(54) Title: AMINOALCOHOL DERIVATIVES USEFUL FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS

(57) Abstract: This invention relates to new aminoalcohol derivatives or salts thereof represented by formula (I) wherein each symbol is as defined in the specification or salts thereof which have gut selective symptomatic, anti-ulcerous, anti-pancreatitis, lipolytic, anti-urinary incontinence and anti-pollakiuria activities, to processes for the preparation thereof, to a pharmaceutical composition comprising the same and to a method for the prevention and/or treatment diseases indicated in the specification to a human being or an animal.
DESCRIPTION

AMINOALCOHOL DERIVATIVES USEFUL FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS

Technical Field

This invention relates to new aminoalcohol derivatives and salts thereof which are $\beta_3$ adrenergic receptor agonists and useful as a medicament.

Background Art

Some ethanolamine derivatives having gut selective sympathomimetic activity and the like have been known as described, for example, in International Publication No. WO 94/25427. Compounds having more potent $\beta_3$ adrenergic receptor agonists activity are desired.

Disclosure of Invention

This invention relates to new aminoalcohol derivatives which are $\beta_3$ adrenergic receptor agonists and salts thereof.

More particularly, it relates to new aminoalcohol derivatives and salts thereof which have gut selective sympathomimetic, anti-ulcerous, anti-pancreatitis, lipolytic, anti-urinary incontinence and anti-pollakiuria activities, to processes for the preparation thereof, to a pharmaceutical composition comprising the same and to a method of using the same therapeutically in the treatment and/or prevention of gastro-intestinal disorders caused by smooth muscle contractions in human beings or animals.

One object of this invention is to provide new and useful aminoalcohol derivatives and salts thereof which have gut selective sympathomimetic, anti-ulcerous, anti-pancreatitis, lipolytic, anti-urinary incontinence and anti-pollakiuria activities.

Another object of this invention is to provide processes for the preparation of said aminoalcohol derivatives and salts thereof.

A further object of this invention is to provide a pharmaceutical composition comprising, as an active ingredient, said aminoalcohol derivatives and salts thereof.

Still further object of this invention is to provide a therapeutical method for the treatment and/or prevention of aforesaid diseases in human beings or animals, using said aminoalcohol derivatives and salts thereof.

The object aminoalcohol derivatives of this invention are new and can be represented by the following general formula [I]:
wherein

A

is phenyl, pyridyl, indolyl, benzimidazolyl or 2,3-dihydro-2-oxobenzimidazolyl, each of which may have 1 to 3 same or different substituent(s) selected from the group consisting of hydroxy, lower alkylcarbonyloxy, lower alkoxy carbonyloxy, amino, halogen atom, lower alkylsulfonylamino, carboxy(lower)alkylsulfonylamino, N-lower alkyl-N-(lower)alkylsulfonylamino, mono(or di or tri)halo(lower)alkylsulfonylamino, phenyl(lower)alkylsulfonylamino, thiienylsulfonylamino, phenyl(lower)alkoxy, lower alkyl, hydroxy(lower)alkyl, amino(lower)alkyl, lower alkylsulfonylamino(lower)alkyl, formylamino, lower alkylcarbonylamino, [N,N-di(lower)alkylsulfamoyl]amino, lower alkoxycarbonylaminosulfonylamino, lower alkoxy carbonylamino, ureido, lower alkyaminocarbonylamino, lower alkoxy carbonyl, formyl, carbamoyl, nitro, lower alkylsulfonylamino wherein amino is protected by amino-protective group, and phenylsulfonylamino wherein phenyl may be substituted by halogen atom, lower alkyl or lower alkoxy,

X

is single bond or –O-CH₂–,

R¹

is hydrogen atom or amino-protective group,

R²

is hydrogen atom, lower alkyl, hydroxy(lower)alkyl or carboxy(lower)alkyl,

R³

is hydrogen atom or hydroxy,

R⁴, R⁵, R⁶ and R⁷ are each independently hydrogen atom, hydroxy, lower alkyl, lower alkoxy, amino, lower alkylsulfonylamino, lower alkoxy carbonylamino, carboxy(lower)alkylamino, lower alkoxy carbonyl(lower)alkylamino, formylamino, lower alkyl carbonylamino, ureido, halogen atom, phenyl(lower)alkoxy,
lower alkoxyacarbonyloxy, lower alkylcarbonyloxy, lower alkoxyacarbonyl[lower]alkoxy, carboxy[lower]alkoxy, carboxamoyl, lower alkylcarbamoyl, lower alkylsulfonylcarbamoyl, morpholinyl, isothiazolidinyl wherein isothiazolidinyl may be substituted by 1 or 2 oxo(s), pyrrolidinyl or imidazolidinyl wherein pyrrolidinyl and imidazolidinyl may be substituted by oxo, and

n

is 0 or 1;

provided that A should be phenyl, pyridyl, indoly1, benzimidazolyl or 2,3-dihydro-2-oxobenzimidazolyl, each of which has at least one substituent selected from the group consisting of lower alkylcarbonyloxy, lower alkoxyacarbonyloxy, carboxy[lower]alkylsulfonylamino, N-lower alkyl-N-[lower]alkylsulfonylamino, mono(or di or tri)halo[lower]alkylsulfonylamino, phenyl[lower]alkylsulfonylamino, thiene[lower]sulfonylamino, hydroxy[lower]alkyl, amino[lower]alkyl, lower alkylsulfonylamino[lower]alkyl, formylamino, lower alkylcarbonylamino, [N,N-di[lower]alkylsulfamoyl]amino, lower alkoxyacarbonylaminosulfonylamino, lower alkoxyacarbonylamino, ureido, lower alkylaminocarbonylamino, lower alkoxyacarbonyl, formyl, carbamoyl, nitro, lower alkylsulfonylamino wherein amino is protected by amino-protective group, and phenylsulfonylamino wherein phenyl may be substituted by halogen atom, lower alkyl or lower alkoxy, when n is 1, R² is hydrogen atom or lower alkyl, and R⁴, R⁵, R⁶ and R⁷ are each independently hydrogen atom, hydroxy, lower alkyl, lower alkoxy, amino, lower alkoxyacarbonylamino, lower alkoxyacarbonylamino, formylamino, lower alkylcarbonylamino, ureido, carbamoyl, lower alkylcarbamoyl or pyrrolidinyl; and

provided that A should be phenyl, pyridyl, indoly1 or benzimidazolyl, each of which has at least one substituent selected from the group consisting of lower alkylsulfonylamino, carboxy[lower]alkylsulfonylamino, N-lower alkyl-N-[lower]alkylsulfonylamino, mono(or di or tri)halo[lower]alkylsulfonylamino, phenyl[lower]alkylsulfonylamino, thiene[lower]sulfonylamino, lower alkyl, hydroxy[lower]alkyl, amino[lower]alkyl, lower alkylsulfonylamino[lower]alkyl, [N,N-di[lower]alkylsulfamoyl]amino, lower alkoxyacarbonylaminosulfonylamino, lower alkoxyacarbonyl, formyl, lower alkylsulfonylamino wherein amino is protected by amino-protective group, and phenylsulfonylamino wherein phenyl may be substituted by halogen atom, lower alkyl or lower alkoxy, when n is 0 or 1, R² is hydrogen atom or lower alkyl, R³ is hydrogen atom, R⁴ and R⁶ are each hydrogen atom and R⁵ and R⁷ are each independently lower alkoxyacarbonyl[lower]alkoxy or carboxy[lower]alkoxy, or a pharmaceutically acceptable salt thereof.
The object compound [I] or a salt thereof can be prepared by the following processes.

**Process 1**

\[
\begin{align*}
[A-X-CHCH_2] & \quad \text{or a salt thereof} \\
[II] & \\
\rightarrow & \\
[A-X-CHCH_2N-CH(CH_2)n-C] & \quad \text{or a salt thereof} \\
[I] & \\
\end{align*}
\]

**Process 2**

\[
\begin{align*}
\text{R}^{1a} \quad \text{R}^2 \\
[A-X-CHCH_2N-CH(CH_2)n-C] & \quad \text{or a salt thereof} \\
[IIa] & \\
\rightarrow & \\
[A-X-CHCH_2N-CH(CH_2)n-C] & \quad \text{or a salt thereof} \\
[IIb] & \\
\end{align*}
\]

[Elimination reaction of amino-protective group]
Process 3

wherein A, X, R¹, R², R³, R⁴, R⁵, R⁶, R⁷ and n are each as defined above, and R⁴, is amino-protective group, R⁵ is lower alkyl, Y is halogen atom, R⁴, is R⁴ or R⁶, and R⁵ is R⁵ or R⁷, wherein R⁴, R⁵, R⁶, and R⁷ are each as defined above.

In the above and subsequent description of the present specification, suitable examples of the various definition to be included within the scope of the invention are explained in detail in the following.

The term "lower" is intended to mean a group having 1 to 6 carbon atom(s), unless otherwise provided.

Suitable example of "lower alkyl" and "lower alkoxy" moiety may include a straight or branched one having 1 to 6 carbon atom(s), such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, 1-methylpentyl, tert-pentyl, neo-pentyl, hexyl, isohexyl and the like.

Suitable "lower alkoxy" and "lower alkoxy" moiety may be a straight or branched one such as methoxy, ethoxy, propoxy, isopropoxy, 1-ethylpropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy, neopentyloxy, tert-pentyloxy, hexyloxy, and the like, in which the preferred one may be C₁-C₄ alkoxy, and the more preferred one may be methoxy, ethoxy and butoxy, and the most preferred one may be methoxy.

Suitable example of "halogen" may be fluoro, chloro, bromo and iodo, and the preferred one may be fluoro and chloro.

Suitable example of "aryl", "aryl" moiety, "arene" and "aryl" moiety in aralkyl may include phenyl, naphthyl, anthryl, and the like, in which the preferred one may be phenyl.

Suitable example of "amino-protective group" moiety may be common
amino-protective group such as aryl(lower)alkyl [e.g. trityl, benzyl, etc.] or acyl, for example, substituted or unsubstituted lower alkanoyl [e.g. formyl, acetyl, propionyl, trifluoroacetoyl, etc.], phthaloyl, lower alkoxy carbonyl [e.g. tert-butoxycarbonyl, tert-amyloxy carbonyl, etc.], substituted or unsubstituted aralkyloxy carbonyl [e.g. benzylloxy carbonyl, p-nitrobenzylloxy carbonyl, etc.], substituted or unsubstituted arenesulfonyl [e.g. benzenesulfonyl, tosyl, etc.], nitrophenylsulfenyl, and the like, in which preferable one is phenyl(lower)alkyl such as benzyl.

Suitable example of "lower alkylsulfonylamino" and "lower alkylsulfonylamino" moiety may include methylsulfonylamino, ethylsulfonylamino, propylsulfonylamino, butylsulfonylamino, pentylsulfonylamino, hexylsulfonylamino, and the like, in which the preferred one may be (C1-C4)alkylsulfonylamino, and the more preferred one may be methylsulfonylamino, ethylsulfonylamino and butylsulfonylamino, and the most preferred one may be methylsulfonylamino.

Suitable example of "carboxyl(lower)alkylsulfonylamino" may be carboxymethylsulfonylamino, carboxyethylsulfonylamino, carboxypropylsulfonylamino, carboxybutylsulfonylamino, carboxypentylsulfonylamino, carboxyhexylsulfonylamino, and the like, in which the preferred one may be carboxy(C1-C4)alkylsulfonylamino, and the most preferred one may be carboxymethylsulfonylamino.

"N-lower alkyl-N-(lower)alkylsulfonylamino" is the above-mentioned lower alkylsulfonylamino wherein amino is substituted by the above-mentioned lower alkyl. The lower alkyl moiety of "N-lower alkyl-N-(lower)alkylsulfonylamino" may be those as described above, and the suitable example of "N-lower alkyl-N-(lower)alkylsulfonylamino" may be N-methyl-N-methylsulfonylamino, N-methyl-N-ethylsulfonylamino, N-methyl-N-propylsulfonylamino, N-methyl-N-butylsulfonylamino, N-methyl-N-pentylsulfonylamino, N-methyl-N-hexylsulfonylamino, N-ethyl-N-methylsulfonylamino, N-propyl-N-methylsulfonylamino, N-butyl-N-methylsulfonylamino, N-pentyl-N-methylsulfonylamino, N-hexyl-N-methylsulfonylamino, N-ethyl-N-ethylsulfonylamino, N-ethyl-N-propylsulfonylamino, N-ethyl-N-butylsulfonylamino, and the like, in which the preferred one may be N-(C1-C4)alkyl-N-(C1-C4)alkylsulfonylamino, and the most preferred one may be N-methyl-N-methylsulfonylamino.

"Lower alkylsulfonylamino wherein amino is protected by amino-protective group" is the above-mentioned lower alkylsulfonylamino wherein amino is protected by the above-mentioned amino-protective group. The
suitable amino-protecting group may be substituted or unsubstituted aralkyloxycarbonyl, in which the preferred one may be benzoyloxy carbonyl. The suitable example of "lower alkylsulfonylamino wherein amino is protected by amino-protective group" may be N-benzoyloxy carbonyl-N-methylsulfonylamino, N-benzoyloxy carbonyl-N-ethylsulfonylamino, N-benzoyloxy carbonyl-N-propylsulfonylamino, N-benzoyloxy carbonyl-N-butylsulfonylamino, N-benzoyloxy carbonyl-N-pentylsulfonylamino, N-benzoyloxy carbonyl-N-hexylsulfonylamino, and the like, in which the preferred one may be N-benzoyloxy carbonyl-N-(C₁-C₄)alkylsulfonylamino, and the most preferred one may be N-benzoyloxy carbonyl-N-methylsulfonylamino.

"Mono(or di or tri)halo(lower)alkyl" moiety is the above-mentioned lower alkyl which is mono(or di or tri)-substituted by halogen atom(s). The suitable example may be lower alkyl which is mono(or di or tri)-substituted by fluorine atom(s), in which the preferred one may be (C₁-C₄)lower alkyl which is mono(or di or tri)-substituted by fluorine atom(s), such as fluoromethyl, difluoromethyl, trifluoromethyl, 1-fluoroethyl, 2-fluoroethyl, 1,2-difluoroethyl, 2,2,2-trifluoroethyl, and the like, and the most preferred one may be trifluoromethyl.

Suitable example of "mono(or di or tri)halo(lower)alkylsulfonylamino" may be mono(or di or tri)fluoromethylsulfonylamino, mono(or di or tri)fluoroethylsulfonylamino, mono(or di or tri)fluoropropylsulfonylamino, mono(or di or tri)fluorobutylsulfonylamino, mono(or di or tri)fluoropentylsulfonylamino, mono(or di or tri)fluorohexylsulfonylamino, and the like, in which the preferred one may be mono(or di or tri)fluoro(C₁-C₄)alkylsulfonylamino, and the more preferred one may be trifluoromethylsulfonylamino and 2,2,2-trifluoroethylsulfonylamino, and the most preferred one may be trifluoromethylsulfonylamino.

The lower alkylsulfonylamino moiety of "phenyl(lower)alkylsulfonylamino" may be those as described above, and the suitable example of "phenyl(lower)alkylsulfonylamino" may be benzylsulfonylamino, phenethylsulfonylamino, phenylpropylsulfonylamino, phenylbutylsulfonylamino, phenylpentylsulfonylamino, phenylhexylsulfonylamino, and the like, in which the preferred one may be phenyl(C₁-C₄)alkylsulfonylamino, and the most preferred one may be benzylsulfonylamino.

"Thienylsulfonylamino" includes 2-thienylsulfonylamino and 3-thienylsulfonylamino.

The lower alkyl moieties of "[N,N-di(lower)alkylsulfamoyl]amino" may be the same or different and the suitable example of lower alkyl moiety may be those as described above. The suitable example of "[N,N-di(lower)alkylsulfamoyl]amino"
may be (N,N-dimethylsulfamoyl)amino, (N,N-diethylsulfamoyl)amino, (N,N-dipropylsulfamoyl)amino, (N,N-dibutylsulfamoyl)amino, (N,N-dipentylsulfamoyl)amino, (N,N-dihexylsulfamoyl)amino, and the like. The preferred example of "[N,N-di(lower)alkylsulfamoyl]amino" may be [N,N-di(C_{1}-C_{4})alkylsulfamoyl]amino, and the most preferred one may be (N,N-dimethylsulfamoyl)amino.

"Phenyl(lower)alkoxy" is the above-mentioned lower alkoxy substituted by phenyl, such as benzyloxy, phenethyloxy, phenylpropoxy, phenylbutoxy, phenylpentyloxy, phenylethoxy, and the like, in which the preferred one may be phenyl(C_{1}-C_{4})alkoxy, and the most preferred one may be benzyloxy.

"Carboxy(lower)alkoxy" is the above-mentioned lower alkoxy substituted by carboxy, such as carboxymethoxy, carboxyethoxy, carboxypropoxy, carboxybutoxy, carboxypentyloxy, carboxyethoxy, and the like, in which the preferred one may be carboxy(C_{1}-C_{4})alkoxy, and the most preferred one may be carboxymethoxy.

Suitable example of "lower alkoxy carbonyl" and "lower alkoxy carbonyl" moiety may be methoxy carbonyl, ethoxy carbonyl, propoxy carbonyl, butoxy carbonyl, pentyloxy carbonyl, hexyloxy carbonyl, and the like, in which the preferred one may be (C_{1}-C_{4})alkoxy carbonyl, and the more preferred one may be methoxy carbonyl, ethoxy carbonyl and butoxy carbonyl.

"Lower alkoxy carbonyl(lower)alkoxy" is the above-mentioned (lower) alkoxy substituted by the above-mentioned lower alkoxy carbonyl, such as, methoxy carbonyl methoxy, methoxy carbonylethoxy, methoxy carbonyl propoxy, methoxy carbonylbutoxy, methoxy carbonylpentyloxy, methoxy carbonyl hexyloxy, ethoxy carbonyl methoxy, propoxy carbonyl methoxy, butoxy carbonyl methoxy, pentyloxy carbonyl methoxy, hexyloxy carbonyl methoxy, ethoxy carbonylethoxy, ethoxy carbonyl propoxy, and the like, in which the preferred one may be (C_{1}-C_{4})alkoxy carbonyl(C_{1}-C_{4})alkoxy, and the most preferred one may be ethoxy carbonyl methoxy.

"Lower alkoxy carbonylamino" is amino substituted by the above-mentioned lower alkoxy carbonyl, such as, methoxy carbonylamino, ethoxy carbonylamino, propoxy carbonylamino, butoxy carbonylamino, pentyloxy carbonylamino, hexyloxy carbonylamino, and the like, in which the preferred one may be (C_{1}-C_{4})alkoxy carbonylamino, and the more preferred one may be methoxy carbonylamino, ethoxy carbonylamino and butoxy carbonylamino.

The lower alkoxy carbonylamino moiety of "lower alkoxy carbonylamino-sulfonylamino" may be those as described above, and the suitable example of "lower alkoxy carbonylaminosulfonylamino" may be methoxy carbonylamino-sulfonylamino, ethoxy carbonylaminosulfonylamino, propoxy carbonylamino-
sulfonylamino, butoxycarbonylaminosulfonylamino, pentyloxy carbonylaminosulfonylamino, hexyloxy carbonylaminosulfonylamino, and the like, in which the preferred one may be (C₁-C₄)alkoxycarbonylaminosulfonylamino, and the most preferred one may be ethoxycarbonylaminosulfonylamino.

The lower alkoxy carbonyl moiety and lower alkyl moiety of "lower alkoxy carbonyl(lower alkylamino)" may be those as described above respectively, and the suitable example of "lower alkoxy carbonyl(lower alkylamino)" may be methoxycarbonylmethylamino, ethoxycarbonylmethylamino, propoxycarbonylmethylamino, butoxycarbonylmethylamino, pentyloxy carbonylmethylamino, hexyloxy carbonylmethylamino, methoxy carbonyl ethylamino, methoxy carbonyl propylamino, methoxy carbonyl butylamino, methoxy carbonyl pentylamino, methoxy carbonyl hexylamino, ethoxycarbonyl ethylamino, propoxycarbonyl ethylamino, and the like, in which the preferred one may be (C₁-C₄)alkoxycarbonyl(C₁-C₄)alkylamino, and the most preferred one may be ethoxycarbonylmethylamino.

The lower alkyl moiety of "hydroxy(lower alkyl)" may be the above-mentioned lower alkyl and the suitable example of "hydroxy(lower alkyl)" may be hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, hydroxypentyl, hydroxyhexyl, and the like, in which the preferred one may be hydroxy(C₁-C₄)alkyl, and the more preferred one may be hydroxymethyl and hydroxyethyl.

"Carboxy(lower alkyl)" is the above-mentioned lower alkyl substituted by carboxy, and the suitable example may be carboxymethyl, carboxyethyl, carboxypropyl, carboxybutyl, carboxypentyl, carboxyhexyl, and the like, in which the preferred one may be carboxy(C₁-C₄)alkyl, and the more preferred one may be carboxymethyl.

"Carboxy(lower alkylamino)" is amino substituted by the above-mentioned carboxy(lower alkyl), and the suitable example may be carboxymethylamino, carboxyethylamino, carboxypropylamino, carboxybutylamino, carboxypentylamino, carboxyhexylamino, and the like, in which the preferred one may be carboxy(C₁-C₄)alkylamino, and the most preferred one may be carboxymethylamino.

Suitable example of "amino(lower alkyl)" may be aminomethyl, aminoethyl, aminopropyl, aminobutyl, aminopentyl, aminohexyl, and the like, in which the preferred one may be amino(C₁-C₄)alkyl, and the most preferred one may be aminomethyl.

"Lower alkylsulfonylamino(lower alkyl)" is the above-mentioned lower alkyl substituted by the above-mentioned lower alkylsulfonylamino, and the suitable example may be methylsulfonylimethyl, ethylsulfonylimethyl,
propylsulfonylaminomethyl, butylsulfonylaminomethyl, pentylsulfonylaminomethyl, hexylsulfonylaminomethyl, methylsulfonylaminopropyl, methylsulfonylaminobutyl, methylsulfonylaminopentyl, methylsulfonylaminohexyl, ethylsulfonylaminooethyl, propylsulfonylaminooethyl, butylsulfonylaminooethyl, and the like, in which the preferred one may be \((C_1-C_4)\)alkylsulfonylamino\((C_1-C_4)\)alkyl, and the most preferred one may be methylsulfonylaminomethyl.

"Lower alkylcarbonyl" moiety is carbonyl substituted by above-mentioned lower alkyl, and the suitable example may be methylcarbonyl, ethylcarbonyl, propylcarbonyl, butylcarbonyl, pentylcarbonyl, hexylcarbonyl, and the like, in which the preferred one may be \((C_1-C_4)\)alkylcarbonyl, and the most preferred one may be methylcarbonyl.

"Lower alkylcarbonylamino" is amino substituted by the above-mentioned lower alkylcarbonyl, and the suitable example may be methylcarbonylamino, ethylcarbonylamino, propylcarbonylamino, butylcarbonylamino, pentylcarbonylamino, hexylcarbonylamino, and the like, in which the preferred one may be \((C_1-C_4)\)alkylcarbonylamino, and the more preferred one may be methylcarbonylamino and ethylcarbonylamino, and the most preferred one may be methylcarbonylamino.

The lower alkyl moiety of "lower alkylaminocarbonylamino" may be those as described above, and the suitable example of "lower alkylaminocarbonylamino" may be methyaminocarbonylamino, ethylaminocarbonylamino, propylaminocarbonylamino, butylaminocarbonylamino, pentylaminocarbonylamino, hexylaminocarbonylamino, and the like, in which the preferred one may be \((C_1-C_4)\)alkylaminocarbonylamino, and the most preferred one may be methyaminocarbonylamino.

The lower alkoxycarbonyl moiety of "lower alkoxycarboxyloxy" may be those as described above, and the suitable example of "lower alkoxycarboxyloxy" may be methoxycarboxyloxy, ethoxycarboxyloxy, propoxycarboxyloxy, butoxycarboxyloxy, pentyloxycarboxyloxy, hexyloxycarboxyloxy, and the like, in which the preferred one may be \((C_1-C_4)\)alkoxycarboxyloxy, and the more preferred one may be methoxycarboxyloxy and propoxycarboxyloxy, and the most preferred one may be methoxycarboxyloxy.

The lower alkyl moiety of "lower alkylcarboxyloxy" may be those as described above, and the suitable example of "lower alkylcarboxyloxy" may be methylcarboxyloxy, ethylcarboxyloxy, propylcarboxyloxy, butylcarboxyloxy, pentylicarboxyloxy, hexylcarboxyloxy, and the like, in which the preferred one may be \((C_1-C_4)\)alkylcarboxyloxy, and the more preferred one may be
methylcarbonyloxy and butylcarbonyloxy, and the most preferred one may be methylcarbonyloxy.

"Lower alkylcarbamoyl" is carbamoyl substituted by the above-mentioned lower alkyl, and the suitable example may be methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, butylcarbamoyl, pentylcarbamoyl, hexylcarbamoyl, and the like, in which the preferred one may be (C<sub>1</sub>-C<sub>4</sub>)alkylcarbamoyl, and the most preferred one may be methylcarbamoyl.

Suitable example of "lower alkylsulfonylcarbamoyl" may be methylsulfonylcarbamoyl, ethylsulfonylcarbamoyl, propylsulfonylcarbamoyl, butylsulfonylcarbamoyl, pentylsulfonylcarbamoyl, hexylsulfonylcarbamoyl, and the like, in which the preferred one may be (C<sub>1</sub>-C<sub>4</sub>)alkylsulfonylcarbamoyl, and the most preferred one may be methylsulfonylcarbamoyl.

The halogen, lower alkyl and lower alkoxy moieties of "phenylsulfonylamino wherein phenyl may be substituted by halogen atom, lower alkyl or lower alkoxy" may be those as described above respectively, and the positions of halogen atom, lower alkyl and lower alkoxy are not limited as long as each position is chemically acceptable. The suitable example of "phenylsulfonylamino wherein phenyl may be substituted by halogen atom, lower alkyl or lower alkoxy" may be phenylsulfonylamino and chlorophenylsulfonylamino, and the more preferred one may be phenylsulfonylamino and p-chlorophenylsulfonylamino.

The morpholiny1 includes 1-morpholiny1, 2-morpholiny1, 3-morpholiny1 and morpholino, and the preferred one is morpholino.

The isothiazolidiny1 includes 2-isothiazolidiny1, 3-isothiazolidiny1, 4-isothiazolidiny1 and 5-isothiazolidiny1, and the preferred one is 2-isothiazolidiny1.

The pyrroldiny1 includes 1-pyrroldiny1, 2-pyrroldiny1 and 3-pyrroldiny1, and the preferred one is 1-pyrroldiny1.

The imidazolidiny1 includes 1-imidazolidiny1, 2-imidazolidiny1, 4-imidazolidiny1 and the preferred one is 1-imidazolidiny1.

The isothiazolidiny1 may be substituted by 1 or 2 oxo(s) and the position(s) of oxo(s) is(are) not limited as long as the position is chemically acceptable. The preferred one is 1,1-dioxoisothiazolidin-2-yl.

The pyrroldiny1 and imidazolidiny1 may be substituted by oxo and the position of oxo is not limited as long as the position is chemically acceptable.

The preferred ones are respectively 2-oxopyrroldiny1 and 2-oxoimidazolidiny1.

The substituents represented by R<sup>2</sup>, R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> may bind at any position of ortho-, meta- and para-positions in each phenyl group in the general formula [II], with preference given to the meta- and/or para-position(s).
The phenyl, pyridyl, indolyl, benzimidazolyl and 2,3-dihydro-2-oxobenzimidazolyl represented by A may have 1 to 3 same or different substituent(s) and the position of the substituent(s) is not limited as long as the position is chemically acceptable.

When A is substituted phenyl, said phenyl may have substituent(s) at any position of ortho-, meta- and para-positions, preferably at the meta- and/or para-position(s).

The pyridyl represented by A includes pyridin-1-yl, pyridin-2-yl, pyridin-3-yl and pyridin-4-yl, and the preferred one is pyridin-3-yl. When A is substituted pyridyl, the substituent(s) may be at any position of the pyridine ring.

The indolyl represented by A includes indol-1-yl, indol-2-yl, indol-3-yl, indol-4-yl, indol-5-yl, indol-6-yl and indol-7-yl, and the preferred one is indol-4-yl. When A is substituted indolyl, the substituent(s) may be at any position of the indole ring.

The benzimidazolyl represented by A includes benzimidazol-1-yl, benzimidazol-2-yl, benzimidazol-4-yl, benzimidazol-5-yl, benzimidazol-6-yl, benzimidazol-7-yl, and the preferred one is benzimidazol-7-yl. When A is substituted benzimidazolyl, the substituent(s) may be at any position of the benzimidazole ring.

The 2,3-dihydro-2-oxobenzimidazolyl represented by A includes 2,3-dihydro-2-oxobenzimidazol-1-yl, 2,3-dihydro-2-oxobenzimidazol-3-yl, 2,3-dihydro-2-oxobenzimidazol-4-yl and 2,3-dihydro-2-oxobenzimidazol-5-yl, and the preferred one is 2,3-dihydro-2-oxobenzimidazol-4-yl. When A is substituted 2,3-dihydro-2-oxobenzimidazolyl, the substituent(s) may be at any position of the 2,3-dihydro-2-oxobenzimidazole ring.

Preferred embodiments of the object compound [I] are as follow:

A is phenyl, pyridyl, indolyl, benzimidazolyl or 2,3-dihydro-2-oxobenzimidazolyl, each of which may have 1 to 3 same or different substituent(s) selected from the group consisting of hydroxy, lower alkylcarbonyloxy, lower alkoxy carbonyloxy, amino, halogen atom, lower alkylsulfonlamino, carboxy(lower)alkylsulfonlamino, N-lower alkyl-N-(lower)alkylsulfonlamino, mono(or di or tri)halo(lower)alkylsulfonlamino, phenyl(lower)alkylsulfonlamino, thieryl(sulfonlamino, phenyl(lower)alkoxy, hydroxy(lower)alkyl, amino(lower)alkyl, lower alkylsulfonlamino(lower)alkyl, formylamino, lower alkylcarbonylamino, [N,N-di(lower)alkylsulfamoylamino, lower
alkoxycarbonylaminosulfonylelamino, lower
alkoxycarbonylamino, ureido, lower alkylaminocarbonylamino,
lower alkoxycarbonyl, formyl, carbamoyl, nitro and
phenylsulfonylelamino wherein phenyl may be substituted by
halogen atom, lower alkyl or lower alkoxy,

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\[ X \]
is single bond or \(-\text{O-CH}_2\)-,

\[ R^1 \]
is hydrogen atom or amino-protective group,

\[ R^2 \]
is hydrogen atom, lower alkyl, hydroxy(lower)alkyl or
  carboxy(lower)alkyl,

\[ R^3 \]
is hydrogen atom or hydroxy,

\[ R^4, R^5, R^6 \text{ and } R^7 \]
are each independently hydrogen atom, hydroxy, lower alkyl,
  lower alkoxy, amino, lower alkylsulfonylelamino, lower
  alkoxycarbonylamino, carboxy(lower)alkylamino, lower
  alkoxycarbonyl(lower)alkylamino, halogen atom,

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\[ R^8 \]
phenyl(lower)alkoxy, lower alkoxycarbonyloxy, lower
  alkycarbonyloxy, lower alkoxycarbonyl(lower)alkoxy,
  carboxy(lower)alkoxy, carbamoyl, lower alkycarbamoyl, lower
  alkylsulfonylecarbamoyl, morpholinyl, pyrrolidinyl or
  imidazolidinyl wherein pyrrolidinyl and imidazolidinyl may be
  substituted by oxo, and

\[ n \]
is 0 or 1;

provided that \( A \) should be phenyl, pyridyl, indolyl, benzimidazolyl or 2,3-dihydro-

\[ \text{2-oxobenzimidazolyl} \]
each of which has at least one substituent selected from the
group consisting of lower alkylcarbonyloxy, lower alkoxycarbonyloxy,

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\[ \text{carboxy(lower)alkylsulfonylelamino, N-lower alkyl-N-(lower)alkylsulfonylelamino,} \]
\[ \text{mono(or di or tri) halo(lower)alkylsulfonylelamino, phenyl(lower)alkylsulfonylelamino,} \]
\[ \text{thienylsulfonylelamino, hydroxy(lower)alkyl, amino(lower)alkyl, lower} \]
\[ \text{alkylsulfonylelamino(lower)alkyl, formylamino, lower alkylcarbonylamino,} \]
\[ \text{[N,N-di(lower)alkylsulfamoyl]amino, lower alkoxycarbonylaminosulfonylelamino,} \]
\[ \text{lower alkoxycarbonylamino, ureido, lower alkylaminocarbonylamino, lower} \]
\[ \text{alkoxycarbonyl, formyl, carbamoyl, nitro and phenylsulfonylelamino wherein} \]
\[ \text{phenyl may be substituted by halogen atom, lower alkyl or lower alkoxy, when } n \]
\[ \text{is 1, } R^2 \text{ is hydrogen atom or lower alkyl, and } R^4, R^5, R^6 \text{ and } R^7 \]
\[ \text{are each} \]

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\[ \text{independently hydrogen atom, hydroxy, lower alkyl, lower alkoxy, amino, lower} \]
\[ \text{alkylsulfonylelamino, lower alkoxycarbonylamino, carbamoyl, lower} \]
\[ \text{alkylcarbamoyl or pyrrolidinyl; and} \]

\[ \text{provided that } A \text{ should be phenyl, pyridyl, indolyl or benzimidazolyl, each of} \]
\[ \text{which has at least one substituent selected from the group consisting of lower} \]

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\[ \text{alkylsulfonylelamino, lower alkoxycarbonylamino, carbamoyl, lower} \]
\[ \text{alkylcarbamoyl or pyrrolidinyl; and} \]

\[ \text{provided that } A \text{ should be phenyl, pyridyl, indolyl or benzimidazolyl, each of} \]
\[ \text{which has at least one substituent selected from the group consisting of lower} \]

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alkylsulfonylamino, carboxy(lower)alkylsulfonylamino, N-lower alkyl-N-(lower)alkylsulfonylamino, mono(or di or tri)halo(lower)alkylsulfonylamino, phenyl(lower)alkylsulfonylamino, thiensulfonylelamino, hydroxy(lower)alkyl, amino(lower)alkyl, lower alkylsulfonylamino(lower)alkyl,

\[N,N-di(lower)alkylsulfamoyl]amino, lower alkoxy carbonylamino sulfonylamino, lower alkoxy carbonyl, formyl and phenylsulfonylelamino wherein phenyl may be substituted by halogen atom, lower alkyl or lower alkoxy, when \( n \) is 0 or 1, \( R^2 \) is hydrogen atom or lower alkyl, \( R^3 \) is hydrogen atom, \( R^4 \) and \( R^6 \) are each hydrogen atom and \( R^5 \) and \( R^7 \) are each independently lower alkoxy carbonyl(lower)alkoxy or carboxy(lower)alkoxy,

or a pharmaceutically acceptable salt thereof.

The preferred embodiments of the object compound [I] are as follow:

A is phenyl which may have 1 to 3 same or different substituent(s) selected from the group consisting of hydroxy, amino, lower alkylsulfonylamino, phenyl(lower)alkoxy, hydroxy(lower)alkyl, amino(lower)alkyl, lower alkylsulfonylamino(lower)alkyl, formylamino, lower alkoxy carbonylamino, [N,N-di(lower)alkylsulfamoyl]amino, lower alkoxy carbonylamino, ureido, lower alkoxy carbonyl, formyl,

nitro and phenylsulfonylelamino wherein phenyl may be substituted by halogen atom,

\( X \) is single bond or \(-O-\text{CH}_2-\),

\( R^1 \) is hydrogen atom or amino-protective group,

\( R^2 \) is hydrogen atom, lower alkyl or hydroxy(lower)alkyl,

\( R^3 \) is hydrogen atom or hydroxy,

\( R^1, R^5, R^6 \) and \( R^7 \) are each independently hydrogen atom, hydroxy, lower alkoxy, amino, lower alkoxy carbonylamino, halogen atom, phenyl(lower)alkoxy, lower alkoxy carbonyl(lower)alkoxy or carboxy(lower)alkoxy, and

\( n \) is 0 or 1;

provided that A should be phenyl which has at least one substituent selected from the group consisting of hydroxy(lower)alkyl, amino(lower)alkyl, lower alkylsulfonylamino(lower)alkyl, formylamino, lower alkoxy carbonylamino, [N,N-di(lower)alkylsulfamoyl]amino, lower alkoxy carbonylamino, ureido, lower alkoxy carbonyl, formyl, nitro and phenylsulfonylelamino wherein phenyl may be substituted by halogen atom, when \( n \) is 1, \( R^2 \) is hydrogen atom or lower alkyl, and \( R^4, R^5, R^6 \) and \( R^7 \) are each independently hydrogen atom, hydroxy, lower alkoxy, amino or lower alkoxy carbonylamino; and
provided that A should be phenyl which has at least one substituent selected from the group consisting of lower alkylsulfonylamino, hydroxy(lower)alkyl, amino(lower)alkyl, lower alkylsulfonylamino(lower)alkyl, [N,N-di(lower)alkylsulfamoyl]amino, lower alkoxy carbonyl, formyl and phenylsulfonylamino wherein phenyl may be substituted by halogen atom, when n is 0 or 1, R² is hydrogen atom or lower alkyl, R³ is hydrogen atom, R⁴ and R⁶ are each hydrogen atom and R⁵ and R⁷ are each independently lower alkoxy carbonyl(lower)alkoxy or carboxy(lower)alkoxy, or a pharmaceutically acceptable salt thereof.

In the object compound [I], the further more preferred ones are recited. Compounds having the formula [I] wherein

A is phenyl which has 1 or 2 same or different substituent(s) selected from the group consisting of hydroxy, lower alkylsulfonylamino, hydroxy(lower)alkyl, formylamino, [N,N-di(lower)alkylsulfamoyl]amino and phenylsulfonylamino wherein phenyl may be substituted by halogen atom,

X is single bond or –O–CH₂–,

R¹, R² and R³ are each hydrogen atom,

R⁴, R⁵, R⁶ and R⁷ are each independently hydrogen atom, lower alkoxy or lower alkoxy carbonylamino, and

n is 0 or 1,

provided that A should be phenyl which has at least one substituent selected from the group consisting of hydroxy(lower)alkyl, formylamino, [N,N-di(lower)alkylsulfamoyl]amino and phenylsulfonylamino wherein phenyl may be substituted by halogen atom, when n is 1, or a pharmaceutically acceptable salt thereof. Compounds having the formula [I] wherein

A is phenyl which has 1 or 2 same or different substituent(s) selected from the group consisting of hydroxy, lower alkylsulfonylamino, hydroxy(lower)alkyl, formylamino, [N,N-di(lower)alkylsulfamoyl]amino and phenylsulfonylamino wherein phenyl may be substituted by halogen atom,

X is single bond or –O–CH₂–,

R¹, R² and R³ are each hydrogen atom,

R⁴, R⁵, R⁶ and R⁷ are each independently hydrogen atom or hydroxy, and

n is 0,

or a pharmaceutically acceptable salt thereof.

Preferred objective compounds [I] are as follows.
(R)-1-(4-hydroxy-3-benzenesulfonylaminophenyl)-2-[[2,2-bis(4-methoxyphenyl)ethyl]amino]ethanol
(RS)-1-(4-hydroxy-3-benzenesulfonylaminophenyl)-2-[[3,3-bis(4-methoxyphenyl)propyl]amino]ethanol
(S)-1-(4-hydroxy-3-formylaminophenoxy)-3-[[3,3-bis(4-methoxyphenyl)propyl]amino]-2-propanol
(R)-2-[[2,2-bis[4-(methoxycarbonyl)amino]phenyl]ethyl]amino]-1-[[4-hydroxy-3-(benzenesulfonyl)phenyl]ethanol
(R)-2-[[2,2-bis[4-(methoxycarbonyl)amino]phenyl]ethyl]amino]-1-[[3-formylamino-4-hydroxyphenyl]ethanol
(R)-1-(4-hydroxy-3-methanesulfonylaminophenyl)-2-[[2,2-bis(4-hydroxyphenyl)ethyl]amino]ethanol
(R)-1-(4-hydroxy-3-ethanesulfonylaminophenyl)-2-[[2,2-bis(4-hydroxyphenyl)ethyl]amino]ethanol
(R)-1-[4-hydroxy-3-[[N,N-dimethylsulfonyl]amino]phenyl]-2-[[2,2-bis(4-hydroxyphenyl)ethyl]amino]ethanol

Suitable salts of the object aminoalcohol derivatives [I] are pharmaceutically acceptable salts and include conventional non-toxic salts such as an inorganic acid addition salt [e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.], an organic acid addition salt [e.g. formate, acetate, trifluoroacetate, oxalate, maleate, fumarate, tartrate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc.], an alkali metal salt [e.g. sodium salt, potassium salt, etc.] or the like.

The processes for preparing the object compound [I] are explained in detail in the following.

Process 1

The object compound [I] or a salt thereof can be prepared by reacting a compound [II] or a salt thereof with a compound [III] or a salt thereof.

Suitable salt of the compounds [II] and [III] may be the same as those exemplified for the compound [I].

The reaction is preferably carried out in the presence of a base such as an alkali metal carbonate [e.g. sodium carbonate, potassium carbonate, etc.], an alkaline earth metal carbonate [e.g. magnesium carbonate, calcium carbonate, etc.], an alkali metal bicarbonate [e.g. sodium bicarbonate, potassium bicarbonate, etc.], tri(lower)alkylamine [e.g. trimethylamine, triethylamine, etc.], picoline or the like.

The reaction is usually carried out in a conventional solvent, such as an alcohol [e.g. methanol, ethanol, propanol, isopropanol, etc.], diethyl ether,
tetrahydrofuran, dioxane, or any other organic solvent which does not adversely influence the reaction.

The reaction temperature is not critical, and the reaction can be carried out under cooling to heating.

5 Process 2

The object compound [lb] or a salt thereof can be prepared by subjecting a compound [la] or a salt thereof to elimination reaction of the amino-protective group.

Suitable salts of the compounds [la] and [lb] may be the same as those exemplified for the compound [l].

This reaction is carried out in accordance with a conventional method such as hydrolysis, reduction or the like.

The hydrolysis is preferably carried out in the presence of a base or an acid including Lewis acid.

Suitable base may include an inorganic base and an organic base such as an alkali metal [e.g. sodium, potassium, etc.], an alkaline earth metal [e.g. magnesium, calcium, etc.], the hydroxide or carbonate or bicarbonate thereof, hydrazine, trialkylamine [e.g. trimethylamine, triethylamine, etc.], picoline, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,4-diazabicyclo[2.2.2]octane, 1,8-diazabicyclo[5.4.0]undec-7-ene, or the like.

Suitable acid may include an organic acid [e.g. formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, etc.], an inorganic acid [e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, hydrogen chloride, hydrogen bromide, hydrogen fluoride, etc.] and an acid addition salt compound [e.g. pyridine hydrochloride, etc.].

The elimination using trihaloacetic acid [e.g. trichloroacetic acid, trifluoroacetic acid, etc.] or the like is preferably carried out in the presence of cation trapping agents [e.g. anisole, phenol, etc.].

The reaction is usually carried out in a solvent such as water, an alcohol [e.g. methanol, ethanol, etc.], methylene chloride, chloroform, tetrachloromethane, tetrahydrofuran, a mixture thereof or any other solvent which does not adversely influence the reaction. A liquid base or acid can be also used as the solvent.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

The reduction method applicable for the elimination reaction may include chemical reduction and catalytic reduction.

Suitable reducing agents to be used in chemical reduction are a combination of metal [e.g. tin, zinc, iron, etc.] or metallic compound [e.g.
chromium chloride, chromium acetate, etc.] and an organic or inorganic acid [e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc.].

Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalysts [e.g. platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.], palladium catalysts [e.g. spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate, etc.], nickel catalysts [e.g. reduced nickel, nickel oxide, Raney nickel, etc.], cobalt catalysts [e.g. reduced cobalt, Raney cobalt, etc.], iron catalysts [e.g. reduced iron, Raney iron, etc.], copper catalysts [e.g. reduced copper, Raney copper, Ullman copper, etc.] and the like.

In case that the amino-protective group is benzyl, the reduction is preferably carried out in the presence of a combination of palladium catalysts [e.g. palladium black, palladium on carbon, etc.] and formic acid or its salt [e.g. ammonium formate, etc.].

The reduction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, an alcohol [e.g. methanol, ethanol, propanol, etc.], chlorobenzene, N,N-dimethylformamide, or a mixture thereof. Additionally, in case that the above-mentioned acids to be used in chemical reduction are in liquid, they can also be used as a solvent. Further, a suitable solvent to be used in catalytic reduction may be the above-mentioned solvent, and other conventional solvent such as diethyl ether, dioxane, tetrahydrofuran, etc. or a mixture thereof.

The reaction temperature of this reduction is not critical and the reaction is usually carried out under cooling to heating.

**Process 3**

The object compound [Ic] or a salt thereof can be prepared by reacting a compound [IV] or a salt thereof with a compound [V] or a salt thereof.

Suitable salt of the compounds [Ic], [IV] and [V] may be the same as those exemplified for the compound [I].

The reaction is carried out in the manner disclosed in Preparation 3 to be described later or similar manners thereto.

In addition to the above-mentioned processes, the object compound [I] or a salt thereof can be obtained by modification of substituent(s) of A and R⁴, R⁵, R⁶, and R⁷, by a known method or according to the methods as described in Preparations or Examples or to the similar manners thereto.

The preparation of the starting compounds [II], [III], [IV] and [V] or salts
thereof can be carried out by the known method or according to the methods as described in Preparations or to the similar manners thereto.

The compounds obtained by the above processes can be isolated and purified by a conventional method such as pulverization, recrystallization, column chromatography, reprecipitation, or the like, and converted to the desired salt in conventional manners, if necessary.

It is to be noted that the compound [I] and the other compounds may include one or more stereoisomers due to asymmetric carbon atoms, and all of such isomers and mixture thereof are included within the scope of this invention.

It is further to be noted that isomerization or rearrangement of the compound [I] and the other compounds may occur due to the effect of the light, acid, base or the like, and the compound obtained as the result of said isomerization or rearrangement is also included within the scope of the present invention.

It is also to be noted that the solvating form of the compound [I] and the other compounds (e.g. hydrate, etc.) and any form of the crystal of the compound [I] and the other compounds are included within the scope of the present invention.

The object compound [I] or a salt thereof possesses gut selective sympathomimetic, anti-ulcerous, anti-pancreatitis, lipolytic, anti-urinary incontinence and anti-pollakiuria activities, and are useful for the treatment and/or prevention of gastro-intestinal disorders caused by smooth muscle contractions in human beings or animals, and more particularly for the treatment and/or prevention of spasm or hyperanakinesia in case of irritable bowel syndrome, gastritis, gastric ulcer, duodenal ulcer, enteritis, cholecystopathy, cholangitis, urinary calculus and the like; for the treatment and/or prevention of ulcer such as gastric ulcer, duodenal ulcer, peptic ulcer, ulcer caused by non steroidal anti-inflammatory drugs, or the like; for the treatment and/or prevention of dysuria such as pollakiuria, urinary incontinence or the like in case of nervous pollakiuria, neurogenic bladder dysfunction, nocturia, unstable bladder, cystospasm, chronic cystitis, chronic prostatitis, prostatic hypertrophy or the like; for the treatment and/or prevention of pancreatitis, obesity, diabetes, glycosuria, hyperlipidemia, hypertension, atherosclerosis, glaucoma, melancholia, depression or the like; for the treatment and/or prevention of diseases as the result of insulin resistance (e.g. hypertension, hyperinsulinemia, etc.); for reducing a wasting condition, and the like.

The pharmaceutical composition of the present invention can be used in
the form of a pharmaceutical preparation, for example, in solid, semisolid or liquid form, which contains an aminoalcohol derivative in the present application or a pharmaceutically acceptable salt thereof, as an active ingredient in admixture with an organic or inorganic pharmaceutically acceptable carrier or excipient suitable for rectal, pulmonary (nasal or buccal inhalation), nasal, ocular, external (topical), oral or parenteral (including subcutaneous, intravenous and intramuscular) administrations or insufflation.

The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, troches, capsules, suppositories, creams, ointments, aerosols, powders for insufflation, solutions, emulsions, suspensions, and any other forms suitable for use. And, if necessary, in addition, auxiliary, stabilizing, thickening and coloring agents and perfumes may be used.

The aminoalcohol derivative in the present invention or a pharmaceutically acceptable salt thereof is included in the pharmaceutical composition in an amount sufficient to produce the desired effect upon the process or condition of the diseases.

The pharmaceutical composition of the present invention can be manufactured by the conventional method in this field of the art. If necessary, the technique generally used in this field of the art for improving the bioavailability of a drug can be applied to the pharmaceutical composition of the present invention.

For applying the composition to a human being or an animal, it is preferable to apply it by intravenous (including i.v. infusion), intramuscular, pulmonary, or oral administration, or insufflation.

While the dosage of therapeutically effective amount of the aminoalcohol derivative in the present invention varies from and also depends upon the age and condition of each individual patient to be treated, in the case of intravenous administration, a daily dose of 0.01-100 mg of the aminoalcohol derivative in the present invention per kg weight of a human being or an animal, in case of intramuscular administration, a daily dose of 0.01-100 mg of the aminoalcohol derivative in the present invention per kg weight of a human being or an animal, in case of oral administration, a daily dose of 0.01-200 mg of the aminoalcohol derivative in the present invention per kg weight of a human being or an animal is generally given for the prophylactic and/or therapeutic treatment of above-mentioned diseases in a human being or an animal.

In order to show the usefulness of the compound [I] for the prophylactic and therapeutic treatment of above-mentioned disease in human beings or
animals, the pharmacological test data of a representative compound thereof are shown in the following.

**Test**

Effect on the increase in intravesical pressure induced by carbachol in anesthetized dog

**Test Compound**

1. (R)-1-{4-hydroxy-3-methanesulfonylaminophenyl}-2-{[2,2-bis(4-hydroxyphenyl)ethyl]amino}ethanol (the object compound of Example 12 in this invention)
2. 2-[[3-(7-carboxymethoxyindol-3-yl)-2-propylamino]-[1R]-1-(3-chlorophenyl)ethanol (the objective compound of Example 15 in WO96/16938)
3. (2R,2R)-3-[2-{2-(3-chlorophenyl)-2-hydroxyethylamino}propyl]-7-indolyloxyacetic acid (the objective compound of Example 6 in Japanese patent publication JP11-255743)

**Test Method**

Female Beagle dogs weighing 8.0-15.0 kg were fasted for 24 hours and maintained under halothane anesthesia. A 12F Foley catheter was lubricated with water soluble jelly, inserted into the urethral orifice and advanced approximately 10 cm until the balloon tip was placed well inside the bladder. The balloon was then inflated with 5 ml of room air and the catheter was slowly withdrawn to just the point where the first resistance was felt at the bladder neck. Urine was completely drained out through the catheter, and 30 ml of biological saline was infused. The catheter was connected to pressure transducer, and intravesical pressure was continuously recorded. The test compound was injected intravenously at 5 minutes before the administration of carbachol (1.8 µg/kg).

**Test Results**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Increase in intravesical pressure (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>9.5 ± 1.6</td>
</tr>
<tr>
<td>Test Compound (1) (0.001 mg/kg)</td>
<td>1.7 ± 0.4*</td>
</tr>
</tbody>
</table>

* P<0.01 vs Control (ANOVA) (N=3)
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Increase in intravesical pressure (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>6.0±0.8</td>
</tr>
<tr>
<td>Test Compound (2)</td>
<td>0.8±0.3**</td>
</tr>
<tr>
<td>(0.001 mg/kg)</td>
<td></td>
</tr>
</tbody>
</table>

** P<0.01 vs Control (ANOVA) (N=3)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Increase in intravesical pressure (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>5.8±0.4</td>
</tr>
<tr>
<td>Test Compound (3)</td>
<td>2.2±0.5***</td>
</tr>
<tr>
<td>(0.00032 mg/kg)</td>
<td></td>
</tr>
</tbody>
</table>

*** P<0.01 vs Control (ANOVA) (N=3)

The above test results show that the test compounds (1), (2) and (3) possess a relaxation effect on the smooth muscle in the urinary bladder and these compounds are useful for the treatment of pollakiuria and urinary incontinence in human beings or animals. The test compounds (2) and (3) have been known as described in the above-mentioned publications. It has not been known, however, that these compounds are useful for the treatment of pollakiuria and urinary incontinence in human beings or animals.

The following Preparations and Examples are given for the purpose of illustrating this invention.

**Preparation 1**

N-Benzyl-2,2-bis(4-methoxyphenyl)ethylamine was obtained from methyl dibenzylaminoacetate and 4-bromoanisole by a similar manner to that of Preparation 3 to be described later, followed by catalytic hydrogenation on palladium on charcoal in a usual manner.

\(^1\text{H}-\text{NMR (CDCl}_3, \delta) : 3.14(2H, d, J=7.7Hz), 3.77(6H, s), 3.79(2H, s), 4.12(1H, t, J=7.5Hz), 6.81(4H, d, J=8.7Hz), 7.11(4H, d, J=8.7Hz), 7.2-7.4(5H, m)\)

MS m/z : 348(M+1)

**Preparation 2**

To a solution of 4-benzyloxy-3-nitrophenyl acetate (4.20 g) in methanol (20 ml), 28% sodium methoxide - methanol solution (2.96 g) was added and evaporated. To the crude residue, N,N-dimethylformamide (20 ml) and (S)-[3-nitrobenzenesulfonyloxy)methyl]oxirane (3.80 g) were added. The mixture was
stirred at room temperature overnight, and worked up in the usual manner to
give (S)-[4-benzyloxy-3-nitrophenoxymethyl]oxirane (4.30 g).

\[ ^1H\text{-NMR (CDCl}_3, \delta) : 2.72-2.77 (1H, m), 2.92 (1H, quintet, J=4.8Hz), 3.32-3.37 (1H, m), 3.91 (1H, quartet, J=5.9Hz), 4.27 (1H, dd, J=2.8 and 11.4Hz), 5.18 (2H, s), 7.07-7.15 (2H, m), 7.34-7.46 (6H, m) \]

**Example 1**

The following compound was obtained according to a similar manner to
that of Preparation 7 to be described later.

(S)-1-(3-Amino-4-benzyloxyphenoxymethyl)-3-[N-benzyl-[2,2-bis(4-methoxy-
phenyl)ethyl]amino]-2-propanol

\[ ^1H\text{-NMR (CDCl}_3, \delta) : 2.66(2H, d, J=6.5Hz), 2.9-3.0(1H, dd), 3.1-3.2(1H, dd), 3.53(1H, d, J=13.6Hz), 3.74(3H, s), 3.76(3H, s), 3.7-4.0(4H, m), 4.10(1H, t), 5.01(2H, s), 6.11-6.26(2H, m), 6.7-6.9(5H, m), 7.0-7.2(6H, m), 7.2-7.5(8H, m) \]

**Example 2**

The following compounds were obtained according to a similar manner to
that of Example 22 to be described later.

1)  (S)-1-(4-Hydroxy-3-methanesulfonylaminophenoxymethyl)-3-[2,2-bis(4-
methoxyphenyl)ethyl]amino]-2-propanol

\[ \text{IR (KBr) : 1610(w), 1512(s), 1460(m), 1325(m), 1248(s), 1176(m), 1151(m), 1034(m), 827(w) cm}^{-1} \]

\[ ^1H\text{-NMR (CD}_3\text{OD, \delta) : 2.7-2.9(2H, m), 2.91(3H, s), 3.1-3.3(2H, m), 3.74(6H, s), 3.81(2H, d, J=5.2Hz), 3.9-4.2(2H, m), 6.58(1H, dd, J=2.9Hz, 8.4Hz), 6.77(1H, d, J=8.4Hz), 6.83(4H, d, J=8.4Hz), 7.17(4H, d, J=8.4Hz) } \]

**Example 3**

The following compound was obtained according to a similar manner to
that of Example 25 to be described later.

(S)-1-(4-Hydroxy-3-fomylaminophenoxymethyl)-3-[2,2-bis(4-methoxy-
phenyl]ethyl[amino]-2-propanol
IR (KBr) : 1678(s), 1608(w), 1512(s), 1446(m), 1248(s), 1180(m), 1034(s),
829(m) cm⁻¹
¹H-NMR (CD₃OD, δ) : 2.7-2.9(2H, m), 3.1-3.2(2H, m), 3.73(6H, s), 3.80(2H, d,
J=5.0Hz), 3.9-4.1(1H, m), 4.04(1H, t, J=7.8Hz), 6.47(1H, dd, J=3.0Hz, 8.8Hz),
6.7-6.8(1H, m), 6.83(4H, d, J=7.6Hz), 7.16(4H, d, J=7.6Hz), 7.70(1H, d, J=2.9Hz),
8.28(1H, s)
MS m/z : 467(M⁺+1)
Example 4

The following compound was obtained according to a similar manner to
that of Preparation 7 to be described later.
(R)-1-[(3-Amino-4-benzylxoyphenyl)-2-[N-benzyl-[2,2-bis(4-methoxyphenyl)ethyl]amino]ethanol
MS m/z : 589(M⁺+1)

Example 5

The following compounds were obtained according to a similar manner to
that of Example 22 to be described later.
(1) (R)-1-[(4-Hydroxy-3-methanesulfonylaminophenyl)-2-[2,2-bis(4-methoxyphenyl)ethyl]amino]ethanol
IR (KBr) : 1610(w), 1512(s), 1460(m), 1323(s), 1248(s), 1153(s), 1115(m), 1034(m),
827(m) cm⁻¹
¹H-NMR (CD₃OD, δ) : 2.75-2.9(2H, m), 2.89(3H, s), 3.17(2H, d, J=7.7Hz),
3.75(6H, s), 4.05(1H, broad t), 4.63(1H, broad t), 6.8-6.9(5H, m), 6.9-7.0(1H, m),
7.12(4H, d, J=6.8Hz), 7.29(1H, brs)
MS m/z : 487(M⁺+1)
(2) (R)-1-[(4-Hydroxy-3-benzenesulfonylaminophenyl)-2-[2,2-bis(4-methoxyphenyl)ethyl]amino]ethanol
IR (KBr) : 1610(m), 1512(s), 1456(m), 1329(m), 1248(s), 1167(s), 1092(m),
1032(m), 827(m) cm⁻¹
¹H-NMR (CD₃OD, δ) : 2.6-3.0(2H, m), 3.14(2H, d, J=7.7Hz), 3.74(6H, s), 4.04(1H,
t, J=7.7Hz), 4.56(1H, broad t), 6.60(1H, d, J=8.2Hz), 6.7-6.9(5H, m), 7.1-7.3(5H,
m), 7.3-7.6(3H, m), 7.74(2H, d, J=7.1Hz)
MS m/z : 549(M⁺+1)

Example 6

The following compound was obtained according to a similar manner to
that of Example 25 to be described later.
(R)-1-[(4-Hydroxy-3-formylaminophenyl)-2-[2,2-bis(4-methoxyphenyl)ethyl]amino]ethanol
IR (KBr): 1676(s), 1512(s), 1456(m), 1248(s), 1178(w), 1034(m), 827(m) cm⁻¹

¹H-NMR (CD₃OD, δ): 2.7-2.9(2H, m), 3.13(2H, d, J=7.9Hz), 3.74(6H, s), 4.03(1H, t, J=7.9Hz), 4.60(1H, t, J=5.6Hz), 6.72-6.88(6H, m), 7.10(4H, d, J=8.7Hz), 7.98(1H, s), 8.29(1H, s)

MS m/z: 437(M⁺+1)

Example 7

To a mixture of (R)-1-(4-benzyloxy-3-aminophenyl)-2-[N-benzyl-[2,2-bis(4-methoxyphenyl)ethyl]amino]ethanol (49 mg), pyridine (40 µl) and dichloromethane (1 ml), methyl chlorocarbonate (10 µl) was added at 0°C. The reaction mixture was stirred at room temperature for 10 minutes and worked up in the usual manner to give (R)-1-(4-benzyloxy-3-methoxycarbonylaminophenyl)-2-[N-benzyl-[2,2-bis(4-methoxyphenyl)ethyl]amino]ethanol. The crude product was hydrogenated on palladium on charcoal in a usual manner and purified by preparative thin-layer chromatography (silica gel, dichloromethane: methanol: concentrated ammonia solution = 9:1:0.1) to afford (R)-1-(4-hydroxy-3-methoxycarbonylaminophenyl)-2-[2,2-bis(4-methoxyphenyl)ethyl]amino]ethanol (27.3 mg).

IR (KBr): 1726(s), 1608(m), 1535(m), 1510(s), 1446(m), 1248(s), 827(m) cm⁻¹

¹H-NMR (CD₃OD, δ): 2.7-2.9(2H, m), 3.13(2H, d, J=7.9Hz), 3.75(6H, s), 4.03(1H, t, J=7.9Hz), 4.60(1H, t, J=7.7Hz), 6.70-6.83(6H, m), 7.10(4H, d, J=8.8Hz), 7.69(1H, s)

MS m/z: 467(M⁺+1)

Example 8

To a solution of (R)-1-(4-benzyloxy-3-aminophenyl)-2-[N-benzyl-[2,2-bis(4-methoxyphenyl)ethyl]amino]ethanol (55 mg) in acetic acid (1 ml), potassium cyanate (10 mg) was added and worked up in the usual manner to give (R)-1-(4-benzyloxy-3-ureidophenyl)-2-[N-benzyl-[2,2-bis(4-methoxyphenyl)ethyl]amino]ethanol. The crude product was hydrogenated on palladium on charcoal in a usual manner and purified by preparative thin-layer chromatography (silica gel, dichloromethane: methanol: concentrated ammonia solution = 9:1:0.1) to afford (R)-1-(4-hydroxy-3-ureidophenyl)-2-[2,2-bis(4-methoxyphenyl)ethyl]amino]ethanol (19.5 mg).

IR (KBr): 1664(s), 1608(s), 1545(s), 1510(s), 1444(m), 1248(s), 1178(m), 1034(m), 827(m) cm⁻¹

¹H-NMR (CD₃OD, δ): 2.7-2.9(2H, m), 3.13(2H, d, J=7.9Hz), 3.75(6H, s), 4.03(1H, t, J=7Hz), 4.59(1H, t, J=6Hz), 6.68-6.84(5H, m), 7.10(4H, d, J=7Hz), 7.63(1H, s)

MS m/z: 452(M⁺+1)

Preparation 3
To a solution of benzyl 4-bromophenyl ether (6.32 g) in tetrahydrofuran (20 ml), butyllithium (1.52M hexane solution, 16.6 ml) was added at -78°C. After 30 minutes, ethyl dibenzylaminoacetate (2.83 g) was added to the reaction mixture and warmed to room temperature. The reaction mixture was worked up in the usual manner, followed by purification by column chromatography (silica gel, hexane : ethyl acetate = 9:1) to give 1,1-bis(4-benzyloxyphenyl)-2-dibenzylaminoethanol (4.34 g).

**Preparation 4**

A mixture of 1,1-bis(4-benzyloxyphenyl)-2-dibenzylaminoethanol (456 mg), methanol (5 ml), 1,4-dioxane (5 ml), 4N hydrogen chloride in 1,4-dioxane (0.36 ml) and 20% palladium hydroxide on charcoal (0.1 g) was stirred under hydrogen (1 atm) at room temperature overnight, followed by addition of ammonium formate (0.5 g) and heating under reflux for 1 hour under nitrogen atmosphere. The reaction mixture was filtered and evaporated to give 2,2-bis(4-hydroxyphenyl)ethylammonium formate (0.28 g) as a crude product.

**1H-NMR (CD$_3$OD, δ)**: 3.49(2H, d, J=8.3Hz), 4.09(1H, t, J=8.0Hz), 6.76(4H, d, J=6.6Hz), 7.12(4H, d, J=6.6Hz)

**Preparation 5**

To a mixture of 2,2-bis(4-hydroxyphenyl)ethylammonium formate (0.28 g), benzaldehyde (0.13 g), acetic acid (0.14 ml), dichloromethane (2 ml), 1,4-dioxane (3 ml) and sodium triacetoxyborohydride (0.39 g), methanol (1 ml) was added at room temperature. After 10 minutes, additional sodium triacetoxyborohydride (0.43 g) and methanol (10 ml) was added. The reaction mixture was worked up in a usual manner followed by purification by column chromatography (silica gel, dichloromethane : methanol : concentrated ammonia solution = 12:1:0.1) to give N-benzyl-2,2-bis(4-hydroxyphenyl)ethylamine (200 mg).

**1H-NMR (CD$_3$OD, δ)**: 3.06(2H, d, J=7.9Hz), 3.74(2H, s), 4.00(1H, t, J=7.6Hz), 6.69(4H, d, J=8.5Hz), 7.00(4H, d, J=8.5Hz), 7.1-7.3(5H, m)

**MS m/z : 320(M++1)**

**Example 9**

A mixture of (R)-(4-benzyloxy-3-nitrophenyl)oxirane (Tetrahedron Lett., 39(1998), p.1705-1708) (0.79 g), N-benzyl-2,2-bis(4-hydroxyphenyl)ethylamine (0.93 g) and ethanol (25 ml) was heated under reflux for 20 hours and evaporated to give (R)-1-(4-benzyloxy-3-nitrophenyl)-2-[N-benzyl-[2,2-bis(4-hydroxyphenyl)-ethyl]amino]ethanol (1.79 g).

**Example 10**

A mixture of (R)-1-(4-benzyloxy-3-nitrophenyl)-2-[N-benzyl-[2,2-bis(4-
hydroxyphenyl]ethyl]amino]ethanol (1.79 g), benzyl bromide (1.1 g), potassium carbonate (1.2 g) and N,N-dimethylformamide (5 ml) was stirred at 60°C for 1 hour. The reaction mixture was worked up in a usual manner and purified by column chromatography (silica gel, hexane : ethyl acetate = 4:1) to give (R)-1-(4-benzyloxy-3-nitrophenyl)-2-[N-benzyl-[2,2-bis(4-benzyloxyphenyl]ethyl]amino]ethanol (1.86 g).

**Example 1**

A mixture of (R)-1-(4-benzyloxy-3-nitrophenyl)-2-[N-benzyl-[2,2-bis(4-
benzyloxyphenyl]ethyl]amino]ethanol (1.86 g), iron powder (3.3 g), ammonium chloride (0.33 g), ethanol (15 ml), 1,4-dioxane (5 ml) and water (2 ml) was heated under reflux for 1 hour. The reaction mixture was filtered and worked up in a usual manner to give (R)-1-(4-benzyloxy-3-aminophenyl)-2-[N-benzyl-[2,2-bis(4-
benzyloxyphenyl]ethyl]amino]ethanol (1.83 g).

**Example 12**

To a mixture of (R)-1-(4-benzyloxy-3-aminophenyl)-2-[N-benzyl-[2,2-bis(4-
benzyloxyphenyl]ethyl]amino]ethanol (1.46 g), pyridine (324 μl) and dichloromethane (10 ml), methanesulfonyl chloride (232 μl) was added at 0°C. The reaction mixture was stirred at room temperature for 30 minutes and worked up in a usual manner to give (R)-1-(4-benzyloxy-3-methanesulfonylaminophenyl)-2-[N-benzyl-[2,2-bis(4-benzyloxyphenyl]ethyl]amino]ethanol. A mixture of the obtained crude product (1.67 g), methanol (20 ml), 1,4-dioxane (10 ml), and palladium on charcoal (0.5 g) was stirred under hydrogen (1 atm) at room temperature for 1 hour, followed by filtration and evaporation. The hydrogenated product was purified by column chromatography (silica gel, dichloromethane : methanol : concentrated ammonia solution = 8:1:0.1→5:1:0.1) to give (R)-1-(4-hydroxy-3-methanesulfonylaminophenyl)-2-[2,2-bis(4-

**Example 13**

**Example 13**

1H-NMR (CDCl₃, δ) : 2.7-2.8(2H, m), 2.92(3H, s), 3.13(2H, d, J=7.8Hz), 3.98(1H, t, J=7.7Hz), 4.62(1H, t, J=7.4Hz), 6.69(4H, ddd, J=3.3Hz, 6.2Hz), 6.82(1H, d, J=8.3Hz), 6.9-7.1(5H, m), 7.30(1H, s)

**Example 13**

The following compounds were obtained according to a similar manner to that of Example 12.

(1) (R)-1-(4-Hydroxy-3-benzenesulfonylaminophenyl)-2-[2,2-bis(4-
hydroxyphenyl]ethyl]amino]ethanol
IR (KBr): 1604(m), 1512(m), 1446(m), 1248(s), 1165(s), 831(m) cm⁻¹
H-NMR (CD₃OD, δ): 2.6-2.8(2H, m), 3.08(2H, d, J=7.9Hz), 3.96(1H, t, J=7.9Hz),
4.55(1H, dd, J=5.1Hz, 7.9Hz), 6.5-6.9(5H, m), 7.0-7.1(5H, m), 7.22(1H, d,
J=2.0Hz), 7.3-7.5(3H, m), 7.6-7.9(2H, m)

MS m/z: 521(M⁺+1)

(R)-1-(4-Hydroxy-3-butanesulfonfylaminophenyl)-2-[[2,2-bis(4-
hydroxyphenyl)ethyl]amino]ethanol
IR (KBr): 1610(s), 1514(s), 1246(s), 1144(m), 829(m) cm⁻¹
H-NMR (CD₃OD, δ): 0.89(3H, t, J=7.4Hz), 1.24(2H, quartet, J=7.4Hz), 1.42(2H, quartet, J=7.4Hz), 2.8-3.0(2H, m), 2.98(1H, d, J=8.0Hz), 3.02(1H, d, J=8.0Hz),
3.18(2H, d, J=8.1Hz), 4.01(1H, t, J=7.6Hz), 4.64(1H, t, J=7.2Hz), 6.70(4H, d,
J=8.5Hz), 6.80(1H, d, J=8.3Hz), 6.95-7.1(5H, m), 7.34(1H, s)
MS m/z: 501(M⁺+1)

Example 14

To a solution of (R)-1-(4-benzylxoy-3-aminophenyl)-2-[N-benzyl-[2,2-bis(4-benzylxyoyphenyl)ethyl]amino]ethanol (43 mg) in dichloromethane, 50 μl of a mixture of acetic anhydride (1.25 ml) and formic acid (1.00 ml) was added and worked up in a usual manner to give (R)-1-[4-benzylxyoy-3-formylaminophenyl]-2-[N-benzyl-[2,2-bis(4-benzylxyoyphenyl)ethyl]amino]ethanol. The crude product was treated with potassium carbonate in methanol and worked up in a usual manner, followed by usual catalytic hydrogenation on palladium on charcoal and purification by preparative thin-layer chromatography (silica gel, dichloromethane : methanol : concentrated ammonia solution = 9:2:0.1) to give (R)-1-(4-hydroxy-3-formylaminophenyl)-2-[2,2-bis(4-hydroxyphenyl)ethyl]amino]ethanol (18.3 mg).

IR (KBr): 1668(s), 1606(s), 1512(m), 1444(m), 1252(s), 831(m) cm⁻¹
H-NMR (CD₃OD, δ): 2.9-3.2(4H, m), 4.05(1H, t, J=7.6Hz), 4.7(1H, m), 6.7-
7.2(10H, m), 8.00(1H, s), 8.29(1H, s)
MS m/z: 409(M⁺+1)

Example 15

A mixture of (R)-1-(4-benzylxoy-3-aminophenyl)-2-[N-benzyl-[2,2-bis(4-benzylxyoyphenyl)ethyl]amino]ethanol (56 mg), 4-dimethylaminopyridine (56 mg), dimethylsulfamoyl chloride (16 μl) and pyridine (0.5 ml) was heated at 110°C for 2 hours, and worked up in a usual manner to give (R)-1-[4-benzylxyoy-3-[N,N-
dimethylsulfamoyl]amino]phenyl]-2-[N-benzyl-[2,2-bis(4-benzylxyoyphenyl)ethyl]-amino]ethanol. The crude product was hydrogenated on palladium on charcoal in a usual manner to afford (R)-1-[4-hydroxy-3-[N,N-dimethylsulfamoyl]amino]phenyl]-2-[2,2-bis(4-hydroxyphenyl)ethyl]amino]ethanol (11.7 mg).
Example 16

To a mixture of (R)-1-(4-benzylxy-3-aminophenyl)-2-[N-benzyl-[2,2-bis(4-methoxyphenyl)ethyl]amino]ethanol (158 mg), pyridine (103 µl) and dichloromethane (3 ml), ethanesulfonyl chloride (40 µl) was added and stirred at room temperature for 1.5 hours. To the reaction mixture, additional pyridine (114 µl) and ethanesulfonyl chloride (85 µl) was added and stirred for 1 hour. The reaction mixture was worked up in the usual manner to give (R)-1-(4-benzylxy-3-ethanesulfonylaminoxyphenyl)-2-[N-benzyl-[2,2-bis(4-methoxyphenyl)ethyl]amino]ethanol. To a solution of the crude product in dichloromethane (2 ml), 1M boron tribromide-dichloromethane solution (1.1 ml) was added at −78°C and stirred at 0°C for 1.5 hours. The reaction mixture was stirred with saturated sodium bicarbonate solution overnight at room temperature and worked up in the usual manner to give (R)-1-(4-benzylxy-3-ethanesulfonylaminoxyphenyl)-2-[N-benzyl-[2,2-bis(4-hydroxyphenyl)ethyl]amino]ethanol. The crude product was hydrogenated on palladium on charcoal in a usual manner followed by purification by preparative thin-layer chromatography (silica gel, dichloromethane : methanol : concentrated ammonia solution = 9:2:0.1) to afford (R)-1-(4-hydroxy-3-ethanesulfonylaminoxyphenyl)-2-[2,2-bis(4-hydroxyphenyl)ethyl]amino]ethanol (43.1 mg).

IR (KBr) : 1608(m), 1592(m), 1248(s), 1146(m), 831(m) cm⁻¹

Example 17

A mixture of (R)-1-(4-benzylxy-3-nitrophenyl)-2-[N-benzyl-[2,2-bis(4-hydroxyphenyl)ethyl]amino]ethanol (136 mg), ethyl bromoacetate (56 µl), potassium carbonate (96 mg) and N,N-dimethylformamide (1 µl) was stirred at 60°C for 1.5 hours and worked up in a usual manner to give (R)-1-(4-benzylxy-3-nitrophenyl)-2-[N-benzyl-[2,2-bis(4-ethoxycarbonylmethoxy)phenyl]ethyl]-amino]ethanol (194 mg).

Example 18

A mixture of (R)-1-(4-benzylxy-3-nitrophenyl)-2-[N-benzyl-[2,2-bis(4-ethoxycarbonylmethoxy)phenyl]ethyl]amino]ethanol (193 mg), ethanol (2 ml),
ethyl acetate (1 ml), water (0.5 ml), iron powder (400 mg) and ammonium chloride (20 mg) was heated under reflux for 20 minutes, filtrated and worked up in the usual manner to give (R)-1-(3-amino-4-benzyloxyphenyl)-2-[N-benzyl-[2,2-bis[4-(ethoxycarbonylmethoxy)phenyl]ethyl]amino]ethanol (182 mg).

Example 19

(R)-1-(4-Benzyl-3-methanesulfonylaminophenyl)-2-[N-benzyl-[2,2-bis[4-(ethoxycarbonylmethoxy)phenyl]ethyl]amino]ethanol was obtained from (R)-1-(3-amino-4-benzyloxyphenyl)-2-[N-benzyl-[2,2-bis[4-(ethoxycarbonylmethoxy)phenyl]ethyl]amino]ethanol and methanesulfonyl chloride in the usual manner.

Example 20

(R)-1-(4-Hydroxy-3-methanesulfonylaminophenyl)-2-[2,2-bis[4-(ethoxycarbonylmethoxy)phenyl]ethyl]amino]ethanol hydrochloride was obtained from (R)-1-(4-benzyloxy-3-methanesulfonylaminophenyl)-2-[N-benzyl-[2,2-bis[4-(ethoxycarbonylmethoxy)phenyl]ethyl]amino]ethanol by usual catalytic hydrogenation on palladium on charcoal.

IR (KBr) : 1745(s), 1610(m), 1512(s), 1400(m), 1317(m), 1294(m), 1211(s), 1186(s), 1153(s), 1080(m), 829(m) cm⁻¹

¹H-NMR (CD₃OD, δ) : 1.27(6H, t, J=7.1Hz), 2.91(3H, s), 3.04-3.15(2H, m), 3.74(2H, d, J=8.3Hz), 4.22(4H, quartet, J=7.1Hz), 4.35(1H, t), 4.68(4H, s), 4.9(1H), 6.87-6.94(5H, m), 7.10(1H, d J=8.3Hz), 7.24-7.35(5H, m)

MS m/z : 631(M⁺+1)

Example 21

(R)-1-(4-Hydroxy-3-methanesulfonylaminophenyl)-2-[2,2-bis[4-carboxymethoxyphenyl]ethyl]amino]ethanol was obtained from (R)-1-(4-benzyloxy-3-methanesulfonylaminophenyl)-2-[N-benzyl-[2,2-bis[4-(ethoxycarbonylmethoxy)phenyl]ethyl]amino]ethanol by usual saponification followed by usual catalytic hydrogenation on palladium on charcoal.

IR (KBr) : 1736(s), 1610(m), 1512(s), 1406(m), 1313(s), 1225(s), 1184(m), 1153(m), 1078(w), 982(w), 831(m) cm⁻¹

¹H-NMR (CD₃OD, δ) : 2.91(3H, s), 3.04-3.16(2H, m), 3.74(2H, d, J=7.4Hz), 4.35(1H, t), 4.64(4H, s), 4.9(1H), 6.87-6.95(5H, m), 7.10(1H, d, J=8.0Hz), 7.24-7.36(5H, m)

Preparation 6

3-Dibenzylamino-1,1-bis[4-methoxyphenyl]-1-propanol, which was obtained from 3-(dibenzylamino)propionic acid ethyl ester and 4-bromoanisole by a similar manner to that of Preparation 15 to be described later, was hydrogenated according to a similar manner to that of Preparation 16 to be described later to give N-benzyl-[3,3-bis[4-methoxyphenyl]propyl]amine.
Preparation 7

A mixture of (RS)-(4-benzyloxy-3-nitrophenyl)oxirane (160 mg), N-benzyl-[3,3-bis(4-methoxyphenyl)propyl]amine (170 mg) and ethanol (2 ml) was heated under reflux for 12 hours, followed addition of iron powder, a small amount of ammonium chloride and a small amount of water, and heating under reflux for 1 hour. The reaction mixture was filtered, worked up in a usual manner and purified by silica gel column chromatography (hexane : ethyl acetate = 2:1) to give (RS)-1-(3-amino-4-benzyloxyphenyl)-2-[N-benzyl-[3,3-bis(4-methoxyphenyl)propyl]amino]ethanol (239 mg).

$^1$H-NMR (CDCl$_3$, $\delta$): 2.1-2.3(2H, m), 2.3-2.7(4H, m), 3.46(1H, d, J=13.3Hz), 3.76(6H, s), 3.8-3.9(3H, m), 4.4-4.5(1H, m), 5.05(2H, s), 6.56-6.67(2H, m), 6.78(5H, d J=8.7Hz), 7.07(4H, dd J=3.3Hz, 8.7Hz), 7.2-7.4(10H, m)

MS m/z: 603(M$^+$+1)

Example 22

To a mixture of (RS)-1-(3-amino-4-benzyloxyphenyl)-2-[N-benzyl-[3,3-bis(4-methoxyphenyl)propyl]amino]ethanol (50 mg), benzenesulfonyl chloride (22 mg) and dichloromethane (1 ml), pyridine (40 $\mu$l) was added. The reaction mixture was stirred at room temperature for 40 minutes and worked up by a usual manner to give (RS)-3-benzenesulfonylamino-4-benzyloxyphenyl]-2-[N-benzyl-[3,3-bis(4-methoxyphenyl)propyl]amino]ethanol. The crude product was hydrogenated on charcoal in a usual manner, worked up and purified by preparative thin-layer chromatography (dichloromethane : methanol = 7:1) to give (RS)-1-(4-hydroxy-3-benzenesulfonylaminophenyl)-2-[3,3-bis(4-methoxyphenyl)propyl]amino]ethanol (8.8 mg).

IR (KBr): 1649(w), 1543(m), 1512(s), 1458(w), 1248(m), 1032(s), 823(s) cm$^{-1}$

$^1$H-NMR (CD$_3$OD, $\delta$): 2.1-2.3(2H, m), 2.6-2.8(4H, m), 3.75(6H, s), 3.87(1H, broad t), 4.6-4.8(1H, broad m), 6.67(1H, d, J=8.1Hz), 6.83(1H, d, J=8.4Hz), 6.7-6.9(1H, m), 7.16(4H, d, J=8.6Hz), 7.26(1H, s), 7.3-7.6(3H, m), 7.74(2H, d J=7.0Hz)

MS m/z: 563(M$^+$+1)

Preparation 8

A mixture of (S)-[4-benzyloxy-3-nitrophenoxymethyl]oxirane (197 mg), N-benzyl-[3,3-bis(4-methoxyphenyl)propyl]amine (236 mg) and ethanol (3 ml) was heated under reflux for 12 hours. Iron powder, ammonium chloride and water were added to the reaction mixture and heating was continued for 1 hour. The reaction mixture was filtrated and worked up in the usual manner to give (2S)-1-(3-amino-4-benzyloxyphenoxy)-3-[N-benzyl-[3,3-bis(4-methoxyphenyl)propyl]amino]-2-propanol (412.7 mg).
\[ ^1H-NMR\ (CDCl_3, \ \delta) : 2.1-2.3\ (2H, m), 2.4-2.7\ (4H, m), 3.50(1H, d, J=14\text{Hz}), 3.75\ (6H, s), 3.7-4.0\ (5H, m), 5.01\ (2H, s), 6.15-6.4(2H, m), 6.71-6.80\ (5H, m), 7.03-7.08\ (4H, m), 7.2-7.4\ (10H, m) \]

MS m/z : 633 (M^+1)

**Example 23**

The following compound was obtained according to a similar manner to that of Example 25 to be described later.

(S)-1-(4-Hydroxy-3-formylaminophenoxy)-3-[[3,3-bis(4-methoxyphenyl)-propyl]amino]-2-propanol

**Example 24**

The following compounds were obtained according to a similar manner to that of Example 22.

1) (S)-1-(4-Hydroxy-3-benzenesulfonylaminophenoxy)-3-[[3,3-bis(4-methoxyphenyl)propyl]amino]-2-propanol

**Preparation 9**

(2S)-1-(3-Amino-4-benzyloxyphenoxy)-3-[[N-benzyl-[(3RS)-1,1-bis(4-methoxyphenyl)-3-butyl]amino]-2-propanol was obtained from (S)-[(4-benzyloxy-3-nitrophenoxy)methyl]oxirane and (RS)-N-benzyl-[1,1-bis(4-methoxyphenyl)-3-butyl]amine by a similar manner to that of Preparation 7.
Example 25

Formic acid (0.13 ml) and acetic anhydride (0.16 ml) was mixed and stood at room temperature for 30 minutes. This mixture was added to a solution of (2S)-1-(3-amino-4-benzylxoyphenoxy)-3-[N-benzyl-[(3RS)-1,1-bis(4-methoxyphenyl)-3-butyllamino]-2-propanol (377 mg) in dichloromethane (3 ml) and worked up by the usual manner to give (2S)-1-(4-benzylxoy-3-formy laminophenoxy)-3-[N-benzyl-[(3RS)-1,1-bis(4-methoxyphenyl)-3-bu tyllamino]-2-propanol. The crude product was treated with potassium carbonate in methanol at room temperature for 30 minutes and worked up by the usual manner. The obtained crude product was hydorogenated on palladium on charcoal by a usual manner and purified by silica gel column chromatography (dichloromethane : methanol : concentrated ammonia solution = 10:1:0.1) to give (2S)-1-(4-hydroxy-3-formy laminophenoxy)-3-[[3RS]-1,1-bis(4-methoxyphenyl)-3-butyllamino]-2-propanol (159 mg).

IR (KBr) : 1674(s), 1608(m), 1510(s), 1442(m), 1248(s), 1036(m) cm⁻¹

Example 26

To a mixture of (2S)-1-(3-amino-4-benzylxoyphenoxy)-3-[N-benzyl-[(3RS)-1,1-bis(4-methoxyphenyl)-3-butyllamino]-2-propanol (245 mg), catalytic amount of 4-dimethylaminopyridine and dichloromethane (3 μl), acetic anhydride (0.14 ml) was added. The reaction mixture was worked up by the usual manner to give (2S)-1-(3-acetyllamino-4-benzylxoyphenoxy)-3-[N-benzyl-[(3RS)-1,1-bis(4-methoxyphenyl)-3-butyllamino]-2-propanol. The crude product was hydorogenated on palladium on charcoal by a usual manner and purified by silica gel column chromatography (dichloromethane : methanol : concentrated ammonia solution = 10:1:0.1) to give (2S)-1-(4-hydroxy-3-acetyllaminophenoxy)-3-[[3RS]-1,1-bis(4-methoxyphenyl)-3-butyllamino]-2-propanol (54 mg).

IR (KBr) : 1653(w), 1608(m), 1510(s), 1441(m), 1248(s), 1035(m), 825(w) cm⁻¹

1H-NMR (CD3OD, δ) : 1.12(3H, d, J=6.1Hz), 1.8-2.0(1H, m), 2.16(3H, s), 2.2-2.4(1H, m), 2.4-2.9(3H, m), 3.73(6H, s), 3.8-4.0(4H, m), 6.5-6.7(1H, m), 6.7-6.9(5H, m), 7.1-7.2(4H, m), 7.76(1H, d), 8.29(1H, s)

MS m/z : 495(M⁺+1)
MS m/z : 509(M⁺+1)

Preparation 10

A mixture of 4-benzyl oxy-3-nitroacetophenone (10 g), iron powder (10 g), ammonium chloride (1 g), ethanol (200 ml) and water (40 ml) was heated under reflux for 30 minutes, filtrated and worked up by the usual manner to afford 3-amino-4-benzyloxyacetophenone. Acetic anhydride (10.4 ml) was added to formic acid (8.3 ml) below 35°C and stood for 30 minutes at room temperature, followed by addition of a solution of the crude product in dichloromethane (50 ml). The reaction mixture was worked up by the usual manner to give 4-benzyloxy-3-formylaminacetophenone (10.3 g).

1H-NMR (CDCl₃, δ) : 2.59(3H, s), 5.18(2H, s), 7.04(1H, d, J=8.6Hz), 7.43(5H, s), 7.71-7.88(2H, m), 8.47(1H, d, J=1.5Hz), 9.03(1H, d, J=2.1Hz)

Preparation 11

A mixture of 4-benzyloxy-3-formylaminacetophenone (0.83 g), pyridinium tribromide (1.08 g) and acetic acid (5 ml) was stirred at 50°C for 30 minutes, worked up by the usual manner and purified by column chromatography (hexane : ethyl acetate = 2:1) to give 4-benzyloxy-3-formylaminophenacyl bromide (0.37 g).

1H-NMR (CDCl₃, δ) : 4.47(2H, s), 5.20(2H, s), 7.06(1H, d, J=8.7Hz), 7.43(5H, s), 7.7-7.9(2H, m), 8.48(1H, s), 9.07(1H, s)

Preparation 12

To a mixture of 4-benzyl oxy-3-formylaminophenacyl bromide (0.45 g), methanol (5 ml) and tetrahydrofuran (5 ml), sodium borohydride (0.05 g) was added at 0°C and worked up by the usual manner to afford 1-(2-bromo-1-hydroxyethyl)-3-formylamino-4-(benzyl oxy) benzene. The crude product was treated with potassium carbonate in methanol, worked up by the usual manner to give (4-benzyloxy-3-formylaminophenyl)oxirane (0.26 g).

1H-NMR (CDCl₃, δ) : 2.81(1H, quartet, J=2.6Hz), 3.11(1H, t J=5.4Hz), 3.82-3.86(1H, m), 5.10(2H, s), 6.91-7.02(2H, m), 7.41(5H, s), 7.7-7.9(1H, m), 8.38(1H, s), 8.43(1H, s)

Preparation 13

To a solution of 4-methoxyphenylmagnesium bromide (1M in tetrahydrofuran, 35 ml) a solution of 3-(dibenzylamino)propionic acid ethyl ester (4.87 g) in tetrahydrofuran (2 ml) was added, stirred under reflux for 1 hour, worked up in the usual manner and purified by silica gel column chromatography (hexane : ethyl acetate = 5:1) to give 3-dibenzylamino-1,1-bis(4-methoxyphenyl)-1-propanol (3.45 g).

Preparation 14
3-(Dibenzylamino)-1,1-bis(4-methoxyphenyl)-1-propanol (2.0 g) was hydrogenated by the usual manner to give N-benzyl-[3,3-bis(4-methoxyphenyl)-propyl]amine, which was further hydrogenated by heating with 20% palladium on charcoal and ammonium formate in methanol to give [3,3-bis(4-methoxyphenyl)propyl]amine (1.65 g).

Example 27

The following compound was obtained according to a similar manner to that of Example 9.

(RS)-1-(4-Benzylxoy-3-formylaminophenyl)-2-[[3,3-bis(4-methoxyphenyl)-propyl]amino]ethanol

Example 28

(RS)-1-(Benzyloxy-3-formylaminophenyl)-2-[[3,3-bis(4-methoxyphenyl)-propyl]amino]ethanol was hydrogenated on palladium on charcoal in a usual manner to give (RS)-1-(4-hydroxy-3-formylaminophenyl)-2-[[3,3-bis(4-methoxyphenyl)propyl]amino]ethanol.

IR (KBr) : 1664(m), 1606(m), 1248(s), 1178(m), 1105(s), 1034(s) cm⁻¹

¹H-NMR (CD₃OD, δ) : 2.1-2.4(2H, m), 2.6-2.9(2H, m), 2.94(2H, d, J=6.5Hz), 3.74(6H, s), 3.88(1H, t, J=8.1Hz), 4.72(1H, t, J=6.4Hz), 6.7-7.2(11H, m), 8.06(1H, s), 8.29(1H, s)

MS m/z : 451(M⁺+1)

Preparation 15

To a solution of benzyl 4-bromophenyl ether (15.0 g) in tetrahydrofuran (60 ml), butyllithium (1.52M hexane solution, 40 ml) was added at -78°C. The reaction mixture was stirred at 30 minutes, followed by addition of 3-dibenzylaminopropionic acid ethyl ester (7.73 g). The reaction mixture was stirred at 0°C for 30 minutes, worked up in a usual manner and purified by column chromatography (silica gel 300 ml, hexane : ethyl acetate = 8:1) to give 1,1-bis(4-benzylxoyphenyl)-3-(dibenzylamino)-1-propanol (7.37 g).

¹H-NMR (CDCl₃, δ) : 2.3-2.5(2H, m), 2.6-2.7(2H, m), 3.53(4H, s), 5.06(4H, s), 6.76(4H, d, J=8.8Hz), 7.1-7.5(24H, m)

Preparation 16

A mixture of 1,1-bis(4-benzylxoyphenyl)-3-(dibenzylamino)-1-propanol (7.35 g), 1,4-dioxane (10 ml), methanol (70 ml), 4N hydrogen chloride in 1,4-dioxane (5.7 ml) and 20% palladium hydroxide on charcoal (0.8 g) was stirred under hydrogen (1 atm) at room temperature overnight. The reaction mixture was filtrated and evaporated to afford N-benzyl-[3,3-bis(4-hydroxyphenyl)propyl]amine (4.42 g).

MS m/z : 334(M⁺+1)
Example 29

The following compound was obtained according to a similar manner to that of Example 38 to be described later.

(R)-1-(4-Benzylxoy-3-nitrophenyl)-2-[N-benzyl-[3,3-bis(4-hydroxyphenyl)-propyl]amino]ethanol

MS m/z : 605(M⁺+1)

Preparation 17

The following compound was obtained according to a similar manner to that of Example 12.

(R)-1-(4-Hydroxy-3-methanesulfonylaminophenyl)-2-[3,3-bis(4-hydroxyphenyl)propyl]amino]ethanol

IR (KBr) : 1604(m), 1510(s), 1244(s), 1149(m), 831(m) cm⁻¹

¹H-NMR (CD₃OD, δ) : 2.1-2.3(2H, m), 2.5-2.7(2H, m), 2.7-2.8(2H, m), 2.91(3H, s), 3.77(1H, t, J=7.8Hz), 4.64(1H, dd, J=5.2Hz, 7.9Hz), 6.68(4H, d, J=8.5Hz), 6.84(1H, d, J=8.3Hz), 6.9-7.1(5H, m), 7.32(1H, s)

MS m/z : 473(M⁺+1)

Preparation 18

To a mixture of 4-benzylxoyphenyl acetate (5.05 g), potassium acetate (3.27 g) and acetic acid (40 ml), bromine (1.4 ml) was added dropwise and stirred at room temperature overnight. Water was added to the reaction mixture and the precipitate was collected by filtration, washed by water and dried to give 4-benzylxoy-3-bromophenyl acetate (3.90 g).

¹H-NMR (CDCl₃, δ) : 2.27(3H, s), 5.14(2H, s), 6.91(1H, d, J=8.9Hz), 6.96(1H, dd, J=2.5Hz, 8.9Hz), 7.33-7.48(6H, m)

Preparation 19

To a solution of 4-benzylxoy-3-bromophenyl acetate (1.05 g) in methanol (5 ml), 28% sodium methoxide - methanol solution (0.66 g) was added and evaporated. The crude residue was dissolved in N,N-dimethylformamide (5 ml) and methoxymethyl chloride (0.3 ml) was added to the solution. The reaction mixture was worked up by the usual manner and purified through a short pad of silica gel (eluent : hexane : ethyl acetate = 6:1) to give 2-benzylxoy-5-(methoxymethoxy)bromobenzene (967 mg).

¹H-NMR (CDCl₃, δ) : 3.47(3H, m), 5.09(4H, s), 6.80-6.95(2H, m), 7.29-7.48(6H, m)

Preparation 20

To a solution of 2-benzylxoy-5-(methoxymethoxy)bromobenzene (959 mg) in tetrahydrofuran (5 ml), butyllithium (1.52M hexane solution, 2.9 ml) was added dropwise at -78°C under a flow of nitrogen followed by stirring at 0°C for
30 minutes and was added N,N-dimethylformamide (2 ml) at -78°C. The reaction mixture was worked up by the usual manner, treated with 4N hydrogen chloride in 1,4-dioxane, worked up by the usual manner and purified by silica gel column chromatography (hexane : ethyl acetate = 3:1) to give 3-formyl-4-benzoxoxyphenol (398 mg).

\[ ^1H\text{-NMR (CDCl}_3, \delta) : 5.14(2H, m), 6.97(1H, d, J=8.9Hz), 7.05(1H, dd, J=3.1Hz, 8.9Hz), 7.30-7.42(6H, m), 10.48(1H, s) \]

Preparation 21

To a solution of 3-formyl-4-benzoxoxyphenol (390 mg) in N,N-dimethylformamide (3 ml), sodium hydride (60% in mineral oil, 75 mg) was added at 0°C. After 30 minutes, (S)-[3-nitrobenzenesulfonyloxy)methyl]oxirane (465 mg) was added to the reaction mixture and stirred at room temperature for 2 hours. After usual work-up, crude (S)-[3-formyl-4-benzoxoxyphenoxo)methyl]oxirane (551 mg) was obtained and was used in the next step without any purification.

\[ ^1H\text{-NMR (CDCl}_3, \delta) : 2.73-2.77(1H, m), 2.88(1H, t, J=4.8Hz), 3.31-3.38(1H, m), 3.91(1H, quartet, J=5.9Hz), 4.27(1H, d, J=2.8Hz, 11.0Hz), 5.16(2H, s), 7.01(1H, d, J=9.1Hz), 7.17(1H, dd, J=3.3Hz, 9.1Hz), 7.34-7.43(6H, m), 10.50(1H, s) \]

Example 30

(S)-1-(3-Formyl-4-benzoxoxyphenoxo)-3-[N-benzyl-[3,3-bis(4-methoxyphenyl)propyl]amino]-2-propanol, which was obtained according to a similar manner to that of Example 31 to be described later, was treated with sodium borohydride in methanol followed by catalytic hydrogenation on palladium on charcoal in a usual manner to give (S)-1-(4-hydroxy-3-hydroxymethylphenoxo)-3-[3,3-bis(4-methoxyphenyl)propyl]amino]-2-propanol.

IR (KBr) : 1608(w), 1510(s), 1456(m), 1442(m), 1248(s), 1178(m), 1034(s), 814(m) cm\(^{-1}\)

\[ ^1H\text{-NMR (CD}_3\text{OD,} \delta) : 2.1-2.3(2H, m), 2.5-2.8(4H, m), 3.73(6H, s), 3.85(2H, d, J=5.1Hz), 3.9-4.1(2H, m), 4.61(2H, s), 6.68(2H, s), 6.81(4H, d, J=8.6Hz), 6.90(1H, s), 7.15(4H, d, J=8.6Hz) \]

MS m/z : 468(M\(^{+}\)+1)

Example 31

A mixture of (S)-[3-formyl-4-benzoxoxyphenoxo)methyl]oxirane (167 mg), N-benzyl-[3,3-bis(4-methoxyphenyl)propyl]amine (264 mg) and ethanol (4 ml) was heated under reflux for 14 hours and evaporated to give (S)-1-(3-formyl-4-benzoxoxyphenoxo)-3-[N-benzyl-[3,3-bis(4-methoxyphenyl)propyl]amino]-2-propanol (436 mg).

MS m/z : 646(M\(^{+}\)+1)
Example 32

To a mixture of \((S)-1-(3\text{-formyl-4-benzyloxyphenoxy})-3-[N\text{-benzyl-}[3,3\text{-bis[4-methoxyphenyl]propyl]amino]-2\text{-propanol}\) (80 mg), ammonium acetate (200 mg), 1,4-dioxane (1 ml) and methanol (3 ml), sodium cyanoborohydride (40 mg) was added and worked up in the usual manner. The crude product was purified by preparative thin-layer chromatography (dichloromethane : methanol : concentrated ammonium solution = 22:1:0.1) to give \((S)-1-(3\text{-aminomethyl-4-benzyloxyphenoxy})-3-[N\text{-benzyl-}[3,3\text{-bis[4-methoxyphenyl]propyl]amino]-2\text{-propanol}\) (41 mg).

MS m/z : 647(M⁺+1)

Example 33

The following compound was obtained according to a similar manner to that of Example 22.

\((S)-1-[\text{4-Hydroxy-3-[(methanesulfonyl]amino]methyl[phenoxy]}}-3-[3,3\text{-bis[4-methoxyphenyl]propyl]amino]-2\text{-propanol}\)

IR (KBr) : 1560(m), 1510(s), 1452(s), 1250(m), 1178(w), 1144(w), 1034(m), 818(m) cm⁻¹

\(^1\text{H-NMR (CD}_3\text{OD, } \delta) : 2.3-2.5(2\text{H, m}), 2.8-3.3(4\text{H, m}), 2.90(3\text{H, s}), 3.73(6\text{H, s),}\)

3.8-4.0(3H, m), 4.0-4.2(1H, m), 4.39(2H, s), 6.69(2H, s), 6.83(5H, d, J=8.6Hz),

7.16(5H, d, J=8.6Hz)

MS m/z : 545(M⁺+1)

Example 34

The following compound was obtained according to a similar manner to that of Example 31.

\((S)-1-[\text{4-Benzyloloxy-3-formyl]phenoxy]}-3-[N\text{-benzyl-}[2,2\text{-bis[4-methoxyphenyl]ethyl]amino}]\text{-2-propanol}\)

Example 35

The following compound was obtained according to a similar manner to that of Example 30.

\((S)-1-[\text{4-Hydroxy-3-hydroxymethyl]phenoxy}]-3-[[2,2\text{-bis[4-methoxyphenyl]ethyl]amino}]\text{-2-propanol}\)

IR (KBr) : 1510(s), 1454(m), 1248(s), 1032(s), 827(m) cm⁻¹

\(^1\text{H-NMR (CD}_3\text{OD, } \delta) : 2.8-3.0(2\text{H, m}), 3.2-3.4(2\text{H, m), 3.74(6H,s), 3.82(2H, d),}\)

J=4.2Hz), 3.9-4.2(2H, m), 4.60(2H, s), 6.61-6.65(2H, m), 6.85(5H, d, J=7.6Hz),

7.17(4H, d, J=8.5Hz)

MS m/z : 454(M⁺+1)

Preparation 22

To a mixture of 4'-benzyloxy-3'-methoxycarbonylacetophenone (2.84 g),
30% hydrogen bromide in acetic acid (4 drops) and chloroform (12 ml), bromine (0.54 ml) was added dropwise at room temperature. Diisopropylether (10 ml) and hexane (10 ml) was added to the reaction mixture. A white powder was precipitated, and the precipitate was collected by filtration, washed by hexane and dried to give 2-bromo-4'-benzyloxy-3'-methoxycarbonylacetophenone (531 mg).

\(^1\text{H-}	ext{NMR} (\text{CDCl}_3, \delta) : 3.94(3H, s), 4.41(2H, s), 5.29(2H, s), 7.09(1H, d, J=8.9Hz), 7.3-7.5(5H, m), 8.10(1H, dd, J=2.4Hz, 8.8Hz), 8.47(1H, d, J=2.4Hz)

Preparation 23

To a solution of 2-bromo-4'-benzyloxy-3'-methoxycarbonylacetophenone (250 mg) in methanol and tetrahydrofuran, sodium borohydride was added at 0°C. The reaction mixture was warmed up to room temperature, followed by addition of potassium carbonate, and worked up in the usual manner to give (RS)-(4-benzyl-oxy-3-methoxycarbonylphenyl)oxirane (164 mg).

\(^1\text{H-}	ext{NMR} (\text{CDCl}_3, \delta) : 2.79(1H, dd, J=2.6Hz, 5.4Hz), 3.13(1H, t, J=5.3Hz), 3.83(1H, t, J=3.9Hz), 3.91(3H, s), 5.19(2H, s), 6.99(1H, d, J=8.6Hz), 7.30-7.5(6H, m), 7.75(1H, d, J=2.3Hz)

Example 36

The following compound was obtained according to a similar manner to that of Example 38 to be described later:

(RS)-1-(4-Benzyloxy-3-methoxycarbonylphenyl)-2-[N-benzyl-[2,2-bis(4-methoxyphenyl)ethyl]amino]ethanol

MS m/z : 632(M\(^{+1}\))

Example 37

The following compound was obtained according to a similar manner to that of Example 39 to be described later.

(RS)-1-(4-Hydroxy-3-hydroxymethylphenyl)-2-[2,2-bis(4-methoxycarbonylphenyl)ethyl]amino]ethanol

IR (KBr) : 1608(m), 1510(s), 1446(w), 1248(s), 1032(m) cm\(^{-1}\)

\(^1\text{H-}	ext{NMR} (\text{CD}_3\text{OD}, \delta) : 2.7-2.9(2H, m), 3.13(2H, d, J=7.9Hz), 3.73(6H, s), 4.04(1H, t, J=8.2Hz), 4.6(1H, m), 4.65(2H, s), 6.6-6.9(5H, m), 7.0-7.3(6H, m)

MS m/z : 424(M\(^{+1}\))

Example 38

A mixture of (RS)-(4-benzyl-oxy-3-methoxycarbonylphenyl)oxirane (60 mg), N-benzyl-[3,3-bis(4-methoxyphenyl)propyl]amine (80 mg) and ethanol (2 ml) was heated under reflux for 14 hours and evaporated to give (RS)-1-(4-benzyl-oxy-3-methoxycarbonylphenyl)-2-[N-benzyl-[3,3-bis(4-methoxyphenyl)propyl]amino]-ethanol (142 mg).
MS m/z : 646(M⁺+1)

Example 39

A solution of (RS)-1-(4-benzyloxy-3-methoxycarbonylphenyl)-2-[N-benzyl-3,3-bis(4-methoxyphenyl)propyl]amino]ethanol (69 mg) in tetrahydrofuran (1 ml) was added to a suspension of lithium aluminium hydride (10 mg) in tetrahydrofuran (1 ml) at 0°C. The reaction mixture was worked up in the usual manner to give (RS)-1-(4-benzyloxy-3-hydroxymethylphenyl)-2-[N-benzyl-3,3-bis(4-methoxyphenyl)propyl]amino]ethanol, which was hydrogenated by using palladium on charcoal in methanol followed by purification by preparative thin-layer chromatography (silica gel, dichloromethane : methanol : concentrated ammonia solution = 9:1:0.1) to afford (RS)-1-(4-hydroxy-3-hydroxymethylphenyl)-2-[3,3-bis(4-methoxyphenyl)propyl]amino]ethanol (32 mg).

IR (KBr) : 1608(m), 1510(s), 1444(w), 1248(s), 1032(m), 823(m) cm⁻¹

¹H-NMR (CD₂OD, δ) : 2.1-2.3(2H, m), 2.3-2.8(4H, m), 3.74(6H, s), 3.82(1H, t, J=8.0Hz), 4.6(1H, m), 4.64(2H, s), 6.6-6.8(5H, m), 7.0-7.2(6H, m)

MS m/z : 438(M⁺+1)

Preparation 24

To a solution of 1,4-dibromobenzene (18.28 g) in tetrahydrofuran, butyllithium (1.54M in hexane) was added at -78°C. After 30 minutes, 3-dibenzylaminopropionic acid ethyl ester (4.61 g) was added and warmed to 0°C. The reaction mixture was worked up in the usual manner and purified by silica gel column chromatography to give 3-(dibenzylamino)-1,1-bis(4-bromophenyl)-1-propanol (8.43 g).

¹H-NMR (CDCl₃, δ) : 2.3-2.4 (2H, m), 2.6-2.7 (2H, m), 3.51(4H, s), 7.07 (2H, d, J=8.5Hz), 7.1-7.4 (16H, m)

MS m/z : 564, 566 (M⁺+1), 568

Preparation 25

A mixture of 3-(dibenzylamino)-1,1-bis(4-bromophenyl)-1-propanol (8.42 g), benzophenone imine (10.8 g), tris(dibenzylideneacetone)dipalladium (546 mg), (RS)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (1.11 g), sodium tert-butoxide (5.7 g) and toluene (90 ml) was stirred at 100°C for 6 hours. The reaction mixture was added to a mixture of tetrahydrofuran (300 ml) and 3N hydrochloric acid (300 ml) and stirred at room temperature for 1.5 hours. The aqueous phase was separated, neutralized by sodium hydroxide and extracted with ethyl acetate. The ethyl acetate solution was evaporated and purified by silica gel column chromatography (hexane : ethyl acetate =1:1) to give 3-(dibenzylamino)-1,1-bis(4-aminophenyl)-1-propanol (1.76 g).

MS m/z : 438 (M⁺+1)
Preparation 26

To a mixture of 3-(dibenzylamino)-1,1-bis(4-aminophenyl)-1-propanol (0.64 g), pyridine (0.5 ml) and dichloromethane (10 ml), methyl chlorocarbonate (0.34 ml) was added at 0°C and the reaction mixture was worked up in a usual manner. The crude product was dissolved in methanol (10 ml), followed by addition of 4N hydrogen chloride in 1,4-dioxane (0.5 ml) and 20% palladium hydroxide on charcoal. The mixture was stirred under hydrogen (1 atm) at room temperature overnight, worked up in a usual manner and purified by silica gel column chromatography (dichloromethane : methanol : concentrated ammonia water = 20:1:0.1) to give N-benzyl-[3,3-bis[4-[(methoxycarbonyl)amino]phenyl]-propyl]amine (466 mg).

MS m/z : 448 (M^+1)

Preparation 27

A mixture of (R)-{4-benzyloxy-3-nitrophenyl}oxirane (34.4 mg), N-benzyl-[3,3-bis[4-(methoxycarbonylamino)phenyl]propyl]amine (56.7 mg) and ethanol (2 ml) was heated under reflux for 12 hours. Iron powder, ammonium chloride and water were added to the reaction mixture and heating was continued for 1 hour. The reaction mixture was filtrated and worked up in the usual manner to give crude (R)-1-(3-amino-4-benzyloxyphenyl)-2-[N-benzyl-[3,3-bis[4-(methoxycarbonylamino)phenyl]propyl]amino]ethanol (111.7 mg).

MS m/z : 689 (M^+1)

Example 40

(R)-1-(4-Hydroxy-3-formylaminophenyl)-2-[3,3-bis[4-(methoxycarbonylamino)phenyl]propyl]amino]ethanol was obtained from (R)-1-(3-amino-4-benzyloxyphenyl)-2-[N-benzyl-[3,3-bis[4-(methoxycarbonylamino)phenyl]propyl]amino]ethanol by a similar manner to that of Example 25.

IR (KBr) : 1707(s), 1678(m), 1604(s), 1415(m), 1241(m), 1072(m) cm⁻¹

¹H-NMR (CD₃OD, δ) : 2.1-2.3(2H, m), 2.5-2.7(2H, m), 2.7-2.8(2H, m), 3.70 (6H, s), 3.85(1H, t, J=7.3Hz), 4.59(1H, dd, J=8.4Hz,14.1Hz), 6.80(1H, d, J=8.3Hz), 6.94(1H, d, J=8.9Hz), 7.14(4H, d, J=8.5Hz), 7.31(4H, d, J=8.3Hz), 8.00(1H, s), 8.28(1H, s)

MS m/z : 537[M^+1]

Preparation 28

The following compound was obtained according to a similar manner to that of Preparation 27.

(2S)-1-(3-Amino-4-benzyloxyphenoxy)-3-[N-benzyl-[3,3-bis[4-(methoxycarbonylamino)phenyl]propyl]amino]-2-propanol

MS m/z : 719
Example 41

(S)-1-(4-Hydroxy-3-formylaminophenoxy)-3-[[3,3-bis[4-(methoxycarbonylamino)phenyl]propyl]amino]-2-propanol was obtained from (S)-1-(3-amino-4-benzoxypyloxy)-3-[N-benzyl-[3,3-bis[4-(methoxycarbonylamino)phenyl]propyl]amino]-2-propanol by a similar manner to that of Example 25.

IR (KBr) : 1711(s), 1682(m), 1537(s), 1441(m), 1240(s), 1072(m) cm⁻¹

¹H-NMR (CD₃OD, δ) : 2.1-2.3(2H, m), 2.5-2.8(4H, m), 3.67(6H, s), 3.8-4.1(4H, m), 6.55(1H, dd, J=2.9Hz, 8.8Hz), 6.74(1H, d, J=8.7Hz), 7.17(4H, d, J=8.6Hz), 7.32(4H, d, J=8.5Hz), 7.72(1H, d, J=2.8Hz), 8.28(1H, s)

MS m/z : 567(M⁺+1)

Example 42

(S)-1-(4-Hydroxy-3-hydroxymethylphenoxy)-3-[[3,3-bis[4-(methoxycarbonylamino)phenyl]propyl]amino]-2-propanol was obtained from (S)-[[3-formyl-4-benzoxypyloxy)methyl]oxiran and N-benzyl-[3,3-bis[4-(methoxycarbonylamino)phenyl]propyl]amine by a similar manner to that of Example 30.

IR (KBr) : 1711(s), 1604(m), 1539(s), 1238(m), 1070(m) cm⁻¹

¹H-NMR (CD₃OD, δ) : 2.2-2.4(2H, m), 2.6-2.9(4H,m), 3.71(6H, s), 3.7-4.1(4H, m), 4.61(2H, s), 6.68(2H, s), 6.90(1H, s), 7.18(4H, d, J=8.6Hz), 7.33(4H, d, J=8.5Hz)

MS m/z : 554(M⁺+1)

Preparation 29

A mixture of methyl 3-aminobutyrate (4.3 g), (S)-(phenoxy)methyl]oxiran (4.59 g) (IL FARMACO, 50(10), p. 643 (1995)), ytterbium(III) trifluoromethanesulfonate (1.8 g) and dichloromethane (25 ml) was stirred at 40°C for 2 hours and at room temperature overnight, worked up in the usual manner and purified by silica gel column chromatography (toluene : ethanol : concentrated ammonia water = 9:1:0.1) to give (3RS)-3-[[2S]-2-hydroxy-3-phenoxypropyl]amino]butyric acid methyl ester (2.59 g).

IR (Neat) : 3400 (br m), 1734 (s), 1599 (m), 1495 (m), 1458 (m), 1298 (m), 1246 (s), 1041 (m), 756 (m) cm⁻¹

¹H-NMR (CDCl₃, δ) : 1.16 (3H, d, J=5.2Hz), 2.41-2.46 (2H, m), 2.6-3.0 (2H, m), 3.14 (1H, quartet, J=6.4Hz), 3.68 (3H, s), 3.9-4.1 (3H, m), 6.90-6.99 (3H, m), 7.24-7.33 (2H, m)

MS m/z : 268(M⁺+1)

Example 43

(2S)-1-Phenoxy-3-[[3RS]-1,1-bis[4-fluorophenyl]-1-hydroxy-3-butyl]amino]-2-propanol was obtained from (3RS)-3-[[2S]-2-hydroxy-3-phenoxypropyl]amino]butyric acid methyl ester and 4-fluorobromobenzene by a
similar manner to that of Preparation 3.
MS m/z : 428(M**+1)

Preparation 30
A mixture benzyl (S)-tetrahydro-5-oxo-3-furanylcarbamate (2.0 g), 4N hydrogen chloride - ethyl acetate (2.3 ml), palladium on charcoal (0.2 g), ethyl acetate (50 ml) and methanol (10 ml) was stirred under hydrogen (1 atm) at room temperature overnight, filtered and evaporated. The crude product was stirred with benzyl bromide (3.05 g), potassium carbonate (5.88 g) and N,N-dimethylformamide (20 ml) at room temperature overnight, worked up by a usual manner and purified by silica gel column chromatography (hexane : ethyl acetate = 4 : 1) to give (S)-N,N-dibenzyl(tetrahydro-5-oxo-3-furanyl)amine (1.49 g).
IR (KBr) : 1772(s), 1454(w), 1259(m), 1165(s), 1126(m), 1070(m), 1028(s), 746(m) cm\(^{-1}\)
\(^1\)H-NMR (CDCl\(_3\), \(\delta\)) : 2.56-2.61(2H, m), 3.53(2H, d, J=13.8Hz), 3.67(2H, d, J=13.8Hz), 3.75-3.84(1H, m), 4.30-4.40(2H, m), 7.28-7.34(10H, m)
MS m/z : 282(M**+1)

Preparation 31
(S)-3-Dibenzylamino-1,1-bis[4-methoxyphenyl]butane-1,4-diol was obtained from (S)-N,N-dibenzyl(tetrahydro-5-oxo-3-furanyl)amine and 4-bromoanisole by a similar manner to that of Preparation 3.
MS m/z : 498(M**+1)

Preparation 32
A mixture (S)-3-dibenzylamino-1,1-bis[4-methoxyphenyl]butane-1,4-diol (0.75 g), methanol (5 ml), palladium on charcoal (0.1 g) and ammonium formate (0.5 g) was heated under reflux for 1.5 hours, filtered and evaporated. To the crude residue, methanol (5 ml), 4N hydrogen chloride in 1,4-dioxane (0.5 ml), palladium on charcoal (0.1 g) was added. The mixture was stirred under hydrogen (1 atm) overnight, filtered and evaporated to afford (S)-2-amino-4,4-bis[4-methoxyphenyl]-1-butanol (388 mg).
\(^1\)H-NMR (CDCl\(_3\), \(\delta\)) : 1.81-1.96(1H, m), 2.05-2.2(1H, m), 2.6-2.8(1H, m), 3.29(1H, dd, J=7.7Hz, 10.5Hz), 3.53(1H, dd, J=4.0Hz, 10.4Hz), 3.76(6H, s), 4.02(1H, dd, J=6.8Hz, 9.3Hz), 6.81(4H, dd, J=2.3Hz, 8.8Hz), 7.14(4H, d, J=8.8Hz)
MS m/z : 302(M**+1)

Example 44
(2S)-1-Phenoxy-3-[[1S]-3,3-bis[4-methoxyphenyl]-1-[hydroxymethyl]propyl]amino]-2-propanol was obtained from (S)-2-amino-4,4-bis[4-methoxyphenyl]-1-butanol and (S)-(phenoxyethyl)oxirane by a similar manner to that of Example 9.
IR (KBr) : 1606(w), 1510(s), 1471(w), 1250(s), 1178(m), 1036(s), 816(m) cm⁻¹

¹H-NMR (CDCl₃, δ) : 2.0-2.2(2H, m), 2.5-2.9(4H, m), 3.41(1H, dd), 3.63(1H, dd),
3.76(6H, s), 3.9-4.0(4H, m), 6.79-7.00(7H, m), 7.14(4H, dd), 7.26-7.33(2H, m)
MS m/z : 452(M⁺+1)

Preparation 33

A suspension of 1-acetoxy-2,2-bis(4-nitrophenyl)ethane (4.96 g)
(Tetrahedron, p. 8001 (1991)) in methanol (50 ml) - 1,4-dioxane (15 ml) was
hydrogenated (3 atm) over 10% palladium on carbon (252 mg) at room
temperature for 3 hours. The catalyst was filtered off and the filtrate was
evaporated to give 1-acetoxy-2,2-bis(4-aminophenyl)ethane (4.13 g) as a pale
brown powder.

¹H-NMR (CDCl₃, δ) : 1.96(3H, s), 4.14(1H, t, J=8Hz), 4.50(2H, d, J=8Hz), 6.61(4H, d, J=8Hz), 6.99(4H, d, J=8Hz)
MS m/z : 271 (M⁺+1)

Preparation 34

To a suspension of 1-acetoxy-2,2-bis(4-nitrophenyl)ethane (1.41 g) in
ethanol (14 ml) - water (2.8 ml) were added powdered iron (1.89 g) and
ammonium chloride (140 mg). The mixture was gently heated to reflux for 3
hours and allowed to cool to room temperature. After the insoluble material was
filtered off, the filtrate was concentrated to give 1-acetoxy-2,2-bis(4-
aminophenyl)ethane (1.23 g) as a pale yellow powder.

¹H-NMR (CDCl₃, δ) : 1.97(3H, s), 3.55(4H, br s), 4.14(1H, t, J=8Hz), 4.50(2H, d, J=8Hz), 6.62(4H, d, J=8Hz), 6.99(4H, d, J=8Hz)
MS m/z : 271 (M⁺+1)

Preparation 35

To an ice-cooled solution of 1-acetoxy-2,2-bis(4-aminophenyl)ethane
(1.33 g) in tetrahydrofuran (16 ml) - dichloromethane (8 ml) were added pyridine
(1.2 ml) and methyl chlorocarbonate (0.92 ml). The mixture was stirred at the
same temperature for 1.5 hours and partitioned between ethyl acetate and water.
The organic layer was separated, washed successively with 1N hydrochloric acid,
saturated sodium bicarbonate solution and brine, dried over magnesium sulfate,
and filtered. The filtrate was evaporated to give 1-acetoxy-2,2-bis[4-
(methoxy carbonylamino) phenyl]ethane (1.64 g) as a pale yellow amorphous
powder.

¹H-NMR (CDCl₃, δ) : 1.97(3H, s), 3.76(6H, s), 4.27(1H, t, J=8Hz), 4.55(2H, d, J=8Hz), 6.59(2H, br s), 7.14(4H, d, J=8Hz), 7.31(4H, d, J=8Hz)
MS m/z : 409 (M⁺+Na)

Preparation 36
To a solution of 1-acetoxy-2,2-bis[4-(methoxycarbonylamino)phenyl]ethane (1.57 g) in methanol (16 ml) was added 1N sodium hydroxide (4.9 ml) at room temperature. The mixture was stirred at the same temperature for 40 minutes and concentrated to half of the original volume. The solution was neutralized with 1N hydrochloric acid (4.9 ml) and extracted with ethyl acetate. The organic layer was separated, washed successively with saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, and filtered. The filtrate was evaporated to give 2,2-bis[4-(methoxycarbonylamino)phenyl]ethanol (1.45 g) as a pale yellow amorphous powder.

$^1$H-NMR (CDCl$_3$, $\delta$) : 3.76(6H, s), 4.02-4.20(3H, m), 6.62(2H, br s), 7.18(4H, d, J=9Hz), 7.32(4H, d, J=9Hz)
MS m/z : 367 (M$^+$+Na)
Preparation 37

To an ice-cooled mixture of 2,2-bis[4-(methoxycarbonylamino)phenyl]ethanol (1.38 g) and triethylamine (1.0 ml) in dichloromethane (14 ml) was added dropwise methanesulfonyl chloride (0.44 ml). The mixture was stirred at room temperature for 3 hours and partitioned between chloroform and water. The organic layer was separated, washed successively with saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, and filtered. The filtrate was evaporated to give 1,1-bis[4-(methoxycarbonylamino)phenyl]-2-(methanesulfonyloxy)ethane (1.87 g) as a pale brown solid.

$^1$H-NMR (CDCl$_3$, $\delta$) : 2.79(3H, s), 3.77(6H, s), 4.35(1H, t, J=8Hz), 4.67(2H, d, J=8Hz), 6.58(2H, br s), 7.16(4H, d, J=9Hz), 7.34(4H, d, J=9Hz)
MS m/z : 445 (M$^+$+Na)
Preparation 38

A mixture of 1,1-bis[4-(methoxycarbonylamino)phenyl]-2-(methanesulfonyloxy)ethane (1.66 g) and sodium azide (344 mg) in N,N-dimethylformamide (5 ml) was heated at 90°C for 28 hours. After allowed to cool to room temperature, the mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed successively with water and brine, dried over magnesium sulfate, and filtered. The filtrate was concentrated and the residue was purified by column chromatography (silica gel, hexane/ethyl acetate) to give 1-azo-2,2-bis[4-(methoxycarbonylamino)phenyl]ethane (1.36 g) as a pale yellow amorphous powder.

$^1$H-NMR (CDCl$_3$, $\delta$) : 3.76(6H, s), 3.81(2H, d, J=8Hz), 4.15(1H, t, J=8Hz), 6.69(2H, br s), 7.15(4H, d, J=9Hz), 7.28(4H, d, J=9Hz)
MS m/z : 392 (M$^+$+Na)
Preparation 39
A solution of 1-azido-2,2-bis[4-(methoxycarbonylamino)phenyl]ethane (1.32 g) in methanol (13 ml) was hydrogenated (3 atm) over 10% palladium on carbon (132 mg) at room temperature for 3 hours. The catalyst was filtered off and the filtrate was evaporated to give 2,2-bis[4-(methoxycarbonylamino)phenyl]-ethylamine (1.18 g) as a pale brown amorphous powder.

$^1$H-NMR (CDCl$_3$, δ): 3.26(2H, d, J=8Hz), 3.76(6H, s), 3.91(1H, t, J=8Hz), 6.63(2H, br s), 7.16(4H, d, J=9Hz), 7.31(4H, d, J=9Hz)
MS m/z: 344 (M$^+$1)
Preparation 40

To an ice-cooled solution of 2,2-bis[4-(methoxycarbonylamino)phenyl]-ethylamine (1.15 g) in dichloromethane (5.8 ml) were added benzaldehyde (0.39 ml), sodium triacetoxyborohydride (1.77 g) and acetic acid (0.58 ml). The mixture was stirred at room temperature for 14 hours and partitioned between ethyl acetate and saturated sodium bicarbonate solution. The organic layer was separated, washed with brine, dried over magnesium sulfate, and filtered. The filtrate was concentrated and the residue was purified by column chromatography (silica gel, hexane/ethyl acetate) to give N-benzyl-[2,2-bis[4-(methoxycarbonylamino)phenyl]ethyl]amine (358 mg) as a white amorphous powder.

$^1$H-NMR (CDCl$_3$, δ): 3.19(2H, d, J=8Hz), 3.75(6H, s), 3.84(2H, s), 4.19(1H, t, J=8Hz), 6.72(2H, br s), 7.09(4H, d, J=8Hz), 7.15-7.42(9H, m)
MS m/z: 434 (M$^+$1)
Preparation 41

A mixture of 1-acetoxy-2,2-bis(4-aminophenyl)ethane (2.70 g) and di-tert-butyl dicarbonate (5.23 g) in tetrahydrofuran (13.5 ml) was heated to reflux for 2 hours. After allowed to cool to room temperature, the mixture was concentrated and the residue was purified by column chromatography (silica gel, hexane/ethyl acetate) to give 1-acetoxy-2,2-bis[4-(tert-butoxycarbonylamino)phenyl]ethane (4.64 g) as a white amorphous powder.

$^1$H-NMR (CDCl$_3$, δ): 1.50(18H, s), 1.96(3H, s), 4.25(1H, t, J=8Hz), 4.54(2H, d, J=8Hz), 6.46(2H, br s), 7.11(4H, d, J=8Hz), 7.28(4H, d, J=8Hz)
Preparation 42

2,2-Bis[4-(tert-butoxycarbonylamino)phenyl]ethanol was obtained according to a similar manner to that of Preparation 36.

$^1$H-NMR (CDCl$_3$, δ): 1.50(18H, s), 4.00-4.18(3H, m), 6.45(2H, br s), 7.15(4H, d, J=9Hz), 7.30(4H, d, J=9Hz)
Preparation 43

1,1-Bis[4-(tert-butoxycarbonylamino)phenyl]-2-
(methanesulfonyloxy)ethane was obtained according to a similar manner to that of Preparation 37.

$^1$H-NMR (CDCl$_3$, $\delta$): 1.51(18H, s), 2.77(3H, s), 4.33(1H, t, J=8Hz), 4.66(2H, d, J=8Hz), 6.45(2H, br s), 7.13(4H, d, J=9Hz), 7.31(4H, d, J=9Hz)

MS m/z: 529 (M$^+$+Na)

Preparation 44

1-Azido-2,2-bis[4-(tert-butoxycarbonylamino)phenyl]ethane was obtained according to a similar manner to that of Preparation 38.

$^1$H-NMR (CDCl$_3$, $\delta$): 1.52(18H, s), 3.80(2H, d, J=8Hz), 4.14(1H, t, J=8Hz), 6.45(2H, br s), 7.13(4H, d, J=9Hz), 7.30(4H, d, J=9Hz)

MS m/z: 476 (M$^+$+Na)

Preparation 45

2,2-Bis[4-(tert-butoxycarbonylamino)phenyl]ethylamine was obtained according to a similar manner to that of Preparation 39.

$^1$H-NMR (CDCl$_3$, $\delta$): 1.50(18H, s), 3.25(2H, d, J=8Hz), 3.90(1H, t, J=8Hz), 6.44(2H, br s), 7.13(4H, d, J=9Hz), 7.28(4H, d, J=9Hz)

MS m/z: 428 (M$^+$+1)

Preparation 46

A mixture of 2,2-bis[4-(tert-butoxycarbonylamino)phenyl]ethylamine (811 mg) and benzaldehyde (224 mg) in dichloromethane (8.1 ml) was stirred at room temperature for 1.5 hours. The mixture was evaporated, and the residual solid was suspended in ethanol (8.1 ml) - dichloromethane (4.1 ml). Sodium borohydride (79 mg) was added to the suspension, and the mixture was stirred at room temperature for 2 hours. The mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed with brine, dried over magnesium sulfate, and filtered. The filtrate was concentrated and the residue was purified by column chromatography (silica gel, hexane/ethyl acetate) to give N-benzyl-[2,2-bis[4-(tert-butoxycarbonylamino)phenyl]ethyl]amine (801 mg) as a white amorphous powder.

$^1$H-NMR (CDCl$_3$, $\delta$): 1.50(18H, s), 3.15(2H, d, J=8Hz), 3.79(2H, s), 4.12(1H, t, J=8Hz), 6.42(2H, br s), 7.10(4H, d, J=9Hz), 7.15-7.38(9H, m)

MS m/z: 518 (M$^+$+1)

Example 45

A mixture of N-benzyl-[2,2-bis[4-(methoxycarbonylamino)phenyl]-ethyl]amine (119 mg) and (R)-[4-benzyloxyl-3-nitrophenyl]oxirane (82 mg) in ethanol (1.2 ml) was heated at 70°C for 15 hours. After allowed to cool to room temperature, the mixture was concentrated and the residue was purified by column chromatography (silica gel, hexane/ethyl acetate) to give (R)-2-[N-benzyl-
[2,2-bis[4-(methoxycarbonylamino)phenyl]ethyl]amino]-1-[4-benzoyloxy-3-nitrophenoxy]ethanol (120 mg) as a pale yellow amorphous powder.

1H-NMR (CDCl3, δ) : 2.42-2.72(2H, m), 2.97(1H, dd, J=13 and 6Hz), 3.21(1H, br s, OH), 3.27(1H, dd, J=13 and 10Hz), 3.51(1H, d, J=13Hz), 3.76(6H, s), 3.92(1H, d, J=13Hz), 4.04-4.22(1H, m), 4.48(1H, dd, J=10 and 4Hz), 5.21(2H, s), 6.57(2H, br s), 6.96-7.42(20H, m), 7.69(1H, d, J=2Hz)

MS m/z : 705 (M+1)

**Example 46**

(R)-2-[N-Benzyl-[2,2-bis[4-(tert-butoxycarbonylamino)phenyl]ethyl]amino]-1-[4-benzoyloxy-3-nitrophenoxy]ethanol was obtained according to a similar manner to that of Example 45.

1H-NMR (CDCl3, δ) : 1.50(18H, s), 2.42-2.70(2H, m), 2.96(1H, dd, J=13 and 6Hz), 3.20(1H, br s, OH), 3.25(1H, dd, J=13 and 10Hz), 3.52(1H, d, J=13Hz), 3.92(1H, d, J=13Hz), 4.03-4.20(1H, m), 4.47(1H, dd, J=10 and 4Hz), 5.20(2H, s), 6.43(2H, br s), 6.97-7.50(20H, m), 7.68(1H, d, J=2Hz)

MS m/z : 789 (M+1)

**Example 47**

To an ice-cooled solution of (R)-2-[N-benzyl-[2,2-bis[4-(tert-butoxycarbonylamino)phenyl]ethyl]amino]-1-[4-benzoyloxy-3-nitrophenoxy]ethanol (626 mg) in dichloromethane (3.1 ml) was added dropwise trifluoroacetic acid (1.2 ml), and the mixture was stirred for 4.5 hours while being allowed to warm to room temperature. The mixture was concentrated and the residue was partitioned between chloroform and saturated sodium bicarbonate solution. The organic layer was separated, washed with brine, dried over magnesium sulfate, and filtered. The filtrate was evaporated to give (R)-2-[N-benzyl-[2,2-bis[4-aminophenyl]ethyl]amino]-1-[4-benzoyloxy-3-nitrophenoxy]ethanol (448 mg) as a pale brown amorphous powder.

1H-NMR (CDCl3, δ) : 2.40-2.68(2H, m), 2.95(1H, dd, J=13 and 6Hz), 3.23(1H, dd, J=13 and 10Hz), 3.45(4H, br s, NH2), 3.53(1H, d, J=13Hz), 3.93(1H, d, J=13Hz), 4.01(1H, dd, J=10 and 6Hz), 4.48(1H, dd, J=10 and 4Hz), 5.20(2H, s), 6.52-7.52(20H, m), 7.67(1H, d, J=2Hz)

MS m/z : 589 (M+1)

**Example 48**

To an ice-cooled mixture of (R)-2-[N-benzyl-[2,2-bis[4-aminophenyl]ethyl]amino]-1-[4-benzoyloxy-3-nitrophenoxy]ethanol (428 mg) and pyridine (0.2 ml) in dichloromethane (3.4 ml) was added dropwise methyl chlorocarbonate (0.12 ml). The mixture was stirred at the same temperature for 30 minutes and partitioned between chloroform and water. The organic layer was separated,
washed successively with saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, and filtered. The filtrate was concentrated and the residue was purified by column chromatography (silica gel, hexane/ethyl acetate) to give (R)-2-[N-benzyl-[2,2-bis[4-(methoxycarbonyl)amino]phenyl]ethyl]amino]-1-(4-benzoxo-3-nitrophenyl)ethanol (451 mg) as a pale red amorphous powder.

\[ ^1H\text{-NMR (CDCl}_3, \delta) : 2.42-2.72(2H, m), 2.97(1H, dd, J=13 \text{ and } 6Hz), 3.21(1H, br s, OH), 3.27(1H, dd, J=13 \text{ and } 10Hz), 3.51(1H, d, J=13Hz), 3.76(6H, s), 3.92(1H, d, J=13Hz), 4.04-4.22(1H, m), 4.48(1H, dd, J=10 \text{ and } 4Hz), 5.20(2H, s), 6.57(2H, br s), 6.96-7.42(20H, m), 7.69(1H, d, J=2Hz) \]

MS m/z : 705 (M\textsuperscript{+}+1)

**Example 49**

To a solution of (R)-2-[N-benzyl-[2,2-bis[4-(methoxycarbonyl)amino]phenyl]ethyl]amino]-1-(4-benzoxo-3-nitrophenyl)ethanol (107 mg) in ethanol (2.1 ml) - water (0.43 ml) were added powdered iron (105 mg) and ammonium chloride (12 mg). The mixture was heated at 70°C for 1.5 hours and allowed to cool to room temperature. After the insoluble material was filtered off, the filtrate was concentrated and the residue was purified by column chromatography (silica gel, hexane/ethyl acetate) to give (R)-1-(3-amino-4-benzoxo-phenyl)-2-[N-benzyl-[2,2-bis[4-(methoxycarbonyl)amino]phenyl]ethyl]amino]ethanol (108 mg) as a pale yellow amorphous powder.

\[ ^1H\text{-NMR (CDCl}_3, \delta) : 2.50-2.74(2H, m), 2.91(1H, dd, J=13 \text{ and } 6Hz), 3.19(1H, br s, OH), 3.24(1H, dd, J=13 \text{ and } 10Hz), 3.46(1H, d, J=13Hz), 3.75(6H, s), 3.82(2H, br s, NH\textsubscript{2}), 3.93(1H, d, J=13Hz), 4.02-4.22(1H, m), 4.38-4.44(1H, m), 5.05(2H, s), 6.48-6.84(5H, m), 6.94-7.48(18H, m) \]

MS m/z : 675 (M\textsuperscript{+}+1)

**Example 50**

To an ice-cooled mixture of (R)-1-(3-amino-4-benzoxo-phenyl)-2-[N-benzyl-[2,2-bis[4-(methoxycarbonyl)amino]phenyl]ethyl]amino]ethanol (32 mg) and pyridine (20 \mu l) in dichloromethane (0.6 ml) was added dropwise benzenesulfonyl chloride (8 \mu l), and the mixture was stirred at room temperature for 2 hours. One drop of ammonia solution (28%) was added to the mixture, and the whole was stirred at the same temperature for 50 minutes before being partitioned between ethyl acetate and water. The organic layer was separated, washed successively with saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, and filtered. The filtrate was concentrated and the residue was purified by column chromatography (silica gel, chloroform/methanol) to give (R)-2-[N-benzyl-[2,2-bis[4-(methoxycarbonyl)amino]phenyl]ethyl]amino]-1-[4-benzoxo-3-(benzenesulfonyl)amino]phenyl]ethanol (38
mg) as a pale yellow amorphous powder.

\(^1\)H-NMR (CDCl\(_3\), \(\delta\)) : 2.42-2.68(2H, m), 2.94(1H, dd, J=13 and 6Hz), 3.21(1H, br s, OH), 3.27(1H, dd, J=13 and 10Hz), 3.49(1H, d, J=13Hz), 3.74(3H, s), 3.76(3H, s), 3.95(1H, d, J=13Hz), 4.02-4.20(1H, m), 4.42-4.56(1H, m), 4.81(2H, s), 6.57(2H, br s), 6.60-7.72(27H, m)

MS m/z : 815(M\(^{+}\)+1)

**Example 51**

A solution of (R)-2-[[N-benzyl-[2,2-bis[4-(methoxycarbonylamino)phenyl]-ethyl]amino]-1-[4-benzylxylo-3-(benzenesulfonylamino)phenyl]ethanol (34 mg) in methanol (1 ml) was hydrogenated (1 atm) over 10% palladium on carbon (4 mg) at room temperature for 6 hours. After the catalyst was filtered off, the filtrate was concentrated and the residue was purified by column chromatography (silica gel, chloroform/methanol) to give (R)-2-[[2,2-bis[4-(methoxycarbonylamino)phenyl]ethyl]amino]-1-[4-hydroxy-3-(benzenesulfonylamino)phenyl]ethanol (18 mg) as a white amorphous powder.

IR (KBr) : 1710 cm\(^{-1}\)

\(^1\)H-NMR (CD\(_3\)OD, \(\delta\)) : 2.64-2.88(2H, m, AB of ABX), 3.21(2H, d, AB of ABX), 3.71(6H, s), 4.08(1H, t, X of ABX), 4.58(1H, dd, J=8 and 5Hz, X of ABX), 6.61(1H, d, J=8Hz), 6.86(1H, dd, J=8 and 2Hz), 7.00-7.82(14H, m)

MS m/z : 635(M\(^{+}\)+1)

**Example 52**

To a solution of (R)-2-[[2,2-bis[4-(methoxycarbonylamino)phenyl]-ethyl]amino]-1-[4-hydroxy-3-(benzenesulfonylamino)phenyl]ethanol (107 mg) in methanol (1.1 ml) was added 4N hydrogen chloride in 1,4-dioxane (0.13 ml) at room temperature, and the mixture was stirred at the same temperature for 5 minutes. The mixture was concentrated, and the residue was triturated with diisopropyl ether (2 ml) to give (R)-2-[[2,2-bis[4-(methoxycarbonylamino)phenyl]-ethyl]amino]-1-[4-hydroxy-3-(benzenesulfonylamino)phenyl]ethanol hydrochloride (95 mg) as a white powder.

IR (KBr) : 1710 cm\(^{-1}\)

\(^1\)H-NMR (CD\(_3\)OD, \(\delta\)) : 2.96-3.24(2H, m, AB of ABX), 3.65-3.90(2H, m, AB of ABX), 3.72(6H, s), 4.37(1H, t, X of ABX), 4.83(1H, t, X of ABX), 6.68(1H, d, J=8Hz), 6.97(1H, dd, J=8 and 2Hz), 7.20-7.82(14H, m)

MS m/z : 635(M\(^{+}\)+1) (free)

**Example 53**

(R)-2-[[N-Benzyl-[2,2-bis[4-(methoxycarbonylamino)phenyl]-ethyl]amino]-1-[4-benzylxylo-3-(methanesulfonylamino)phenyl]ethanol was obtained according to a similar manner to that of Example 50.
1H-NMR (CDCl3, δ) : 2.48-2.68(2H, m), 2.87-3.04(1H, m), 2.88(3H, s), 3.12-3.35(2H, m), 3.48(1H, d, J=13Hz), 3.75(6H, s), 3.95(1H, d, J=13Hz), 4.02-4.22(1H, m), 4.42-4.58(1H, m), 5.08(2H, s), 6.58(2H, br s), 6.77(1H, br s), 6.86-7.48(21H, m)

5 MS m/z : 753 (M+1)

Example 54

(R)-2-[[2,2-Bis[4-(methoxycarbonylamino)phenyl]ethyl]amino]-1-[4-hydroxy-3-(methanesulfonylamino)phenyl]ethanol was obtained according to a similar manner to that of Example 51.

10 IR (KBr) : 1710 cm⁻¹

1H-NMR (CD3OD, δ) : 2.90(3H, s), 3.02(2H, d, AB of ABX), 3.55(2H, d, AB of ABX), 3.72(6H, s), 4.24(1H, t, X of ABX), 4.78(1H, t, X of ABX), 6.86(1H, d, J=8Hz), 7.05(1H, dd, J=8 and 2Hz), 7.14-7.54(9H, m)

MS m/z : 573 (M+1)

Example 55

To an ice-cooled solution of (R)-1-[3-amino-4-benzylxoyphenyl]-2-[N- benzy1-[2,2-bis[4-(methoxycarbonylamino)phenyl]ethyl]amino]ethanol (32 mg) in dichloromethane (0.6 ml) was added acetic formic anhydride [prepared in situ by mixing formic acid (11 µl) and acetic anhydride (13 µl)], and the mixture was stirred for 2.5 hours, while being allowed to warm to room temperature. Methanol (1 ml) and potassium carbonate (20 mg) were added to the mixture, and the whole was stirred at the same temperature for 2 hours before being partitioned between ethyl acetate and water. The organic layer was separated, washed with brine, dried over magnesium sulfate, and filtered. The filtrate was concentrated and the residue was purified by column chromatography (silica gel, chloroform/methanol) to give (R)-2-[N-benzyl-[2,2-bis[4-(methoxycarbonylamino)phenyl]ethyl]amino]-1-[4-benzylxoy-3-(formylamino)phenyl]ethanol (37 mg) as a white amorphous powder.

1H-NMR (CDCl3, δ) : 2.48-2.74(2H, m), 2.84-3.06(1H, m), 3.11-3.36(2H, m), 3.47(1H, d, J=13Hz), 3.76(6H, s), 3.95(1H, d, J=13Hz), 4.02-4.20(1H, m), 4.40-4.60(1H, m), 5.07(2H, s), 6.58(2/3 of 2H, br s), 6.68(1/3 of 2H, br s), 6.82-7.50(20H+1/3H, m), 7.68(1/3H, br d, J=12Hz), 7.78(2/3H, br s), 8.26(2/3H, d, J=2Hz), 8.42(2/3H, d, J=2Hz), 8.69(1/3H, d, J=12Hz)

MS m/z : 703 (M⁺+1)

Example 56

(R)-2-[[2,2-Bis[4-(methoxycarbonylamino)phenyl]ethyl]amino]-1-(3-formylamino-4-hydroxyphenyl)ethanol was obtained according to a similar manner to that of Example 51.
IR (KBr) : 1710, 1678 cm⁻¹

\(^1\)H-NMR (CD\textsubscript{3}OD, δ) : 2.92-3.12(2H, m, AB of ABX), 3.59(2H, d, AB of ABX), 3.72(6H, s), 4.25(1H, t, X of ABX), 4.78(1H, t, X of ABX), 6.82(1H, d, J=8Hz), 6.96(1H, dd, J=8 and 2Hz), 7.22(4H, d, J=9Hz), 7.40(4H, d, J=9Hz), 8.05(1H, d, J=2Hz), 8.30(1H, s)

MS m/z : 523 (M\textsuperscript{+}+1)

**Example 57**

(S)-1-Phenoxy-3-[N-benzyl-[2,2-bis[4-(methoxycarbonylamino)phenyl]-ethyl]amino]-2-propanol was obtained according to a similar manner to that of Example 45.

\(^1\)H-NMR (CDCl\textsubscript{3}, δ) : 2.62-2.78(2H, m), 3.01(1H, dd, J=13 and 6Hz), 3.18(1H, dd, J=13 and 10Hz), 3.55(1H, d, J=13Hz), 3.75(6H, s), 3.80(1H, d, J=13Hz), 3.86-4.32(4H, m), 6.50(1H, br s), 6.55(1H, br s), 6.76-7.42(18H, m)

MS m/z : 584 (M\textsuperscript{+}+1)

**Example 58**

(S)-1-Phenoxy-3-[[2,2-bis[4-(methoxycarbonylamino)phenyl]ethyl]amino]-2-propanol was obtained according to a similar manner to that of Example 51.

\(^1\)H-NMR (CDCl\textsubscript{3}, δ) : 2.79(1H, dd, J=12 and 7Hz), 2.91(1H, dd, J=12 and 4Hz), 3.22(2H, d, AB of ABX), 3.76(6H, s), 3.86-4.20(4H, m), 6.60(2H, br s), 6.78-7.02(3H, m), 7.08-7.40(10H, m)

MS m/z : 494(M\textsuperscript{+}+1)

**Example 59**

(S)-1-[4-Benzylxoy-3-nitrophenoxy]-3-[N-benzyl-[2,2-bis[4-(methoxycarbonylamino)phenyl]ethyl]amino]-2-propanol was obtained according to a similar manner to that of Example 45.

\(^1\)H-NMR (CDCl\textsubscript{3}, δ) : 2.64(2H, d, AB of ABX), 3.00(1H, dd, J=13 and 7Hz), 3.17(1H, dd, J=13 and 9Hz), 3.50-4.00(5H, m), 3.74(3H, s), 3.75(3H, s), 4.12(1H, t, X of ABX), 5.18(2H, s), 3.54(1H, br s), 6.56(1H, br s), 6.88-7.52(21H, m)

MS m/z : 735 (M\textsuperscript{+}+1)

**Example 60**

(S)-1-[3-Amino-4-benzylxoyphenoxy]-3-[N-benzyl-[2,2-bis[4-(methoxycarbonylamino)phenyl]ethyl]amino]-2-propanol was obtained according to a similar manner to that of Example 49.

\(^1\)H-NMR (CDCl\textsubscript{3}, δ) : 2.33-3.33(4H, m), 3.33-4.28(6H, m), 3.75(6H, s), 5.01(2H, s), 6.12(1H, dd, J=9 and 3Hz), 6.26(1H, d, J=3Hz), 6.56(1H, br s), 6.59(1H, br s), 6.73(1H, d, J=9Hz), 6.92-7.51(18H, m)

MS m/z : 705 (M\textsuperscript{+}+1)

**Example 61**
(S)-1-[4-Benzyl-3-(formylamino)phenoxy]-3-[N-benzyl-2,2-bis[4-(methoxycarbonylamino)phenyl]ethyl]amino]-2-propanol was obtained according to a similar manner to that of Example 55.

\[ ^1H-NMR \text{ (CDCl}_3, \delta): 2.66 \text{ (2H, d, AB of ABX), 3.00 (1H, dd, J=13 and 7Hz), 3.17 (1H, dd, J=13 and 9Hz), 3.46-3.99 (5H, m), 3.74 (3H, s), 3.75 (3H, s), 4.10 (1H, t, X of ABX), 5.05 (2H, s), 6.42-7.50(22H+1/4H, m), 7.70 (1/4H, br d, J=12Hz), 7.80 (3/4H, br s), 7.99 (3/4H, d, J=2Hz), 8.40 (3/4H, d, J=2Hz), 8.68 (1/4H, br d, J=12Hz) }\]

MS m/z : 733 (M+1)

**Example 62**

(S)-1-[3-Formylamino-4-hydroxyphenoxy]-3-[2,2-bis[4-(methoxycarbonylamino)phenyl]ethyl]amino]-2-propanol was obtained according to a similar manner to that of Example 51.

IR (KBr) : 1710, 1678 cm\(^{-1}\)

\[ ^1H-NMR \text{ (CD}_3\text{OD, } \delta): 2.66-2.95(2H, m), 3.13-3.35(2H, m), 3.71(6H, s), 3.72-4.22(4H, m), 6.50(1H, dd, J=9 and 3Hz), 6.74(1H, d, J=9Hz), 7.19(4H, d, J=8Hz), 7.35(4H, d, J=8Hz), 7.69(1H, d, J=3Hz), 8.28(1H, s) \]

MS m/z : 553 (M+1)

**Example 63**

(S)-1-[4-Benzyl-3-(benzenesulfonylamino)phenoxy]-3-[N-benzyl-2,2-bis[4-(methoxycarbonylamino)phenyl]ethyl]amino]-2-propanol was obtained according to a similar manner to that of Example 50.

\[ ^1H-NMR \text{ (CDCl}_3, \delta): 2.66(2H, d, AB of ABX), 3.00(1H, dd, J=13 and 7Hz), 3.20(1H, dd, J=13 and 9Hz), 3.48-4.22(6H, m), 3.73(3H, s), 3.75(3H, s), 4.77(2H, s), 6.45(1H, dd, J=9 and 2Hz), 6.56(2H, br s), 6.66(1H, d, J=9Hz), 6.93-8.00(25H, m) \]

MS m/z : 845 (M+1)

**Example 64**

(S)-1-[4-Hydroxy-3-(benzenesulfonylamino)phenoxy]-3-[2,2-bis[4-(methoxycarbonylamino)phenyl]ethyl]amino]-2-propanol was obtained according to a similar manner to that of Example 51.

IR (KBr) : 1710 cm\(^{-1}\)

\[ ^1H-NMR \text{ (CD}_3\text{OD, } \delta): 2.63-2.95(2H, m), 3.12-3.38(2H, m), 3.60-3.88(2H, m), 3.71(6H, s), 3.88-4.22(2H, m), 6.46(1H, dd, J=9 and 3Hz), 6.58(1H, d, J=9Hz), 6.91(1H, d, J=3Hz), 7.11-7.85(13H, m) \]

MS m/z : 665 (M+1)

**Example 65**

To a mixture of (S)-1-phenoxy-3-[N-benzyl-3,3-bis(4-aminophenyl)-
propyl]amino]-2-propanol (60 mg), dichloromethane (1 ml) and pyridine (60 µl), ethyl chloroformate (36 µl) was added with cooling by ice-bath. The reaction mixture was stirred at room temperature for 1 hour, diluted with ethyl acetate (40 ml), washed by water followed by saturated sodium chloride solution, dried over magnesium sulfate, evaporated and purified by preparative TLC (silica gel, hexane : ethyl acetate = 1:1) to afford an oily product. A mixture of the product, methanol (2 ml) and 10% palladium on charcoal (10 mg) was stirred under hydrogen (1 atm) for 1 hour, filtrated and evaporated to afford (S)-1-phenoxy-3-[[3,3-bis[4-(ethoxycarbonyl)amino][phenyl]propyl]amino]-2-propanol (23 mg).

\[ \text{H-NMR (CD}_3\text{OD, } \delta) : 1.28(6H, t, J=7.1Hz), 2.1-2.3(2H, m), 2.6-2.85(4H, m), 3.86-4.1(4H, m), 4.14(4H, quartet, } J=7.1Hz), 6.88-6.94(3H, m), 7.14-7.35(10H, m) \]

MS m/z : 536 (M+1)

**Example 66**

To a mixture of (S)-1-phenoxy-3-[[N-benzyl-[3,3-bis[4-aminophenyl]-propyl]amino]-2-propanol (60 mg), dichloromethane (1 ml) and pyridine (60 µl), acetic anhydride (35 µl) was added with cooling by ice-bath. The reaction mixture was stirred at room temperature for 1 hour, diluted with ethyl acetate (40 ml), washed by water followed by saturated sodium chloride solution, dried over magnesium sulfate, evaporated and purified by preparative TLC (silica gel, ethyl acetate) to afford an oily product. A mixture of the product, methanol (2 ml) and 10% palladium on charcoal (10 mg) was stirred under hydrogen (1 atm) for 1 hour, filtrated and evaporated to afford (S)-1-phenoxy-3-[[3,3-bis[4-(acetylamino)[phenyl]propyl]amino]-2-propanol (10 mg).

\[ \text{H-NMR (CD}_3\text{OD, } \delta) : 2.09(6H, s), 2.1-2.3(2H, m), 2.6-2.85(4H, m), 3.9-4.1(4H, m), 6.86-6.95(3H, m), 7.1-7.3(6H, m), 7.44(4H, d, } J=8.4Hz) \]

MS m/z : 476 (M+1)

**Example 67**

The following compounds were obtained according to a similar manner to that of Example 66.

(1) (S)-1-Phenoxy-3-[[3,3-bis[4-(propionylamino)[phenyl]propyl]amino]-2-propanol

\[ \text{H-NMR (CD}_3\text{OD, } \delta) : 1.14(6H, t, J=8.9Hz), 2.10-2.3(2H, m), 2.34(4H, quartet, } J=8.9Hz), 2.47-2.81(4H, m), 3.89-4.1(4H, m), 6.88-6.94(3H, m), 7.14-7.31(6H, m), 7.45(4H, d, } J=8.5Hz) \]

MS m/z : 504 (M+1)

(2) (S)-1-Phenoxy-3-[[2,2-bis[4-(acetylamino)[phenyl]ethyl]amino]-2-propanol

\[ \text{H-NMR (CD}_3\text{OD, } \delta) : 2.09(6H, s), 2.73-2.88(2H, m), 3.22(2H, dd, } J=2.9Hz, } 5.4Hz) \]
7.4Hz), 3.87(2H, d, J=5.2Hz), 3.9-4.2(2H, m), 6.82-6.94(3H, m), 7.20-7.27(6H, m), 7.47(4H, d, J=8.4Hz)
MS m/z : 462 (M+1)

Example 68

The following compounds were obtained according to a similar manner to that of Example 65.

(1)  (S)-1-Phenoxy-3-[[3,3-bis[4-(methanesulfonlamino)phenyl]propyl]amino]-2-propanol

$^1$H-NMR (CD$_3$OD, $\delta$) : 2.1-2.3(2H, m), 2.6-2.8(4H, m), 2.89(6H, s), 3.90-4.1(4H, m), 6.87-6.94(3H, m), 7.14-7.29(10H, m)
MS m/z : 548 (M+1)

(2)  (S)-1-Phenoxy-3-[[2,2-bis[4-(methanesulfonlamino)phenyl]ethyl]amino]-2-propanol

$^1$H-NMR (CD$_3$OD, $\delta$) : 2.73-2.88(2H, m), 2.89(6H, s), 3.22(2H, dd, J=2.9Hz, 7.4Hz), 3.87(2H, d, J=5.2Hz), 3.9-4.2(2H, m), 6.87-6.94(3H, m), 7.1-7.3(10H, m)
MS m/z : 534 (M+1)

(3)  (R)-1-(4-Benzzyloxy-3-nitrophenyl)-2-[N-benzyl-[2,2-bis[4-(2,2-dimethylpropionyloxy)phenyl]ethyl]amino]ethanol

$^1$H-NMR (CDCl$_3$, $\delta$) : 1.33(9H, s), 1.35(9H, s), 2.48-2.7(2H, m), 3.00(1H, dd, J=6.1Hz, 13.0Hz), 3.28(1H, dd, J=10.0Hz, 12.9Hz), 3.52(1H, d, J=13.3Hz), 3.93(1H, d, J=13.3Hz), 4.20(1H, dd, J=6.2Hz, 9.7Hz), 4.52(1H, dd, J=3.8Hz, 9.7Hz), 5.21(2H, s), 6.94-7.02(4H, m), 7.06-7.17(7H, m), 7.29-7.46(9H, m), 7.72(1H, d, J=2.1Hz)
MS m/z : 781 (M+Na), 759 (M+1)

(4)  (S)-1-(3-Hydroxymethyl-4-hydroxyphenoxo)-3-[[2,2-bis[4-(2,2-dimethylpropionyloxy)phenyl]ethyl]amino]-2-propanol

$^1$H-NMR (CD$_3$OD, $\delta$) : 1.33(18H, s), 2.69-2.91(2H, m), 3.17-3.3(2H, m), 3.83(2H, d, J=5.3Hz), 3.93-4.02(1H, m), 4.24(1H, t, J=7.8Hz), 4.61(2H, s), 6.60-6.76(2H, m), 6.88(1H, d, J=1.8Hz), 6.98(4H, d, J=8.5Hz), 7.32(4H, d, J=8.5Hz)
MS m/z : 594 (M+1)

Example 69

To a mixture of (S)-1-phenoxy-3-[N-benzyl-[3,3-bis[4-aminophenyl]-propyl]amino]-2-propanol (60 mg) and acetic acid (2 ml), potassium isocyanate (50 mg) was added at once. The reaction mixture was stirred at room temperature for 1 hour, diluted with ethyl acetate (40 ml), washed by water followed by saturated sodium chloride solution, dried over magnesium sulfate, evaporated and purified by preparative TLC (silica gel, ethyl acetate) to afford an oily product. A mixture of the product, methanol (2 ml) and 10% palladium on
charcoal (10 mg) was stirred under hydrogen (1 atm) for 1 hour, filtered and evaporated to afford (S)-1-phenoxo-3-[[3,3-bis[4-ureidophenyl]propyl]amino]-2-propanol (16 mg).

$^1$H-NMR (CD$_3$OD, $\delta$): 2.1-2.3(2H, m), 2.6-2.8(4H, m), 3.90-4.1(4H, m), 6.87-6.94(3H, m), 7.14-7.29(10H, m)

MS m/z : 477 (M$^+$)

**Example 70**

To a mixture of (S)-1-phenoxo-3-[N-benzyl-[3,3-bis[4-aminophenyl]-propyl]amino]-2-propanol (60 mg) and dichloromethane (2 ml), a mixture of formic acid (22 $\mu$L) and acetic anhydride (28 $\mu$L) was added with cooling by ice-bath. The reaction mixture was stirred at room temperature for 1 hour, diluted with ethyl acetate (40 ml), washed by water followed by saturated sodium chloride solution, dried over magnesium sulfate, evaporated and purified by preparative TLC (silica gel, ethyl acetate) to afford an oily product. A mixture of the product, methanol (2 ml) and 10% palladium on charcoal (10 mg) was stirred under hydrogen (1 atm) for 1 hour, filtered and evaporated to afford (S)-1-phenoxo-3-[[3,3-bis[4-(formylamino)phenyl]propyl]amino]-2-propanol (30 mg).

$^1$H-NMR (CD$_3$OD, $\delta$): 2.18-2.30(2H, m), 2.54-2.81(4H, m), 3.89-4.1(4H, m), 6.88-6.94(3H, m), 7.21-7.29(6H, m), 7.48(4H, d, J = 8.5 Hz), 8.21(2H, s)

MS m/z : 448 (M+1)

**Example 71**

To a mixture of (S)-1-phenoxo-3-[N-benzyl-[3,3-bis[4-aminophenyl]-propyl]amino]-2-propanol (120 mg), N,N-dimethylformamide (2 ml) and potassium carbonate (0.5g), 4-chlorobutyryl chloride (84 $\mu$L) was added with cooling by ice-bath. The reaction mixture was stirred at room temperature for 1 hour, diluted with ethyl acetate (40 ml), washed by water followed by saturated sodium chloride solution, dried over magnesium sulfate and evaporated to afford a crude product. A mixture of the product, methanol (5 ml) and 28% sodium methoxide - methanol solution (0.29 g) was heated under reflux for 4 hours, worked up in the usual manner as described above, purified by preparative TLC (silica gel, ethyl acetate) to afford an oily product. A mixture of the purified oily product, methanol (2 ml), 1,4-dioxane (2 ml) and 10% palladium on charcoal (10 mg) was stirred under hydrogen (1 atm) for 2 hours, filtered and evaporated to afford (S)-1-phenoxo-3-[[3,3-bis[4-(pyrrolidin-2-one-1-yl)phenyl]propyl]amino]-2-propanol (46 mg).

$^1$H-NMR (CD$_3$OD, $\delta$): 2.00-2.30(6H, m), 2.59-2.76(8H, m), 3.82-4.04(8H, m), 6.88-6.94(3H, m), 7.21-7.31(6H, m), 7.49(4H, d, J = 6.6 Hz)

MS m/z : 528 (M+1)
Example 72

The following compound was obtained according to a similar manner to that of Example 71.

(S)-1-Phenoxy-3-[[3,3-bis[4-(1,1-dioxoisothiazolidin-2-yl)phenyl]propyl]amino]-2-propanol

$^1$H-NMR (CD$_3$OD, $\delta$) : 2.00-2.40(2H, broad m), 2.46(4H, quintet, $\text{J}=6.7\text{Hz}$), 3.36(4H, t, $\text{J}=7.5\text{Hz}$), 3.6-3.8(4H, m), 3.9-4.1(4H, m), 6.87-6.94(3H, m), 7.1-7.4(10H, m)

MS m/z : 600 (M+1)

Example 73

To a mixture of (S)-1-phenoxy-3-[N-benzyl-[3,3-bis[4-aminophenyl]-propyl]amino]-2-propanol (120 mg), dichloromethane (2 ml) and acetic acid (1 drop), 2-chloroethyl isocyanate (63 $\mu$l) was added with cooling by ice-bath. The reaction mixture was stirred at room temperature for 1 hour, diluted with ethyl acetate (40 ml), washed by water followed by saturated sodium chloride solution, dried over magnesium sulfate and evaporated to afford a crude product. A mixture of the product, methanol (5 ml) and 28% sodium methoxide - methanol solution (0.29 g) was heated under reflux for 5 hours, worked up in the usual manner as described above, purified by preparative TLC (silica gel, dichloromethane : methanol = 20:1) to afford an oily product. A mixture of the purified oily product, methanol (2 ml), 1,4-dioxane (2 ml) and 10% palladium on charcoal (10 mg) was stirred under hydrogen (1 atm) for 2 hours, filtrated and evaporated to afford (S)-1-phenoxy-3-[[3,3-bis[4-(imidazolidin-2-one-1-yl)phenyl]propyl]amino]-2-propanol (79mg).

$^1$H-NMR (CD$_3$OD, $\delta$) : 2.1-2.4(2H, broad m), 2.5-2.6(2H, broad m), 2.7-2.9(2H, m), 3.49(4H, dd, $\text{J}=6.0\text{Hz}$, 8.8Hz), 3.85-4.08(8H, m), 6.88-6.94(3H, m), 7.1-7.29(6H,m), 7.39-7.45 (4H, m)

MS m/z : 530 (M+1), 503, 476

Example 74

The following compounds were obtained according to a similar manner to that of Example 9.

1. (R)-1-(3-Chlorophenyl)-2-[N-benzyl-[3,3-bis[4-(methoxycarbonylamino)phenyl]propyl]amino]ethanol

MS m/z : 602 (M$^+$)

2. (S)-1-(3-Formyl-4-benzoyloxyphenoxy)-3-[N-benzyl-[2,2-bis[4-hydroxyphenyl]ethyl]amino]-2-propanol

MS m/z : 604 (M+1)

3. (R)-2-[N-Benzyl-[3,3-bis[4-(methoxycarbonylamino)phenyl]propyl]amino]-
1-(benzyloxy-3-nitrophenyl)ethanol
$^1$H-NMR (CDCl$_3$, $\delta$) : 2.04-2.73 (6H, m), 3.49 (1H, d, J=13Hz), 3.72-3.92 (1H, m), 3.75 (6H, s), 3.84 (1H, d, J=13Hz), 4.45 (1H, dd, J=10 and 3Hz), 5.21 (2H, s), 6.56 (2H, br s), 6.98-7.53 (20H, m), 7.72 (1H, d, J=2Hz)

MS m/z : 719 (M$^+$+1)

(4) (R)-2-[N-Benzyl-[3,3-bis[4-(1-pyrrolidinyl)phenyl]propyl]amino]-1-(4-benzyloxy-3-nitrophenyl)ethanol
$^1$H-NMR (CDCl$_3$, $\delta$) : 1.78-2.14 (8H, m), 2.05-2.75 (6H, m), 3.06-3.40 (8H, m), 3.50 (1H, d, J=13Hz), 3.63-3.81 (1H, m), 3.85 (1H, d, J=13Hz), 4.45 (1H, dd, J=10 and 4Hz), 5.20 (2H, s), 6.47 (4H, d, J=9Hz), 6.90-7.60 (16H, m), 7.72 (1H, d, J=2Hz)

(5) (S)-1-Phenoxy-3-[N-benzyl-[2,2-bis[3-methoxycarbonylamino]phenyl]-2-hydroxyethyl]amino]-2-propanol
$^1$H-NMR (CDCl$_3$, $\delta$) : 2.73 (2H, d, AB of ABX), 3.44-3.82 (6H, m), 3.74 (6H, s), 3.84-4.06 (1H, m), 5.22 (1H, br s, OH), 6.59 (2H, br s), 6.68-7.50 (18H, m)

MS m/z : 600 (M$^+$+1)

(6) (R)-2-[N-Benzyl-[2,2-bis[4-methoxy-3-methylphenyl]ethyl]amino]-1-(4-benzyloxy-3-nitrophenyl)ethanol
(+ ) APCI-MS m/z : 647 (M+H)$^+$

(7) (R)-2-[N-Benzyl-[2,2-bis[4-hydroxy-3-methylphenyl]ethyl]amino]-1-[4-benzyloxy-3-[N-(benzyloxycarbonyl)methanesulfonylamino]phenyl]ethanol
(+ ) ESI-MS m/z : 801 (M+H)$^+$

(8) (S)-1-Phenoxy-3-[N-benzyl-[2,2-bis[4-hydroxyphenyl]ethyl]amino]-2-propanol
(+ ) APCI-MS m/z : 470 (M+H)$^+$

(9) (S)-1-Phenoxy-3-[N-benzyl-[3,3-bis[4-hydroxyphenyl]propyl]amino]-2-propanol
(+ ) APCI-MS m/z : 483 (M+H)$^+$

(10) (S)-1-[1H-Indol-4-yloxy]-3-[N-benzyl-[2,2-bis[4-hydroxyphenyl]ethyl]-amino]-2-propanol
(+ ) APCI-MS m/z : 509 (M+H)$^+$

(11) (S)-1-[1H-Indol-4-yloxy]-3-[N-benzyl-[3,3-bis[4-hydroxyphenyl]propyl]-amino]-2-propanol
(+ ) APCI-MS m/z : 523 (M+H)$^+$

(12) (R)-2-[N-Benzyl-[3,3-bis[4-methoxyphenyl]propyl]amino]-1-[4-benzyloxy-3-nitrophenyl]ethanol

MS (m/z) : 633 (M+1)

(13) (S)-3-[(2-Hydroxy-2,2-diphenylethyl)amino]-1-phenoxy-2-propanol hydrochloride
\(^1\)H-NMR (DMSO-d\(_6\), \(\delta\)) : 2.95-3.25(2H, m), 3.80-4.10(4H, m), 4.20-4.30(1H, m), 6.80-7.05(3H, m), 7.20-7.60(12H, m)

MS (m/z) : 364 (M+1)

(14) (R)-2-[N-Benzyl-[2,2-bis(4-benzyloxy-3-chlorophenyl)ethyl]amino]-1-(4-benzyloxy-3-nitrophenyl)ethanol

\(^1\)H-NMR (DMSO-d\(_6\), \(\delta\)) : 2.61(2H, br d, CH\(_2\)), 2.90-3.00(2H, m, CH\(_2\)), 3.51(1H, d, J=13.3Hz, CH\(_2\)), 3.76(1H, d, J=13.3Hz, CH\(_2\)), 4.19(1H, t, J=7.3Hz, CHAr\(_2\)), 4.65(1H, m, CH), 5.02(1H, d, J=3.8Hz, OH), 5.14(2H, s, CH\(_2\)), 5.15(2H, s, CH\(_2\)), 5.25(2H, s, CH\(_2\)), 6.96-7.71(29H, m, aromatic H)

(+) ESI MS m/z : 839, 841, 843 (M+1)

Example 75

A mixture of (R)-1-(3-chlorophenyl)-2-[N-benzyl-[3,3-bis(4-methoxy-carbonylamino)phenyl]propyl]amino]ethanol (112 mg), methanol (6 ml), chlorobenzene (6 ml) and 10% palladium on charcoal (100 mg) was stirred under hydrogen (1 atm) for 40 minutes, filtrated, and evaporated to afford (R)-1-(3-chlorophenyl)-2-[3,3-bis(4-methoxy-carbonylamino)phenyl]propyl]amino]ethanol hydrochloride (96 mg).

\(^1\)H-NMR (CD\(_3\)OD, \(\delta\)) : 2.18-2.49(2H, m), 2.93-3.24(4H, m), 3.71(6H, s), 3.91(1H, t, J=7.6Hz), 4.9-5.0(1H, m), 7.12-7.2(5H, m), 7.29-7.39(7H, m)

MS m/z : 512, 514 (free form, M+1)

Preparation 47

To a mixture of 2,2-bis(4-(tert-butoxycarbonylamino)phenyl)ethanol (500 mg), dichloromethane (5 ml) and triethylamine (0.45 ml), methanesulfonyl chloride (0.12 ml) was added dropwise with cooling by ice-bath. The reaction mixture was stirred at room temperature for 10 minutes, diluted with ethyl acetate (50 ml), washed by water followed by saturated sodium chloride solution, dried over magnesium sulfate and evaporated to afford a crude product. A mixture of the product and benzylamine (2.6 ml) was heated at 120°C for 1.5 hours, diluted with ethyl acetate (50 ml), washed by 1N hydrochloric acid solution (30 ml, twice) followed by saturated sodium bicarbonate solution, dried over potassium carbonate and evaporated to afford a crude product, which was purified by column chromatography (silica gel, hexane : ethyl acetate = 1:2) to afford N-benzyl-2,2-bis(4-(tert-butoxycarbonylamino)phenyl)ethylamine (263 mg).

\(^1\)H-NMR (CD\(_3\)OD, \(\delta\)) : 1.49(18H, s), 3.10(2H, d, J=7.9Hz), 3.75(2H, s), 4.80(1H, t, J=7.3Hz), 7.10(4H, d, J=6.7Hz), 7.2-7.34(9H, m)

MS m/z : 518 (M+1), 503, 476

Example 76

The following compound was obtained according to a similar manner to
that of Example 70.

\( (S\text{-1-Phenoxy-3-[[2,2-bis[4-(formylamino)phenyl]ethyl]amino]-2-propanol} \)

\(^1\text{H-NMR} (\text{CD}_3\text{OD}, \delta) : 2.73-2.88(2\text{H, m}), 3.22(2\text{H, dd, J=2.9Hz, 7.4Hz}), 3.87(2\text{H, d, J=5.2Hz}), 3.9-4.2(2\text{H, m}), 6.87-6.94(3\text{H, m}), 7.1-7.4(6\text{H, m}), 7.51(4\text{H, d, J=7.4Hz}), 8.22(2\text{H, s}) \)

MS m/z : 434 (M+1)

**Example 77**

The following compound was obtained according to a similar manner to that of Example 67.

\( (S\text{-1-Phenoxy-3-[[2,2-bis[4-ureidophenyl]ethyl]amino]-2-propanol} \)

\(^1\text{H-NMR} (\text{CD}_3\text{OD}, \delta) : 2.73-2.88(2\text{H, m}), 3.22(2\text{H, dd, J=2.9Hz, 7.4Hz}), 3.87(2\text{H, d, J=5.2Hz}), 3.9-4.2(2\text{H, m}), 6.83-6.94(3\text{H, m}), 7.16-7.32(8\text{H, m}), 7.46(2\text{H, d, J=8.5Hz}) \)

MS m/z : 463 (M+)

**Example 78**

A mixture of \((R\text{-1-[4-benzylxy-3-nitrophenyl]-2-[N-benzyl-[2,2-bis[4-(2,2-dimethylpropioxy)phenyl]ethyl]amino]ethanol (193 mg), ethanol (5 ml), water (0.5 ml)}, iron powder (0.2 g) and ammonium chloride (0.1 g) was refluxed for 0.5 hour. The reaction mixture was filtrated, diluted with ethyl acetate (40 ml), washed by saturated sodium chloride solution, dried over magnesium sulfate and evaporated to afford a crude product. To a mixture of the crude product, dichloromethane (4 ml) and pyridine (123 \( \mu l \)), methanesulfonyl chloride (60 \( \mu l \)) was added with cooling by ice-bath. The reaction mixture was stirred at room temperature for 10 minutes, diluted with ethyl acetate (40 ml), washed by water followed by saturated sodium chloride solution, dried over magnesium sulfate and evaporated to afford a crude product which was purified by column chromatography (silica gel, hexane : ethyl acetate = 2:1) to afford \((R\text{-1-[4-benzylxy-3-(methanesulfonylamino)phenyl]-2-[N-benzyl-[2,2-bis[4-(2,2-dimethylpropioxy)phenyl]ethyl]amino]ethanol (191 mg)} \)

\(^1\text{H-NMR} (\text{CDCl}_3, \delta) : 1.33(9\text{H, s}), 1.34(9\text{H, s}), 2.61-2.64(2\text{H, d, J=5.7Hz}), 2.89(3\text{H, s}), 2.96(1\text{H, dd, J=5.9Hz, 13.1Hz}), 3.28(1\text{H, dd, J=10.5Hz, 12.8Hz}), 3.48(1\text{H, d, J=13.4Hz}), 3.94(1\text{H, d, J=13.4Hz}), 4.21(1\text{H, dd, J=5.8Hz, 10.1Hz}), 4.54(1\text{H, dd, J=5.8Hz, 7.7Hz}), 5.08(2\text{H, s}), 6.77(1\text{H, s}), 6.92-7.2(12\text{H, m}), 7.25-7.42(9\text{H, m}) \)

MS m/z : 829 (M+Na), 807 (M+1)

**Example 79**

A mixture of \((R\text{-1-[4-benzylxy-3-(methanesulfonylamino)phenyl]-2-[N-benzyl-[2,2-bis[4-(2,2-dimethylpropioxy)phenyl]ethyl]amino]ethanol (185 mg), methanol (5 ml), 1,4-dioxane (5 ml), 4N hydrogen chloride solution in 1,4-dioxane} \)
(57 μl) and 10% palladium on charcoal (50 mg) was stirred under hydrogen (1 atm) for 20 minutes, filtrated and evaporated to afford (R)-1-[4-hydroxy-3-(methanesulfonylamino)phenyl]-2-[[2,2-bis[4-(2,2-dimethylpropionyloxy)phenyl]ethyl]amino]ethanol hydrochloride (141 mg).

\[^{1}H\text{-NMR (CD}_{3}\text{OD, } \delta): 1.34 (18H, s), 2.91 (3H, s), 3.1-3.3 (2H, m), 3.83 (2H, dd, J=3.1Hz, 8.1Hz), 4.51 (1H, t, J=8.0Hz), 4.9-5.0 (1H, m), 6.90 (1H, d, J=8.3Hz), 7.06-7.14 (5H, m), 7.38-7.46 (5H, m)\]

MS m/z : 627 (M+1), 609

**Example 80**

To a mixture of (R)-1-(4-benzyl-3-nitrophenyl)-2-[N-benzyl-[2,2-bis(4-hydroxyphenyl)ethyl]amino]ethanol (422 mg), N,N-dimethylformamide (1 ml) and potassium carbonate (128 mg), isopropyl chloroformate (80 μl) was added. The reaction mixture was stirred at room temperature for 3 hours, diluted with ethyl acetate (40 ml), washed by water followed by saturated sodium chloride solution, dried over magnesium sulfate and evaporated to afford (R)-1-(4-benzyl-3-nitrophenyl)-2-[N-benzyl-[2,2-bis[4-(isopropoxycarbonyloxy)phenyl]ethyl]amino]ethanol (126 mg).

MS m/z : 785 (M+Na), 763 (M+1)

**Example 81**

The following compound was obtained according to a similar manner to that of Example 78.

(R)-1-[4-Benzylroxy-3-(methanesulfonylamino)phenyl]-2-[N-benzyl-[2,2-bis[4-(isopropoxycarbonyloxy)phenyl]ethyl]amino]ethanol

MS m/z : 833 (M+Na), 811 (M+1)

**Example 82**

The following compound was obtained according to a similar manner to that of Example 79.

(R)-1-[4-Hydrox-3-(methanesulfonylamino)phenyl]-2-[[2,2-bis[4-(isopropoxycarbonyloxy)phenyl]ethyl]amino]ethanol hydrochloride

\[^{1}H\text{-NMR (CD}_{3}\text{OD, } \delta): 1.33 (12H, d, J=6.2Hz), 2.92 (3H, s), 3.04-3.3 (2H, m), 3.83 (2H, dd, J=3.1Hz, 8.1Hz), 4.53 (1H, t, J=7.9Hz), 4.9-5.0 (1H, m), 6.90 (1H, d, J=8.3Hz), 7.08-7.21 (5H, m), 7.38-7.47 (5H, m)\]

MS m/z : 631 (M+1), 613

**Example 83**

A mixture of tert-butyl N-benzyl-N-[2,2-bis[3-chloro-4-hydroxyphenyl]ethyl]carbamate (112 mg) and 4N hydrogen chloride solution in 1,4-dioxane (1 ml) was stood at room temperature for 3 hours, diluted with ethyl acetate (40 ml), washed by saturated sodium bicarbonate solution, dried over sodium sulfatae and
evaporated to afford a free amine. A mixture of the amine, (S)-[3-formyl-4-benzyloxyphenoxy)methyl]oxirane (73 mg) and isopropanol (2 ml) was refluxed for 16 hours. To the reaction mixture, methanol (2 ml) and sodium borohydride (50 mg) were added with ice-bath cooling. The reaction mixture was diluted with ethyl acetate (40 ml), washed by water followed by saturated sodium chloride solution, dried over sodium sulfate, evaporated and purified by preparative TLC (silica gel, hexane:ethyl acetate = 1:1) to afford an oily product. A mixture of the oily product, methanol (2 ml) and 10% palladium on charcoal (10 mg) was stirred under hydrogen (1 atm) for 15 minutes, filtrated, evaporated to afford (S)-1-[3-methyl-4-hydroxyphenoxy]-3-[2,2-bis(4-hydroxyphenyl)ethyl]amino]-2-propanol hydrochloride (50.3 mg).

$^1$H-NMR (CD$_3$OD, $\delta$) : 2.15(3H, s), 3.12-3.3(2H, m), 3.70(2H, d, J=8.0Hz), 3.81-3.97(2H, m), 4.16-4.31(2H, m), 6.52(1H, dd, J=2.9Hz, 8.5Hz), 6.61(1H, d, J=2.9Hz), 6.64(1H, d, J=8.5Hz), 6.76(4H, dd, J=2.2Hz, 8.6Hz), 7.16(4H, dd, 2.2Hz, 8.6Hz)

MS m/z : 410 (free form, M+1)

Example 84

A mixture of (RS)-1-(4-benzyloxy-3-methoxycarbonylphenyl)-2-[N-benzyl-2,2-bis(4-methoxyphenyl)ethyl]amino]ethanol (72 mg), formamide (50 mg), N,N-dimethylformamide (1 ml) and 28% sodium methoxide - methanol solution (15 mg) was heated at 100$^\circ$C. After 1 hour, formamide (50 mg) and 28% sodium methoxide - methanol solution (30 mg) was added and heated at 100$^\circ$C for 0.5 hour. The reaction mixture was diluted with ethyl acetate (40 ml), washed by water followed by saturated sodium chloride solution, dried over magnesium sulfate and evaporated to afford (RS)-1-(4-benzyloxy-3-carbamoylphenyl)-2-[N-benzyl-2,2-bis(4-methoxyphenyl)ethyl]amino]ethanol (64 mg).

MS m/z : 617 (M+1)

Example 85

A mixture of (RS)-1-(4-benzyloxy-3-carbamoylphenyl)-2-[N-benzyl-2,2-bis(4-methoxyphenyl)ethyl]amino]ethanol (24 mg), methanol (2 ml) and 10% palladium on charcoal (10 mg) was stirred under hydrogen (1 atm) for 20 minutes, filtrated, evaporated and purified by preparative TLC (silica gel, dichloromethane : methanol : concentrated ammonia solution = 9:1:0.1) to afford (RS)-1-(4-hydroxy-3-carbamoylphenyl)-2-[2,2-bis(4-methoxyphenyl)ethyl]-amino]ethanol (8.5 mg).

$^1$H-NMR (CD$_3$OD, $\delta$) : 2.78-2.9(2H, m), 3.15(2H, d, J=7.9Hz), 3.75(6H, s), 4.0-4.2(1H, m), 4.64(1H, t, J=7.5Hz), 6.78-6.84(5H, m), 7.08-7.30(5H, m), 7.71(1H, m)
MS m/z : 437 (M+1)

Preparation 48

The following compound was obtained according to a similar manner to that of preparation 21.

(S)-[4-Nitrophenoxy)methyl]oxirane

MS m/z : 218 (M+Na)

Example 86

A mixture of N-benzyl-[3,3-bis(4-methoxyphenyl)propyl]amine (21.5 mg), (S)-[4-nitrophenoxymethyl]oxirane (13 mg) and ethanol (1 ml) was refluxed for 12 hours. To the reaction mixture, water (0.1 ml), iron powder (10 mg) and ammonium chloride (10 mg) were added and refluxed for 1 hour. The reaction mixture was filtrated, diluted with ethyl acetate (40 ml), washed by saturated sodium chloride solution, dried over magnesium sulfate and evaporated to afford a crude product. To a mixture of the crude product, dichloromethane (1 ml) and pyridine (30 µl), methanesulfonyl chloride (7 µl) was added with cooling by ice-bath. The reaction mixture was stirred at room temperature for 10 minutes, diluted with ethyl acetate (40 ml), washed by water followed by saturated sodium chloride solution, dried over magnesium sulfate and evaporated to afford a crude product. A mixture of the crude product, methanol (2 ml) and 10% palladium on charcoal (10 mg) was stirred under hydrogen (1 atm) for 20 minutes, filtrated, evaporated and purified by preparative TLC (silica gel, dichloromethane: methanol: concentrated ammonia solution = 9:1:0.1) to afford (S)-1-[4-(methanesulfonylamino)phenoxy]-3-[3,3-bis(4-methoxyphenyl)propyl]amino]-2-propanol (16 mg).

1H-NMR (CD3OD, δ) : 2.2-2.4(2H, m), 2.7-3.0(4H, m), 2.87(3H, s), 3.74(6H, s), 3.8-4.2(4H, m), 6.82(4H, d, J=8.6Hz), 6.92(2H, d, J=9.0Hz), 7.14-7.20(6H, m)

MS m/z : 515 (M+1)

Example 87

The following compounds were obtained according to a similar manner to that of Example 49.

(1) (R)-1-[3-Amino-4-benzylxyphenyl]-2-[N-benzyl-[3,3-bis[4-(methoxycarbonylamino)phenyl]propyl]amino]ethanol

1H-NMR (CDCl3, δ) : 2.04-2.70(6H, m), 3.46(1H, d, J=13Hz), 3.75(6H, s), 3.75-3.92(1H, m), 3.85(1H, d, J=13Hz), 4.42(1H, dd, J=9 and 5Hz), 5.05(2H, s), 6.55-6.85(3H, m), 6.56(2H, br s), 7.00-7.50(18H, m)

MS m/z : 689 (M+1)

(2) (R)-1-[3-Amino-4-benzylxyphenyl]-2-[N-benzyl-[3,3-bis[4-(1-pyrrolidinyl)phenyl]propyl]amino]ethanol
$^1$H-NMR (CDCl$_3$, $\delta$): 1.84-2.08 (8H, m), 2.08-2.78 (6H, m), 3.10-3.36 (8H, m), 3.47 (1H, d, J=13Hz), 3.62-3.80 (1H, m), 3.87 (1H, d, J=13Hz), 4.44 (1H, dd, J=9 and 5Hz), 5.05 (2H, s), 6.46 (4H, d, J=9Hz), 6.50-7.50 (17H, m)
MS m/z: 681 (M$^+$+1)

(3) (R)-1-(3-Amino-4-benzoyloxyphenyl)-2-[N-benzyl-[2,2-bis(4-methoxy-3-methylphenyl)ethyl]amino]ethanol
(+) APCI-MS m/z: 617 [M+H]$^+$

(4) (R)-1-(3-Amino-4-benzoyloxyphenyl)-2-[N-benzyl-[3,3-bis(4-benzyloxyphenyl)propyl]amino]ethanol

(5) (S)-1-(3-Amino-4-benzoyloxyphenoxo)-3-[N-benzyl-[2,2-bis(4-benzyloxyphenyl)ethyl]amino]-2-propanol
$^1$H-NMR (CDCl$_3$, $\delta$): 2.66 (2H, d, J=6.7Hz), 2.90-3.00 (1H, m), 3.50-3.90 (7H, m), 4.98 (2H, s), 5.01 (4H, s), 6.60-7.40 (23H, m)

(6) (S)-1-(3-Amino-4-benzoyloxyphenoxo)-3-[N-benzyl-[3,3-bis(4-benzyloxyphenyl)propyl]amino]-2-propanol
MS m/z: 815 (M$^+$+1)

(7) (R)-2-[N-Benzyl-[2,2-bis(4-benzyloxy-3-chlorophenyl)ethyl]amino]-1-(3-amino-4-benzoyloxyphenyl)ethanol
$^1$H-NMR (DMSO-d$_6$, $\delta$): 2.51 (2H, m, CH$_2$), 3.03-3.13 (2H, m, CH$_2$), 3.64 (1H, d, J=13.9Hz, CH$_2$), 3.74 (1H, d, J=13.9Hz, CH$_2$), 4.22 (1H, t, J=7.7Hz, CHAr$_2$), 4.29 (1H, d, J=2.8Hz, OH), 4.49 (1H, m, CH), 4.64 (2H, brs, NH$_2$), 5.04 (2H, s, CH$_2$), 5.16 (4H, s, CH$_2$), 6.31 (1H, dd, J=8.3, 1.7Hz, aromatic H), 6.58 (1H, d, J=1.7Hz, aromatic H), 6.73 (1H, d, J=8.3Hz), 7.05-7.48 (26H, m, aromatic H)
Example 88

The following compounds were obtained according to a similar manner to that of Example 50.

(1) (R)-2-[N-Benzyl-[3,3-bis[4-(methoxycarbonylamino)phenyl]propyl]amino]-1-[4-benzyloxy-3-[benzenesulfonylamino]phenyl]ethanol
$^1$H-NMR (CDCl$_3$, $\delta$): 2.04-2.73 (6H, m), 3.48 (1H, d, J=13Hz), 3.75 (6H, s), 3.75-3.94 (1H, m), 3.85 (1H, d, J=13Hz), 4.43 (1H, dd, J=10 and 3Hz), 4.81 (2H, s), 6.57 (1H, br s), 6.61 (1H, br s), 6.71 (1H, d, J=8Hz), 6.90-7.75 (25H, m)
MS m/z: 829 (M$^+$+1)

(2) (R)-2-[N-Benzyl-[2,2-bis(4-benzyloxyphenyl)ethyl]amino]-1-[4-benzyloxy-3-[(2,2,2-trifluoroethyl)sulfonylamino]phenyl]ethanol
$^1$H-NMR (CDCl$_3$, $\delta$): 2.44-2.74 (2H, m), 2.92 (1H, dd, J=13 and 6Hz), 3.27 (1H, dd, J=13 and 10Hz), 3.29 (1H, br s, OH), 3.46 (1H, d, J=13Hz), 3.73 (2H, q, JFH=9Hz), 3.95 (1H, d, J=13Hz), 4.02-4.22 (1H, m), 4.51 (1H, dd, J=10 and 4Hz), 5.01 (2H, s), 5.03 (2H, s), 5.08 (2H, s), 6.80-7.50 (32H, m)
MS m/z : 887 (M+1)

(3)  (R)-2-[N-Benzyl-[3,3-bis[4-(1-pyrrolidinyl)phenyl]propyl]amino]-1-[4-benzylxloxy-3-(methanesulfonlamino)phenyl]ethanol

1H-NMR (CDCl3, δ) : 1.81-2.11(8H, m), 2.10-2.80(6H, m), 2.88(3H, s), 3.08-3.38(8H, m), 3.50(1H, d, J=13Hz), 3.60-3.82(1H, m), 3.91(1H, d, J=13Hz), 4.61(1H, dd, J=10 and 4Hz), 5.08(2H, s), 6.47(4H, d, J=9Hz), 6.75(1H, br s), 6.85-7.52(17H, m)

MS m/z : 759 (M+1)

(4)  (R)-2-[N-Benzyl-[2,2-bis(4-methoxy-3-methylphenyl)ethyl]amino]-1-[4-benzylxloxy-3-(methanesulfonlamino)phenyl]ethanol

(+ APCI-MS m/z : 695(M+H)+

(5)  (R)-1-[3-Benzenesulfonlamino-4-benzylxloxyphenyl]-2-[N-benzyl-[3,3-bis(4-benzylxloxyphenyl)propyl]amino]ethanol

(6)  (R)-1-[4-Benzylxloxy-3-(methanesulfonlamino)phenyl]-2-[N-benzyl-[2,2-bis(4-benzylxloxy-3-chlorophenyl)ethyl]amino]ethanol

1H-NMR (DMSO-d6, δ) : 2.56(2H, m, CH2), 2.82(3H, s, CH3), 3.07(2H, m, CH2), 3.68(2H, s, CH2), 4.19(1H, m, CHAr), 4.58(1H, br s, OH), 4.60(1H, m, CH), 5.13(2H, s, CH2), 5.15(4H, s, CH2), 6.87-7.54(29H, m, aromatic H), 8.91(1H, br s, NH)

(+ ESI MS m/z : 909, 911, 913 (M+Na)

Example 89

The following compounds were obtained according to a similar manner to that of Example 51.

(1)  (R)-2-[[3,3-Bis[4-(methoxycarbonylamino)phenyl]propyl]amino]-1-[4-hydroxy-3-(benzenesulfonlamino)phenyl]ethanol

IR (KBr) : 1710, 1602 cm⁻¹

1H-NMR (CD3OD, δ) : 2.10-2.40(2H, m, AB of ABX), 2.60-2.85(4H, m), 3.70(6H, s), 3.90(1H, t, X of ABX), 4.64(1H, t, X of ABX), 6.67(1H, d, J=8Hz), 6.93(1H, dd, J=8 and 2Hz), 7.10-7.55(12H, m), 7.66-7.82(2H, m)

MS m/z : 649 (M+1)

(2)  (R)-2-[[3,3-Bis[4-(1-pyrrolidinyl)phenyl]propyl]amino]-1-[4-hydroxy-3-(methanesulfonlamino)phenyl]ethanol

IR (KBr) : 1612, 1518 cm⁻¹

1H-NMR (CDCl3, δ) : 1.74-2.10(8H, m), 2.20-2.50(2H, m), 2.50-3.00(4H, m), 2.72(3H, s), 3.00-3.32(8H, m), 3.63-3.83(1H, m), 4.60-5.00(1H, m), 6.40(4H, d, J=8Hz), 6.63-6.90(2H, m), 7.00(4H, d, J=8Hz), 7.14(1H, br s), 7.20-7.40(1H, m)

MS m/z : 573 (M+1)

(3)  (S)-1-Phenoxy-3-[[2,2-bis[3-(methoxycarbonylamino)phenyl]-2-
hydroxyethylamino]-2-propanol

\[^1^H\text{-NMR (CDC\textsubscript{13}, } \delta\text{):} \begin{align*}
2.75-2.96 & (2\text{H, m}, 3.35(1\text{H, d, } J=12\text{Hz}), 3.42(1\text{H, d, } J=12\text{Hz}), 3.73(6\text{H, s}, 3.82-4.20(3\text{H, m}), 6.60-7.52(15\text{H, m})
\end{align*}
\]

MS m/z : 510 (M\(^{+1}\))

5

\((R)-2-[[2,2-Bis(4-methoxy-3-methylphenyl)ethyl]amino]-1-[4-hydroxy-3-(methanesulfonyl)amino]phenyl]ethanol

\[^1^H\text{-NMR (DMSO-d\textsubscript{6}, } \delta\text{):} \begin{align*}
2.09(6\text{H, s}, 2.60(2\text{H, d, } J=6.1\text{Hz}), 2.90(3\text{H, s}, 3.06(2\text{H, d, } J=7.5\text{Hz}), 3.72(6\text{H, s}, 3.89(1\text{H, t, } J=7.5 \text{ Hz}), 4.45(1\text{H, t, } J=6.1\text{Hz}), 6.7-7.1(8\text{H, m}), 7.14(1\text{H, d, } J=1.8\text{Hz})
\end{align*}
\]

MS m/z : 515 (M+H\(^{+}\))

Preparation 49

The following compounds were obtained according to a similar manner to that of Preparation 16.

(1) N-Benzyl-3,3-bis[4-(1-pyrrolidinyl)phenyl]propylamine

\[^1^H\text{-NMR (CDC\textsubscript{13}, } \delta\text{):} \begin{align*}
1.82-2.10 & (8\text{H, m}, 2.19(2\text{H, t, } J=7\text{Hz}), 2.63(2\text{H, q, } J=7\text{Hz}), 3.08-3.38(8\text{H, m}), 3.71(2\text{H, s}, 3.82(1\text{H, t, } J=7\text{Hz}), 6.47(4\text{H, d, } J=9\text{Hz}), 7.07(4\text{H, d, } J=9\text{Hz}), 7.14-7.42(5\text{H, m})
\end{align*}
\]

MS m/z : 440 (M\(^{+1}\))

(2) 2-Benzylamino-1,1-bis[3-(methoxycarbonyl)amino]phenyl]ethanol

\[^1^H\text{-NMR (CDC\textsubscript{13}, } \delta\text{):} \begin{align*}
3.30(2\text{H, s}, 3.75(6\text{H, s}, 3.80(2\text{H, s}, 6.61(2\text{H, br s}, 7.04-7.44(13\text{H, m})
\end{align*}
\]

MS m/z : 450 (M\(^{+1}\))

Preparation 50

To a solution of 1,3-dibromobenzene (23.30 g) in tetrahydrofuran (90 ml) was added dropwise 1.54 M n-butyllithium/hexane (62 ml) at -65°C over 40 minutes. The resulting suspension was allowed to warm to about -30°C before cooled to -70°C again. To the suspension was added dropwise ethyl 2-(dibenzylation)acetate (12.76 g) in tetrahydrofuran (4.5 ml) below -50°C over 10 minutes. The mixture was allowed to warm to room temperature for 1 hour.

The mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed successively with water and brine, dried over magnesium sulfate, and filtered. The filtrate was concentrated and the residue was purified by column chromatography (silica gel, hexane/ethyl acetate) followed by recrystallization from ethyl acetate - hexane to give 2-dibenzylamino-1,1-bis[3-bromophenyl]ethanol (8.47 g) as a white powder.

\[^1^H\text{-NMR (CDC\textsubscript{13}, } \delta\text{):} \begin{align*}
3.38(2\text{H, s}, 3.46(4\text{H, s), 5.25(1\text{H, s, OH}, 7.02-7.62(18\text{H, m})
\end{align*}
\]

MS m/z : 550, 552, 554 (M\(^{+1}\))

Preparation 51
A mixture of 2-dibenzylamino-1,1-bis(3-bromophenyl)ethanol (553 mg), benzophenone imine (539 mg), tris(dibenzyldieneacetone)dipalladium (0) (46 mg), racemic 2,2'-'-bis(diphenyolphosphino)-1,1'-binaphthyl (74 mg), and sodium tert-butoxide (126 mg) in toluene (2.5 ml) was heated at 80°C for 6 hours. The mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed with brine, dried over magnesium sulfate, and filtered. The filtrate was concentrated and the residual oil was dissolved in tetrahydrofuran (2.5 ml). To the solution was added 6N hydrochloric acid, and the mixture was stirred at room temperature for 3 hours. The mixture was partitioned between ethyl acetate and water. The water layer was neutralized with saturated sodium bicarbonate solution and extracted twice with ethyl acetate. The combined extract was washed with brine, dried over magnesium sulfate, and filtered. The filtrate was evaporated to give 1,1-bis(3-aminophenyl)-2-(dibenzylamino)ethanol (488 mg) as a pale yellow powder.

1H-NMR (CDCl₃, δ): 3.39(2H, s), 3.46(4H, s), 3.53(4H, br s, NH₂), 5.17(1H, br s, OH), 6.35-7.68(18H, m)
MS m/z : 424 (M⁺+1)

Preparation 52

The following compound was obtained according to a similar manner to that of Preparation 51.

3-Dibenzylamino-1,1-bis[4-(1-pyrrolidinyl)phenyl]propanol

1H-NMR(CDCl₃, δ): 1.84-2.08(8H, m), 2.40(2H, t, J=6Hz), 2.66(2H, t, J=6Hz), 3.22(8H, t, J=6Hz), 3.56(4H, s), 6.40(4H, d, J=8Hz), 7.14(4H, d, J=8Hz), 7.20-7.40(10H, m)

Preparation 53

The following compound was obtained according to a similar manner to that of Preparation 35.

2-Dibenzylamino-1,1-bis[3-(methoxycarbonylamino)phenyl]ethanol

1H-NMR (CDCl₃, δ): 3.43(2H, s), 3.46(4H, s), 3.75(6H, s), 5.27(1H, s, OH), 6.51(2H, br s), 7.02-7.44(18H, m)
MS m/z : 540 (M⁺+1)

Preparation 54

To an ice-cooled suspension of (1R, 2S)-(−)-cis-1-amino-2-indanol (2.98 g) in anhydrous tetrahydrofuran (60 ml) was added dropwise borane - methyl sulfide complex (10.0-10.2 M, 4 ml) at such a rate that the internal temperature remained below 10°C. The resulting suspension was stirred at room temperature for 25 minutes. To the suspension were added a solution of 4'-benzylxoxy-2-bromo-3'-nitroacetophenone (140.08 g) in anhydrous...
tetrachlorofuran (1120 ml) and more borane - methyl sulfide complex (10.0-10.2 M, 27.7 ml) simultaneously over 1.5 hours at 19-21°C. The mixture was stirred at room temperature for 30 minutes and cooled with an ice bath. Methanol (100 ml) was added dropwise for 5 minutes, and the mixture was stirred at room temperature for 20 minutes. The mixture was concentrated and the residue was diluted with toluene (560 ml). The solution was washed twice with 0.5N hydrochloric acid (120 ml), three times with water (120 ml), twice with brine (120 ml), then dried over magnesium sulfate, and filtered. The filtrate was concentrated to give (R)-1-(4-benzzyloxy-3-nitrophenyl)-2-bromoethanol (157.11 g) as an oil. The enantiomeric excess of the product was determined to be 87.3%ee by HPLC analysis using a chiral stationary phase column (Daicel CHIRALCEL OJ, 4.6×250 mm, hexane/2-propanol=75/25).

1H-NMR (CDCl₃, δ): 2.71(1H, d, J=4Hz, OH), 3.50(1H, dd, J=11 and 8Hz), 3.62(1H, dd, J=11 and 4Hz), 4.92(1H, dt, J=8 and 4Hz), 5.25(2H, s), 7.12(1H, d, J=9Hz), 7.26-7.50(5H, m), 7.53(1H, dd, J=9 and 2Hz), 7.91(1H, d, J=2Hz)

MS m/z: 374, 376 (M⁺+Na)

Preparation 55

To an ice-cooled mixture of (R)-1-(4-benzzyloxy-3-nitrophenyl)-2-bromoethanol (140.86 g, 87.3%ee), pyridine (65 ml), and 4-(dimethylamino)pyridine (2.44 g) in toluene (705 ml) was added (1S)-(−)-camphanic chloride (95.21 g) in portions over 15 minutes. The mixture was stirred at room temperature for 22 hours. The mixture was cooled with an ice bath and partitioned between toluene and water. The organic layer was separated, washed twice with water (430 ml), once with sodium hydrogen carbonate solution (430 ml), once with brine (430 ml), dried over magnesium sulfate, and filtered. The filtrate was concentrated and the residual oil was crystallized from ethyl acetate (107 ml) - 2-propanol (1070 ml) to give crude (1S,4R)-camphanic acid (R)-2-bromo-1-(4-benzzyloxy-3-nitrophenyl)ethyl ester (193.48 g) as a white powder.

1H-NMR (CDCl₃, δ): 1.02(3H, s), 1.07(3H, s), 1.13(3H, s), 1.60-1.80(1H, m), 1.85-2.12(2H, m), 2.32-2.56(1H, m), 3.52-3.80(2H, m, AB of ABX), 5.25(2H, s), 6.07(1H, dd, J=8 and 5Hz, X of ABX), 7.15(1H, d, J=9Hz), 7.28-7.52(5H, m), 7.57(1H, dd, J=9 and 2Hz), 7.89(1H, d, J=2Hz)

MS m/z: 554, 556 (M⁺+Na)

Preparation 56

The crude powder (245.78 g) of the objective compound of Preparation 55 was recrystallized from ethyl acetate (490 ml) - hexane (740 ml) to give pure ester (186.23 g) as white crystals. The diastereomeric excess of the product was
determined to be 98.2%de by HPLC analysis using a chiral stationary phase column (Daicel CHIRALPAK AD, 4.6×250 mm, hexane/2-propanol=50/50). The second crop was obtained from the mother liquor by the same method (37.84 g, 97.6%de).

mp 149-150°C

Preparation 57

To an ice-cooled solution of (1S,4R)-camphamic acid (R)-2-bromo-1-(4-benzylxyloxy-3-nitrophenoxy)ethyl ester (229.14 g, 98%de) in tetrahydrofuran (460 ml) - methanol (460 ml) was added dropwise 6N sodium hydroxide solution (158 ml) over 10 minutes. The mixture was stirred at room temperature for 1 hour. The mixture was cooled with an ice bath and partitioned between toluene and water. The organic layer was separated, washed twice with water (460 ml), once with brine (460 ml), dried over magnesium sulfate, and filtered. The filtrate was concentrated to give a solid. The solid was recrystallized from ethyl acetate (120 ml) - hexane (820 ml) to give (R)-(4-benzylxyloxy-3-nitrophenoxy)oxirane (110.80 g) as a white powder. The enantiomeric excess of the product was determined to be 98.2%ee by HPLC analysis using a chiral stationary phase column (Daicel CHIRALPAK AS, 4.6×250 mm, hexane/2-propanol=70/30).

^1H-NMR (CDCl₃, δ): 2.76(1H, dd, J=5 and 2Hz), 3.16(1H, dd, J=5 and 4Hz), 3.85(1H, dd, J=4 and 2Hz), 5.24(2H, s), 7.10(1H, d, J=9Hz), 7.25-7.52(6H, m), 7.78(1H, d, J=2Hz).

MS m/z : 294 (M+Na)

Preparation 58

To a solution of 2-methylanisole (10 ml) and concentrated sulfonic acid (4.1 g) in acetic acid (40 ml) was added dropwise glyoxylic acid monohydrate (3.5 g) during 30 minutes at room temperature. The mixture was stirred at the same temperature overnight. The resulting mixture was poured into ice-cold water to give precipitates. After being stirred for 1 hour, the precipitates were collected by filtration, followed by washing with water. The dryness in vacuo afforded bis(4-methoxy-3-methylphenyl)acetic acid (11 g).

(+ ESI-MS m/z : 323 (M+Na)^+ 

Preparation 59

Under nitrogen, to a solution of bis(4-methoxy-3-methylphenyl)acetic acid (11 g) in N,N-dimethylformamide (110 ml) were added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (7.7 g), 1-hydroxybenzotriazole (5.4 g) and benzylamine (4.4 ml) at 5°C, and the mixture was stirred at room temperature for 4 hours. The resulting mixture was poured into water and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed with water and
brine, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (chloroform : ethyl acetate = 50:1 to 20:1) to give N-benzyl-2,2-bis(4-methoxy-3-methylphenyl)acetamide (13 g).

5 (+) APCI-MS m/z : 390 (M+H)^+

Preparation 60

Under nitrogen, to a solution of N-benzyl-2,2-bis(4-methoxy-3-methylphenyl)acetamide (13 g) in tetrahydrofuran (250 ml) was added 1M boron trifluoride etherate in tetrahydrofuran (99 ml) at 5°C, and the mixture was stirred at room temperature for 20 hours. The resulting mixture was cooled to 5°C, and methanol (200 ml) and aqueous hydrochloric acid were added dropwise. The mixture was stirred at room temperature for 2.5 days. After the mixture was evaporated under reduced pressure, the residue was dissolved into a mixture of water and ethyl acetate, followed by being adjusted to pH 9 with 5N aqueous sodium hydroxide. After separation, the organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The residue was dissolved in ethyl acetate (65 ml), and the mixture was cooled to 5°C. To this mixture was added dropwise 4N hydrogen chloride in ethyl acetate (16 ml) to give precipitates, and the mixture was stirred at room temperature for 1 hour. The precipitates were collected by filtration and washed successively with ethyl acetate and hexane. The dryness in vacuo afforded N-benzyl-[2,2-bis(4-methoxy-3-methylphenyl)]ethylamine hydrochloride (9.7 g).

(+) APCI-MS m/z : 376 (M-HCl+H)^+

Preparation 61

Under nitrogen, to a solution of N-benzyl-[2,2-bis(4-methoxy-3-methylphenyl)]ethylamine hydrochloride (2.0 g) in dichloromethane (20 ml) was added dropwise 1M boron tribromide in dichloromethane (19 ml) at −10°C, and the mixture was stirred at the same temperature for 2 hours. The resulting mixture was evaporated under reduced pressure. The residue was dissolved in a mixture of water and ethyl acetate, followed by being adjusted to pH 9 with 5N aqueous sodium hydroxide. After separation, the organic layer was washed with brine, dried over anhydrous magnesium sulfate, evaporated under reduced pressure, and dried in vacuo to give N-benzyl-[2,2-bis(4-hydroxy-3-methylphenyl)]ethylamine (1.8 g).

(+) APCI-MS m/z : 348 (M+H)^+

Example 90

A mixture of N-benzyl-[2,2-bis[4-(tert-butoxycarbonylamino)phenyl]ethyl]-
amine (255mg), (S)-2-(phenoxy)methyl]oxirane (89mg) and ethanol (3 ml) was refluxed for 14 hours and evaporated to afford a crude product. A mixture of the product, dichloromethane (1 ml) and trifluoroacetic acid (1 ml) was stood at room temperature for 1.5 hours, diluted with ethyl acetate (30 ml), washed by water followed by saturated sodium chloride solution, dried over magnesium sulfate and evaporated to afford (S)-1-phenoxy-3-[[N-benzyl-[2,2-bis(4-aminophenyl)-ethyl]amino]-2-propanol (253 mg) which was used without any further purification.

MS m/z : 468 (M+1)

Example 91

A mixture of (R)-2-[[N-benzyl-[2,2-bis(4-hydroxy-3-methylphenyl)ethyl]-amino]-1-[4-benzyl]-3-[N-benzyl]methanesulfonamido[phenyl]-ethanol (85 mg) and 10% palladium on activated carbon (50% wet, 40 mg) in methanol (3 ml) was stirred at room temperature in the presence of hydrogen at an atmospheric pressure for 2 hours. After filtration, the filtrate was evaporated under reduced pressure. The residue was triturated with hexane and dried in vacuo to give (R)-2-[[2,2-bis(4-hydroxy-3-methylphenyl)ethyl]amino]-1-[4-hydroxy-3-(methanesulfonyl)amino]phenyl]ethanol (40 mg).

1H-NMR (DMSO-d6, δ) : 2.08(6H, s), 2.85-3.1(5H, m), 3.45-3.8(2H, m), 4.1-4.2(1H, m), 4.75-4.85(1H, m), 6.70(1H, d, J=2.8Hz), 6.74(1H, d, J=2.8Hz), 6.85-7.1(6H, m), 7.21(1H, d, J=1.8Hz)

(+) APCI-MS m/z : 487 (M+H)+

Preparation 62

Under nitrogen, to a solution of (R)-1-[4-benzyl]-3-[methanesulfonamido][phenyl]-2-bromoethanol (500 mg) in N,N-dimethylformamide (5 ml) were added imidazole (190 mg), chlorotriethylsilane (0.44 ml) and 4-dimethylaminopyridine (15 mg) at 5°C, and the mixture was stirred at the same temperature for 5 hours. The resulting mixture was poured into 0.1N hydrochloric acid and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium hydrogencarbonate and brine, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The residue was triturated with hexane, followed by dryness in vacuo to give (R)-N-[2-benzyl]-5-[[2-bromo-1-(triethyl)silyloxy]ethyl]phenyl|methanesulfonamide (500 mg).

(+) ESI-MS m/z : 536 (M+Na)+

Preparation 63

Under nitrogen, to a suspension of sodium hydride (60% in oil, 32 mg) in tetrahydrofuran (10 ml) was added (R)-N-[2-benzyl]-5-[[2-bromo-1-
(triethylsilyloxy)ethyl[phenyl]methanesulfonamide (390 mg) at 5°C, and the mixture was stirred at the same temperature for 40 minutes. To this reaction mixture was added benzyl chloroformate (0.12 ml), and the mixture was stirred at 5°C for 3 hours. The resulting mixture was poured into saturated aqueous sodium hydrogen carbonate and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 10:1 to 5:1) to give (R)-N-[2-benzyloxy-5-[2-bromo-1-(triethylsilyloxy)ethyl][phenyl]-N-(benzyloxy carbonyl)]methanesulfonamide (420 mg).

(+) ESI-MS m/z : 670, 672 (M+Na)+

**Preparation 64**

To a solution of (R)-N-[2-benzyloxy-5-[2-bromo-1-(triethylsilyloxy)ethyl][phenyl]-N-(benzyloxy carbonyl)]methanesulfonamide (490 mg) in a mixture of tetrahydrofuran (3 ml) and methanol (3 ml) was added concentrated hydrochloric acid (0.32 ml) at room temperature, and the mixture was stirred at the same temperature for 30 minutes. The resulting mixture was poured into ice-cold saturated aqueous sodium hydrogen carbonate and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 3:1 to 1:1) to give (R)-1-[4-benzyloxy-3-[N-benzyloxy carbonyl-N-(methanesulfonyl)amino][phenyl]-2-bromoethanol (360 mg).

(+) ESI-MS m/z : 556, 558 (M+Na)+

**Preparation 65**

To a solution of (R)-1-[4-benzyloxy-3-[N-benzyloxy carbonyl-N-(methanesulfonyl)amino][phenyl]-2-bromoethanol (340 mg) in methanol (5 ml) was added 28% sodium methoxide in methanol (0.19 ml) at 5°C, and the mixture was stirred at the same temperature for 1.5 hours. The resulting mixture was poured into brine and the aqueous mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 2:1 to 1:1) to give (R)-N-benzyloxy carbonyl-N-[2-benzyloxy-5-oxiranyl][phenyl]methanesulfonamide (120 mg).

(+) ESI-MS m/z : 476 (M+Na)+

**Example 92**

The following compounds were obtained according to a similar manner to that of Example 91.
(1) (S)-1-Phenoxy-3-[[2,2-bis(4-hydroxyphenyl)ethyl]amino]-2-propanol

$^1$H-NMR (DMSO-d$_6$, $\delta$) : 2.65-2.9 (2H, m), 3.1-3.3 (2H, m), 3.8-4.1 (4H, m), 6.67 (4H, d, J=8.4 Hz), 6.8-7.0 (3H, m), 7.06 (4H, m), 7.2-7.35 (2H, m)

(+) APCI-MS m/z : 380 (M+H)$^+$

(2) (S)-1-Phenoxy-3-[[3,3-bis(4-hydroxyphenyl)propyl]amino]-2-propanol

$^1$H-NMR (DMSO-d$_6$, $\delta$) : 2.0-2.2 (2H, m), 2.4-2.8 (4H, m), 3.7-4.0 (4H, m), 6.64 (4H, d, J=8.3 Hz), 6.8-7.1 (7H, m), 7.2-7.35 (2H, m)

(+) APCI-MS m/z : 394 (M+H)$^+$

(3) (S)-1-(1H-Indol-4-yloxy)-3-[[2,2-bis(4-hydroxyphenyl)ethyl]amino]-2-propanol

$^1$H-NMR (DMSO-d$_6$, $\delta$) : 2.9-3.2 (2H, m), 3.35-3.6 (2H, m), 3.95-4.3 (4H, m), 6.4-6.5 (2H, m), 6.72 (4H, d, J=7.9 Hz), 6.9-7.2 (6H, m), 7.22 (1H, d, J=3.1 Hz)

(+) APCI-MS m/z : 419 (M+H)$^+$

(4) (S)-1-(1H-Indol-4-yloxy)-3-[[3,3-bis(4-hydroxyphenyl)propyl]amino]-2-propanol

$^1$H-NMR (DMSO-d$_6$, $\delta$) : 2.0-2.2 (2H, m), 2.45-2.9 (4H, m), 3.85-3.9 (1H, m), 3.95-4.15 (3H, m), 6.4-6.5 (2H, m), 6.65 (4H, d, J=8.3 Hz), 6.85-7.1 (6H, m), 7.15-7.25 (1H, m)

(+) ESI-MS m/z : 433 (M+H)$^+$

Example 93

To a solution of (R)-2-[[N-benzyl-[3,3-bis(4-hydroxyphenyl)propyl]amino]-1-(4-benzoyloxy-3-nitrophenyl)ethanol (492 mg) in acetone (5.0 ml) were added successively potassium carbonate powder (338 mg) and benzyl bromide (213 $\mu$l). The mixture was heated to 50°C and stirred for 3 hours. After cooling to room temperature, the mixture was quenched by the addition of water (30 ml) and extracted with ethyl acetate (30 ml x 1). The organic layer was separated, washed with water (30 ml x 1), brine (30 ml x 1), dried over magnesium sulfate, and evaporated to give a pale brown oil (686 mg). The crude oil was purified by a recycling preparative HPLC equipped with a GPC (gel permeation chromatography) column (elucent : chloroform/triethylamine = 99.5/0.5) to give (R)-2-[[N-benzyl-[3,3-bis(4-benzoyloxyphenyl)propyl]amino]-1-(4-benzoyloxy-3-nitrophenyl)ethanol (336 mg) as a yellow solid.

$^1$H-NMR (CDCl$_3$, $\delta$) : 2.16-2.65 (m, 6H), 3.48 (d, J=13.3 Hz, 1H), 3.76-3.88 (m, 2H), 3.85 (d, J=13.3 Hz, 1H), 4.46 (dd, J=3.4, 10.1 Hz, 1H), 5.01 (s, 4H), 5.21 (s, 2H), 6.85-7.40 (m, 31H)

Example 94

To a solution of (R)-1-(3-benzenesulfonylamino-4-benzoyloxyphenyl)-2-[N-benzyl-[3,3-bis(4-benzoyloxyphenyl)propyl]amino]ethanol (121 mg) in a mixed
solvent of methanol (3.0 ml) and ethyl acetate (1.0 ml) was added 10% palladium on activated carbon (50% wet, 60 mg) and the mixture was hydrogenated at 1 atm for 3 hours. The catalyst was removed by filtration and washed with methanol. The filtrate was concentrated in vacuo and the residual solid was tritratated with hexane and dried under reduced pressure to give (R)-1-(3-benzenesulfonylamino-4-hydroxyphenyl)-2-[[3,3-bis(4-hydroxyphenyl)propyl]-amino]ethanol (71.1 mg) as a light brown solid.

IR (KBr) : 3369, 1670, 1662, 1604, 1512, 1442, 1246, 833 cm⁻¹

¹H-NMR (DMSO-d₆, δ) : 1.90-2.06(m, 2H), 2.42-2.51(m, 4H), 3.76 (t, J=7.6Hz, 1H), 4.38 (t, J=6.1Hz, 1H), 6.58-6.78(m, 6H), 6.94-7.04(m, 5H), 7.35-7.50(m, 3H), 7.68-7.73(m, 2H)

MS m/z : 535 (M⁺+1)

Example 95

To a solution of (R)-1-(3-amino-4-benzoyloxyphenyl)-2-[N-benzyl-[3,3-bis(4-benzoyloxyphenyl)propyl]amino]ethanol (148 mg) in dichloromethane (3.0 ml) was added a mixed anhydride of formic acid (200 µl, which was prepared by mixing formic acid (1.0 ml) with acetic anhydride (1.25 ml) at room temperature. After stirring for 2.5 hours, the reaction mixture was diluted with ethyl acetate (10 ml) and washed with water (10 ml x 2), brine (10 ml x 1), dried over magnesium sulfate, filtered, and evaporated to give a pale yellow solid (161 mg). The solid was dissolved in a mixed solvent of methanol (3.0 ml) and ethyl acetate (1.0 ml). The solution was added potassium carbonate (100 mg) and the mixture was stirred at room temperature for 30 minutes. The insoluble solid was filtered off and washed with ethyl acetate. The filtrate was concentrated in vacuo to give a pale yellow solid. The solid was dissolved in ethyl acetate (10 ml), and then washed with brine (10 ml x 1), dried over magnesium sulfate, filtered, and evaporated to give (R)-2-[N-benzyl-[3,3-bis(4-benzoyloxyphenyl)propyl]amino]-1-[4-benzoyloxy-3-(formylamino)phenyl]ethanol (138 mg) as a pale yellow solid.

MS m/z : 783 (M⁺+1)

Example 96

The following compounds were obtained according to a similar manner to that of Example 94.

(1) (R)-1-(3-Formylamino-4-hydroxyphenyl)-2-[[3,3-bis(4-hydroxyphenyl)propyl]amino]ethanol

IR (KBr) : 3448, 3425, 1662, 1604, 1512, 1444, 1246 cm⁻¹

¹H-NMR (DMSO-d₆, δ) : 1.91-2.09(m, 2H), 2.32-2.46(m, 4H), 3.75(t, J=7.4Hz, 1H), 4.08(br, 1H), 4.41(t, J=5.8Hz, 1H), 5.04(br, 1H), 6.63(d, J=8.4Hz, 2H), 6.75-6.87(m, 2H), 7.00(d, J=8.4 Hz, 2H), 7.99(s, 1H), 8.25(s, 1H), 9.11(br, 3H), 9.53(br,
1H)
MS m/z : 423 (M⁺+1)

(2)  (R)-2-[[2,2-Bis(4-hydroxyphenyl)ethyl]amino]-1-[4-hydroxy-3-[(2,2,2-
trifluoroethyl)sulfonyl]amino]phenyl]ethanol

IR (KBr) : 1612, 1514 cm⁻¹

1H-NMR (CD₃OD, δ) : 2.75-2.95(2H, m, AB of ABX), 3.12-3.40(4H, m), 4.03(1H, t,
X of ABX), 4.67(1H, t, X of ABX), 6.71(4H, d, J=9Hz), 6.82(1H, d, J=8Hz), 7.00(1H,
dd, J=8 and 2Hz), 7.05(4H, d, J=9Hz), 7.28(1H, d, J=2Hz)
MS m/z : 527 (M⁺+1)

Example 97

To a solution of (S)-3-[N-benzyl-[2,2-bis(4-hydroxyphenyl)ethyl]amino]-1-
(3-formyl-4-benzoxoxyphenoxy)-2-propanol (286 mg) in a mixed solvent of
tetrahydrofuran (3.0 ml) and ethanol (3.0 ml) was added sodium borohydride
(35.8 mg) at room temperature and the mixture was stirred for 1 hour. The
reaction mixture was diluted with ethyl acetate (20 ml) and washed with water
(20 ml x 2), brine (20 ml x 1), dried over magnesium sulfate, filtered, and
evaporated to give (S)-3-[N-benzyl-[2,2-bis(4-hydroxyphenyl)ethyl]amino]-1-[4-
benzoxoxy-3-[hydroxymethyl]phenoxy]-2-propanol (239 mg) as a white solid.
MS m/z : 606 (M⁺+1)

Example 98

To a solution of (S)-3-[N-benzyl-[2,2-bis(4-hydroxyphenyl)ethyl]amino]-1-
[4-benzoxoxy-3-[hydroxymethyl]phenoxy]-2-propanol (234 mg) in methanol (5.0
ml) was added 10% palladium on activated carbon (50% wet, 100 mg) and the
mixture was hydrogenated at 1 atm for 2 hours. The catalyst was removed by
filtration and washed with methanol. The filtrate was concentrated in vacuo to
give (S)-1-[4-hydroxy-3-[hydroxymethyl]phenoxy]-3-[2,2-bis(4-hydroxyphenyl)ethyl]amino]-2-propanol (164 mg) as a yellow solid.
IR (KBr) : 3417, 2929, 1608, 1510, 1444, 1242, 831 cm⁻¹

1H-NMR (DMSO-d₆, δ) : 2.58-2.71(m, 2H), 3.08(d, J=7.5Hz, 2H), 3.73(brs, 2H),
3.89(t, J = 7.4 Hz, 1H), 4.43(d, J = 5.0 Hz, 2H), 4.85(br, 1H), 4.97(br, 1H), 6.52-
6.58(m, 2H), 6.65(d, J=8.5 Hz, 2H), 6.85(d, J=2.7Hz, 1H), 7.03(d, J=8.5 Hz, 2H),
8.84(br, 1H), 9.16(br, 2H)
MS m/z : 426 (M⁺+1)

Example 99

0.5 ml of a mixture of acetic anhydride (1.25 ml) and formic acid (1.00 ml)
was added to a solution of (S)-1-(3-amino-4-benzoxoxyphenoxy)-3-[N-benzyl-[2,2-
bis(4-benzoxoxyphenyl)ethyl]amino]-2-propanol (314 mg) and pyridine (0.1 ml) in
dichloromethane (6 ml) under ice water cooling over 10 minutes and the mixture
was stirred at room temperature for a further 1 hour. To this reaction mixture was added aqueous saturated solution of sodium bicarbonate (5.0 ml). The mixture was stirred at the same temperature for 18 hours, and which was dissolved in ethyl acetate, washed with aqueous saturated sodium bicarbonate solution and brine, dried over sodium sulfate, and evaporated in vacuo.

A mixture of the residue and 10% palladium on activated carbon (50% wet, 10 mg) in methanol (2.0 ml) and chlorobenzene (2.0 ml) was stirred at room temperature in the presence of hydrogen at an atmospheric pressure for 1 hour, and filtered. The filtrate was evaporated in vacuo. The residue was chromatographed (chloroform - methanol) over silica gel to afford (S)-1-(3-formylamino-4-hydroxyphenoxy)-3-[2,2-bis(4-hydroxyphenyl)ethyl]amino]-2-propanol (103 mg) as a yellow foam.

IR (KBr) : 3300-3150, 1671, 1664, 1604, 1598, 1444, 1247, 1203 cm⁻¹

¹H-NMR (CD₃OD, δ) : 2.70-2.90(2H, m), 3.05-3.30(2H, m), 3.80-3.90(2H, m), 4.00-4.10(2H, m), 6.40-6.50(1H, m), 6.60-6.80(5H, m), 7.00-7.20(4H, m), 7.70(1H, d, J=2.9Hz), 8.28(1H, s)

MS (m/z) : 439 (M+1).

Example 100

Benzenesulfonfyl chloride (63 mg) was added to a solution of (S)-1-(3-amino-4-benzylphenoxy)-3-[N-benzyl-[2,2-bis(4-benzylphenoxy)ethyl]amino]-2-propanol (230 mg) and pyridine (0.1 ml) in dichloromethane (5 ml) under ice water cooling over 10 minutes and the mixture was stirred at room temperature for a further 1 hour. To this reaction mixture was added aqueous saturated solution of sodium bicarbonate (5.0 ml). The mixture was stirred at the same temperature for 18 hours, and which was dissolved in ethyl acetate, washed with aqueous saturated sodium bicarbonate solution and brine, dried over sodium sulfate, and evaporated in vacuo.

A mixture of the residue and 10% palladium on activated carbon (50% wet, 10 mg) in methanol (2.0 ml) was stirred at room temperature in the presence of hydrogen at an atmospheric pressure for 1 hour, and filtered. The filtrate was evaporated in vacuo. The residue was chromatographed (chloroform - methanol) over silica gel to afford (S)-1-(3-benzenesulfonfylamino-4-hydroxyphenoxy)-3-[2,2-bis(4-hydroxyphenyl)ethyl]amino]-2-propanol (60 mg) as a brown foam.

IR (KBr) : 3380-3000, 1610, 1513, 1450, 1324, 1444, 1247, 1157 cm⁻¹

¹H-NMR (CD₃OD, δ) : 2.60-2.95(2H, m), 3.10-3.20(2H, m), 3.75(2H, d, J=5.3Hz), 3.90-4.10(2H, m), 6.40-6.80(6H, m), 6.90(1H, d, J=2.8Hz), 7.00-7.20(4H, m), 7.30-7.60(3H, m), 7.70-7.90(2H, m)

MS (m/z) : 551 (M+1)
Example 101

The following compounds were obtained according to a similar manner to that of Example 100.

(1) (S)-1-[3-Benzenesulfonfylamino-4-hydroxyphenoxy]-3-[[3,3-bis(4-
hydroxyphenyl)propyl]amino]-2-propanol
IR (KBr) : 3380-3000, 1610, 1513, 1450, 1324, 1444, 1247, 1157 cm⁻¹
¹H-NMR (CD₃OD, δ) : 2.20-2.40(2H, m), 2.60-3.00(4H, m), 3.42(1H, s), 3.80(2H,
d, J=5.0 Hz), 4.00-4.15(1H, m), 6.47-6.70(5H, m), 6.95-7.10(5H, m), 7.25-7.50(4H,
m), 7.70-7.80(2H, m)

10 MS (m/z) : 565 (M+1)

(2) (R)-2-[[3,3-Bis(4-methoxyphenyl)propyl]amino]-1-[3-
benzenesulfonfylamino-4-hydroxyphenyl]ethanol hydrochloride
IR (KBr) : 3300-2960, 1608, 1509, 1448, 1245, 1162 cm⁻¹
¹H-NMR (CD₃OD, δ) : 2.30-2.45(2H, m), 2.80-3.10(3H, m), 3.62(6H, s), 4.00-
4.10(1H, m), 6.90-7.80(16H, m)

15 MS (m/z) : 563 (M+1)

(3) (R)-1-[4-Hydroxy-3-(methanesulfonfylamino)phenyl]-2-[[2,2-bis(3-chloro-4-
hydroxyphenyl)ethyl]amino]ethanol
IR (KBr) : 3420 (br), 1608, 1290, 1149 cm⁻¹
¹H-NMR (DMSO-d₆, δ) : 2.60(2H, br d, CH₂), 2.91(3H, s, CH₃), 3.10(2H, m, CH₂),
3.94(1H, t, CHAr), 4.47(1H, m, CH), 5.12 (1H, br s, OH), 6.77-7.26(9H, m,
aromatic H), 9.97(3H, br, OH)

20 (+) APCI MS m/z : 527, 529, 531 (M⁺+1)

Example 102

The following compound was obtained according to a similar manner to that of Example 99.

(S)-1-[3-Formylamino-4-hydroxyphenoxy]-3-[[3,3-bis(4-
hydroxyphenyl)propyl]amino]-2-propanol
IR (KBr) : 3300-3000, 1671, 1664, 1606, 1509, 1461, 1240, 1207 cm⁻¹
¹H-NMR (CD₃OD, δ) : 2.10-2.30(2H, m), 2.60-3.00(3H, m), 3.32(1H, s), 3.60-
3.90(3H, m), 4.00-4.10(1H, m), 6.50-6.80(6H, m), 7.05-7.15(4H, m), 7.75(1H, d,
J=2.8 Hz), 8.28(1H, s)

25 MS (m/z) : 453 (M+1)

Preparation 66

1.0 M solution of boron tribromide in dichloromethane (25.2 ml) was
added dropwise to a stirred suspension of N-benzyl-[2,2-bis(4-methoxyphenyl)-
ethyl]amine hydrochloride (3.07 g) in dichloromethane (31 ml) under ice cooling
and in an atmosphere of nitrogen over 20 minutes, and the resulting mixture was
stirred under the same conditions for 1 hour and 30 minutes. The reaction mixture was evaporated in vacuo and the residue was partitioned between ethyl acetate and aqueous solution of sodium bicarbonate. The organic layer was washed with brine, dried over sodium sulfate, and evaporated in vacuo. The residue was powdered from diisopropyl ether to afford N-benzyl-[2,2-bis(4-hydroxyphenyl)ethyl]amine (2.47 g) as a colorless powder.

mp 161.5-163.5°C

$^1$H-NMR (DMSO-d$_6$, $\delta$): 1.65(1H, br, NH), 2.97(2H, d, J=7.6Hz, CH$_2$), 3.69(2H, s, CH$_2$), 3.91(1H, t, J=7.6Hz, CHAr$_2$), 6.64(4H, d, J=8.4 Hz, aromatic H), 7.00(4H, d, J=8.4Hz, aromatic H), 7.22(5H, m, aromatic H), 9.15(2H, s, OH)

(+) ESI MS m/z : 320 (M$^+$+1)

Preparation 67

A mixture of N-benzyl-[2,2-bis(4-hydroxyphenyl)ethyl]amine (319 mg) and di-tert-butyl dicarbonate (240 mg) in tetrahydrofuran (3.2 ml) was stirred at room temperature for 2 hours and partitioned between ethyl acetate and aqueous solution of sodium bicarbonate. The organic layer was separated, washed with brine, dried over sodium sulfate, and evaporated in vacuo. The residue was chromatographed (toluene - ethyl acetate (85/15)) over silica gel (2.3 g) to afford tert-butyl N-benzyl-N-[2,2-bis(4-hydroxyphenyl)ethyl]carbamate (427 mg) as a colorless amorphous powder.

$^1$H-NMR (DMSO-d$_6$, $\delta$): 1.29 and 1.36(1H, each s, CH$_3$), 3.60 (2H, m, CH$_2$), 4.06(1H, m, CHAr$_2$), 4.18(2H, m, CH$_2$), 6.66(4H, d, J=8.4Hz, aromatic H), 7.03 (4H, d, J=8.4Hz, aromatic H), 7.12 -7.35(5H, m, aromatic H), 9.20(2H, br s, OH)

(+) ESI MS m/z : 442 (M$^+$+Na)

Preparation 68

A mixture of tert-butyl N-benzyl-N-[2,2-bis(4-hydroxyphenyl)ethyl]-carbamate (419 mg) and N-chlorosuccinimide (267 mg) in 1,4-dioxane (4.5 ml) was stirred under reflux for 8 hours and 30 minutes. The reaction mixture was partitioned between ethyl acetate and brine. The organic layer was separated, washed twice with brine, dried over sodium sulfate, and evaporated in vacuo. The residue was chromatographed (toluene – ethyl acetate) over silica gel (9.8 g) to afford tert-butyl N-benzyl-N-[2,2-bis(3-chloro-4-hydroxyphenyl)ethyl]-carbamate (320 mg) as a colorless amorphous powder.

$^1$H-NMR (DMSO-d$_6$, $\delta$): 1.29 and 1.34 (1H, each br s, CH$_3$), 3.65(2H, m, CH$_2$), 4.15(1H, m, CHAr$_2$), 4.28(2H, m, CH$_2$), 6.87(2H, d, J=8.4Hz, aromatic H), 7.03(2H, d, J=8.4Hz, aromatic H), 7.15-7.36(7H, m, aromatic H), 10.02(2H, br s, OH)

(-)ESI MS m/z : 486, 488, 490 (M$^-$ - 1)

Preparation 69
Benzyl bromide (224 mg) was added to a stirred suspension of tert-butyl N-benzyl-N-[2,2-bis[3-chloro-4-hydroxyphenyl]ethyl]carbamate (304 mg) and potassium carbonate (258 mg) in N,N-dimethylformamide (5 ml) under ice cooling and the resulting mixture was stirred at the same temperature for 1 hour and 40 minutes and at room temperature for 2 hours and 15 minutes. The reaction mixture was poured into 1N sodium hydroxide solution and the mixture was extracted with toluene. The extract was washed three times with brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was chromatographed (toluene - ethyl acetate) over silica gel (8.1 g) to afford tert-butyl N-benzyl-N-[2,2-bis[4-benzyloxy-3-chlorophenyl]ethyl]carbamate (382 mg).

$^1$H-NMR (DMSO-d$_6$, δ): 1.30 and 1.32 (1H, each br s, CH$_3$), 3.73(2H, m, CH$_2$), 4.15(1H, m, CHAr$_2$), 4.28(2H, m, CH$_2$), 5.17(4H, s, CH$_2$), 7.11-7.47(21H, m, aromatic H)

(+) ESI MS m/z: 690, 692, 694 (M$^+$+Na)

**Preparation 70**

4N Hydrogen chloride in ethyl acetate (4 ml) was added to tert-butyl N-benzyl-N-[2,2-bis[4-benzyloxy-3-chlorophenyl]ethyl]carbamate (369 mg) under ice cooling and the resulting mixture was stirred at the same temperature and then room temperature for 3 hours and 15 minutes in all. The reaction mixture was concentrated in vacuo and the solid residue was washed with ethyl acetate to afford N-benzyl-[2,2-bis[4-benzyloxy-3-chlorophenyl]ethyl]amine hydrochloride (322 mg) as a colorless powder.

mp 221-226°C

$^1$H-NMR (DMSO-d$_6$, δ): 3.58(2H, m, CH$_2$), 4.12(2H, br s, CH$_2$), 4.40(1H, t, J=7.2Hz, CHAr$_2$), 5.18(4H, s, CH$_2$), 7.18(2H, J=8.6Hz, aromatic H), 7.25-7.60(19H, m, aromatic H)

(+) ESI MS m/z: 568, 570, 572 (M$^+$+1)

**Example 103**

Under nitrogen, a solution of N-benzyl-[2,2-bis[4-hydroxyphenyl]ethyl]-amine (400 mg) and (S)-[4-benzyloxy-3-nitrobenzoxy]methyl]oxirane (415 mg) in ethanol (10 ml) was refluxed for 24 hours. The mixture was evaporated in vacuo. A mixture of the residue, potassium carbonate (476 mg) and benzyl bromide (0.328 ml) in N,N-dimethylformamide (10 ml) was stirred at room temperature for 18 hours. The mixture was diluted with ethyl acetate, and insoluble materials were filtered off. The filtrate was evaporated in vacuo. The residue was dissolved in ethyl acetate, washed with aqueous saturated sodium bicarbonate solution and brine, dried over sodium sulfate, and evaporated in vacuo. The residue was purified by column chromatography on silica gel (n-hexane : ethyl
acetate = 1:1) to give (S)-3-[N-benzyl-[2,2-bis(4-benzoxylphenyl)ethyl]amino]-1-(4-benzoxyl-3-nitrophenoxy)-2-propanol (820 mg) as a yellow foam.

$^1$H-NMR (CHCl₃, δ) : 2.60-2.70(2H, m), 2.95-3.00(1H, m), 3.10-3.25(1H, m), 3.40-3.90(4H, m), 4.98(2H, s), 5.01(2H, s), 5.13(2H, s), 6.70-6.95(4H, m), 7.00-7.45(19H, m)

Example 104

Under nitrogen, a solution of N-benzyl-[3,3-bis(4-hydroxyphenyl)propyl]amine (300 mg) and (S)-[(4-benzoxyl-3-nitrophenoxy)methyl]oxirane (271 mg) in ethanol (10 ml) was refluxed for 24 hours. The mixture was evaporated in vacuo. A mixture of the residue, potassium carbonate (310 mg) and benzyl bromide (0.214 ml) in N,N-dimethylformamide (10 ml) was stirred at room temperature for 18 hours. The mixture was diluted with ethyl acetate, and insoluble materials were filtered off. The filtrate was evaporated in vacuo. The residue was dissolved in ethyl acetate, washed with aqueous saturated sodium bicarbonate solution and brine, dried over sodium sulfate, and evaporated in vacuo. The residue was purified by column chromatography on silica gel (n-hexane : ethyl acetate = 1:1) to give (S)-3-[N-benzyl-[3,3-bis(4-benzoxylphenyl)propyl]amino]-1-(4-benzoxyl-3-nitrophenoxy)-2-propanol (820 mg) as a yellow foam.

MS (m/z) : 815(M+1)

Example 105

A mixture of (S)-1-phenoxy-3-[N-benzyl-[3,3-bis[4-(methoxycarbonyl)amino]phenyl]propyl]amino]-2-propanol (7.4 g), potassium hydroxide (2.5 g) and ethylene glycol (50 ml) was heated at 100°C for 6 hours. The reaction mixture was worked up in a usual manner and purified by column chromatography (silica gel, hexane : ethyl acetate = 1:1 to 1:2) to afford (S)-1-phenoxy-3-[N-benzyl-[3,3-bis(4-aminophenyl)propyl]amino]-2-propanol (2.53 g).

MS m/z : 482 (M+1)

Example 106

To a mixture of (S)-1-phenoxy-3-[N-benzyl-[3,3-bis(4-aminophenyl)propyl]amino]-2-propanol (120 mg), dichloromethane (1 ml) and pyridine (60 µl), methyl chloroformate (19 µl) was added with cooling by ice-bath. The reaction mixture was stirred at room temperature for 1 hour, diluted with ethyl acetate (40 ml), washed by water followed by saturated sodium chloride solution, dried over magnesium sulfate, evaporated and purified by preparative TLC (silica gel, hexane : ethyl acetate = 1:2) to afford an oily product. A mixture of the product, methanol (2 ml) and 10% palladium on charcoal (10 mg) was stirred under hydrogen (1 atm) for 1 hour, filtrated and evaporated to afford (S)-1-phenoxy-3-[[3RS]-3-[4-(methoxycarbonylamino)phenyl]-3-(4-aminophenyl)propyl]amino]-2-
propanol (27 mg).

$^1$H-NMR (CD$_3$OD, $\delta$): 2.14-2.26(2H, m), 2.56-2.84(4H, m), 3.70(3H, s), 3.78-
4.15(4H, m), 6.65(2H, dd, J=1.7Hz, 6.5Hz), 6.87-7.02(5H, m), 7.13-7.33(6H, m)
MS m/z : 450 (M+1)

Industrial Applicability

The compound of the formula [I] and a salt thereof possesses gut selective
sympathomimetic, anti-ulcerous, anti-pancreatitis, lipolytic, anti-urinary
incontinence and anti-pollakiuria activities. These compounds are useful for the
treatment and/or prevention of gastro-intestinal disorders caused by smooth
muscle contractions in human beings or animals, and more particularly for the
treatment and/or prevention of spasm or hyperanakinesia in case of irritable
bowel syndrome, gastritis, gastric ulcer, duodenal ulcer, enteritis,
cholecystopathy, cholangitis, urinary calculus and the like; for the treatment
and/or prevention of ulcer such as gastric ulcer, duodenal ulcer, peptic ulcer,
under caused by non steroidal anti-inflammatory drugs, or the like; for the
treatment and/or prevention of dysuria such as pollakiuria, urinary incontinence
or the like in case of nervous pollakiuria, neurogenic bladder dysfunction,
nocturia, unstable bladder, cystospasm, chronic cystitis, chronic prostatitis,
prostatic hypertrophy or the like; for the treatment and/or prevention of
pancreatitis, obesity, diabetes, glycosuria, hyperlipidemia, hypertension,
atherosclerosis, glaucoma, melancholia, depression or the like; for the treatment
and/or prevention of diseases as the result of insulin resistance (e.g.
hypertension, hyperinsulinemia, etc.); for reducing a wasting condition, and the
like.

This invention is based on application No. PQ4076 filed in Australia, the
content of which is incorporated hereinto by reference.
CLAIMS

1. A compound of the general formula [I]:

\[
\begin{array}{c}
\text{OH} \\
A-X-\text{CH-CH}_2-N-\text{CH-(CH}_2)\text{n-C-} \\
\end{array}
\]

\[\text{[I]}\]

wherein

- A is phenyl, pyridyl, indolyl, benzimidazolyl or 2,3-dihydro-2-oxobenzimidazolyl, each of which may have 1 to 3 same or different substituent(s) selected from the group consisting of hydroxy, lower alkylicarbonyloxy, lower alkoxy carbonyloxy, amino, halogen atom, lower alkylsulfonylamino, carboxy(lower)alkyl sulfonylamino, N-lower alkyl-N-(lower)alkyl sulfonylamino, mono(or di or tri)halo(lower)alkyl sulfonylamino, phenyl(lower)alkyl sulfonylamino, thienyl sulfonylamino, phenyl(lower)alkoxy, lower alkyl, hydroxy(lower)alkyl, amino(lower)alkyl, lower alkylicarbonylamino(lower)alkyl, formylamino, lower alkylicarbonylamino, lower alkylcarboxamidinamino, lower alkoxy carbonylamino, ureido, lower alkylicarboxamidinocarbonylamino, lower alkoxy carbonyl, formyl, carbamoyl, nitro, lower alkyl sulfonylamino wherein amino is protected by amino-protective group, and phenyl sulfonylamino wherein phenyl may be substituted by halogen atom, lower alkyl or lower alkoxy,

- X is single bond or \(-\text{O-CH}_2-\),

- \(R^1\) is hydrogen atom or amino-protective group,

- \(R^2\) is hydrogen atom, lower alkyl, hydroxy(lower)alkyl or carboxy(lower)alkyl,

- \(R^3\) is hydrogen atom or hydroxy,

- \(R^4, R^5, R^6\) and \(R^7\) are each independently hydrogen atom, hydroxy, lower alkyl, lower alkoxy, amino, lower alkyl sulfonylamino, lower
alkoxycarbonylamino, carboxyl(lower)alkylamino, lower
alkoxycarbonyl(lower)alkylamino, formylamino, lower
alkylcarbamoylamino, ureido, halogen atom, phenyl(lower)alkoxy,
lower alkoxycarbonyloxy, lower alkylcarbonyloxy, lower
alkoxycarbonyl(lower)alkoxy, carboxyl(lower)alkoxy, carbamoyl,
lower alkylcarbamoyl, lower alkylsulfonylcarbamoyl,
morpholinyl, isothiazolidinyl wherein isothiazolidinyl may be
substituted by 1 or 2 oxo(s), pyrrolidinyl or imidazolidinyl
wherein pyrrolidinyl and imidazolidinyl may be substituted by
oxo, and

\[ n \]

provided that \( A \) should be phenyl, pyridyl, indolyl, benzimidazolyl or 2,3-dihydro-2-oxobenzimidazolyl, each of which has at least one substituent selected from the group consisting of lower alkylcarbonyloxy, lower alkoxycarbonyloxy,
carboxyl(lower)alkylsulfonlamino, N-lower alkyl-N-(lower)alkylsulfonlamino,
mono(or di or tri)halo(lower)alkylsulfonlamino, phenyl(lower)alkylsulfonlamino,
thienylsulfonlamino, hydroxy(lower)alkyl, amino(lower)alkyl, lower
alkylsulfonlamino(lower)alkyl, formylamino, lower alkylcarbonylamino,
[N,N-di(lower)alkylsulfamoyl]amino, lower alkoxycarbonylamino-sulfonlamino,
lower alkoxycarbonylamino, ureido, lower alkylaminocarbonylamino, lower
alkoxycarbonyl, formyl, carbamoyl, nitro, lower alkylsulfonlamino wherein
amino is protected by amino-protective group, and phenylsulfonlamino wherein
phenyl may be substituted by halo atom, lower alkyl or lower alkoxy, when \( n \)
is 1, \( R^2 \) is hydrogen atom or lower alkyl, and \( R^4, R^5, R^6 \) and \( R^7 \) are each
independently hydrogen atom, hydroxy, lower alkyl, lower alkoxy, amino, lower
alkylsulfonlamino, lower alkoxycarbonylamino, formylamino, lower
alkylcarbonylamino, ureido, carbamoyl, lower alkylcarbamoyl or pyrrolidinyl; and
provided that \( A \) should be phenyl, pyridyl, indolyl or benzimidazolyl, each of
which has at least one substituent selected from the group consisting of lower
alkylsulfonlamino, carboxyl(lower)alkylsulfonlamino, N-lower alkyl-N-
(lower)alkylsulfonlamino, mono(or di or tri)halo(lower)alkylsulfonlamino,
phenyl(lower)alkylsulfonlamino, thienylsulfonlamino, lower alkyl,
hydroxy(lower)alkyl, amino(lower)alkyl, lower alkylsulfonlamino(lower)alkyl,
[N,N-di(lower)alkylsulfamoyl]amino, lower alkoxycarbonylamino-sulfonlamino,
lower alkoxycarbonyl, formyl, lower alkylsulfonlamino wherein amino is
protected by amino-protective group, and phenylsulfonlamino wherein phenyl
may be substituted by halo atom, lower alkyl or lower alkoxy, when \( n \) is 0 or
1, \( R^2 \) is hydrogen atom or lower alkyl, \( R^4 \) is hydrogen atom, \( R^5 \) and \( R^6 \) are each
hydrogen atom and R⁵ and R⁷ are each independently lower alkoxy carbonyl(lower)alkoxy or carboxy(lower)alkoxy, or a pharmaceutically acceptable salt thereof.

5 2. A compound of claim 1, wherein
A is phenyl, pyridyl, indolyl, benzimidazolyl or 2,3-dihydro-2-oxobenzimidazolyl, each of which may have 1 to 3 same or different substituent(s) selected from the group consisting of hydroxy, lower alkylcarbonyloxy, lower alkoxy carbonyloxy, amino, halogen atom, lower alkylsulfonfylamino, carboxy(lower)alkylsulfonfylamino, N-lower alkyl-N-(lower)alkylsulfonfylamino, mono(or di or tri)halo(lower)alkylsulfonfylamino, phenyl(lower)alkylsulfonfylamino, thienylsulfonfylamino, phenyl(lower)alkoxy, hydroxy(lower)alkyl, amino(lower)alkyl, lower alkylsulfonfylamino(lower)alkyl, formylamino, lower alkylcarbonylamino, [N,N-di(lower)alkylsulfamoyl]amino, lower alkoxy carbonylamino, lower alkoxy carbonylamino, ureido, lower alky lamino carbonylamino, lower alkoxy carbonyl, formyl, carbamoyl, nitro and phenylsulfonfylamino wherein phenyl may be substituted by halogen atom, lower alkyl or lower alkoxy,
X is single bond or −O−CH₂−,
R¹ is hydrogen atom or amino-protective group,
R² is hydrogen atom, lower alkyl, hydroxy(lower)alkyl or carboxy(lower)alkyl,
R³ is hydrogen atom or hydroxy,
R⁴, R⁵, R⁶ and R⁷ are each independently hydrogen atom, hydroxy, lower alkyl, lower alkoxy, amino, lower alkylsulfonfylamino, lower alkoxy carbonylamino, carboxy(lower)alkylamino, lower alkoxy carbonyl(lower)alkylamino, halogen atom, phenyl(lower)alkoxy, lower alkoxy carbonyloxy, lower alkylcarbonyloxy, lower alkoxy carbonyl(lower)alkoxy, carboxy(lower)alkoxy, carbamoyl, lower alkyl carbamoyl, lower alkylsulfonfyl carbamoyl, morpholiny, pyrrolidiny or imidazolidinyl wherein pyrrolidiny and imidazolidinyl may be substituted by oxo, and
n is 0 or 1;
provided that A should be phenyl, pyridyl, indolyl, benzimidazolyl or 2,3-dihydro-2-oxobenzimidazolyl, each of which has at least one substituent selected from the group consisting of lower alkylcarbonyloxy, lower alkoxy carbonyloxy, carboxy(lower)alkylsulfonylamino, N-lower alkyl-N-(lower)alkylsulfonylamino, mono(or di or tri)halo(lower)alkylsulfonylamino, phenyl(lower)alkylsulfonylamino, thienylsulfonylamino, hydroxy(lower)alkyl, amino(lower)alkyl, lower alkylsulfonylamino(lower)alkyl, formylamino, lower alkylcarbonylamino, [N,N-di(lower)alkylsulfamoyl]amino, lower alkoxy carbonylamino, ureido, lower alkylaminocarbonylamino, lower alkoxy carbonyl, formyl, carbamoyl, nitro and phenylsulfonylamino wherein phenyl may be substituted by halogen atom, lower alkyl or lower alkoxy, when n is 1, R^2 is hydrogen atom or lower alkyl, and R^4, R^5, R^6 and R^7 are each independently hydrogen atom, hydroxy, lower alkyl, lower alkoxy, amino, lower alkylsulfonylamino, lower alkoxy carbonylamino, carbamoyl, lower alkyl carbamoyl or pyrrolidinyl; and provided that A should be phenyl, pyridyl, indolyl or benzimidazolyl, each of which has at least one substituent selected from the group consisting of lower alkylsulfonylamino, carboxy(lower)alkylsulfonylamino, N-lower alkyl-N-(lower)alkylsulfonylamino, mono(or di or tri)halo(lower)alkylsulfonylamino, phenyl(lower)alkylsulfonylamino, thienylsulfonylamino, hydroxy(lower)alkyl, amino(lower)alkyl, lower alkylsulfonylamino(lower)alkyl, formyl and phenylsulfonylamino wherein phenyl may be substituted by halogen atom, lower alkyl or lower alkoxy, when n is 0 or 1, R^2 is hydrogen atom or lower alkyl, R^3 is hydrogen atom, R^4 and R^6 are each hydrogen atom and R^5 and R^7 are each independently lower alkoxy carbonyl(lower)al koxy or carboxy(lower)al koxy, or a pharmaceutically acceptable salt thereof.

3. A compound of claim 2, wherein A is phenyl which may have 1 to 3 same or different substituent(s) selected from the group consisting of hydroxy, amino, lower alkylsulfonylamino, phenyl(lower)al koxy, hydroxy(lower)alkyl, amino(lower)alkyl, lower alkylsulfonylamino(lower)alkyl, formylamino, lower alkyl carbonylamino, [N,N-di(lower)alkylsulfamoyl]amino, lower alkoxy carbonylamino, ureido, lower alkoxy carbonyl, formyl, nitro and phenylsulfonylamino wherein phenyl may be
substituted by halogen atom,

X is single bond or \(-\text{O-CH}_2\),

R\(^1\) is hydrogen atom or amino-protective group,

R\(^2\) is hydrogen atom, lower alkyl or hydroxy(lower)alkyl,

R\(^3\) is hydrogen atom or hydroxy,

R\(^4\), R\(^5\), R\(^6\) and R\(^7\) are each independently hydrogen atom, hydroxy, lower alkoxy, amino, lower alkoxy carbonylamino, halogen atom, phenyl(lower)alkoxy, lower alkoxy carbonyl(lower)alkoxy or carboxy(lower)alkoxy, and

n is 0 or 1;

provided that A should be phenyl which has at least one substituent selected from the group consisting of hydroxy(lower)alkyl, amino(lower)alkyl, lower alkylsulfonlamino(lower)alkyl, formylamino, lower alkylcarbonylamino, [N,N-di(lower)alkylsulfamoyl]amino, lower alkoxy carbonylamino, ureido, lower alkoxy carbonyl, formyl, nitro and phenyl sulfonlamino wherein phenyl may be substituted by halogen atom, when n is 1, R\(^2\) is hydrogen atom or lower alkyl, and R\(^4\), R\(^5\), R\(^6\) and R\(^7\) are each independently hydrogen atom, hydroxy, lower alkoxy, amino or lower alkoxy carbonylamino; and

provided that A should be phenyl which has at least one substituent selected from the group consisting of lower alkylsulfonlamino, hydroxy(lower)alkyl, amino(lower)alkyl, lower alkylsulfonlamino(lower)alkyl, [N,N-di(lower)alkylsulfamoyl]amino, lower alkoxy carbonyl, formyl and phenyl sulfonlamino wherein phenyl may be substituted by halogen atom, when n is 0 or 1, R\(^2\) is hydrogen atom or lower alkyl, R\(^3\) is hydrogen atom, R\(^4\) and R\(^6\) are each hydrogen atom and R\(^5\) and R\(^7\) are each independently lower alkoxy carbonyl(lower)alkoxy or carboxy(lower)alkoxy, or a pharmaceutically acceptable salt thereof.

4. A compound of claim 3, wherein

A is phenyl which has 1 or 2 same or different substituent(s) selected from the group consisting of hydroxy, lower alkyl sulfonlamino, hydroxy(lower)alkyl, formylamino, [N,N-di(lower)alkylsulfamoyl]amino and phenyl sulfonlamino wherein phenyl may be substituted by halogen atom,

X is single bond or \(-\text{O-CH}_2\),

R\(^1\), R\(^2\) and R\(^3\) are each hydrogen atom,

R\(^1\), R\(^5\), R\(^6\) and R\(^7\) are each independently hydrogen atom, lower alkoxy or lower alkoxy carbonylamino, and
n is 0 or 1,
provided that A should be phenyl which has at least one substituent selected from the group consisting of hydroxy(lower)alkyl, formylamino, [N,N-di(lower)alkylsulfamoyl]amino and phenylsulfonylamino wherein phenyl may be substituted by halogen atom, when n is 1, or a pharmaceutically acceptable salt thereof.

5. A compound of claim 3, wherein
A is phenyl which has 1 or 2 same or different substituent(s) selected from the group consisting of hydroxy, lower alkylsulfonlamino, hydroxy(lower)alkyl, formylamino, [N,N-di(lower)alkylsulfamoyl]amino and phenylsulfonylamino wherein phenyl may be substituted by halogen atom,
X is single bond or —O-CH₂—,
R¹, R² and R³ are each hydrogen atom,
R⁴, R⁵, R⁶ and R⁷ are each independently hydrogen atom or hydroxy, and n is 0,
or a pharmaceutically acceptable salt thereof.

6. A compound of claim 4, which is a member selected from the group consisting of
(R)-1-(4-hydroxy-3-benzenesulfonylamidophenyl)-2-[[2,2-bis(4-methoxyphenyl)ethyl]amino]ethanol,
(RS)-1-(4-hydroxy-3-benzenesulfonylamidophenyl)-2-[[3,3-bis(4-methoxyphenyl)propyl]amino]ethanol,
(S)-1-(4-hydroxy-3-formylaminophenoxy)-3-[[3,3-bis(4-methoxyphenyl)propyl]amino]-2-propanol,
(R)-2-[[2,2-bis[4-(methoxycarbonylamino)phenyl]ethyl]amino]-1-[[4-hydroxy-3-(benzenesulfonylamido)phenyl]ethanol and
(R)-2-[[2,2-bis[4-(methoxycarbonylamino)phenyl]ethyl]amino]-1-(3-formylamino-4-hydroxyphenyl]ethanol,
or a salt thereof.

7. A compound of claim 5, which is a member selected from the group consisting of
(R)-1-(4-hydroxy-3-methanesulfonylamidophenyl)-2-[[2,2-bis(4-hydroxyphenyl)ethyl]amino]ethanol,
(R)-1-(4-hydroxy-3-ethanesulfonylamidophenyl)-2-[[2,2-bis(4-
hydroxyphenyl]ethyl]amino]ethanol and
(R)-1-[4-hydroxy-3-[[N,N-dimethylsulfamoyl]amino]phenyl]-2-[[2,2-bis(4-
hydroxyphenyl]ethyl]amino]ethanol,
or a salt thereof.

8. A process for preparing a compound of claim 1 or a salt thereof, which
comprises
(i) reacting a compound [II] of the formula:

\[
\begin{align*}
A - \text{X} - \text{CH}_2 - \\
\text{II}
\end{align*}
\]

wherein A and X are each as defined in claim 1, or a salt thereof,
with a compound [III] of the formula:

\[
\begin{align*}
\text{R}^1 & \quad \text{R}^2 \\
\text{R}^3 & \quad \text{R}^4 \\
\text{R}^5 & \quad \text{R}^6 \\
\text{R}^7 & \quad \text{R}^8 \\
\text{R}^n & \quad \text{R}^n
\end{align*}
\]

wherein R\(^1\), R\(^2\), R\(^3\), R\(^4\), R\(^5\), R\(^6\), and n are each as defined in
claim 1, or a salt thereof, to give a compound [I] of the formula:

\[
\begin{align*}
\text{OH} & \quad \text{R}^1_a \\
A - \text{X} - \text{CH}_2 - \text{N} - \text{CH}_2 - \\
\text{R}^2 & \quad \text{R}^3 \\
\text{R}^4 & \quad \text{R}^5 \\
\text{R}^6 & \quad \text{R}^7 \\
\text{R}^n & \quad \text{R}^n
\end{align*}
\]

wherein A, X, R\(^1\), R\(^2\), R\(^3\), R\(^4\), R\(^5\), R\(^6\), R\(^7\) and n are each as defined in claim
1, or a salt thereof,
(ii) subjecting a compound [Ia] of the formula:
wherein A, X, R², R³, R⁴, R⁵, R⁶, R⁷ and n are each as defined in claim 1, and R¹ₐ is amino-protective group, or a salt thereof, to elimination reaction of the amino-protective group, to give a compound [Ib] of the formula:

wherein A, X, R², R³, R⁴, R⁵, R⁶, R⁷ and n are each as defined in claim 1, or a salt thereof, or

(iii) reacting a compound [IV] of the formula:

wherein A, X, R¹, R² and n are each as defined in claim 1, and R⁸ is lower alkyl, or a salt thereof, with a compound [V] of the formula:

wherein Y is halogen atom, R⁴ₐ is R⁴ or R⁵, and R⁵ₐ is R⁵ or R⁷, wherein R⁴, R⁵, R⁶, and R⁷ are each as defined in claim 1, or a salt thereof, to give a compound of the formula [Ic]:

wherein A, X, R¹, R², R⁴, R⁵, R⁶, R⁷ and n are each as defined in claim 1, or a salt thereof.
9. A pharmaceutical composition which comprises, as an active ingredient, a compound of claim 1 or a pharmaceutically acceptable salt thereof in admixture with pharmaceutically acceptable carriers or excipients.

10. Use of a compound of claim 1 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament.

11. A compound of claim 1 or a pharmaceutically acceptable salt thereof for use as a medicament.

12. A method for the prophylactic and/or therapeutic treatment of pollakiuria or urinary incontinence, which comprises administering a compound of claim 1 or a pharmaceutically acceptable salt thereof to a human being or an animal.

13. A prophylactic or therapeutic agent for pollakiuria or urinary incontinence, which comprises 2-[3-(7-carboxymethoxyindol-3-yl)-2-propylamino]-1-(3-chlorophenyl)ethanol or (2R,2R)-3-[2-(3-chlorophenyl)-2-hydroxyethylamino]propyl]-7-indolylxoyacetic acid or a pharmaceutically acceptable salt thereof as an active ingredient.

14. A method for the prophylactic and/or therapeutic treatment of pollakiuria or urinary incontinence, which comprises administering 2-[3-(7-carboxymethoxyindol-3-yl)-2-propylamino]-1-(3-chlorophenyl)ethanol or (2R,2R)-3-[2-(3-chlorophenyl)-2-hydroxyethylamino]propyl]-7-indolylxoyacetic acid or a pharmaceutically acceptable salt thereof to a human being or an animal.

15. Use of 2-[3-(7-carboxymethoxyindol-3-yl)-2-propylamino]-1-(3-chlorophenyl)ethanol or (2R,2R)-3-[2-(3-chlorophenyl)-2-hydroxyethylamino]propyl]-7-indolylxoyacetic acid or a pharmaceutically acceptable salt thereof for manufacturing a medicament for the prophylactic and/or therapeutic treatment of pollakiuria or urinary incontinence.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C217/60 C07C217/62 C07C217/72 C07D209/14 C07D213/61
A61K31/135 A61K31/44 A61K31/415

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 7 C07C C07D A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>P, X</td>
<td>WO 00 12462 A (TANIGUCHI KIYOSHI; FUJII NAOAKI (JP); SAKURAI MINORU (JP); FUJISAW)</td>
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<td></td>
<td>9 March 2000 (2000-03-09) claims 1-11; examples 7,18,20</td>
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<td>10 November 1994 (1994-11-10) cited in the application</td>
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Further documents are listed in the continuation of box C.

X Patient family members are listed in annex.

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

Date of the actual completion of the international search

8 January 2001

Date of mailing of the international search report

17. 4. 01

Name and mailing address of the ISA
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) 340-3018

Authorized officer

RUFET J.
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<td>A</td>
<td>EP 0 714 883 A (SQUIBB BRISTOL MYERS CO) 5 June 1996 (1996-06-05) abstract; claims 1-4</td>
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</tr>
</tbody>
</table>
1. Claims: 1-12

The provision of aminoalcohol derivatives according to formula (I) useful for the treatment and/or prevention of gastro-intestinal disorders

2. Claims: 13-15

The use of known indolyloxyacetic derivatives for the treatment and/or prevention of gastro-intestinal disorders
INTERNATIONAL SEARCH REPORT

Box I  Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
   Although claims 12 and 14 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II  Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
   1-12

Remark on Protest  
[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.
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