under ice-cooling. The reaction mixture was
diluted with water and extracted with ethyl acetate. The extract
was washed with brine and dried over anhydrous magnesium sulfate,
and the solvent was removed *in vacuo*. Purification of the residue
20 by medium pressure liquid column chromatography on silica gel
(eluent: hexane/ethyl acetate = 2/1) gave 2-[[4-(2-bromoethyl)-
2,6-dichlorophenyl]amino]-*N,N*-dimethylacetamide (795mg).
¹H-NMR (CDCl₃) δ ppm: 2.95-3.05 (8H, m), 3.49 (2H, t, *J*=7.4Hz), 4.14
(2H, d, *J*=4.4Hz), 5.65-5.75 (1H, m), 7.08 (2H, s)

25

Reference Example 10

Ethyl *N*-[2,6-dichloro-4-(2-hydroxyethyl)phenyl]aminoacetate

To a stirred solution of ethyl *N*-[4-(2-hydroxyethyl)-phenyl]aminoacetate (1.0g) in dichloromethane (20ml) were added concentrated hydrochloric acid (373μl) and ethanol (3.0ml) at room temperature, and a solution of *tert*-butyl hypochlorite (1.04ml) in dichloromethane (6ml) was added dropwise over 10 minutes period under ice-cooling with stirring. The mixture was stirred for 10 minutes, and the reaction mixture was concentrated *in vacuo*. A saturated aqueous sodium bicarbonate solution was added to the residue, and the resulting mixture was extracted with ethyl acetate. The extract was washed with brine and dried over anhydrous magnesium sulfate, and the solvent was removed *in vacuo*. Purification of the residue by medium pressure liquid column chromatography on silica gel (eluent: hexane/ethyl acetate = 3/1) gave ethyl *N*-[2,6-dichloro-4-(2-hydroxyethyl)phenyl]aminoacetate (695mg).

¹H-NMR (CDCl₃) δ ppm: 1.28 (3H, t, *J*=7.1Hz), 2.74 (2H, t, *J*=6.4Hz), 3.82 (2H, t, *J*=6.4Hz), 4.14 (2H, s), 4.23 (2H, q, *J*=7.1Hz), 7.12 (2H, s)

Reference Example 11

Ethyl 4-[[2,6-dichloro-4-(2-hydroxyethyl)phenyl]amino]butyrate

Ethyl 4-[[2,6-dichloro-4-(2-hydroxyethyl)phenyl]amino]-butyrate was prepared according to a similar manner to that described in Reference Example 10 using ethyl 4-[[4-(2-hydroxyethyl)-phenyl]amino]butyrate.

¹H-NMR (CDCl₃) δ ppm: 1.26 (3H, t, *J*=7.1Hz), 1.44 (1H, br), 1.85-1.95 (2H, m), 2.43 (2H, t, *J*=7.4Hz), 2.74 (2H, t, *J*=6.4Hz), 3.33 (2H, t, *J*=7.1Hz), 3.75-3.95 (3H, m), 4.14 (2H, q, *J*=7.1Hz), 7.12 (2H, s)

Reference Example 12

Ethyl N-[4-(2-hydroxyethyl)phenyl]-N-methylaminoacetate

To a solution of ethyl N-[4-(2-hydroxyethyl)phenyl]-
5 aminoacetate (1.15g) in *N,N*-dimethylformamide (10ml) were added
potassium carbonate (1.17g) and methyl iodide (420 μ l), and the
mixture was stirred for 9 hours at room temperature. The reaction
mixture was poured into water and extracted with ethyl acetate. The
extract was washed with brine and dried over anhydrous magnesium
10 sulfate, and the solvent was removed *in vacuo*. Purification of the
residue by flash column chromatography on silica gel (eluent:
dichloromethane/diethyl ether = 10/1) gave ethyl N-[4-(2-
hydroxyethyl)phenyl]-N-methylaminoacetate (820 mg).

¹H-NMR (CDCl₃) δ ppm: 1.25 (3H, t, *J*=7.1Hz), 1.51 (1H, br), 2.77 (2H,
15 t, *J*=6.5Hz), 3.05 (3H, s), 3.80 (2H, t, *J*=6.5Hz), 4.04 (2H, s), 4.18
(2H, q, *J*=7.1Hz), 6.65 (2H, d, *J*=8.8Hz), 7.09 (2H, d, *J*=8.8Hz)

Reference Example 13

Ethyl N-[2,6-dichloro-4-(2-hydroxyethyl)phenyl]-N-methylamino-
20 acetate

Ethyl N-[2,6-dichloro-4-(2-hydroxyethyl)phenyl]-N-methyl-
aminoacetate was prepared according to a similar manner to that
described in Reference Example 12 using the corresponding ethyl
aminoacetate derivative.

25 ¹H-NMR (CDCl₃) δ ppm: 1.26 (3H, t, *J*=7.1Hz), 1.41 (1H, br), 2.70-2.80
(2H, m), 2.94 (3H, s), 3.80-3.90 (4H, m), 4.17 (2H, q, *J*=7.1Hz),
7.10-7.20 (2H, m)

Reference Example 14

Ethyl N-[2-chloro-4-(2-hydroxyethyl)phenyl]aminoacetate

To a stirred solution of 4-amino-3-chlorophenethyl alcohol
5 (950mg) and triethylamine (2.3ml) in tetrahydrofuran (5.5ml) was
added a solution of trifluoroacetic anhydride (1.6ml) in
tetrahydrofuran (2.0ml) under ice-cooling, and the mixture was
stirred for 10 minutes. To the reaction mixture was added methanol
(2.0ml), and the resulting mixture was stirred for 5 minutes. 1N
10 Hydrochloric acid (10ml) was added to the stirred mixture, and the
resulting mixture was extracted with ethyl acetate. The extract was
washed with a saturated aqueous sodium bicarbonate solution and brine
subsequently, and dried over anhydrous magnesium sulfate. Removal
of the solvent *in vacuo* gave 2'-chloro-4'-(2-hydroxyethyl)-
15 2,2,2-trifluoroacetanilide (1.4g).

¹H-NMR (CDCl₃) δ ppm: 2.86 (2H, t, J=6.4Hz), 3.87 (2H, t, J=6.4Hz),
7.22 (1H, dd, J=8.4, 2.0Hz), 7.35 (1H, d, J=2.0Hz), 8.24 (1H, d,
J=8.4Hz), 8.36 (1H, br)

20 To a solution of 2'-chloro-4'-(2-hydroxyethyl)-2,2,2-
trifluoroacetanilide (1.4g) and 3,4-dihydro-2H-pyran (1.4ml) in
dichloromethane (15ml) was added pyridinium *p*-toluenesulfonate
(14mg), and the mixture was heated under reflux for 1 hour with
stirring. After concentration of the reaction mixture *in vacuo*, the
25 residue was dissolved in ethyl acetate. The solution was washed with
a saturated aqueous sodium bicarbonate solution and brine, and dried
over anhydrous magnesium sulfate, and the solvent was removed *in vacuo*.

Purification of the residue by medium pressure liquid column chromatography on silica gel (eluent: hexane/diethyl ether = 3/1) gave 2'-chloro-4'-[2-((*RS*)-tetrahydropyran-2-yloxy)ethyl]-2,2,2-trifluoroacetanilide (1.4 g).

5 $^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.40-1.90 (6H, m), 2.88 (2H, t, $J=6.7\text{Hz}$), 3.40-3.50 (1H, m), 3.60 (1H, dt, $J=9.8, 6.7\text{Hz}$), 3.65-3.80 (1H, m), 3.94 (1H, dt, $J=9.8, 6.7\text{Hz}$), 4.55-4.60 (1H, m), 7.23 (1H, dd, $J=8.4, 1.9\text{Hz}$), 7.36 (1H, d, $J=1.9\text{Hz}$), 8.22 (1H, d, $J=8.4\text{Hz}$), 8.36 (1H, br)

10 To a stirred solution of 2'-chloro-4'-[2-((*RS*)-tetrahydropyran-2-yloxy)ethyl]-2,2,2-trifluoroacetanilide (352mg) in *N,N*-dimethylformamide (3ml) was added sodium hydride (48mg) under ice-cooling, and the mixture was stirred for 30 minutes at room temperature. Ethyl bromoacetate (133 μ l) was added to the reaction
15 mixture, and the mixture was stirred for 16 hours. Ethyl acetate was added to the reaction mixture, and the resulting mixture was washed with brine and dried over anhydrous magnesium sulfate. After the solvent was removed *in vacuo*, purification of the residue by
20 medium pressure liquid column chromatography on silica gel (eluent: hexane/diethyl ether = 2/1) gave ethyl *N*-[2-chloro-4-[2-((*RS*)-tetrahydropyran-2-yloxy)ethyl]phenyl]-*N*-trifluoroacetyl-amino-acetate (250mg).

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.28 (3H, t, $J=7.1\text{Hz}$), 1.40-1.85 (6H, m), 2.91 (2H, t, $J=6.6\text{Hz}$), 3.40-3.50 (1H, m), 3.55-3.70 (2H, m), 3.72 (1H, d, $J=17.2\text{Hz}$), 3.90-4.00 (1H, m), 4.15-4.30 (2H, m), 4.55-4.65 (1H, m), 4.98 (1H, d, $J=17.2\text{Hz}$), 7.15-7.25 (1H, m), 7.35-7.45 (1H, m), 7.56 (1H, d, $J=8.1\text{Hz}$)

A solution of ethyl *N*-[2-chloro-4-[2-((*RS*)-tetrahydro-
pyran-2-yloxy)ethyl]phenyl]-*N*-trifluoroacetylaminacetate (830mg)
and *p*-toluenesulfonic acid monohydrate (80mg) in ethanol (9.0ml) was
5 stirred for 2 hours at 40°C. To the reaction mixture was added
potassium carbonate (314mg), and the resulting mixture was heated
under reflux for 5 hours with stirring. The insoluble material was
filtered off, the filtrate was concentrated *in vacuo*, and the residue
was dissolved in ethyl acetate. The solution was washed with a
10 saturated aqueous sodium bicarbonate solution and brine, and dried
over anhydrous magnesium sulfate, and the solvent was removed *in vacuo*.
Purification of the residue by medium pressure liquid column
chromatography on silica gel (eluent: hexane/ethyl acetate = 2/1)
gave ethyl *N*-[2-chloro-4-(2-hydroxyethyl)phenyl]aminoacetate
15 (315mg).

¹H-NMR (CDCl₃) δ ppm: 1.30 (3H, t, *J*=7.1Hz), 1.37 (1H, br s), 2.74 (2H,
t, *J*=6.5Hz), 3.75-3.85 (2H, m), 3.93 (2H, d, *J*=5.5Hz), 4.26 (2H, q,
J=7.1Hz), 4.80-4.90 (1H, m), 6.49 (1H, d, *J*=8.2Hz), 7.00 (1H, dd,
J=8.2, 2.0Hz), 7.17 (1H, d, *J*=2.0Hz)

20

Reference Example 15

Ethyl *N*-[2-chloro-4-(2-hydroxyethyl)phenyl]-*N*-methylaminoacetate

Ethyl *N*-[2-chloro-4-(2-hydroxyethyl)phenyl]-*N*-methyl-
aminoacetate was prepared according to a similar manner to that
25 described in Reference Example 12 using the corresponding ethyl
aminoacetate derivative.

¹H-NMR (CDCl₃) δ ppm: 1.24 (3H, t, *J*=7.1Hz), 1.35-1.50 (1H, m), 2.78

(2H, t, $J=6.5\text{Hz}$), 2.97 (3H, s), 3.75-3.90 (2H, m), 3.96 (2H, s), 4.15 (2H, q, $J=7.1\text{Hz}$), 7.07 (1H, dd, $J=8.2, 1.9\text{Hz}$), 7.14 (1H, d, $J=8.2\text{Hz}$), 7.21 (1H, d, $J=1.9\text{Hz}$)

5 Reference Example 16

Ethyl N-[4-(2-bromoethyl)-2,6-dichlorophenyl]aminoacetate

To a stirred solution of ethyl N-[2,6-dichloro-4-(2-hydroxyethyl)phenyl]aminoacetate (650mg) and triphenylphosphine (700mg) in dichloromethane (10ml) was added carbon tetrabromide
10 (886mg) under ice-cooling, and the mixture was stirred for 1 hour. Rough purification of the reaction mixture by flash column chromatography on silica gel (eluent: hexane/ethyl acetate = 3/1) and further purification of the fraction by medium pressure liquid column chromatography on silica gel (eluent: hexane/dichloromethane
15 = 1/1) gave ethyl N-[4-(2-bromoethyl)-2,6-dichlorophenyl]-aminoacetate (708mg).

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.28 (3H, t, $J=7.2\text{Hz}$), 3.03 (2H, t, $J=7.4\text{Hz}$), 3.50 (2H, t, $J=7.4\text{Hz}$), 4.16 (2H, d, $J=5.7\text{Hz}$), 4.23 (2H, q, $J=7.2\text{Hz}$), 4.80-4.90 (1H, m), 7.10 (2H, s)

20

Reference Example 17

The following compounds were prepared according to a similar manner to that described in Reference Example 16 using the corresponding hydroxyethyl derivative.

25

Ethyl N-[4-(2-bromoethyl)phenyl]aminoacetate

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.29 (3H, t, $J=7.1\text{Hz}$), 3.04 (2H, t, $J=7.8\text{Hz}$),

3.50 (2H, t, $J=7.8\text{Hz}$), 3.88 (2H, s), 4.24 (2H, q, $J=7.1\text{Hz}$), 6.56 (2H, d, $J=8.5\text{Hz}$), 7.02 (2H, d, $J=8.5\text{Hz}$)

Ethyl N-[4-(2-bromoethyl)phenyl]-N-methylaminoacetate

5 $^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.24 (3H, t, $J=7.1\text{Hz}$), 3.00-3.10 (5H, m), 3.50 (2H, t, $J=7.9\text{Hz}$), 4.04 (2H, s), 4.17 (2H, q, $J=7.1\text{Hz}$), 6.64 (2H, d, $J=8.8\text{Hz}$), 7.07 (2H, d, $J=8.8\text{Hz}$)

Ethyl N-[4-(2-bromoethyl)-2-chlorophenyl]-N-methylaminoacetate

10 $^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.30 (3H, t, $J=7.1\text{Hz}$), 3.03 (2H, t, $J=7.6\text{Hz}$), 3.49 (2H, t, $J=7.6\text{Hz}$), 3.93 (2H, d, $J=5.5\text{Hz}$), 4.26 (2H, q, $J=7.1\text{Hz}$), 4.85-4.95 (1H, m), 6.49 (1H, d, $J=8.3\text{Hz}$), 6.98 (1H, dd, $J=8.3, 2.0\text{Hz}$), 7.14 (1H, d, $J=2.0\text{Hz}$)

15 Ethyl N-[4-(2-bromoethyl)-2-chlorophenyl]-N-methylaminoacetate

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.24 (3H, t, $J=7.1\text{Hz}$), 2.97 (3H, s), 3.07 (2H, t, $J=7.6\text{Hz}$), 3.52 (2H, t, $J=7.6\text{Hz}$), 3.97 (2H, s), 4.15 (2H, q, $J=7.1\text{Hz}$), 7.04 (1H, dd, $J=8.2, 2.0\text{Hz}$), 7.13 (1H, d, $J=8.2\text{Hz}$), 7.18 (1H, d, $J=2.0\text{Hz}$)

20

Ethyl N-[4-(2-bromoethyl)-2,6-dichlorophenyl]-N-methylaminoacetate

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.26 (3H, t, $J=7.1\text{Hz}$), 2.95 (3H, s), 3.06 (2H, t, $J=7.3\text{Hz}$), 3.52 (2H, t, $J=7.3\text{Hz}$), 3.88 (2H, s), 4.17 (2H, q, $J=7.1\text{Hz}$),
25 7.14 (2H, s)

Ethyl 4-[[4-(2-bromoethyl)-2,6-dichlorophenyl]aminol]butyrate

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.26 (3H, t, $J=7.1\text{Hz}$), 1.85-1.95 (2H, m), 2.43 (2H, t, $J=7.4\text{Hz}$), 3.02 (2H, t, $J=7.4\text{Hz}$), 3.30-3.40 (2H, m), 3.50 (2H, t, $J=7.4\text{Hz}$), 3.93 (1H, br), 4.14 (2H, q, $J=7.1\text{Hz}$), 7.09 (2H, s)

5 Reference Example 18

Ethyl *N*-[4-(2-bromoethyl)-3-chlorophenyl]aminoacetate

To a stirred solution of 2-chloro-4-nitrophenethyl alcohol (1.17g) in dichloromethane (15ml) were added carbon tetrabromide (2.12g) and triphenylphosphine (1.67g) at room temperature, and the
10 mixture was stirred for 15 minutes. The solvent was removed *in vacuo*, and purification of the residue by flash column chromatography on silica gel (eluent: hexane/ethyl acetate = 9/1) gave 1-(2-bromoethyl)-2-chloro-4-nitrobenzene (1.30 g).

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 3.40 (2H, t, $J=7.0\text{Hz}$), 3.64 (2H, t, $J=7.0\text{Hz}$),
15 7.48 (1H, d, $J=8.4\text{Hz}$), 8.11 (1H, dd, $J=8.4, 2.2\text{Hz}$), 8.27 (1H, d, $J=2.2\text{Hz}$)

To a solution of 1-(2-bromoethyl)-2-chloro-4-nitrobenzene (1.24g) in methanol (20ml) were added 2N hydrochloric acid (7.0ml)
20 and iron powder (785mg), and the mixture was heated under reflux for 50 minutes with stirring. After the insoluble material was filtered off, the filtrate was alkalized with 2N aqueous sodium hydroxide solution and extracted with dichloromethane. The extract was washed with brine and dried over anhydrous magnesium sulfate, and the solvent
25 was removed *in vacuo*. The residue was dissolved in *N,N*-dimethylformamide (10ml), and potassium carbonate (647mg) and ethyl bromoacetate (520 μl) were added to the solution. After the mixture

was stirred for 14 hours at room temperature, water was added to the reaction mixture, and the resulting mixture was extracted with a mixed solution of diethyl ether and ethyl acetate (3/1). The extract was washed with water and brine subsequently, and dried over anhydrous magnesium sulfate, and the solvent was removed *in vacuo*.

Purification of the residue by flash column chromatography on silica gel (eluent: hexane/ethyl acetate = 4/1) gave ethyl *N*-[4-(2-bromoethyl)-3-chlorophenyl]aminoacetate (426mg).

¹H-NMR (CDCl₃) δ ppm: 1.30 (3H, t, *J*=7.1Hz), 3.00-3.20 (2H, m), 3.45-3.70 (2H, m), 3.86 (2H, d, *J*=5.3Hz), 4.25 (2H, q, *J*=7.1Hz), 4.34 (1H, br), 6.40-6.50 (1H, m), 6.55-6.65 (1H, m), 7.00-7.10 (1H, m)

Reference Example 19

Ethyl *N*-[4-(2-bromoethyl)-2,3-dichlorophenyl]aminoacetate

15 Ethyl *N*-[4-(2-bromoethyl)-2,5-dichlorophenyl]aminoacetate

To a stirred solution of ethyl *N*-[4-(2-bromoethyl)-3-chlorophenyl]aminoacetate (79mg) in dichloromethane (2ml) was added *tert*-butyl hypochlorite (31μl) under ice-cooling, and the mixture was stirred for 6 hours at room temperature. The solvent was removed *in vacuo*, and purification of the residue by flash column chromatography on silica gel (eluent: hexane/ethyl acetate = 15/1) gave ethyl *N*-[4-(2-bromoethyl)-2,3-dichlorophenyl]aminoacetate (31 mg) as a high-polar regioisomer and ethyl *N*-[4-(2-bromoethyl)-2,5-dichlorophenyl]aminoacetate (34mg) as a low-polar regioisomer.

25

Ethyl *N*-[4-(2-bromoethyl)-2,3-dichlorophenyl]aminoacetate

¹H-NMR (CDCl₃) δ ppm: 1.30 (3H, t, *J*=7.1Hz), 3.05-3.25 (2H, m),

3.50-3.70 (2H, m), 3.94 (2H, d, $J=5.4\text{Hz}$), 4.26 (2H, q, $J=7.1\text{Hz}$), 5.04 (1H, br), 6.41 (1H, d, $J=8.4\text{Hz}$), 7.05 (1H, d, $J=8.4\text{Hz}$)

Ethyl N-[4-(2-bromoethyl)-2,5-dichlorophenyl]aminoacetate

5 $^1\text{H-NMR}(\text{CDCl}_3)$ δ ppm: 1.31 (3H, t, $J=7.1\text{Hz}$), 3.00-3.20 (2H, m), 3.45-3.70 (2H, m), 3.90 (2H, d, $J=5.3\text{Hz}$), 4.27 (2H, q, $J=7.1\text{Hz}$), 4.95 (1H, br), 6.53 (1H, s), 7.17 (1H, s)

Reference Example 20

10 Ethyl N-[4-(2-bromoethyl)-2,3,6-trichlorophenyl]aminoacetate

To a stirred solution of ethyl N-[4-(2-bromoethyl)-3-chlorophenyl]aminoacetate (513mg) in dichloromethane (4ml) was added *tert*-butyl hypochlorite (370 μ l) under ice-cooling, and the mixture was stirred for 10 minutes. The solvent was removed *in vacuo*,
15 and purification of the residue by flash column chromatography on silica gel (eluent: hexane/ethyl acetate = 10/1) gave ethyl N-[4-(2-bromoethyl)-2,3,6-trichlorophenyl]aminoacetate (453mg).
 $^1\text{H-NMR}(\text{CDCl}_3)$ δ ppm: 1.29 (3H, t, $J=7.1\text{Hz}$), 3.21 (2H, t, $J=7.3\text{Hz}$), 3.54 (2H, t, $J=7.3\text{Hz}$), 4.17 (2H, s), 4.24 (2H, q, $J=7.1\text{Hz}$), 4.98 (1H, br),
20 7.17 (1H, s)

Reference Example 21

Ethyl N-[4-(2-bromoethyl)-2,5-dimethylphenyl]aminoacetate

To a stirred solution of 2,5-dimethylaniline (5.30g) and
25 4-dimethylaminopyridine (6.41g) in dichloromethane (90ml) was added acetic anhydride (4.13ml) under ice-cooling, and the mixture was stirred for 4 hours. The reaction mixture was washed with 1N

hydrochloric acid and a saturated aqueous sodium bicarbonate solution subsequently, and dried over anhydrous magnesium sulfate. Removal of the solvent *in vacuo* gave 2',5'-dimethylacetanilide (6.09g).

¹H-NMR (CDCl₃) δppm: 2.20 (3H, s), 2.21 (3H, s), 2.31 (3H, s),
5 6.80-7.00 (2H, m), 7.06 (1H, d, J=7.7Hz), 7.59 (1H, s)

To a stirred suspension of aluminum chloride (13.4g) in carbon disulfide (68ml) was added bromoacetyl bromide (8.8ml) under ice-cooling, and the mixture was stirred for 30 minutes. 2',5'-
10 Dimethylacetanilide (5.57g) was added to the stirred mixture, and the mixture was heated under reflux for 12 hours. After cooling, the reaction mixture was poured into ice-water, and the resulting precipitate were collected by filtration and washed with water. The cake was dissolved in ethyl acetate, and the solution was dried over
15 anhydrous magnesium sulfate. After removal of the solvent, the residue was washed with diethyl ether to give 4'-(2-bromoacetyl)-2',5'-dimethylacetanilide (5.65g).

¹H-NMR (CDCl₃) δppm: 2.24 (3H, s), 2.29 (3H, s), 2.52 (3H, s), 4.38
(2H, s), 7.03 (1H, br), 7.53 (1H, s), 7.98 (1H, br)

20

To a stirred solution of 4'-(2-bromoacetyl)-2',5'-dimethylacetanilide (4.57g) in ethanol (80ml) was added sodium borohydride (608mg) under ice-cooling, and the mixture was stirred for 1 hour. Acetic acid (3.7ml) and water (200ml) were added to the
25 reaction mixture, and the resulting mixture was extracted with ethyl acetate. The extract was washed with water and brine, and dried over anhydrous magnesium sulfate, and the solvent was removed *in vacuo*.

The residue was dissolved in tetrahydrofuran (80ml), and 5N aqueous sodium hydroxide solution (6.4ml) was added to the solution under ice-cooling with stirring. The mixture was stirred for 30 minutes at room temperature, water was added to the reaction mixture, and the resulting mixture was extracted with ethyl acetate. The extract was washed with water and dried over anhydrous magnesium sulfate, and the solvent was removed *in vacuo*. To the residue was added diethyl ether, and collection of the insoluble material by filtration gave 2',5'-dimethyl-4'-oxiranylacetanilide (1.72g).

¹H-NMR (CDCl₃) δ ppm: 2.20 (6H, s), 2.37 (3H, s), 2.60-2.70 (1H, m), 3.10-3.20 (1H, m), 3.90-4.00 (1H, m), 6.90 (1H, br), 7.00 (1H, s), 7.61 (1H, s)

2',5'-Dimethyl-4'-oxiranylacetanilide (1.61g) and 10% palladium carbon (13mg) was suspended in ethanol (90ml), and the mixture was stirred for 2.5 hours at room temperature under a hydrogen atmosphere. The insoluble material was filtered off, and the filtrate was concentrated *in vacuo*. 6N Hydrochloric acid (15ml) was added to the residue, and the mixture was heated under reflux for 2 hours. After cooling, water was added to the reaction mixture, and the mixture was washed with ethyl acetate. 5N Aqueous sodium hydroxide solution (20ml) was added to the mixture and the resulting mixture was extracted with ethyl acetate. The extract was washed with brine and dried over anhydrous magnesium sulfate, and the solvent was removed *in vacuo*. The residue was dissolved in 48% hydrobromic acid (10ml), and the solution was stirred for 3.5 hours at 120°C. The reaction mixture was poured into a saturated aqueous sodium

bicarbonate solution under ice-cooling with stirring, and the resulting mixture was extracted with ethyl acetate. The extract was washed with brine and dried over anhydrous magnesium sulfate, and the solvent was removed *in vacuo*. After the residue was dissolved
5 in *N,N*-dimethylformamide (35ml), potassium carbonate (1.61g) and ethyl bromoacetate (785 μ l) were added to the solution at room temperature with stirring. After the mixture was stirred for 15.5 hours, water was added to the reaction mixture, and the resulting mixture was extracted with ethyl acetate. The extract was washed
10 with water and dried over anhydrous magnesium sulfate, and the solvent was removed *in vacuo*. Purification of the residue by flash column chromatography on silica gel (eluent: hexane/ethyl acetate = 10/1) gave ethyl *N*-[4-(2-bromoethyl)-2,5-dimethylphenyl]aminoacetate (592mg).

15 $^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.31 (3H, t, $J=7.1\text{Hz}$), 2.16 (3H, s), 2.26 (3H, s), 3.00-3.10 (2H, m), 3.40-3.50 (2H, m), 3.91 (2H, d, $J=5.2\text{Hz}$), 4.05-4.15 (1H, m), 4.26 (2H, q, $J=7.1\text{Hz}$), 6.28 (1H, s), 6.85 (1H, s)

20 Example 1

Ethyl *N*-[2,6-dichloro-4-[2-[[[(1*S*,2*R*)-2-hydroxy-2-(4-hydroxy-phenyl)]-1-methylethyl]amino]ethyl]phenyl]aminoacetate (Compound 1)

To a solution of (1*R*,2*S*)-2-amino-1-(4-hydroxyphenyl)-
25 propan-1-ol (495mg) and ethyl *N*-[4-(2-bromoethyl)-2,6-dichloro-phenyl]aminoacetate (700mg) in *N,N*-dimethylformamide (6ml) was added *N,N*-diisopropylethylamine (343 μ l), and the mixture was stirred

for 7 hours at 70°C. The reaction mixture was concentrated *in vacuo*, and purification of the residue by medium pressure liquid column chromatography on aminopropyl silica gel (eluent: dichloromethane/ethanol = 20/1) gave ethyl *N*-[2,6-dichloro-4-[2-
 5 [[(1*S*,2*R*)-2-hydroxy-2-(4-hydroxyphenyl)-1-methylethyl]amino]-ethyl]phenyl]aminoacetate (510mg).

¹H-NMR (CDCl₃) δ ppm: 0.95 (3H, d, *J*=6.4Hz), 1.30 (3H, t, *J*=7.2Hz), 2.55-3.05 (5H, m), 4.16 (2H, d, *J*=6.0Hz), 4.25 (2H, q, *J*=7.2Hz), 4.51 (1H, d, *J*=5.3Hz), 4.78 (1H, t, *J*=6.0Hz), 6.75 (2H, d, *J*=8.5Hz), 7.00
 10 (2H, s), 7.10 (2H, d, *J*=8.5Hz)

Example 2

Ethyl *N*-[2,6-dichloro-4-[2-[[[(1*S*,2*R*)-2-hydroxy-2-(4-hydroxyphenyl)-1-methylethyl]amino]ethyl]phenyl]aminoacetate
 15 hydrochloride (Compound 2)

To a stirred solution of ethyl *N*-[2,6-dichloro-4-[2-[[[(1*S*,2*R*)-2-hydroxy-2-(4-hydroxyphenyl)-1-methylethyl]amino]-ethyl]phenyl]aminoacetate (87ml) in ethyl acetate (2.0ml) was added 2.6 M hydrogen chloride diethyl ether solution (2.0ml) at room
 20 temperature. Collection of the resulting precipitates by filtration gave ethyl *N*-[2,6-dichloro-4-[2-[[[(1*S*,2*R*)-2-hydroxy-2-(4-hydroxyphenyl)-1-methylethyl]amino]ethyl]phenyl]aminoacetate hydrochloride (81mg).

¹H-NMR (DMSO-*d*₆) δ ppm: 0.95 (3H, d, *J*=6.7Hz), 1.16 (3H, t, *J*=7.1Hz), 2.85-3.00 (2H, m), 3.15-3.40 (3H, m), 4.08 (2H, q, *J*=7.1Hz), 4.20 (2H, s), 5.05 (1H, br s), 5.35 (1H, br), 5.94 (1H, br s), 6.76 (2H, d, *J*=8.6Hz), 7.16 (2H, d, *J*=8.6Hz), 7.28 (2H, s), 8.70 (2H, br), 9.39

(1H, br s)

Specific Rotation: $[\alpha]_D^{30} = -6.3^\circ$ (c=0.67, Methanol)

Example 3

- 5 The following compounds were prepared according to a similar manner to that described in Example 1 or Examples 1-2 using the corresponding aminoacetate derivative.

10 Ethyl N-[4-[2-[[[(1S,2R)-2-hydroxy-2-(4-hydroxyphenyl)-1-methyl-ethylamino]ethyl]phenyl]amino]acetate hydrobromide (Compound 3)

¹H-NMR (DMSO-*d*₆) δ ppm: 0.94 (3H, d, *J*=6.7Hz), 1.19 (3H, t, *J*=7.1Hz), 2.82 (2H, t, *J*=8.3Hz), 3.05-3.40 (3H, m), 3.86 (2H, d, *J*=6.4Hz), 4.10 (2H, q, *J*=7.1Hz), 4.98 (1H, br s), 5.90-6.00 (2H, m), 6.52 (2H, d, *J*=8.5Hz), 6.75 (2H, d, *J*=8.5Hz), 6.98 (2H, d, *J*=8.5Hz), 7.16 (2H, d, *J*=8.5Hz), 8.47 (2H, br), 9.38 (1H, s)

Ethyl 4-[[2,6-dichloro-4-[2-[[[(1S,2R)-2-hydroxy-2-(4-hydroxyphenyl)-1-methylethylamino]ethyl]phenyl]aminol]butyrate (Compound 4)

20 ¹H-NMR (CD₃OD) δ ppm: 1.09 (3H, d, *J*=6.4Hz), 1.23 (3H, t, *J*=7.1Hz), 1.80-1.90 (2H, m), 2.43 (2H, t, *J*=7.3Hz), 2.50-2.95 (5H, m), 3.25-3.35 (2H, m), 4.11 (2H, q, *J*=7.1Hz), 4.35 (1H, d, *J*=6.4Hz), 6.71 (2H, d, *J*=8.6Hz), 7.04 (2H, s), 7.07 (2H, d, *J*=8.6Hz)

25 Ethyl N-[2-chloro-4-[2-[[[(1S,2R)-2-hydroxy-2-(4-hydroxyphenyl)-1-methylethylamino]ethyl]phenyl]amino]acetate (Compound 5)

¹H-NMR (CDCl₃) δ ppm: 0.96 (3H, d, *J*=6.4Hz), 1.32 (3H, t, *J*=7.1Hz),

2.55-3.00 (5H, m), 3.96 (2H, d, $J=5.9\text{Hz}$), 4.29 (2H, q, $J=7.1\text{Hz}$), 4.47 (1H, d, $J=5.6\text{Hz}$), 4.82 (1H, t, $J=5.9\text{Hz}$), 6.40 (1H, d, $J=8.2\text{Hz}$), 6.70 (2H, d, $J=8.6\text{Hz}$), 6.87 (1H, dd, $J=8.2, 1.9\text{Hz}$), 7.02 (1H, d, $J=1.9\text{Hz}$), 7.06 (2H, d, $J=8.6\text{Hz}$)

5

Ethyl N-[4-[2-[[[(1S,2R)-2-hydroxy-2-(4-hydroxyphenyl)-1-methylethylamino]ethyl]phenyl]-N-methylaminoacetate (Compound 6)

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.10 (3H, d, $J=6.3\text{Hz}$), 1.23 (3H, t, $J=7.1\text{Hz}$), 2.45-2.75 (4H, m), 2.80-2.90 (1H, m), 3.02 (3H, s), 4.10 (2H, s), 4.16 (2H, q, $J=7.1\text{Hz}$), 4.31 (1H, d, $J=6.8\text{Hz}$), 6.53 (2H, d, $J=8.7\text{Hz}$), 6.68 (2H, d, $J=8.5\text{Hz}$), 6.85 (2H, d, $J=8.7\text{Hz}$), 7.03 (2H, d, $J=8.5\text{Hz}$)

10

Ethyl N-[2,6-dichloro-4-[2-[[[(1S,2R)-2-hydroxy-2-(4-hydroxyphenyl)-1-methylethylamino]ethyl]phenyl]-N-methylaminoacetate (Compound 7)

15

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 0.92 (3H, d, $J=6.4\text{Hz}$), 1.29 (3H, t, $J=7.1\text{Hz}$), 2.67 (2H, t $J=6.7\text{Hz}$), 2.75-3.20 (6H, m), 3.87 (2H, s), 4.21 (2H, q, $J=7.1\text{Hz}$), 4.53 (1H, d, $J=4.9\text{Hz}$), 6.76 (2H, d, $J=8.5\text{Hz}$), 7.08 (2H, s), 7.11 (2H, d, $J=8.5\text{Hz}$)

20

Ethyl N-[2-chloro-4-[2-[[[(1S,2R)-2-hydroxy-2-(4-hydroxyphenyl)-1-methylethylamino]ethyl]phenyl]-N-methylaminoacetate (Compound 8)

25

$^1\text{H-NMR}$ (CD_3OD) δ ppm: 1.10 (3H, d, $J=6.3\text{Hz}$), 1.23 (3H, t, $J=7.1\text{Hz}$), 2.50-2.95 (8H, m), 3.90 (2H, s), 4.15 (2H, q, $J=7.1\text{Hz}$), 4.33 (1H, d, $J=6.6\text{Hz}$), 6.69 (2H, d, $J=8.5\text{Hz}$), 6.88 (1H, d, $J=8.2\text{Hz}$), 7.00-7.10 (4H, m)

Ethyl N-[2,3-dichloro-4-[2-[[[(1S,2R)-2-hydroxy-2-(4-hydroxy-phenyl)]-1-methylethyl]amino]ethyl]phenyl]aminoacetate (Compound 9)

- 5 $^1\text{H-NMR}$ (CD_3OD) δ ppm: 1.10 (3H, d, $J=6.3\text{Hz}$), 1.27 (3H, t, $J=7.1\text{Hz}$), 2.60-2.90 (5H, m), 4.01 (2H, s), 4.22 (2H, q, $J=7.1\text{Hz}$), 4.34 (1H, d, $J=6.6\text{Hz}$), 6.36 (1H, d, $J=8.4\text{Hz}$), 6.70 (2H, d, $J=8.5\text{Hz}$), 6.81 (1H, d, $J=8.4\text{Hz}$), 7.07 (2H, d, $J=8.5\text{Hz}$)

10 Ethyl N-[2,5-dichloro-4-[2-[[[(1S,2R)-2-hydroxy-2-(4-hydroxy-phenyl)]-1-methylethyl]amino]ethyl]phenyl]aminoacetate (Compound 10)

- $^1\text{H-NMR}$ (CD_3OD) δ ppm: 1.09 (3H, d, $J=6.4\text{Hz}$), 1.28 (3H, t, $J=7.1\text{Hz}$), 2.60-2.90 (5H, m), 3.99 (2H, s), 4.23 (2H, q, $J=7.1\text{Hz}$), 4.36 (1H, d, $J=6.5\text{Hz}$), 6.51 (1H, s), 6.70 (2H, d, $J=8.6\text{Hz}$), 7.00-7.15 (3H, m)
- 15

Ethyl N-[2,3,6-trichloro-4-[2-[[[(1S,2R)-2-hydroxy-2-(4-hydroxy-phenyl)]-1-methylethyl]amino]ethyl]phenyl]aminoacetate (Compound 11)

- 20 $^1\text{H-NMR}$ (CD_3OD) δ ppm: 1.09 (3H, d, $J=6.4\text{Hz}$), 1.25 (3H, t, $J=7.1\text{Hz}$), 2.65-2.95 (5H, m), 4.10-4.25 (4H, m), 4.37 (1H, d, $J=6.4\text{Hz}$), 6.71 (2H, d, $J=8.5\text{Hz}$), 7.08 (2H, d, $J=8.5\text{Hz}$), 7.11 (1H, s)

Ethyl N-[4-[2-[[[(1S,2R)-2-hydroxy-2-(4-hydroxyphenyl)]-1-methyl-ethyl]amino]ethyl]-2,5-dimethylphenyl]aminoacetate (Compound 12)

25

- $^1\text{H-NMR}$ (CDCl_3) δ ppm: 0.96 (3H, d, $J=6.4\text{Hz}$), 1.34 (3H, t, $J=7.1\text{Hz}$), 2.10 (3H, s), 2.22 (3H, s), 2.55-2.95 (5H, m), 3.90-4.10 (3H, m),

4.30 (2H, q, $J=7.1\text{Hz}$), 4.49 (1H, d, $J=5.6\text{Hz}$), 6.22 (1H, s), 6.60-6.70
(3H, m), 7.06 (2H, d, $J=8.6\text{Hz}$)

5 Ethyl N-[2-bromo-4-[2-[[[(1S,2R)-2-hydroxy-2-(4-hydroxyphenyl)-1-
methylethyllamino]ethyllphenyllaminoacetate (Compound 13)

$^1\text{H-NMR}$ ($\text{DMSO-}d_6$) δ ppm: 0.79 (3H, d, $J=6.4\text{Hz}$), 1.15-1.30 (4H, m),
2.20-2.75 (5H, m), 3.97 (2H, d, $J=6.0\text{Hz}$), 4.13 (2H, q, $J=7.1\text{Hz}$),
4.35-4.45 (1H, m), 4.82 (1H, d, $J=3.9\text{Hz}$), 5.31 (1H, t, $J=6.0\text{Hz}$), 6.44
(1H, d, $J=8.3\text{Hz}$), 6.67 (2H, d, $J=8.5\text{Hz}$), 6.95 (1H, dd, $J=8.3, 1.8\text{Hz}$),
10 7.06 (2H, d, $J=8.5\text{Hz}$), 7.26 (1H, d, $J=1.8\text{Hz}$), 9.13 (1H, br s)

Specific Rotation: $[\alpha]_D^{29} = -7.1^\circ$ ($c=0.65$, Methanol)

15 Ethyl N-[2,6-dibromo-4-[2-[[[(1S,2R)-2-hydroxy-2-(4-hydroxy-
phenyl)-1-methylethyllamino]ethyllphenyllaminoacetate (Compound
14)

$^1\text{H-NMR}$ ($\text{DMSO-}d_6$) δ ppm: 0.79 (3H, d, $J=6.4\text{Hz}$), 1.17 (3H, t, $J=7.1\text{Hz}$),
1.20-1.35 (1H, m), 2.30-2.80 (5H, m), 4.05-4.20 (4H, m), 4.35-4.45
(1H, m), 4.83 (1H, d, $J=3.9\text{Hz}$), 4.90 (1H, t, $J=6.4\text{Hz}$), 6.67 (2H, d,
 $J=8.5\text{Hz}$), 7.06 (2H, d, $J=8.5\text{Hz}$), 7.38 (2H, s), 9.13 (1H, br s)

20 Specific Rotation: $[\alpha]_D^{29} = -4.3^\circ$ ($c=0.47$, Methanol)

Ethyl N-[4-[2-[[[(1S,2R)-2-hydroxy-2-(4-hydroxyphenyl)-1-
methylethyllamino]ethyll-2-iodophenyllaminoacetate (Compound 15)

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 0.96 (3H, d, $J=6.3\text{Hz}$), 1.33 (3H, t, $J=7.1\text{Hz}$),
25 2.55-3.00 (6H, m), 3.95 (2H, d, $J=5.7\text{Hz}$), 4.29 (2H, q, $J=7.1\text{Hz}$), 4.47
(1H, d, $J=5.5\text{Hz}$), 4.65-4.75 (1H, m), 6.31 (1H, d, $J=8.2\text{Hz}$), 6.71 (2H,
d, $J=8.4\text{Hz}$), 6.90-7.00 (1H, m), 7.07 (2H, d, $J=8.4\text{Hz}$), 7.44 (1H, d,

$J=1.8\text{Hz}$)

Specific Rotation: $[\alpha]_D^{29} = -6.1^\circ$ ($c=0.56$, Methanol)

2-[[2,6-Dichloro-4-[2-[[[(1S,2R)-2-hydroxy-2-(4-hydroxyphenyl)-1-methylethylamino]ethyl]phenyl]amino]-N,N-dimethylacetamide hydrochloride (Compound 16)

$^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ ppm: 0.95 (3H, d, $J=6.7\text{Hz}$), 2.85-3.00 (8H, m), 3.10-3.40 (3H, m), 4.14 (2H, s), 5.04 (1H, br s), 5.95 (1H, br), 6.76 (2H, d, $J=8.6\text{Hz}$), 7.16 (2H, d, $J=8.6\text{Hz}$), 7.29 (2H, s), 8.70 (2H, br), 9.40 (1H, br)

Specific Rotation: $[\alpha]_D^{31} = -5.3^\circ$ ($c=0.60$, Methanol)

Example 4

N-[2,6-Dichloro-4-[2-[[[(1S,2R)-2-hydroxy-2-(4-hydroxyphenyl)-1-methylethylamino]ethyl]phenyl]amino]acetic acid (Compound 17)

Ethyl N-[2,6-dichloro-4-[2-[[[(1S,2R)-2-hydroxy-2-(4-hydroxyphenyl)-1-methylethyl]amino]ethyl]phenyl]aminoacetate (500mg) was dissolved in 1N aqueous sodium hydroxide solution (5.0ml), and the solution was stirred for 1 hour at room temperature. To the reaction mixture was added 1N hydrochloric acid (5.0ml) under ice-cooling with stirring, and collection of the resulting precipitates by filtration gave N-[2,6-dichloro-4-[2-[[[(1S,2R)-2-hydroxy-2-(4-hydroxyphenyl)-1-methylethyl]amino]ethyl]phenyl]-aminoacetic acid (464mg).

$^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ ppm: 0.90 (3H, d, $J=6.6\text{Hz}$), 2.65-2.80 (2H, m), 2.95-3.20 (3H, m), 3.76 (2H, s), 4.93 (1H, br s), 5.55 (1H, br), 6.72 (2H, d, $J=8.5\text{Hz}$), 7.13 (2H, d, $J=8.5\text{Hz}$), 7.16 (2H, s)

Specific Rotation: $[\alpha]_D^{30} = -3.5^\circ$ ($c=1.00$, Acetic acid)

Example 5

The following compounds were prepared according to a similar
5 manner to that described in Example 4 using the corresponding ester
derivative.

N-[4-[2-[[[(1S,2R)-2-hydroxy-2-(4-hydroxyphenyl)-1-methylethyl]-
aminoethyl]phenyllaminoacetic acid (Compound 18)

10 $^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ ppm: 0.87 (3H, d, $J=6.4\text{Hz}$), 2.50-3.20 (5H, m), 3.51
(2H, s), 4.86 (1H, br s), 6.45 (2H, d, $J=8.1\text{Hz}$), 6.70 (2H, d, $J=8.4\text{Hz}$),
6.83 (2H, d, $J=8.1\text{Hz}$), 7.11 (2H, d, $J=8.4\text{Hz}$)

Specific Rotation: $[\alpha]_D^{25} = -6.7^\circ$ ($c=0.75$, Acetic acid)

15 4-[[[2,6-Dichloro-4-[2-[[[(1S,2R)-2-hydroxy-2-(4-hydroxyphenyl)-1-
methylethyllaminoethyl]phenyllaminolbutyric acid (Compound 19)

$^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ ppm: 0.83 (3H, d, $J=6.4\text{Hz}$), 1.60-1.75 (2H, m), 2.19
(2H, t, $J=7.4\text{Hz}$), 2.45-2.85 (5H, m), 3.22 (2H, t, $J=6.9\text{Hz}$), 4.40-4.60
(2H, m), 6.66 (2H, d, $J=8.5\text{Hz}$), 7.04 (2H, d, $J=8.5\text{Hz}$), 7.16 (2H, s)

20 Specific Rotation: $[\alpha]_D^{25} = -3.3^\circ$ ($c=0.60$, Acetic acid)

N-[2-Chloro-4-[2-[[[(1S,2R)-2-hydroxy-2-(4-hydroxyphenyl)-1-
methylethyllaminoethyl]phenyllaminoacetic acid (Compound 20)

$^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ ppm: 0.90 (3H, d, $J=6.4\text{Hz}$), 2.60-2.80 (2H, m),
25 2.90-3.20 (3H, m), 3.52 (2H, s), 4.95 (1H, br s), 5.35 (1H, br), 6.46
(1H, d, $J=8.4\text{Hz}$), 6.72 (2H, d, $J=8.6\text{Hz}$), 6.91 (1H, dd, $J=8.4, 1.8\text{Hz}$),
7.05-7.20 (3H, m)

Specific Rotation: $[\alpha]_D^{30} = -6.7^\circ$ ($c=1.00$, Acetic acid)

N-[4-[2-[[[(1*S*,2*R*)-2-Hydroxy-2-(4-hydroxyphenyl)-1-methylethyl]-amino]ethyl]phenyl]-*N*-methylaminoacetic acid (Compound 21)

5 $^1\text{H-NMR}$ (CD_3OD) δ ppm: 1.07 (3H, d, $J=6.7\text{Hz}$), 2.84 (2H, t, $J=8.1\text{Hz}$), 3.03 (3H, s), 3.10-3.25 (2H, m), 3.30-3.40 (1H, m), 3.86 (2H, s), 4.99 (1H, d, $J=3.4\text{Hz}$), 6.64 (2H, d, $J=8.8\text{Hz}$), 6.78 (2H, d, $J=8.6\text{Hz}$), 7.02 (2H, d, $J=8.8\text{Hz}$), 7.17 (2H, d, $J=8.6\text{Hz}$)

Specific Rotation: $[\alpha]_D^{25} = -6.9^\circ$ ($c=0.96$, Acetic acid)

10

N-[2,6-Dichloro-4-[2-[[[(1*S*,2*R*)-2-hydroxy-2-(4-hydroxyphenyl)-1-methylethyl]amino]ethyl]phenyl]-*N*-methylaminoacetic acid (Compound 22)

15 $^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ ppm: 0.84 (3H, d, $J=6.6\text{Hz}$), 2.30-2.95 (8H, m), 3.76 (2H, s), 4.64 (1H, br s), 6.69 (2H, d, $J=8.5\text{Hz}$), 7.09 (2H, d, $J=8.5\text{Hz}$), 7.22 (2H, s)

Specific Rotation: $[\alpha]_D^{32} = -5.9^\circ$ ($c=0.54$, Methanol)

20 *N*-[2-Chloro-4-[2-[[[(1*S*,2*R*)-2-hydroxy-2-(4-hydroxyphenyl)-1-methylethyl]amino]ethyl]phenyl]-*N*-methylaminoacetic acid (Compound 23)

$^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ ppm: 0.87 (3H, d, $J=6.4\text{Hz}$), 2.65-2.90 (5H, m), 2.89 (3H, s), 3.60-3.70 (2H, m), 4.56 (1H, br), 6.65 (2H, d, $J=8.5\text{Hz}$), 6.81 (1H, dd, $J=8.3, 1.9\text{Hz}$), 6.95-7.05 (4H, m)

25 Specific Rotation: $[\alpha]_D^{25} = -4.5^\circ$ ($c=0.75$, Acetic acid)

N-[2,3-Dichloro-4-[2-[[[(1*S*,2*R*)-2-hydroxy-2-(4-hydroxyphenyl)-1-

methylethyllaminoethyllphenyllaminoacetic acid (Compound 24)

¹H-NMR (DMSO-*d*₆) δ ppm: 0.89 (3H, d, *J*=6.5Hz), 2.75-3.25 (5H, m), 3.53 (2H, s), 4.90 (1H, br s), 5.62 (1H, br s), 6.45 (1H, d, *J*=8.5Hz), 6.71 (2H, d, *J*=8.4Hz), 7.01 (1H, d, *J*=8.5Hz), 7.13 (2H, d, *J*=8.4Hz)

5 Specific Rotation: $[\alpha]_D^{25} = -4.3^\circ$ (*c*=0.47, Acetic acid)

N-[2,5-Dichloro-4-[2-[[[(1*S*,2*R*)-2-hydroxy-2-(4-hydroxyphenyl)-1-methylethyllaminoethyllphenyllaminoacetic acid (Compound 25)

¹H-NMR (DMSO-*d*₆) δ ppm: 0.89 (3H, d, *J*=6.5Hz), 2.65-3.25 (5H, m), 3.55 (2H, s), 4.93 (1H, br s), 5.58 (1H, br s), 6.53 (1H, s), 6.71 (2H, d, *J*=8.4Hz), 7.13 (2H, d, *J*=8.4Hz), 7.19 (1H, s), 9.30 (1H, br)

Specific Rotation: $[\alpha]_D^{25} = -3.4^\circ$ (*c*=0.83, Acetic acid)

N-[2,3,6-Trichloro-4-[2-[[[(1*S*,2*R*)-2-hydroxy-2-(4-hydroxyphenyl)-1-methylethyllaminoethyllphenyllaminoacetic acid (Compound 26)

¹H-NMR (DMSO-*d*₆) δ ppm: 0.89 (3H, d, *J*=6.4Hz), 2.75-3.20 (5H, m), 3.70-3.90 (2H, m), 4.92 (1H, br s), 5.72 (1H, br), 6.71 (2H, d, *J*=8.4Hz), 7.13 (2H, d, *J*=8.4Hz), 7.25 (1H, s), 9.25 (1H, br)

Specific Rotation: $[\alpha]_D^{25} = -2.0^\circ$ (*c*=0.60, Acetic acid)

20

N-[4-[2-[[[(1*S*,2*R*)-2-Hydroxy-2-(4-hydroxyphenyl)-1-methylethyllaminoethyll-2,5-dimethylphenyllaminoacetic acid (Compound 27)

¹H-NMR (DMSO-*d*₆) δ ppm: 0.95 (3H, d, *J*=6.7Hz), 2.05 (3H, s), 2.19 (3H, s), 2.75-3.10 (4H, m), 3.20-3.40 (1H, m), 3.77 (2H, s), 5.02 (1H, br s), 6.21 (1H, s), 6.65-6.85 (3H, m), 7.16 (2H, d, *J*=8.5Hz), 9.40 (2H, br)

25

Specific Rotation: $[\alpha]_D^{32} = -6.9^\circ$ (*c*=0.29, Methanol)

N-[2-Bromo-4-[2-[[[(1S,2R)-2-hydroxy-2-(4-hydroxyphenyl)-1-methylethyl]amino]ethyl]phenyl]aminoacetic acid (Compound 28)

¹H-NMR (DMSO-*d*₆) δ ppm: 0.92 (3H, d, *J*=6.5Hz), 2.70-2.90 (2H, m),
 5 3.00-3.40 (3H, m), 3.75 (2H, s), 4.93 (1H, br s), 5.36 (1H, br), 6.50
 (1H, d, *J*=8.3Hz), 6.74 (2H, d, *J*=8.5Hz), 7.04 (1H, dd, *J*=8.3, 1.8Hz),
 7.14 (2H, d, *J*=8.5Hz), 7.34 (1H, d, *J*=1.8Hz)
 Specific Rotation: $[\alpha]_D^{27} = -4.7^\circ$ (c=0.51, Acetic acid)

10 N-[2,6-Dibromo-4-[2-[[[(1S,2R)-2-hydroxy-2-(4-hydroxyphenyl)-1-methylethyl]amino]ethyl]phenyl]aminoacetic acid (Compound 29)

¹H-NMR (DMSO-*d*₆) δ ppm: 0.89 (3H, d, *J*=6.6Hz), 2.65-3.20 (5H, m), 3.75
 (2H, s), 4.75-4.90 (1H, m), 5.40 (1H, br), 6.71 (2H, d, *J*=8.3Hz),
 7.11 (2H, d, *J*=8.3Hz), 7.38 (2H, s)
 15 Specific Rotation: $[\alpha]_D^{29} = -3.4^\circ$ (c=1.29, Acetic acid)

N-[4-[2-[[[(1S,2R)-2-Hydroxy-2-(4-hydroxyphenyl)-1-methylethyl]amino]ethyl]-2-iodophenyl]aminoacetic acid (Compound 30)

¹H-NMR (DMSO-*d*₆) δ ppm: 0.92 (3H, d, *J*=6.6Hz), 2.70-2.80 (2H, m),
 20 3.00-3.25 (3H, m), 3.68 (2H, s), 4.93 (1H, br s), 5.15 (1H, br), 6.39
 (1H, d, *J*=8.3Hz), 6.73 (2H, d, *J*=8.6Hz), 7.00-7.10 (1H, m), 7.14 (2H,
 d, *J*=8.6Hz), 7.53 (1H, d, *J*=1.8Hz)
 Specific Rotation: $[\alpha]_D^{27} = -4.7^\circ$ (c=0.51, Acetic acid)

25 Example 6

2-[[[2,6-Dichloro-4-[2-[[[(1S,2R)-2-hydroxy-2-(4-hydroxyphenyl)-1-methylethyl]amino]ethyl]phenyl]amino]-N-(2-methoxyethyl)-

acetamide (Compound 31)

Ethyl *N*-[2,6-dichloro-4-[2-[[*(1S,2R)*-2-hydroxy-2-(4-hydroxyphenyl)-1-methylethyl]amino]ethyl]phenyl]aminoacetate (44.3mg) was dissolved in 2-methoxyethylamine (886 μ l), and the solution was stirred for 48 hours at 80°C. The reaction mixture was concentrated *in vacuo*, and purification of the residue by medium pressure liquid column chromatography on aminopropyl silica gel (eluent: dichloromethane / methanol = 10 / 1) gave 2-[[2,6-dichloro-4-[2-[[*(1S,2R)*-2-hydroxy-2-(4-hydroxyphenyl)-1-methylethyl]amino]ethyl]phenyl]amino]-*N*-(2-methoxyethyl)-acetamide (27.7mg).

¹H-NMR (DMSO-*d*₆) δ ppm : 0.80 (3H, d, *J*=6.4Hz), 1.15-1.35 (1H, m), 2.40-2.80 (5H, m), 3.15-3.40 (7H, m), 3.86 (2H, d, *J*=5.7Hz), 4.35-4.45 (1H, m), 4.85 (1H, d, *J*=3.9Hz), 5.25 (1H, t, *J*=5.7Hz), 6.67 (2H, d, *J*=8.5Hz), 7.06 (2H, d, *J*=8.5Hz), 7.16 (2H, s), 8.05-8.15 (1H, m), 9.15 (1H, br)

Example 7

4-[2-[[2,6-Dichloro-4-[2-[[*(1S,2R)*-2-hydroxy-2-(4-hydroxyphenyl)-1-methylethyl]amino]ethyl]phenyl]amino]acetyl]morpholine (Compound 32)

4-[2-[[2,6-Dichloro-4-[2-[[*(1S,2R)*-2-hydroxy-2-(4-hydroxyphenyl)-1-methylethyl]amino]ethyl]phenyl]amino]acetyl]-morpholine was prepared according to a similar manner to that described in Example 6 using morpholine instead of 2-methoxyethylamine.

¹H-NMR (CDCl₃) δ ppm: 0.96 (3H, d, *J*=6.4Hz), 2.55-3.00 (6H, m),

3.40-3.45 (2H, m), 3.65-3.80 (7H, m), 4.17 (2H, d, $J=4.9\text{Hz}$), 4.47 (1H, d, $J=5.4\text{Hz}$), 5.40-5.50 (1H, m), 6.74 (2H, d, $J=8.5\text{Hz}$), 6.98 (2H, s), 7.08 (2H, d, $J=8.5\text{Hz}$)

Specific Rotation: $[\alpha]_D^{30} = +4.4^\circ$ ($c=1.01$, DMSO)

5

Test Example 1

The experiment for measuring β_3 -adrenoceptor stimulating effects

Urinary bladders of male ferrets (1100 to 1400g in body weight) were isolated and urinary bladder smooth muscle strips of approximately 10 mm in length and approximately 2 mm in width were prepared. The experiment was conducted according to the Magnus method. The preparations with a tension of 1g were exposed to Krebs-Henseleit solution maintained at 37°C and gassed with a mixture of 95% oxygen and 5% carbon dioxide. Basal tensions of urinary bladder were measured isometrically with a force-displacement transducer and recorded on a rectigram. The drug was added cumulatively to the Magnus bath every 5 minutes. The drug efficacy was evaluated as the molar concentration of the drug required to produce 50% of the relaxation of urinary bladder smooth muscle before the addition of the drug (i.e., EC_{50} value). In this experiment, tension of urinary bladder smooth muscle before the addition of the drug was expressed as 100% and tension of maximal relaxation after the addition of 10^{-5} molar concentration of forskolin was expressed as 0%. The result was shown in the following Table 1.

25

[Table 1]

Compound No.	EC ₅₀ (M)
2	4.9X10 ⁻⁸
16	1.3X10 ⁻⁷
17	1.9X10 ⁻⁸
18	2.4X10 ⁻⁸
20	9.3X10 ⁻¹⁰
21	5.2X10 ⁻⁸
29	8.1X10 ⁻⁸
32	7.9X10 ⁻⁸
BRL-37344	1.6X10 ⁻⁹

Test Example 2

The experiment for measuring β_1 -adrenoceptor stimulating effects

5 Atria of male SD rats (250 to 400g in body weight) were isolated and the experiment was conducted according to the Magnus method. The preparations with a tension of 0.5g were exposed to Krebs-Henseleit solution maintained at 37°C and gassed with a mixture of 95% oxygen and 5% carbon dioxide. The cardiac contractility was measured

10 isometrically with a force-displacement transducer, and heart rate was recorded on a rectigram via a tachometer, and the drug was added cumulatively. The drug efficacy was evaluated as the molar concentration of the drug required to produce 50% increase of heart rate per minute (i.e., EC₅₀ value). In this experiment, increase of

15 heart rate per minute after addition of 10⁻⁸ molar concentration of isoproterenol was expressed as 100%. The result was shown in the following Table 2.

[Table 2]

Compound No.	EC ₅₀ (M)
2	5.0X10 ⁻⁸
16	>10 ⁻⁴
17	>10 ⁻⁴
18	8.3X10 ⁻⁸
20	2.3X10 ⁻⁵
21	3.4X10 ⁻⁵
29	>10 ⁻⁴
32	>10 ⁻⁴
BRL-37344	2.7X10 ⁻⁷

Test Example 3

The experiment for measuring β_2 -adrenoceptor stimulating effects

5 Uteri of pregnant SD rats (pregnancy day 21) were isolated and longitudinal uterine muscle strips of approximately 15 mm in length and approximately 5 mm in width free from the basal plate were prepared. The experiment was conducted according to the Magnus method. The preparations with a tension of 0.5g were exposed to

10 Locke-Ringer solution maintained at 37°C and gassed with a mixture of 95% oxygen and 5% carbon dioxide. Spontaneous contractions of myometrium were measured isometrically with a force-displacement transducer and recorded on a rectigram. The drug was added cumulatively to the Magnus bath every 5 minutes. The drug efficacy

15 was evaluated as the molar concentration of the drug required to produce 50% of the inhibition of uterine contraction (i.e., EC₅₀ value) by comparing the total degree of uterine contraction during 5 minutes before the addition of the drug (100%) with the total degree of uterine contraction during 5 minutes after the addition of the

20 drug. The result was shown in the following Table 3.

[Table 3]

Compound No.	EC ₅₀ (M)
2	6.5X10 ⁻⁷
17	1.4X10 ⁻⁵
18	6.5X10 ⁻⁷
20	3.3X10 ⁻⁶
21	1.6X10 ⁻⁶
32	1.7X10 ⁻⁶
BRL-37344	9.0X10 ⁻⁹

Test Example 4

Acute toxicity test

5 To male ICR rats of 4 weeks age was administered intravenously *N*-[2,6-dichloro-4-[2-[[*(1S, 2R)*-2-hydroxy-2-(4-hydroxyphenyl)-1-methylethyl]amino]ethyl]phenyl]aminoacetic acid at a dose of 250mg/kg. No death of animals was observed during 24 hours after the administration.

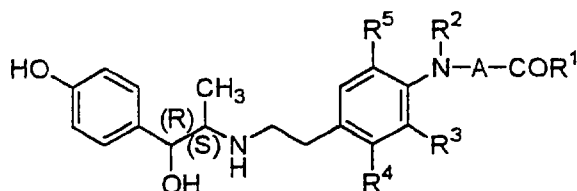
10

Industrial Applicability

The phenylaminoalkylcarboxylic acid derivative represented by the above general formula (I) and pharmaceutically acceptable salts thereof of the present invention have excellent β_3 -adrenoceptor
15 stimulating effects and are extremely useful as medicaments such as agents for the prevention or treatment of obesity, hyperglycemia, the diseases caused by intestinal hypermotility, pollakiuria, urinary incontinence, depression, or the diseases caused by biliary calculi or hypermotility of biliary tract.

CLAIMS

1. A phenylaminoalkylcarboxylic acid derivative represented by the general formula:



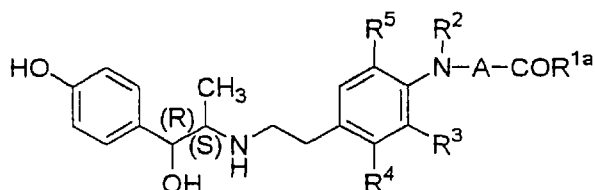
5

(wherein R^1 represents a hydroxy group, a lower alkoxy group, an aralkoxy group, an amino group, an alicyclic amino group or a mono or di(lower alkyl)amino group which may have a hydroxy group or a lower alkoxy group as a substituent; R^2 represents a hydrogen atom or a lower alkyl group; R^3 represents a hydrogen atom or a halogen atom; R^4 and R^5 are the same or different and each represents a hydrogen atom, a halogen atom or a lower alkyl group; A represents a lower alkylene group; the carbon atom marked with (R) represents a carbon atom in (R) configuration; and the carbon atom marked with (S) represents a carbon atom in (S) configuration) or a pharmaceutically acceptable salt thereof.

15

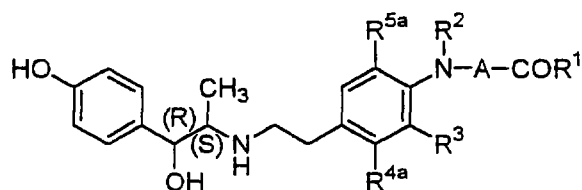
2. A phenylaminoalkylcarboxylic acid derivative as claimed in claim 1, represented by the general formula:

20



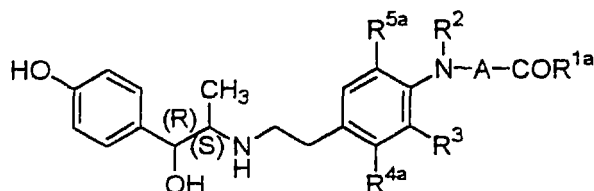
(wherein R^{1a} represents a hydroxy group or a lower alkoxy group; R^2 represents a hydrogen atom or a lower alkyl group; R^3 represents a hydrogen atom or a halogen atom; R^4 and R^5 are the same or different and each represents a hydrogen atom, a halogen atom or a lower alkyl group; A represents a lower alkylene group; the carbon atom marked with (R) represents a carbon atom in (R) configuration; and the carbon atom marked with (S) represents a carbon atom in (S) configuration) or a pharmaceutically acceptable salt thereof.

3. A phenylaminoalkylcarboxylic acid derivative as claimed in claim 1, represented by the general formula:



(wherein R^1 represents a hydroxy group, a lower alkoxy group, an aralkoxy group, an amino group, an alicyclic amino group or a mono or di(lower alkyl)amino group which may have a hydroxy group or a lower alkoxy group as a substituent; R^2 represents a hydrogen atom or a lower alkyl group; R^3 , R^{4a} and R^{5a} are the same or different and each represents a hydrogen atom or a halogen atom; A represents a lower alkylene group; the carbon atom marked with (R) represents a carbon atom in (R) configuration; and the carbon atom marked with (S) represents a carbon atom in (S) configuration) or a pharmaceutically acceptable salt thereof.

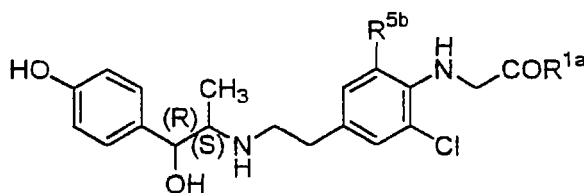
4. A phenylaminoalkylcarboxylic acid derivative as claimed in claim 2 or 3, represented by the general formula:



5 (wherein R^{1a} represents a hydroxy group or a lower alkoxy group; R^2 represents a hydrogen atom or a lower alkyl group; R^3 , R^{4a} and R^{5a} are the same or different and each represents a hydrogen atom or a halogen atom; A represents a lower alkylene group; the carbon atom marked with (R) represents a carbon atom in (R) configuration; and
10 the carbon atom marked with (S) represents a carbon atom in (S) configuration) or a pharmaceutically acceptable salt thereof.

5. A phenylaminoalkylcarboxylic acid derivative as claimed in claim 4, represented by the general formula:

15



(wherein R^{1a} represents a hydroxy group or a lower alkoxy group; R^{5b} represents a hydrogen atom or a chlorine atom; the carbon atom marked with (R) represents a carbon atom in (R) configuration; and the carbon
20 atom marked with (S) represents a carbon atom in (S) configuration) or a pharmaceutically acceptable salt thereof.

6. A pharmaceutical composition comprising a phenylamino-alkylcarboxylic acid derivative or a pharmaceutically acceptable salt thereof as claimed in claim 1, 2, 3, 4 or 5.

7. A β_3 -adrenoceptor stimulant comprising as the active ingredient a phenylaminoalkylcarboxylic acid derivative or a pharmaceutically acceptable salt thereof as claimed in claim 1, 2, 3, 4 or 5.

8. An agent for the prevention or treatment of obesity, hyperglycemia, the diseases caused by intestinal hypermotility, pollakiuria, urinary incontinence, depression, or the diseases caused by biliary calculi or hypermotility of biliary tract which comprises as the active ingredient a phenylaminoalkylcarboxylic acid derivative or a pharmaceutically acceptable salt thereof as claimed in claim 1, 2, 3, 4 or 5.

9. A use of a phenylaminoalkylcarboxylic acid derivative or a pharmaceutically acceptable salt thereof as claimed in claim 1, 2, 3, 4 or 5 for the manufacture of a pharmaceutical composition for the prevention or treatment of obesity, hyperglycemia, the diseases caused by intestinal hypermotility, pollakiuria, urinary incontinence, depression, or the diseases caused by biliary calculi or hypermotility of biliary tract.

10. A use of a phenylaminoalkylcarboxylic acid derivative or a pharmaceutically acceptable salt thereof as claimed in claim 1, 2, 3, 4 or 5 as an agent for the prevention or treatment of obesity, hyperglycemia, the diseases caused by intestinal hypermotility, pollakiuria, urinary incontinence, depression, or the diseases caused by biliary calculi or hypermotility of biliary tract.

11. A process for the manufacture of a pharmaceutical composition for the prevention or treatment of obesity, hyperglycemia, the diseases caused by intestinal hypermotility, pollakiuria, urinary incontinence, depression, or the diseases caused by biliary calculi or hypermotility of biliary tract, characterized in the use, as an essential constituent of said pharmaceutical composition, of a phenylaminoalkylcarboxylic acid derivative or a pharmaceutically acceptable salt as claimed in claim 1, 2, 3, 4 or 5.