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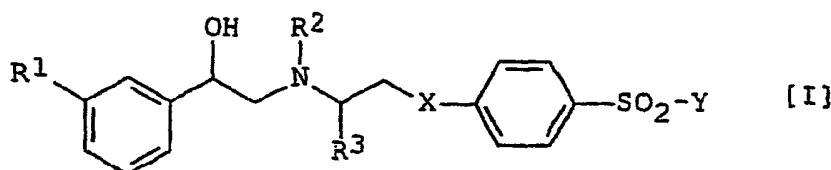
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(54) Title: AMINOALCOHOL DERIVATIVES AND THEIR USE AS BETA-3 ADRENERGIC RECEPTOR AGONISTS



(57) Abstract: The present invention relates to a compound formula [I] or a salt thereof. The compound [I] of the present invention and pharmaceutically acceptable salts thereof are useful for the prophylactic and/or the therapeutic treatment of pollakiuria or urinary incontinence.

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## DESCRIPTION

## AMINOALCOHOL DERIVATIVES AND THEIR USE AS BETA-3 ADRENERGIC RECEPTOR AGONISTS

## 5 TECHNICAL FIELD

This invention relates to new aminoalcohol derivatives and salts thereof which are beta-3 ( $\beta_3$ ) adrenergic receptor agonists and useful as a medicament.

## 10 BACKGROUND OF THE INVENTION

International Publication No. WO 02/094770, published November 28, 2002, describes aminoalcohol derivatives useful as  $\beta_3$  adrenergic receptor agonists.

## 15 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 sympathomimetic, anti-ulcerous, anti-pancreatitis, lipolytic, anti-urinary incontinence, anti-pollakiuria activities, anti-diabetes and anti-obesity, 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 a human being or an animal.

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

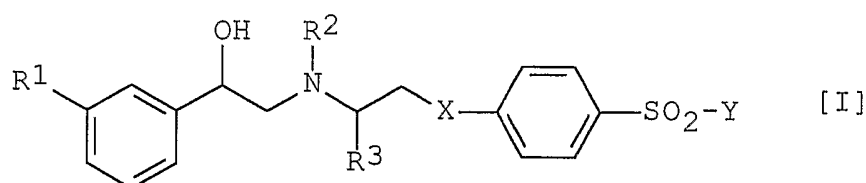
Another object of this invention is to provide processes for the preparation of said aminoalcohol derivatives and salts thereof.

35 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 therapeutic method for the treatment and/or prevention of aforesaid diseases in a human being or an animal, using said aminoalcohol derivatives and salts thereof.

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



wherein

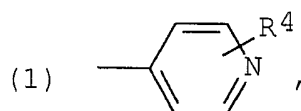
$R^1$  is hydrogen or halogen,

$R^2$  is hydrogen or an amino protective group,

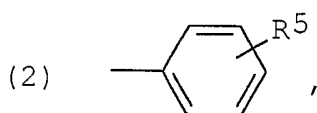
$R^3$  is hydrogen or lower alkyl,

X is bond,  $-\text{CH}_2-$  or  $-\text{O}-$ , and

Y is

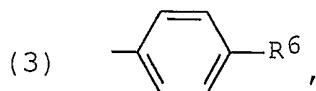


in which  $R^4$  is lower alkoxy carbonyl,



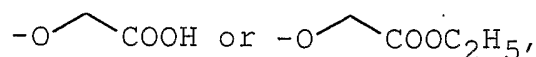
in which  $R^5$  is carboxy(lower)alkyl, (lower alkoxy)-carbonyl(lower)alkyl, lower alkanoyl, mono(or di or tri)halo(lower)alkylsulfonyloxy, carboxyphenoxy, (lower alkoxy)carbonylphenoxy, carboxypyridyloxy, (lower alkanoyl)pyridyl, carboxypyrrolidinyl(lower)alkyl, (lower alkoxy)carbonylpyrrolidinyl(lower)alkyl,

carboxyphenyl or (lower alkyl)phenyl,



5

in which  $R^6$  is  $-\text{OH}$ ,  $-\text{COOH}$ ,  $-\text{COOC}_2\text{H}_5$ ,



provided that (i) when  $R^6$  is  $-\text{OH}$ , then X is  $-\text{CH}_2-$ ,

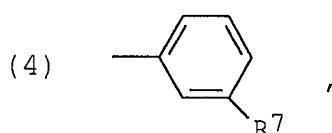
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(ii) when  $R^6$  is  $-\text{COOH}$ , then  $R^1$  is  $-\text{H}$ ,

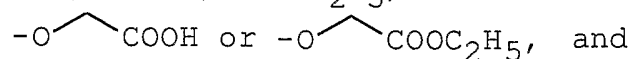
or

(iii) when  $R^6$  is  $-\text{COOC}_2\text{H}_5$ ,  $-\text{O}-\text{CH}_2-\text{COOH}$  or  
 $-\text{O}-\text{CH}_2-\text{COOC}_2\text{H}_5$ , then X is  $-\text{O}-$ ,

15

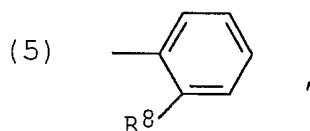


in which  $R^7$  is  $-\text{OH}$ ,  $-\text{COOH}$ ,  $-\text{COOC}_2\text{H}_5$ ,



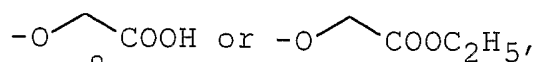
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X is  $-\text{CH}_2-$ ,

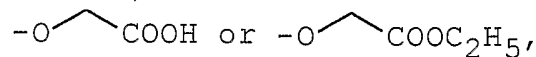


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in which  $R^8$  is  $-\text{OH}$ ,  $-\text{COOH}$ ,  $-\text{COOC}_2\text{H}_5$ ,

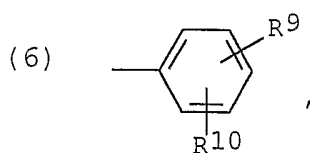


provided that when  $R^8$  is  $-\text{OH}$ ,



then  $R^3$  is  $-\text{CH}_3$ ,

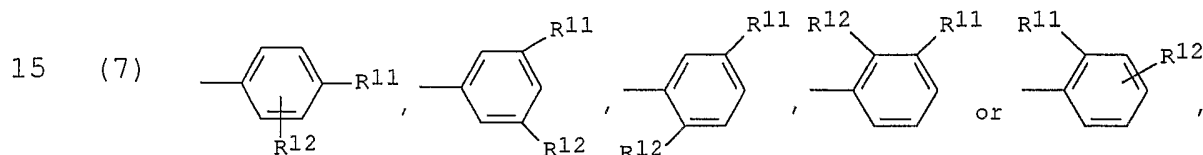
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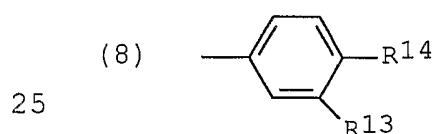
in which  $R^9$  is hydroxy, cyclo(lower)alkyl, mono(or di  
 35 or tri)halo(lower)alkyl, hydroxy(lower)alkoxy, lower

alkoxy(lower)alkoxy, carboxy(lower)alkoxy, lower  
 alkoxy carbonyl(lower)alkoxy, phenoxy, nitro, amino,  
 lower alkylamino, [lower alkoxy(lower)alkyl]amino,  
 [hydroxy(lower)alkyl]amino, [lower alkoxy carbonyl]amino,  
 5 lower alkanoylamino, [hydroxy(lower)alkanoyl]amino,  
 benzoylamino, (lower alkylsulfonyl)amino, lower  
 alkylthio or phenyl, and

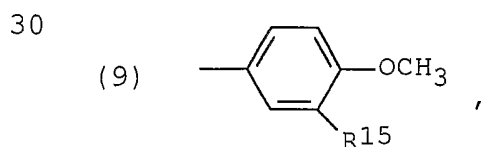
$R^{10}$  is carboxy, lower alkanoyl, lower alkoxy carbonyl,  
 carbamoyl, lower alkylcarbamoyl, carboxy(lower)alkyl,  
 10 (lower alkoxy carbonyl)(lower)alkyl, carboxy(lower)-  
 alkenyl, (lower alkoxy carbonyl)(lower)alkenyl or  
 phenyl optionally substituted with carboxy or lower  
 alkoxy carbonyl,



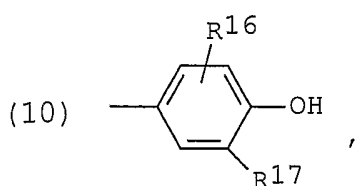
in which  $R^{11}$  is halogen or lower alkyl, and  
 $R^{12}$  is carboxy, lower alkanoyl, lower alkoxy carbonyl,  
 20 carbamoyl, lower alkylcarbamoyl, carboxy(lower)alkyl,  
 (lower alkoxy carbonyl)(lower)alkyl, carboxy(lower)-  
 alkenyl or (lower alkoxy carbonyl)(lower)alkenyl,



in which  $R^{13}$  is -Cl or -CH<sub>3</sub>,  
 $R^{14}$  is -COOH or -COOC<sub>2</sub>H<sub>5</sub>, and  
 X is -CH<sub>2</sub>-,



in which  $R^{15}$  is -COOH or -COOC<sub>2</sub>H<sub>5</sub>, and  
 35 X is -CH<sub>2</sub>-, or

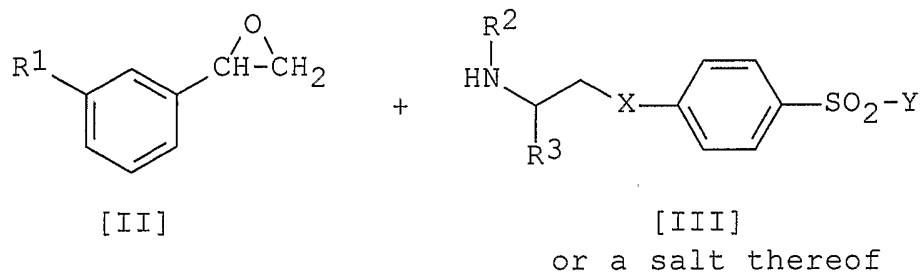


5 in which R<sup>16</sup> is lower alkyl or lower alkoxy, and  
R<sup>17</sup> is carboxy or lower alkoxycarbonyl,  
or a prodrug thereof or a pharmaceutially acceptable salt  
thereof.

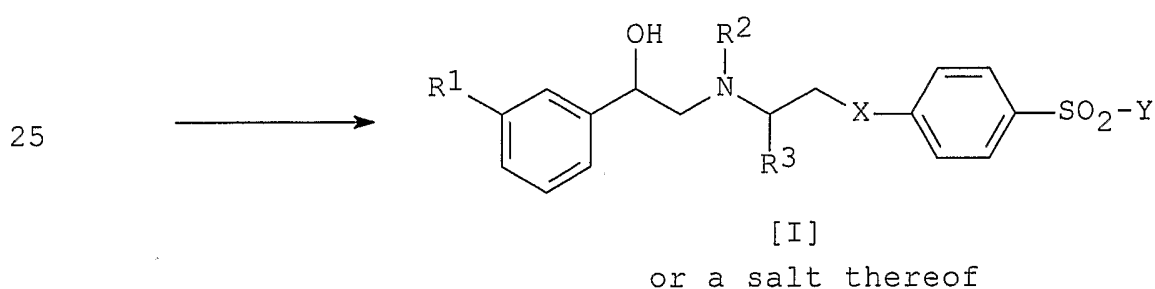
10 According to this invention, the object compounds can  
be prepared by processes which are illustrated in the  
following schemes.

Process 1

15



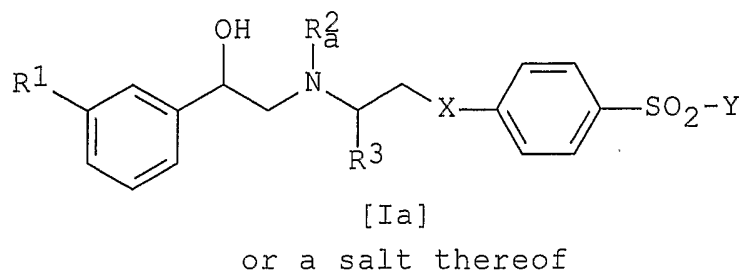
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Process 2

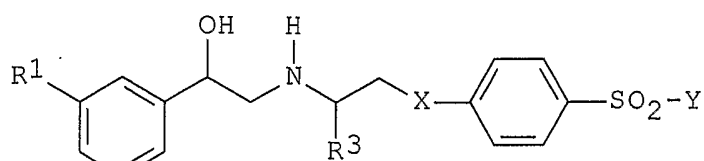
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35

6

elimination reaction  
of the amino  
protective group



[Ib]

or a salt thereof

## Process 3

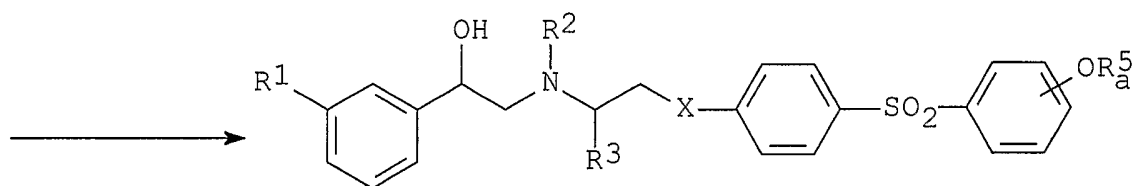
$$\text{R}^1\text{-C}_6\text{H}_4\text{-CH(OH)-CH}_2\text{-N(R}^2\text{)-CH(R}^3\text{)-CH}_2\text{-X-C}_6\text{H}_4\text{-SO}_2\text{-C}_6\text{H}_4\text{-OH} + \text{Z-R}_a^5$$

[IC]

or a salt thereof

[IV]

or a salt thereof



[Id]

or a salt thereof

25 wherein  $R^1$ ,  $R^2$ ,  $R^3$ , X and Y are each as defined above,  
 $R_a^2$  is an amino protective group, and  
 $R_a^5$  is lower alkyl optionally substituted with  
carboxy or lower alkoxycarbonyl; phenyl  
substituted with lower alkanoyl, carboxy or  
30 lower alkoxycarbonyl; or pyridyl optionally  
substituted with lower alkanoyl, carboxy or  
lower alkoxycarbonyl, and  
Z is halogen.

35

As to the starting compounds [II], [III], [Ia], [Ic] and [IV], some of them are novel and can be prepared by the procedures described in the Preparations and Examples mentioned later or a conventional manner.

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, preferably 1 to 4, carbon atom(s), unless otherwise indicated.

Suitable "lower alkyl" and "lower alkyl" moiety in the term of "mono(or di or tri)halo(lower)alkylsulfonyloxy" may include 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, in which more preferable one is C<sub>1</sub>-C<sub>4</sub> alkyl, and the most preferable one is methyl, ethyl, propyl or isobutyl.

Suitable "cyclo(lower)alkyl" may include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like, in which the preferred one is cyclo(C<sub>3</sub>-C<sub>6</sub>)alkyl and the most preferred one is cyclohexyl.

The term "lower alkenyl" means one having one or two double bond(s) in the straight or branched lower alkyl group as defined above.

Suitable "lower alkenyl" moiety in the terms of "carboxy(lower)alkenyl" and "(lower alkoxy-carbonyl)(lower)-alkenyl" may include one having 2 to 6 carbon atoms such as



vinyl, 1-propenyl, 2-propenyl, 1,3-butadienyl, 1-methylvinyl and the like, in which the preferred one is vinyl.

Suitable "lower alkoxy" and "lower alkoxy" moiety in the term of "lower alkoxy" may include methoxy, ethoxy, propoxy, isopropoxy, butoxy, iso-butoxy, t-butoxy, pentyloxy, t-pentyloxy, hexyloxy and the like, in which preferable one is C<sub>1</sub>-C<sub>4</sub> alkoxy, and the most preferable one is methoxy or ethoxy.

10

Suitable "lower alkanoyl" may include formyl, acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl, 2,2-dimethylpropanoyl, hexanoyl and the like, in which preferable one is C<sub>2</sub>-C<sub>4</sub> alkanoyl, and the most preferable one is formyl.

15

Suitable "halogen" may be fluoro, chloro, bromo and iodo, in which preferable one is fluoro or chloro.

Suitable "mono(or di or tri)halo(lower)alkyl" and "mono(or di or tri)halo(lower)alkyl" moiety in the term of "mono(or di or tri)halo(lower)alkylsulfonyloxy" may include chloromethyl, dichloromethyl, trichloromethyl, bromomethyl, dibromomethyl, tribromomethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 1 or 2-chloroethyl, 1 or 2-bromoethyl, 1 or 2-fluoroethyl, 1,1-difluoroethyl, 2,2-difluoroethyl and the like, in which more preferable one is mono(or di or tri)halo(C<sub>1</sub>-C<sub>4</sub>)alkyl, and the most preferable one is trifluoromethyl.

20

25

30

Suitable example of "amino protective group" moiety may be common amino protective group such as substituted or unsubstituted lower alkanoyl [e.g. formyl, acetyl, propionyl, trifluoroacetyl, etc.], phthaloyl, lower alkoxy carbonyl [e.g. tert-butoxycarbonyl, tert-amylloxycarbonyl, etc.],

35

substituted or unsubstituted aralkyloxycarbonyl [e.g. benzyloxycarbonyl, p-nitrobenzyloxycarbonyl, etc.], substituted or unsubstituted arenesulfonyl [e.g. benzenesulfonyl, tosyl, etc.], nitrophenylsulfenyl, ar(lower)alkyl [e.g. trityl, benzyl, etc.], and the like, in which preferable one is benzyl or tert-butoxycarbonyl.

Suitable salts of the object aminoalcohol derivative [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, citrate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc., an alkali metal salt [e.g. sodium salt, potassium salt, etc.] or the like.

The Processes 1 to 3 for preparing the object compounds of the present invention 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] with a compound [III] or a salt thereof.

Suitable salt of the compound [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.

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

#### Process 2

10       The object compound [Ib] or a salt thereof can be prepared by subjecting a compound [Ia] or a salt thereof to elimination reaction of the amino protective group.

Suitable salts of the compounds [Ia] and [Ib] may be the same as those exemplified for the compound [I].

15       This reaction can be carried out in a similar manner to that of Example 7 or 25 mentioned below.

#### Process 3

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

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

This reaction can be carried out in a similar manner to that of Example 22 or 24.

25

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.

30       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.

35       It is further to be noted that isomerization or

rearrangement of the object compound [I] 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 if also included within the scope of the present invention.

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

10

The object compound [I] or a salt thereof possesses gut 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 hyperanakisia 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 overactive bladder disorder, stress incontinence, urge incontinence, mixed incontinence, functional incontinence, overflow incontinence; 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 the treatment and/or prevention of neurogenetic inflammation; and for reducing a wasting condition, and the like.

5        Additionally,  $\beta_3$  adrenergic receptor agonists are known to lower triglyceride and cholesterol levels and to raise high density lipoprotein levels in mammals (US Patent No. 5,451,677). Accordingly, the object compound [I] is useful in the treatment and/or prevention of conditions such as  
10   hyper-triglyceridaemia, hypercholesterolaemia and in lowering high density lipoprotein levels as well as in the treatment of atherosclerotic and cardiovascular diseases and relates conditions.

15        Moreover, the object compound [I] is useful for inhibiting uterine contractions, preventing premature labor, and treating and preventing dysmenorrhea.

For therapeutic purpose, the compound (I) and a  
20   pharmaceutically acceptable salt thereof of the present invention can be used in a form of pharmaceutical preparation containing one of said compounds, as an active ingredient, in admixture with a pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid  
25   excipient suitable for oral, parenteral, external including topical, internal, intravenous, intramuscular, inhalant, nasal, intraarticular, intraspinal, transtracheal or transocular administration. The pharmaceutical preparations may be solid, semi-solid or solutions such as capsules,  
30   tablets, pellets, dragees, powders, granules, suppositories, ointments, creams, lotions, inhalants, injections, cataplasms, gels, tapes, eye drops, solution, syrups, aerosols, suspension, emulsion, or the like. If desired, there may be included in these preparations, auxiliary  
35   substances, stabilizing agents, wetting or emulsifying

agents, buffers and other commonly used additives.

While the dosage of the compound (I) will vary depending upon the age and condition of a patient, an average single dose of about 0.1 mg, 1 mg, 10 mg, 50 mg, 100 mg, 250 mg, 500 mg and 1000 mg of the compound (I) may be effective for treating diseases such as pollakiurea, urinary incontinence and the like. In general, amounts between 0.1 mg/body and about 1,000 mg/body may be administered per day.

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

15

#### Test

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

#### 20 Test Compound

- (1) [[4-[[4-[(2R)-2-[[ (2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]benzoyl]-(methyl)amino]acetic acid hydrochloride (the object compound of Example 25 mentioned below)

25

#### 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 catheter slowly withdrawn just past the first resistance that is felt at the bladder neck. Urine was completely drained out through the catheter, and 30 ml

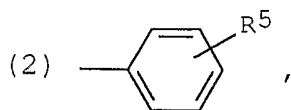
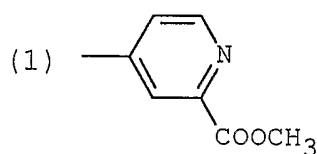
of biological saline was infused. The catheter was connected to pressure transducer, and intravesical pressure was continuously recorded. Intravenous administration of test compound (I) inhibited carbachol (1.8  $\mu\text{g/kg}$ )-induced increase in intravesical pressure (IVP).

### Test Results

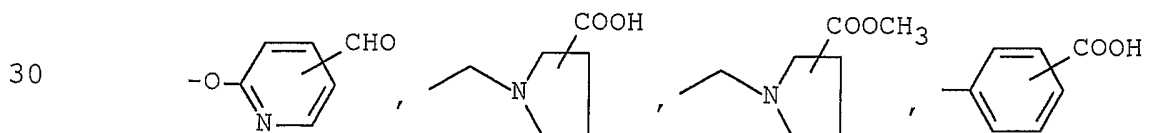
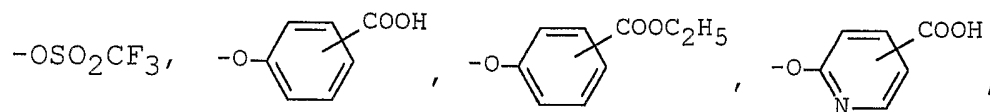
Treatment	% inhibition of carbachol-induced increase in IVP
Test Compound (1) (0.032 mg/kg)	80.8%

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

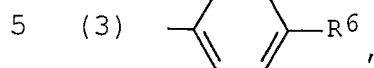
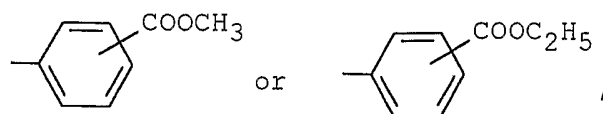
$R^1$  is hydrogen or chloride,  
 $R^2$  is hydrogen or benzyl,  
 $R^3$  is hydrogen or methyl,  
X is bond,  $-\text{CH}_2-$  or  $-\text{O}-$ , and  
Y is



in which  $R^5$  is  $-\text{CH}_2\text{COOH}$ ,  $-\text{CH}_2\text{COOC}_2\text{H}_5$ ,  $-\text{CHO}$ ,



15



in which  $R^6$  is  $-OH$ ,  $-COOH$ ,  $-COOC_2H_5$ ,

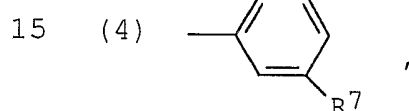
$-OCH_2COOH$  or  $-OCH_2COOC_2H_5$ ,

10 provided that (i) when  $R^6$  is  $-OH$ , then  $X$  is  $-CH_2-$ ,

(ii) when  $R^6$  is  $-COOH$ , then  $R^1$  is  $-H$ ,

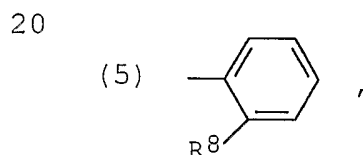
or

(iii) when  $R^6$  is  $-COOC_2H_5$ ,  $-OCH_2COOH$  or  
 $-OCH_2COOC_2H_5$ , then  $X$  is  $-O-$ ,



in which  $R^7$  is  $-OH$ ,  $-COOH$ ,  $-COOC_2H_5$ ,

$-OCH_2COOH$  or  $-OCH_2COOC_2H_5$ , and  $X$  is  $-CH_2-$ ,

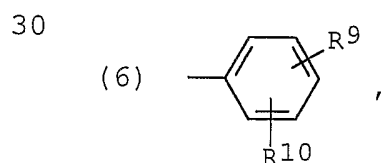



in which  $R^8$  is  $-OH$ ,  $-COOH$ ,  $-COOC_2H_5$ ,

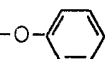
25  $-OCH_2COOH$  or  $-OCH_2COOC_2H_5$ ,

provided that when  $R^8$  is  $-OH$ ,

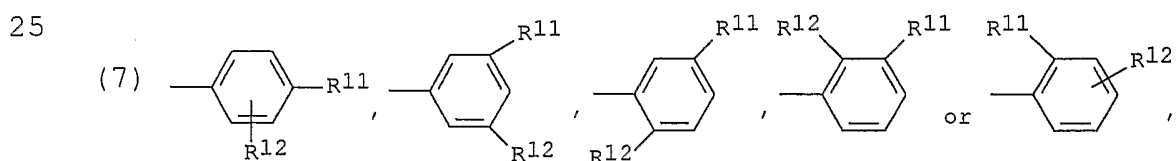
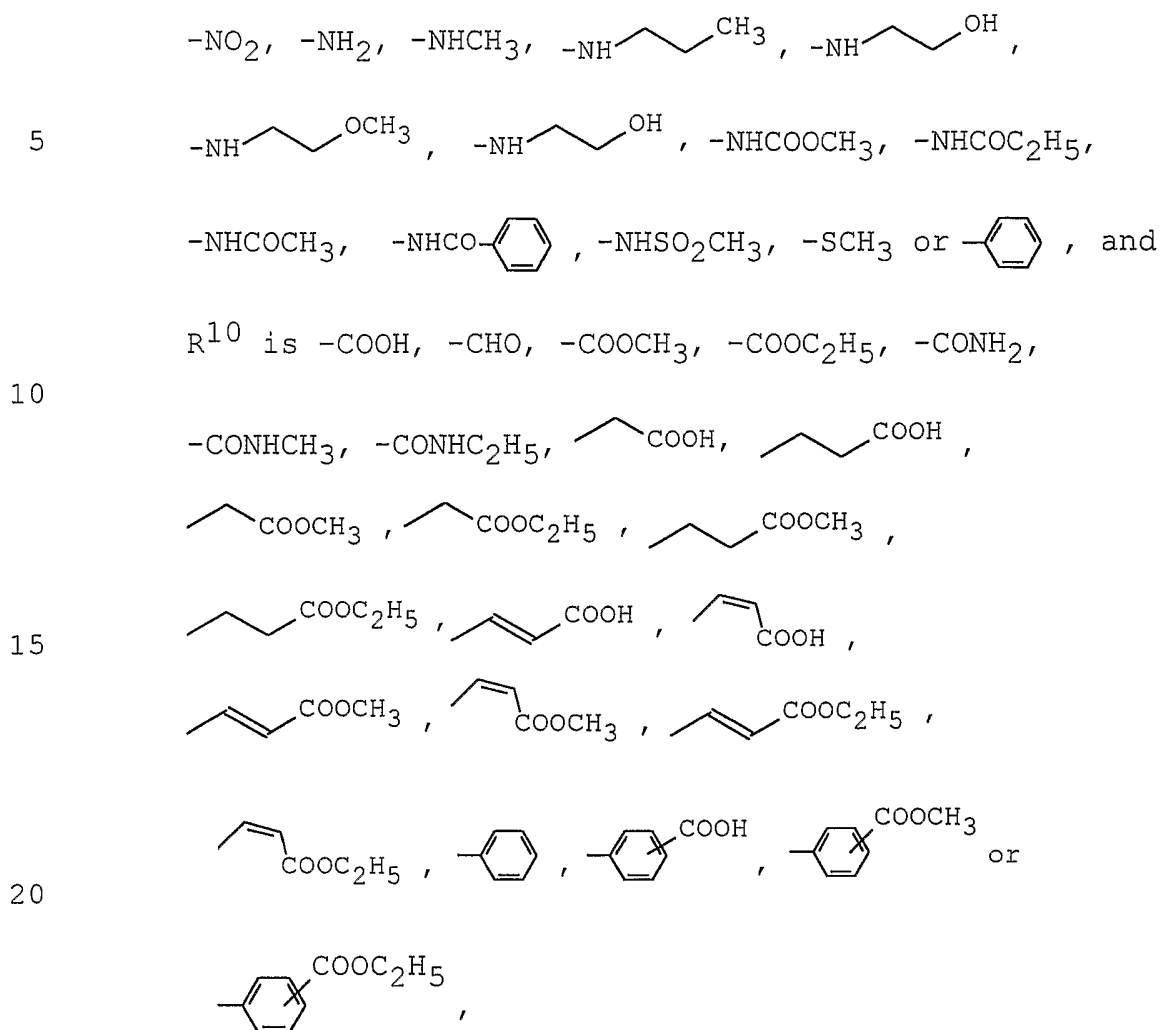
$-OCH_2COOH$  or  $-OCH_2COOC_2H_5$ ,  
then  $R^3$  is  $-CH_3$ ,



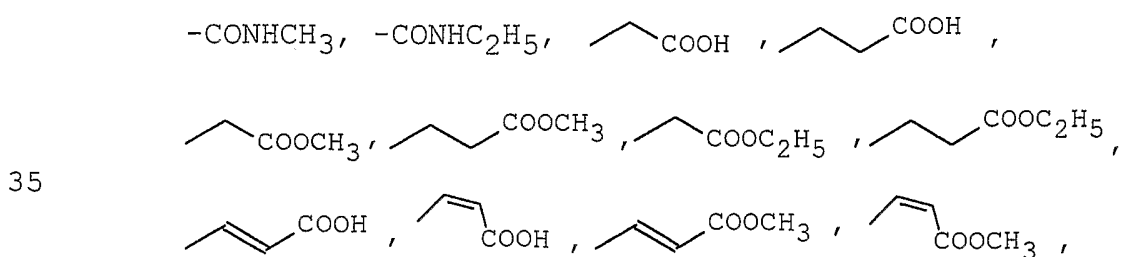
in which  $R^9$  is  $-OH$ , ,  $-CF_3$ ,  $-OCH_2CH_2OH$ ,

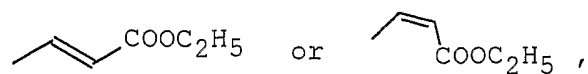
35  $-OCH_2OCH_3$ ,  $-OCH_2COOH$ ,  $-OCH_2COOC_2H_5$ ,  $-O$ -,



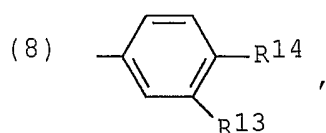


in which  $\text{R}^{11}$  is  $-\text{F}$ ,  $-\text{Cl}$  or  $-\text{CH}_3$ , and  
 30  $\text{R}^{12}$  is  $-\text{COOH}$ ,  $-\text{CHO}$ ,  $-\text{COOCH}_3$ ,  $-\text{COOC}_2\text{H}_5$ ,  $-\text{CONH}_2$ ,



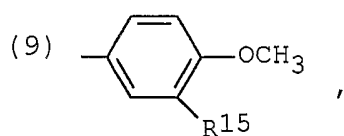


5



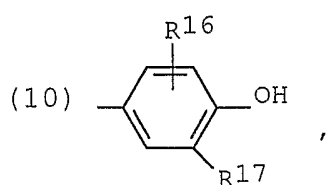
in which  $R^{13}$  is  $-Cl$  or  $-CH_3$ ,  
 10  $R^{14}$  is  $-COOH$  or  $-COOC_2H_5$ , and  
 $X$  is  $-CH_2-$ ,

15



20

in which  $R^{15}$  is  $-COOH$  or  $-COOC_2H_5$ , and  
 $X$  is  $-CH_2-$ , or



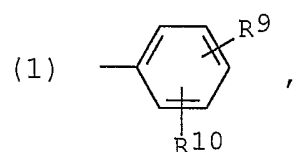
25

in which  $R^{16}$  is  $-CH_3$  or  $-OCH_3$ , and  
 $R^{17}$  is  $-COOH$ ,  $-COOCH_3$  or  $-COOC_2H_5$ .


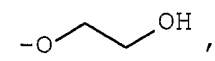
More preferred embodiments of the object compound [I]  
 are as follows:

30

$Y$  is



35

in which  $R^9$  is  $-OH$ ,  ,  $-CF_3$ ,  ,

18

$-OCH_2OCH_3$ ,  $-OCH_2COOH$ ,  $-OCH_2COOC_2H_5$ ,  $-O-C_6H_5$ ,  
 $-NO_2$ ,  $-NH_2$ ,  $-NHCH_3$ ,  $-NHCH_2CH_2CH_3$ ,  $-NHCH_2CH_2OH$ ,  
 $-NHCH_2CH_2OCH_3$ ,  $-NHCH_2CH_2OH$ ,  $-NHCOOCH_3$ ,  $-NHCOC_2H_5$ ,  
 $-NHCOCH_3$ ,  $-NHCO-C_6H_5$ ,  $-NHSO_2CH_3$ ,  $-SCH_3$  or  $-C_6H_5$ , and

$R^{10}$  is  $-COOH$ ,  $-CHO$ ,  $-COOCH_3$ ,  $-COOC_2H_5$ ,  $-CONH_2$ ,

$-CONHCH_3$ ,  $-CONHC_2H_5$ ,  $-CH_2CH_2COOH$ ,  $-CH_2CH_2CH_2COOH$ ,

$-CH_2CH_2COOCH_3$ ,  $-CH_2CH_2COOC_2H_5$ ,  $-CH_2CH_2CH_2COOCH_3$ ,

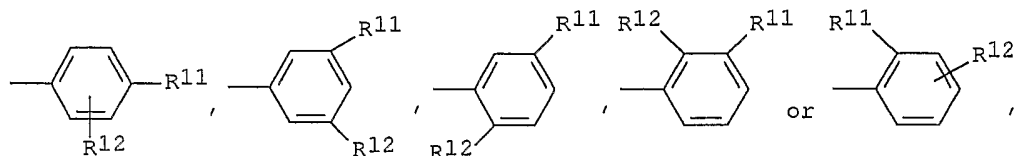
$-CH_2CH_2CH_2COOC_2H_5$ ,  $-CH=CHCOOH$ ,  $-CH=CHCOOH$ ,

$-CH=CHCOOCH_3$ ,  $-CH=CHCOOCH_3$ ,  $-CH=CHCOOC_2H_5$ ,

$-CH=CHCOOC_2H_5$ ,  $-C_6H_5$ ,  $-C_6H_4COOH$ ,  $-C_6H_4COOCH_3$  or

$-C_6H_4COOC_2H_5$ , or

(2)



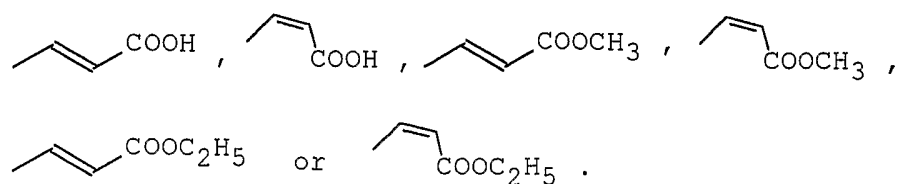
in which  $R^{11}$  is  $-F$ ,  $-Cl$  or  $-CH_3$ , and

$R^{12}$  is  $-COOH$ ,  $-CHO$ ,  $-COOCH_3$ ,  $-COOC_2H_5$ ,  $-CONH_2$ ,

$-CONHCH_3$ ,  $-CONHC_2H_5$ ,  $-CH_2CH_2COOH$ ,  $-CH_2CH_2CH_2COOH$ ,

$-CH_2CH_2COOCH_3$ ,  $-CH_2CH_2CH_2COOCH_3$ ,  $-CH_2CH_2COOC_2H_5$ ,  $-CH_2CH_2CH_2COOC_2H_5$ ,

19

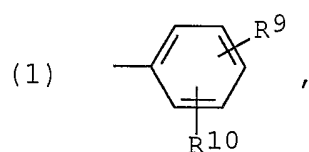


5

And, more preferred embodiments of the object compound [I] are as follows:

Y is

10



in which  $R^9$  is  $-\text{OH}$ ,  $-\text{OCH}_2\text{CH}_2\text{OH}$ ,  $-\text{OCH}_2\text{OCH}_3$ ,

15

$-\text{OCH}_2\text{COOH}$ ,  $-\text{OCH}_2\text{COOC}_2\text{H}_5$ ,  $-\text{O}-\text{C}_6\text{H}_5$ ,

$-\text{NH}_2$ ,  $-\text{NHCH}_3$ ,  $-\text{NHCH}_2\text{CH}_2\text{CH}_3$ ,  $-\text{NHCH}_2\text{CH}_2\text{OH}$ ,

20

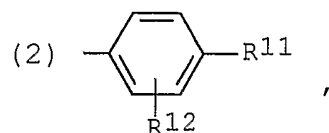
$-\text{NHCH}_2\text{CH}_2\text{OCH}_3$ ,  $-\text{NHCH}_2\text{CH}_2\text{OH}$ ,  $-\text{NHCOOCH}_3$ ,  $-\text{NHCOC}_2\text{H}_5$ ,

$-\text{NHCOCH}_3$ ,  $-\text{NHCO}-\text{C}_6\text{H}_5$ ,  $-\text{NHSO}_2\text{CH}_3$  or  $-\text{C}_6\text{H}_5$ , and

$R^{10}$  is  $-\text{COOH}$ ,  $-\text{COOCH}_3$ ,  $-\text{COOC}_2\text{H}_5$ ,  $-\text{CONH}_2$ ,

25

$-\text{CONHCH}_3$ ,  $-\text{CONHC}_2\text{H}_5$ ,  $\text{CH}_3\text{CH}=\text{CHCOOH}$  or  $\text{CH}_3\text{CH}=\text{CHCOOH}$ , or

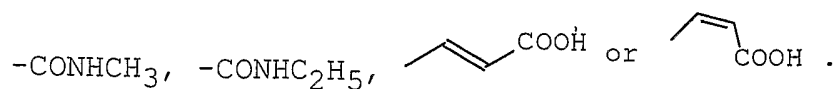


30

in which  $R^{11}$  is  $-\text{CH}_3$ , and

$R^{12}$  is  $-\text{COOH}$ ,  $-\text{COOCH}_3$ ,  $-\text{COOC}_2\text{H}_5$ ,  $-\text{CONH}_2$ ,

35



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

Preparation 1 .

Under nitrogen, to a mixture of 2-phenylethanamine (40 g) and triethylamine (59.8 ml) in tetrahydrofuran (250 ml)  
10 was added trifluoromethanesulfonic anhydride (51.3 ml) dropwise under ice-water cooling, and the mixture was stirred at the same temperature for 1 hour. The resulting mixture was poured into saturated aqueous sodium bicarbonate and the aqueous mixture was extracted with ethyl acetate.  
15 The organic layer was dried over anhydrous magnesium sulfate, evaporated under reduced pressure and dried in vacuo to give 2,2,2-trifluoro-N-(2-phenylethyl)acetamide (67.73 g).

NMR (CHCl<sub>3</sub>,  $\delta$ ): 2.89 (2H, t, J=7Hz), 3.64 (2H, q, J=7Hz), 7.20-7.40 (5H, m)

20

Preparation 2

The following compound was obtained according to a similar manner to that of Preparation 48.

25 (R)-[2-[(Trifluoroacetyl)amino]propyl]benzenesulfonyl chloride

NMR (DMSO-d<sub>6</sub>,  $\delta$ ): 2.83 (2H, t, J=7Hz), 3.40 (2H, q, J=7Hz), 7.10-7.20 (2H, m), 7.40-7.60 (2H, m)

30 Preparation 3

Under nitrogen atmosphere, to a suspension of zinc powder (2.29 g) in 1,2-dichloroethane (10 ml) was added dichlorodimethylsilane (4.3 ml). The mixture was heated to 55°C whereupon a solution of 4-[2-[(trifluoroacetyl)amino]-  
35 ethyl]benzenesulfonyl chloride (3.15 g) and 1,3-dimethyl-2-

imidazolidinone (3.3 ml) in 1,2-dichloroethane (10 ml) was added dropwise while keeping the temperature below 75°C. The mixture was stirred at 70°C for 1.5 hours and allowed to cool to room temperature. Methanol (5 ml) was added to the mixture and the mixture was stirred at room temperature for 30 minutes. 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 2,2,2-trifluoro-N-[2-(4-mercaptophenyl)ethyl]acetamide (1.48 g) as a white powder.

NMR (CDCl<sub>3</sub>, δ): 2.84 (2H, t, J=7Hz), 3.44 (1H, s), 3.59 (2H, q, J=7Hz), 6.27 (1H, br s), 7.06 (2H, d, J=8Hz), 7.25 (2H, d, J=8Hz)  
(+)ESI-MS (m/z): 272 (M+Na)<sup>+</sup>

#### Preparation 4

Under nitrogen at room temperature, to a solution of 2,2,2-trifluoro-N-[2-(4-mercaptophenyl)ethyl]acetamide (1.0 g) in N,N-dimethylformamide (20 ml) were added 4-chloro-2-pyridinecarboxylic acid (695 mg) and potassium carbonate (1.22 g), and the mixture was stirred at 100°C for 26 hours. The mixture was cooled to room temperature, and iodoethane (0.355 ml) was added. After being stirred at the same temperature for 12 hours, the resulting mixture was poured into saturated aqueous sodium bicarbonate and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed successively with water two times and 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 1:2) to give ethyl 4-[[2-[2-[(trifluoroacetyl)amino]ethyl]-phenyl]thio]-2-pyridinecarboxylate (713 mg).

NMR (CDCl<sub>3</sub>, δ): 1.41 (3H, t, J=7.1Hz), 2.97 (2H, t,

J=7.1Hz), 3.6-3.7 (2H, m), 4.43 (2H, q, J=7.1Hz),  
7.0-7.05 (1H, m), 7.31 (2H, d, J=8.1Hz), 7.53 (2H,  
d, J=8.1Hz), 7.76 (1H, d, J=1.9Hz), 8.44 (1H, d,  
J=5.4Hz)

5 (+)ESI-MS (m/z): 399 (M+H)<sup>+</sup>

#### Preparation 5

To a solution of ethyl 4-[[4-[2-[(trifluoroacetyl)-  
amino]ethyl]phenyl]thio]-2-pyridinecarboxylate (631 mg) in a  
10 mixture of ethanol (6.3 ml) and methanol (10 ml) was added  
1N sodium hydroxide at room temperature, and the mixture was  
stirred at the same temperature overnight. To the resulting  
mixture was added 1N hydrochloric acid (6.3 ml) and the  
mixture was evaporated under reduced pressure. Under  
15 nitrogen, the mixture of the obtained product and a reagent  
of 10-20% hydrogen chloride in methanol (20 ml) was refluxed  
for 24 hours. After evaporation, to a mixture of the  
residue in a mixture of tetrahydrofuran (5 ml) and water (5  
ml) was added a solution of di-tert-butyl dicarbonate (691  
20 mg) in tetrahydrofuran (3 ml) with adjusting pH to around 8  
by 5N sodium hydroxide at room temperature. After being  
stirred at the same temperature for 1.5 hours, to the  
resulting mixture was added ethyl acetate followed by  
separation. The organic layer was washed with brine, dried  
25 over anhydrous magnesium sulfate and evaporated under  
reduced pressure. The residue was purified by column  
chromatography on silica gel (hexane/ethyl acetate = 1:1 to  
1:5) to give methyl 4-[[4-[2-[(tert-butoxycarbonyl)amino]-  
ethyl]phenyl]thio]-2-pyridinecarboxylate (470 mg).

30 NMR (CDCl<sub>3</sub>, δ): 1.44 (9H, s), 2.87 (2H, t, J=7.0Hz),  
3.35-3.5 (2H, m), 3.97 (3H, s), 7.0-7.05 (1H, m),  
7.32 (2H, d, J=8.1Hz), 7.50 (2H, d, J=8.1Hz), 7.82  
(1H, d, J=1.9Hz), 8.44 (1H, d, J=5.2Hz)

(+)ESI-MS (m/z): 411 (M+Na)<sup>+</sup>

Preparation 6

Under nitrogen at 5°C, to a solution of methyl 4-[[4-[2-  
[(tert-butoxycarbonyl)amino]ethyl]phenyl]thio]-2-  
pyridinecarboxylate (461 mg) in dichloromethane (10 ml) was  
5 added m-chloroperoxybenzoic acid (655 mg), and the mixture  
was stirred at room temperature for 3.5 hours. The  
resulting mixture was poured into aqueous sodium thiosulfate  
and the aqueous mixture was extracted with ethyl acetate.  
The organic layer was washed successively with saturated  
10 aqueous sodium bicarbonate two times and brine, dried over  
anhydrous magnesium sulfate, evaporated under reduced  
pressure and dried in vacuo to give methyl 4-[[4-[2-[(tert-  
butoxycarbonyl)amino]ethyl]phenyl]sulfonyl]-2-  
pyridinecarboxylate (514 mg).

15 NMR (CDCl<sub>3</sub>, δ): 1.39 (9H, s), 2.88 (2H, d, J=6.9Hz),  
3.3-3.45 (2H, m), 4.04 (3H, s), 7.40 (2H, d,  
J=8.3Hz), 7.85-8.0 (3H, m), 8.54 (1H, m), 8.95 (1H,  
d, J=5.1Hz)  
(+)ESI-MS (m/z): 443 (M+Na)<sup>+</sup>

20

Preparation 7

Under nitrogen at room temperature, a solution of  
methyl 4-[[4-[2-[(tert-butoxycarbonyl)amino]ethyl]phenyl]-  
sulfonyl]-2-pyridinecarboxylate (500 mg) and hydrogen  
25 chloride (4N in ethyl acetate, 4 ml) in ethyl acetate (4 ml)  
was stirred for 3 hours. The resulting mixture was  
evaporated under reduced pressure. The residue was  
dissolved into a mixture of saturated aqueous sodium  
bicarbonate and chloroform. After separation, the organic  
30 layer was dried over anhydrous magnesium sulfate, evaporated  
under reduced pressure and dried in vacuo to give methyl 4-  
[[4-(2-aminoethyl)phenyl]sulfonyl]-2-pyridinecarboxylate (346  
mg).

35 NMR (DMSO-d<sub>6</sub>, δ): 2.6-2.85 (4H, m), 3.8-3.9 (3H, m),  
7.05-7.2 (2H, m), 7.35-7.5 (2H, m), 7.75-8.2 (3H,



m)

(+)ESI-MS (m/z): 321 (M+H)<sup>+</sup>Preparation 8

5 The following compound was obtained according to a similar manner to that of Preparation 44.

N-[2-[4-[(3,4-Dihydroxyphenyl)sulfonyl]phenyl]ethyl]-2,2,2-trifluoroacetamide

10 NMR (DMSO-d<sub>6</sub>, δ): 2.86 (2H, t, J=7.0Hz), 3.2-3.5 (2H, m), 6.89 (1H, d, J=8.4Hz), 7.2-7.3 (2H, m), 7.42 (2H, d, J=8.3Hz), 7.78 (2H, d, J=8.3Hz)

(+)ESI-MS (m/z): 412 (M+Na)<sup>+</sup>

15 Preparation 9

Under nitrogen at 5°C, to a solution of N-[2-[4-[(3,4-dihydroxyphenyl)sulfonyl]phenyl]ethyl]-2,2,2-trifluoroacetamide (8.68 g) in N,N-dimethylformamide (86 ml) were added potassium carbonate (3.39 g) and benzyl bromide (2.92 ml), and the mixture was stirred at room temperature for 36 hours. The resulting mixture was poured into 1N hydrochloric acid and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed successively with water two times and brine, 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 4:3) to give N-[2-[4-[(benzyloxy)-3-hydroxyphenyl]sulfonyl]phenyl]ethyl]-2,2,2-trifluoroacetamide (4.38 g).

30 NMR (CDCl<sub>3</sub>, δ): 2.93 (2H, t, J=7.1Hz), 3.5-3.7 (2H, m), 5.15 (2H, s), 6.95-7.1 (1H, m), 7.2-7.6 (9H, m), 7.8-7.9 (2H, m)

(+)ESI-MS (m/z): 502 (M+Na)<sup>+</sup>

35 Preparation 10

Under nitrogen at 5°C, to a solution of N-[2-[4-[[4-(benzyloxy)-3-hydroxyphenyl]sulfonyl]phenyl]ethyl]-2,2,2-trifluoroacetamide (1.68 g) and 2,6-lutidine (0.527 ml) in dichloromethane (50 ml) was added trifluoromethanesulfonic anhydride (0.648 ml), and the mixture was stirred at the same temperature for 1 hour. The resulting mixture was poured into aqueous ammonia and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed successively with 1N hydrochloric acid, water, saturated aqueous sodium bicarbonate and brine, 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 4:3) to give 2-(benzyloxy)-5-[[4-[2-[(trifluoroacetyl)amino]ethyl]phenyl]-sulfonyl]phenyl trifluoromethanesulfonate (1.59 g).

NMR (CDCl<sub>3</sub>, δ): 2.9-3.0 (2H, m), 3.55-3.7 (2H, m), 5.23 (2H, s), 7.15 (1H, d, J=8.7Hz), 7.3-7.45 (7H, m), 7.75-7.9 (4H, m)

(+)ESI-MS (m/z): 634 (M+Na)<sup>+</sup>

#### Preparation 11

Under nitrogen at room temperature, to a solution of 2-(benzyloxy)-5-[[4-[2-[(trifluoroacetyl)amino]ethyl]phenyl]-sulfonyl]phenyl trifluoromethanesulfonate (1.58 g) in N,N-dimethylformamide (12 ml) were added palladium(II) acetate (29 mg), 1,3-bis(diphenylphosphino)propane (53 mg), ethanol (6 ml) and triethylamine (1.08 ml), and under carbon monoxide (1 atm), the mixture was stirred at 60°C for 2 hours. The resulting mixture was poured into water and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed successively with water two times and brine, 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 4:3) to give ethyl 2-(benzyloxy)-5-[[4-[2-

[(trifluoroacetyl)amino]ethyl]phenyl]sulfonyl]benzoate (959 mg).

NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.34 (3H, t, J=7.1Hz), 2.85-3.0 (2H, m),  
3.5-3.65 (2H, m), 4.37 (2H, q, J=7.1Hz), 5.22 (2H,  
5 s), 7.10 (1H, d, J=8.9Hz), 7.25-7.5 (5H, m), 7.85-  
7.9 (2H, m), 7.99 (1H, dd, J=2.5, 8.7Hz), 8.33 (1H,  
d, J=2.5Hz)

(+)ESI-MS (m/z): 558 (M+Na)<sup>+</sup>

#### 10 Preparation 12

Under nitrogen at 5°C, to a solution of ethyl 2-(benzyloxy)-5-[[4-[2-[(trifluoroacetyl)amino]ethyl]phenyl]-sulfonyl]benzoate (957 mg) in N,N-dimethylformamide (15 ml) was added sodium hydride (60% in oil, 78.6 mg), and the  
15 mixture was stirred at room temperature for 30 minutes. The mixture was cooled to 5°C, and benzyl bromide (0.234 ml) was added. After being stirred at room temperature overnight, the resulting mixture was poured into water and the aqueous mixture was extracted with ethyl acetate. The organic layer  
20 was washed successively with water two times and brine, 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 give ethyl 2-(benzyloxy)-5-[[4-[2-[benzyl(trifluoroacetyl)-  
25 amino]ethyl]phenyl]sulfonyl]benzoate (965 mg).

NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.33 (3H, t, J=7.1Hz), 2.75-2.95 (2H, m), 3.4-3.55 (2H, m), 4.36 (2H, q, J=7.1Hz), 4.45-4.70 (2H, m), 5.20 (2H, s), 7.07 (1H, d, J=8.9Hz), 7.1-7.5 (12H, m), 7.8-8.0 (3H, m), 8.32 (1H, d,  
30 J=2.4Hz)

(+)ESI-MS (m/z): 648 (M+Na)<sup>+</sup>

#### Preparation 13

A mixture of ethyl 2-(benzyloxy)-5-[[4-[2-[benzyl(trifluoroacetyl)amino]ethyl]phenyl]sulfonyl]benzoate  
35

(963 mg) and 10% palladium on activated carbon (50% wet, 100 mg) in ethanol (15 ml) was stirred at room temperature in the presence of hydrogen at an atmospheric pressure for 3 hours. After filtration, the filtrate was evaporated under reduced pressure followed by dryness in vacuo to give ethyl 5-[[4-[2-[benzyl(trifluoroacetyl)amino]ethyl]phenyl]-sulfonyl]-2-hydroxybenzoate (848 mg).

NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.45 (3H, t, J=7.1Hz), 2.75-2.95 (2H, m), 3.4-3.55 (2H, m), 4.4-4.7 (3H, m), 7.05 (1H, d, J=8.9Hz), 7.1-7.45 (7H, m), 7.8-7.95 (3H, m), 8.47 (1H, d, J=2.4Hz)

(+)ESI-MS (m/z): 558 (M+Na)<sup>+</sup>

#### Preparation 14

Under nitrogen, the mixture of ethyl 5-[[4-[2-[benzyl(trifluoroacetyl)amino]ethyl]phenyl]sulfonyl]-2-hydroxybenzoate (845 mg) and hydrogen chloride (7N in ethanol, 6 ml) in ethanol (3 ml) was refluxed for 2.5 days. The resulting mixture was evaporated under reduced pressure. The residue was dissolved into a mixture of saturated aqueous sodium bicarbonate and chloroform/methanol (10:1). After separation, the organic layer was washed with brine, dried over anhydrous magnesium sulfate, evaporated under reduced pressure and dried in vacuo to give ethyl 5-[[4-[2-(benzylamino)ethyl]phenyl]sulfonyl]-2-hydroxybenzoate (630 mg).

NMR (DMSO-d<sub>6</sub>,  $\delta$ ): 1.33 (3H, t, J=7.1Hz), 2.65-2.9 (4H, m), 3.71 (2H, s), 4.35 (2H, q, J=7.1Hz), 7.09 (1H, d, J=8.8Hz), 7.15-7.3 (5H, m), 7.44 (2H, d, J=8.3Hz), 7.82 (2H, d, J=8.3Hz), 7.95 (1H, dd, J=2.5, 8.8Hz), 8.20 (1H, d, J=2.5Hz)

(+)ESI-MS (m/z): 440 (M+H)<sup>+</sup>

#### Preparation 15

Under nitrogen at room temperature, to a solution of N-

[2-[4-[[4-(benzyloxy)-3-hydroxyphenyl]sulfonyl]phenyl]ethyl]-2,2,2-trifluoroacetamide (1.0 g) in N,N-dimethylformamide (10 ml) were added potassium carbonate (346 mg) and chloromethyl methyl ether (0.339 ml), and the mixture was stirred at the same temperature overnight. The resulting mixture was poured into water and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed successively with water two times and brine, dried over anhydrous magnesium sulfate, evaporated under reduced pressure and dried in vacuo to give N-[2-[4-[[4-(benzyloxy)-3-(methoxymethoxy)phenyl]sulfonyl]phenyl]ethyl]-2,2,2-trifluoroacetamide (1.1 g).

NMR (CDCl<sub>3</sub>,  $\delta$ ): 2.85-3.0 (2H, m), 3.45-3.7 (5H, m), 5.15-5.3 (4H, m), 6.97 (1H, d, J=8.6Hz), 7.2-7.9 (11H, m)  
(+)ESI-MS (m/z): 546 (M+Na)<sup>+</sup>

#### Preparation 16

The following compounds were obtained according to a similar manner to that of Preparation 13.

(1) 2,2,2-Trifluoro-N-[2-[4-[[4-hydroxy-3-(methoxymethoxy)phenyl]sulfonyl]phenyl]ethyl]acetamide  
NMR (CDCl<sub>3</sub>,  $\delta$ ): 2.85-3.0 (3H, m), 3.45-3.65 (5H, m), 5.2 (2H, m), 7.02 (1H, d, J=8.4Hz), 7.31 (2H, d, J=8.2Hz), 7.45-7.65 (2H, m), 7.87 (2H, d, J=8.2Hz)  
(-)ESI-MS (m/z): 432 (M-H)<sup>-</sup>

(2) Ethyl (R)-4'-[[4-[2-(trifluoroacetyl)amino]propyl]phenyl]sulfonyl]-1,1'-biphenyl-3-carboxylate  
NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.22 (3H, d, J=6.5Hz), 1.41 (3H, q, J=7.1Hz), 2.75-3.1 (2H, m), 4.15-4.5 (3H, m), 7.2-7.4 (2H, m), 7.54 (1H, t, J=7.7Hz), 7.65-8.15 (5H, m), 8.24 (1H, s)  
(+)ESI-MS (m/z): 542 (M+Na)<sup>+</sup>

(3) Ethyl 5-[[4-[3-[benzyl(trifluoroacetyl)amino]propyl]-phenyl]sulfonyl]-2-hydroxybenzoate

NMR (CDCl<sub>3</sub>, δ): 1.45 (3H, t, J=7Hz), 1.68-2.02 (2H, m),  
5 2.60 (2H, t, J=7Hz), 3.30 (2H, t, J=7Hz), 4.46 (2H, q, J=7Hz), 4.57, 4.61 (2H, a pair of s), 6.95-7.45 (9H, m), 7.83 (2H, m), 7.92 (1H, dd, J=9, 2Hz), 8.48 (1H, d, J=2Hz), 11.41 (1H, s, OH)  
(+)ESI-MS (m/z): 572 (M+Na)<sup>+</sup>

10

(4) 2,2,2-Trifluoro-N-[3-[4-[[4-hydroxy-3-(methoxymethoxy)phenyl]sulfonyl]phenyl]propyl]acetamide

NMR (CDCl<sub>3</sub>, δ): 1.92 (2H, quintet, J=7Hz), 2.72 (2H, t, J=7Hz), 3.38 (2H, q, J=7Hz), 3.52 (3H, s), 5.24  
15 (2H, s), 6.33 (1H, br s), 6.43 (1H, s, OH), 7.03 (1H, d, J=9Hz), 7.29 (2H, d, J=8Hz), 7.55 (1H, dd, J=9, 2Hz), 7.66 (1H, d, J=2Hz), 7.83 (2H, d, J=8Hz)

(+)ESI-MS (m/z): 470 (M+Na)<sup>+</sup>

20

(5) Methyl 5-[[4-2-benzyl(trifluoroacetyl)amino]ethoxy]-phenyl]sulfonyl]-2-hydroxybenzoate

NMR (CDCl<sub>3</sub>, δ): 3.60-3.85 (2H, m), 4.00 (3H, s), 4.04-4.25 (2H, m), 4.77, 4.81 (total 2H, a pair of s),  
25 6.92 (2H, d, J=9Hz), 7.06 (1H, d, J=9Hz), 7.12-7.50 (5H, m), 7.85 (2H, d, J=8Hz), 7.93 (1H, dd, J=9, 2Hz), 8.46 (1H, d, J=2Hz), 11.25 (1H, br s, OH)

(+)ESI-MS (m/z): 560 (M+Na)<sup>+</sup>

30

#### Preparation 17

The following compounds were obtained according to a similar manner to that of Preparation 10.

35 (1) 2-(Methoxymethoxy)-4-[[4-[2-[(trifluoroacetyl)amino]-

ethyl]phenyl]sulfonyl]phenyl trifluoromethanesulfonate

NMR (CDCl<sub>3</sub>, δ): 2.9-3.05 (2H, m), 3.5 (3H, m), 3.55-3.7  
(2H, m), 5.30 (2H, s), 7.3-7.45 (3H, m), 7.60 (1H,  
dd, J=2.0, 8.5Hz), 7.8-7.95 (3H, m)

5 (+)ESI-MS (m/z): 588 (M+Na)<sup>+</sup>

(2) 2-Methyl-4-[[4-[3-[(trifluoroacetyl)amino]propyl]-  
phenyl]sulfonyl]phenyl trifluoromethanesulfonate

10 NMR (CDCl<sub>3</sub>, δ): 1.8-2.1 (2H, m), 2.43 (3H, s), 2.65-2.8  
(2H, m), 3.35-3.5 (2H, m), 7.3-7.4 (3H, m), 7.8-  
7.95 (4H, m)

(+)ESI-MS (m/z): 556 (M+Na)<sup>+</sup>

15 (3) tert-Butyl [4-[[[(trifluoromethyl)sulfonyl]oxy]phenyl]-  
acetate

NMR (CDCl<sub>3</sub>, δ): 1.44 (9H, s), 3.55 (2H, s), 7.2-7.4 (4H,  
m)

(+)ESI-MS (m/z): 363 (M+Na)<sup>+</sup>

20 (4) (R)-2-Chloro-4-[[4-[2-(trifluoroacetyl)amino]propyl]-  
phenyl]sulfonyl]phenyl trifluoromethanesulfonate

25 NMR (CDCl<sub>3</sub>, δ): 1.24 (3H, d, J=6.8Hz), 2.87 (1H, dd,  
J=7.3, 13.5Hz), 3.00 (1H, dd, J=6.2, 13.5Hz), 4.28  
(1H, heptuplet, J=7.0Hz), 6.13 (1H, d, J=7.6Hz),  
7.38 (2H, d, J=8.4Hz), 7.49 (1H, d, J=8.7Hz),  
7.87-7.92 (3H, m), 8.09 (1H, d, J=2.2Hz)

(+)APCI-MS (m/z): 576 (M+Na)<sup>+</sup>

30 (5) (R)-3-[[4-[2-[(2,2,2-Trifluoroacetyl)amino]propyl]-  
phenyl]sulfonyl]phenyl trifluoromethanesulfonate

NMR (CDCl<sub>3</sub>, δ): 1.22 (3H, d, J=6.8Hz), 2.8-3.05 (2H, m),  
4.15-4.4 (1H, m), 7.36 (2H, d, J=8.3Hz), 7.45-7.5  
(1H, m), 7.63 (1H, t, J=8.2Hz), 7.8-8.0 (4H, m)

(+)ESI-MS (m/z): 542 (M+Na)<sup>+</sup>

- (6) 2-Benzyloxy-5-[[4-[3-[(trifluoroacetyl)amino]propyl]-phenyl]sulfonyl]phenyl trifluoromethanesulfonate  
NMR (CDCl<sub>3</sub>, δ): 1.93 (2H, quintet, J=7Hz), 2.73 (2H, t, J=7Hz), 3.39 (2H, q, J=7Hz), 5.23 (2H, s), 6.29 (1H, br s), 7.08-7.50 (9H, m), 7.75-7.93 (3H, m)  
(+)ESI-MS (m/z): 648 (M+Na)<sup>+</sup>
- (7) 2-Methoxymethoxy-4-[[4-[3-[(trifluoroacetyl)amino]-propyl]phenyl]sulfonyl]phenyl trifluoromethanesulfonate  
NMR (CDCl<sub>3</sub>, δ): 1.94 (2H, quintet, J=7Hz), 2.75 (2H, t, J=7Hz), 3.40 (2H, q, J=7Hz), 3.51 (3H, s), 5.30 (2H, s), 6.31 (1H, br s), 6.95 (1H, d, J=8Hz), 7.33 (2H, d, J=8Hz), 7.60 (1H, dd, J=8, 2Hz), 7.86 (1H, d, J=2Hz), 7.88 (2H, d, J=8Hz)  
(+)ESI-MS (m/z): 602 (M+H)<sup>+</sup>
- (8) 2-Chloro-4-[[4-[3-[(trifluoroacetyl)amino]propyl]-phenyl]sulfonyl]phenyl trifluoromethanesulfonate  
NMR (CDCl<sub>3</sub>, δ): 1.95 (2H, quintet, J=7Hz), 2.76 (2H, t, J=7Hz), 3.40 (2H, q, J=7Hz), 6.31 (1H, br s), 7.38 (2H, d, J=8Hz), 7.49 (1H, d, J=9Hz), 7.88 (2H, d, J=8Hz), 7.91 (1H, dd, J=9, 2Hz), 8.09 (1H, d, J=2Hz)  
(+)ESI-MS (m/z): 576 (M+H)<sup>+</sup>

#### Preparation 18

The following compounds were obtained according to a similar manner to that of Preparation 11.

- (1) Ethyl 2-(methoxymethoxy)-4-[[4-[2-[(trifluoroacetyl)amino]ethyl]phenyl]sulfonyl]benzoate  
NMR (CDCl<sub>3</sub>, δ): 1.36 (3H, t, J=7.1Hz), 2.96 (2H, t, J=7.1Hz), 3.50 (3H, s), 3.55-3.7 (2H, m), 4.36 (2H, q, J=7.1Hz), 5.28 (2H, s), 7.35 (2H, d, J=8.3Hz), 7.57 (1H, dd, J=1.5, 8.1Hz), 7.75 (1H, d, J=1.5Hz),



7.80 (1H, d, J=8.1Hz), 7.85-7.95 (2H, m)

(+)ESI-MS (m/z): 512 (M+Na)<sup>+</sup>

- (2) Ethyl 2-methyl-4-[[4-[3-[(trifluoroacetyl)amino]-  
propyl]phenyl]sulfonyl]benzoate

NMR (CDCl<sub>3</sub>, δ): 1.30 (3H, t, J=7.1Hz), 1.7-1.9 (2H, m),  
2.55 (3H, m), 2.6-2.75 (2H, m), 3.1-3.25 (2H, m),  
4.31 (2H, d, J=7.1Hz), 7.55-7.65 (2H, m), 7.8-8.0  
(5H, m)

(+)ESI-MS (m/z): 480 (M+Na)<sup>+</sup>

- (3) Ethyl 2-benzyloxy-5-[[4-[3-[(trifluoroacetyl)amino]-  
propyl]phenyl]sulfonyl]benzoate

NMR (CDCl<sub>3</sub>, δ): 1.34 (3H, t, J=7Hz), 1.91 (2H, quintet,  
J=7Hz), 2.71 (2H, t, J=7Hz), 3.37 (2H, q, J=7Hz),  
4.36 (2H, q, J=7Hz), 5.21 (2H, s), 6.39 (1H, br s),  
7.08 (1H, d, J=9Hz), 7.20-7.55 (7H, m), 7.84 (2H,  
d, J=8Hz), 7.98 (1H, dd, J=9, 2Hz), 8.33 (1H, d,  
J=2Hz)

(+)ESI-MS (m/z): 572 (M+Na)<sup>+</sup>

- (4) Ethyl 2-methoxymethoxy-4-[[4-[3-[(trifluoroacetyl)-  
amino]propyl]phenyl]sulfonyl]benzoate

NMR (CDCl<sub>3</sub>, δ): 1.36 (3H, t, J=7Hz), 1.92 (2H, quintet,  
J=7Hz), 2.73 (2H, t, J=7Hz), 3.38 (2H, q, J=7Hz),  
3.50 (3H, s), 4.36 (2H, q, J=7Hz), 5.28 (2H, s),  
6.37 (1H, br s), 7.33 (2H, d, J=8Hz), 7.55 (1H, dd,  
J=8, 2Hz), 7.75 (1H, d, J=2Hz), 7.79 (1H, d,  
J=2Hz), 7.86 (2H, d, J=8Hz)

(+)ESI-MS (m/z): 526 (M+Na)<sup>+</sup>

- (5) Ethyl 2-chloro-4-[[4-[3-[(trifluoroacetyl)amino]-  
propyl]phenyl]sulfonyl]benzoate

NMR (CDCl<sub>3</sub>, δ): 1.39 (3H, t, J=7Hz), 1.93 (2H, quintet,  
J=7Hz), 2.74 (2H, t, J=7Hz), 3.39 (2H, q, J=7Hz),

4.41 (2H, q, J=7Hz), 6.31 (1H, br s), 7.35 (2H, d, J=8Hz), 7.75-7.94 (4H, m), 8.00 (1H, d, J=2Hz)  
(+)ESI-MS (m/z): 500 (M+Na)<sup>+</sup>

5 Preparation 19

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

- (1) Ethyl 4-[[4-[2-[benzyl(trifluoroacetyl)amino]ethyl]-phenyl]sulfonyl]-2-(methoxymethoxy)benzoate  
10 NMR (CDCl<sub>3</sub>, δ): 1.35 (3H, t, J=7.2Hz), 2.75-2.95 (2H, m), 3.4-3.55 (5H, m), 4.36 (2H, q, J=7.2Hz), 4.45-4.7 (2H, m), 5.27 (2H, s), 7.1-7.4 (7H, m), 7.45-7.55 (1H, m), 7.7-7.9 (4H, m)  
15 (+)ESI-MS (m/z): 602 (M+Na)<sup>+</sup>
- (2) Ethyl 4'-[[4-[2-[benzyl(trifluoroacetyl)amino]ethyl]-phenyl]sulfonyl]-2'-(methoxymethoxy)1,1'-biphenyl-3-carboxylate  
20 NMR (CDCl<sub>3</sub>, δ): 1.38 (3H, t, J=7.1Hz), 2.8-2.95 (2H, m), 3.37 (3H, s), 3.45-3.55 (2H, m), 4.36 (2H, q, J=7.1Hz), 4.5-4.7 (2H, m), 5.36 (2H, s), 7.15-7.5 (9H, m), 7.6-7.65 (2H, m), 7.75 (1H, m), 7.85-7.90 (2H, m), 8.05-8.1 (1H, m), 8.13 (1H, m)  
25 (+)ESI-MS (m/z): 678 (M+Na)<sup>+</sup>
- (3) Ethyl 4-[[4-[3-[benzyl(trifluoroacetyl)amino]propyl]-phenyl]sulfonyl]-2-(methoxymethoxy)benzoate  
30 NMR (CDCl<sub>3</sub>, δ): 1.36 (3H, t, J=7Hz), 1.72-2.00 (2H, m), 2.59-2.66 (2H, a pair of t, J=7Hz), 3.31, 3.33 (2H, a pair of t, J=7Hz), 3.50 (3H, s), 4.36 (2H, q, J=7Hz), 4.57, 4.61 (2H, a pair of s), 5.28 (2H, s), 7.10-7.42 (7H, m), 7.55 (1H, dd, J=8, 2Hz), 7.70-7.95 (4H, m)

- (4) Ethyl 2-benzyloxy-5-[[4-[3-[benzyl(trifluoroacetyl)-amino]propyl]phenyl]sulfonyl]benzoate

NMR (CDCl<sub>3</sub>, δ): 1.34 (3H, t, J=7Hz), 1.65-2.00 (2H, m),  
2.58 (2H, t, J=7Hz), 3.30 (2H, m), 4.36 (2H, q,  
J=7Hz), 4.56, 4.61 (2H, a pair of s), 5.21 (2H, s),  
7.00-7.50 (13H, m), 7.81 (2H, m), 7.97 (1H, dd,  
J=9, 2Hz), 8.34 (1H, d, J=2Hz)

(+)ESI-MS (m/z): 662 (M+Na)<sup>+</sup>

10 Preparation 20

The following compounds were obtained according to a similar manner to that of Preparation 14.

- (1) Ethyl 4-[[4-[2-(benzylamino)ethyl]phenyl]sulfonyl]-2-hydroxybenzoate

NMR (CDCl<sub>3</sub>, δ): 1.30 (3H, t, J=7.1Hz), 2.65-2.9 (4H, m),  
3.68 (2H, s), 4.33 (2H, q, J=7.1Hz), 7.1-7.3 (5H, m),  
7.35-7.05 (4H, m), 7.8-7.9 (3H, m)

(+)ESI-MS (m/z): 440 (M+H)<sup>+</sup>

- (2) Ethyl (R)-3-[4-[[4-(2-aminopropyl)phenyl]sulfonyl]-phenoxy]benzoate

NMR (CDCl<sub>3</sub>, δ): 1.12 (3H, d, J=6.2Hz), 1.38 (3H, t, J=7.2Hz), 2.5-2.7 (2H, m), 3.1-3.2 (1H, m), 4.37  
(2H, q, J=7.2Hz), 6.95-7.1 (2H, m), 7.2-7.4 (3H, m), 7.47 (1H, t, J=8.0Hz), 7.7 (1H, m), 7.8-8.0  
(5H, m)

(+)ESI-MS (m/z): 440 (M+H)<sup>+</sup>

- (3) Ethyl 4-[[4-(3-aminopropyl)phenyl]sulfonyl]-2-methylbenzoate

NMR (CDCl<sub>3</sub>, δ): 1.38 (3H, t, J=7.1Hz), 1.6-1.85 (2H, m),  
2.62 (3H, s), 2.65-2.8 (4H, m), 4.36 (2H, q, J=7.1Hz), 7.33 (2H, d, J=8.3Hz), 7.7-7.9 (4H, m),  
7.96 (1H, d, J=8.1Hz)

(+)ESI-MS (m/z): 362 (M+H)<sup>+</sup>

(4) (R)-Ethyl 3-[3-[[4-(2-aminopropyl)phenyl]sulfonyl]-phenoxy]benzoate

5 NMR (CDCl<sub>3</sub>, δ): 1.12 (3H, d, J=6.4Hz), 1.39 (3H, t, J=7.2Hz), 2.55-2.8 (2H, m), 3.1-3.3 (1H, m), 4.38 (2H, q, J=7.2Hz), 7.1-7.7 (9H, m), 7.8-7.9 (3H, m)

(+)ESI-MS (m/z): 440 (M+H)<sup>+</sup>

10 (5) Ethyl (R)-4'-[[4-(2-aminopropyl)phenyl]sulfonyl]-1,1'-biphenyl-3-carboxylate

NMR (CDCl<sub>3</sub>, δ): 1.12 (3H, d, J=6.2Hz), 1.41 (3H, t, J=7.2Hz), 2.5-2.8 (2H, m), 3.1-3.3 (1H, m), 4.41 (2H, q, J=7.2Hz), 7.35 (2H, d, J=8.3Hz), 7.54 (1H, t, J=7.8Hz), 7.7-8.15 (8H, m), 8.24 (1H, m)

15

(+)ESI-MS (m/z): 424 (M+H)<sup>+</sup>

(6) Ethyl (R)-3'-[[4-(2-aminopropyl)phenyl]sulfonyl]-1,1'-biphenyl-3-carboxylate

20 NMR (CDCl<sub>3</sub>, δ): 1.11 (3H, d, J=6.3Hz), 1.41 (3H, t, J=7.2Hz), 2.5-2.8 (2H, m), 3.1-3.25 (1H, m), 4.43 (2H, q, J=7.2Hz), 7.34 (2H, d, J=8.3Hz), 7.4-8.3 (10H, m)

(+)ESI-MS (m/z): 424 (M+H)<sup>+</sup>

25

(7) Ethyl 4'-[[4-[2-(benzylamino)ethyl]phenyl]sulfonyl]-2'-hydroxy-1,1'-biphenyl-3-carboxylate

NMR (DMSO-d<sub>6</sub>, δ): 1.31 (3H, t, J=7.1Hz), 2.65-2.8 (4H, m), 3.69 (2H, s), 4.33 (2H, q, J=7.1Hz), 7.15-7.65 (11H, m), 7.75-8.0 (4H, m), 8.1-8.15 (1H, m)

30

(+)ESI-MS (m/z): 516 (M+H)<sup>+</sup>

(8) Ethyl (R)-4-[[4-[(2-aminopropyl)oxy]phenyl]sulfonyl]benzoate

35 NMR (CDCl<sub>3</sub>, δ): 1.17 (3H, d, J=6.5Hz), 1.39 (3H, t,

J=7.2Hz), 3.25-3.45 (1H, m), 3.65-3.8 (1H, m),  
3.85-3.95 (1H, m), 4.39 (2H, q, J=7.2Hz), 6.95-7.0  
(2H, m), 7.8-8.0 (4H, m), 8.1-8.2 (2H, m)  
(+)ESI-MS (m/z): 364 (M+H)<sup>+</sup>

5

- (9) Ethyl 5-[[4-[3-(benzylamino)propyl]phenyl]sulfonyl]-2-hydroxybenzoate

NMR (DMSO-d<sub>6</sub>, δ): 1.32 (3H, t, J=7Hz), 1.78 (2H, quintet, J=7Hz), 2.61 (2H, t, J=7Hz), 2.69 (2H, t, J=7Hz), 3.82 (2H, s), 4.33 (2H, q, J=7Hz), 7.07 (1H, d, J=9Hz), 7.20-7.42 (5H, m), 7.42 (2H, d, J=8Hz), 7.82 (2H, d, J=8Hz), 7.91 (1H, dd, J=9, 2Hz), 8.19 (1H, d, J=2Hz)  
(+)APCI-MS (m/z): 454 (M+H)<sup>+</sup>

15

- (10) Ethyl 4-[[4-[3-(benzylamino)propyl]phenyl]sulfonyl]-2-hydroxybenzoate

NMR (DMSO-d<sub>6</sub>, δ): 1.30 (3H, t, J=7Hz), 1.82 (2H, quintet, J=7Hz), 2.65 (2H, t, J=7Hz), 2.72 (2H, t, J=7Hz), 3.87 (2H, s), 4.33 (2H, q, J=7Hz), 7.10-7.55 (9H, m), 7.87 (2H, d, J=8Hz), 7.88 (1H, d, J=8Hz)

20

- (11) Ethyl 5-[[4-[2-(benzylamino)ethoxy]phenyl]sulfonyl]-2-hydroxybenzoate

NMR (CDCl<sub>3</sub>, δ): 1.45 (3H, t, J=7Hz), 3.03 (2H, t, J=5Hz), 3.87 (2H, s), 4.13 (2H, t, J=5Hz), 4.45 (2H, q, J=7Hz), 6.92 (2H, d, J=9Hz), 7.04 (1H, d, J=9Hz), 7.15-7.47 (5H, m), 7.84 (2H, d, J=9Hz), 7.90 (1H, dd, J=9, 2Hz), 8.46 (1H, d, J=2Hz)  
(+)ESI-MS (m/z): 456 (M+H)<sup>+</sup>

25

30

- (12) Ethyl 4-[[4-(3-aminopropyl)phenyl]sulfonyl]-2-chlorobenzoate

NMR (DMSO-d<sub>6</sub>, δ): 1.30 (3H, t, J=7Hz), 1.84 (2H,

35

quintet,  $J=7\text{Hz}$ ), 2.60-2.88 (4H, m), 4.35 (2H, q,  $J=7\text{Hz}$ ), 7.51 (2H, d,  $J=8\text{Hz}$ ), 7.85-8.10 (4H, m), 8.14 (1H, s)

(+)ESI-MS ( $m/z$ ): 382 ( $M+H$ )<sup>+</sup>

5

(13) Ethyl 5-[[4-(3-aminopropyl)phenyl]sulfonyl]-2-methoxybenzoate

NMR (DMSO- $d_6$ ,  $\delta$ ): 1.29 (3H, t,  $J=7\text{Hz}$ ), 1.67 (2H, quintet,  $J=7\text{Hz}$ ), 2.35-2.80 (4H, m), 3.90 (3H, s), 4.28 (2H, q,  $J=7\text{Hz}$ ), 7.36 (1H, d,  $J=9\text{Hz}$ ), 7.44 (2H, d,  $J=8\text{Hz}$ ), 7.86 (2H, d,  $J=8\text{Hz}$ ), 8.09 (1H, dd,  $J=9$ , 2Hz), 8.12 (1H, d,  $J=2\text{Hz}$ )

10

(+)ESI-MS ( $m/z$ ): 378 ( $M+H$ )<sup>+</sup>

15 Preparation 21

To a solution of 2,2,2-trifluoro-N-[(1R)-1-methyl-2-phenylethyl]acetamide (3.75 g) in acetic acid (32 ml) - water (6.5 ml) - sulfuric acid (0.97 ml) were added iodine (1.65 g) and periodic acid dihydrate (740 mg) at room temperature, and the mixture was heated to 60-80°C for 5 hours. After being allowed to cool to room temperature, the mixture was partitioned between hexane/ethyl acetate and water. The organic layer was separated, washed successively with water, sodium sulfite solution, water, and brine, dried over magnesium sulfate, and filtered. The filtrate was concentrated and the residue was recrystallized from diisopropyl ether (44 ml) to give 2,2,2-trifluoro-N-[(1R)-2-(4-iodophenyl)-1-methylethyl]acetamide (2.15 g) as a colorless needle.

20

25

30 NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 1.21 (3H, d,  $J=7\text{Hz}$ ), 2.74 (1H, dd,  $J=14$ , 7Hz), 2.85 (1H, dd,  $J=14$ , 6Hz), 4.26 (1H, m), 6.04 (1H, br s), 6.92 (2H, d,  $J=8\text{Hz}$ ), 7.65 (2H, d,  $J=8\text{Hz}$ )

(+)ESI-MS ( $m/z$ ): 380 ( $M+\text{Na}$ )<sup>+</sup>

35

Preparation 22

Under nitrogen at room temperature, to a mixture of bis(dibenzylideneacetone)palladium(0) (403 mg) and bis(2-diphenylphosphinophenyl)ether (407 mg) was added toluene (90 ml). After being stirred at the same temperature for 15 minutes, (R)-2,2,2-trifluoro-N-[2-(4-iodophenyl)-1-methylethyl]acetamide (5 g), potassium tert-butoxide (1.89 g) and 4-methoxybenzenethiol (1.89 ml) were added, and the mixture was stirred at 80°C for 3 hours. The resulting mixture was poured into water and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed successively with water and 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)-2,2,2-trifluoro-N-[2-[4-[(4-methoxyphenyl)thio]phenyl]-1-methylethyl]acetamide (4.39 g).

NMR (DMSO- $d_6$ ,  $\delta$ ): 1.14 (3H, d,  $J=6.7\text{Hz}$ ), 2.73 (2H, d,  $J=7.1\text{Hz}$ ), 3.77 (3H, s), 3.9-4.1 (1H, m), 6.9-7.2 (6H, m), 7.3-7.4 (2H, m)

(+)ESI-MS ( $m/z$ ): 392 ( $M+H$ )<sup>+</sup>

Preparation 23

Under nitrogen at 5°C, to a solution of (R)-2,2,2-trifluoro-N-[2-[4-[(4-methoxyphenyl)thio]phenyl]-1-methylethyl]acetamide (4.38 g) in dichloromethane (88 ml) was added boron tribromide (1M in dichloromethane, 35.6 ml) dropwise, and the mixture was stirred at room temperature overnight. The resulting mixture was evaporated under reduced pressure. The residue was dissolved into a mixture of saturated aqueous sodium bicarbonate and ethyl acetate. After separation, the organic layer was washed successively with water and brine, dried over anhydrous magnesium sulfate, evaporated under reduced pressure and dried in vacuo to give (R)-2,2,2-trifluoro-N-[2-[4-[(4-hydroxyphenyl)thio]phenyl]-

1-methylethyl]acetamide (3.97 g).

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 1.20 (3H, d,  $J=6.6\text{Hz}$ ), 2.65-2.9 (2H, m),  
4.1-4.35 (1H, m), 6.75-6.9 (2H, m), 6.95-7.15 (4H,  
m), 7.3-7.4 (2H, m)

5 (+)ESI-MS ( $m/z$ ): 378 ( $M+\text{Na}$ )<sup>+</sup>

#### Preparation 24

A mixture of (R)-2,2,2-trifluoro-N-[2-[4-[(4-hydroxyphenyl)thio]phenyl]-1-methylethyl]acetamide (500 mg),  
10 3-ethoxycarbonylphenylboronic acid (546 mg), copper(II)  
acetate (256 mg), powdered molecular sieves 4 Å (500 mg) and  
pyridine (0.569 ml) in dichloromethane (15 ml) was stirred  
at room temperature for 4 days. After the resulting mixture  
was filtered with celite, the filtrate was poured into 0.1N  
15 hydrochloric acid and the aqueous mixture was extracted with  
ethyl acetate. The organic layer was washed successively  
with saturated aqueous sodium bicarbonate and brine, dried  
over anhydrous magnesium sulfate and evaporated under  
reduced pressure. The residue was purified by column  
20 chromatography on silica gel (hexane/ethyl acetate = 5:1) to  
give ethyl (R)-3-[4-[[4-[2-[(trifluoroacetyl)amino]propyl]-  
phenyl]thio]phenoxy]benzoate (463 mg).

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 1.22 (3H, d,  $J=6.6\text{Hz}$ ), 1.39 (3H, t,  
 $J=6.9\text{Hz}$ ), 2.7-2.95 (2H, m), 4.15-4.45 (3H, m),  
25 6.9-7.85 (12H, m)

(+)ESI-MS ( $m/z$ ): 526 ( $M+\text{Na}$ )<sup>+</sup>

#### Preparation 25

The following compounds were obtained according to a  
30 similar manner to that of Preparation 6.

(1) Ethyl (R)-3-[4-[[4-[2-[(trifluoroacetyl)amino]propyl]-  
phenyl]sulfonyl]phenoxy]benzoate

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 1.22 (3H, d,  $J=6.6\text{Hz}$ ), 1.37 (3H, t,  
35  $J=7.1\text{Hz}$ ), 2.75-3.05 (2H, m), 4.15-4.45 (3H, m),



6.95-7.1 (2H, m), 7.2-7.4 (3H, m), 7.47 (1H, t,  $J=8.0\text{Hz}$ ), 7.7 (1H, m), 7.85-7.95 (5H, m)  
(+)ESI-MS (m/z): 558 (M+Na)<sup>+</sup>

5 (2) tert-Butyl benzyl[2-[4-[[4-(2-formylphenoxy)phenyl]-sulfonyl]phenyl]ethyl]carbamate  
NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.41 (9H, s), 2.7-2.9 (2H, m), 3.25-3.5  
(2H, m), 4.25-4.5 (2H, m), 6.95-7.4 (10H, m), 7.5-  
7.65 (1H, m), 7.75-8.0 (6H, m), 10.31 (1H, s)  
10 (+)ESI-MS (m/z): 594 (M+Na)<sup>+</sup>

(3) tert-Butyl benzyl[2-[4-[[3-(2-formylphenoxy)phenyl]-sulfonyl]phenyl]ethyl]carbamate  
NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.40 (9H, s), 2.7-2.9 (2H, m), 3.25-3.5  
15 (2H, m), 4.25-4.5 (2H, m), 6.85-8.0 (17H, m),  
10.40 (1H, s)  
(+)ESI-MS (m/z): 594 (M+H)<sup>+</sup>

(4) tert-Butyl [4-[[4-[2-[benzyl(tert-butoxycarbonyl)-amino]ethyl]phenyl]sulfonyl]phenyl]acetate  
20 NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.39 (9H, br s), 1.42 (9H, s), 2.7-2.9  
(2H, m), 3.25-3.5 (2H, m), 3.56 (2H, s), 4.25-4.45  
(2H, m), 7.1-7.35 (9H, m), 7.8-7.95 (4H, m)  
(+)ESI-MS (m/z): 588 (M+Na)<sup>+</sup>

25 (5) Ethyl (R)-3-[3-[[4-[2-[(trifluoroacetyl)amino]propyl]-phenyl]sulfonyl]phenoxy]benzoate  
NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.21 (3H, d,  $J=6.6\text{Hz}$ ), 1.39 (3H, t,  $J=7.2\text{Hz}$ ), 2.8-3.05 (2H, m), 4.2-4.45 (3H, m), 7.1-  
30 7.7 (9H, m), 7.8-7.9 (3H, m)  
(+)ESI-MS (m/z): 558 (M+Na)<sup>+</sup>

(6) tert-Butyl benzyl[2-[4-[(3-hydroxyphenyl)sulfonyl]-phenyl]ethyl]carbamate  
35 NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.38 (9H, br s), 2.7-2.9 (2H, m), 3.25-

3.5 (2H, m), 4.37 (2H, br s), 6.95-7.05 (1H, m),  
7.15-7.5 (10H, m), 7.75-7.85 (2H, m)  
(+)ESI-MS (m/z): 490 (M+Na)<sup>+</sup>

5 (7) Ethyl 4-[3-[[4-[2-[benzyl(tert-butoxycarbonyl)amino]-  
ethyl]phenyl]sulfonyl]phenoxy]benzoate  
NMR (CDCl<sub>3</sub>, δ): 1.3-1.45 (12H, m), 2.7-2.9 (2H, m),  
3.3-3.5 (2H, m), 4.3-4.5 (4H, m), 6.95-7.05 (2H,  
m), 7.1-7.75 (13H, m), 7.82 (2H, d, J=8.2Hz), 8.0-  
10 8.1 (2H, m)  
(+)ESI-MS (m/z): 638 (M+Na)<sup>+</sup>

(8) Ethyl 3-[3-[[4-[2-[benzyl(tert-butoxycarbonyl)amino]-  
ethyl]phenyl]sulfonyl]phenoxy]benzoate  
15 NMR (CDCl<sub>3</sub>, δ): 1.3-1.5 (12H, m), 2.7-2.95 (2H, m),  
3.3-3.5 (2H, m), 4.25-4.5 (4H, m), 7.1-7.7 (14H,  
m), 7.75-7.9 (3H, m)  
(+)ESI-MS (m/z): 638 (M+Na)<sup>+</sup>

20 (9) tert-Butyl benzyl[2-[4-[(4-hydroxyphenyl)sulfonyl]-  
phenyl]ethyl]carbamate  
(+)ESI-MS (m/z): 490 (M+Na)<sup>+</sup>

(10) 2,2,2-Trifluoro-N-[3-[4-[(3-methoxyphenyl)sulfonyl]-  
25 phenyl]propyl]acetamide  
NMR (CDCl<sub>3</sub>, δ): 1.92 (2H, quintet, J=7Hz), 2.72 (2H, t,  
J=7Hz), 3.39 (2H, q, J=7Hz), 3.84 (3H, s), 6.31  
(1H, br s), 7.00-7.16 (1H, m), 7.20-7.58 (5H, m),  
7.86 (2H, d, J=8Hz)  
30 (+)ESI-MS (m/z): 424 (M+Na)<sup>+</sup>

(11) tert-Butyl benzyl[2-[4-[(4-hydroxyphenyl)sulfonyl]-  
phenoxy]ethyl]carbamate  
NMR (CDCl<sub>3</sub>, δ): 1.45 (9H, s), 3.58 (2H, br s), 4.08 (2H,  
35 br s), 4.53 (2H, s), 6.86 (2H, d, J=8Hz), 6.89 (2H,

d, J=8Hz), 7.10-7.42 (5H, m), 7.64-7.90 (4H, m)  
(+)ESI-MS (m/z): 506 (M+Na)<sup>+</sup>

(12) Methyl 2-benzyloxy-5-[[4-[2-[benzyl(trifluoroacetyl)-  
5 amino]ethoxy]phenyl]sulfonyl]benzoate  
NMR (CDCl<sub>3</sub>, δ): 3.60-3.85 (2H, m), 3.91 (3H, s), 4.03-  
4.23 (2H, m), 4.77, 4.81 (total 2H, a pair of s),  
5.23 (2H, s), 6.91 (2H, d, J=9Hz), 7.07 (1H, d,  
J=9Hz), 7.14-7.52 (10H, m), 7.85 (2H, d, J=8Hz),  
10 7.96 (1H, dd, J=9, 2Hz), 8.35 (1H, d, J=2Hz)  
(+)ESI-MS (m/z): 650 (M+Na)<sup>+</sup>

#### Preparation 26

Under nitrogen at room temperature, to a solution of 4-  
15 fluorobenzaldehyde (3.0 g) in N,N-dimethylformamide (60 ml)  
was added 4-methoxybenzenethiol (3.3 ml) and potassium  
carbonate (3.7 g), and the mixture was stirred at 120°C for 6  
hours. The resulting mixture was poured into water and the  
aqueous mixture was extracted with ethyl acetate. The  
20 organic layer was washed successively with water and 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  
give 4-[(4-methoxyphenyl)thio]benzaldehyde (4.9 g).

25 NMR (CDCl<sub>3</sub>, δ): 3.86 (3H, s), 6.95-7.0 (2H, m), 7.1-7.2  
(2H, m), 7.45-7.5 (2H, m), 7.65-7.7 (2H, m), 9.89  
(1H, s)  
(+)APCI-MS (m/z): 245 (M+H)<sup>+</sup>

#### Preparation 27

Under nitrogen at room temperature, to a solution of 4-  
[(4-methoxyphenyl)thio]benzaldehyde (5.1 g) in methanol (51  
ml) were added nitromethane (1.7 ml), acetic acid (0.60 ml)  
and butylamine (1.0 ml), and the mixture was stirred at the  
35 same temperature overnight to give precipitates. Water (51

ml) was poured into the resulting mixture and the mixture was the mixture was stirred for 30 minutes. The deposits were collected by filtration and the filter cake was washed with water followed by air-drying to give 1-methoxy-4-[[4-(2-nitroethenyl)phenyl]thio]benzene (5.4 g).

NMR (CDCl<sub>3</sub>, δ): 3.86 (3H, s), 6.9-7.15 (4H, m), 7.3-7.6 (5H, m), 7.85-7.95 (1H, m)

(+)ESI-MS (m/z): 310 (M+Na)<sup>+</sup>

#### 10 Preparation 28

Under nitrogen at 5°C, to a suspension of lithium aluminum hydride (3.2 g) in tetrahydrofuran (80 ml) was added dropwise 1-methoxy-4-[[4-(2-nitroethenyl)phenyl]thio]benzene (4.8 g) in tetrahydrofuran (50 ml), and the mixture was refluxed for 6.5 hours. The resulting mixture was cooled to 5°C, and to this one was added sodium fluoride (14 g) followed by water (4.5 ml) dropwise carefully. The mixture was vigorously stirred at room temperature for 30 minutes. The precipitates were removed by filtration, and the filter cake was washed with a mixture of ethyl acetate and ethanol (95:5). The filtrate was evaporated under reduced pressure. The residue was dissolved into ethyl acetate (40 ml) and cooled to 5°C. To this one was added 4N hydrogen chloride in 1,4-dioxane (8.4 ml) and the mixture was stirred at room temperature for 30 minutes to deposit the corresponding salt followed by collection by filtration. The filter cake was washed with ethyl acetate and dissolved into a mixture of ethyl acetate and 1N sodium hydroxide. After separation, the organic layer was dried over anhydrous magnesium sulfate, evaporated under reduced pressure and dried to give 2-[4-[(4-methoxyphenyl)thio]phenyl]ethylamine (2.0 g).

NMR (CDCl<sub>3</sub>, δ): 2.69 (2H, t, J=6.8Hz), 2.93 (2H, t, J=6.8Hz), 3.81 (3H, s), 6.85-6.95 (2H, m), 7.05-7.2 (4H, m), 7.35-7.45 (2H, m)

(+)APCI-MS (m/z): 260 (M+H)<sup>+</sup> \*

#### Preparation 29

Under nitrogen at room temperature, to a solution of 2-  
5 [4-[(4-methoxyphenyl)thio]phenyl]ethylamine (2.0 g) in  
dichloromethane (20 ml) was added benzaldehyde (0.78 ml),  
and the mixture was stirred at the same temperature for 20  
minutes. To this one was added toluene and evaporated under  
reduced pressure. Under nitrogen at 5°C, to a solution of  
10 the residue in tetrahydrofuran (20 ml) was added sodium  
borohydride (0.32 g) followed by methanol (10 ml) dropwise  
and the mixture was stirred at room temperature for 40  
minutes. The resulting mixture was poured into a mixture of  
ethyl acetate and water, and stirred for 10 minutes. After  
15 separation, 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 (chloroform:methanol = 100:1 to  
20:1) to give N-benzyl-N-[2-[4-[(4-methoxyphenyl)thio]-  
20 phenyl]ethyl]amine (2.0 g).

NMR (CDCl<sub>3</sub>, δ): 2.7-2.9 (4H, m), 3.81 (2H, s), 3.83 (3H,  
s), 6.85-6.95 (2H, m), 7.05-7.45 (11H, m)

(+)APCI-MS (m/z): 350 (M+H)<sup>+</sup>

#### 25 Preparation 30

The following compounds were obtained according to a  
similar manner to that of Preparation 23.

(1) 4-[[4-[2-(Benzylamino)ethyl]phenyl]thio]phenol

30 NMR (DMSO-d<sub>6</sub>, δ): 2.65-2.75 (4H, m), 3.71 (2H, s),  
6.75-6.85 (2H, m), 6.95-7.35 (11H, m)

(+)APCI-MS (m/z): 336 (M+H)<sup>+</sup>

(2) 3-[[4-[2-(Benzylamino)ethyl]phenyl]thio]phenol

35 NMR (DMSO-d<sub>6</sub>, δ): 2.7-2.85 (4H, m), 3.74 (2H, s), 7.55-

7.75 (3H, m), 7.05-7.4 (10H, m)

(+)APCI-MS (m/z): 336 (M+H)<sup>+</sup>

- (3) 2,2,2-Trifluoro-N-[3-[4-[(4-hydroxy-3-methylphenyl)sulfonyl]phenyl]propyl]acetamide

NMR (CDCl<sub>3</sub>, δ): 1.8-2.0 (2H, m), 2.24 (3H, s), 2.6-2.75 (2H, m), 3.3-3.45 (2H, m), 6.83 (1H, d, J=8.3Hz), 7.25-7.3 (2H, m), 7.6-7.7 (2H, m), 7.75-7.9 (2H, m)

(+)ESI-MS (m/z): 424 (M+Na)<sup>+</sup>

- (4) (R)-2,2,2-Trifluoro-N-[2-[4-[(3-hydroxyphenyl)thio]-phenyl]-1-methylethyl]acetamide

NMR (CDCl<sub>3</sub>, δ): 1.30 (3H, d, J=6.7Hz), 2.65-2.95 (2H, m), 4.15-4.4 (1H, m), 6.3 (1H, m), 6.6-6.65 (1H, m), 6.8-6.85 (1H, m), 7.05-7.2 (3H, m), 7.35-7.45 (2H, m)

(+)ESI-MS (m/z): 378 (M+Na)<sup>+</sup>

- (5) (R)-N-[2-[4-[(3-Chloro-4-hydroxyphenyl)sulfonyl]-phenyl]-1-methylethyl]-2,2,2-trifluoroacetamide

(+)APCI-MS (m/z): 444 (M+Na)<sup>+</sup>

- (6) 3-[[4-[3-(Benzylamino)propyl]phenyl]sulfonyl]phenol

NMR (DMSO-d<sub>6</sub>, δ): 1.75 (2H, quintet, J=7Hz), 2.55 (2H, t, J=7Hz), 2.66 (2H, t, J=7Hz), 3.76 (2H, s), 6.95-7.11 (1H, m), 7.11-7.55 (10H, m), 7.81 (2H, d, J=8Hz)

(+)ESI-MS (m/z): 382 (M+H)<sup>+</sup>

- (7) 2-[[4-[(2R)-2-(Benzylamino)propyl]phenyl]sulfonyl]phenol

NMR (DMSO-d<sub>6</sub>, δ): 0.95 (3H, d, J=7Hz), 2.40-3.00 (3H, m), 3.76 (1H, d, J=14Hz), 3.80 (1H, d, J=14Hz), 6.88 (1H, d, J=8Hz), 7.00 (1H, t, J=8Hz), 7.05-

7.35 (5H, m), 7.37 (2H, d, J=8Hz), 7.48 (1H, t, J=8Hz), 7.80 (2H, d, J=8Hz), 7.89 (1H, d, J=8Hz)  
(+)ESI-MS (m/z): 382 (M+H)<sup>+</sup>

- 5 (8) N-[3-[4-[(3-Chloro-4-hydroxyphenyl)sulfonyl]phenyl]-propyl]-2,2,2-trifluoroacetamide  
NMR (CDCl<sub>3</sub>, δ): 1.92 (2H, quintet, J=7Hz), 2.72 (2H, t, J=7Hz), 3.38 (2H, q, J=7Hz), 6.15 (1H, s, OH),  
6.33 (1H, br s), 7.10 (1H, d, J=9Hz), 7.32 (2H, d, J=8Hz),  
10 7.75 (1H, dd, J=9, 2Hz), 7.83 (2H, d, J=8Hz), 7.93 (1H, d, J=2Hz)  
(+)ESI-MS (m/z): 444 (M+Na)<sup>+</sup>

#### Preparation 31

- 15 Under nitrogen at room temperature, to a solution of 4-[[4-[2-(benzylamino)ethyl]phenyl]thio]phenol (794 mg) in tetrahydrofuran (8 ml) was added di-tert-butyl dicarbonate (775 mg) in tetrahydrofuran (2 ml), and the mixture was stirred at the same temperature for 9.5 hours. The  
20 resulting mixture was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 10:1 to 2:1) to give tert-butyl benzyl[2-[4-[(4-hydroxyphenyl)thio]phenyl]ethyl]carbamate (849 mg).

- 25 NMR (CDCl<sub>3</sub>, δ): 1.45 (9H, s), 2.6-2.85 (2H, m), 3.25-3.45 (2H, m), 4.3-4.45 (2H, m), 6.75-6.85 (2H, m), 6.9-7.4 (11H, m)  
(+)ESI-MS (m/z): 458 (M+Na)<sup>+</sup>

#### Preparation 32

- 30 Under nitrogen at room temperature, to a solution of tert-butyl benzyl[2-[4-[(4-hydroxyphenyl)thio]phenyl]ethyl]carbamate (1.8 g) in N,N-dimethylformamide (20 ml) were added potassium carbonate (628 mg) and 2-  
35 fluorobenzaldehyde (0.497 ml), and the mixture was stirred

at 130°C for 1.5 hours. The resulting mixture was poured into water and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed successively with water two times and 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 tert-butyl benzyl[2-[4-[4-(2-formylphenoxy)phenyl]thio]phenyl]ethyl]-carbamate (1.76 g).

10 NMR (CDCl<sub>3</sub>, δ): 1.46 (9H, s), 2.6-2.9 (2H, m), 3.25-3.5 (2H, m), 4.25-4.45 (2H, m), 6.9-7.4 (15H, m), 7.45-7.6 (1H, m), 7.9-8.0 (1H, m), 10.47 (1H, s)  
(+)ESI-MS (m/z): 562 (M+Na)<sup>+</sup>

15 Preparation 33

To a solution of tert-butyl benzyl[2-[4-[4-(2-formylphenoxy)phenyl]sulfonyl]phenyl]ethyl]carbamate (1.17 g) in acetonitrile (18 ml) were added sodium dihydrogenphosphate (51.6 mg) and 30% hydrogen peroxide (0.232 ml) at room temperature. After the mixture was cooled to 5°C, sodium chlorite (333 mg) in water (18 ml) was added dropwise and the mixture was stirred at room temperature for 2.5 days. To the resulting mixture was added sodium sulfite, and the mixture was stirred for 10 minutes, followed by being adjusted pH to around 2.5 with 1N hydrochloric acid to give deposits. The precipitates were collected and washed with water followed by dryness in vacuo to give 2-[4-[4-[2-[benzyl(tert-butoxycarbonyl)amino]-ethyl]phenyl]sulfonyl]phenoxy]benzoic acid (1.0 g).

30 NMR (DMSO-d<sub>6</sub>, δ): 1.0-1.4 (9H, m), 2.7-2.9 (2H, m), 3.1-3.45 (2H, m), 4.25-4.5 (2H, m), 6.8-7.5 (10H, m), 7.55-8.0 (7H, m)  
(-)ESI-MS (m/z): 586 (M-H)<sup>-</sup>

35 Preparation 34



Under nitrogen at room temperature, to a solution of 2-[4-[[4-[2-[benzyl(tert-butoxycarbonyl)amino]ethyl]-phenyl]sulfonyl]phenoxy]benzoic acid (1.0 g) in N,N-dimethylformamide (10 ml) were added potassium carbonate  
5 (282 mg) and iodoethane (0.15 ml), and the mixture was stirred at the same temperature for 2.5 hours. The resulting mixture was poured into water and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed successively with water two times and brine,  
10 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 12:5) to give ethyl 2-[4-[[4-[2-[benzyl(tert-butoxycarbonyl)amino]ethyl]phenyl]sulfonyl]-  
15 phenoxy]benzoate (783 mg).

NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.06 (3H, t, J=7.1Hz), 1.41 (9H, s),  
2.7-2.9 (2H, m), 3.25-3.5 (2H, m), 4.16 (2H, q, J=7.1Hz), 4.25-4.5 (2H, m), 6.85-7.4 (11H, m),  
7.5-7.6 (1H, m), 7.75-8.0 (5H, m)  
20 (+)ESI-MS (m/z): 638 (M+Na)<sup>+</sup>

#### Preparation 35

The following compounds were obtained according to a similar manner to that of Preparation 7.

25

- (1) Ethyl 2-[4-[[4-[2-(benzylamino)ethyl]phenyl]sulfonyl]-phenoxy]benzoate

NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.06 (3H, t, J=7.1Hz), 2.8-2.95 (4H, m),  
3.79 (2H, s), 4.16 (2H, q, J=7.1Hz), 6.85-7.1 (3H,  
30 m), 7.2-7.4 (8H, m), 7.5-7.6 (1H, m), 7.75-9.9 (5H, m)

(+)ESI-MS (m/z): 516 (M+H)<sup>+</sup>

- (2) Ethyl 2-[3-[[4-[2-(benzylamino)ethyl]phenyl]-sulfonyl]phenoxy]benzoate  
35

NMR (CDCl<sub>3</sub>, δ): 1.04 (3H, t, J=7.2Hz), 2.8-2.95 (4H, m),  
3.79 (2H, s), 4.05-4.2 (2H, m), 6.95-7.1 (2H, m),  
7.2-7.65 (12H, m), 7.75-7.85 (2H, m), 7.9-8.0 (1H,  
m)

5 (+)ESI-MS (m/z): 516 (M+H)<sup>+</sup>

(3) 3-[[4-[2-(Benzylamino)ethyl]phenyl]sulfonyl]phenol

NMR (CDCl<sub>3</sub>, δ): 2.7-3.0 (4H, m), 3.81 (2H, s), 6.9-7.0  
(1H, m), 7.1-7.5 (10H, m), 7.75-7.85 (2H, m)

10 (-)APCI-MS (m/z): 366 (M-H)<sup>-</sup>

(4) Ethyl 4-[3-[[4-[2-(benzylamino)ethyl]phenyl]-  
sulfonyl]phenoxy]benzoate

15 NMR (CDCl<sub>3</sub>, δ): 1.40 (3H, t, J=7.1Hz), 2.8-2.95 (4H, m),  
3.79 (2H, s), 4.38 (2H, q, J=7.1Hz), 6.95-7.05 (2H,  
m), 7.15-7.4 (8H, m), 7.48 (1H, t, J=8.0Hz), 7.55-  
7.75 (2H, m), 7.84 (2H, d, J=8.4Hz), 8.0-8.1 (2H,  
m)

(+)ESI-MS (m/z): 516 (M+H)<sup>+</sup>

20

(5) Ethyl 3-[3-[[4-[2-(benzylamino)ethyl]phenyl]-  
sulfonyl]phenoxy]benzoate

25 NMR (CDCl<sub>3</sub>, δ): 1.38 (3H, t, J=7.1Hz), 2.8-2.95 (4H, m),  
3.79 (2H, s), 4.37 (2H, q, J=7.1Hz), 7.1-7.7 (14H,  
m), 7.8-7.9 (3H, m)

(+)ESI-MS (m/z): 516 (M+H)<sup>+</sup>

(6) (R)-1-Phenoxy-2-propanamine

30 NMR (DMSO-d<sub>6</sub>, δ): 1.05 (3H, d, J=6.4Hz), 3.05-3.2 (1H,  
m), 3.65-3.8 (2H, m), 6.85-7.0 (3H, m), 7.25-7.4  
(2H, m)

(+)ESI-MS (m/z): 152 (M+H)<sup>+</sup>

(7) 4-[[4-[2-(Benzylamino)ethyl]phenyl]sulfonyl]phenol

35 (+)ESI-MS (m/z): 368 (M+H)<sup>+</sup>

(8) 4-[[4-[2-(Benzylamino)ethoxy]phenyl]sulfonyl]phenol

NMR (DMSO- $d_6$ ,  $\delta$ ): 2.85 (2H, t,  $J=6\text{Hz}$ ), 3.57 (2H, s),  
4.10 (2H, t,  $J=6\text{Hz}$ ), 6.90 (2H, d,  $J=8\text{Hz}$ ), 7.09 (2H,  
5 d,  $J=8\text{Hz}$ ), 7.15-7.40 (5H, m), 7.72 (2H, d,  $J=8\text{Hz}$ ),  
7.79 (2H, d,  $J=8\text{Hz}$ )

(+)ESI-MS ( $m/z$ ): 384 ( $M+H$ )<sup>+</sup>

#### Preparation 36

10 The following compound was obtained according to a  
similar manner to that of Preparation 26.

4-[(3-Methoxyphenyl)thio]benzaldehyde

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 3.81 (3H, s), 6.9-7.0 (1H, m), 7.05-  
15 7.15 (2H, m), 7.25-7.4 (3H, m), 7.7-7.8 (2H, m),  
9.92 (1H, s)

(+)APCI-MS ( $m/z$ ): 245 ( $M+H$ )<sup>+</sup>

#### Preparation 37

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

1-Methoxy-3-[[4-(2-nitroethenyl)phenyl]thio]benzene

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 3.80 (3H, s), 6.85-7.15 (3H, m), 7.2-  
25 7.55 (6H, m), 7.9-8.0 (1H, m)

(+)ESI-MS ( $m/z$ ): 310 ( $M+Na$ )<sup>+</sup>

#### Preparation 38

30 The following compound was obtained according to a  
similar manner to that of Preparation 28.

2-[4-[(3-Methoxyphenyl)thio]phenyl]ethylamine

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 2.74 (2H, t,  $J=6.9\text{Hz}$ ), 2.97 (2H, t,  
 $J=6.9\text{Hz}$ ), 3.75 (3H, s), 6.7-6.9 (3H, m), 7.1-7.4  
35 (5H, m)

(+)ESI-MS (m/z): 260 (M+H)<sup>+</sup>

### Preparation 39

The following compounds were obtained according to a similar manner to that of Preparation 29.

(1) N-Benzyl-N-[2-[4-[(3-methoxyphenyl)thio]phenyl]ethyl]-amine

NMR (CDCl<sub>3</sub>, δ): 2.75-3.0 (4H, m), 3.78 (3H, s), 3.80 (2H, s), 6.7-6.95 (3H, m), 7.1-7.4 (10H, m)

(+)APCI-MS (m/z): 350 (M+H)<sup>+</sup>

(2) N-Benzyl-N-[3-[4-[(3-methoxyphenyl)sulfonyl]phenyl]-propyl]amine

NMR (CDCl<sub>3</sub>, δ): 1.81 (2H, quintet, J=7Hz), 2.52-2.80 (4H, m), 3.77 (2H, s), 3.84 (3H, s), 7.00-7.12 (1H, m), 7.15-7.55 (10H, m), 7.83 (2H, d, J=8Hz)

(+)ESI-MS (m/z): 396 (M+H)<sup>+</sup>

(3) N-Benzyl-N-[(1R)-2-[4-[(2-methoxyphenyl)sulfonyl]-phenyl]-1-methylethyl]amine

NMR (CDCl<sub>3</sub>, δ): 1.07 (3H, d, J=6Hz), 2.68 (1H, dd, J=13, 6Hz), 2.82 (1H, dd, J=13, 7Hz), 2.94 (1H, m), 3.72 (1H, d, J=13Hz), 3.73 (3H, s), 3.83 (1H, d, J=13Hz), 6.89 (1H, d, J=8Hz), 7.10-7.43 (7H, m), 7.14 (1H, t, J=8Hz), 7.54 (1H, t, J=8Hz), 7.88 (2H, d, J=8Hz), 8.15 (1H, d, J=8Hz)

(+)ESI-MS (m/z): 396 (M+H)<sup>+</sup>

### Preparation 40

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

tert-Butyl benzyl[2-[4-[(3-hydroxyphenyl)thio]phenyl]ethyl]carbamate

NMR (CDCl<sub>3</sub>, δ): 1.45 (9H, br s), 2.7-2.85 (2H, m), 3.3-3.5 (2H, m), 4.37 (2H, s), 6.55-6.7 (2H, m), 6.75-6.85 (1H, m), 7.05-7.4 (10H, m)  
(+)ESI-MS (m/z): 458 (M+Na)<sup>+</sup>

5

#### Preparation 41

The following compound was obtained according to a similar manner to that of Preparation 32.

10       tert-Butyl benzyl[2-[4-[[3-(2-formylphenoxy)phenyl]thio]phenyl]ethyl]carbamate

NMR (CDCl<sub>3</sub>, δ): 1.47 (9H, s), 2.65-2.9 (2H, m), 3.25-3.5 (2H, m), 4.25-4.5 (2H, m), 6.8-7.6 (16H, m), 7.85-7.95 (1H, m), 10.45 (1H, s)

15       (+)ESI-MS (m/z): 562 (M+H)<sup>+</sup>

#### Preparation 42

The following compound was obtained according to a similar manner to that of Preparation 33.

20

2-[3-[[4-[2-[Benzyl(tert-butoxycarbonyl)amino]ethyl]-phenyl]sulfonyl]phenoxy]benzoic acid

NMR (CDCl<sub>3</sub>, δ): 1.0-1.4 (9H, m), 2.7-2.95 (2H, m), 3.2-3.5 (2H, m), 4.25-4.45 (2H, m), 6.8-8.0 (17H, m)

25       (-)ESI-MS (m/z): 586 (M-H)<sup>-</sup>

#### Preparation 43

The following compound was obtained according to a similar manner to that of Preparation 34.

30

Ethyl 2-[3-[[4-[2-[benzyl(tert-butoxycarbonyl)amino]-ethyl]phenyl]sulfonyl]phenoxy]benzoate

NMR (CDCl<sub>3</sub>, δ): 1.06 (3H, t, J=7.1Hz), 1.42 (9H, s), 2.7-2.9 (2H, m), 3.25-3.5 (2H, m), 4.15 (2H, q,

35       J=7.1Hz), 4.25-4.5 (2H, m), 7.0-7.1 (2H, m), 7.1-

7.6 (12H, m), 7.75-7.85 (2H, m), 7.9-8.0 (1H, m)  
(+)ESI-MS (m/z): 638 (M+Na)<sup>+</sup>

#### Preparation 44

5 Under nitrogen at room temperature, to a solution of  
(R)-2,2,2-trifluoro-N-(1-methyl-2-phenylethyl)acetamide (1.5  
g) and methyl 5-(chlorosulfonyl)-2-hydroxybenzoate (2.18 g)  
in 1,2-dichloroethane (15 ml) was added aluminum chloride  
(3.03 g), and the mixture was stirred at 60-65°C for 4.5  
10 hours. After the resulting mixture was cooled to room  
temperature, chloroform and water were added, followed by  
being stirred for 30 minutes. After separation, the organic  
layer was dried over anhydrous magnesium sulfate and  
evaporated under reduced pressure. The residue was purified  
15 by column chromatography on silica gel (chloroform/ethyl  
acetate = 20:1) to give methyl (R)-2-hydroxy-5-[[4-[2-  
[(trifluoroacetyl)amino]propyl]phenyl]sulfonyl]benzoate  
(2.12 g).

NMR (CDCl<sub>3</sub>, δ): 1.21 (3H, d, J=6.7Hz), 2.75-3.05 (2H,  
20 m), 3.98 (3H, s), 4.15-4.4 (1H, m), 7.07 (1H, d,  
J=8.8Hz), 7.32 (2H, d, J=8.3Hz), 7.87 (2H, d,  
J=8.3Hz), 7.95 (1H, dd, J=2.4, 8.9Hz), 8.48 (1H, d,  
J=2.4Hz)

(+)ESI-MS (m/z): 468 (M+Na)<sup>+</sup>

25

#### Preparation 45

Under nitrogen at room temperature, a mixture of methyl  
(R)-2-hydroxy-5-[[4-[2-[(trifluoroacetyl)amino]propyl]-  
phenyl]sulfonyl]benzoate (2.1 g) and 7N hydrogen chloride in  
30 ethanol (40 ml) was refluxed for 12 hours. The resulting  
mixture was evaporated under reduced pressure followed by  
dryness in vacuo to give ethyl (R)-5-[[4-(2-aminopropyl)-  
phenyl]sulfonyl]-2-hydroxybenzoate hydrochloride (1.97 g).

NMR (DMSO-d<sub>6</sub>, δ): 1.11 (3H, d, J=6.5Hz), 1.34 (3H, t,  
35 J=7.1Hz), 2.8-3.55 (3H, m), 4.37 (2H, q, J=7.1Hz),

7.22 (1H, d, J=8.7Hz), 7.51 (2H, d, J=8.3Hz),  
7.85-8.3 (3H, m)

(+)ESI-MS (m/z): 364 (M-HCl+H)<sup>+</sup>

5 Preparation 46

Ethyl (R)-5-[[4-(2-aminopropyl)phenyl]sulfonyl]-2-hydroxybenzoate hydrochloride (1.96 g) was dissolved into a mixture of chloroform/methanol (4:1) and water, and sodium bicarbonate (412 mg) was added. After separation, the  
10 organic layer was dried over anhydrous magnesium sulfate and evaporated under reduced pressure. Under nitrogen, a mixture of the residue and (R)-2-(3-chlorophenyl)oxirane (758 mg) in ethanol (34 ml) was stirred at 70°C for 19.5 hours. The resulting mixture was evaporated under reduced  
15 pressure. The residue was purified by column chromatography on silica gel (chloroform/methanol = 20:1) to give ethyl 5-[[4-[(2R)-2-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-propyl]phenyl]sulfonyl]-2-hydroxybenzoate (810 mg).

NMR (CDCl<sub>3</sub>, δ): 1.05 (3H, d, J=6.1Hz), 1.45 (3H, t, J=7.2Hz), 2.55-3.0 (5H, m), 4.35-4.6 (3H, m), 7.06  
20 (1H, d, J=8.9Hz), 7.1-7.35 (6H, m), 7.8-8.0 (3H, m), 8.50 (1H, d, J=2.3Hz)

(+)ESI-MS (m/z): 518, 520 (M+H)<sup>+</sup>

25 Preparation 47

Under nitrogen at room temperature, to a solution of 3-phenyl-1-propylamine (100 g) in methanol (500 ml) was added ethyl trifluoroacetate (106 ml) dropwise, and the mixture was stirred at the same temperature for 4 hours. The  
30 resulting mixture was evaporated under reduced pressure and dried in vacuo to give 2,2,2-trifluoro-N-(3-phenylpropyl)-acetamide (171 g).

NMR (CDCl<sub>3</sub>, δ): 1.85-2.0 (2H, m), 2.69 (2H, t, J=7.4Hz),  
3.3-3.5 (2H, m), 7.15-7.4 (5H, m)

35 (+)ESI-MS (m/z): 254 (M+Na)<sup>+</sup>

Preparation 48

Under nitrogen at 5°C, to a solution of 2,2,2-trifluoro-N-(3-phenylpropyl)acetamide (100 g) in chloroform (800 ml) was added chlorosulfonic acid (144 ml) dropwise, and the mixture was stirred at the same temperature for 1 hour and at room temperature for 36 hours. The resulting mixture was carefully poured into a stirred mixture of water and chloroform under ice-water cooling. After separation, the organic layer was washed with water, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 4:1 to 2:1) to give 4-[3-[(trifluoroacetyl)amino]propyl]benzenesulfonyl chloride (109 g).

NMR (CDCl<sub>3</sub>, δ): 1.9-2.1 (2H, m), 2.81 (2H, t, J=7.4Hz), 3.35-3.55 (2H, m), 7.4-7.5 (2H, m), 7.95-8.05 (2H, m)

Preparation 49

The following compounds were obtained according to a similar manner to that of Preparation 44.

(1) 2,2,2-Trifluoro-N-[3-[4-[(4-methoxy-3-methylphenyl)sulfonyl]phenyl]propyl]acetamide  
NMR (CDCl<sub>3</sub>, δ): 1.8-2.0 (2H, m), 2.21 (3H, s), 2.6-2.75 (2H, m), 3.3-3.45 (2H, m), 3.86 (3H, s), 6.87 (1H, d, J=8.6Hz), 7.25-7.3 (2H, m), 7.65 (1H, m), 7.75-7.9 (3H, m)

(+)ESI-MS (m/z): 438 (M+Na)<sup>+</sup>

(2) (R)-N-[2-[4-[(3-Chloro-4-methoxyphenyl)sulfonyl]-phenyl]-1-methylethyl]-2,2,2-trifluoroacetamide  
(+)APCI-MS (m/z): 458 (M+Na)<sup>+</sup>



- (3) (R)-4-[[4-[[2-[(Trifluoroacetyl)amino]propyl]oxy]-phenyl]sulfonyl]benzoic acid  
NMR (DMSO-d<sub>6</sub>, δ): 1.1-1.3 (3H, m), 3.9-4.4 (3H, m),  
7.1-7.3 (2H, m), 7.85-8.2 (6H, m)  
5 (-)ESI-MS (m/z): 430 (M-H)<sup>-</sup>
- (4) N-[3-[4-[(3,4-Dihydroxyphenyl)sulfonyl]phenyl]propyl]-2,2,2-trifluoroacetamide  
NMR (DMSO-d<sub>6</sub>, δ): 1.78 (2H, quintet, J=7Hz), 2.65 (2H,  
10 t, J=7Hz), 3.18 (2H, t, J=7Hz), 6.88 (1H, d,  
J=8Hz), 7.22 (1H, s), 7.24 (1H, d, J=8Hz), 7.43  
(2H, d, J=8Hz), 7.76 (2H, d, J=8Hz)  
(-)ESI-MS (m/z): 402 (M-H)<sup>-</sup>
- 15 (5) Methyl 5-[[4-[(2R)-2-(formylamino)propyl]oxy]-phenyl]sulfonyl]-2-hydroxybenzoate  
NMR (CDCl<sub>3</sub>, δ): 1.33, 1.35 (total 3H, J=7Hz, a pair of  
d), 3.90-4.25 (2H, m), 4.00, 3.99 (total 3H, a  
pair of s), 4.49 (1H, m), 5.76 (1H, br d, J=6Hz),  
20 6.80-7.15 (3H, m), 7.86 (2H, d, J=9Hz), 7.92, 8.11  
(total 1H, J=9, 2Hz, a pair of dd), 8.16, 8.23  
(total 1H, a pair of br s), 8.46, 8.50 (total 1H,  
J=2Hz, a pair of d), 11.25, 11.29 (total 1H, a  
pair of s, OH)  
25 (+)ESI-MS (m/z): 416 (M+Na)<sup>+</sup>
- (6) N-[3-[4-[(3-Chloro-4-methoxyphenyl)sulfonyl]phenyl]-propyl]-2,2,2-trifluoroacetamide  
NMR (CDCl<sub>3</sub>, δ): 1.92 (2H, quintet, J=7Hz), 2.72 (2H, t,  
30 J=7Hz), 3.38 (2H, q, J=7Hz), 3.94 (3H, s), 6.36  
(1H, br s), 7.00 (1H, d, J=9Hz), 7.31 (2H, d,  
J=8Hz), 7.83 (2H, d, J=8Hz), 7.83 (1H, dd, J=9,  
2Hz), 7.91 (1H, d, J=2Hz)  
(+)ESI-MS (m/z): 458 (M+Na)<sup>+</sup>

(7) Methyl 2-hydroxy-5-[[4-[3-[(trifluoroacetyl)amino]-propyl]phenyl]sulfonyl]benzoate

NMR (CDCl<sub>3</sub>, δ): 1.92 (2H, quintet, J=7Hz), 2.72 (2H, t, J=7Hz), 3.38 (2H, q, J=7Hz), 4.00 (3H, s), 6.33 (1H, br s), 7.07 (1H, d, J=9Hz), 7.31 (2H, d, J=8Hz), 7.85 (1H, d, J=8Hz), 7.95 (1H, dd, J=9 and 2Hz), 8.48 (1H, d, J=2Hz), 11.28 (1H, s, OH)

(+)ESI-MS (m/z): 468 (M+Na)<sup>+</sup>

#### 10 Preparation 50

Under nitrogen at room temperature, to a solution of methyl (4-hydroxyphenyl)acetate (10 g) in N,N-dimethylformamide (50 ml) were added potassium carbonate (9.3 g) and benzyl bromide (8.0 ml), and the mixture was stirred at 60°C for 1 hour. The resulting mixture was poured into water and the aqueous mixture was extracted with hexane/ethyl acetate (1:1). The organic layer was washed successively with water and brine, dried over anhydrous magnesium sulfate, evaporated under reduced pressure and dried in vacuo to give methyl [4-(benzyloxy)phenyl]acetate (16 g).

NMR (CDCl<sub>3</sub>, δ): 3.56 (2H, s), 3.68 (3H, s), 5.05 (2H, s), 6.9-7.0 (2H, m), 7.1-7.5 (7H, m)

(+)ESI-MS (m/z): 279 (M+Na)<sup>+</sup>

25

#### Preparation 51

To a solution of methyl [4-(benzyloxy)phenyl]acetate (16 g) in methanol (160 ml) was added 1N sodium hydroxide (68.5 ml) at room temperature, and the mixture was stirred at the same temperature for 2 hours. After removal of methanol under reduced pressure, the residue was dissolved into a mixture of water and ethyl acetate. The aqueous layer was adjusted to pH 2-3 with 6N hydrochloric acid to give deposits. The precipitates were collected and washed with water followed by dryness in vacuo to give [4-

(benzyloxy)phenyl]acetic acid (11 g).

NMR (DMSO- $d_6$ ,  $\delta$ ): 3.48 (2H, s), 5.08 (2H, s), 6.9-7.0

(2H, m), 7.15-7.2 (2H, m), 7.25-7.5 (5H, m)

(-)ESI-MS (m/z): 241 (M-H)<sup>-</sup>

5

#### Preparation 52

Under nitrogen, to a suspension of [4-(benzyloxy)-phenyl]acetic acid (10.8 g) in dichloromethane (300 ml) were added concentrated sulfuric acid (0.5 ml) and the excess  
10 amount of isobutene in dryice-acetone bath, and the mixture was raised to room temperature slowly followed by being stirred at the same temperature for 3.5 days. The resulting mixture was poured into saturated aqueous sodium bicarbonate and the aqueous mixture was extracted with ethyl acetate.

15 The organic layer was washed successively with saturated aqueous sodium bicarbonate two times and 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 give tert-  
20 butyl [4-(benzyloxy)phenyl]acetate (11.3 g).

NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.43 (9H, s), 3.46 (2H, s), 5.05 (2H, s), 6.9-6.95 (2H, m), 7.15-7.5 (7H, m)

(+)ESI-MS (m/z): 321 (M+Na)<sup>+</sup>

#### 25 Preparation 53

A mixture of tert-butyl [4-(benzyloxy)phenyl]acetate (11.3 g) and 10% palladium on activated carbon (50% wet, 550 mg) in methanol (110 ml) was stirred at room temperature in the presence of hydrogen at an atmospheric pressure for 5.5  
30 hours. After filtration, the filtrate was evaporated under reduced pressure and dried in vacuo to give tert-butyl (4-hydroxyphenyl)acetate (8.56 g).

NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.44 (9H, s), 3.45 (2H, s), 6.7-6.9 (2H, m), 7.05-7.15 (2H, m)

35 (+)ESI-MS (m/z): 231 (M+Na)<sup>+</sup>

Preparation 54

Under nitrogen at room temperature, to a solution of tert-butyl benzyl[2-[4-[(triisopropylsilyl)thio]phenyl]-ethyl]carbamate (210 mg) in toluene (3 ml) were added tert-butyl [4-[[4-[(trifluoromethyl)sulfonyl]oxy]phenyl]acetate (157 mg), bis(dibenzylideneacetone)palladium(0) (24.2 mg) bis(2-diphenylphosphinophenyl)ether (22.6 mg) and cesium fluoride (70.2 mg), and the mixture was stirred at 80°C for 17 hours. The resulting mixture was poured into water 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 give tert-butyl [4-[[4-[2-[benzyl(tert-butoxycarbonyl)amino]ethyl]phenyl]thio]phenyl]acetate (136 mg).

NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.43 (9H, s), 1.46 (9H, s), 2.65-2.9 (2H, m), 3.25-3.5 (4H, m), 4.3-4.45 (2H, m), 6.95-7.4 (13H, m)  
(+)ESI-MS (m/z): 556 (M+Na)<sup>+</sup>

Preparation 55

Under nitrogen at room temperature, to a solution of tert-butyl [4-[[4-[2-[benzyl(tert-butoxycarbonyl)amino]-ethyl]phenyl]sulfonyl]phenyl]acetate (725 mg) in dichloromethane (5 ml) was added trifluoroacetic acid (1 ml), and the mixture was stirred at the same temperature for 4 hours. The resulting mixture was evaporated under reduced pressure. Under nitrogen at room temperature, to the residue in ethanol (10 ml) was added 4N hydrogen chloride in 1,4-dioxane (2 ml), and the mixture was stirred at the same temperature overnight. The resulting mixture was evaporated under reduced pressure. The residue was dissolved into a mixture of saturated aqueous sodium bicarbonate and ethyl

acetate. After separation, the organic layer was dried over anhydrous magnesium sulfate, evaporated under reduced pressure and dried in vacuo to give ethyl [4-[[4-[2-(benzylamino)ethyl]phenyl]sulfonyl]phenyl]acetate (573 mg).

5        NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.24 (3H, t, J=7.1Hz), 2.75-2.95 (4H, m), 3.65 (2H, s), 3.79 (2H, s), 4.14 (2H, q, J=7.1Hz), 7.15-7.5 (9H, m), 7.8-7.95 (4H, m)  
      (+)ESI-MS (m/z): 438 (M+H)<sup>+</sup>

#### 10    Preparation 56

      Under nitrogen at room temperature, to a mixture of bis(dibenzylideneacetone)palladium(0) (13.1 mg) and bis(2-diphenylphosphinophenyl)ether (13.3 mg) was added toluene (2 ml). After being stirred at the same temperature for 15  
15    minutes, tert-butyl benzyl[2-(4-iodophenyl)ethyl]carbamate (200 mg) in toluene (2 ml), potassium tert-butoxide (61.6 mg) and triisopropylsilanethiol (0.108 ml) were added, and the mixture was stirred at 80°C for 1 hour. The resulting mixture was poured into saturated aqueous sodium bicarbonate  
20    and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed successively with water and brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 20:1)  
25    to give tert-butyl benzyl[2-4-[(triisopropylsilyl)thio]-phenyl]ethyl carbamate (210 mg).

      NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.07 (18H, d, J=6.3Hz), 1.1-1.3 (3H, m), 1.4-1.6 (9H, m), 2.65-2.85 (2H, m), 3.2-3.45 (2H, m), 4.2-4.35 (2H, m), 6.9-7.45 (9H, m)

30

#### Preparation 57

      Under nitrogen, a mixture of formic acid (0.828 ml) and acetic anhydride (2.07 ml) was stirred at 5°C for 30 minutes. To this one was added (R)-1-phenoxy-2-propanamine (1.66 g)  
35    in dichloromethane (5 ml), and the mixture was stirred at

room temperature for 2 hours. The resulting mixture was poured into water and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed successively with saturated aqueous sodium bicarbonate, water and brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 1:1 to 1:2) to give (R)-1-methyl-2-phenoxyethylformamide (147 g).

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 1.3-1.4 (3H, m), 3.8-4.1 (2H, m), 4.35-4.5 (1H, m), 6.8-7.05 (3H, m), 7.2-7.4 (2H, m), 8.17 (1H, s)

(+)ESI-MS ( $m/z$ ): 202 ( $M+\text{Na}$ )<sup>+</sup>

#### Preparation 58

A mixture of 4-mercaptophenol (16.2 g) in dimethyl sulfoxide (15 ml) was stirred at 80°C for 5 hours. The resulting mixture was poured into a mixture of water and the aqueous mixture was extracted with hexane/ethyl acetate (1:1). After separation, the organic layer was washed successively with water two times and brine, dried over anhydrous magnesium sulfate, evaporated under reduced pressure and dried in vacuo to give di(4-hydroxyphenyl)-disulfide (16.54 g).

(-)ESI-MS ( $m/z$ ): 249 ( $M-\text{H}$ )<sup>-</sup>

#### Preparation 59

Under nitrogen at room temperature, to a solution of N-benzylethanolamine (50 g) in methanol (250 ml) was added ethyl trifluoroacetate (59 ml) dropwise, and the mixture was stirred at 45°C for 2 hours. The resulting mixture was evaporated under reduced pressure. The residue was dissolved into a mixture of 1N hydrochloric acid and hexane/ethyl acetate (1:1). After separation, the organic layer was washed successively with water, saturated aqueous sodium bicarbonate and brine, dried over anhydrous magnesium

sulfate, evaporated under reduced pressure and dried in vacuo to give N-benzyl-2,2,2-trifluoro-N-(2-hydroxyethyl)-acetamide (64 g).

(+)ESI-MS (m/z): 270 (M+Na)<sup>+</sup>

5

#### Preparation 60

To a solution of (R)-2-chloro-4-[[4-[2-  
[(trifluoroacetyl)amino]propyl]phenyl]sulfonyl]phenyl  
trifluoromethanesulfonate (1.0 g) and 3-  
10 ethoxycarbonylphenylboronic acid (455 mg) in 1,2-  
dimethoxyethane (10 ml) were added  
tetrakis(triphenylphosphine)palladium(0) (104 mg) and 2M  
sodium carbonate (1.90 ml) at room temperature, and the  
mixture was stirred at 80°C for 4 hours. The resulting  
15 mixture was poured into water 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  
20 = 3:1 to 2:1) to give ethyl (R)-2'-chloro-4'-[[4-[2-  
[(trifluoroacetyl)amino]propyl]phenyl]sulfonyl]-1,1'-  
biphenyl-3-carboxylate (783 mg).

NMR (CDCl<sub>3</sub>, δ): 1.23 (3H, d, J=6.7Hz), 1.39 (3H, t,  
J=7.1Hz), 2.8-3.1 (2H, m), 4.2-4.5 (3H, m), 7.38  
25 (2H, d, J=8.3Hz), 7.4-7.6 (3H, m), 7.8-8.2 (6H, m)

(+)ESI-MS (m/z): 576 (M+Na)<sup>+</sup>

#### Preparation 61

Under nitrogen at room temperature, to a solution of  
30 (R)-1-phenoxy-2-propanamine (1.4 g) in methanol (7 ml) was  
added ethyl trifluoroacetate (1.32 ml) dropwise, and the  
mixture was stirred at the same temperature overnight. The  
resulting mixture was evaporated under reduced pressure and  
dried in vacuo to give (R)-2,2,2-trifluoro-N-(1-methyl-2-  
35 phenoxyethyl)acetamide (2.13 g).

NMR (CDCl<sub>3</sub>, δ): 1.41 (3H, d, J=6.9Hz), 3.9-4.1 (2H, m),  
4.3-4.55 (1H, m), 6.85-7.05 (3H, m), 7.2-7.4 (2H,  
m)

(+)ESI-MS (m/z): 270 (M+Na)<sup>+</sup>

5

#### Preparation 62

To a solution of 2,2,2-trifluoro-N-[3-[4-[(3-methoxyphenyl)sulfonyl]phenyl]propyl]acetamide (6.13 g) in 1,4-dioxane (61 ml) was added 1N sodium hydroxide solution  
10 (23 ml), and the mixture was stirred at room temperature for 12 hours. After being concentrated, the mixture was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over magnesium sulfate, and filtered. The filtrate was concentrated to give 3-[4-  
15 [(3-methoxyphenyl)sulfonyl]phenyl]propylamine (3.46 g) as a pale yellow oil.

NMR (CDCl<sub>3</sub>, δ): 1.76 (2H, quintet, J=7Hz), 2.60-2.82  
(4H, m), 3.84 (3H, s), 7.01-7.13 (1H, m), 7.20-  
7.55 (5H, m), 7.85 (2H, d, J=8Hz)

20 (+)ESI-MS (m/z): 306 (M+H)<sup>+</sup>

#### Preparation 63

Under nitrogen atmosphere, to an ice-cooled solution of 4-iodophenol (15.40 g), triphenylphosphine (22.03 g), and  
25 tert-butyl benzyl(2-hydroxyethyl)carbamate (21.05 g) in tetrahydrofuran (123 ml) was added diethyl azodicarboxylate (14.58 g) in tetrahydrofuran (31 ml) for 25 minutes, and the mixture was stirred at room temperature for 2 hours. After being concentrated, the mixture was treated with  
30 hexane/ethyl acetate (5/1, 180 ml). The precipitate formed was filtered off, the filtrate was concentrated, and the residue was purified by column chromatography (silica gel, hexane/ethyl acetate) to give tert-butyl benzyl[2-(4-iodophenoxy)ethyl]carbamate (7.17 g) as a colorless oil.

35 NMR (CDCl<sub>3</sub>, δ): 1.45 (9H, s), 3.58 (2H, br s), 4.07 (2H,



br s), 4.55 (2H, s), 6.62 (2H, d, J=8Hz), 7.10-  
7.40 (5H, m), 7.53 (2H, d, J=8Hz)  
(+)ESI-MS (m/z): 476 (M+Na)<sup>+</sup>

#### 5 Preparation 64

To a solution of N-[2-[4-[[4-[2-[benzyl(2,2,2-  
trifluoroacetyl)amino]ethoxy]phenyl]dithio]phenoxy]ethyl]-N-  
benzyl-2,2,2-trifluoroacetamide (359 mg) in  
ethanol/tetrahydrofuran (2/1, 5.4 ml) was added  
10 triphenylphosphine (142 mg), and the mixture was stirred at  
room temperature for 6 hours. 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  
15 concentrated to give N-benzyl-2,2,2-trifluoro-N-[2-(4-  
mercaptophenoxy)ethyl]acetamide (525 mg) as a colorless oil.  
NMR (CDCl<sub>3</sub>, δ): 3.37 (1H, s), 3.55-3.85 (2H, m), 4.00-  
4.20 (2H, m), 4.80, 4.84 (total 2H, a pair of s),  
6.75 (2H, d, J=9Hz), 7.05-7.85 (7H, m)  
20 (-)APCI-MS (m/z): 354 (M-H)<sup>-</sup>

#### Preparation 65

To a solution of methyl 5-iodosalicylate (5.56 g) in  
N,N-dimethylformamide (56 ml) were added powdered potassium  
25 carbonate (3.04 g) and benzyl bromide (2.6 ml), and the  
mixture was stirred at room temperature for 45 hours. The  
mixture was partitioned between hexane/ethyl acetate (1/2)  
and water. The organic layer was separated, washed  
successively with water and brine, dried over magnesium  
30 sulfate, and filtered. The solvent was evaporated to give  
methyl 2-benzyloxy-5-iodobenzoate (8.07 g) as a pale yellow  
oil.

NMR (CDCl<sub>3</sub>, δ): 3.90 (3H, s), 5.17 (2H, s), 6.78 (1H, d,  
J=9Hz), 7.26-7.52 (5H, m), 7.69 (1H, dd, J=9, 2Hz),  
35 8.10 (1H, d, J=2Hz)

(+)ESI-MS (m/z): 391 (M+Na)<sup>+</sup>

#### Preparation 66

Chlorosulfonic acid (10 ml) was cooled in an ice bath  
5 whereupon methyl salicylate (7.60 g) was added dropwise over  
20 minutes. The mixture was heated to 40°C for 30 minutes,  
allowed to cool to room temperature, and poured onto crashed  
ice. The precipitate formed was collected, washed with  
water, and dried in vacuo to give methyl 5-chlorosulfonyl-2-  
10 hydroxybenzoate (7.89 g) as a white powder.

NMR (CDCl<sub>3</sub>, δ): 4.04 (3H, s), 7.18 (1H, d, J=9Hz), 8.09  
(1H, dd, J=9, 2Hz), 8.57 (1H, d, J=2Hz), 11.55 (1H,  
s, OH)

#### 15 Preparation 67

Methyl 5-[[4-[[[(2R)-2-(formylamino)propyl]oxy]phenyl]-  
sulfonyl]-2-hydroxybenzoate (1.60 g) and hydrogen chloride  
in methanol (10-20%, 16 ml) were mixed and stirred at room  
temperature for 12 hours. The solvent was evaporated to  
20 give methyl 5-[[4-[[[(2R)-2-aminopropyl]oxy]phenyl]sulfonyl]-  
2-hydroxybenzoate hydrochloride (1.67 g) as a white solid.

NMR (DMSO-d<sub>6</sub>, δ): 1.28 (3H, d, J=7Hz), 3.35-3.75 (1H,  
m), 3.89 (3H, s), 3.92-4.32 (2H, m), 7.18 (1H, d,  
J=9Hz), 7.19 (2H, d, J=9Hz), 7.90 (2H, d, J=9Hz),  
25 7.97 (1H, dd, J=9, 2Hz), 8.21 (1H, d, J=2Hz),  
11.27 (1H, s, OH)

(+)ESI-MS (m/z): 366 (free, M+H)<sup>+</sup>

#### Preparation 68

30 To a solution of methyl 2-hydroxy-5-[[4-[3-  
[(trifluoroacetyl)amino]propyl]phenyl]sulfonyl]benzoate  
(4.43 g) in N,N-dimethylformamide (35 ml) were added  
powdered potassium carbonate (2.73 g) and iodomethane (0.93  
ml), and the mixture was stirred at 50°C for 2 hours. After  
35 being allowed to cool to room temperature, the mixture was

partitioned between hexane/ethyl acetate (1/2) and water. The organic layer was separated, washed successively with water and brine, dried over magnesium sulfate, and filtered. The filtrate was concentrated to give methyl 2-methoxy-5-  
5 [[4-[3-[(trifluoroacetyl)amino]propyl]phenyl]sulfonyl]-benzoate (4.81 g) as a pale yellow solid.

NMR (CDCl<sub>3</sub>, δ): 1.92 (2H, quintet, J=7Hz), 2.68 (2H, t, J=7Hz), 3.38 (2H, q, J=7Hz), 3.86 (3H, s), 3.95 (3H, s), 6.40 (1H, br s), 7.06 (1H, d, J=9Hz),  
10 7.31 (2H, d, J=8Hz), 7.85 (2H, d, J=8Hz), 8.03 (1H, dd, J=9, 2Hz), 8.34 (1H, d, J=2Hz)  
(-)ESI-MS (m/z): 458 (M-H)<sup>-</sup>

#### Preparation 69

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

(1) (R)-2,2,2-Trifluoro-N-[2-[4-[(3-methoxyphenyl)thio]-phenyl]-1-methylethyl]acetamide

20 NMR (CDCl<sub>3</sub>, δ): 1.22 (3H, d, J=6.7Hz), 2.7-2.95 (2H, m), 3.75 (3H, s), 4.2-4.35 (1H, m), 6.7-6.95 (3H, m), 7.05-7.35 (5H, m)  
(+)ESI-MS (m/z): 392 (M+Na)<sup>+</sup>

25 (2) 2,2,2-Trifluoro-N-[3-[4-[(3-methoxyphenyl)thio]-phenyl]propyl]acetamide

NMR (CDCl<sub>3</sub>, δ): 1.92 (2H, quintet, J=7Hz), 2.67 (2H, t, J=7Hz), 3.40 (2H, q, J=7Hz), 3.76 (3H, s), 6.25 (1H, br s), 6.65-6.95 (3H, m), 7.13 (2H, d, J=8Hz),  
30 7.20 (1H, t, J=8Hz), 7.32 (2H, d, J=8Hz)  
(+)ESI-MS (m/z): 392 (M+Na)<sup>+</sup>

(3) tert-Butyl benzyl[2-[4-[(4-hydroxyphenyl)thio]-phenoxy]ethyl]carbamate

35 NMR (CDCl<sub>3</sub>, δ): 1.45 (9H, s), 3.58 (2H, br s), 4.07 (2H,

br s), 4.55 (2H, s), 5.20 (1H, br s, OH), 6.77 (4H, d, J=8Hz), 7.10-7.42 (9H, m)  
(+)ESI-MS (m/z): 474 (M+Na)<sup>+</sup>

- 5 (4) Methyl 2-benzyloxy-5-[[4-[2-[benzyl(trifluoroacetyl)-amino]ethoxy]phenyl]thio]benzoate  
NMR (CDCl<sub>3</sub>, δ): 3.60-3.83 (2H, m), 3.88 (3H, s), 4.02-4.22 (2H, m), 4.81, 4.85 (total 2H, a pair of s),  
5.16 (2H, s), 6.80 (2H, d, J=9Hz), 6.93 (1H, d, J=9Hz),  
10 7.15-7.55 (13H, m), 7.80 (1H, d, J=2Hz)  
(+)ESI-MS (m/z): 618 (M+Na)<sup>+</sup>

#### Preparation 70

The following compounds were obtained according to a  
15 similar manner to that of Preparation 24.

- (1) Ethyl (R)-3-[3-[[4-[2-[(trifluoroacetyl)amino]propyl]phenyl]thio]phenoxy]benzoate  
NMR (CDCl<sub>3</sub>, δ): 1.21 (3H, d, J=6.6Hz), 1.39 (3H, t, J=7.3Hz), 2.7-2.95 (2H, m), 4.2-4.45 (3H, m),  
20 6.75-7.85 (12H, m)  
(+)ESI-MS (m/z): 526 (M+Na)<sup>+</sup>
- (2) Ethyl 4-[3-[[4-[2-[benzyl(tert-butoxycarbonyl)amino]ethyl]phenyl]thio]phenoxy]benzoate  
25 NMR (CDCl<sub>3</sub>, δ): 1.38 (3H, t, J=7.2Hz), 1.4-1.55 (9H, m), 2.7-2.9 (2H, m), 3.3-3.5 (2H, m), 4.3-4.5 (4H, m), 6.8-7.4 (15H, m), 7.95-8.0 (2H, m)  
(+)ESI-MS (m/z): 606 (M+Na)<sup>+</sup>  
30
- (3) Ethyl 3-[3-[[4-[2-[benzyl(tert-butoxycarbonyl)amino]ethyl]phenyl]thio]phenoxy]benzoate  
NMR (CDCl<sub>3</sub>, δ): 1.39 (3H, t, J=7.2Hz), 1.4-1.55 (9H, m), 2.65-2.85 (2H, m), 3.25-3.5 (2H, m), 4.3-4.5 (4H, m),  
35 6.75-7.4 (15H, m), 7.64 (1H, m), 7.76 (1H, m)

(+)ESI-MS (m/z): 606 (M+Na)<sup>+</sup>

#### Preparation 71

The following compound was obtained according to a  
5 similar manner to that of Preparation 48.

(R)-4-[2-[(Trifluoroacetyl)amino]propyl]benzenesulfonyl  
chloride

NMR (CDCl<sub>3</sub>, δ): 1.27 (3H, d, J=6.7Hz), 2.92 (1H, dd,  
10 J=7.3, 13.6Hz), 3.07 (1H, dd, J=6.1, 13.6Hz), 4.32  
(1H, h, J=7.0Hz), 6.19 (1H, br), 7.44 (2H, d,  
J=8.5Hz), 8.00 (2H, d, J=8.5Hz)

#### Preparation 72

15 The following compounds were obtained according to a  
similar manner to that of Preparation 60.

(1) Ethyl (R)-3'-[[4-[2-[(trifluoroacetyl)amino]propyl]-  
phenyl]sulfonyl]-1,1'-biphenyl-3-carboxylate

20 NMR (CDCl<sub>3</sub>, δ): 1.21 (3H, d, J=6.7Hz), 1.42 (3H, t,  
J=7.1Hz), 2.75-3.05 (2H, m), 4.15-4.35 (1H, m),  
4.43 (2H, q, J=7.1Hz), 7.33 (2H, d, J=8.3Hz),  
7.45-8.3 (10H, m)

(+)ESI-MS (m/z): 542 (M+Na)<sup>+</sup>

25

(2) Ethyl 2'-(methoxymethoxy)-4'-[[4-[2-[(trifluoroacetyl)-  
amino]ethyl]phenyl]sulfonyl]-1,1'-biphenyl-3-  
carboxylate

30 NMR (CDCl<sub>3</sub>, δ): 1.26 (3H, t, J=7.1Hz), 2.97 (2H, t,  
J=7.1Hz), 3.93 (3H, s), 2.6-2.65 (2H, m), 4.38 (2H,  
q, J=7.1Hz), 5.18 (2H, s), 7.36 (2H, d, J=8.4Hz),  
7.45-7.55 (2H, m), 7.6-7.7 (2H, m), 7.76 (1H, m),  
7.96 (2H, d, J=8.4Hz), 8.05 (1H, d, J=7.8Hz), 8.15  
(1H, m)

35 (+)ESI-MS (m/z): 588 (M+Na)<sup>+</sup>

Preparation 73

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

5

2,2,2-Trifluoro-N-[3-(4-iodophenyl)propyl]acetamide

NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.90 (2H, quintet, J=7Hz), 2.62 (2H, t, J=7Hz), 3.38 (2H, q, J=7Hz), 6.26 (1H, br s), 6.93 (2H, d, J=8Hz), 7.62 (2H, d, J=8Hz)

10 (+)ESI-MS (m/z): 380 (M+Na)<sup>+</sup>

Preparation 74

The following compound was obtained according to a similar manner to that of Preparation 62.

15

(1R)-2-[4-[(2-Methoxyphenyl)sulfonyl]phenyl]-1-methylethylamine

NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.12 (3H, d, J=6Hz), 2.62 (1H, dd, J=13, 8Hz), 2.75 (1H, dd, J=13, 6Hz), 3.08-3.34 (1H, m),  
20 3.77 (3H, s), 6.91 (1H, d, J=8Hz), 7.10 (1H, t, J=8Hz), 7.30 (2H, d, J=8Hz), 7.44-7.64 (1H, m), 7.90 (2H, d, J=8Hz), 8.15 (1H, d, J=8Hz)

(+)ESI-MS (m/z): 306 (M+H)<sup>+</sup>

25 Preparation 75

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

N-[3-[4-[[4-(Benzyloxy)-3-hydroxyphenyl]sulfonyl]-phenyl]propyl]-2,2,2-trifluoroacetamide

30 NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.89 (2H, quintet, J=7Hz), 2.69 (2H, t, J=7Hz), 3.36 (2H, q, J=7Hz), 5.14 (2H, s), 5.93 (1H, s, OH), 6.60 (1H, br s), 6.97 (1H, d, J=8Hz), 7.15-7.60 (9H, m), 7.80 (2H, d, J=8Hz)

35 (-)ESI-MS (m/z): 492 (M-H)<sup>-</sup>

Preparation 76

The following compound was obtained according to a similar manner to that of Preparation 15.

5

N-[3-[4-[4-Benzyloxy-3-(methoxymethoxy)phenyl]-sulfonyl]phenyl]propyl]-2,2,2-trifluoroacetamide

NMR (CDCl<sub>3</sub>, δ): 1.95 (2H, quintet, J=7Hz), 2.71 (2H, t, J=7Hz), 3.37 (2H, q, J=7Hz), 3.50 (3H, s), 5.17 (2H, s), 5.24 (2H, s), 6.34 (1H, br s), 6.96 (1H, d, J=9Hz), 7.16-7.50 (7H, m), 7.54 (1H, dd, J=9, 2Hz), 7.67 (1H, d, J=2Hz), 7.83 (2H, d, J=8Hz)  
(+)ESI-MS (m/z): 560 (M+Na)<sup>+</sup>

15 Preparation 77

The following compound was obtained according to a similar manner to that of Preparation 63.

N-[2-[4-[4-[2-[Benzyl(2,2,2-trifluoroacetyl)amino]-ethoxy]phenyl]dithio]phenoxy]ethyl]-N-benzyl-2,2,2-trifluoroacetamide

NMR (CDCl<sub>3</sub>, δ): 3.55-3.85 (4H, m), 4.00-4.25 (4H, m), 4.80, 4.84 (total 4H, a pair of s), 6.79 (4H, d, J=8Hz), 7.10-7.50 (14H, m)  
(+)ESI-MS (m/z): 731 (M+Na)<sup>+</sup>

25

Example 1

Under nitrogen at room temperature, to a solution of methyl 4-[[4-(2-aminoethyl)phenyl]sulfonyl]-2-pyridinecarboxylate (335 mg) in dimethylsulfoxide (5 ml) was added N,O-bis(trimethylsilyl)acetamide (0.127 ml), and the mixture was stirred at the same temperature for 1 hour. To this one was added (R)-2-(3-chlorophenyl)oxirane (194 mg) and the mixture was stirred at 80°C for 20 hours. The resulting mixture was cooled to room temperature and 10%

35

aqueous acetic acid was added. After being stirred for 20 minutes, the mixture was poured into saturated aqueous sodium bicarbonate and the aqueous mixture was extracted with chloroform. The organic layer was washed successively  
5 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/methanol = 20:1 to 15:1) to give methyl (R)-4-  
[[4-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]-  
10 phenyl]sulfonyl]-2-pyridinecarboxylate (158 mg).

NMR (CDCl<sub>3</sub>,  $\delta$ ): 2.6-3.1 (6H, m), 4.03 (3H, s), 4.6-4.7  
(1H, m), 7.15-8.05 (8H, m), 8.45-8.75 (2H, m),  
8.95 (1H, d, J=5.0Hz)

(+)ESI-MS (m/z): 475, 477 (M+H)<sup>+</sup>

15

#### Example 2

To a suspension of methyl (R)-4-[[4-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-2-pyridinecarboxylate (155 mg) in a mixture of ethanol (3 ml)  
20 and tetrahydrofuran (1.5 ml) was added 1N sodium hydroxide (0.326 ml) at room temperature, and the mixture was stirred at the same temperature for 3.5 hours. The resulting mixture was evaporated under reduced pressure. The residue was purified by reversed phase chromatography to give sodium  
25 (R)-4-[[4-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]-ethyl]phenyl]sulfonyl]-2-pyridinecarboxylate (3.9 mg).

NMR (DMSO-d<sub>6</sub>,  $\delta$ ): 2.55-2.85 (6H, m), 4.5-4.65 (1H, m),  
7.2-7.35 (4H, m), 7.48 (2H, d, J=8.3Hz), 7.75-7.8  
(1H, m), 7.87 (2H, d, J=8.3Hz), 8.15 (1H, br s),  
30 8.72 (1H, d, J=5.0Hz)

(-)ESI-MS (m/z): 459, 461 (M-Na)<sup>-</sup>

#### Example 3

The following compounds were obtained according to a  
35 similar manner to that of Example 6.



- (1) Ethyl 5-[[4-[2-[benzyl[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-2-hydroxybenzoate
- 5 NMR (CDCl<sub>3</sub>, δ): 1.45 (3H, t, J=7Hz), 2.45-3.00 (6H, m), 3.54 (1H, d, J=13Hz), 3.63 (1H, br s, OH), 3.90 (1H, d, J=13Hz), 4.45 (2H, q, J=7Hz), 4.60 (1H, dd, J=10, 4Hz), 7.05 (1H, d, J=9Hz), 7.05-7.40 (11H, m), 7.80 (2H, d, J=8Hz), 7.92 (1H, dd, J=9, 2Hz), 8.49 (1H, d, J=2Hz), 11.40 (1H, s, OH)
- 10 (+)ESI-MS (m/z): 594 (M+H)<sup>+</sup>
- (2) Ethyl 3-[4-[[4-[(2R)-2-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]phenoxy]-benzoate
- 15 NMR (CDCl<sub>3</sub>, δ): 1.06 (3H, d, J=6.2Hz), 1.37 (3H, t, J=7.1Hz), 2.6-3.0 (5H, m), 4.37 (2H, q, J=7.1Hz), 4.55 (1H, dd, J=3.8, 8.5Hz), 6.95-7.1 (2H, m), 7.1-7.55 (8H, m), 7.7 (1H, m), 7.8-7.95 (5H, m)
- 20 (+)ESI-MS (m/z): 594, 596 (M+H)<sup>+</sup>
- (3) Ethyl (R)-2-[4-[[4-[2-[benzyl[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]phenoxy]-benzoate
- 25 NMR (CDCl<sub>3</sub>, δ): 1.06 (3H, t, J=7.1Hz), 2.5-2.95 (6H, m), 3.55 (1H, d, J=13.4Hz), 3.91 (1H, d, J=13.4Hz), 4.16 (2H, q, J=7.1Hz), 4.62 (1H, dd, J=3.5, 9.8Hz), 6.85-7.35 (15H, m), 7.5-7.6 (1H, m), 7.7-8.0 (5H, m)
- 30 (+)ESI-MS (m/z): 670, 672 (M+H)<sup>+</sup>
- (4) Ethyl (R)-2-[3-[[4-[2-[benzyl[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]phenoxy]-benzoate
- 35 NMR (CDCl<sub>3</sub>, δ): 1.06 (3H, t, J=7.1Hz), 2.5-2.95 (6H, m),

3.56 (1H, d, J=13.4Hz), 3.92 (1H, d, J=13.4Hz),  
4.15 (2H, d, J=7.1Hz), 4.62 (1H, dd, J=3.7, 9.8Hz),  
6.95-7.6 (18H, m), 7.75-7.85 (2H, m), 7.9-8.0 (1H,  
m)

5 (+)ESI-MS (m/z): 670 (M+H)<sup>+</sup>

(5) Ethyl (R)-[4-[4-[2-[benzyl[2-(3-chlorophenyl)-2-  
hydroxyethyl]amino]ethyl]phenyl]sulfonyl]phenyl]acetate

10 NMR (CDCl<sub>3</sub>, δ): 1.25 (3H, t, J=7.3Hz), 2.52-2.95 (6H, m),  
3.55 (1H, d, J=13.4Hz), 3.64 (2H, s), 3.90 (1H, d,  
J=13.4Hz), 4.12 (2H, t, J=7.3Hz), 4.61 (1H, dd,  
J=3.7, 9.8Hz), 7.1-7.35 (11H, m), 7.41 (2H, d,  
J=8.3Hz), 7.75-7.95 (4H, m)

(+)ESI-MS (m/z): 592, 594 (M+H)<sup>+</sup>

15

(6) (R)-4-[4-[2-[Benzyl[2-(3-chlorophenyl)-2-  
hydroxyethyl]amino]ethyl]phenyl]sulfonylphenol

20 NMR (CDCl<sub>3</sub>, δ): 2.5-2.95 (6H, m), 3.5-3.95 (2H, m),  
4.55-4.65 (1H, m), 6.85-6.95 (2H, m), 7.1-7.4 (11H,  
m), 7.75-7.9 (4H, m)

(+)ESI-MS (m/z): 522, 524 (M+H)<sup>+</sup>

(7) Ethyl 3-[3-[4-[(2R)-2-[(2R)-2-(3-chlorophenyl)-2-  
hydroxyethyl]amino]propyl]phenyl]sulfonyl]phenoxy]-  
25 benzoate

NMR (CDCl<sub>3</sub>, δ): 1.07 (3H, d, J=6.2Hz), 1.38 (3H, t,  
J=7.2Hz), 2.6-3.0 (5H, m), 4.37 (2H, q, J=7.2Hz),  
4.5-4.6 (1H, m), 7.1-7.7 (13H, m), 7.8-7.9 (3H, m)

(+)APCI-MS (m/z): 594 (M+H)<sup>+</sup>

30

(8) Ethyl 4'-[4-[(2R)-2-[(2R)-2-(3-chlorophenyl)-2-  
hydroxyethyl]amino]propyl]phenyl]sulfonyl]-1,1'-  
biphenyl-3-carboxylate

35 NMR (CDCl<sub>3</sub>, δ): 1.06 (3H, d, J=6.1Hz), 1.44 (3H, t,  
J=7.1Hz), 2.6-3.0 (5H, m), 4.41 (2H, q, J=7.1Hz),

7.1-7.35 (6H, m), 7.55 (1H, t, J=7.7Hz), 7.65-8.1  
(8H, m), 8.2-8.25 (1H, m)  
(+)ESI-MS (m/z): 578, 580 (M+H)<sup>+</sup>

5 (9) Ethyl 3'-[[4-[(2R)-2-[[[(2R)-2-(3-chlorophenyl)-2-  
hydroxyethyl]amino]propyl]phenyl]sulfonyl]-1,1'-  
biphenyl-3-carboxylate  
NMR (CDCl<sub>3</sub>, δ): 1.05 (3H, d, J=6.1Hz), 1.42 (3H, t,  
J=7.2Hz), 2.55-3.0 (5H, m), 4.42 (2H, q, J=7.2Hz),  
10 4.45-4.55 (1H, m), 7.1-7.35 (6H, m), 7.45-7.65 (2H,  
m), 7.7-8.3 (8H, m)  
(+)ESI-MS (m/z): 578 (M+H)<sup>+</sup>

(10) (R)-3-[[4-[2-[Benzyl[2-(3-chlorophenyl)-2-  
15 hydroxyethyl]amino]ethyl]phenyl]sulfonyl]phenol  
NMR (CDCl<sub>3</sub>, δ): 2.45-3.0 (6H, m), 3.5-4.0 (2H, m),  
4.45-4.55 (1H, m), 6.9-7.45 (14H, m), 7.5-7.55 (1H,  
m), 7.8-7.9 (2H, m)  
(+)APCI-MS (m/z): 522, 524 (M+H)<sup>+</sup>

20 (11) Ethyl (R)-3-[3-[[4-[2-[benzyl[2-(3-chlorophenyl)-2-  
hydroxyethyl]amino]ethyl]phenyl]sulfonyl]phenoxy]-  
benzoate  
NMR (CDCl<sub>3</sub>, δ): 1.38 (3H, t, J=7.1Hz), 2.5-2.95 (6H, m),  
25 3.55 (1H, d, J=13.4Hz), 3.91 (1H, d, J=13.4Hz),  
4.37 (2H, q, J=7.1Hz), 7.1-7.5 (15H, m), 7.55-7.7  
(3H, m), 7.75-7.9 (3H, m)  
(+)ESI-MS (m/z): 670, 672 (M+H)<sup>+</sup>

30 (12) Ethyl 5-[[4-[3-[[[(2R)-2-(3-chlorophenyl)-2-  
hydroxyethyl]amino]propyl]phenyl]sulfonyl]-2-  
methoxybenzoate  
NMR (CDCl<sub>3</sub>, δ): 1.38 (3H, t, J=7Hz), 1.82 (2H, quintet,  
J=7Hz), 2.55-3.00 (6H, m), 3.93 (3H, s), 4.36 (2H,  
35 q, J=7Hz), 4.69 (1H, dd, J=9, 4Hz), 7.04 (1H, d,

J=9Hz), 7.10-7.45 (6H, m), 7.83 (2H, d, J=8Hz),  
8.02 (1H, dd, J=9, 2Hz), 8.32 (1H, d, J=2Hz)  
(+)ESI-MS (m/z): 532 (M+H)<sup>+</sup>

- 5 (13) Ethyl (R)-4-[3-[[4-[2-[benzyl[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]phenoxy]-benzoate  
NMR (CDCl<sub>3</sub>, δ): 1.39 (3H, t, J=7.1Hz), 2.55-2.95 (6H, m), 3.55 (1H, d, J=13.4Hz), 3.91 (1H, d, J=13.4Hz),  
10 4.38 (2H, q, J=7.1Hz), 4.61 (1H, dd, J=3.6, 9.8Hz), 6.95-7.05 (2H, m), 7.1-7.35 (12H, m), 7.4-7.75 (3H, m), 7.80 (2H, d, J=8.2Hz), 8.0-8.1 (2H, m)  
(+)ESI-MS (m/z): 670, 672 (M+H)<sup>+</sup>

- 15 (14) Ethyl 4'-[[4-[2-[benzyl[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-2'-hydroxy-1,1'-biphenyl-3-carboxylate  
NMR (CDCl<sub>3</sub>, δ): 1.38 (3H, t, J=7.1Hz), 2.45-3.0 (6H, m), 3.54 (1H, d, J=13.4Hz), 3.92 (1H, d, J=13.4Hz),  
20 4.38 (2H, q, J=7.1Hz), 4.53 (1H, dd, J=3.8, 9.9Hz), 7.0-7.7 (16H, m), 7.90 (2H, d, J=8.3Hz), 8.0-8.2 (2H, m)  
(+)ESI-MS (m/z): 670, 672 (M+H)<sup>+</sup>

- 25 (15) Ethyl 4-[[4-[[[(2R)-2-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]oxy]phenyl]sulfonyl]benzoate  
NMR (CDCl<sub>3</sub>, δ): 1.19 (3H, d, J=6.5Hz), 1.39 (3H, t, J=7.1Hz), 2.71 (1H, dd, J=9.0, 12.2Hz), 2.97 (1H, dd, J=3.7, 12.2Hz), 3.05-3.2 (1H, m), 3.8-4.0 (2H, m),  
30 4.39 (2H, q, J=7.1Hz), 4.63 (1H, dd, J=3.6, 8.9Hz), 6.9-7.0 (2H, m), 7.15-7.4 (4H, m), 7.8-8.0 (4H, m), 8.1-8.2 (2H, m)  
(+)ESI-MS (m/z): 518, 520 (M+H)<sup>+</sup>

- 35 (16) 3-[[4-[3-[Benzyl[(2R)-2-(3-chlorophenyl)-2-

hydroxyethyl]amino]propyl]phenyl]sulfonyl]phenol

NMR (CDCl<sub>3</sub>, δ): 1.81 (2H, quintet, J=7Hz), 2.35-2.80  
(6H, m), 3.48 (1H, d, J=13Hz), 3.86 (1H, d,  
J=13Hz), 4.59 (1H, dd, J=10, 4Hz), 6.90-7.60 (15H,  
m), 7.80 (2H, d, J=8Hz)

(+)ESI-MS (m/z): 536 (M+H)<sup>+</sup>

(17) 4-[[4-[2-[Benzyl[(2R)-2-(3-chlorophenyl)-2-  
hydroxyethyl]amino]ethoxy]phenyl]sulfonyl]phenol

NMR (CDCl<sub>3</sub>, δ): 2.65 (1H, dd, J=13, 10Hz), 2.82-3.22  
(2H, m), 2.85 (1H, dd, J=13, 4Hz), 3.69 (1H, d,  
J=13Hz), 3.86-4.18 (2H, m), 3.94 (1H, d, J=13Hz),  
4.64 (1H, dd, J=10, 3Hz), 6.85 (2H, d, J=8Hz),  
6.91 (2H, d, J=8Hz), 7.05-7.40 (9H, m), 7.76 (2H,  
d, J=8Hz), 7.81 (2H, d, J=8Hz)

(+)ESI-MS (m/z): 538 (M+H)<sup>+</sup>

(18) 2-[[4-[(2R)-2-[Benzyl[(2R)-2-(3-chlorophenyl)-2-  
hydroxyethyl]amino]propyl]phenyl]sulfonyl]phenol

NMR (CDCl<sub>3</sub>, δ): 1.03 (3H, d, J=6Hz), 2.40-2.90 (4H, m),  
3.00-3.25 (1H, m), 3.47 (1H, d, J=13Hz), 3.56 (1H,  
br s, OH), 3.80 (1H, d, J=13Hz), 4.56 (1H, dd,  
J=10, 4Hz), 6.85-7.55 (14H, m), 7.66 (1H, t,  
J=8Hz), 7.77 (2H, d, J=8Hz), 9.23 (1H, br s)

(-)ESI-MS (m/z): 534 (M-H)<sup>-</sup>

(19) Ethyl 5-[[4-[3-[benzyl[(2R)-2-(3-chlorophenyl)-2-  
hydroxyethyl]amino]propyl]phenyl]sulfonyl]-2-  
hydroxybenzoate

NMR (CDCl<sub>3</sub>, δ): 1.45 (3H, t, J=7Hz), 1.80 (2H, quintet,  
J=7Hz), 2.32-2.80 (6H, m), 3.48 (1H, d, J=13Hz),  
3.87 (1H, d, J=13Hz), 3.90 (1H, br s, OH), 4.46 (2H,  
q, J=7Hz), 4.60 (1H, dd, J=10, 4Hz), 7.05 (1H, d,  
J=9Hz), 7.05-7.45 (11H, m), 7.80 (2H, d, J=8Hz),  
7.93 (1H, dd, J=9, 2Hz), 8.49 (1H, d, J=2Hz),

11.40 (1H, s, OH)

(20) Ethyl 4-[[4-[3-[benzyl[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-2-hydroxybenzoate

5 NMR (CDCl<sub>3</sub>, δ): 1.41 (3H, t, J=7Hz), 1.80 (2H, quintet, J=7Hz), 2.32-2.80 (6H, m), 3.48 (1H, d, J=13Hz), 3.87 (1H, d, J=13Hz), 3.88 (1H, br s, OH), 4.43 (2H, q, J=7Hz), 4.60 (1H, dd, J=10, 4Hz), 7.05-7.45 (11H, m), 7.41 (1H, dd, J=8, 2Hz), 7.51 (1H, d, J=2Hz), 7.82 (2H, d, J=8Hz), 7.96 (1H, d, J=8Hz), 11.01 (1H, s, OH)  
10 (+)ESI-MS (m/z): 608 (M+H)<sup>+</sup>

15 (21) Ethyl 5-[[4-[2-[benzyl[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethoxy]phenyl]sulfonyl]-2-hydroxybenzoate

NMR (CDCl<sub>3</sub>, δ): 1.49 (3H, t, J=7Hz), 2.64 (1H, dd, J=13, 10Hz), 2.83-3.20 (2H, m), 2.85 (1H, dd, J=13, 4Hz),  
20 3.69 (1H, d, J=13Hz), 3.90-4.10 (2H, m), 3.94 (1H, d, J=13Hz), 4.46 (2H, q, J=7Hz), 4.64 (1H, dd, J=10, 4Hz), 6.93 (2H, d, J=9Hz), 7.05 (1H, d, J=9Hz), 7.10-7.38 (9H, m), 7.85 (2H, d, J=9Hz), 7.92 (1H, dd, J=9, 2Hz), 8.47 (1H, d, J=2Hz),  
25 11.38 (1H, s, OH)  
(+)ESI-MS (m/z): 610 (M+H)<sup>+</sup>

(22) Ethyl 5-[[4-[[[(2R)-2-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]oxy]phenyl]sulfonyl]-2-hydroxybenzoate

30 NMR (CDCl<sub>3</sub>, δ): 1.19 (3H, d, J=6Hz), 1.45 (3H, t, J=7Hz), 2.70 (1H, dd, J=12, 9Hz), 2.97 (1H, dd, J=12, 4Hz), 3.00-3.25 (1H, m), 3.72-4.00 (2H, m), 4.45 (2H, q, J=7Hz), 4.63 (1H, dd, J=9, 4Hz), 6.96 (2H, d, J=9Hz), 7.05 (1H, d, J=9Hz), 7.12-7.45 (4H,  
35

m), 7.86 (2H, d, J=9Hz), 7.91 (1H, dd, J=9, 2Hz),  
8.46 (1H, d, J=2Hz)

(-)ESI-MS (m/z): 532 (M-H)<sup>-</sup>

- 5 (23) Ethyl 2-chloro-4-[[4-[3-[[[(2R)-2-(3-chlorophenyl)-2-  
hydroxyethyl]amino]propyl]phenyl]sulfonyl]benzoate  
NMR (CDCl<sub>3</sub>, δ): 1.39 (3H, t, J=7Hz), 1.94 (2H, quintet,  
J=7Hz), 2.60-3.10 (6H, m), 4.40 (2H, q, J=7Hz),  
4.89 (1H, dd, J=9, 4Hz), 7.10-7.45 (6H, m), 7.70-  
10 7.97 (4H, m), 7.99 (1H, s)  
(+)ESI-MS (m/z): 536 (M+H)<sup>+</sup>

#### Example 4

The following compound was obtained according to a  
15 similar manner to that of Example 23.

Ethyl 5-[[4-[2-[[[(2R)-2-(3-chlorophenyl)-2-  
hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-2-hydroxybenzoate  
hydrochloride

- 20 NMR (DMSO-d<sub>6</sub>, δ): 1.34 (3H, t, J=7Hz), 2.92-3.32 (6H,  
m), 4.37 (2H, q, J=7Hz), 4.98 (1H, m), 6.33 (1H,  
br s, OH), 7.19 (1H, d, J=9Hz), 7.25-7.60 (6H, m),  
7.91 (2H, d, J=8Hz), 8.00 (1H, dd, J=9, 2Hz), 8.23  
(1H, d, J=2Hz)  
25 (+)ESI-MS (m/z): 504 (free, M+H)<sup>+</sup>

#### Example 5

The following compounds were obtained according to a  
similar manner to that of Example 8.

30

- (1) Sodium [5-[[4-[3-[[[(2R)-2-(3-chlorophenyl)-2-  
hydroxyethyl]amino]propyl]phenyl]sulfonyl]-2-  
hydroxybenzoate  
NMR (DMSO-d<sub>6</sub>, δ): 2.50-2.85 (6H, m), 4.60 (1H, m), 5.39  
35 (1H, br s, OH), 6.72 (1H, d, J=9Hz), 7.12-7.50 (6H,

m), 7.65 (1H, dd, J=9, 2Hz), 7.73 (2H, d, J=8Hz),  
8.13 (1H, d, J=2Hz), 18.20 (1H, br s, OH)  
(-)ESI-MS (m/z): 474 (free, M-H)<sup>-</sup>

5 (2) Sodium (R)-2-[4-[[4-[2-[[2-(3-chlorophenyl)-2-  
hydroxyethyl]amino]ethyl]phenyl]sulfonyl]phenoxy]-  
benzoate  
NMR (DMSO-d<sub>6</sub>, δ): 2.65-2.85 (6H, m), 4.5-4.65 (2H, m),  
6.8-6.95 (3H, m), 7.1-7.6 (9H, m), 7.75-7.9 (4H,  
10 m)  
(-)ESI-MS (m/z): 550, 552 (M-Na)<sup>-</sup>

(3) Sodium 3-[4-[[4-[(2R)-2-[[2-(3-chlorophenyl)-2-  
hydroxyethyl]amino]propyl]phenyl]sulfonyl]phenoxy]-  
15 benzoate  
NMR (DMSO-d<sub>6</sub>, δ): 0.90 (3H, d, J=5.9Hz), 2.4-2.95 (5H,  
m), 4.45-4.55 (1H, m), 6.95-7.5 (11H, m), 7.65-  
7.95 (5H, m)  
(-)ESI-MS (m/z): 564, 566 (M-Na)<sup>-</sup>

20 (4) Sodium (R)-2-[3-[[4-(2-[[2-(3-chlorophenyl)-2-  
hydroxyethyl]amino]ethyl]phenyl]sulfonyl]phenoxy]-  
benzoate  
NMR (DMSO-d<sub>6</sub>, δ): 2.55-2.85 (6H, m), 4.55-4.7 (1H, m),  
25 6.85-7.6 (14H, m), 7.80 (2H, d, J=8.2Hz)  
(-)ESI-MS (m/z): 550, 552 (M-Na)<sup>-</sup>

(5) Sodium 5-[[4-[(2R)-2-[[2-(3-chlorophenyl)-2-  
hydroxyethyl]amino]propyl]phenyl]sulfonyl]-2-  
30 hydroxybenzoate  
NMR (DMSO-d<sub>6</sub>, δ): 1.06 (3H, d, J=6.2Hz), 2.6-3.3 (5H,  
m), 4.8-4.95 (1H, m), 6.74 (1H, d, J=8.8Hz), 7.25-  
7.55 (6H, m), 7.68 (1H, dd, J=2.6, 8.6Hz), 7.82  
(2H, d, J=8.3Hz), 8.15 (1H, m)  
35 (-)ESI-MS (m/z): 488, 490 (M-Na)<sup>-</sup>



- (6) Sodium 3-[3-[4-[(2R)-2-[[2-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]phenoxy]-benzoate  
5 NMR (DMSO- $d_6$ ,  $\delta$ ): 1.04 (3H, d,  $J=6.1\text{Hz}$ ), 2.4-2.9 (5H, m), 4.5-4.6 (1H, m), 7.0-7.05 (1H, m), 7.2-7.9 (15H, m)  
(-)ESI-MS (m/z): 564, 566 (M-Na) $^-$
- 10 (7) Sodium 4'-[[4-[(2R)-2-[[2-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-1,1'-biphenyl-3-carboxylate  
NMR (DMSO- $d_6$ ,  $\delta$ ): 0.92 (3H, d,  $J=5.9\text{Hz}$ ), 2.4-2.95 (5H, m), 4.55-4.65 (1H, m), 7.2-7.55 (7H, m), 7.75-8.1  
15 (8H, m), 8.2 (1H, m)  
(-)ESI-MS (m/z): 548, 550 (M-Na) $^-$
- (8) Sodium 3'-[[4-[(2R)-2-[[2-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-1,1'-  
20 biphenyl-3-carboxylate  
NMR (DMSO- $d_6$ ,  $\delta$ ): 0.89 (3H, d,  $J=5.9\text{Hz}$ ), 2.5-2.9 (5H, m), 4.5-4.9 (1H, m), 7.15-7.45 (7H, m), 7.55-7.75 (2H, m), 7.85-8.0 (5H, m), 8.1-8.15 (2H, m)  
(-)ESI-MS (m/z): 548, 550 (M-Na) $^-$   
25
- (9) Sodium (R)-3'-[[4-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-1,1'-biphenyl-4-carboxylate  
NMR (DMSO- $d_6$ ,  $\delta$ ): 2.55-2.9 (6H, m), 4.55-4.65 (1H, m),  
30 7.2-7.5 (6H, m), 7.6-7.8 (3H, m), 7.85-8.1 (6H, m), 8.18 (1H, m)  
(-)ESI-MS (m/z): 535 (M-Na) $^-$
- (10) Sodium (R)-3'-[[4-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-1,1'-  
35

biphenyl-3-carboxylate

NMR (DMSO- $d_6$ ,  $\delta$ ): 2.5-2.8 (6H, m), 4.5-4.6 (1H, m),  
7.2-7.5 (7H, m), 7.6-7.8 (2H, m), 7.85-8.0 (5H, m),  
8.1-8.15 (2H, m)

5 (-)ESI-MS (m/z): 534 (M-Na)<sup>-</sup>

(11) Sodium (R)-3'-[[4-(2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl)phenyl]sulfonyl]-1,1'-biphenyl-2-carboxylate

10 NMR (DMSO- $d_6$ ,  $\delta$ ): 2.5-2.9 (6H, m), 4.55-4.7 (1H, m),  
7.15-8.0 (16H, m)

(-)ESI-MS (m/z): 534, 536 (M-Na)<sup>-</sup>

(12) Sodium (R)-4-[3-[[4-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]phenoxy]-benzoate

15 NMR (DMSO- $d_6$ ,  $\delta$ ): 2.5-2.9 (6H, m), 4.45-4.6 (1H, m),  
6.85-7.0 (2H, m), 7.15-7.5 (8H, m), 7.5-7.7 (2H, m), 7.7-8.0 (4H, m)

20 (-)ESI-MS (m/z): 550, 552 (M-Na)<sup>-</sup>

(13) Sodium (R)-3-[3-[[4-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]phenoxy]-benzoate

25 NMR (DMSO- $d_6$ ,  $\delta$ ): 2.55-2.85 (6H, m), 4.55-4.7 (1H, m),  
7.0-7.1 (1H, m), 7.2-7.5 (10H, m), 7.55-7.9 (5H, m)

(-)ESI-MS (m/z): 550, 552 (M-Na)<sup>-</sup>

30 (14) Sodium (R)-4'-[[4-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-2'-hydroxy-1,1'-biphenyl-3-carboxylate

NMR (DMSO- $d_6$ ,  $\delta$ ): 2.4-3.0 (6H, m), 4.2-4.4 (1H, m),  
7.2-7.65 (11H, m), 7.75-7.9 (3H, m), 8.07 (1H, m)

35 (-)ESI-MS (m/z): 550, 552 (M-Na)<sup>-</sup>

- (15) Sodium [3-[[4-[3-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]phenoxy]-acetate  
5 NMR (DMSO- $d_6$ ,  $\delta$ ): 1.67 (2H, quintet,  $J=7\text{Hz}$ ), 2.40-2.80 (6H, m), 4.17 (2H, s), 4.60 (1H, m), 5.51 (1H, br s, OH), 6.92-7.60 (1H, m), 7.82 (2H, d,  $J=8\text{Hz}$ )  
(-)ESI-MS (m/z): 502 (free,  $M-H$ )<sup>-</sup>
- 10 (16) Sodium 3-[[4-[3-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]benzoate  
NMR (DMSO- $d_6$ ,  $\delta$ ): 1.66 (2H, quintet,  $J=7\text{Hz}$ ), 2.40-2.80 (6H, m), 4.60 (1H, m), 5.44 (1H, br s, OH), 7.15-7.60 (7H, m), 7.72-7.92 (3H, m), 8.07 (1H, d,  $J=8\text{Hz}$ ), 8.30 (1H, s)  
15 (-)ESI-MS (m/z): 472 (free,  $M-H$ )<sup>-</sup>
- (17) Sodium [4-[[4-[2-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethoxy]phenyl]sulfonyl]phenoxy]-acetate  
20 NMR (DMSO- $d_6$ ,  $\delta$ ): 2.55-3.00 (4H, m), 4.08 (2H, m), 4.20 (2H, s), 4.63 (1H, m), 5.50 (1H, br s, OH), 6.93 (2H, d,  $J=8\text{Hz}$ ), 7.08 (2H, d,  $J=8\text{Hz}$ ), 7.15-7.45 (4H, m), 7.75 (2H, d,  $J=8\text{Hz}$ ), 7.80 (2H, d,  $J=8\text{Hz}$ )  
25 (+)ESI-MS (m/z): 504 (free,  $M+H$ )<sup>+</sup>
- (18) Sodium 4-[[4-[2-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethoxy]phenyl]sulfonyl]benzoate  
NMR (DMSO- $d_6$ ,  $\delta$ ): 2.58-3.00 (4H, m), 4.08 (2H, m), 4.63 (1H, m), 5.47 (1H, br s, OH), 7.11 (2H, d,  $J=8\text{Hz}$ ), 7.20-7.45 (4H, m), 7.79 (2H, d,  $J=8\text{Hz}$ ), 7.84 (2H, d,  $J=8\text{Hz}$ ), 7.98 (2H, d,  $J=8\text{Hz}$ )  
30 (+)ESI-MS (m/z): 474 (free,  $M+H$ )<sup>+</sup>
- 35 (19) Sodium [2-[[4-[(2R)-2-[[[(2R)-2-(3-chlorophenyl)-2-

hydroxyethyl]amino]propyl]phenyl]sulfonyl]phenoxy]-  
acetate

NMR (DMSO- $d_6$ ,  $\delta$ ): 0.93 (3H, d,  $J=6\text{Hz}$ ), 2.40-3.10 (5H,  
m), 4.03 (2H, s), 4.54 (1H, m), 6.04 (1H, br s,  
OH), 6.82-7.62 (9H, m), 7.78-8.05 (3H, m)

(-)ESI-MS ( $m/z$ ): 502 (free,  $M-H$ )<sup>-</sup>

(20) Sodium 2-[[4-[(2R)-2-[(2R)-2-(3-chlorophenyl)-2-  
hydroxyethyl]amino]propyl]phenyl]sulfonyl]benzoate

NMR (DMSO- $d_6$ ,  $\delta$ ): 0.74 (3H, d,  $J=6\text{Hz}$ ), 2.50-3.20 (5H,  
m), 4.72 (1H, m), 7.10-7.60 (9H, m), 7.80-8.15 (3H,  
m)

(-)ESI-MS ( $m/z$ ): 472 (free,  $M-H$ )<sup>-</sup>

(21) Sodium 4'-[[4-[2-[(2R)-2-(3-chlorophenyl)-2-  
hydroxyethyl]amino]ethoxy]phenyl]sulfonyl]-1,1'-  
biphenyl-3-carboxylate

NMR (DMSO- $d_6$ ,  $\delta$ ): 2.58-3.02 (4H, m), 4.10 (2H, m), 4.64  
(1H, m), 5.56 (1H, br s, OH), 7.05-7.75 (8H, m),  
7.75-8.10 (7H, m), 8.20 (1H, s)

(-)ESI-MS ( $m/z$ ): 550 (free,  $M-H$ )<sup>-</sup>

(22) Sodium 4'-[[4-[2-[(2R)-2-(3-chlorophenyl)-2-  
hydroxyethyl]amino]ethoxy]phenyl]sulfonyl]-1,1'-  
biphenyl-4-carboxylate

NMR (DMSO- $d_6$ ,  $\delta$ ): 2.60-3.05 (4H, m), 4.12 (2H, m), 4.66  
(1H, m), 5.58 (1H, br s, OH), 7.15 (2H, d,  $J=8\text{Hz}$ ),  
7.17-7.50 (4H, m), 7.63 (2H, d,  $J=8\text{Hz}$ ), 7.80-8.18  
(8H, m)

(+)ESI-MS ( $m/z$ ): 550 (free,  $M+H$ )<sup>+</sup>

(23) Sodium 4'-[[4-[3-[(2R)-2-(3-chlorophenyl)-2-  
hydroxyethyl]amino]propyl]phenyl]sulfonyl]-1,1'-  
biphenyl-3-carboxylate

NMR (DMSO- $d_6$ ,  $\delta$ ): 1.67 (2H, quintet,  $J=7\text{Hz}$ ), 2.40-2.80

(6H, m), 4.60 (1H, m), 5.48 (1H, br s, OH), 7.10-8.28 (16H, m)  
(+)ESI-MS (m/z): 550 (free, M+H)<sup>+</sup>

5 (24) Sodium 4'-[[4-[3-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-1,1'-biphenyl-4-carboxylate  
NMR (DMSO-d<sub>6</sub>, δ): 1.67 (2H, quintet, J=7Hz), 2.40-2.80  
10 (6H, m), 4.61 (1H, m), 5.53 (1H, br s, OH), 7.05-8.20 (16H, m)  
(+)ESI-MS (m/z): 550 (free, M+H)<sup>+</sup>

(25) Sodium 3-[4-[4-[3-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]phenoxy]-benzoate  
15 NMR (DMSO-d<sub>6</sub>, δ): 1.67 (2H, quintet, J=7Hz), 2.40-2.80  
(6H, m), 4.60 (1H, m), 5.51 (1H, br s, OH), 6.95-8.00 (16H, m)  
(+)ESI-MS (m/z): 566 (free, M+H)<sup>+</sup>

20 (26) Sodium 3'-[[4-[3-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-1,1'-biphenyl-3-carboxylate  
NMR (DMSO-d<sub>6</sub>, δ): 1.65 (2H, quintet, J=7Hz), 2.40-2.80  
25 (6H, m), 4.61 (1H, m), 5.68 (1H, br s, OH), 7.10-8.30 (1H, m)  
(+)ESI-MS (m/z): 550 (free, M+H)<sup>+</sup>

30 (27) Sodium 3-[3-[4-[3-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]phenoxy]-benzoate  
NMR (DMSO-d<sub>6</sub>, δ): 1.65 (2H, quintet, J=7Hz), 2.40-2.80  
(6H, m), 4.61 (1H, m), 6.90-8.05 (16H, m)  
(+)ESI-MS (m/z): 566 (free, M+H)<sup>+</sup>

- (28) Sodium 5-[[4-[3-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-2-hydroxybenzoate  
NMR (DMSO-d<sub>6</sub>, δ): 1.64 (2H, quintet, J=7Hz), 2.40-2.90  
5 (6H, m), 4.63 (1H, m), 6.73 (1H, d, J=9Hz), 7.10-7.50 (6H, m), 7.66 (1H, dd, J=9, 2Hz), 7.75 (2H, d, J=8Hz), 8.14 (1H, d, J=2Hz)  
(+)ESI-MS (m/z): 490 (free, M+H)<sup>+</sup>
- 10 (29) Sodium 4-[[4-[3-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-2-hydroxybenzoate  
NMR (DMSO-d<sub>6</sub>, δ): 1.77 (2H, quintet, J=7Hz), 2.50-2.90  
15 (6H, m), 4.72 (1H, m), 7.00-7.55 (8H, m), 7.83 (2H, d, J=8Hz), 7.84 (1H, d, J=8Hz)  
(+)ESI-MS (m/z): 490 (free, M+H)<sup>+</sup>
- (30) Sodium 5-[[4-[2-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethoxy]phenyl]sulfonyl]-2-hydroxybenzoate  
20 NMR (DMSO-d<sub>6</sub>, δ): 2.55-3.05 (4H, m), 4.08 (2H, m), 4.64 (1H, m), 5.45 (1H, br s, OH), 6.72 (1H, d, J=9Hz), 7.09 (2H, d, J=9Hz), 7.15-7.45 (4H, m), 7.64 (1H, dd, J=9, 2Hz), 7.77 (2H, d, J=9Hz), 8.12 (1H, d, J=2Hz)  
25 J=2Hz)  
(-)ESI-MS (m/z): 490 (free, M-H)<sup>-</sup>
- (31) Sodium 5-[[4-[[[(2R)-2-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]oxy]phenyl]sulfonyl]-2-hydroxybenzoate  
30 NMR (DMSO-d<sub>6</sub>, δ): 1.21 (3H, d, J=6Hz), 2.75-3.55 (3H, m), 4.09 (2H, m), 4.80 (1H, m), 5.91 (1H, br s, OH), 6.70 (1H, d, J=9Hz), 7.11 (2H, d, J=9Hz), 7.22-7.50 (4H, m), 7.63 (1H, dd, J=9, 2Hz), 7.80  
35 (2H, d, J=9Hz), 8.09 (1H, d, J=2Hz)

(-)ESI-MS (m/z): 504 (free, M-H)<sup>-</sup>

(32) Sodium 2-chloro-4-[[4-[3-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]benzoate

5 NMR (DMSO-d<sub>6</sub>, δ): 1.69 (2H, quintet, J=7Hz), 2.32-2.82 (6H, m), 4.63 (1H, m), 5.55 (1H, br s, OH), 7.17-7.55 (7H, m), 7.60-7.86 (2H, m), 7.86 (2H, d, J=8Hz)

(+)ESI-MS (m/z): 508 (free, M+H)<sup>+</sup>

10

(33) Sodium 5-[[4-[3-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-2-methoxybenzoate

15 NMR (DMSO-d<sub>6</sub>, δ): 1.66 (2H, quintet, J=7Hz), 2.32-2.75 (6H, m), 3.73 (3H, s), 4.56 (1H, m), 5.47 (1H, br s, OH), 7.02 (1H, d, J=9Hz), 7.15-7.48 (6H, m), 7.55 (1H, d, J=2Hz), 7.69 (1H, dd, J=9, 2Hz), 7.76 (2H, d, J=8Hz)

(+)ESI-MS (m/z): 504 (free, M+H)<sup>+</sup>

20

#### Example 6

Under nitrogen, a mixture of ethyl 4-[[4-[2-(benzylamino)ethyl]phenyl]sulfonyl]-2-hydroxybenzoate (215 mg) and (R)-2-(3-chlorophenyl)oxirane (90.7 mg) in ethanol

25 (10 ml) was refluxed for 48 hours. The resulting mixture was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel

(hexane/ethyl acetate = 3:1 to 3:2) to give ethyl (R)-4-[[4-[2-[benzyl[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]-phenyl]sulfonyl]-2-hydroxybenzoate (208 mg).

30

NMR (CDCl<sub>3</sub>, δ): 1.40 (3H, t, J=7.1Hz), 2.55-2.9 (6H, m), 3.55 (1H, d, J=13.4Hz), 3.96 (1H, d, J=13.4Hz), 4.42 (2H, q, J=7.1Hz), 4.6-4.65 (1H, m), 7.15-7.35 (11H, m), 7.4-7.45 (1H, m), 7.5 (1H, m), 7.82 (2H, d, J=8.4Hz), 7.95 (1H, d, J=8.3Hz)

35

(+)ESI-MS (m/z): 594, 596 (M+H)<sup>+</sup>

Example 7

To a solution of ethyl (R)-4-[[4-[2-[benzyl[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-2-hydroxybenzoate (204 mg) in ethyl acetate (3 ml) was added 4N hydrogen chloride in ethyl acetate (0.5 ml) at room temperature, and the mixture was evaporated under reduced pressure. A mixture of the residue and 10% palladium on activated carbon (50% wet, 10 mg) in a mixture of ethanol (1.5 ml) and chlorobenzene (3.5 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 dissolved into a mixture of saturated aqueous sodium bicarbonate and ethyl acetate which contained a little of methanol. After separation, the organic layer was dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (chloroform/methanol = 20:1 to 15:1) to give ethyl (R)-4-[[4-[2-[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-2-hydroxybenzoate (149 mg).

NMR (CDCl<sub>3</sub>, δ): 1.41 (3H, t, J=7.2Hz), 2.65-3.0 (6H, m), 4.43 (2H, q, J=7.2Hz), 4.6-4.65 (1H, m), 7.15-7.45 (7H, m), 7.52 (1H, m), 7.85-7.9 (2H, m), 7.97 (1H, d, J=8.4Hz)

(+)ESI-MS (m/z): 504, 506 (M+H)<sup>+</sup>

Example 8

To a suspension of ethyl (R)-4-[[4-[2-[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-2-hydroxybenzoate (145 mg) in methanol (3 ml) was added 1N sodiumhydroxide (0.72 ml) at room temperature, and the mixture was stirred at the same temperature for 4 days. To



the resulting mixture was added 1N hydrochloric acid (0.43 ml), and the mixture was evaporated under reduced pressure. The residue was purified by reversed phase chromatography to give sodium (R)-4-[[4-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-2-hydroxybenzoate (110 mg).

NMR (DMSO- $d_6$ ,  $\delta$ ): 2.85-3.2 (6H, m), 4.75-4.9 (1H, m), 7.0-7.1 (2H, m), 7.25-7.55 (6H, m), 7.75-7.9 (3H, m)

(-)ESI-MS (m/z): 474, 476 (M-Na)<sup>-</sup>

#### Example 9

The following compounds were obtained according to a similar manner to that of Example 7.

15

(1) Ethyl (R)-2-[4-[[4-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]phenoxy]-benzoate

NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.08 (3H, t, J=7.1Hz), 2.6-3.0 (6H, m), 4.17 (2H, q, J=7.1Hz), 4.64 (1H, dd, J=3.6, 8.7Hz), 6.85-7.0 (2H, m), 7.05-7.4 (8H, m), 7.5-7.6 (1H, m), 7.8-8.0 (5H, m)

(+)ESI-MS (m/z): 580, 582 (M+H)<sup>+</sup>

25 (2) Ethyl (R)-2-[3-[[4-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]phenoxy]-benzoate

NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.07 (3H, t, J=7.1Hz), 2.6-3.0 (6H, m), 4.15 (2H, q, J=7.1Hz), 4.64 (1H, dd, J=3.6, 8.8Hz), 7.0-7.1 (2H, m), 7.15-7.65 (11H, m), 7.8-7.9 (2H, m), 7.95-8.0 (1H, m)

(+)ESI-MS (m/z): 580 (M+H)<sup>+</sup>

35 (3) Ethyl (R)-[4-[[4-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]phenyl]acetate

NMR (CDCl<sub>3</sub>, δ): 1.24 (3H, t, J=7.1Hz), 2.6-3.0 (6H, m),  
3.65 (2H, s), 4.14 (2H, q, J=7.1Hz), 4.63 (1H, dd,  
J=3.7, 8.8Hz), 7.15-7.35 (6H, m), 7.42 (2H, d,  
J=8.3Hz), 7.8-7.95 (4H, m)

5 (+)ESI-MS (m/z): 502, 504 (M+H)<sup>+</sup>

(4) Methyl (R)-3'-[[4-[2-[[2-(3-chlorophenyl)-2-  
hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-1,1'-  
biphenyl-4-carboxylate

10 NMR (CDCl<sub>3</sub>, δ): 2.6-3.0 (6H, m), 3.95 (3H, s), 4.62 (1H,  
dd, J=3.6, 8.7Hz), 7.1-7.4 (6H, m), 7.55-7.7 (3H,  
m), 7.75-8.0 (4H, m), 8.1-8.2 (3H, m)

(+)ESI-MS (m/z): 550, 552 (M+H)<sup>+</sup>

15 (5) Ethyl (R)-3'-[[4-[2-[[2-(3-chlorophenyl)-2-  
hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-1,1'-  
biphenyl-3-carboxylate

NMR (CDCl<sub>3</sub>, δ): 1.42 (3H, t, J=7.2Hz), 2.6-3.0 (6H, m),  
4.42 (2H, q, J=7.2Hz), 4.63 (1H, dd, J=3.6, 8.7Hz),  
20 7.1-7.4 (6H, m), 7.5-7.7 (2H, m), 7.7-8.0 (5H, m),  
8.05-8.3 (3H, m)

(+)ESI-MS (m/z): 564, 566 (M+H)<sup>+</sup>

(6) Ethyl (R)-3'-[[4-[2-[[2-(3-chlorophenyl)-2-  
25 hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-1,1'-  
biphenyl-2-carboxylate

NMR (CDCl<sub>3</sub>, δ): 0.87 (3H, t, J=7.1Hz), 2.6-2.7 (1H, m),  
2.8-3.0 (5H, m), 3.96 (2H, q, J=7.1Hz), 4.64 (1H,  
dd, J=3.5, 8.9Hz), 7.15-7.35 (7H, m), 7.45-7.6 (4H,  
30 m), 7.85-8.0 (5H, m)

(+)ESI-MS (m/z): 564 (M+H)<sup>+</sup>

(7) Ethyl (R)-4-[3-[[4-[2-[[2-(3-chlorophenyl)-2-  
hydroxyethyl]amino]ethyl]phenyl]sulfonyl]phenoxy]-  
35 benzoate

NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.40 (3H, t, J=7.1Hz), 2.6-3.05 (6H, m),  
4.38 (2H, q, J=7.1Hz), 4.64 (1H, dd, J=3.7, 8.8Hz),  
6.95-7.05 (2H, m), 7.15-7.35 (7H, m), 7.4-7.75 (3H,  
m), 7.8-7.9 (2H, m), 8.0-8.1 (2H, m)

5 (-)ESI-MS (m/z): 578, 580 (M-H)<sup>-</sup>

(8) Ethyl (R)-3-[3-[4-[2-[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]phenoxy]-benzoate

10 NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.38 (3H, t, J=7.1Hz), 2.6-3.0 (6H, m),  
4.37 (2H, q, J=7.1Hz), 4.64 (1H, dd, J=3.7, 8.8Hz),  
7.1-7.7 (13H, m), 7.8-7.9 (3H, m)

(+)ESI-MS (m/z): 580, 582 (M+H)<sup>+</sup>

15 (9) Ethyl (R)-4'-[[4-[2-[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-2'-hydroxy-1,1'-biphenyl-3-carboxylate

NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.37 (3H, t, J=7.1Hz), 2.6-3.0 (6H, m),  
4.38 (2H, q, J=7.1Hz), 4.65 (1H, dd, J=3.6, 8.8Hz),  
20 7.1-7.7 (10H, m), 7.90 (2H, d, J=8.3Hz), 8.0-8.1  
(1H, m), 8.16 (1H, m)

(+)ESI-MS (m/z): 580, 582 (M+H)<sup>+</sup>

(10) Ethyl [2-[4-[(2R)-2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]phenoxy]-acetate

NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.07 (3H, d, J=6Hz), 1.24 (3H, t, J=7Hz), 2.50-3.05 (5H, m), 4.18 (2H, q, J=7Hz),  
4.52 (1H, dd, J=9, 4Hz), 4.59 (2H, s), 6.80 (1H, d, J=8Hz),  
30 7.02-7.40 (7H, m), 7.52 (1H, t, J=8Hz),  
7.99 (2H, d, J=8Hz), 8.20 (1H, d, J=8Hz)

(+)ESI-MS (m/z): 532 (free, M+H)<sup>+</sup>

(11) Ethyl 2-[4-[(2R)-2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]benzoate

35

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 1.06 (3H, d,  $J=6\text{Hz}$ ), 1.38 (3H, t,  $J=7\text{Hz}$ ), 2.50-3.05 (5H, m), 4.42 (2H, q,  $J=7\text{Hz}$ ), 4.53 (1H, dd,  $J=9, 4\text{Hz}$ ), 7.00-8.20 (12H, m)  
(+)ESI-MS ( $m/z$ ): 502 ( $M+H$ )<sup>+</sup>

5

#### Example 10

Under nitrogen, a mixture of ethyl 4-[[4-(3-aminopropyl)phenyl]sulfonyl]-2-methylbenzoate (3.42 g) and (R)-2-(3-chlorophenyl)oxirane (731 mg) in ethanol (34 ml) was refluxed for 24 hours. The resulting mixture was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (chloroform/methanol = 20:1 to 40:3) to give ethyl (R)-4-[[4-[3-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-2-methylbenzoate (1.44 g).

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 1.38 (3H, t,  $J=7.1\text{Hz}$ ), 1.7-1.9 (2H, m), 2.55-2.9 (7H, m), 4.36 (2H, q,  $J=7.1\text{Hz}$ ), 4.64 (1H, dd,  $J=3.6, 8.7\text{Hz}$ ), 7.15-7.4 (6H, m), 7.7-8.0 (5H, m)  
(+)ESI-MS ( $m/z$ ): 516, 518 ( $M+H$ )<sup>+</sup>

20

#### Example 11

To a suspension of ethyl (R)-4-[[4-[3-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-2-methylbenzoate (1.42 g) in ethanol (14 ml) was added 1N sodiumhydroxide (2.75 ml) at room temperature, and the mixture was stirred at 60°C for 1.3 hours. The resulting mixture was evaporated under reduced pressure and dried in vacuo to give sodium (R)-4-[[4-[3-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-2-methylbenzoate (1.42g).

NMR ( $\text{DMSO}-d_6$ ,  $\delta$ ): 1.55-1.75 (2H, m), 2.35-2.7 (9H, m), 4.55-4.65 (1H, m), 7.2-7.65 (9H, m), 7.81 (2H, d,  $J=8.2\text{Hz}$ )  
(-)ESI-MS ( $m/z$ ): 486, 488 ( $M-\text{Na}$ )<sup>-</sup>

35

Example 12

The following compound was obtained according to a similar manner to that of Example 11.

5

Sodium (R)-[4-[[4-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]phenyl]acetate

NMR (DMSO- $d_6$ ,  $\delta$ ): 2.55-2.8 (6H, m), 3.23 (2H, s), 4.55-4.65 (1H, m), 7.2-7.45 (8H, m), 7.7-7.85 (4H, m)

10 

(+)ESI-MS (m/z): 472, 474 (M-Na)<sup>-</sup>

Example 13

A mixture of (R)-4-[[4-[2-[benzyl[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]phenol (1.31 g),  
15 triethylamine (3.3 ml) and 10% palladium on activated carbon (50% wet, 0.65 g) in a mixture of methanol (13 ml) and chlorobenzene (13 ml) was stirred at room temperature in the presence of hydrogen at an atmospheric pressure for 5 hours. After filtration, the filtrate was evaporated under reduced  
20 pressure. The residue was dissolved into a mixture of ethyl acetate and saturated aqueous sodium hydrogencarbonate. After separation, the organic layer was washed with brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column  
25 chromatography on silica gel (chloroform:methanol = 20:1 to 8:1) to give (R)-4-[[4-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]phenol (789 mg).

NMR (DMSO- $d_6$ ,  $\delta$ ): 2.55-2.85 (6H, m), 4.55-4.6 (1H, m), 6.9-6.95 (2H, m), 7.2-7.8 (4H, m)

30 

(+)ESI-MS (m/z): 432, 434 (M+H)<sup>+</sup>

Example 14

Under nitrogen at room temperature, to a solution of (R)-4-[[4-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]-ethyl]phenyl]sulfonyl]phenol (1.0 g) in tetrahydrofuran (8  
35

ml) was added di-tert-butyl dicarbonate (0.56 g) in tetrahydrofuran (2 ml), and the mixture was stirred at the same temperature for 12 hours. The resulting mixture was poured into water 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 = 2:1 to 1:1) to give tert-butyl (R)-[2-(3-chlorophenyl)-2-hydroxyethyl][2-[4-[(4-hydroxyphenyl)sulfonyl]phenyl]-ethyl]carbamate (1.1 g).

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 1.2-1.5 (9H, m), 2.6-2.95 (2H, m), 3.15-3.6 (4H, m), 4.8-4.95 (1H, m), 6.8-6.95 (2H, m), 7.15-7.45 (6H, m), 7.7-7.9 (2H, m)  
(+)ESI-MS (m/z): 554, 556 ( $\text{M}+\text{Na}$ )<sup>+</sup>

#### Example 15

A mixture of (R)-3-[[4-[2-[benzyl[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]phenol (202 mg) and 10% palladium on activated carbon (50% wet, 100 mg) in a mixture of methanol (2 ml) and chlorobenzene (2 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 dissolved into a mixture of saturated aqueous sodium bicarbonate and ethyl acetate. After separation, the organic layer was dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (chloroform:methanol = 20:1 to 8:1) followed by treatment with 4N hydrogen chloride in 1,4-dioxane and dryness to give (R)-3-[[4-[2-[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]-sulfonyl]phenol hydrochloride (90 mg).

NMR ( $\text{DMSO}-d_6$ ,  $\delta$ ): 2.9-3.5 (6H, m), 4.85-5.0 (1H, m), 7.0-7.1 (1H, m), 7.2-7.6 (9H, m), 7.85-7.95 (2H,

m)

(+)APCI-MS (m/z): 432, 434 (M-HCl+H)<sup>+</sup>Example 16

5 Under nitrogen, to a solution of (R)-3-[[4-[2-[benzyl[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]-phenyl]sulfonyl]phenol (3.55 g) and 2,6-lutidine (1.09 ml) in dichloromethane (35 ml) was added

10 trifluoromethanesulfonic anhydride (1.26 ml) in dryice-acetone bath, and the mixture was stirred at the same temperature for 1 hour. The resulting mixture was poured into 1N hydrochloric acid and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed successively with water, saturated aqueous sodium

15 bicarbonate and brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 5:1 to 2:1) to give (R)-3-[[4-[2-[benzyl[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]-phenyl]sulfonyl]phenyl trifluoromethanesulfonate (3.95 g).

20 NMR (CDCl<sub>3</sub>, δ): 2.5-2.9 (6H, m), 3.55 (1H, d, J=13.4Hz), 3.90 (1H, d, J=13.4Hz), 4.60 (1H, dd, J=3.7, 9.9Hz), 7.1-7.35 (11H, m), 7.4-7.7 (2H, m), 7.8-8.0 (4H, m)

25 (+)ESI-MS (m/z): 654 (M+H)<sup>+</sup>

Example 17

To a solution of (R)-3-[[4-[2-[benzyl[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-phenyl trifluoromethanesulfonate (480 mg) and 2-carboxyphenylboronic acid (480 mg) in 1,2-dimethoxyethane (7 ml) were added tetrakis(triphenylphosphine)palladium(0) (42.4 mg) and 2M sodium carbonate (1.14 ml) at room temperature, and the mixture was stirred at 80°C for 10 hours.

35 The resulting mixture was poured into pH 4 phosphate buffer

and the aqueous mixture was extracted with chloroform. The organic layer was dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (chloroform/methanol  
5 = 30:1 to 20:1) to give (R)-3'-[[4-[2-[benzyl[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-1,1'-biphenyl-2-carboxylic acid (354 mg).

NMR (DMSO- $d_6$ ,  $\delta$ ): 2.55-2.8 (6H, m), 3.58 (1H, d,  $J=13.9\text{Hz}$ ), 3.73 (1H, d,  $J=13.9\text{Hz}$ ), 4.6-4.75 (1H, m), 6.95-8.0 (21H, m)  
10 (-)ESI-MS (m/z): 624 (M-H)<sup>-</sup>

#### Example 18

To a solution of methyl 4'-[[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-1,1'-biphenyl-3-carboxylate (125 mg) in 1,4-dioxane (1.3 ml) was added 1N sodium hydroxide solution (0.48 ml), and the mixture was stirred at 50°C for 19 hours. After the solution was made  
20 acidic with 1N hydrochloric acid, the mixture was extracted with chloroform-methanol. The organic layer was washed with brine, dried over magnesium sulfate, and filtered. The filtrate was concentrated to give 4'-[[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]-amino]ethyl]phenyl]sulfonyl]-1,1'-biphenyl-3-carboxylic acid  
25 (104 mg) as a white amorphous.

NMR (DMSO- $d_6$ ,  $\delta$ ): 1.07, 1.19 (total 9H, a pair of s), 2.70-2.95 (2H, m), 2.95-3.45 (4H, m), 4.71 (1H, m), 5.58 (1H, br s, OH), 7.10-7.53 (6H, m), 7.64 (1H, t,  $J=8\text{Hz}$ ), 7.82-8.12 (8H, s), 8.20 (1H, s)  
30 (-)ESI-MS (m/z): 634 (M-H)<sup>-</sup>

#### Example 19

4'[[4-[2-[(tert-Butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-  
35



1,1'-biphenyl-3-carboxylic acid (91 mg) and 4N hydrogen chloride in 1,4-dioxane (0.92 ml) were mixed and stirred at room temperature for 15.5 hours. The solvent was evaporated and the residual powder was treated with ethanol (0.92 ml) -  
5 1N sodium hydroxide solution (0.35 ml). The solvent was evaporated to give sodium 4'-[[4-[2-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-1,1'-biphenyl-3-carboxylate (54 mg) as a white powder.

NMR (DMSO-d<sub>6</sub>,  $\delta$ ): 2.50-2.90 (6H, m), 4.60 (1H, m), 5.48  
10 (1H, br s, OH), 7.10-7.55 (7H, m), 7.55-7.72 (1H, m), 7.72-8.10 (7H, m), 8.20 (1H, s)  
(-)ESI-MS (m/z): 534 (free, M-H)<sup>-</sup>

#### Example 20

15 Ethyl 3-[4-[[4-[2-[(tert-butoxycarbonyl) [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-phenoxy]benzoate (48 mg) and 4N hydrogen chloride in 1,4-dioxane (1 ml) were mixed and stirred at room temperature for 6.5 hours. The solvent was evaporated and the residual  
20 powder was treated with ethanol (1 ml) - 1N sodium hydroxide solution (0.16 ml). After the mixture was heated to reflux for 9 hours, the solvent was evaporated to give sodium 3-[4-[[4-[2-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-ethyl]phenyl]sulfonyl]phenoxy]benzoate (46 mg) as a white  
25 powder.

NMR (DMSO-d<sub>6</sub>,  $\delta$ ): 2.50-2.90 (6H, m), 4.60 (1H, m), 5.50  
(1H, br s, OH), 6.95-7.16 (3H, m), 7.16-7.60 (8H, m), 7.65-8.00 (5H, m)

(+)ESI-MS (m/z): 552 (free, M+H)<sup>+</sup>

30

#### Example 21

Under nitrogen atmosphere, a mixture of 4-[[4-[2-[(tert-butoxycarbonyl) [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]phenyl  
35 trifluoromethanesulfonate (265 mg), palladium(II) acetate (5

- mg), 2-[bis(tert-butyl)phosphino]biphenyl (12 mg), and powdered potassium phosphate (177 mg) in toluene (2.6 ml) was heated to 100°C for 10 hours. After being 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 ethyl 4-[4-[[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]-amino]ethyl]phenyl]sulfonyl]phenoxy]benzoate (93 mg) as a white amorphous.
- 10 NMR (CDCl<sub>3</sub>, δ): 1.36 (9H, br s), 1.40 (3H, t, J=7Hz), 2.60-3.05 (2H, m), 3.05-3.60 (4H, m), 4.27 (1H, br s, OH), 4.38 (2H, q, J=7Hz), 4.86 (1H, m), 6.90-7.45 (10H, m), 7.86 (2H, d, J=8Hz), 7.90 (2H, d, J=8Hz), 8.07 (2H, d, J=8Hz)
- 15 (+)ESI-MS (m/z): 702 (M+Na)<sup>+</sup>

#### Example 22

- To a solution of 3-[[4-[3-[benzyl[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-phenol (282 mg) in N,N-dimethylformamide (2.3 ml) were added powdered potassium carbonate (88 mg) and ethyl bromoacetate (0.07 ml), and the mixture was stirred at 60°C for 1.5 hours. After being allowed to cool to room temperature, the mixture was partitioned between hexane/ethyl acetate (1/2) and water.
- 20 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 ethyl [3-[[4-[3-[benzyl[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]phenoxy]acetate
- 30 (270 mg) as a colorless oil.
- NMR (CDCl<sub>3</sub>, δ): 1.29 (3H, t, J=7Hz), 1.80 (2H, quintet, J=7Hz), 2.35-2.80 (6H, m), 3.48 (1H, d, J=13Hz), 3.87 (1H, d, J=13Hz), 4.26 (2H, q, J=7Hz), 4.61
- 35 (1H, dd, J=10, 4Hz), 4.65 (2H, s), 7.00-7.62 (15H,

m), 7.80 (2H, d, J=8Hz)  
(+)ESI-MS (m/z): 622 (M+H)<sup>+</sup>

#### Example 23

5 To a solution of ethyl [3-[[4-[3-[benzyl[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-phenoxy]acetate (252 mg) in ethyl acetate (2.5 ml) was added  
4N hydrogen chloride/ethyl acetate (0.5 ml). After the  
solvent was evaporated, the residue was dissolved in  
10 chlorobenzene (3.5 ml) - ethanol (1.5 ml), and the solution  
was hydrogenated (1 atm) over 10% palladium on carbon (12  
mg) at room temperature for 3.5 hours. After the catalyst  
was filtered off, the filtrate was concentrated to give  
ethyl [3-[[4-[3-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]-  
15 amino]propyl]phenyl]sulfonyl]phenoxy]acetate hydrochloride  
(221 mg) as a white powder.

NMR (DMSO-d<sub>6</sub>, δ): 1.19 (3H, t, J=7Hz), 1.96 (2H,  
quintet, J=7Hz), 2.73 (2H, t, J=7Hz), 2.80-3.25  
(4H, m), 4.15 (2H, q, J=7Hz), 4.92 (2H, s), 4.95  
20 (1H, m), 6.29 (1H, br s, OH), 7.15-7.62 (10H, m),  
7.92 (2H, d, J=8Hz)

(+)ESI-MS (m/z): 532 (free, M+H)<sup>+</sup>

#### Example 24

25 To a solution of 3-[[4-[3-[benzyl[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-phenol (287 mg) in dimethyl sulfoxide (1.5 ml) were added  
powdered potassium carbonate (115 mg) and 2-  
fluorobenzaldehyde (79 mg), and the mixture was stirred at  
30 100°C for 4 hours. After being allowed to cool to room  
temperature, the mixture was partitioned between  
hexane/ethyl acetate (1/2) and water. The organic layer was  
separated, washed successively with water and brine, dried  
over magnesium sulfate, and filtered. The filtrate was  
35 concentrated and the residue was purified by column

chromatography (silica gel, hexane/ethyl acetate) to give 2-[3-[[4-[3-[benzyl[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]-amino]propyl]phenyl]sulfonyl]phenoxy]benzaldehyde (166 mg) as a colorless oil.

- 5       NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.81 (2H, quintet, J=7Hz), 2.35-2.80 (6H, m), 3.49 (1H, d, J=13Hz), 3.88 (1H, d, J=13Hz), 4.61 (1H, dd, J=10, 4Hz), 6.80-8.10 (21H, m), 10.40 (1H, s)  
      (+)-ESI-MS (m/z): 640 (M+H)<sup>+</sup>

10

#### Example 25

2-[3-[[4-[3-[(tert-Butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-phenoxy]benzoic acid (171 mg) and 4N hydrogen chloride in  
15 1,4-dioxane (1.7 ml) were mixed and stirred at room temperature for 15 hours. The solvent was evaporated to give 2-[3-[[4-[3-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]-amino]propyl]phenyl]sulfonyl]phenoxy]benzoic acid hydrochloride (163 mg) as a white amorphous.

- 20       NMR (DMSO-d<sub>6</sub>,  $\delta$ ): 1.82-2.12 (2H, m), 2.74 (2H, t, J=7Hz), 2.83-3.30 (4H, m), 4.96 (1H, m), 6.31 (1H, br s, OH), 7.08-7.98 (16H, m)  
      (-)-ESI-MS (m/z): 564 (free, M-H)<sup>-</sup>

#### 25 Example 26

To a suspension of 3-[[4-[2-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]phenol hydrochloride (324 mg) in tetrahydrofuran (3.2 ml) were added 1N sodium hydroxide solution (0.7 ml) and di-tert-  
30 butyl dicarbonate (169 mg), and the mixture was stirred at 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  
35 concentrated and the residue was purified by column

chromatography (silica gel, hexane/ethyl acetate) to give tert-butyl [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl][2-[4-[(3-hydroxyphenyl)sulfonyl]phenyl]ethyl]carbamate (318 mg) as a white amorphous.

5 NMR (CDCl<sub>3</sub>, δ): 1.33 (9H, s), 2.45-3.00 (2H, m) 3.00-3.65 (4H, m), 4.55 (1H, br s, OH), 4.71 (1H, m), 6.50-8.00 (12H, m)  
(+)ESI-MS (m/z): 554 (M+Na)<sup>+</sup>

#### 10 Example 27

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

(1) 4-[[4-[2-[(tert-Butoxycarbonyl)[(2R)-2-(3-  
15 chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]-sulfonyl]phenyl trifluoromethanesulfonate  
NMR (DMSO-d<sub>6</sub>, δ): 1.31 (9H, br s), 2.60-3.05 (2H, m), 3.05-3.60 (4H, m), 4.24 (1H, br s, OH), 4.87 (1H, m), 7.05-7.48 (8H, m), 7.87 (2H, d, J=8Hz), 8.03  
20 (2H, d, J=9Hz)

(+)APCI-MS (m/z): 564 (M-Boc+H)<sup>+</sup>

(2) 3-[[4-[3-[Benzyl[(2R)-2-(3-chlorophenyl)-2-  
hydroxyethyl]amino]propyl]phenyl]sulfonyl]phenyl  
25 trifluoromethanesulfonate  
NMR (CDCl<sub>3</sub>, δ): 1.87 (2H, quintet, J=7Hz), 2.43-2.90 (6H, m), 3.62 (1H, d, J=13Hz), 3.92 (1H, d, J=13Hz), 4.66 (1H, dd, J=10, 4Hz), 7.05-8.00 (17H, m)  
(+)ESI-MS (m/z): 668 (M+H)<sup>+</sup>

30 (3) 4-[[4-[2-[Benzyl[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethoxy]phenyl]sulfonyl]phenyl trifluoromethanesulfonate  
NMR (CDCl<sub>3</sub>, δ): 2.65 (1H, dd, J=13, 10Hz), 2.84-3.22  
35 (2H, m), 2.86 (1H, dd, J=13, 4Hz), 3.69 (1H, d,

J=13Hz), 3.95 (1H, d, J=13Hz), 3.97-4.09 (2H, m),  
4.65 (1H, dd, J=10, 4Hz), 6.95 (2H, d, J=8Hz),  
7.10-7.38 (9H, m), 7.39 (2H, d, J=8Hz), 7.87 (2H,  
d, J=8Hz), 8.02 (2H, d, J=8Hz)

5 (+)ESI-MS (m/z): 670 (M+H)<sup>+</sup>

(4) 2-[[4-[(2R)-[Benzyl[(2R)-2-(3-chlorophenyl)-2-  
hydroxyethyl]amino]propyl]phenyl]sulfonyl]phenyl  
trifluoromethanesulfonate

10 NMR (CDCl<sub>3</sub>, δ): 1.03 (3H, d, J=6Hz), 2.35-2.95 (4H, m),  
3.00-3.26 (1H, m), 3.51 (1H, d, J=13Hz), 3.84 (1H,  
d, J=13Hz), 4.53 (1H, dd, J=10, 4Hz), 6.85-7.95  
(16H, m), 8.29 (1H, d, J=8Hz)

(+)ESI-MS (m/z): 668 (M+H)<sup>+</sup>

15

(5) 4-[[4-[3-[Benzyl[(2R)-2-(3-chlorophenyl)-2-  
hydroxyethyl]amino]propyl]phenyl]sulfonyl]phenyl  
trifluoromethanesulfonate

20 NMR (CDCl<sub>3</sub>, δ): 1.81 (2H, quintet, J=7Hz), 2.38-2.80  
(6H, m), 3.49 (1H, d, J=13Hz), 3.88 (1H, d,  
J=13Hz), 4.61 (1H, dd, J=10, 4Hz), 7.05-7.50 (13H,  
m), 7.82 (2H, d, J=8Hz), 8.03 (2H, d, J=8Hz)

(+)ESI-MS (m/z): 668 (M+H)<sup>+</sup>

25 Example 28

The following compound was obtained according to a  
similar manner to that of Example 11.

Sodium 4-[[4-[[[(2R)-2-[[[(2R)-2-(3-chlorophenyl)-2-  
30 hydroxyethyl]amino]propyl]oxy]phenyl]sulfonyl]benzoate

NMR (DMSO-d<sub>6</sub>, δ): 1.0-1.1 (3H, m), 2.65-2.75 (2H, m),  
2.9-3.05 (1H, m), 3.75-3.9 (2H, m), 4.55-4.65 (1H,  
m), 7.05-7.15 (2H, m), 7.2-7.4 (4H, m), 7.75-7.9  
(4H, m), 7.95-8.0 (2H, m)

35 (-)ESI-MS (m/z): 488 (M-Na)<sup>-</sup>

Example 29

The following compound was obtained according to a similar manner to that of Example 18.

5

4'-[[4-[2-[(tert-Butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-1,1'-biphenyl-4-carboxylic acid

NMR (DMSO-d<sub>6</sub>, δ): 1.07, 1.19 (total 9H, a pair of s),  
10           2.70-2.95 (2H, m), 2.95-3.45 (4H, m), 4.72 (1H, m),  
             5.59 (1H, br s, OH), 7.10-7.52 (6H, m), 7.75-8.12  
             (10H, m)  
             (-)ESI-MS (m/z): 634 (M-H)<sup>-</sup>

15   Example 30

The following compound was obtained according to a similar manner to that of Example 19.

Sodium 4'-[[4-[2-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-1,1'-biphenyl-4-carboxylate

NMR (DMSO-d<sub>6</sub>, δ): 2.50-2.90 (6H, m), 4.60 (1H, m), 5.49  
             (1H, br s, OH), 7.10-7.72 (8H, m), 7.72-8.10 (8H,  
             m)  
25           (-)ESI-MS (m/z): 534 (free, M-H)<sup>-</sup>

Example 31

The following compounds were obtained according to a similar manner to that of Example 20.

30

(1) Sodium 3-[4-[[4-[2-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]phenoxy]-benzoate

NMR (DMSO-d<sub>6</sub>, δ): 2.50-2.90 (6H, m), 4.63 (1H, m),  
35           7.00-7.20 (3H, m), 7.20-7.55 (8H, m), 7.65-8.00

(5H, m)

(-)ESI-MS (m/z): 550 (free, M-H)<sup>-</sup>

(2) Sodium 4-[4-[4-[2-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]phenoxy]-benzoate

NMR (DMSO-d<sub>6</sub>, δ): 2.50-2.90 (6H, m), 4.61 (1H, m), 6.31 (1H, br s, OH), 6.90-8.10 (16H, m)

(-)ESI-MS (m/z): 550 (free, M-H)<sup>-</sup>

(3) Sodium 2-[3-[4-[3-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]phenoxy]-nicotinate

NMR (DMSO-d<sub>6</sub>, δ): 1.67 (2H, quintet, J=7Hz), 2.30-2.80 (6H, m), 4.61 (1H, m), 5.54 (1H, br s, OH), 7.00-8.10 (15H, m)

(+)ESI-MS (m/z): 567 (free, M+H)<sup>+</sup>

### Example 32

The following compounds were obtained according to a similar manner to that of Example 21.

(1) Methyl 3-[4-[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]phenoxy]benzoate

NMR (CDCl<sub>3</sub>, δ): 1.36 (9H, br s), 2.60-3.05 (2H, m), 3.05-3.60 (4H, m), 3.91 (3H, s), 4.31 (1H, br s, OH), 4.86 (1H, m), 7.00 (2H, d, J=9Hz), 7.10-7.40 (7H, m), 7.48 (1H, t, J=8Hz), 7.67 (1H, s), 7.75-7.98 (5H, m)

(+)ESI-MS (m/z): 688 (M+Na)<sup>+</sup>

(2) Ethyl 3-[4-[4-[3-[benzyl[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]phenoxy]-benzoate



NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.41 (3H, t, J=7Hz), 1.81 (2H, quintet, J=7Hz), 2.37-2.80 (6H, m), 3.49 (1H, d, J=13Hz), 3.87 (1H, d, J=13Hz), 4.37 (2H, q, J=7Hz), 4.61 (1H, dd, J=10, 4Hz), 7.01 (2H, d, J=8Hz), 7.05-7.70 (15H, m), 7.81 (2H, d, J=8Hz), 7.89 (2H, d, J=8Hz)

(+)ESI-MS (m/z): 684 (M+H)<sup>+</sup>

### Example 33

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

(1) Ethyl [2-[[4-[(2R)-2-[benzyl[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]phenoxy]-acetate

NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.02 (3H, d, J=6Hz), 1.24 (3H, t, J=7Hz), 2.40-2.90 (4H, m), 2.98-3.22 (1H, m), 3.48 (1H, d, J=13Hz), 3.82 (1H, d, J=13Hz), 4.19 (2H, q, J=7Hz), 4.52 (1H, dd, J=10, 4Hz), 4.59 (2H, s), 6.81 (1H, d, J=8Hz), 6.92-7.40 (12H, m), 7.51 (1H, t, J=8Hz), 7.94 (2H, d, J=8Hz), 8.17 (1H, d, J=8Hz)

(+)ESI-MS (m/z): 644 (M+Na)<sup>+</sup>

(2) Ethyl [4-[[4-[2-[benzyl[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethoxy]phenyl]sulfonyl]phenoxy]-acetate

NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.29 (3H, t, J=7Hz) 2.64 (1H, dd, J=13, 10Hz), 2.80-3.22 (2H, m), 2.85 (1H, dd, J=13, 4Hz), 3.69 (1H, d, J=13Hz), 3.94-4.10 (2H, m), 4.01 (1H, d, J=13Hz), 4.26 (2H, q, J=7Hz), 4.64 (1H, dd, J=10, 3Hz), 4.65 (2H, s), 6.91 (2H, d, J=8Hz), 6.95 (2H, d, J=8Hz), 7.06-7.40 (9H, m), 7.83 (2H, d, J=8Hz), 7.86 (2H, d, J=8Hz)

(+)ESI-MS (m/z): 624 (M+H)<sup>+</sup>

Example 34

The following compounds were obtained according to a similar manner to that of Example 23.

5

- (1) Ethyl 4-[[4-[2-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethoxy]phenyl]sulfonyl]benzoate hydrochloride

10 NMR (DMSO- $d_6$ ,  $\delta$ ): 1.32 (3H, t, J=7Hz), 2.95-3.55 (4H, m), 4.34 (2H, q, J=7Hz), 4.40 (2H, m), 5.02 (1H, m), 6.32 (1H, br s, OH), 7.20 (2H, d, J=8Hz), 7.30-7.50 (4H, m), 7.95 (2H, d, J=8Hz), 8.06 (2H, d, J=8Hz), 8.14 (2H, d, J=8Hz)  
(+)ESI-MS (m/z): 534 (free, M+H)<sup>+</sup>

15

- (2) Ethyl [4-[[4-[2-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethoxy]phenyl]sulfonyl]phenoxy]-acetate hydrochloride

20 NMR (DMSO- $d_6$ ,  $\delta$ ): 1.20 (3H, t, J=7Hz), 2.95-3.50 (4H, m), 4.16 (2H, q, J=7Hz), 4.39 (2H, m), 4.90 (2H, s), 5.01 (1H, m), 6.32 (1H, br s, OH), 7.11 (2H, d, J=8Hz), 7.17 (2H, d, J=8Hz), 7.30-7.50 (4H, m), 7.84 (2H, d, J=8Hz), 7.89 (2H, d, J=8Hz)  
(+)ESI-MS (m/z): 534 (free, M+H)<sup>+</sup>

25

- (3) Ethyl 3-[[4-[3-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]benzoate hydrochloride

30 NMR (DMSO- $d_6$ ,  $\delta$ ): 1.34 (3H, t, J=7Hz), 1.96 (2H, quintet, J=7Hz), 2.74 (2H, t, J=7Hz), 2.80-3.25 (4H, m), 4.36 (2H, q, J=7Hz), 4.96 (1H, m), 6.30 (1H, br s, OH), 7.26-7.60 (6H, m), 7.80 (1H, t, J=8Hz), 7.95 (2H, d, J=8Hz), 8.23 (1H, d, J=8Hz), 8.23 (1H, d, J=8Hz), 8.39 (1H, s)  
35 (+)ESI-MS (m/z): 502 (free, M+H)<sup>+</sup>

- (4) Ethyl 4'-[[4-[2-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethoxy]phenyl]sulfonyl]-1,1'-biphenyl-3-carboxylate hydrochloride
- 5 NMR (DMSO-d<sub>6</sub>, δ): 1.34 (3H, t, J=7Hz), 2.95-3.55 (4H, m), 4.35 (2H, q, J=7Hz), 4.40 (2H, m), 5.00 (1H, m), 6.33 (1H, br s, OH), 7.20 (2H, d, J=8Hz), 7.30-7.53 (5H, m), 7.67 (1H, t, J=8Hz), 7.85-8.13 (7H, m), 8.20 (1H, s)
- 10 (+)ESI-MS (m/z): 580 (free, M+H)<sup>+</sup>
- (5) Methyl 4'-[[4-[2-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethoxy]phenyl]sulfonyl]-1,1'-biphenyl-4-carboxylate hydrochloride
- 15 NMR (DMSO-d<sub>6</sub>, δ): 2.98-3.50 (4H, m), 3.88 (3H, s), 4.40 (2H, m), 5.01 (1H, m), 6.32 (1H, br s, OH), 7.20 (2H, d, J=8Hz), 7.28-7.50 (4H, m), 7.80-8.15 (10H, m)
- (+)ESI-MS (m/z): 566 (free, M+H)<sup>+</sup>
- 20
- (6) Ethyl 4'-[[4-[3-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-1,1'-biphenyl-3-carboxylate hydrochloride
- 25 NMR (DMSO-d<sub>6</sub>, δ): 1.34 (3H, t, J=7Hz), 1.97 (2H, quintet, J=7Hz), 2.74 (2H, t, J=7Hz), 2.82-3.25 (4H, m), 4.35 (2H, q, J=7Hz), 4.95 (1H, m), 6.29 (1H, br s, OH), 7.20-8.28 (16H, m)
- (+)ESI-MS (m/z): 578 (free, M+H)<sup>+</sup>
- 30
- (7) Methyl 4'-[[4-[3-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-1,1'-biphenyl-4-carboxylate hydrochloride
- 35 NMR (DMSO-d<sub>6</sub>, δ): 1.97 (2H, quintet, J=7Hz), 2.74 (2H, t, J=7Hz), 2.82-3.22 (4H, m), 3.88 (3H, s), 4.97 (1H, m), 6.29 (1H, br s, OH) 7.20-7.60 (6H, m),

7.80-8.15 (10H, m)

(+)ESI-MS (m/z): 564 (free, M+H)<sup>+</sup>

- (8) Ethyl 3-[4-[4-[3-[[2R)-2-(3-chlorophenyl)-  
5 hydroxyethyl]amino]propyl]phenyl]sulfonyl]phenoxy]-  
benzoate hydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 1.30 (3H, t, J=7Hz), 1.96 (2H,  
quintet, J=7Hz), 2.73 (2H, t, J=7Hz), 2.80-3.30  
(4H, m), 4.28 (2H, q, J=7Hz), 4.94 (1H, m), 6.30  
10 (1H, br s, OH), 7.16 (2H, d, J=8Hz), 7.22-8.05  
(14H, m)

(+)ESI-MS (m/z): 594 (free, M+H)<sup>+</sup>

- (9) Ethyl 3'-[[4-[3-[[2R)-2-(3-chlorophenyl)-2-  
15 hydroxyethyl]amino]propyl]phenyl]sulfonyl]-1,1'-  
biphenyl-3-carboxylate hydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 1.35 (3H, t, J=7Hz), 1.97 (2H,  
quintet, J=7Hz), 2.73 (2H, t, J=7Hz), 2.79-3.30  
(4H, m), 4.37 (2H, q, J=7Hz), 4.95 (1H, m), 6.30  
20 (1H, br s, OH), 7.25-8.30 (16H, m)

(+)ESI-MS (m/z): 578 (free, M+H)<sup>+</sup>

- (10) Ethyl 3-[3-[4-[3-[[2R)-2-(3-chlorophenyl)-2-  
hydroxyethyl]amino]propyl]phenyl]sulfonyl]phenoxy]-  
25 benzoate hydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 1.30 (3H, t, J=7Hz), 1.97 (2H,  
quintet, J=7Hz), 2.74 (2H, t, J=7Hz), 2.80-3.30  
(4H, m), 4.31 (2H, q, J=7Hz), 4.95 (1H, m), 6.30  
(1H, br s, OH), 7.20-8.00 (16H, m)

30 (+)ESI-MS (m/z): 594 (free, M+H)<sup>+</sup>

- (11) Sodium 2-[3-[4-[3-[[2R)-2-(3-chlorophenyl)-2-  
hydroxyethyl]amino]propyl]phenyl]sulfonyl]phenoxy]-  
benzoate

35 NMR (DMSO-d<sub>6</sub>, δ): 1.66 (2H, quintet, J=7Hz), 2.35-2.80

(6H, m), 4.60 (1H, m), 5.54 (1H, br s, OH), 6.80-7.95 (16H, m)

(-)ESI-MS (m/z): 564 (free, M-H)<sup>-</sup>

- 5 (12) 3-[[4-[3-[[[(2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]phenol hydrochloride

10 NMR (DMSO-d<sub>6</sub>, δ): 1.97 (2H, quintet, J=7Hz), 2.73 (2H, t, J=7Hz), 2.75-3.30 (4H, m), 4.96 (1H, m), 6.30 (1H, br s, OH), 6.95-7.60 (10H, m), 7.86 (2H, d, J=8Hz), 8.75 (1H, br s), 9.03 (1H, br s), 10.32 (1H, s, OH)

(+)ESI-MS (m/z): 446 (free, M+H)<sup>+</sup>

- 15 (13) Ethyl 5-[[4-[3-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-2-hydroxybenzoate hydrochloride

20 NMR (DMSO-d<sub>6</sub>, δ): 1.34 (3H, t, J=7Hz), 2.00 (2H, quintet, J=7Hz), 2.60-3.25 (6H, m), 4.37 (2H, q, J=7Hz), 4.96 (1H, m), 6.28 (1H, br s, OH) 7.19 (1H, d, J=9Hz), 7.25-7.60 (6H, m), 7.88 (2H, d, J=8Hz), 8.00 (1H, dd, J=9, 2Hz), 8.23 (1H, d, J=2Hz)

(+)ESI-MS (m/z): 518 (free, M+H)<sup>+</sup>

- 25 (14) Ethyl 4-[[4-[3-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-2-hydroxybenzoate hydrochloride

30 NMR (DMSO-d<sub>6</sub>, δ): 1.30 (3H, t, J=7Hz), 1.97 (2H, quintet, J=7Hz), 2.60-3.30 (6H, m), 4.33 (2H, q, J=7Hz), 4.96 (1H, m), 6.29 (1H, br s, OH), 7.20-7.62 (8H, m), 7.77-8.03 (3H, m)

(+)ESI-MS (m/z): 518 (free, M+H)<sup>+</sup>

- 35 (15) Ethyl 5-[[4-[2-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethoxy]phenyl]sulfonyl]-2-

hydroxybenzoate hydrochloride

NMR (DMSO- $d_6$ ,  $\delta$ ): 1.34 (3H, t,  $J=7\text{Hz}$ ), 2.95-3.55 (4H, m), 4.37 (2H, q,  $J=7\text{Hz}$ ), 4.38 (2H, m), 5.01 (1H, m), 6.33 (1H, br s, OH), 7.18 (2H, d,  $J=9\text{Hz}$ ),  
5 7.25-7.55 (5H, m), 7.91 (2H, d,  $J=9\text{Hz}$ ), 7.98 (1H, dd,  $J=9$ , 2Hz), 8.21 (12H, d,  $J=2\text{Hz}$ ), 11.27 (1H, br s, OH)

(+)ESI-MS ( $m/z$ ): 520 (free,  $M+H$ )<sup>+</sup>

10 Example 35

The following compounds were obtained according to a similar manner to that of Example 24.

- (1) tert-Butyl [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl] [3-  
15 [4-[[3-(2-formylphenoxy)phenyl]sulfonyl]phenyl]propyl]-  
carbamate

NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.44 (9H, s), 1.60-1.95 (2H, m), 2.61  
(2H, t,  $J=7\text{Hz}$ ), 2.90-3.60 (4H, m), 4.47 (1H, br s,  
OH), 4.89 (1H, m), 6.91 (1H, d,  $J=8\text{Hz}$ ), 7.10-8.02  
20 (15H, m), 10.39 (1H, s)

(+)ESI-MS ( $m/z$ ): 672 ( $M+Na$ )<sup>+</sup>

- (2) tert-Butyl [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl] [2-  
25 [4-[[3-[(3-formyl-2-pyridyl)oxy]phenyl]sulfonyl]-  
phenyl]ethyl]carbamate

NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.36 (9H, s), 2.60-3.02 (2H, m), 3.02-  
3.60 (4H, m), 4.29 (1H, br s, OH), 4.87 (1H, m),  
7.05-7.65 (9H, m), 7.70-8.00 (4H, m), 8.20-8.40  
(2H, m)

30 (-)ESI-MS ( $m/z$ ): 635 ( $M-H$ )<sup>-</sup>

- (3) tert-Butyl [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl] [2-  
[4-[[4-[(3-formyl-2-pyridyl)oxy]phenyl]sulfonyl]-  
phenyl]ethyl]carbamate

35 NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.36 (9H, s), 2.60-3.00 (2H, m), 3.05-

3.60 (4H, m), 4.30 (1H, br s, OH), 4.88 (1H, m),  
7.10-7.45 (9H, m), 7.89 (2H, d, J=8Hz), 8.00 (2H,  
d, J=8Hz), 8.20-8.40 (2H, m)

(-)ESI-MS (m/z): 635 (M-H)<sup>-</sup>

5

(4) tert-Butyl [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl][3-  
[4-[[3-[(3-formyl-2-pyridyl)oxy]phenyl]sulfonyl]-  
phenyl]propyl]carbamate

NMR (CDCl<sub>3</sub>, δ): 1.44 (9H, s), 1.76 (2H, quintet, J=7Hz),  
2.61 (2H, m), 2.85-3.55 (4H, m), 4.48 (1H, br s,  
OH), 4.88 (1H, m), 7.05-7.65 (9H, m), 7.70-8.00  
(4H, m), 8.20-8.36 (2H, m), 10.51 (1H, s)

10

(-)ESI-MS (m/z): 649 (M-H)<sup>-</sup>

15 Example 36

The following compounds were obtained according to a  
similar manner to that of Example 25.

(1) 2-[3-[[4-[2-[[[(2R)-2-(3-Chlorophenyl)-2-  
hydroxyethyl]amino]ethyl]phenyl]sulfonyl]phenoxy]-  
nicotinic acid dihydrochloride

20

NMR (DMSO-d<sub>6</sub>, δ): 2.90-3.40 (6H, m), 4.99 (1H, m) 6.34  
(1H, br s, OH), 7.20-7.90 (11H, m), 7.97 (2H, d,  
J=8Hz), 8.20-8.40 (2H, m)

25

(+)ESI-MS (m/z): 553 (free, M+H)<sup>+</sup>

(2) 2-[4-[[4-[2-[[[(2R)-2-(3-Chlorophenyl)-2-  
hydroxyethyl]amino]ethyl]phenyl]sulfonyl]phenoxy]-  
nicotinic acid dihydrochloride

30

NMR (DMSO-d<sub>6</sub>, δ): 2.90-3.40 (6H, m), 4.99 (1H, m), 6.34  
(1H, br s, OH), 7.22-7.62 (9H, m), 7.96 (2H, d,  
J=8Hz), 7.99 (2H, d, J=8Hz), 8.23-8.40 (2H, m)

(-)ESI-MS (m/z): 551 (free, M-H)<sup>-</sup>

35 Example 37

The following compound was obtained according to a similar manner to that of Example 26.

tert-Butyl [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl][3-  
5 [4-[(3-hydroxyphenyl)sulfonyl]phenyl]propyl]carbamate  
NMR (CDCl<sub>3</sub>, δ): 1.43 (9H, s), 1.78 (2H, quintet, J=7Hz),  
2.60 (2H, t, J=7Hz), 2.85-3.50 (4H, m), 4.58 (1H,  
br s, OH), 4.86 (1H, m), 6.84 (1H, br s, OH),  
6.92-7.52 (10H, m), 7.81 (2H, d, J=8Hz)  
10 (+)ESI-MS (m/z): 568 (M+Na)<sup>+</sup>

#### Example 38

The following compound was obtained according to a similar manner to that of Preparation 24 starting from the  
15 object compound of Example 14.

Ethyl 3-[4-[[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-  
chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-  
phenoxy]benzoate  
20 NMR (CDCl<sub>3</sub>, δ): 1.37 (9H, br s), 1.38 (3H, t, J=7Hz),  
2.60-3.05 (2H, m), 3.05-3.60 (4H, d), 4.33 (1H, br  
s, OH), 4.37 (2H, q, J=7Hz), 4.87 (1H, m), 7.00  
(2H, d, J=9Hz), 7.10-7.42 (7H, m), 7.47 (1H, t,  
J=8Hz), 7.69 (1H, s), 7.74-7.96 (5H, m)  
25 (+)ESI-MS (m/z): 702 (M+Na)<sup>+</sup>

#### Example 39

The following compound was obtained according to a similar manner to that of Preparation 24 starting from the  
30 object compound of Example 3-(16).

Ethyl 3-[3-[[4-[3-[benzyl[(2R)-2-(3-chlorophenyl)-2-  
hydroxyethyl]amino]propyl]phenyl]sulfonyl]phenoxy]benzoate  
NMR (CDCl<sub>3</sub>, δ): 1.38 (3H, t, J=7Hz), 1.81 (2H, quintet,  
35 J=7Hz), 2.35-2.83 (6H, m), 3.49 (1H, d, J=13Hz),



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3.87 (1H, d, J=13Hz), 3.91 (1H, br s, OH), 4.37  
(2H, q, J=7Hz), 4.61 (1H, dd, J=10 and 4Hz), 7.05-  
7.95 (21H, m)  
(+)ESI-MS (m/z): 684 (M+H)<sup>+</sup>

5

Example 40

The following compounds were obtained according to a similar manner to that of Preparation 60 starting from the object compound of Example 16.

10

(1) Methyl (R)-3'-[[4-[2-[benzyl[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-1,1'-biphenyl-4-carboxylate

NMR (CDCl<sub>3</sub>, δ): 2.5-2.9 (6H, m), 3.53 (1H, d, J=13.4Hz),  
15 3.90 (1H, d, J=13.4Hz), 3.95 (3H, s), 4.59 (1H, dd, J=3.7, 9.8Hz), 7.1-7.35 (11H, m), 7.55-7.7 (3H, m), 7.75-8.0 (4H, m), 8.1-8.2 (3H, m)  
(+)ESI-MS (m/z): 640, 642 (M+H)<sup>+</sup>

20 (2) Ethyl (R)-3'-[[4-[2-[benzyl[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-1,1'-biphenyl-3-carboxylate

NMR (CDCl<sub>3</sub>, δ): 1.42 (3H, t, J=7.2Hz), 2.5-2.9 (6H, m),  
3.54 (1H, d, J=13.4Hz), 3.89 (1H, d, J=13.4Hz),  
25 4.42 (2H, q, J=7.2Hz), 4.60 (1H, dd, J=3.6, 9.9Hz), 7.1-7.35 (11H, m), 7.45-7.65 (2H, m), 7.75-8.0 (5H, m), 8.05-8.3 (3H, m)  
(+)ESI-MS (m/z): 654, 656 (M+H)<sup>+</sup>

30 Example 41

The following compounds were obtained according to a similar manner to that of Preparation 60 starting from the object compound of Example 27-(1).

35 (1) Methyl 4'-[[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-

chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]-  
sulfonyl]-1,1'-biphenyl-3-carboxylate

NMR (CDCl<sub>3</sub>, δ): 1.34 (9H, br s) 2.60-3.00 (2H, m),  
3.00-3.70 (4H, m), 3.95 (3H, s), 4.30 (1H, br s,  
5 OH), 4.85 (1H, m), 7.10-7.42 (6H, m), 7.55 (1H, t,  
J=8Hz), 7.63-7.82 (3H, m), 7.90 (2H, d, J=8Hz),  
8.00 (2H, d, J=8Hz), 8.08 (1H, d, J=8Hz), 8.23 (1H,  
s)

(+)ESI-MS (m/z): 672 (M+Na)<sup>+</sup>

10

(2) Methyl 4'-[[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-  
chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]-  
sulfonyl]-1,1'-biphenyl-4-carboxylate

NMR (CDCl<sub>3</sub>, δ): 1.34 (9H, br s), 2.60-3.04 (2H, m),  
15 3.04-3.70 (4H, m), 3.95 (3H, s), 4.28 (1H, br s,  
OH), 4.84 (1H, m), 7.08-7.42 (6H, m), 7.61 (2H, d,  
J=8Hz), 7.70 (2H, d, J=8Hz), 7.90 (2H, d, J=8Hz),  
8.01 (2H, d, J=8Hz), 8.12 (2H, d, J=8Hz)

(+)ESI-MS (m/z): 672 (M+Na)<sup>+</sup>

20

#### Example 42

The following compounds were obtained according to a  
similar manner to that of Preparation 60 starting from the  
object compound of Example 27-(3).

25

(1) Ethyl 4'-[[4-[2-[benzyl[(2R)-2-(3-chlorophenyl)-2-  
hydroxyethyl]amino]ethoxy]phenyl]sulfonyl]-1,1'-  
biphenyl-3-carboxylate

NMR (CDCl<sub>3</sub>, δ): 1.41 (3H, t, J=7Hz), 2.64 (1H, dd, J=13,  
10Hz), 2.85 (1H, dd, J=13, 4Hz), 2.86-3.20 (2H, m),  
30 3.69 (1H, d, J=13Hz), 3.94 (1H, d, J=13Hz), 3.96  
(br s, OH), 3.96-4.10 (2H, m), 4.41 (2H, q, J=7Hz),  
4.64 (1H, dd, J=10, 3Hz), 6.94 (2H, d, J=8Hz),  
7.08-7.40 (9H, m), 7.53 (1H, t, J=8Hz), 7.63-7.82  
35 (3H, m), 7.90 (2H, d, J=8Hz), 8.00 (2H, d, J=8Hz),

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8.08 (1H, d, J=8Hz), 8.23 (1H, s)  
(+)ESI-MS (m/z): 670 (M+H)<sup>+</sup>

(2) Methyl 4'-[[4-[2-[benzyl[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethoxy]phenyl]sulfonyl]-1,1'-biphenyl-4-carboxylate

5 NMR (CDCl<sub>3</sub>, δ): 2.64 (1H, dd, J=13, 10Hz), 2.85 (1H, dd, J=13, 4Hz), 2.86-3.20 (2H, m), 3.68 (1H, d, J=13Hz), 3.94 (3H, s), 3.94 (1H, d, J=13Hz), 3.96-4.10 (2H, m), 4.64 (1H, dd, J=10, 3Hz), 6.94 (2H, d, J=8Hz), 7.08-7.42 (9H, m), 7.63 (2H, d, J=8Hz), 7.72 (2H, d, J=8Hz), 7.90 (2H, d, J=8Hz), 8.00 (2H, d, J=8Hz), 8.12 (2H, d, J=8Hz)  
10  
(+)ESI-MS (m/z): 656 (M+H)<sup>+</sup>

15

#### Example 43

The following compounds were obtained according to a similar manner to that of Preparation 60 starting from the object compound of Example 27-(5).

20

(1) Ethyl 4'-[[4-[3-[benzyl[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-1,1'-biphenyl-3-carboxylate

25 NMR (CDCl<sub>3</sub>, δ): 1.41 (3H, t, J=7Hz), 1.81 (2H, quintet, J=7Hz), 2.32-2.80 (6H, m), 3.48 (1H, d, J=13Hz), 3.87 (1H, d, J=13Hz), 3.90 (1H, br s, OH), 4.41 (2H, q, J=7Hz), 4.60 (1H, dd, J=10, 4Hz), 7.05-7.40 (11H, m), 7.53 (1H, t, J=8Hz), 7.62-7.84 (3H, m), 7.86 (2H, d, J=8Hz), 8.02 (2H, d, J=8Hz), 8.08 (1H, d, J=8Hz), 8.23 (1H, s)  
30  
(+)ESI-MS (m/z): 668 (M+H)<sup>+</sup>

(2) Methyl 4'-[[4-[3-[benzyl[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-1,1'-biphenyl-4-carboxylate

35

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NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.81 (2H, quintet, J=7Hz), 2.35-2.80  
(6H, m), 3.48 (1H, d, J=13Hz), 3.87 (1H, d,  
J=13Hz), 3.95 (3H, s), 4.60 (1H, dd, J=10, 4Hz),  
7.05-7.40 (11H, m), 7.62 (2H, d, J=8Hz), 7.72 (2H,  
5 d, J=8Hz), 7.86 (2H, d, J=8Hz), 8.02 (2H, d,  
J=8Hz), 8.12 (2H, d, J=8Hz)  
(+)ESI-MS (m/z): 654 (M+Na)<sup>+</sup>

#### Example 44

10 The following compound was obtained according to a  
similar manner to that of Preparation 60 starting from the  
object compound of Example 27-(2).

Ethyl 3'-[[4-[3-[benzyl[(2R)-2-(3-chlorophenyl)-2-  
15 hydroxyethyl]amino]propyl]phenyl]sulfonyl]-1,1'-biphenyl-3-  
carboxylate

NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.42 (3H, t, J=7Hz), 1.80 (2H, quintet,  
J=7Hz), 2.32-2.78 (6H, m), 3.48 (1H, d, J=13Hz),  
3.86 (1H, d, J=13Hz), 4.43 (2H, q, J=7Hz), 4.60  
20 (1H, dd, J=10, 4Hz), 7.03-8.30 (21H, m)  
(+)ESI-MS (m/z): 668 (M+H)<sup>+</sup>

#### Example 45

25 The following compound was obtained according to a  
similar manner to that of Preparation 11 starting from the  
object compound of Example 27-(3).

Ethyl 4-[[4-[2-[benzyl[(2R)-2-(3-chlorophenyl)-2-  
hydroxyethyl]amino]ethoxy]phenyl]sulfonyl]benzoate

30 NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.39 (3H, t, J=7Hz), 2.64 (1H, dd, J=13,  
10Hz), 2.84-3.22 (2H, m), 2.85 (1H, dd, J=13, 4Hz),  
3.68 (1H, d, J=13Hz), 3.94 (1H, d, J=13Hz), 3.94-  
4.10 (2H, m), 4.39 (2H, q, J=7Hz), 4.64 (1H, dd,  
J=10, 3Hz), 6.93 (2H, d, J=8Hz), 7.05-7.40 (9H, m),  
35 7.87 (2H, d, J=8Hz), 7.97 (2H, d, J=8Hz), 8.14 (2H,

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d, J=8Hz)

(+)ESI-MS (m/z): 594 (M+H)<sup>+</sup>Example 46

5       The following compound was obtained according to a similar manner to that of Preparation 11 starting from the object compound of Example 27-(2).

Ethyl 3-[[4-[3-[benzyl[(2R)-2-(3-chlorophenyl)-2-  
10   hydroxyethyl]amino]propyl]phenyl]sulfonyl]benzoate  
NMR (CDCl<sub>3</sub>, δ): 1.41 (3H, t, J=7Hz), 1.80 (2H, quintet, J=7Hz), 2.32-2.75 (6H, m), 3.48 (1H, d, J=13Hz), 3.87 (1H, d, J=13Hz), 4.41 (2H, q, J=7Hz), 4.60 (1H, dd, J=10, 4Hz), 7.03-7.40 (11H, m), 7.59 (1H, 15   t, J=8Hz), 7.84 (2H, d, J=8Hz), 8.11 (1H, d, J=8Hz), 8.22 (1H, d, J=8Hz), 8.59 (1H, s)  
(+)ESI-MS (m/z): 592 (M+H)<sup>+</sup>

Example 47

20       The following compound was obtained according to a similar manner to that of Preparation 11 starting from the object compound of Example 27-(4).

Ethyl 2-[[4-[(2R)-2-[benzyl[(2R)-2-(3-chlorophenyl)-2-  
25   hydroxyethyl]amino]propyl]phenyl]sulfonyl]benzoate  
NMR (CDCl<sub>3</sub>, δ): 1.01 (3H, d, J=6Hz), 1.38 (3H, t, J=7Hz), 2.40-2.90 (4H, m), 2.98-3.22 (1H, m), 3.49 (1H, d, J=13Hz), 3.57 (1H, br s, OH), 3.83 (1H, d, J=13Hz), 4.43 (2H, q, J=7Hz), 4.58 (1H, dd, J=10, 30   4Hz), 6.85-8.20 (17H, m)  
(+)ESI-MS (m/z): 592 (M+H)<sup>+</sup>

Example 48

35       The following compound was obtained according to a similar manner to that of Preparation 33 starting from the

object compound of Example 24.

2-[3-[[4-[3-[Benzyl[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]phenoxy]benzoic  
5 acid

NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.96 (2H, quintet, J=7Hz), 2.35-3.00  
(6H, m), 3.86 (1H, d, J=13Hz), 3.89 (1H, d,  
J=13Hz), 4.66 (1H, dd, J=10, 3Hz), 6.80-8.10 (21H,  
m)

10 (+)ESI-MS (m/z): 656 (M+H)<sup>+</sup>

#### Example 49

The following compound was obtained according to a  
similar manner to that of Preparation 33 starting from the  
15 object compound of Example 35-(1).

2-[3-[[4-[3-[(tert-Butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-  
phenoxy]benzoic acid

20 NMR (DMSO-d<sub>6</sub>,  $\delta$ ): 1.28 (9H, s), 1.60-1.88 (2H, m), 2.58  
(2H, t, J=7Hz), 2.98-3.44 (4H, m), 4.72 (1H, m),  
5.56 (1H, br s, OH), 7.05-8.00 (16H, m)  
(-)ESI-MS (m/z): 664 (M-H)<sup>-</sup>

#### 25 Example 50

The following compound was obtained according to a  
similar manner to that of Preparation 33 starting from the  
object compound of Example 9-(7).

30 2-[3-[[4-[2-[(tert-Butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-  
phenoxy]nicotinic acid

NMR (DMSO-d<sub>6</sub>,  $\delta$ ): 1.08, 1.21 (total 9H, a pair of s),  
2.65-3.00 (2H, m), 3.00-3.60 (4H, m), 4.73 (1H, m),  
35 5.59 (1H, br s, OH), 7.10-8.00 (13H, m), 8.20-8.40

(2H, m)

(-)ESI-MS (m/z): 651 (M-H)<sup>-</sup>

#### Example 51

5       The following compound was obtained according to a similar manner to that of Preparation 33 starting from the object compound of Example 35-(3).

2-[4-[4-[2-[(tert-Butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-phenoxy]nicotinic acid

NMR (DMSO-d<sub>6</sub>, δ): 1.09, 1.21 (total 9H, a pair of s),  
2.65-3.00 (2H, m), 3.00-3.55 (4H, m), 4.75 (1H, m),  
5.59 (1H, br s, OH), 7.10-7.60 (9H, m), 7.89 (2H,  
15       d, J=8Hz), 7.96 (2H, d, J=8Hz), 8.20-8.40 (2H, m)  
(-)ESI-MS (m/z): 651 (M-H)<sup>-</sup>

#### Example 52

20       The following compound was obtained according to a similar manner to that of Preparation 33 starting from the object compound of Example 35-(4).

2-[3-[4-[3-[(tert-Butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-phenoxy]nicotinic acid

NMR (DMSO-d<sub>6</sub>, δ): 1.25, 1.28 (total 9H, a pair of s),  
1.74 (2H, quintet, J=7Hz), 2.48-2.70 (2H, m),  
2.95-3.55 (4H, m), 4.71 (1H, m), 5.56 (1H, br s,  
OH), 7.10-8.00 (13H, m), 8.15-8.40 (2H, m)  
30       (-)ESI-MS (m/z): 665 (M-H)<sup>-</sup>

#### Example 53

35       The following compound was obtained according to a similar manner to that of Preparation 34 starting from the object compound of Example 17.

Ethyl (R)-3'-[[4-[2-[benzyl[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-1,1'-biphenyl-2-carboxylate

5 NMR (CDCl<sub>3</sub>,  $\delta$ ): 0.85 (3H, t, J=7.1Hz), 2.5-2.9 (6H, m),  
3.55 (1H, d, J=13.4Hz), 3.85-4.0 (3H, m), 4.62 (1H,  
dd, J=3.7, 9.9Hz), 7.15-7.35 (12H, m), 7.4-7.6 (4H,  
m), 7.8-7.95 (5H, m)  
(+)ESI-MS (m/z): 654, 656 (M+H)<sup>+</sup>

10

#### Preparation 78

Under nitrogen at 5°C, to a solution of 4-iodophenylacetic acid (11.6 g) in N,N-dimethylformamide (110 ml) were added (1R)-2-amino-1-(3-chlorophenyl)ethanol  
15 hydrochloride (9.19 g), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (7.54 g) and 1-hydroxybenzotriazole (6.56 g), and the mixture was stirred at room temperature for 12 hours. The resulting mixture was poured into 1N sodium hydroxide and the aqueous mixture was extracted with a  
20 mixture of hexane and ethyl acetate (1:1). The organic layer was washed successively with water (two times) and brine, dried over anhydrous magnesium sulfate, evaporated under reduced pressure and dried in vacuo to give N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]-2-(4-iodophenyl)acetamide  
25 (16.7 g).

(+)ESI-MS (m/z): 438 (M+Na)<sup>+</sup>

#### Preparation 79

Under nitrogen at 5°C, to a solution of N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]-2-(4-iodophenyl)acetamide  
30 (16.7 g) in tetrahydrofuran (170 ml) was added dropwise a solution of borane-methyl sulfide complex (12.8 ml) in tetrahydrofuran (13 ml), and the mixture was refluxed for 1 hour. The resulting mixture was cooled to 5°C, and to this  
35 one was added 6N hydrochloric acid (82 ml) dropwise, and the



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mixture was stirred at room temperature for 2.5 days. The mixture was cooled to 5°C, adjusted to pH 8.7 with 3N sodium hydroxide, and to this one was added dropwise a solution of di-tert-butyl dicarbonate (9.64 g) in tetrahydrofuran (30 ml) with controlling pH. The mixture was stirred at room temperature for 2 hours. The resulting mixture was diluted with ethyl acetate. After separation, the organic layer was washed successively with water and brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 7:1 to 4:1) to give tert-butyl [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl][2-(4-iodophenyl)ethyl]carbamate (18.9 g).

(+)ESI-MS (m/z): 524 (M+Na)<sup>+</sup>

15

#### Preparation 80

The following compounds were obtained according to a similar manner to that of Preparation 56.

(1) tert-Butyl [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl][2-[4-[(triisopropylsilyl)thio]phenyl]ethyl]carbamate  
NMR (CDCl<sub>3</sub>, δ): 1.05 (3H, d, J=6.3Hz), 1.1-1.3 (3H, m), 1.48 (9H, s), 2.6-2.8 (2H, m), 3.1-3.4 (4H, m), 4.8-4.9 (1H, m), 6.9-7.1 (2H, m), 7.15-7.5 (6H, m)

25

(2) tert-Butyl [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]-[(1R)-1-methyl-2-[4-[(triisopropylsilyl)thio]phenyl]-ethyl]carbamate  
NMR (CDCl<sub>3</sub>, δ): 0.95-1.2 (24H, m), 1.43 (9H, br s), 2.45-2.8 (3H, m), 3.05-2.15 (1H, m), 3.3-3.55 (1H, m), 4.7-4.8 (1H, m), 6.9-7.0 (2H, m), 7.2-7.45 (6H, m)

30

#### Preparation 81

Under nitrogen at room temperature, to a solution of

35

tert-butyl [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl] [2-[4-  
[(triisopropylsilyl)thio]phenyl]ethyl]carbamate (2.12 g) in  
N,N-dimethylformamide (20 ml) were added potassium carbonate  
(571 mg), 5-fluoro-2-nitrobenzoic acid (730 mg) and cesium  
5 fluoride (628 mg), and the mixture was stirred at 60°C for  
1.5 hours. The mixture was cooled to room temperature and  
to this one was added iodoethane (0.33 ml). After stirred  
for 3 days, the mixture was poured into water and the  
aqueous mixture was extracted with ethyl acetate. The  
10 organic layer was washed successively with water (two times)  
and 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 3:1.25) to give ethyl 5-[[4-[2-[(tert-  
15 butoxycarbonyl) [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]-  
amino]ethyl]phenyl]thio]-2-nitrobenzoate (2.13 g).

(+)ESI-MS (m/z): 623, 625 (M+Na)<sup>+</sup>

#### Preparation 82

20 The following compounds were obtained according to a  
similar manner to that of Preparation 81.

(1) tert-Butyl [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl] [2-  
[4-[(4-formylphenyl)thio]phenyl]ethyl]carbamate

25 (+)ESI-MS (m/z): 534, 536 (M+Na)<sup>+</sup>

(2) tert-Butyl [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]-  
[(1R)-2-[4-[[2-formyl-4-(trifluoromethyl)phenyl]thio]-  
phenyl]-1-methylethyl]carbamate

30 (+)ESI-MS (m/z): 616, 618 (M+Na)<sup>+</sup>

#### Preparation 83

Under nitrogen at 5°C, to a solution of 2-  
methoxyethanol (1.0 g) in dichloromethane (10 ml) were added  
35 pyridine (1.25 g) and p-nitrobenzenesulfonyl chloride (3.2

g), and the mixture was stirred at the same temperature for 2 hours. The resulting mixture was poured into 1N hydrochloric acid and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed successively  
5 with saturated aqueous sodium bicarbonate, water and brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (chloroform) to give 2-methoxyethyl 4-nitrobenzenesulfonate (2.56 g).  
10 NMR (CDCl<sub>3</sub>,  $\delta$ ): 3.28 (3H, s), 3.5-3.65 (2H, m), 4.25-4.35 (2H, m), 8.05-8.2 (2H, m), 8.35-8.45 (2H, m)

#### Preparation 84

The following compound was obtained according to a  
15 similar manner to that of Preparation 58.

2-(2-Iodoethoxy)tetrahydro-2H-pyran  
(+)ESI-MS (m/z): 279 (M+Na)<sup>+</sup>

#### 20 Preparation 85

Under nitrogen at room temperature, to a solution of 4-[2-[(trifluoroacetyl)amino]ethyl]benzenesulfonyl chloride (2.0 g) and methyl (2-methoxyphenyl)acetate (1.37 g) in 1,2-dichloroethane (10 ml) was added aluminum chloride (2.11 g),  
25 and the mixture was refluxed for 4 days. The resulting mixture was poured into a mixture of ice-cold water and ethyl acetate, and the mixture was stirred for 10 minutes. After separation, the organic layer was washed with brine, dried over anhydrous magnesium sulfate and evaporated under  
30 reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 2:1 to 1:1) to give methyl [2-methoxy-5-[[4-[2-[(trifluoroacetyl)amino]ethyl]phenyl]sulfonyl]phenyl]acetate (1.2 g).

(+)ESI-MS (m/z): 482 (M+Na)<sup>+</sup>

Preparation 86

The following compounds were obtained according to a similar manner to that of Preparation 85.

- 5 (1) Methyl 2-hydroxy-4-methyl-5-[[4-[(2R)-2-  
[(trifluoroacetyl)amino]propyl]phenyl]sulfonyl]benzoate  
(+)ESI-MS (m/z): 482 (M+Na)<sup>+</sup>
- (2) Methyl 2-hydroxy-4-methoxy-5-[[4-[(2R)-2-  
10 [(trifluoroacetyl)amino]propyl]phenyl]sulfonyl]benzoate  
(+)ESI-MS (m/z): 498 (M+Na)<sup>+</sup>
- (3) A mixture of N-[(1R)-2-[4-[(4-chloro-2-  
methoxyphenyl)sulfonyl]phenyl]-1-methylethyl]-2,2,2-  
15 trifluoroacetamide and N-[(1R)-2-[4-[(2-chloro-4-  
methoxyphenyl)sulfonyl]phenyl]-1-methylethyl]-2,2,2-  
trifluoroacetamide  
(+)ESI-MS (m/z): 458 (M+Na)<sup>+</sup>

20 Preparation 87

- Under nitrogen at 5°C, to a solution of methyl [2-  
methoxy-5-[[4-[2-[(trifluoroacetyl)amino]ethyl]phenyl]-  
sulfonyl]phenyl]acetate (1.17 g) in dichloromethane (23 ml)  
was added boron tribromide (1M in dichloromethane, 10 ml),  
25 and the mixture was stirred at the same temperature for 30  
minutes. The resulting mixture was evaporated under reduced  
pressure. The residue was dissolved into a mixture of water  
and ethyl acetate. After separation, the organic layer was  
washed successively with water and brine, dried over  
30 anhydrous magnesium sulfate and evaporated under reduced  
pressure. The residue was purified by column chromatography  
on silica gel (hexane/ethyl acetate = 1:1 to 1:2) to give  
methyl [2-hydroxy-5-[[4-[2-[(trifluoroacetyl)amino]ethyl]-  
phenyl]sulfonyl]phenyl]acetate (787 mg).  
35 (+)ESI-MS (m/z): 468 (M+Na)<sup>+</sup>

Preparation 88

The following compounds were obtained according to a similar manner to that of Preparation 87.

5

- (1) N-[(1R)-2-[4-[(4-Chloro-2-hydroxyphenyl)sulfonyl]-phenyl]-1-methylethyl]-2,2,2-trifluoroacetamide

NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.23 (3H, d, J=6.7Hz), 2.8-3.05 (2H, m),  
4.15-4.4 (1H, m), 6.8-7.0 (3H, m), 7.30 (2H, d,  
10 J=8.3Hz), 7.86 (2H, d, J=8.3Hz), 8.15-8.20 (1H, m)  
(+)ESI-MS (m/z): 444 (M+Na)<sup>+</sup>

- (2) N-[(1R)-2-[4-[(2-Chloro-4-hydroxyphenyl)sulfonyl]-phenyl]-1-methylethyl]-2,2,2-trifluoroacetamide

NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.22 (3H, d, J=6.8Hz), 2.75-3.1 (2H, m),  
15 4.1-4.4 (1H, m), 6.9-7.05 (2H, m), 7.35 (2H, d,  
J=8.3Hz), 7.57 (1H, d, J=8.5Hz), 7.8-7.9 (2H, m)  
(+)ESI-MS (m/z): 444 (M+Na)<sup>+</sup>

20 Preparation 89

Under nitrogen at room temperature, to methyl [2-hydroxy-5-[[4-[2-[(trifluoroacetyl)amino]ethyl]phenyl]-sulfonyl]phenyl]acetate (775 mg) was added 5.5N hydrogen chloride in ethanol (15 ml), and the mixture was refluxed  
25 for 19 hours. The resulting mixture was evaporated under reduced pressure. The residue was dissolved into a mixture of aqueous sodium bicarbonate and chloroform/methanol (4:1). After separation, the organic layer was dried over anhydrous magnesium sulfate, evaporated and dried in vacuo to give  
30 ethyl [5-[[4-(2-aminoethyl)phenyl]sulfonyl]-2-hydroxyphenyl]acetate (463 mg).

(+)ESI-MS (m/z): 364 (M+H)<sup>+</sup>

Preparation 90

35 The following compounds were obtained according to a

similar manner to that of Preparation 89.

- (1) Ethyl 2-[[4-[(2R)-2-aminopropyl]phenyl]sulfonyl]-5-chlorobenzoate  
5 (+)ESI-MS (m/z): 382 (M+H)<sup>+</sup>
- (2) Ethyl 4-[[4-[(2R)-2-aminopropyl]phenyl]sulfonyl]-3-chlorobenzoate  
10 (+)ESI-MS (m/z): 382 (M+H)<sup>+</sup>
- (3) Methyl 2-[[4-[(2R)-2-aminopropyl]phenyl]sulfonyl]-4-chlorobenzoate  
(+)ESI-MS (m/z): 368 (M+H)<sup>+</sup>
- 15 (4) Ethyl 5-methoxy-2-[[4-[(2R)-2-[(trifluoroacetyl)amino]propyl]phenyl]sulfonyl]benzoate  
(+)ESI-MS (m/z): 404 (M+Na)<sup>+</sup>
- (5) Methyl 2-[[4-[(2R)-2-aminopropyl]phenyl]sulfonyl]-5-methylbenzoate  
20 (+)ESI-MS (m/z): 348 (M+H)<sup>+</sup>
- (6) Ethyl 2-[[4-[(2R)-2-aminopropyl]phenyl]sulfonyl]-5-methoxybenzoate  
25 (+)ESI-MS (m/z): 400 (M+Na)<sup>+</sup>
- (7) Ethyl 2-[[4-[(2R)-2-aminopropyl]phenyl]sulfonyl]-5-phenoxybenzoate  
30 (+)ESI-MS (m/z): 461 (M+Na)<sup>+</sup>
- (8) Ethyl 2-[[4-[(2R)-2-aminopropyl]phenyl]sulfonyl]-5-propylbenzoate  
(+)ESI-MS (m/z): 390 (M+H)<sup>+</sup>
- 35 (9) Ethyl 2-[[4-[(2R)-2-aminopropyl]phenyl]sulfonyl]-5-(3-

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methylbutyl)benzoate

(+)ESI-MS (m/z): 418 (M+H)<sup>+</sup>

(10) Ethyl 2-[[4-[(2R)-2-aminopropyl]phenyl]sulfonyl]-5-cyclohexylbenzoate

(+)ESI-MS (m/z): 430 (M+H)<sup>+</sup>

(11) Ethyl 2-[[4-[(2R)-2-aminopropyl]phenyl]sulfonyl]-4-propylbenzoate

(+)ESI-MS (m/z): 412 (M+Na)<sup>+</sup>

(12) Ethyl 4-[[4-[(2R)-2-aminopropyl]phenyl]sulfonyl]-3-biphenylcarboxylate

(+)ESI-MS (m/z): 424 (M+H)<sup>+</sup>

(13) Ethyl 5-[[4-[(2R)-2-aminopropyl]phenyl]sulfonyl]-2-hydroxy-4-methylbenzoate

(+)ESI-MS (m/z): 378 (M+H)<sup>+</sup>

(14) Ethyl 5-[[4-[(2R)-2-aminopropyl]phenyl]sulfonyl]-2-hydroxy-4-methoxybenzoate

(+)ESI-MS (m/z): 394 (M+H)<sup>+</sup>

(15) Ethyl 4-[[4-[(2R)-2-aminopropyl]phenyl]sulfonyl]-benzoate

(+)ESI-MS (m/z): 348 (M+H)<sup>+</sup>

(16) Ethyl 5-[[4-[(2R)-2-aminopropyl]phenyl]sulfonyl]-2-hydroxybenzoate

(+)ESI-MS (m/z): 364 (M+H)<sup>+</sup>

#### Preparation 91

Under nitrogen at room temperature, to a suspension of ethyl [5-[[4-(2-aminoethyl)phenyl]sulfonyl]-2-

hydroxyphenyl]acetate (460 mg) in chloroform (10 ml) was

added benzaldehyde (141 mg), and the mixture was stirred at the same temperature for 1 hour. After the resulting mixture was evaporated under reduced pressure, to a suspension of the residue in tetrahydrofuran (5 ml) was added sodium borohydride (53 mg) at 5°C under nitrogen, followed by methanol (5 ml) dropwise, and the mixture was stirred at room temperature for 12 hours. The resulting mixture was poured into water 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 (chloroform/methanol = 20:1 to 15:1) to give ethyl [5-[[4-[2-(benzylamino)ethyl]-phenyl]sulfonyl]-2-hydroxyphenyl]acetate (385 mg).

(+)ESI-MS (m/z): 454 (M+H)<sup>+</sup>

#### Preparation 92

Under nitrogen at 5°C, to a solution of N-[(1R)-2-[4-[(4-chloro-2-hydroxyphenyl)sulfonyl]phenyl]-1-methylethyl]-2,2,2-trifluoroacetamide (1.0 g) in dichloromethane (10 ml) were added 2,6-lutidine (330 mg) and trifluoromethanesulfonic anhydride (736 mg), and the mixture was stirred at the same temperature for 1.5 hours. The resulting mixture was poured into 1N hydrochloric acid and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed successively with saturated aqueous sodium bicarbonate and brine, dried over anhydrous magnesium sulfate, evaporated and dried in vacuo to give 5-chloro-2-[[4-[(2R)-2-[(trifluoroacetyl)amino]propyl]phenyl]sulfonyl]-phenyl trifluoromethanesulfonate (1.17 g).

(+)ESI-MS (m/z): 576 (M+Na)<sup>+</sup>

#### Preparation 93

The following compounds were obtained according to a similar manner to that of Preparation 92.



- (1) 3-Chloro-4-[[4-[(2R)-2-[(trifluoroacetyl)amino]propyl]-phenyl]sulfonyl]phenyl trifluoromethanesulfonate  
(+)ESI-MS (m/z): 576 (M+Na)<sup>+</sup>

5

- (2) Methyl 4-chloro-2-[[[(trifluoromethyl)sulfonyl]oxy]-benzoate  
(+)ESI-MS (m/z): 341 (M+Na)<sup>+</sup>

- 10 (3) Methyl 5-methyl-2-[[[(trifluoromethyl)sulfonyl]oxy]-benzoate  
(+)ESI-MS (m/z): 321 (M+Na)<sup>+</sup>

#### Preparation 94

- 15 The following compounds were obtained according to a similar manner to that of Preparation 11.

- (1) Ethyl 5-chloro-2-[[4-[(2R)-2-[(trifluoroacetyl)amino]-propyl]phenyl]sulfonyl]benzoate  
20 (+)ESI-MS (m/z): 500 (M+Na)<sup>+</sup>

- (2) Ethyl 3-chloro-4-[[4-[(2R)-2-[(trifluoroacetyl)amino]-propyl]phenyl]sulfonyl]benzoate  
(+)ESI-MS (m/z): 500 (M+Na)<sup>+</sup>

25

#### Preparation 95

- To a solution of 2,2,2-trifluoro-N-[(1R)-2-(4-iodophenyl)-1-methylethyl]acetamide (10 g) in 1,4-dioxane (100 ml) was added 1N sodium hydroxide (56 ml), and the  
30 mixture was stirred at 50°C for 1 hour. 1,4-Dioxane was removed by evaporation, and the aqueous mixture was extracted with a mixture of chloroform and methanol (5:1). The organic layer was dried over anhydrous magnesium sulfate, evaporated and dried in vacuo to give (2R)-1-(4-iodophenyl)-  
35 2-propanamine (7.75 g).

129

(+)ESI-MS (m/z): 262 (M+H)<sup>+</sup>

Preparation 96

The following compound was obtained according to a  
5 similar manner to that of Example 83.

(1R)-1-(3-Chlorophenyl)-2-[[ (1R)-2-(4-iodophenyl)-1-methylethyl]amino]ethanol

(+)ESI-MS (m/z): 415 (M+H)<sup>+</sup>

10

Preparation 97

To a suspension of (1R)-1-(3-chlorophenyl)-2-[[ (1R)-2-(4-iodophenyl)-1-methylethyl]amino]ethanol (6.65g) in a mixture of tetrahydrofuran (66 ml) and water (66 ml) was  
15 added dropwise a solution of di-tert-butyl dicarbonate (3.84 g) in tetrahydrofuran (10 ml) with adjusting pH to 8 by 1N sodium hydroxide, and the mixture was stirred at room temperature for 2 hours. The resulting mixture was diluted with ethyl acetate. After separation, the organic layer was  
20 washed with water, dried over anhydrous magnesium sulfate, evaporated and dried in vacuo to give tert-butyl [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl][(1R)-2-(4-iodophenyl)-1-methylethyl]carbamate (8.32 g).

(+)ESI-MS (m/z): 537 (M+Na)<sup>+</sup>

25

Preparation 98

Under nitrogen at room temperature, to a solution of tert-butyl [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl][(1R)-1-methyl-2-[4-[(triisopropylsilyl)thio]phenyl]ethyl]carbamate  
30 (227 mg) in N,N-dimethylformamide (5 ml) was added 2-chloro-6-fluorobenzaldehyde (69 mg) and cesium fluoride (66 mg), and the mixture was stirred at 60°C for 1 hour. The resulting mixture was poured into water and the aqueous mixture was extracted with ethyl acetate. The organic layer  
35 was washed successively with water (two times) and brine,

dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 5:1 to 3:1) to give tert-butyl [(1R)-2-[4-[(3-chloro-2-formylphenyl)thio]phenyl]-1-methylethyl][(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]carbamate (184 mg).

(+)ESI-MS (m/z): 582, 584 (M+Na)<sup>+</sup>

#### Preparation 99

10 A solution of 4-chloro-2-hydroxybenzoic acid (3.6 g) and concentrated sulfonic acid (3.6 ml) in methanol (36 ml) was refluxed for 3 days. The resulting mixture was poured into water and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed successively with  
15 saturated aqueous sodium bicarbonate and brine, dried over anhydrous magnesium sulfate, evaporated and dried in vacuo to give methyl 4-chloro-2-hydroxybenzoate (3.59 g).

NMR (CDCl<sub>3</sub>, δ): 3.95 (3H, s), 6.87 (1H, dd, J=2.0, 8.5Hz), 7.01 (1H, d, J=2.0Hz), 7.76 (1H, d, J=8.5Hz)  
20

#### Preparation 100

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

25

Methyl 2-hydroxy-4-methylbenzoate

NMR (CDCl<sub>3</sub>, δ): 2.34 (3H, s), 3.92 (3H, s), 6.65-6.7 (1H, m), 6.79 (1H, m), 7.70 (1H, d, J=8.1Hz)

#### 30 Preparation 101

The following compound was obtained according to a similar manner to that of Preparation 3.

2,2,2-Trifluoro-N-[(1R)-2-(4-mercaptophenyl)-1-methylethyl]acetamide  
35

(+)ESI-MS (m/z): 286 (M+Na)<sup>+</sup>

#### Preparation 102

Under nitrogen at room temperature, to a mixture of  
5 bis(dibenzylideneacetone)palladium(0) (328 mg) and bis(2-  
diphenylphosphinophenyl)ether (307 mg) was added toluene (30  
ml). After being stirred at the same temperature for 10  
minutes, 2,2,2-trifluoro-N-[(1R)-2-(4-mercaptophenyl)-1-  
methylethyl]acetamide (1.5 g), methyl 4-chloro-2-  
10 [[(trifluoromethyl)sulfonyl]oxy]benzoate (2.0 g) and  
potassium tert-butoxide (703 mg) were added, and the mixture  
was stirred at 100°C for 1 hour. The resulting mixture was  
poured into water and the aqueous mixture was extracted with  
ethyl acetate. The organic layer was dried over anhydrous  
15 magnesium sulfate and evaporated under reduced pressure.  
The residue was purified by column chromatography on silica  
gel (hexane/ethyl acetate = 5:1 to 3:1) to give methyl 4-  
chloro-2-[[4-[(2R)-2-[(trifluoroacetyl)amino]propyl]phenyl]-  
thio]benzoate (650 mg).

20 (+)ESI-MS (m/z): 454 (M+Na)<sup>+</sup>

#### Preparation 103

The following compound was obtained according to a  
similar manner to that of Preparation 102.

25

Methyl 5-methyl-2-[[4-[(2R)-2-[(trifluoroacetyl)amino]-  
propyl]phenyl]thio]benzoate

(+)ESI-MS (m/z): 434 (M+Na)<sup>+</sup>

#### 30 Preparation 104

The following compounds were obtained according to a  
similar manner to that of Example 91.

(1) Methyl 4-chloro-2-[[4-[(2R)-2-[(trifluoroacetyl)amino]-  
35 propyl]phenyl]sulfonyl]benzoate

132

(+) ESI-MS (m/z): 486 (M+Na)<sup>+</sup>

(2) N-[(1R)-2-[4-[(2-Chloro-6-formylphenyl)sulfonyl]-phenyl]-1-methylethyl]-2,2,2-trifluoroacetamide

5 (-) ESI-MS (m/z): 432, 434 (M-H)<sup>-</sup>

(3) Methyl 5-methyl-2-[[4-[(2R)-2-[(trifluoroacetyl)amino]-propyl]phenyl)sulfonyl]benzoate

(+) ESI-MS (m/z): 466 (M+Na)<sup>+</sup>

10

(4) 2,2,2-Trifluoro-N-[(1R)-2-[4-[(2-formyl-4-methoxyphenyl)sulfonyl]phenyl]-1-methylethyl]acetamide

(+) ESI-MS (m/z): 452 (M+Na)<sup>+</sup>

15 (5) 2,2,2-Trifluoro-N-[(1R)-2-[4-[(4-fluoro-2-formylphenyl)sulfonyl]phenyl]-1-methylethyl]acetamide

(+) ESI-MS (m/z): 440 (M+Na)<sup>+</sup>

20 (6) 2,2,2-Trifluoro-N-[(1R)-2-[4-[(2-formyl-4-iodophenyl)sulfonyl]phenyl]-1-methylethyl]acetamide

(+) ESI-MS (m/z): 548 (M+Na)<sup>+</sup>

(7) 2,2,2-Trifluoro-N-[(1R)-2-[4-[(2-formyl-5-iodophenyl)sulfonyl]phenyl]-1-methylethyl]acetamide

25 (+) ESI-MS (m/z): 548 (M+Na)<sup>+</sup>

(8) 2,2,2-Trifluoro-N-[(1R)-2-[4-[(4-formylphenyl)sulfonyl]phenyl]-1-methylethyl]acetamide

(+) ESI-MS (m/z): 422 (M+Na)<sup>+</sup>

30

#### Preparation 105

Under nitrogen at room temperature, to a solution of 2,2,2-trifluoro-N-[(1R)-2-(4-mercaptophenyl)-1-methylethyl]-acetamide (700 mg) in N,N-dimethylformamide (10 ml) were  
35 added 3-chloro-2-fluorobenzaldehyde (464 mg) and potassium

carbonate (404 mg), and the mixture was stirred at 60°C for 1 hour. The resulting mixture was poured into water and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed successively with water and brine, dried over anhydrous magnesium sulfate, evaporated under reduced pressure. The residue was triturated with diisopropyl ether and collected by filtration followed by dryness to give N-[(1R)-2-[4-[(2-chloro-6-formylphenyl)-thio]phenyl]-1-methylethyl]-2,2,2-trifluoroacetamide (824 mg).

(+)ESI-MS (m/z): 424 (M+Na)<sup>+</sup>

#### Preparation 106

The following compounds were obtained according to a similar manner to that of Preparation 33.

(1) 3-Chloro-2-[[4-[(2R)-2-[(trifluoroacetyl)amino]propyl]-phenyl]sulfonyl]benzoic acid  
(-)ESI-MS (m/z): 404 (M-COOH)<sup>-</sup>

(2) 5-Methoxy-2-[[4-[(2R)-2-[(trifluoroacetyl)amino]-propyl]phenyl]sulfonyl]benzoic acid  
(-)ESI-MS (m/z): 400 (M-COOH)<sup>-</sup>

(3) 5-Phenoxy-2-[[4-[(2R)-2-[(trifluoroacetyl)amino]-propyl]phenyl]sulfonyl]benzoic acid  
(-)ESI-MS (m/z): 506 (M-H)<sup>-</sup>

(4) 5-Iodo-2-[[4-[(2R)-2-[(trifluoroacetyl)amino]propyl]-phenyl]sulfonyl]benzoic acid  
(-)ESI-MS (m/z): 540 (M-H)<sup>-</sup>

(5) 4-Iodo-2-[[4-[(2R)-2-[(trifluoroacetyl)amino]propyl]-phenyl]sulfonyl]benzoic acid  
(-)ESI-MS (m/z): 540 (M-H)<sup>-</sup>

(6) 4-[[4-[(2R)-2-[(trifluoroacetyl)amino]propyl]phenyl]-sulfonyl]benzoic acid

(-)ESI-MS (m/z): 414 (M-H)<sup>-</sup>

5

#### Preparation 107

Under nitrogen at room temperature, to a solution of 3-chloro-2-[[4-[(2R)-2-[(trifluoroacetyl)amino]propyl]phenyl]-sulfonyl]benzoic acid (629 mg) in N,N-dimethylformamide (6  
10 ml) were added iodoethane (240 mg) and potassium carbonate (213 mg), and the mixture was stirred at the same temperature for 4 hours. The resulting mixture was poured into saturated aqueous sodium bicarbonate and the aqueous mixture was extracted with ethyl acetate. The organic layer  
15 was washed successively with water (two times) and brine, 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 ethyl 3-chloro-2-[[4-[(2R)-2-  
20 [(trifluoroacetyl)amino]propyl]phenyl]sulfonyl]benzoate (395 mg).

(+)ESI-MS (m/z): 500 (M+Na)<sup>+</sup>

#### Preparation 108

25 The following compounds were obtained according to a similar manner to that of Preparation 107.

(1) Ethyl 5-methoxy-2-[[4-[(2R)-2-[(trifluoroacetyl)amino]-propyl]phenyl]sulfonyl]benzoate

30 (+)ESI-MS (m/z): 495 (M+Na)<sup>+</sup>

(2) Ethyl 5-phenoxy-2-[[4-[(2R)-2-[(trifluoroacetyl)amino]-propyl]phenyl]sulfonyl]benzoate

(+)ESI-MS (m/z): 557 (M+Na)<sup>+</sup>

35

- (3) Ethyl 5-iodo-2-[[4-[(2R)-2-[(trifluoroacetyl)amino]-propyl]phenyl]sulfonyl]benzoate  
(+)ESI-MS (m/z): 592 (M+Na)<sup>+</sup>
- 5 (4) Ethyl 4-iodo-2-[[4-[(2R)-2-[(trifluoroacetyl)amino]-propyl]phenyl]sulfonyl]benzoate  
(+)ESI-MS (m/z): 592 (M+Na)<sup>+</sup>
- 10 (5) Ethyl 4-[[4-[(2R)-2-[(trifluoroacetyl)amino]-propyl]phenyl]sulfonyl]benzoate  
(+)ESI-MS (m/z): 466 (M+Na)<sup>+</sup>

#### Preparation 109

Under nitrogen at room temperature, to a solution of  
15 tert-butyl [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl][(1R)-1-methyl-2-[4-[(triisopropylsilyl)thio]phenyl]ethyl]carbamate (1.7 g) in N,N-dimethylformamide (17 ml) were added 3-fluoro-5-methoxybenzaldehyde (1.1 g) and potassium carbonate (982 mg), and the mixture was stirred at 60°C for 1.5 hours.  
20 The resulting mixture was poured into water and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed successively with water and brine, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The residue was purified by column chromatography  
25 on silica gel (hexane/ethyl acetate = 4:1 to 3:1) to give 2,2,2-trifluoro-N-[(1R)-2-[4-[(2-formyl-4-methoxyphenyl)-thio]phenyl]-1-methylethyl]acetamide (2.0 g).  
(+)ESI-MS (m/z): 420 (M+Na)<sup>+</sup>

#### 30 Preparation 110

Under nitrogen at room temperature, to a solution of  
tert-butyl [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl][(1R)-1-methyl-2-[4-[(triisopropylsilyl)thio]phenyl]ethyl]carbamate (1.01 g) in N,N-dimethylformamide (10 ml) was added 2,5-  
35 difluorobenzaldehyde (273 mg) and cesium fluoride (292 mg),



and the mixture was stirred at 60°C for 1.5 hours. The resulting mixture was poured into water and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed successively with water (two times) and brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 5:1 to 3:1) to give tert-butyl [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl] [(1R)-2-[4-[(4-fluoro-2-formylphenyl)thio]phenyl]-1-methylethyl]carbamate (803 mg).

(+)ESI-MS (m/z): 566 (M+Na)<sup>+</sup>

#### Preparation 111

Under nitrogen at 5°C, to a solution of tert-butyl [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl] [(1R)-2-[4-[(4-fluoro-2-formylphenyl)thio]phenyl]-1-methylethyl]carbamate (790 mg) in N,N-dimethylformamide (10 ml) were added imidazole (158 mg) and tert-butyldimethylsilyl chloride (350 mg), and the mixture was stirred at room temperature for 22 hours. The resulting mixture was poured into 1N hydrochloric acid and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed successively with water, saturated aqueous sodium bicarbonate and 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 give tert-butyl [(2R)-2-[[tert-butyl(dimethyl)silyl]oxy]-2-(3-chlorophenyl)ethyl] [(1R)-2-[4-[(4-fluoro-2-formylphenyl)thio]phenyl]-1-methylethyl]carbamate (886 mg).

(+)ESI-MS (m/z): 680 (M+Na)<sup>+</sup>

#### Preparation 112

Under nitrogen at room temperature, to a solution of 2,2,2-trifluoro-N-[(1R)-2-(4-mercaptophenyl)-1-methylethyl]acetamide (2.0 g) in N,N-dimethylformamide (20

ml) were added 2,5-difluorobenzaldehyde (1.19 g) and potassium carbonate (1.15 g), and the mixture was stirred at 60°C for 1 hour. The resulting mixture was poured into water and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed successively with water and brine, dried over anhydrous magnesium sulfate, evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (chloroform/ethyl acetate = 100:1) to give 2,2,2-trifluoro-N-[(1R)-2-[4-[(4-fluoro-2-formylphenyl)thio]phenyl]-1-methylethyl]acetamide (2.28 g).

(+)ESI-MS (m/z): 408 (M+Na)<sup>+</sup>

#### Preparation 113

Under nitrogen at 5°C, to a suspension of sodium hydride (60% in oil, 32 mg) in N,N-dimethylformamide (5 ml) was added phenol (74 mg), and the mixture was stirred at room temperature for 30 minutes. To this one was added 2,2,2-trifluoro-N-[(1R)-2-[4-[(4-fluoro-2-formylphenyl)sulfonyl]phenyl]-1-methylethyl]acetamide (300 mg), and the mixture was stirred at 60°C for 1.5 hours. The resulting mixture was poured into water and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed successively with water (two times) and brine, dried over anhydrous magnesium sulfate, evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (chloroform/ethyl acetate = 30:1 to 20:1) to give 2,2,2-trifluoro-N-[(1R)-2-[4-[(2-formyl-4-phenoxyphenyl)sulfonyl]phenyl]-1-methylethyl]acetamide (288 mg).

(+)ESI-MS (m/z): 514 (M+Na)<sup>+</sup>

#### Preparation 114

Under nitrogen in acetone-dry ice bath, to a solution of 2-fluoro-6-methoxybenzaldehyde (3.0 g) in dichloromethane

(15 ml) was added boron tribromide (1M in dichloromethane, 21.4 ml), and the temperature of the mixture was raised to 5°C over a period of 2 hours. The resulting mixture was poured into a mixture of ice-cold water and ethyl acetate, and stirred for 5 minutes, followed by adjusting pH to ca. 6.5 with 5N sodium hydroxide. After separation, the organic layer was washed successively with water and brine, dried over anhydrous magnesium sulfate, evaporated and dried in vacuo to give 2-fluoro-6-hydroxybenzaldehyde (2.18 g).

10 NMR (CDCl<sub>3</sub>, δ): 6.55-6.65 (1H, m), 6.75-6.8 (1H, m), 7.4-7.55 (1H, m), 10.27 (1H, s)

#### Preparation 115

Under nitrogen at room temperature, to a solution of 2-fluoro-6-hydroxybenzaldehyde (1.04 g) in N,N-dimethylformamide (10 ml) were added chloromethyl methyl ether (1.28 g) and potassium carbonate (1.13 g), and the mixture was stirred at 45°C for 2 hours. The resulting mixture was poured into water and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed successively with water (two times) and brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 5:1 to 3:1) to give 2-fluoro-6-(methoxymethoxy)benzaldehyde (842 mg).

20 25

(+)ESI-MS (m/z): 207 (M+Na)<sup>+</sup>

#### Preparation 116

Under nitrogen at room temperature, to a solution of tert-butyl [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl][(1R)-1-methyl-2-[4-[(triisopropylsilyl)thio]phenyl]ethyl]carbamate (437 mg) in N,N-dimethylformamide (4 ml) was added 2-fluoro-6-(methoxymethoxy)benzaldehyde (153 mg) and cesium fluoride (126 mg), and the mixture was stirred at 55°C for 5 hours.

30 35

The resulting mixture was poured into water and the aqueous

mixture was extracted with ethyl acetate. The organic layer was washed successively with water (two times) and brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 4:1 to 3:1) to give tert-butyl [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl] [(1R)-2-[4-[[2-formyl-3-(methoxymethoxy)-phenyl]thio]phenyl]-1-methylethyl]carbamate (326 mg).

(+)ESI-MS (m/z): 608, 610 (M+Na)<sup>+</sup>

10

#### Preparation 117

Under nitrogen at room temperature, to a solution of 2,2,2-trifluoro-N-[(1R)-2-(4-mercaptophenyl)-1-methylethyl]acetamide (2.0 g) in N,N-dimethylformamide (20 ml) was added 2-fluoro-5-iodobenzaldehyde (2.09 g) and potassium carbonate (1.15 g), and the mixture was stirred at 60°C for 2 hours. The resulting mixture was poured into water and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed successively with water (two times) and brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/chloroform = 1:3 to only chloroform) to give 2,2,2-trifluoro-N-[(1R)-2-[4-[(2-formyl-4-iodophenyl)thio]phenyl]-1-methylethyl]acetamide (3.06 g).

(+)ESI-MS (m/z): 516 (M+Na)<sup>+</sup>

15

20

25

#### Preparation 118

Under nitrogen at room temperature, to a suspension of indium (68 mg) in N,N-dimethylformamide (1 ml) was added allyl iodide (149 mg), and the mixture was stirred at room temperature for 100 minutes. Under nitrogen at room temperature, to a mixture of ethyl 5-iodo-2-[[4-[(2R)-2-[(trifluoroacetyl)amino]propyl]phenyl]sulfonyl]benzoate (336 mg), tris(dibenzylideneacetone)dipalladium(0)-chloroform

30

35

adduct (27 mg), triphenylphosphine (50 mg) and lithium chloride (75 mg) was added N,N-dimethylformamide (4 ml), and the mixture was stirred at the same temperature for 15 minutes. To this one was added the allylic indium reagent which was obtained above, and the mixture was stirred at 80°C for 1.5 hours. The resulting mixture was poured into a mixture of saturated aqueous sodium bicarbonate and ethyl acetate, and the mixture was stirred for 5 minutes. After separation, the organic layer was washed successively with water (two times) 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 = 20:1 to 10:1) to give ethyl 5-allyl-2-[[4-[(2R)-2-[(trifluoroacetyl)amino]propyl]phenyl]sulfonyl]benzoate (231 mg).

(+)ESI-MS (m/z): 506 (M+Na)<sup>+</sup>

#### Preparation 119

The following compounds were obtained according to a similar manner to that of Preparation 118.

(1) Ethyl 5-(3-methyl-2-buten-1-yl)-2-[[4-[(2R)-2-[(trifluoroacetyl)amino]propyl]phenyl]sulfonyl]benzoate  
(+)ESI-MS (m/z): 534 (M+Na)<sup>+</sup>

(2) Ethyl 5-(2-cyclohexen-1-yl)-2-[[4-[(2R)-2-[(trifluoroacetyl)amino]propyl]phenyl]sulfonyl]benzoate  
(+)ESI-MS (m/z): 546 (M+Na)<sup>+</sup>

(3) Ethyl 4-allyl-2-[[4-[(2R)-2-[(trifluoroacetyl)amino]propyl]phenyl]sulfonyl]benzoate  
(+)ESI-MS (m/z): 506 (M+Na)<sup>+</sup>

#### Preparation 120

A mixture of ethyl 5-allyl-2-[[4-[(2R)-2-

[(trifluoroacetyl)amino]propyl]phenyl]sulfonyl]benzoate (318 mg) and 10% palladium on activated carbon (50% wet, 30 mg) in ethanol (4 ml) was stirred at room temperature in the presence of hydrogen at an atmospheric pressure for 2 hours. After filtration, the filtrate was evaporated and dried in vacuo to give ethyl 5-propyl-2-[[4-[(2R)-2-[(trifluoroacetyl)amino]propyl]phenyl]sulfonyl]benzoate (321 mg).

(+)ESI-MS (m/z): 508 (M+Na)<sup>+</sup>

10

#### Preparation 121

The following compounds were obtained according to a similar manner to that of Preparation 120.

- (1) Ethyl 5-(3-methylbutyl)-2-[[4-[(2R)-2-[(trifluoroacetyl)amino]propyl]phenyl]sulfonyl]benzoate  
(+)ESI-MS (m/z): 536 (M+Na)<sup>+</sup>
- (2) Ethyl 4-propyl-2-[[4-[(2R)-2-[(trifluoroacetyl)amino]propyl]phenyl]sulfonyl]benzoate  
(+)ESI-MS (m/z): 508 (M+Na)<sup>+</sup>

20

#### Preparation 122

A mixture of ethyl 5-(2-cyclohexen-1-yl)-2-[[4-[(2R)-2-[(trifluoroacetyl)amino]propyl]phenyl]sulfonyl]benzoate (186 mg) and 10% palladium on activated carbon (50% wet, 38 mg) in ethanol (5 ml) was stirred at room temperature in the presence of hydrogen at an atmospheric pressure for 5 hours. After filtration, the filtrate was evaporated under reduced pressure. The residue was dissolved into a mixture of 1N hydrochloric acid and ethyl acetate. After separation, the organic layer was washed successively with saturated aqueous sodium bicarbonate and brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel

35

(hexane/ethyl acetate = 3:1 to 2:1 to give ethyl 5-cyclohexyl-2-[[4-[(2R)-2-[(trifluoroacetyl)amino]propyl]-phenyl]sulfonyl]benzoate (108 mg).

(+)ESI-MS (m/z): 548 (M+Na)<sup>+</sup>

5

#### Preparation 123

Under nitrogen at room temperature, to a solution of 4-bromo-2-fluorobenzaldehyde (5.0 g) in toluene (50 ml) were added ethylene glycol (4.59 g) and p-toluenesulfonic acid monohydrate (468 mg), and the mixture was refluxed for 2.5 hours to remove water by azeotropic distillation. The resulting mixture was poured into aqueous sodium bicarbonate and the aqueous mixture was extracted with toluene. The organic layer was washed successively with saturated aqueous sodium bicarbonate and brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 20:1) to give 2-(4-bromo-2-fluorophenyl)-1,3-dioxolane (5.5 g).

20 NMR (CDCl<sub>3</sub>, δ): 3.95-4.2 (4H, m), 6.03 (1H, s), 7.2-7.5 (3H, m)

#### Preparation 124

Under nitrogen in dry ice-acetone bath, to a solution of 2-(4-bromo-2-fluorophenyl)-1,3-dioxolane (5.5 g) in tetrahydrofuran (80 ml) was added butyl lithium (1.58M in hexane, 14.8 ml), and the mixture was stirred at the same temperature for 40 minutes. To this one was added a solution of iodine (17 g) in tetrahydrofuran (30 ml) in dry ice-acetone bath, and the mixture was stirred at the same temperature for 40 minutes and then at 5°C for 1.5 hours. To the resulting mixture was added aqueous sodium thiosulfate and ethyl acetate at 5°C, and the mixture was stirred at the same temperature for 5 minutes. After separation, the organic layer was washed successively with

35

saturated aqueous sodium bicarbonate and 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 give iodo compounds. To the solution of the iodo compounds in a mixture of tetrahydrofuran (20 ml) and methanol (20 ml) was added 6N hydrochloric acid (10 ml) at room temperature, and the mixture was stirred at the same temperature for 12 hours. The volatile solvents were removed by evaporation to give precipitates. To this one was added water, and the mixture was stirred for 1 hour. The precipitates were collected by filtration and dried in vacuo to give 2-fluoro-4-iodobenzaldehyde (1.79 g).

NMR (CDCl<sub>3</sub>,  $\delta$ ): 7.5-7.75 (3H, m), 10.31 (1H, s)

#### Preparation 125

Under nitrogen at room temperature, to a solution of 2,2,2-trifluoro-N-[(1R)-2-(4-mercaptophenyl)-1-methylethyl]acetamide (4.0 g) in N,N-dimethylformamide (40 ml) was added 2-fluoro-4-iodobenzaldehyde (4.18 g) and potassium carbonate (2.31 g), and the mixture was stirred at 60°C for 2 hours. The resulting mixture was poured into water and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed successively with water (two times) 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 = 10:1) to give 2,2,2-trifluoro-N-[(1R)-2-[4-[(2-formyl-5-iodophenyl)thio]phenyl]-1-methylethyl]acetamide (5.02 g).

(+)ESI-MS (m/z): 516 (M+Na)<sup>+</sup>

#### Preparation 126

Under nitrogen at room temperature, to a solution of ethyl 5-iodo-2-[[4-[(2R)-2-[(trifluoroacetyl)amino]propyl]-



phenyl]sulfonyl]benzoate (500 mg) and phenylboronic acid (300 mg) in 1,2-dimethoxyethane (5 ml) were added tetrakis(triphenylphosphine)palladium(0) (101 mg) and 2M sodium carbonate (1.8 ml), and the mixture was stirred at 80°C for 7.5 hours. The resulting mixture was poured into water 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 = 2:1 to 3:2) to give ethyl 4-[[4-[(2R)-2-[(trifluoroacetyl)amino]-propyl]phenyl]sulfonyl]-3-biphenylcarboxylate (416 mg).  
(+)ESI-MS (m/z): 542 (M+Na)<sup>+</sup>

#### 15 Preparation 127

Under nitrogen at room temperature, to a solution of tert-butyl [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl][(1R)-1-methyl-2-[4-[(triisopropylsilyl)thio]phenyl]ethyl]carbamate (0.92 g) in N,N-dimethylformamide (10 ml) was added 2-fluoro-5-methylbenzaldehyde (242 mg) and cesium fluoride (266 mg), and the mixture was stirred at 55°C for 2 hours. The resulting mixture was poured into water and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed successively with water (two times) and brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 6:1 to 4:1) to give tert-butyl [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl][(1R)-2-[4-[(2-formyl-4-methylphenyl)thio]-phenyl]-1-methylethyl]carbamate (512 mg).  
(+)ESI-MS (m/z): 562, 564 (M+Na)<sup>+</sup>

#### Preparation 128

Under nitrogen at 5°C, to methyl 2-hydroxy-4-methylbenzoate (16.1 g) was added chlorosulfonic acid (33.8

g) dropwise, and the mixture was stirred at 70°C for 3 hours. The resulting mixture was poured into ice-cold water and the aqueous mixture was extracted with chloroform. The organic layer was dried over anhydrous magnesium sulfate and  
5 evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (chloroform) to give methyl 5-(chlorosulfonyl)-2-hydroxy-4-methylbenzoate (6.96 g).

10 NMR (CDCl<sub>3</sub>, δ): 2.77 (3H, s), 4.01 (3H, s), 6.99 (1H, s),  
8.58 (1H, s)

#### Preparation 129

The following compound was obtained according to a similar manner to that of Preparation 128.

15

Methyl 5-(chlorosulfonyl)-2-hydroxy-4-methoxybenzoate

NMR (CDCl<sub>3</sub>, δ): 3.98 (3H, s), 4.07 (3H, s), 6.60 (1H, s), 8.50 (1H, s)

#### 20 Preparation 130

Under nitrogen at room temperature, to a solution of 2,2,2-trifluoro-N-[(1R)-2-(4-mercaptophenyl)-1-methylethyl]-acetamide (2.0 g) in N,N-dimethylformamide (20 ml) was added 4-fluorobenzaldehyde (1.04 g) and potassium carbonate (1.15  
25 g), and the mixture was stirred at 60°C for 2 hours. The resulting mixture was poured into water and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed successively with water (two times) and brine, dried over anhydrous magnesium sulfate and evaporated under  
30 reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 4:1 to 3:1) to give 2,2,2-trifluoro-N-[(1R)-2-[4-[(4-formylphenyl)-thio]phenyl]-1-methylethyl]acetamide (2.19 g).

(+)ESI-MS (m/z): 390 (M+Na)<sup>+</sup>

35

Preparation 131

Under nitrogen at room temperature, to (2-phenylethyl)amine (20 g) was added dropwise ethyl formate (49.6 g), and the mixture was stirred at 50°C for 1.5 hours.  
5 The resulting mixture was evaporated and dried in vacuo to give (2-phenylethyl)formamide (25 mg).

(-)ESI-MS (m/z): 148 (M-H)<sup>-</sup>

Preparation 132

10 Under nitrogen at room temperature, to a mixture of (2-phenylethyl)formamide (500 mg) and methyl 5-(chlorosulfonyl)-2-hydroxybenzoate (840 mg) in nitrobenzene (5 ml) was added aluminum chloride (1.56 g), and the mixture was stirred at 100°C for 4 hours. To the resulting mixture  
15 were added ice-cold 1N hydrochloric acid and ethyl acetate, and the mixture was stirred for 20 minutes. After separation, the organic layer was dried over anhydrous magnesium sulfate and evaporated under reduced pressure. To the residue was added hydrogen chloride methanol reagent  
20 (5 ml) at room temperature under nitrogen, and the mixture was stirred at 40°C for 2.5 hours. The resulting mixture was evaporated under reduced pressure. To the residue was added diisopropyl ether (20 ml), and the mixture was stirred for 1 hour. The precipitates were collected by filtration  
25 and dried in vacuo to give methyl 5-[[4-(2-aminoethyl)-phenyl]sulfonyl]-2-hydroxybenzoate hydrochloride (1.03 g).

(+)ESI-MS (m/z): 336 (M-HCl+H)<sup>+</sup>

Preparation 133

30 To a suspension of methyl 5-[[4-(2-aminoethyl)phenyl]sulfonyl]-2-hydroxybenzoate hydrochloride (3.0 g) in a mixture of tetrahydrofuran (30 ml) and water (30 ml) was added dropwise a solution of di-tert-butyl dicarbonate (1.85 g) in tetrahydrofuran (5 ml) with adjusting pH to 8 by 5N  
35 sodium hydroxide, and the mixture was stirred at room

temperature for 1.5 hours. The resulting mixture was diluted with ethyl acetate. After separation, the organic layer was washed with brine, dried over anhydrous magnesium sulfate, evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 2:1 to 1:1) to give methyl 5-[[4-[2-[(tert-butoxycarbonyl)amino]ethyl]phenyl]sulfonyl]-2-hydroxybenzoate (3.04 g).

(+)ESI-MS (m/z): 458 (M+Na)<sup>+</sup>

#### Preparation 134

Under nitrogen at room temperature, to a solution of methyl 5-[[4-[2-[(tert-butoxycarbonyl)amino]ethyl]phenyl]sulfonyl]-2-hydroxybenzoate (3.03 g) in N,N-dimethylformamide (30 ml) was added potassium carbonate (1.06 g) and ethyl bromoacetate (1.28 g), and the mixture was stirred at 60°C for 1 hour. The resulting mixture was poured into water and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed successively with water and brine, dried over anhydrous magnesium sulfate, evaporated and dried in vacuo to give methyl 5-[[4-[2-[(tert-butoxycarbonyl)amino]ethyl]phenyl]sulfonyl]-2-(2-ethoxy-2-oxoethoxy)benzoate (3.71 g).

(+)ESI-MS (m/z): 544 (M+Na)<sup>+</sup>

#### Preparation 135

Under nitrogen at room temperature, to methyl 5-[[4-[2-[(tert-butoxycarbonyl)amino]ethyl]phenyl]sulfonyl]-2-(2-ethoxy-2-oxoethoxy)benzoate (1.53 g) was added 4N hydrogen chloride in ethyl acetate (15 ml), and the mixture was stirred at the same temperature for 12 hours. The resulting mixture was evaporated under reduced pressure. The residue was dissolved into a mixture of saturated aqueous sodium bicarbonate and chloroform/methanol (4:1). After separation, the organic layer was dried over anhydrous magnesium sulfate,

evaporated and dried in vacuo to give methyl 5-[[4-(2-aminoethyl)phenyl]sulfonyl]-2-(2-ethoxy-2-oxoethoxy)benzoate (1.04 g).

(+)ESI-MS (m/z): 422 (M+H)<sup>+</sup>

5

#### Preparation 136

The following compound was obtained according to a similar manner to that of Preparation 135.

10 Methyl 5-[[4-(2-aminoethyl)phenyl]sulfonyl]-2-(2-hydroxyethoxy)benzoate.

(+)ESI-MS (m/z): 380 (M+H)<sup>+</sup>

#### Preparation 137

15 Under nitrogen at 5°C, to a solution of methyl 5-[[4-[2-[(tert-butoxycarbonyl)amino]ethyl]phenyl]sulfonyl]-2-(2-ethoxy-2-oxoethoxy)benzoate (2.18 g) in tetrahydrofuran (22 ml) was added sodium borohydride (174 mg) followed by methanol (10 ml) dropwise, and the mixture was stirred at  
20 room temperature for 12 hours. The resulting mixture was poured into saturated aqueous sodium bicarbonate and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed successively with water and brine, dried over anhydrous magnesium sulfate and evaporated under  
25 reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 1:1 to 1:5) to give methyl 5-[[4-[2-[(tert-butoxycabonyl)amino]-ethyl]phenyl]sulfonyl]-2-(2-hydroxyethoxy)benzoate (852 mg).

(+)ESI-MS (m/z): 502 (M+Na)<sup>+</sup>

30

#### Preparation 138

Under nitrogen at room temperature, to a suspension of methyl 5-[[4-(2-aminoethyl)phenyl]sulfonyl]-2-hydroxybenzoate hydrochloride (10 g) in methanol (300 ml)  
35 was added potassium carbonate (3.82 g), and the mixture was

stirred at the same temperature for 1.5 hours. The resulting mixture was concentrated to ca. 150 ml and diluted with chloroform (150 ml). The insoluble materials were removed by filtration, and the filtrate was evaporated under reduced pressure. Under nitrogen at room temperature, to a suspension of the residue in tetrahydrofuran (300 ml) was added benzaldehyde (5.71 g), and the mixture was stirred at 50°C for 2 hours. The resulting mixture was evaporated under reduced pressure. Under nitrogen at 5°C, to a suspension of the residue in tetrahydrofuran (300 ml) was added sodium borohydride (3.05 g) followed by methanol (300 ml) dropwise, and the mixture was stirred at room temperature for 2 hours. The resulting mixture was poured into a mixture of water and chloroform/methanol (4:1). After separation, the organic layer was washed with brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. To the residue was added ethyl acetate, and the mixture was stirred for 12 hours. The precipitates were collected by filtration and dried in vacuo to give methyl 5-[[4-[2-(benzylamino)ethyl]phenyl]sulfonyl]-2-hydroxybenzoate (8.28 g).

(+)ESI-MS (m/z): 426 (M+H)<sup>+</sup>

#### Preparation 139

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

Methyl 2-(benzyloxy)-5-[[4-[2-[(tert-butoxycarbonyl)-amino]ethyl]phenyl]sulfonyl]benzoate

(+)ESI-MS (m/z): 548 (M+Na)<sup>+</sup>

#### Preparation 140

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

Methyl 5-[[4-[2-[benzyl(tert-butoxycarbonyl)amino]ethyl]phenyl]sulfonyl]-2-(benzyloxy)benzoate  
(+)ESI-MS (m/z): 638 (M+Na)<sup>+</sup>

5 Preparation 141

To a solution of methyl 5-[[4-[2-[benzyl(tert-butoxycarbonyl)amino]ethyl]phenyl]sulfonyl]-2-(benzyloxy)benzoate (559 mg) in ethanol (10 ml) was added 1N sodium hydroxide (2.72 ml) at room temperature, and the mixture was  
10 stirred at 45°C for 2 hours. The resulting mixture was poured into 1N hydrochloric acid and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, evaporated and dried in vacuo to give 5-[[4-[2-[benzyl(tert-butoxycarbonyl)amino]ethyl]phenyl]sulfonyl]-2-(benzyloxy)-  
15 benzoic acid (551 mg).

(-)ESI-MS (m/z): 600 (M-H)<sup>-</sup>

Preparation 142

20 Under nitrogen at 5°C, to a solution of 5-[[4-[2-[benzyl(tert-butoxycarbonyl)amino]ethyl]phenyl]sulfonyl]-2-(benzyloxy)benzoic acid (537 mg) in N,N-dimethylformamide (6 ml) were added methylamine hydrochloride (72 mg), 1-hydroxybenzotriazole (145 mg) and 1-(3-dimethylaminopropyl)-  
25 3-ethylcarbodiimide (166 mg), and the mixture was stirred at room temperature for 3 days. The resulting mixture was poured into water and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed successively with water (two times) and brine, dried over anhydrous  
30 magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 2:1 to 1:2) to give tert-butyl benzyl[2-[4-[[4-(benzyloxy)-3-[(methylamino)carbonyl]-phenyl]sulfonyl]phenyl]ethyl]carbamate (497 mg).

35 (+)ESI-MS (m/z): 637 (M+Na)<sup>+</sup>

Preparation 143

A mixture of tert-butyl benzyl [2-[4-[4-(benzyloxy)-3-  
[(methylamino)carbonyl]phenyl]sulfonyl]phenyl]ethyl]-  
5 carbamate (492 mg) and 10% palladium on activated carbon  
(50% wet, 25 mg) in methanol (5 ml) was stirred at room  
temperature in the presence of hydrogen at an atmospheric  
pressure for 2 hours. After filtration, the filtrate was  
evaporated and dried in vacuo to give tert-butyl benzyl [2-  
10 [4-[4-hydroxy-3-[(methylamino)carbonyl]phenyl]sulfonyl]-  
phenyl]ethyl]carbamate (398 mg).

(+)ESI-MS (m/z): 547 (M+Na)<sup>+</sup>

Preparation 144

15 The following compound was obtained according to a  
similar manner to that of Preparation 135.

5-[4-[2-(Benzylamino)ethyl]phenyl]sulfonyl]-2-hydroxy-  
N-methylbenzamide

20 (+)ESI-MS (m/z): 425 (M+H)<sup>+</sup>

Example 54

The following compound was obtained according to a  
similar manner to that of Preparation 6.

25

Ethyl 5-[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-  
chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-2-  
nitrobenzoate

(+)ESI-MS (m/z): 655 (M+Na)<sup>+</sup>

30

Example 55

Under nitrogen at room temperature, to a solution of  
ethyl 5-[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-  
chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-2-  
35 nitrobenzoate (1.85 g) in a mixture of ethanol (15 ml) and



water (5 ml) were added reduced iron (490 mg) and ammonium chloride (78 mg), and the mixture was refluxed for 1 hour. The insoluble materials were filtered with celite and the filtrate was concentrated under reduced pressure. The residue was dissolved into a mixture of saturated aqueous sodium bicarbonate and ethyl acetate. After separation, the organic layer was washed successively with water and brine, dried over anhydrous magnesium sulfate, evaporated under reduced pressure and dried in vacuo to give ethyl 2-amino-5-  
10 [[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]benzoate (1.6 g).  
(+)ESI-MS (m/z): 625, 627 (M+Na)<sup>+</sup>

#### Example 56

15 To a solution of ethyl 2-amino-5-[[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]-amino]ethyl]phenyl]sulfonyl]benzoate (200 mg) in ethanol (5 ml) was added 1N sodium hydroxide (0.663 ml) at room temperature, and the mixture was stirred at the same  
20 temperature for 21 hours. To the resulting mixture was added 1N hydrochloric acid (0.663 ml) and the mixture was evaporated under reduced pressure. The residue was dissolved into a mixture of water and chloroform/methanol (5:1). After separation, the organic layer was dried over anhydrous  
25 magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (chloroform/methanol = 20:1 to 10:1) to give 2-amino-5-[[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]benzoic acid (159  
30 mg).  
(-)ESI-MS (m/z): 573 (M-H)<sup>-</sup>

#### Example 57

Under nitrogen at room temperature, to a solution of 2-  
35 amino-5-[[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-

chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-benzoic acid (157 mg) in ethyl acetate (2 ml) was added 4N hydrogen chloride in ethyl acetate (2 ml), and the mixture was stirred at the same temperature for 3.5 hours. The  
5 resulting mixture was diluted with diethyl ether, and the precipitates were collected by filtration, followed by dryness to give 2-amino-5-[[4-[2-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]benzoic acid dihydrochloride (126 mg).

10 NMR (DMSO- $d_6$ ,  $\delta$ ): 2.9-3.3 (6H, m), 4.9-5.05 (1H, m), 6.88 (1H, d,  $J=8.9\text{Hz}$ ), 7.25-7.5 (6H, m), 7.69 (1H, dd,  $J=2.4, 9.0\text{Hz}$ ), 7.84 (2H, d,  $J=8.3\text{Hz}$ ), 8.21 (1H, d,  $J=2.4\text{Hz}$ )

(-)ESI-MS ( $m/z$ ): 473 ( $M-2\text{HCl}-\text{H}$ )<sup>-</sup>

15

#### Example 58

Under nitrogen at room temperature, to a solution of 5-[[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]thio]-2-nitrobenzoate (203  
20 mg) in dichloromethane (3 ml) were added 3,4-dihydro-2H-pyran (54 mg) and pyridinium p-toluenesulfonate (8.1 mg), and the mixture was stirred at the same temperature for 4 hours. The resulting mixture was poured into water and the aqueous mixture was extracted with ethyl acetate. The  
25 organic layer was washed successively with saturated aqueous sodium bicarbonate and brine, dried over anhydrous magnesium sulfate, evaporated and dried in vacuo to give ethyl 5-[[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]amino]ethyl]phenyl]-sulfonyl]-2-nitrobenzoate (266 mg).

30 (+)ESI-MS ( $m/z$ ): 739, 741 ( $M+\text{Na}$ )<sup>+</sup>

#### Example 59

Under nitrogen at room temperature, to a solution of  
35 ethyl 5-[[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-

chlorophenyl)-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]amino]-  
ethyl]phenyl]sulfonyl]-2-nitrobenzoate (261 mg) in a mixture  
of ethanol (6 ml) and water (2 ml) were added reduced iron  
(61 mg) and ammonium chloride (9.7 mg), and the mixture was  
5 refluxed for 30 minutes. The insoluble materials were  
removed by filtration with celite and the filtrate was  
concentrated under reduced pressure. The residue was  
dissolved into a mixture of saturated aqueous sodium  
bicarbonate and ethyl acetate. After separation, the  
10 organic layer was washed successively with water and 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  
2:1) to give ethyl 2-amino-5-[[4-[2-[(tert-butoxycarbonyl)-  
15 [(2R)-2-(3-chlorophenyl)-2-(tetrahydro-2H-pyran-2-yloxy)-  
ethyl]amino]ethyl]phenyl]sulfonyl]benzoate (168 mg).

(+)ESI-MS (m/z): 709, 711 (M+Na)<sup>+</sup>

#### Example 60

20 Under nitrogen at 5°C, to a suspension of sodium  
hydride (60% in oil, 13 mg) in N,N-dimethylformamide (6 ml)  
was added ethyl 2-amino-5-[[4-[2-[(tert-butoxycarbonyl)-  
[(2R)-2-(3-chlorophenyl)-2-(tetrahydro-2H-pyran-2-  
yloxy)ethyl]amino]ethyl]phenyl]sulfonyl]benzoate (200 mg),  
25 and the resulting mixture was stirred at the same  
temperature for 20 minutes. To this one was added  
iodomethane (45 mg) at 5°C and the mixture was stirred at  
the same temperature for 80 minutes. The resulting mixture  
was poured into water and the aqueous mixture was extracted  
30 with ethyl acetate. The organic layer was washed  
successively with water (two times) and 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 2:1) to give  
35 ethyl 5-[[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-

chlorophenyl)-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]amino]-ethyl]phenyl]sulfonyl]-2-(methylamino)benzoate (167 mg).

(+)ESI-MS (m/z): 723, 725 (M+Na)<sup>+</sup>

5 Example 61

The following compound was obtained according to a similar manner to that of Example 60.

Ethyl 5-[[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]amino]-ethyl]phenyl]sulfonyl]-2-(ethylamino)benzoate

(+)ESI-MS (m/z): 737, 739 (M+Na)<sup>+</sup>

Example 62

15 Under nitrogen at room temperature, to a solution of ethyl 5-[[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]amino]-ethyl]phenyl]sulfonyl]-2-(methylamino)benzoate (164 mg) in methanol (3 ml) was added a catalytic amount of p-  
20 toluenesulfonic acid monohydrate, and the mixture was stirred at the same temperature for 8.5 hours. The resulting mixture was poured into saturated aqueous sodium bicarbonate and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed successively with  
25 saturated aqueous sodium bicarbonate and brine, dried over anhydrous magnesium sulfate, evaporated under reduced pressure and dried in vacuo to give ethyl 5-[[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]-amino]ethyl]phenyl]sulfonyl]-2-(methylamino)benzoate (140  
30 mg).

(+)ESI-MS (m/z): 639, 641 (M+Na)<sup>+</sup>

Example 63

The following compounds were obtained according to a similar manner to that of Example 62.

- (1) Ethyl 5-[[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]-sulfonyl]-2-(ethylamino)benzoate  
5 (+)ESI-MS (m/z): 653, 655 (M+Na)<sup>+</sup>
- (2) Ethyl 5-[[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]-sulfonyl]-2-(propylamino)benzoate  
10 (+)ESI-MS (m/z): 667, 669 (M+Na)<sup>+</sup>
- (3) Ethyl 5-[[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]-sulfonyl]-2-[(2-methoxyethyl)amino]benzoate  
15 (+)ESI-MS (m/z): 683, 685 (M+Na)<sup>+</sup>
- (4) Ethyl 5-[[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]-sulfonyl]-2-[(2-hydroxyethyl)amino]benzoate  
20 (+)ESI-MS (m/z): 669, 671 (M+Na)<sup>+</sup>
- (5) Methyl 5-[[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]-sulfonyl]-2-[(methoxycarbonyl)amino]benzoate  
25 (+)ESI-MS (m/z): 669, 671 (M+Na)<sup>+</sup>
- (6) Ethyl 5-[[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]-sulfonyl]-2-[(methylsulfonyl)amino]benzoate  
30 (-)ESI-MS (m/z): 679, 681 (M-H)<sup>-</sup>

#### Example 64

To a solution of ethyl 5-[[4-[2-[(tert-butoxycarbonyl)-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]-sulfonyl]-2-(methylamino)benzoate (137 mg) in ethanol (3 ml)

35

was added 1N sodium hydroxide (0.444 ml) at room temperature, and the mixture was stirred at 45°C for 4 hours. To the resulting mixture was added 1N hydrochloric acid (0.444 ml) and the mixture was evaporated under reduced pressure. The residue was dissolved into a mixture of water and chloroform/methanol (5:1). After separation, the organic layer was dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (chloroform/methanol = 20:1 to 10:1) to give 5-[[4-[2-[(tert-butoxycarbonyl)-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]-sulfonyl]-2-(methylamino)benzoic acid (129 mg).

(-)ESI-MS (m/z): 587, 589 (M-H)<sup>-</sup>

#### 15 Example 65

The following compounds were obtained according to a similar manner to that of Example 64.

- (1) 5-[[4-[2-[(tert-Butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]-sulfonyl]-2-(ethylamino)benzoic acid
- (-)ESI-MS (m/z): 601, 603 (M-H)<sup>-</sup>
- (2) 5-[[4-[2-[(tert-Butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]-sulfonyl]-2-(propylamino)benzoic acid
- (-)ESI-MS (m/z): 615, 617 (M-H)<sup>-</sup>
- (3) (2S)-1-[4-[[4-[2-[(tert-Butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]-sulfonyl]benzyl]-2-pyrrolidinecarboxylic acid
- (-)ESI-MS (m/z): 641, 643 (M-H)<sup>-</sup>

#### Example 66

35 Under nitrogen at room temperature, to a solution of 5-

[[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-2-(methylamino)-benzoic acid (125 mg) in ethyl acetate (1 ml) was added 4N hydrogen chloride in ethyl acetate (2 ml), and the mixture  
5 was stirred at the same temperature for 2.5 hours. The resulting mixture was decanted and the residue was washed with ethyl acetate, followed by dryness to give 5-[[4-[2-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]-phenyl]sulfonyl]-2-(methylamino)benzoic acid hydrochloride  
10 (94 mg).

NMR (DMSO- $d_6$ ,  $\delta$ ): 2.88 (3H, s), 2.95-3.45 (6H, m), 4.9-5.0 (1H, m), 6.84 (1H, d,  $J=9.2\text{Hz}$ ), 7.3-7.55 (6H, m), 7.75-7.9 (3H, m), 8.26 (1H, d,  $J=2.4\text{Hz}$ )  
(-)ESI-MS (m/z): 487 (M-HCl-H)<sup>-</sup>

15

#### Example 67

Under nitrogen at room temperature, to a solution of 5-[[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-2-(ethylamino)-benzoic acid (82 mg) in ethyl acetate (1 ml) was added 4N hydrogen chloride in ethyl acetate (2 ml), and the mixture  
20 was stirred at the same temperature for 2 hours. The resulting mixture was evaporated under reduced pressure and dried in vacuo to give 5-[[4-[2-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-2-(ethylamino)-benzoic acid hydrochloride (67 mg).  
25

NMR (DMSO- $d_6$ ,  $\delta$ ): 1.18 (3H, t,  $J=7.1\text{Hz}$ ), 2.95-3.45 (8H, m), 4.9-5.0 (1H, m), 6.88 (1H, d,  $J=9.2\text{Hz}$ ), 7.3-7.5 (6H, m), 7.75-7.9 (3H, m), 8.27 (1H, d,  $J=2.4\text{Hz}$ )  
30

(-)ESI-MS (m/z): 501, 503 (M-HCl-H)<sup>-</sup>

#### Example 68

The following compounds were obtained according to a  
35 similar manner to that of Example 67.

- (1) 5-[[4-[2-[[[(2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]-amino]ethyl]phenyl]sulfonyl]-2-(propylamino)benzoic acid hydrochloride  
5 NMR (DMSO- $d_6$ ,  $\delta$ ): 0.92 (3H, t,  $J=7.2\text{Hz}$ ), 1.5-1.7 (2H, m), 2.95-3.45 (8H, m), 4.9-5.0 (1H, m), 6.89 (1H, d,  $J=9.2\text{Hz}$ ), 7.3-7.5 (6H, m), 7.75-7.9 (3H, m), 8.27 (1H, d,  $J=2.4\text{Hz}$ )  
(-)ESI-MS (m/z): 515, 517 (M-HCl-H)<sup>-</sup>  
10
- (2) 5-[[4-[2-[[[(2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]-amino]ethyl]phenyl]sulfonyl]-2-[(2-methoxyethyl)amino]-benzoic acid hydrochloride  
NMR (DMSO- $d_6$ ,  $\delta$ ): 2.95-3.7 (13H, m), 4.9-5.0 (1H, m),  
15 6.92 (1H, d,  $J=9.2\text{Hz}$ ), 7.3-7.5 (6H, m), 7.75-7.9 (3H, m), 8.27 (1H, d,  $J=2.4\text{Hz}$ )  
(-)ESI-MS (m/z): 531, 533 (M-HCl-H)<sup>-</sup>
- (3) 5-[[4-[2-[[[(2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]-amino]ethyl]phenyl]sulfonyl]-2-[(2-hydroxyethyl)amino]-benzoic acid hydrochloride  
20 NMR (DMSO- $d_6$ ,  $\delta$ ): 2.95-3.65 (10H, m), 4.9-5.0 (1H, m), 6.92 (1H, d,  $J=9.2\text{Hz}$ ), 7.3-7.55 (6H, m), 7.75-7.9 (3H, m), 8.27 (1H, d,  $J=2.4\text{Hz}$ )  
25 (-)ESI-MS (m/z): 517, 519 (M-HCl-H)<sup>-</sup>
- (4) 5-[[4-[2-[[[(2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]-amino]ethyl]phenyl]sulfonyl]-2-(propionylamino)benzoic acid hydrochloride  
30 NMR (DMSO- $d_6$ ,  $\delta$ ): 1.10 (3H, t,  $J=7.5\text{Hz}$ ), 2.95-3.6 (6H, m), 4.9-5.0 (1H, m), 7.3-7.55 (6H, m), 7.93 (2H, d,  $J=8.3\text{Hz}$ ), 8.12 (1H, dd,  $J=2.4, 8.9\text{Hz}$ ), 8.44 (1H, d,  $J=2.3\text{Hz}$ ), 8.69 (1H, d,  $J=8.9\text{Hz}$ )  
35 (-)ESI-MS (m/z): 529, 531 (M-HCl-H)<sup>-</sup>



- (5) 5-[[4-[2-[[[(2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]-amino]ethyl]phenyl]sulfonyl]-2-(glycoloylamino)benzoic acid hydrochloride  
NMR (DMSO-d<sub>6</sub>, δ): 2.9-3.6 (6H, m), 4.0-4.05 (2H, m),  
5 4.9-5.0 (1H, m), 7.3-7.6 (6H, m), 7.94 (2H, d, J=8.3Hz), 8.16 (1H, dd, J=2.4, 8.9Hz), 8.47 (1H, d, J=2.4Hz), 8.89 (1H, d, J=9.0Hz)  
(-)ESI-MS (m/z): 531 (M-HCl-H)<sup>-</sup>
- 10 (6) 5-[[4-[2-[[[(2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]-amino]ethyl]phenyl]sulfonyl]-2-[(methoxycarbonyl)-amino]benzoic acid hydrochloride  
NMR (DMSO-d<sub>6</sub>, δ): 2.9-3.6 (6H, m), 4.9-5.0 (1H, m),  
7.3-7.6 (6H, m), 7.92 (2H, d, J=8.3Hz), 8.12 (1H,  
15 dd, J=2.3, 9.0Hz), 8.4-8.5 (2H, m)  
(-)ESI-MS (m/z): 531, 533 (M-HCl-H)<sup>-</sup>
- (7) 5-[[4-[2-[[[(2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]-amino]ethyl]phenyl]sulfonyl]-2-[(methylsulfonyl)-amino]benzoic acid hydrochloride  
NMR (DMSO-d<sub>6</sub>, δ): 2.3-3.6 (9H, m), 4.9-5.0 (1H, m),  
20 7.3-7.6 (6H, m), 7.69 (1H, d, J=8.8Hz), 7.92 (2H, d, J=8.3Hz), 8.07 (1H, dd, J=2.4, 8.9Hz), 8.43 (1H, d, J=2.3Hz)  
25 (-)ESI-MS (m/z): 551, 553 (M-HCl-H)<sup>-</sup>
- (8) (2S)-1-[4-[[4-[2-[[[(2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]benzyl]-2-pyrrolidinecarboxylic acid dihydrochloride  
NMR (DMSO-d<sub>6</sub>, δ): 1.7-2.1 (4H, m), 2.9-3.6 (8H, m),  
30 4.15-4.6 (3H, m), 4.9-5.0 (1H, m), 7.25-7.6 (6H, m), 7.76 (2H, d, J=8.3Hz), 7.95 (2H, d, J=8.3Hz), 8.03 (2H, d, J=8.3Hz)  
(-)ESI-MS (m/z): 541, 543 (M-2HCl-H)<sup>-</sup>

- (9) 2-Chloro-6-[[4-[2-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]benzoic acid hydrochloride  
NMR (DMSO- $d_6$ ,  $\delta$ ): 1.10 (3H, d,  $J=6.3\text{Hz}$ ), 2.7-2.9 (2H, m), 3.0-3.6 (3H, m), 5.0-5.1 (1H, m), 7.3-7.6 (6H, m), 7.67 (1H, t,  $J=8.0\text{Hz}$ ), 7.88 (1H, d,  $J=7.4\text{Hz}$ ), 7.95 (2H, d,  $J=6.7\text{Hz}$ ), 8.05-8.15 (1H, m)  
(-)ESI-MS ( $m/z$ ): 506, 508 ( $M\text{-HCl-H}$ )<sup>-</sup>
- 10 (10) (2E)-3-[2-[[4-[(2R)-2-[(2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-5-methylphenyl]acrylic acid hydrochloride  
NMR (DMSO- $d_6$ ,  $\delta$ ): 1.06 (3H, d,  $J=6.3\text{Hz}$ ), 2.40 (3H, s), 2.65-2.9 (1H, m), 3.0-3.6 (4H, m), 4.9-5.05 (1H, m), 6.34 (1H, d,  $J=15.7\text{Hz}$ ), 7.3-7.6 (7H, m), 7.7-7.85 (3H, m), 8.07 (1H, d,  $J=8.1\text{Hz}$ ), 8.25 (1H, d,  $J=15.8\text{Hz}$ )  
(-)ESI-MS ( $m/z$ ): 512 ( $M\text{-HCl-H}$ )<sup>-</sup>
- 20 (11) (2Z)-3-[2-[[4-[(2R)-2-[(2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-5-methylphenyl]acrylic acid hydrochloride  
NMR (DMSO- $d_6$ ,  $\delta$ ): 1.05 (3H, d,  $J=6.3\text{Hz}$ ), 2.34 (3H, s), 2.6-2.9 (1H, m), 3.0-3.55 (4H, m), 4.9-5.0 (1H, m), 5.96 (1H, d,  $J=12.0\text{Hz}$ ), 7.15 (1H, s), 7.25-7.5 (8H, m), 7.76 (2H, d,  $J=8.2\text{Hz}$ ), 8.00 (1H, d,  $J=8.1\text{Hz}$ )  
(-)ESI-MS ( $m/z$ ): 512 ( $M\text{-HCl-H}$ )<sup>-</sup>
- 25

#### Example 69

- 30 Under nitrogen at 5°C, to a suspension of ethyl 2-amino-5-[[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]amino]-ethyl]phenyl]sulfonyl]benzoate (134 mg) in N,N-dimethylformamide (3 ml) was added sodium hydride (60% in  
35 oil, 8.6 mg), and the resulting mixture was stirred at the

same temperature for 15 minutes. To this one was added 1-bromopropane (120 mg) and potassium iodide (162 mg) at 5°C and the mixture was stirred at room temperature for 3 days. The resulting mixture was poured into water and the aqueous  
5 mixture was extracted with ethyl acetate. The organic layer was washed successively with water (two times) and 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  
10 2:1) to give ethyl 5-[[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]amino]ethyl]phenyl]sulfonyl]-2-(propylamino)benzoate (72 mg).  
(+)ESI-MS (m/z): 751, 753 (M+Na)<sup>+</sup>

15 Example 70

Under nitrogen at 5°C, to a solution of 2-amino-5-[[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]amino]ethyl]phenyl]sulfonyl]benzoate (200 mg) in N,N-dimethylformamide (4 ml)  
20 was added sodium hydride (60% in oil, 13 mg), and the resulting mixture was stirred at the same temperature for 20 minutes. To this one was added 2-methoxyethyl 4-nitrobenzenesulfonate (228 mg) at 5°C and the mixture was stirred at the same temperature for 6 hours. The resulting  
25 mixture was poured into water and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed successively with water (two times) and brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography  
30 on silica gel (hexane/ethyl acetate = 3:2) to give ethyl 5-[[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]amino]ethyl]phenyl]sulfonyl]-2-[(2-methoxyethyl)amino]benzoate (124 mg).  
(+)ESI-MS (m/z): 767, 769 (M+Na)<sup>+</sup>

Example 71

To a solution of ethyl 5-[[4-[2-[(tert-butoxycarbonyl)-  
[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]-  
sulfonyl]-2-[(2-methoxyethyl)amino]benzoate (42 mg) in  
5 ethanol (2 ml) was added 1N sodium hydroxide (0.19 ml) at  
room temperature, and the mixture was stirred at 45°C for 2  
hours. The resulting mixture was poured into 1N  
hydrochloric acid and the aqueous mixture was extracted with  
chloroform/methanol (4:1). After separation, the organic  
10 layer was dried over anhydrous magnesium sulfate and  
evaporated under reduced pressure. The residue was purified  
by column chromatography on silica gel (chloroform/methanol  
= 20:1 to 10:1) to give 5-[[4-[2-[(tert-butoxycarbonyl)-  
[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]-  
15 sulfonyl]-2-[(2-methoxyethyl)amino]benzoic acid (33 mg).

(-)ESI-MS (m/z): 631, 633 (M-H)<sup>-</sup>

Example 72

The following compounds were obtained according to a  
20 similar manner to that of Example 71.

(1) 5-[[4-[2-[(tert-Butoxycarbonyl)[(2R)-2-(3-  
chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]-  
sulfonyl]-2-[(2-hydroxyethyl)amino]benzoic acid  
25 (-)ESI-MS (m/z): 617, 619 (M-H)<sup>-</sup>

(2) 5-[[4-[2-[(tert-Butoxycarbonyl)[(2R)-2-(3-  
chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]-  
sulfonyl]-2-[(methoxycarbonyl)amino]benzoic acid  
30 (-)ESI-MS (m/z): 631, 633 (M-H)<sup>-</sup>

(3) 5-[[4-[2-[(tert-Butoxycarbonyl)[(2R)-2-(3-  
chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]-  
sulfonyl]-2-[(methylsulfonyl)amino]benzoic acid  
35 (-)ESI-MS (m/z): 651, 653 (M-H)<sup>-</sup>

Example 73

Under nitrogen at 5°C, to a solution of ethyl 2-amino-5-[[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]amino]ethyl]phenyl]-sulfonyl]benzoate (200 mg) in N,N-dimethylformamide (4 ml) was added sodium hydride (60% in oil, 13 mg), and the resulting mixture was stirred at the same temperature for 20 minutes. To this one was added 2-(2-iodoethoxy)tetrahydro-2H-pyran (224 mg) at 5°C and the mixture was stirred at the same temperature for 5 hours. The resulting mixture was poured into water and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed successively with water (two times) and brine, 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 3:2) to give ethyl 5-[[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]amino]ethyl]phenyl]-sulfonyl]-2-[[2-(tetrahydro-2H-pyran-2-yloxy)ethyl]amino]-benzoate (177 mg).

(+)ESI-MS (m/z): 837, 839 (M+Na)<sup>+</sup>

Example 74

To a solution of ethyl 2-amino-5-[[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]amino]ethyl]phenyl]sulfonyl]benzoate (200 mg) in ethanol (8 ml) was added 1N sodium hydroxide (0.58 ml) at room temperature, and the mixture was stirred at 45°C for 4 hours. To the resulting mixture was added 1N hydrochloric acid (0.58 ml) and the mixture was evaporated and dried in vacuo. To a solution of the residue in dichloromethane (3 ml) were added pyridine (230 mg) and acetyl chloride (48 mg) at 5°C under nitrogen, and the mixture was stirred at the same temperature for 3.5 hours.

The resulting mixture was poured into a mixture of 1N hydrochloric acid and ethyl acetate, and the mixture was stirred for 15 minutes. After separation, the organic layer was dried over anhydrous magnesium sulfate, evaporated under reduced pressure and dried in vacuo to give 2-(acetylamino)-5-[[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]benzoic acid (199 mg).

(-)ESI-MS (m/z): 615, 617 (M-H)<sup>-</sup>

10

#### Example 75

Under nitrogen at room temperature, to a solution of 2-(acetylamino)-5-[[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-benzoic acid (197 mg) in ethyl acetate (1 ml) was added 4N hydrogen chloride in ethyl acetate (3 ml), and the mixture was stirred at the same temperature for 3 hours. The precipitates were collected by filtration, followed by dryness to give 2-(acetylamino)-5-[[4-[2-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-benzoic acid hydrochloride (139 mg).

NMR (DMSO-d<sub>6</sub>, δ): 2.17 (3H, s), 2.9-3.6 (6H, m), 4.9-5.0 (1H, m), 7.3-7.6 (6H, m), 7.93 (2H, d, J=8.2Hz), 8.14 (1H, dd, J=2.4, 8.9Hz), 8.43 (1H, d, J=2.3Hz), 8.65 (1H, d, J=8.9Hz)

25

(-)ESI-MS (m/z): 515, 517 (M-HCl-H)<sup>-</sup>

#### Example 76

The following compounds were obtained according to a similar manner to that of Example 75.

30

(1) 2-(Benzoylamino)-5-[[4-[2-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]benzoic acid hydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 2.9-3.6 (6H, m), 4.9-5.0 (1H, m),

35

7.3-7.7 (9H, m), 7.9-8.0 (4H, m), 8.21 (1H, dd, J=2.4, 8.9Hz), 8.51 (1H, d, J=2.4Hz), 8.90 (1H, d, J=8.9Hz)

(-)ESI-MS (m/z): 577, 579 (M-HCl-H)<sup>-</sup>

5

(2) 2-[[4-[(2R)-2-[[[(2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-5-(methylthio)benzoic acid hydrochloride

10 NMR (DMSO-d<sub>6</sub>, δ): 1.05-1.15 (3H, m), 2.55 (3H, s), 2.7-3.6 (5H, m), 4.95-5.1 (1H, m), 7.3-7.6 (8H, m), 7.92 (2H, d, J=8.3Hz), 8.00 (1H, d, J=8.5Hz)

(-)ESI-MS (m/z): 518, 520 (M-HCl-H)<sup>-</sup>

15 (3) 2-[[4-[(2R)-2-[[[(2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-5-(trifluoromethyl)benzoic acid hydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 1.05-1.15 (3H, m), 2.7-2.9 (1H, m), 3.0-3.65 (4H, m), 4.95-5.1 (1H, m), 7.35-7.6 (6H, m), 7.9-8.2 (4H, m), 8.39 (1H, d, J=8.3Hz)

20 (-)ESI-MS (m/z): 540, 542 (M-HCl-H)<sup>-</sup>

#### Example 77

To a solution of ethyl 2-amino-5-[[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]amino]ethyl]phenyl]sulfonyl]benzoate  
25 (800 mg) in ethanol (10 ml) was added 1N sodium hydroxide (2.32 ml) at room temperature, and the mixture was stirred at 45°C for 2.5 hours. To the resulting mixture was added 1N hydrochloric acid (2.32 ml) and the mixture was evaporated  
30 under reduced pressure. To the residue was added a mixture of chloroform and methanol (4:1), and the mixture was stirred for 30 minutes. The insoluble materials were removed by filtration, and the filtrate was evaporated and dried in vacuo to give 2-amino-5-[[4-[2-[(tert-  
35 butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-(tetrahydro-2H-

pyran-2-yloxy)ethyl]amino]ethyl]phenyl]sulfonyl]benzoic acid  
(822 mg).

(-)ESI-MS (m/z): 657, 659 (M-H)<sup>-</sup>

5 Example 78

Under nitrogen at 5°C, to a solution of 2-amino-5-[[4-  
[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-  
(tetrahydro-2H-pyran-2-yloxy)ethyl]amino]ethyl]phenyl]-  
sulfonyl]benzoic acid (150 mg) in dichloromethane (3 ml)  
10 were added pyridine (180 mg) and propionyl chloride (51 mg),  
and the mixture was stirred at the same temperature for 4.5  
hours. The resulting mixture was poured into a mixture of  
1N hydrochloric acid and ethyl acetate, and the mixture was  
stirred for 15 minutes. After separation, the organic layer  
15 was dried over anhydrous magnesium sulfate and evaporated  
under reduced pressure. To a solution of the residue in a  
mixture of methanol (3 ml) and water (0.5 ml) was added a  
catalytic amount of p-toluenesulfonic acid monohydrate at  
room temperature, and the mixture was stirred at the same  
20 temperature for 43 hours. The resulting mixture was poured  
into 1N hydrochloric acid and the aqueous mixture was  
extracted with a mixture of chloroform and methanol (4:1).  
The organic layer was dried over anhydrous magnesium sulfate  
and evaporated under reduced pressure. The residue was  
25 purified by column chromatography on silica gel  
(chloroform/methanol = 10:1 to 6:1) to give 5-[[4-[2-[(tert-  
butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]-  
amino]ethyl]phenyl]sulfonyl]-2-(propionylamino)benzoic acid  
(51 mg).

30 (-)ESI-MS (m/z): 629, 631 (M-H)<sup>-</sup>

Example 79

Under nitrogen at 5°C, to a solution of 2-amino-5-[[4-  
[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-  
35 (tetrahydro-2H-pyran-2-yloxy)ethyl]amino]ethyl]phenyl]-



sulfonyl]benzoic acid (150 mg) in dichloromethane (3 ml) were added pyridine (180 mg) and benzoyl chloride (77 mg), and the mixture was stirred at room temperature for 4 days. The resulting mixture was poured into 1N hydrochloric acid and the aqueous mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and evaporated under reduced pressure. To a solution of the residue in tetrahydrofuran (4 ml) was added 1N sodium hydroxide at room temperature, and the mixture was stirred at the same temperature for 2 hours. The resulting mixture was poured into 1N hydrochloric acid and the aqueous mixture was extracted with a mixture of chloroform and methanol (4:1). The organic layer was dried over anhydrous magnesium sulfate and evaporated under reduced pressure. To a solution of the residue in a mixture of methanol (4 ml) and water (0.5 ml) was added a catalytic amount of p-toluenesulfonic acid monohydrate at room temperature, and the mixture was stirred at the same temperature for 36 hours. The resulting mixture was poured into 1N hydrochloric acid and the aqueous mixture was extracted with a mixture of chloroform and methanol (4:1). The organic layer was dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (chloroform/methanol = 10:1 to 8:1) to give 2-(benzoylamino)-5-[[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]-amino]ethyl]phenyl]sulfonyl]benzoic acid (85 mg).

(-)ESI-MS (m/z): 677, 679 (M-H)<sup>-</sup>

### 30 Example 80

Under nitrogen at 5°C, to a solution of 2-amino-5-[[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]amino]ethyl]phenyl]-sulfonyl]benzoic acid (311 mg) in dichloromethane (5 ml) were added pyridine (373 mg) and acetoxyacetyl chloride (135

mg), and the mixture was stirred at the same temperature for 100 minutes. The resulting mixture was poured into a mixture of 1N hydrochloric acid and ethyl acetate, and the mixture was stirred for 30 minutes. After separation, the organic layer was dried over anhydrous magnesium sulfate and evaporated under reduced pressure. To a solution of the residue in methanol (3 ml) was added Amberlyst 15 at room temperature, and the mixture was stirred at the same temperature for 12 hours. Amberlyst 15 was removed by filtration, and the filtrate was evaporated under reduced pressure. To a solution of the residue in tetrahydrofuran (5 ml) was added 1N sodium hydroxide (1.4 ml) at 5°C, and the mixture was stirred at the same temperature for 3 hours. The resulting mixture was poured into 1N hydrochloric acid and the aqueous mixture was extracted with a mixture of chloroform and methanol (4:1). The organic layer was dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (chloroform/methanol = 10:1 to 5:1) to give 5-[[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-2-(glycoloylamino)benzoic acid (196 mg).

(-)-ESI-MS (m/z): 631, 633 (M-H)<sup>-</sup>

#### 25 Example 81

Under nitrogen at 5°C, to a solution of ethyl 2-amino-5-[[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]amino]ethyl]phenyl]sulfonyl]benzoate (300 mg) in N,N-dimethylformamide (5 ml) was added sodium hydride (60% in oil, 18 mg), and the resulting mixture was stirred at the same temperature for 20 minutes. After the mixture was cooled in dry ice-acetone bath, dimethyl carbonate (79 mg) was added, and the mixture was stirred at 5°C for 1 hour. The resulting mixture was poured into water and the aqueous mixture was extracted with

ethyl acetate. The organic layer was washed successively with water (two times) and 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 2:1) to give methyl 5-  
5 [[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]amino]ethyl]phenyl]-sulfonyl]-2-[(methoxycarbonyl)amino]benzoate (106 mg).

(+)ESI-MS (m/z): 753, 755 (M+Na)<sup>+</sup>

10

#### Example 82

Under nitrogen at 5°C, to a solution of ethyl 2-amino-5-[[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]amino]ethyl]phenyl]-sulfonyl]benzoate (200 mg) in dichloromethane (4 ml) were  
15 added pyridine (230 mg) and methanesulfonyl chloride (90 mg), and the mixture was stirred at room temperature for 19.5 hours. The resulting mixture was poured into a mixture of 1N hydrochloric acid and the aqueous mixture was extracted  
20 with ethyl acetate. The organic layer was washed successively with 1N hydrochloric acid, saturated aqueous sodium bicarbonate and brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel  
25 (hexane/ethyl acetate = 2:1 to 3:2) to give 5-[[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]amino]ethyl]phenyl]sulfonyl]-2-[(methylsulfonyl)amino]benzoate (125 mg).

(-)ESI-MS (m/z): 763, 765 (M-H)<sup>-</sup>

30

#### Example 83

A solution of ethyl [5-[[4-[2-(benzylamino)ethyl]-phenyl]sulfonyl]-2-hydroxyphenyl]acetate (375 mg) and (2R)-2-(3-chlorophenyl)oxirane (141 mg) in ethanol (5 ml) was  
35 refluxed for 47.5 hours. The resulting mixture was

evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 2:1 to 4:3) to give ethyl 5-[[4-[2-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-2-hydroxyphenyl]acetate (346 mg).

(+)ESI-MS (m/z): 608, 610 (M+H)<sup>+</sup>

#### Example 84

The following compounds were obtained according to a similar manner to that of Example 83.

(1) Ethyl 5-chloro-2-[[4-[(2R)-2-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]benzoate  
(+)ESI-MS (m/z): 536, 538 (M+H)<sup>+</sup>

15

(2) Ethyl 3-chloro-4-[[4-[(2R)-2-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]benzoate  
(+)ESI-MS (m/z): 536, 538 (M+H)<sup>+</sup>

(3) Methyl 4-chloro-2-[[4-[(2R)-2-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]benzoate  
(+)ESI-MS (m/z): 522, 524 (M+H)<sup>+</sup>

(4) Ethyl 3-chloro-2-[[4-[(2R)-2-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]benzoate  
(+)ESI-MS (m/z): 535, 537 (M+H)<sup>+</sup>

(5) Methyl 2-[[4-[(2R)-2-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-5-methylbenzoate  
(+)ESI-MS (m/z): 502, 504 (M+H)<sup>+</sup>

(6) Ethyl 2-[[4-[(2R)-2-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-5-

35

172

methoxybenzoate

(+)ESI-MS (m/z): 532 (M+H)<sup>+</sup>

- 5 (7) Ethyl 2-[[4-[(2R)-2-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-5-phenoxybenzoate  
(+)ESI-MS (m/z): 594, 596 (M+H)<sup>+</sup>
- 10 (8) Ethyl 2-[[4-[(2R)-2-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-5-propylbenzoate  
(+)ESI-MS (m/z): 544, 546 (M+H)<sup>+</sup>
- 15 (9) Ethyl 2-[[4-[(2R)-2-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-5-(3-methylbutyl)benzoate  
(+)ESI-MS (m/z): 572, 574 (M+H)<sup>+</sup>
- 20 (10) Ethyl 2-[[4-[(2R)-2-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-5-cyclohexylbenzoate  
(+)ESI-MS (m/z): 584, 586 (M+H)<sup>+</sup>
- 25 (11) Ethyl 2-[[4-[(2R)-2-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-4-propylbenzoate  
(+)ESI-MS (m/z): 544, 546 (M+H)<sup>+</sup>
- 30 (12) Ethyl 4-[[4-[(2R)-2-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-3-biphenylcarboxylate  
(+)ESI-MS (m/z): 578, 580 (M+H)<sup>+</sup>
- 35 (13) Ethyl 5-[[4-[(2R)-2-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-2-hydroxy-4-

methylbenzoate

(+)ESI-MS (m/z): 532, 534 (M+H)<sup>+</sup>

(14) Ethyl 5-[[4-[(2R)-2-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-2-hydroxy-4-methoxybenzoate

(+)ESI-MS (m/z): 548, 550 (M+H)<sup>+</sup>

(15) Methyl 5-[[4-[2-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-2-(2-ethoxy-2-oxoethoxy)benzoate

(+)ESI-MS (m/z): 576 (M+H)<sup>+</sup>

(16) Methyl 5-[[4-[2-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-2-(2-hydroxyethoxy)benzoate

(+)ESI-MS (m/z): 534, 536 (M+H)<sup>+</sup>

#### Example 85

To a solution of ethyl [5-[[4-[2-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-2-hydroxyphenyl]acetate (343 mg) in ethanol (5 ml) was added 4N hydrogenchloride in ethyl acetate (0.5 ml), and the mixture was evaporated under reduced pressure. A mixture of the residue and 10% palladium on activated carbon (50% wet, 17 mg) in a mixture of ethanol (3 ml) and chlorobenzene (7 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 dissolved into a mixture of saturated aqueous sodium bicarbonate and ethyl acetate. After separation, 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 (chloroform/methanol = 20:1 to

15:1) to give ethyl [5-[[4-[2-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-2-hydroxyphenyl]-acetate (258 mg).

(+)ESI-MS (m/z): 518, 520 (M+H)<sup>+</sup>

5

#### Example 86

To a solution of ethyl [5-[[4-[2-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-2-hydroxyphenyl]acetate (255 mg) in methanol (5 ml) was added  
10 1N sodium hydroxide (1.48 ml) at room temperature, and the mixture was stirred at 45°C for 3 hours. To the resulting mixture was added 1N hydrochloric acid (2.46 ml) and the mixture was evaporated under reduced pressure. The residue was purified by reversed phase chromatography to give [5-  
15 [[4-[2-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-ethyl]phenyl]sulfonyl]-2-hydroxyphenyl]acetic acid hydrochloride (222 mg).

NMR (DMSO-d<sub>6</sub>, δ): 2.95-3.4 (6H, m), 3.54 (2H, s), 4.9-5.0 (1H, m), 6.98 (1H, d, J=8.4Hz), 7.3-7.55 (6H, m), 7.65-7.8 (2H, m), 7.86 (2H, d, J=8.2Hz)  
20

(-)ESI-MS (m/z): 488, 490 (M-HCl-H)<sup>-</sup>

#### Example 87

Under nitrogen at 5°C, to a solution of tert-butyl  
25 [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl][2-[4-[(4-formylphenyl)thio]phenyl]ethyl]carbamate (1.33 g) in dichloromethane (15 ml) was added m-chloroperbenzoic acid (1.34 g), and the mixture was stirred at room temperature for 5.5 hours. The resulting mixture was poured into water  
30 which was adjusted to pH 7.2 by sodium sulfite and sodium bicarbonate and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous magnesium sulfate, evaporated and dried in vacuo to give tert-butyl [(2R)-2-(3-chlorophenyl)-2-  
35 hydroxyethyl][2-[4-[(4-formylphenyl)sulfonyl]phenyl]ethyl]-

carbamate (1.25 g).

(+)ESI-MS (m/z): 566, 568 (M+Na)<sup>+</sup>

#### Example 88

5 Under nitrogen at 5°C, to a solution of tert-butyl [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl][2-[4-[(4-formylphenyl)sulfonyl]phenyl]ethyl]carbamate (300 mg) and L-proline methyl ester (78 mg) in 1,2-dichloroethane (6 ml) was added sodium triacetoxyborohydride (292 mg), and the  
10 mixture was stirred at room temperature for 12 hours. The resulting mixture was poured into a mixture of 1N hydrochloric acid and ethyl acetate, and the mixture was stirred for 20 minutes. After separation, the organic layer was washed successively with water, saturated aqueous sodium  
15 bicarbonate and brine, 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 methyl (2S)-1-[4-[[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]benzyl]-2-pyrrolidinecarboxylate (183 mg).

(+)ESI-MS (m/z): 679, 681 (M+Na)<sup>+</sup>

#### Example 89

25 To a solution of ethyl 5-chloro-2-[[4-[(2R)-2-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]-sulfonyl]benzoate (88 mg) in ethanol (2 ml) was added 1N sodium hydroxide (0.25 ml) at room temperature, and the mixture was stirred at 50°C for 5 hours. To the resulting  
30 mixture was added 1N hydrochloric acid (0.082 ml) and the mixture was evaporated under reduced pressure. The residue was purified by reversed phase chromatography to give sodium 5-chloro-2-[[4-[(2R)-2-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]benzoate (27 mg).

35 NMR (DMSO-d<sub>6</sub>, δ): 0.94 (3H, d, J=6.0Hz), 2.4-3.0 (5H,



m), 4.55-4.7 (1H, m), 7.2-7.5 (8H, m), 7.90 (1H, d, J=8.5Hz), 7.98 (2H, d, J=8.3Hz).

(-)ESI-MS (m/z): 506, 508 (M-Na)<sup>-</sup>

5 Example 90

The following compounds were obtained according to a similar manner to that of Example 89.

(1) Sodium 3-chloro-4-[4-[(2R)-2-[[ (2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]-sulfonyl]benzoate  
10 NMR (DMSO-d<sub>6</sub>, δ): 0.93 (3H, d, J=6.0Hz), 2.4-3.0 (5H, m), 4.55-4.7 (1H, m), 7.2-7.5 (6H, m), 7.78 (2H, d, J=8.2Hz), 7.87 (1H, d, J=1.2Hz), 7.99 (1H, dd, J=1.3, 8.0Hz), 8.19 (1H, d, J=8.1Hz)  
15 (-)ESI-MS (m/z): 506, 508 (M-Na)<sup>-</sup>

(2) Sodium 4-chloro-2-[4-[(2R)-2-[[ (2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]-sulfonyl]benzoate  
20 NMR (DMSO-d<sub>6</sub>, δ): 1.00 (3H, d, J=5.9Hz), 2.6-3.6 (5H, m), 4.9-5.1 (1H, m), 7.2-7.5 (7H, m), 7.66 (1H, dd, J=2.1, 8.2Hz), 8.00 (1H, d, J=2.0Hz), 8.04 (2H, d, J=8.3Hz)  
25 (-)ESI-MS (m/z): 506, 508 (M-Na)<sup>-</sup>

(3) Sodium 2-[4-[(2R)-2-[[ (2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-5-methylbenzoate  
30 NMR (DMSO-d<sub>6</sub>, δ): 0.94 (3H, d, J=6.0Hz), 2.30 (3H, s), 2.5-3.6 (5H, m), 4.65-4.85 (1H, m), 7.05-7.5 (8H, m), 7.79 (1H, d, J=8.1Hz), 7.97 (2H, d, J=8.2Hz)  
(-)ESI-MS (m/z): 486 (M-Na)<sup>-</sup>

35 (4) Sodium 2-[4-[(2R)-2-[[ (2R)-2-(3-chlorophenyl)-2-

hydroxyethyl] amino] propyl] phenyl] sulfonyl] -5-  
phenoxybenzoate

NMR (DMSO- $d_6$ ,  $\delta$ ): 0.96 (3H, d,  $J=5.9\text{Hz}$ ), 2.5-3.6 (5H,  
m), 4.75-4.95 (1H, m), 6.70 (1H, d,  $J=2.4\text{Hz}$ ), 6.97  
5 (1H, dd,  $J=2.6, 8.7\text{Hz}$ ), 7.05-7.5 (11H, m), 7.9-8.0  
(3H, m)

(-)ESI-MS (m/z): 564, 566 (M-Na) $^-$

(5) Sodium 5-[[4-[(2R)-2-[[[(2R)-2-(3-chlorophenyl)-2-  
10 hydroxyethyl] amino] propyl] phenyl] sulfonyl]-2-hydroxy-4-  
methylbenzoate

NMR (DMSO- $d_6$ ,  $\delta$ ): 1.01 (3H, d,  $J=6.2\text{Hz}$ ), 2.20 (3H, s),  
2.55-2.75 (1H, m), 2.8-3.5 (4H, m), 4.7-4.85 (1H,  
m), 6.50 (1H, s), 7.25-7.5 (6H, m), 7.68 (2H, d,  
15  $J=8.2\text{Hz}$ ), 8.38 (1H, s)

(-)ESI-MS (m/z): 502, 504 (M-Na) $^-$

(6) Sodium 5-[[4-[(2R)-2-[[[(2R)-2-(3-chlorophenyl)-2-  
20 hydroxyethyl] amino] propyl] phenyl] sulfonyl]-2-hydroxy-4-  
methoxybenzoate

NMR (DMSO- $d_6$ ,  $\delta$ ): 0.97 (3H, d,  $J=6.1\text{Hz}$ ), 2.5-3.4 (5H,  
m), 3.63 (3H, s), 4.6-4.8 (1H, m), 6.15 (1H, s),  
7.25-7.5 (6H, m), 7.72 (2H, d,  $J=8.2\text{Hz}$ ), 8.25 (1H,  
s)

25 (-)ESI-MS (m/z): 518, 520 (M-Na) $^-$

#### Example 91

Under nitrogen at 5°C, to a solution of tert-butyl  
[(1R)-2-[4-[(3-chloro-2-formylphenyl)thio]phenyl]-1-  
30 methylethyl][(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]-  
carbamate (173 mg) in dichloromethane (4 ml) was added m-  
chloroperbenzoic acid (160 mg), and the mixture was stirred  
at room temperature for 2.5 hours. The resulting mixture  
was poured into saturated aqueous sodium bicarbonate and the  
35 aqueous mixture was extracted with ethyl acetate. The

organic layer was washed successively with saturated aqueous sodium bicarbonate (two times) and brine, dried over anhydrous magnesium sulfate, evaporated and dried in vacuo to give tert-butyl [(1R)-2-[4-[(3-chloro-2-formylphenyl)-sulfonyl]phenyl]-1-methylethyl][(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]carbamate (204 mg).

(+)ESI-MS (m/z): 614, 616 (M+Na)<sup>+</sup>

#### Example 92

10 The following compounds were obtained according to a similar manner to that of Preparation 33.

(1) 2-[[4-[(2R)-2-[(tert-Butoxycarbonyl][(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]-sulfonyl]-6-chlorobenzoic acid

15 (-)ESI-MS (m/z): 606, 608 (M-H)<sup>-</sup>

(2) 2-[[4-[(2R)-2-[(tert-Butoxycarbonyl][(2R)-2-[[tert-butyl(dimethyl)silyl]oxy]-2-(3-chlorophenyl)ethyl]-amino]propyl]phenyl]sulfonyl]-5-fluorobenzoic acid

20 (-)ESI-MS (m/z): 704, 706 (M-H)<sup>-</sup>

(3) 2-[[4-[(2R)-2-[(tert-Butoxycarbonyl][(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]-sulfonyl]-5-(trifluoromethyl)benzoic acid

25 (-)ESI-MS (m/z): 640, 642 (M-H)<sup>-</sup>

(4) 2-[[4-[(2R)-2-[(tert-Butoxycarbonyl][(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]-sulfonyl]-6-(methoxymethoxy)benzoic acid

30 (-)ESI-MS (m/z): 632, 634 (M-H)<sup>-</sup>

#### Example 93

To a solution of ethyl 3-chloro-2-[[4-[(2R)-2-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]-

35

sulfonyl]benzoate (172 mg) in 1,4-dioxane (4 ml) was added  
6N hydrochloric acid (6 ml) at room temperature, and the  
mixture was refluxed for 42 hours. The resulting mixture  
was evaporated under reduced pressure. The residue was  
5 purified by reversed phase chromatography to give sodium 3-  
chloro-2-[[4-[(2R)-2-[[[(2R)-2-(3-chlorophenyl)-2-  
hydroxyethyl]amino]propyl]phenyl]sulfonyl]benzoate (55 mg).  
NMR (DMSO- $d_6$ ,  $\delta$ ): 0.89 (3H, d,  $J=5.9\text{Hz}$ ), 2.45-2.9 (5H,  
m), 4.5-4.6 (1H, m), 7.1-7.5 (9H, m), 8.22 (2H, d,  
10  $J=8.3\text{Hz}$ )

#### Example 94

To a solution of ethyl 2-[[4-[(2R)-2-[[[(2R)-2-(3-  
chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-  
15 5-methoxybenzoate (211 mg) in ethanol (5 ml) was added 1N  
sodium hydroxide (0.79 ml) at room temperature, and the  
mixture was refluxed for 2.5 hours. To the resulting  
mixture was added 1N hydrochloric acid (0.79 ml) and the  
mixture was evaporated under reduced pressure. The residue  
20 was purified by column chromatography on silica gel  
(chloroform/methanol = 10:1 to 5:1), followed by treatment  
of 4N hydrogen chloride in ethyl acetate to give 2-[[4-  
[(2R)-2-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-  
propyl]phenyl]sulfonyl]-5-methoxybenzoic acid hydrochloride  
25 (77 mg).

NMR (DMSO- $d_6$ ,  $\delta$ ): 1.09 (3H, d,  $J=6.3\text{Hz}$ ), 2.65-2.9 (1H,  
m), 3.0-3.6 (4H, m), 3.86 (3H, s), 4.95-5.1 (1H,  
m), 7.12 (1H, d,  $J=2.5\text{Hz}$ ), 7.23 (1H, dd,  $J=2.6$ ,  
8.9Hz), 7.5-7.55 (6H, m), 7.91 (2H, d,  $J=8.3\text{Hz}$ ),  
30 8.07 (1H, d,  $J=8.9\text{Hz}$ )  
(-)ESI-MS (m/z): 502, 504 (M-HCl-H)<sup>-</sup>

#### Example 95

The following compounds were obtained according to a  
35 similar manner to that of Example 91.

- (1) tert-Butyl [(2R)-2-[[tert-butyl(dimethyl)silyl]oxy]-2-(3-chlorophenyl)ethyl][(1R)-2-[4-[4-fluoro-2-formylphenyl)sulfonyl]phenyl]-1-methylethyl]carbamate  
5 (-)ESI-MS (m/z): 704, 706 (M+H<sub>2</sub>O-H)<sup>-</sup>
- (2) tert-Butyl [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]-[(1R)-2-[4-[[2-formyl-4-(trifluoromethyl)]phenyl]-sulfonyl]phenyl]-1-methylethyl]carbamate  
10 (+)ESI-MS (m/z): 648, 650 (M+Na)<sup>+</sup>
- (3) tert-Butyl [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]-[(1R)-2-[4-[[2-formyl-3-(methoxymethoxy)phenyl]-sulfonyl]phenyl]-1-methylethyl]carbamate  
15 (+)ESI-MS (m/z): 640, 642 (M+Na)<sup>+</sup>
- (4) tert-Butyl [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]-[(1R)-2-[4-[[2-formyl-3-methoxyphenyl)sulfonyl]phenyl]-1-methylethyl]carbamate  
20 (+)ESI-MS (m/z): 594, 596 (M+Na)<sup>+</sup>

#### Example 96

Under nitrogen at room temperature, to a solution of 2-[4-[(2R)-2-[(tert-butoxycarbonyl][(2R)-2-[[tert-butyl(dimethyl)silyl]oxy]-2-(3-chlorophenyl)ethyl]amino]-propyl]phenyl)sulfonyl]-5-fluorobenzoic acid (150 mg) in N,N-dimethylformamide (3 ml) was added sodium thiomethoxide (33 mg), and the mixture was stirred at 60°C for 1.5 hours. The mixture was cooled to room temperature, and n-tetrabutylammonium fluoride (1M in tetrahydrofuran, 0.64 ml) was added. The mixture was stirred at room temperature for 1.5 hours. The resulting mixture was poured into 1N hydrochloric acid and the aqueous mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and evaporated under reduced pressure.  
35

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The residue was purified by column chromatography on silica gel (chloroform/methanol = 10:1 to 8:1) to give 2-[[4-[(2R)-2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-5-(methylthio)benzoic acid (149 mg).

(-)ESI-MS (m/z): 618, 620 (M-H)<sup>-</sup>

#### Example 97

Under nitrogen at room temperature, to a solution of 2-[[4-[(2R)-2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-6-(methoxymethoxy)benzoic acid (208 mg) in 1,4-dioxane (2 ml) was added 6N hydrochloric acid (2 ml), and the mixture was stirred at the same temperature for 12 hours. The resulting mixture was evaporated and dried in vacuo to give 2-[[4-[(2R)-2-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-6-hydroxybenzoic acid hydrochloride (181 mg).

NMR (DMSO-d<sub>6</sub>, δ): 1.10 (3H, d, J=6.5Hz), 2.65-2.9 (1H, m), 3.0-3.6 (4H, m), 4.95-5.1 (1H, m), 7.18 (1H, dd, J=2.7, 6.4Hz), 7.3-7.6 (8H, m), 7.92 (2H, d, J=8.3Hz)

(-)ESI-MS (m/z): 488, 490 (M-HCl-H)<sup>-</sup>

#### Example 98

Under nitrogen at room temperature, to a solution of ethyl 2-[[4-[(2R)-2-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-5-propylbenzoate (179 mg) in 1,4-dioxane (2 ml) was added a solution of di-tert-butyl dicarbonate (79 mg) in 1,4-dioxane (1 ml), and the mixture was stirred at the same temperature for 7 hours. To this one was added 1N sodium hydroxide (0.99 ml) and 1,4-dioxane (2 ml), and the mixture was stirred at 50°C for 2.5 days. The resulting mixture was poured into a mixture of 1N hydrochloric acid and chloroform/methanol (5:1), and the

mixture was stirred for 20 minutes. After separation, the organic layer was dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (chloroform/methanol  
5 = 20:1 to 10:1) to give 2-[[4-[(2R)-2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]-amino]propyl]phenyl]sulfonyl]-5-propylbenzoic acid (183 mg).  
(-)ESI-MS (m/z): 614, 616 (M-H)<sup>-</sup>

#### 10 Example 99

Under nitrogen at room temperature, to a solution of 2-[[4-[(2R)-2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-5-propylbenzoic acid (180 mg) in ethyl acetate (1 ml) was added 4N hydrogen  
15 chloride in ethyl acetate (2 ml), and the mixture was stirred at the same temperature for 9 hours. The resulting mixture was evaporated under reduced pressure. The residue was purified by reversed phase chromatography, followed by treatment with 1N hydrochloric acid to give 2-[[4-[(2R)-2-  
20 [[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-phenyl]sulfonyl]-5-propylbenzoic acid hydrochloride (93 mg).

NMR (DMSO-d<sub>6</sub>, δ): 0.87 (3H, t, J=7.3Hz), 1.10 (3H, d, J=6.3Hz), 1.45-1.7 (2H, m), 2.55-2.9 (3H, m), 3.0-3.6 (4H, m), 4.95-5.1 (1H, m), 7.35-7.6 (8H, m),  
25 7.93 (2H, d, J=8.3Hz), 8.04 (1H, d, J=8.2Hz)  
(-)ESI-MS (m/z): 514, 516 (M-HCl-H)<sup>-</sup>

#### Example 100

To a solution of ethyl 2-[[4-[(2R)-2-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-5-(3-methylbutyl)benzoate (44 mg) in ethanol (2 ml) was added 1N sodium hydroxide (0.387 ml), and the mixture was stirred at 45°C for 4.5 hours. The resulting mixture was cooled to room temperature, 1N hydrochloric acid (0.542 ml)  
35 was added, and the mixture was purified by reversed phase

chromatography, followed by treatment with 1N hydrochloric acid to give 2-[[4-[(2R)-2-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-5-(3-methylbutyl)benzoic acid hydrochloride (41 mg).

5        NMR (DMSO- $d_6$ ,  $\delta$ ): 0.90 (6H, d,  $J=6.0\text{Hz}$ ), 1.10 (3H, d,  $J=6.3\text{Hz}$ ), 1.35-1.65 (3H, m), 2.6-2.9 (3H, m), 3.0-3.6 (4H, m), 4.95-5.1 (1H, m), 7.35-7.6 (8H, m), 7.93 (2H, d,  $J=8.3\text{Hz}$ ), 8.03 (1H, d,  $J=8.1\text{Hz}$ )  
(-)ESI-MS (m/z): 542, 544 (M-HCl-H)<sup>-</sup>

10

#### Example 101

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

15    (1) 2-[[4-[(2R)-2-[[[(2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-5-cyclohexylbenzoic acid hydrochloride  
NMR (DMSO- $d_6$ ,  $\delta$ ): 1.10 (3H, d,  $J=6.3\text{Hz}$ ), 1.15-1.9 (10H, m), 2.55-2.9 (2H, m), 3.0-3.6 (4H, m), 4.95-5.1  
20        (1H, m), 7.35-7.6 (8H, m), 7.94 (2H, d,  $J=8.2\text{Hz}$ ), 8.04 (1H, d,  $J=8.3\text{Hz}$ )  
(-)ESI-MS (m/z): 554, 556 (M-HCl-H)<sup>-</sup>

25    (2) 2-[[4-[(2R)-2-[[[(2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-4-propylbenzoic acid hydrochloride  
NMR (DMSO- $d_6$ ,  $\delta$ ): 0.89 (9H, t,  $J=7.3\text{Hz}$ ), 1.10 (3H, d,  $J=6.3\text{Hz}$ ), 1.5-1.7 (2H, m), 2.6-2.9 (3H, m), 3.0-3.6 (4H, m), 4.95-5.1 (1H, m), 7.35-7.65 (8H, m),  
30        7.9-8.0 (3H, m)  
(-)ESI-MS (m/z): 514, 516 (M-HCl-H)<sup>-</sup>

35    (3) 4-[[4-[(2R)-2-[[[(2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-3-biphenylcarboxylic acid hydrochloride



NMR (DMSO- $d_6$ ,  $\delta$ ): 1.11 (3H, d,  $J=6.3\text{Hz}$ ), 2.7-2.9 (1H, m), 3.0-3.6 (4H, m), 4.95-5.1 (1H, m), 7.3-7.6 (9H, m), 7.7-7.8 (2H, m), 7.88 (1H, d,  $J=1.7\text{Hz}$ ), 7.9-8.05 (3H, m), 8.21 (1H, d,  $J=8.4\text{Hz}$ )

5 (-)ESI-MS ( $m/z$ ): 548, 550 ( $M\text{-HCl-H}$ )<sup>-</sup>

(4) 4-[[4-[(2R)-2-[(2R)-2-Hydroxy-2-phenylethyl]amino]-propyl]phenyl]sulfonyl]benzoic acid hydrochloride

10 NMR (DMSO- $d_6$ ,  $\delta$ ): 1.09 (3H, d,  $J=6.3\text{Hz}$ ), 2.75-2.9 (1H, m), 3.0-3.6 (4H, m), 4.9-5.0 (1H, m), 7.25-7.5 (5H, m), 7.53 (2H, d,  $J=8.3\text{Hz}$ ), 7.97 (2H, d,  $J=8.3\text{Hz}$ ), 8.0-8.2 (4H, m)

(-)ESI-MS ( $m/z$ ): 438 ( $M\text{-HCl-H}$ )<sup>-</sup>

15 Example 102

Under nitrogen at room temperature, to a solution of tert-butyl [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl][(1R)-2-[4-[(2-formyl-4-methylphenyl)sulfonyl]phenyl]-1-methylethyl]carbamate (490 mg) in tetrahydrofuran (10 ml) was added (carboethoxymethylene)triphenylphosphorane (328 mg), and the mixture was stirred at 50°C for 2.5 hours. The resulting mixture was poured into saturated aqueous sodium bicarbonate 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 (chloroform/ethyl acetate = 20:1 to 10:1) to give a mixture (327 mg) of ethyl (2E)-3-[2-[[4-[(2R)-2-[(tert-butoxycarbonyl][(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-5-methylphenyl]acrylate and ethyl (2Z)-3-[2-[[4-[(2R)-2-[(tert-butoxycarbonyl][(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-5-methylphenyl]acrylate.

35 (+)ESI-MS ( $m/z$ ): 664 ( $M\text{+Na}$ )<sup>+</sup>

Example 103

Under nitrogen at 5°C, to a solution of a mixture (225 mg) of ethyl (2E)-3-[2-[[4-[(2R)-2-[(tert-butoxycarbonyl)-  
5 [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-phenyl]sulfonyl]-5-methylphenyl]acrylate and ethyl (2Z)-3-[2-[[4-[(2R)-2-[(tert-butoxycarbonyl) [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-5-methylphenyl]acrylate, and copper(I) chloride (52 mg) in  
10 methanol (8 ml) was added sodium borohydride (133 mg) in small portions over a period of 30 minutes, and the mixture was stirred at the same temperature for 1 hour. The resulting mixture was poured into a mixture of 1N hydrochloric acid and ethyl acetate and the mixture was  
15 stirred for 5 minutes. After separation, the organic layer was washed successively with saturated aqueous sodium bicarbonate and brine, dried over anhydrous magnesium sulfate, evaporated and dried in vacuo to give ethyl 3-[2-[[4-[(2R)-2-[(tert-butoxycarbonyl) [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-5-methylphenyl]propanoate (215 mg).

(+)ESI-MS (m/z): 666 (M+Na)<sup>+</sup>

Example 104

25 To a solution of ethyl 3-[2-[[4-[(2R)-2-[(tert-butoxycarbonyl) [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]-amino]propyl]phenyl]sulfonyl]-5-methylphenyl]propanoate (210 mg) in ethanol (5 ml) was added 1N sodium hydroxide (0.652 ml) at room temperature, and the mixture was stirred at the  
30 same temperature for 2.5 days. The resulting mixture was poured into 1N hydrochloric acid and the aqueous mixture was extracted with a mixture of chloroform and methanol (5:1). The organic layer was dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was  
35 purified by column chromatography on silica gel

(chloroform/methanol = 30:1 to 20:1) to give 3-[2-[[4-[(2R)-2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-5-methylphenyl]-propanoic acid (167 mg).

5           (-)ESI-MS (m/z): 614, 616 (M-H)<sup>-</sup>

#### Example 105

The following compound was obtained according to a similar manner to that of Example 57.

10

3-[2-[[4-[(2R)-2-[[[(2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-5-methylphenyl]propanoic acid hydrochloride

15           NMR (DMSO-d<sub>6</sub>, δ): 1.08 (3H, d, J=6.3Hz), 2.15-2.3 (2H, m), 2.40 (3H, s), 2.65-3.6 (7H, m), 4.95-5.1 (1H, m), 7.25-7.55 (8H, m), 7.78 (2H, d, J=8.3Hz), 8.00 (1H, d, J=8.1Hz)

          (-)ESI-MS (m/z): 514, 516 (M-HCl-H)<sup>-</sup>

#### 20   Example 106

The following compounds were obtained according to a similar manner to that of Example 104.

25   (1)   (2E)-3-[2-[[4-[(2R)-2-[(tert-Butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-5-methylphenyl]acrylic acid

          (-)ESI-MS (m/z): 612, 614 (M-H)<sup>-</sup>

30   (2)   (2Z)-3-[2-[[4-[(2R)-2-[(tert-Butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-5-methylphenyl]acrylic acid

          (-)ESI-MS (m/z): 612, 614 (M-H)<sup>-</sup>

#### Example 107

35           A solution of ethyl 4-[[4-[(2R)-2-aminopropyl]phenyl]-

sulfonyl]benzoate (212 mg) and (R)-styrene oxide (73 mg) in a mixture of ethanol (10 ml) and chloroform (3 ml) was refluxed for 22 hours. The resulting mixture was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (chloroform/methanol = 50:1 to 20:1) to give ethyl 4-[[4-[(2R)-2-[[[(2R)-2-hydroxy-2-phenylethyl]amino]propyl]phenyl]sulfonyl]benzoate (85 mg).

(+)ESI-MS (m/z): 468 (M+H)<sup>+</sup>

10 Example 108

A solution of ethyl 5-[[4-[(2R)-2-aminopropyl]phenyl]-sulfonyl]-2-hydroxybenzoate (277 mg) and (R)-styrene oxide (128 mg) in a mixture of methanol (4 ml) and chloroform (4 ml) was refluxed for 47 hours. The resulting mixture was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (chloroform/methanol = 50:1 to 30:1). Under nitrogen at room temperature, to a solution of the product which was obtained above, in tetrahydrofuran (2 ml) was added di-tert-butyl dicarbonate (79 mg), and the mixture was stirred at the same temperature for 12 hours. The resulting mixture was poured into water 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 2:1) to give 5-[[4-[(2R)-2-[(tert-butoxycarbonyl)[(2R)-2-hydroxy-2-phenylethyl]amino]propyl]phenyl]sulfonyl]-2-hydroxybenzoate (68 mg).

30 (+)ESI-MS (m/z): 606 (M+Na)<sup>+</sup>

Example 109

To a solution of 5-[[4-[(2R)-2-[(tert-butoxycarbonyl)-[(2R)-2-hydroxy-2-phenylethyl]amino]propyl]phenyl]sulfonyl]-2-hydroxybenzoate (62 mg) in ethanol (2 ml) was added 1N

sodium hydroxide (0.53 ml) at room temperature, and the mixture was stirred at 45°C for 4 hours. The resulting mixture was poured into 1N hydrochloric acid and the aqueous mixture was extracted with a mixture of chloroform and methanol (4:1). After separation, the organic layer was dried over anhydrous magnesium sulfate, evaporated and dried in vacuo to give 5-[[4-[(2R)-2-[(tert-butoxycarbonyl)[(2R)-2-hydroxy-2-phenylethyl]amino]propyl]phenyl]sulfonyl]-2-hydroxybenzoic acid (65 mg).

(-)ESI-MS (m/z): 554 (M-H)<sup>-</sup>

#### Example 110

The following compound was obtained according to a similar manner to that of Example 66.

2-Hydroxy-5-[[4-[(2R)-2-[[[(2R)-2-hydroxy-2-phenylethyl]amino]propyl]phenyl]sulfonyl]benzoic acid hydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 1.10 (3H, d, J=6.3Hz), 2.65-3.6 (5H, m), 4.85-5.0 (1H, m), 6.85-7.0 (1H, m), 7.25-7.6 (7H, m), 7.75-7.95 (3H, m), 8.20 (1H, d, J=2.5Hz)  
(-)ESI-MS (m/z): 454 (M-HCl-H)<sup>-</sup>

#### Example 111

To a solution of methyl 5-[[4-[2-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-2-(2-ethoxy-2-oxoethoxy)benzoate (349 mg) in ethanol (7 ml) was added 1N sodium hydroxide (1.21 ml) at room temperature, and the mixture was stirred at 60°C for 110 minutes. The resulting mixture was evaporated under reduced pressure. The residue was triturated with ethanol, and the precipitates were collected by filtration, followed by dryness in vacuo to give disodium 5-[[4-[2-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-2-(2-oxido-2-oxoethoxy)benzoate (315 mg).

NMR (DMSO- $d_6$ ,  $\delta$ ): 2.35-2.85 (6H, m), 4.12 (2H, s),  
4.55-4.7 (1H, m), 7.0-7.1 (1H, m), 7.15-7.55 (5H,  
m), 7.6-7.85 (4H, m), 7.9-8.0 (1H, m)  
(-)ESI-MS (m/z): 532 (M-2Na)<sup>-</sup>

5

Example 112

To a solution of methyl 5-[[4-[2-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-2-(2-hydroxyethoxy)benzoate (207 mg) in ethanol (2 ml) was  
10 added 1N sodium hydroxide (0.388 ml) at room temperature, and the mixture was stirred at 60°C for 2 hours. The resulting mixture was evaporated and dried in vacuo to give sodium 5-[[4-[2-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]-amino]ethyl]phenyl]sulfonyl]-2-(2-hydroxyethoxy)benzoate  
15 (213 mg).

NMR (DMSO- $d_6$ ,  $\delta$ ): 2.55-2.8 (6H, m), 3.4-3.55 (2H, m),  
4.1-4.2 (2H, m), 4.55-4.65 (1H, m), 7.1-7.45 (7H,  
m), 7.7-7.85 (4H, m)  
(-)ESI-MS (m/z): 518, 520 (M-Na)<sup>-</sup>

20

Example 113

The following compound was obtained according to a similar manner to that of Example 107.

25 Methyl 5-[[4-[2-[benzyl[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]sulfonyl]-2-hydroxybenzoate  
(+)ESI-MS (m/z): 546 (M+H)<sup>+</sup>

Example 114

30 To a solution of methyl 5-[[4-[2-[benzyl[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]sulfonyl]-2-hydroxybenzoate (158 mg) in methanol (5 ml) was added hydrogen chloride methanol reagent 10 (0.5 ml), and the mixture was evaporated under reduced pressure. A mixture of  
35 the residue and 10% palladium on activated carbon (50% wet,

8 mg) in methanol (3 ml) was stirred at room temperature in the presence of hydrogen at an atmospheric pressure for 5 hours. After filtration, the filtrate was evaporated under reduced pressure. The residue was dissolved into a mixture of saturated aqueous sodium bicarbonate and chloroform/methanol (4:1). After separation, the organic layer was dried over anhydrous magnesium sulfate and evaporated under reduced pressure. Under nitrogen at room temperature, to a solution of the residue in a mixture of tetrahydrofuran (5 ml) and N,N-dimethylformamide (5 ml) was added di-tert-butyl dicarbonate (65 mg), and the mixture was stirred at the same temperature for 2.5 hours. The resulting mixture was poured into water and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed successively with water (two times) and brine, 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 4:3) to give methyl 5-[[4-[2-[(tert-butoxycarbonyl)[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]sulfonyl]-2-hydroxybenzoate (112 mg).

(+)ESI-MS (m/z): 578 (M+Na)<sup>+</sup>

#### Example 115

The following compound was obtained according to a similar manner to that of Example 109.

5-[[4-[2-[(tert-Butoxycarbonyl)[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]sulfonyl]-2-hydroxybenzoic acid

(-)ESI-MS (m/z): 540 (M-H)<sup>-</sup>

#### Example 116

The following compound was obtained according to a similar manner to that of Example 75.

2-Hydroxy-5-[[4-[2-[[[(2R)-2-hydroxy-2-phenylethyl]-  
amino]ethyl]phenyl]sulfonyl]benzoic acid hydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 2.9-3.35 (6H, m), 4.85-5.0 (1H, m),  
5 7.05-7.15 (1H, m), 7.25-7.45 (5H, m), 7.50 (2H, d,  
J=8.3Hz), 7.8-8.0 (3H, m), 8.25-8.3 (1H, m)  
(-)ESI-MS (m/z): 440 (M-HCl-H)<sup>-</sup>

#### Example 117

10 The following compound was obtained according to a  
similar manner to that of Example 83.

5-[[4-[2-[Benzyl[(2R)-2-(3-chlorophenyl)-2-  
hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-2-hydroxy-N-  
15 methylbenzamide

(+)ESI-MS (m/z): 579, 581 (M+H)<sup>+</sup>

#### Example 118

To a solution of 5-[[4-[2-[benzyl[(2R)-2-(3-  
20 chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-2-  
hydroxy-N-methylbenzamide (143 mg) in methanol (3 ml) was  
added hydrogen chloride methanol reagent 10 (0.5 ml), and  
the mixture was evaporated under reduced pressure. A  
mixture of the residue and 10% palladium on activated carbon  
25 (50% wet, 7 mg) in a mixture of chlorobenzene (2.1 ml) and  
methanol (0.9 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 dissolved into a mixture of  
30 saturated aqueous sodium bicarbonate and chloroform/methanol  
(5:1). After separation, the organic layer was dried over  
anhydrous magnesium sulfate and evaporated under reduced  
pressure. The residue was purified by column chromatography  
on silica gel (chloroform/methanol = 20:1 to 8:1) followed  
35 by treatment of hydrogen chloride methanol reagent 10 to



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give 5-[[4-[2-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]-amino]ethyl]phenyl]sulfonyl]-2-hydroxy-N-methylbenzamide hydrochloride (71 mg).

5 NMR (DMSO- $d_6$ ,  $\delta$ ): 2.83 (3H, d,  $J=4.5\text{Hz}$ ), 2.95-3.5 (6H, m), 4.9-5.0 (1H, m), 7.10 (1H, d,  $J=8.7\text{Hz}$ ), 7.3-7.6 (6H, m), 7.85-7.95 (3H, m), 8.49 (1H, d,  $J=2.3\text{Hz}$ )

(+)ESI-MS ( $m/z$ ): 489, 491 ( $M-\text{HCl}+\text{H}$ )<sup>+</sup>

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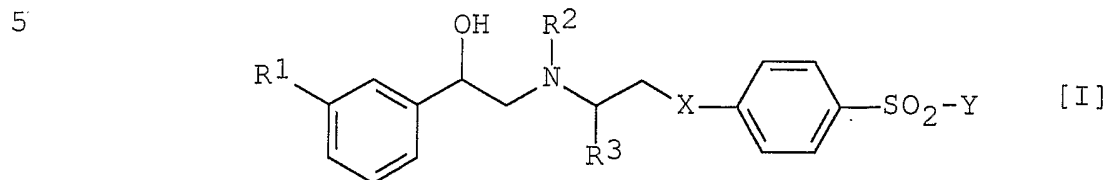
30

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## C L A I M S

1. A compound of the formula [I]:



10 wherein

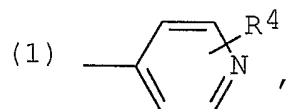
$R^1$  is hydrogen or halogen,

$R^2$  is hydrogen or an amino protective group,

$R^3$  is hydrogen or lower alkyl,

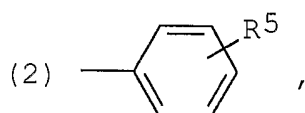
X is bond,  $-CH_2-$  or  $-O-$ , and

15 Y is

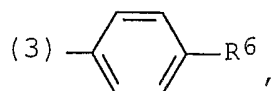


in which  $R^4$  is lower alkoxy carbonyl,

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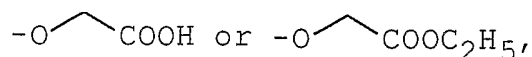


in which  $R^5$  is carboxy(lower)alkyl, (lower  
 25 alkoxy)carbonyl(lower)alkyl, lower alkanoyl, mono(or  
 di or tri)halo(lower)alkylsulfonyloxy,  
 carboxyphenoxy, (lower alkoxy)carbonylphenoxy,  
 carboxypyridyloxy, (lower alkanoyl)pyridyl,  
 carboxypyrrolidinyl(lower)alkyl, (lower  
 30 alkoxy)carbonylpyrrolidinyl(lower)alkyl,  
 carboxyphenyl or (lower alkyl)phenyl,



35

in which  $R^6$  is  $-OH$ ,  $-COOH$ ,  $-COOC_2H_5$ ,



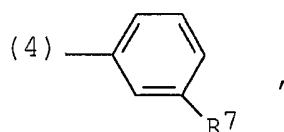
provided that (i) when  $\text{R}^6$  is  $-\text{OH}$ , then X is  $-\text{CH}_2-$ ,

(ii) when  $\text{R}^6$  is  $-\text{COOH}$ , then  $\text{R}^1$  is  $-\text{H}$ ,

or

(iii) when  $\text{R}^6$  is  $-\text{COOC}_2\text{H}_5$ ,  $-\text{O}-\text{CH}_2-\text{COOH}$  or

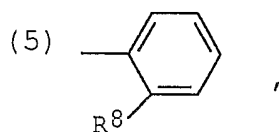
$-\text{O}-\text{CH}_2-\text{COOC}_2\text{H}_5$ , then X is  $-\text{O}-$ ,



in which  $\text{R}^7$  is  $-\text{OH}$ ,  $-\text{COOH}$ ,  $-\text{COOC}_2\text{H}_5$ ,

$-\text{O}-\text{CH}_2-\text{COOH}$  or  $-\text{O}-\text{CH}_2-\text{COOC}_2\text{H}_5$ , and

X is  $-\text{CH}_2-$ ,

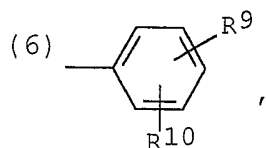


in which  $\text{R}^8$  is  $-\text{OH}$ ,  $-\text{COOH}$ ,  $-\text{COOC}_2\text{H}_5$ ,

$-\text{O}-\text{CH}_2-\text{COOH}$  or  $-\text{O}-\text{CH}_2-\text{COOC}_2\text{H}_5$ ,

provided that when  $\text{R}^8$  is  $-\text{OH}$ ,

$-\text{O}-\text{CH}_2-\text{COOH}$  or  $-\text{O}-\text{CH}_2-\text{COOC}_2\text{H}_5$ , then  $\text{R}^3$  is  $-\text{CH}_3$ ,



in which  $\text{R}^9$  is hydroxy, cyclo(lower)alkyl, mono(or di or tri)halo(lower)alkyl, hydroxy(lower)alkoxy,

lower alkoxy(lower)alkoxy, carboxy(lower)alkoxy,

lower alkoxycarbonyl(lower)alkoxy, phenoxy, nitro,

amino, lower alkylamino, [lower alkoxy(lower)-

alkyl]amino, [hydroxy(lower)alkyl]amino, [lower

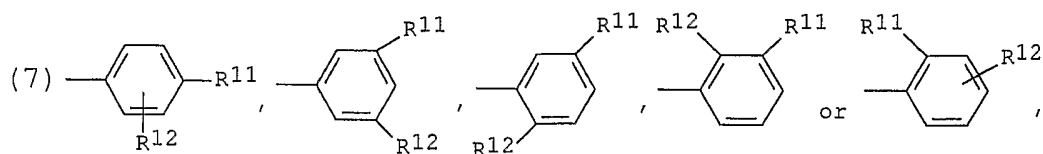
alkoxycarbonyl]amino, lower alkanoylamino,

[hydroxy(lower)alkanoyl]amino, benzoylamino, (lower

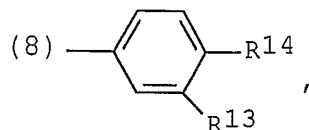
alkylsulfonyl)amino, lower alkylthio or phenyl, and

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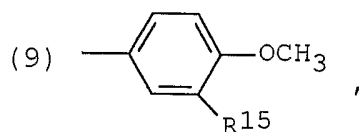
$R^{10}$  is carboxy, lower alkanoyl, lower alkoxycarbonyl, carbamoyl, lower alkylcarbamoyl, carboxy(lower)alkyl, (lower alkoxycarbonyl)(lower)alkyl, carboxy(lower)-alkenyl, (lower alkoxycarbonyl)(lower)alkenyl or phenyl optionally substituted with carboxy or lower alkoxycarbonyl,



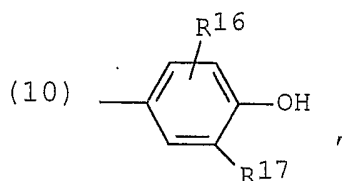
in which  $R^{11}$  is halogen or lower alkyl, and  $R^{12}$  is carboxy, lower alkanoyl, lower alkoxycarbonyl, carbamoyl, lower alkylcarbamoyl, carboxy(lower)alkyl, (lower alkoxycarbonyl)(lower)alkyl, carboxy(lower)-alkenyl or (lower alkoxycarbonyl)(lower)alkenyl,



in which  $R^{13}$  is  $-Cl$  or  $-CH_3$ ,  $R^{14}$  is  $-COOH$  or  $-COOC_2H_5$ , and  $X$  is  $-CH_2-$ ,



in which  $R^{15}$  is  $-COOH$  or  $-COOC_2H_5$ , and  $X$  is  $-CH_2-$ , or



in which  $R^{16}$  is lower alkyl or lower alkoxy, and

$R^{17}$  is carboxy or lower alkoxy carbonyl,  
or a prodrug thereof or a pharmaceutically acceptable  
salt thereof.

5 2. A compound of claim 1, wherein

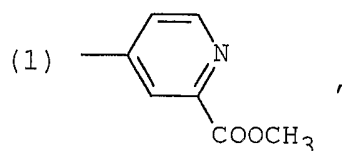
$R^1$  is hydrogen or chloride,

$R^2$  is hydrogen or benzyl,

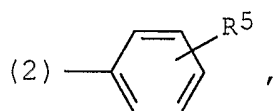
$R^3$  is hydrogen or methyl,

X is bond,  $-CH_2-$  or  $-O-$ , and

10 Y is

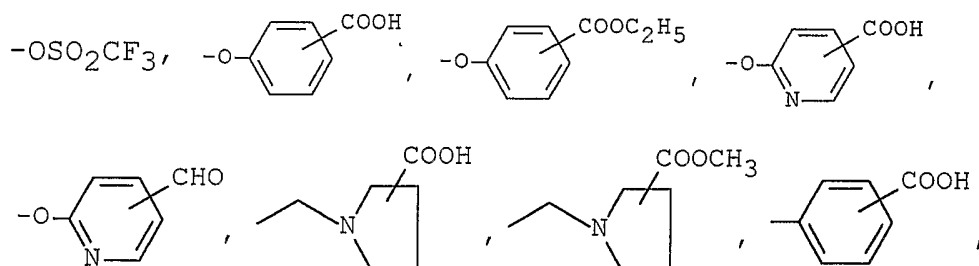


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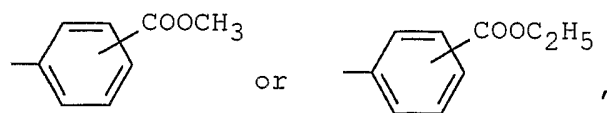


in which  $R^5$  is  $-CH_2COOH$ ,  $-CH_2COOC_2H_5$ ,  $-CHO$ ,

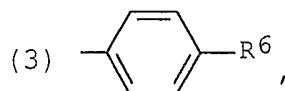
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in which  $R^6$  is  $-OH$ ,  $-COOH$ ,  $-COOC_2H_5$ ,

$-OCH_2COOH$  or  $-OCH_2COOC_2H_5$ ,

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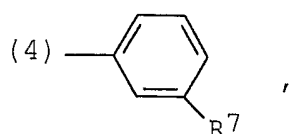
provided that (i) when  $R^6$  is  $-OH$ , then X is  $-CH_2-$ ,

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(ii) when  $R^6$  is  $-\text{COOH}$ , then  $R^1$  is  $-\text{H}$ ,  
or

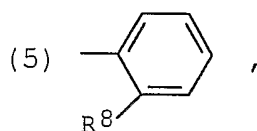
(iii) when  $R^6$  is  $-\text{COOC}_2\text{H}_5$ ,  $-\text{O}-\text{CH}_2-\text{COOH}$  or  
 $-\text{O}-\text{CH}_2-\text{COOC}_2\text{H}_5$ , then  $X$  is  $-\text{O}-$ ,

5



in which  $R^7$  is  $-\text{OH}$ ,  $-\text{COOH}$ ,  $-\text{COOC}_2\text{H}_5$ ,  
 $-\text{O}-\text{CH}_2-\text{COOH}$  or  $-\text{O}-\text{CH}_2-\text{COOC}_2\text{H}_5$ , and  
 $X$  is  $-\text{CH}_2-$ ,

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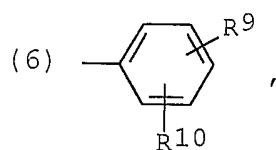


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

in which  $R^8$  is  $-\text{OH}$ ,  $-\text{COOH}$ ,  $-\text{COOC}_2\text{H}_5$ ,  
 $-\text{O}-\text{CH}_2-\text{COOH}$  or  $-\text{O}-\text{CH}_2-\text{COOC}_2\text{H}_5$ ,

provided that when  $R^8$  is  $-\text{OH}$ ,  
 $-\text{O}-\text{CH}_2-\text{COOH}$  or  $-\text{O}-\text{CH}_2-\text{COOC}_2\text{H}_5$ ,  
then  $R^3$  is  $-\text{CH}_3$ ,

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






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


in which  $R^9$  is  $-\text{OH}$ , ,  $-\text{CF}_3$ ,  $-\text{O}-\text{CH}_2-\text{CH}_2-\text{OH}$ ,  
 $-\text{O}-\text{CH}_2-\text{OCH}_3$ ,  $-\text{O}-\text{CH}_2-\text{COOH}$ ,  $-\text{O}-\text{CH}_2-\text{COOC}_2\text{H}_5$ ,  $-\text{O}-\text{C}_6\text{H}_5$ ,  
 $-\text{NO}_2$ ,  $-\text{NH}_2$ ,  $-\text{NHCH}_3$ ,  $-\text{NH}-\text{CH}_2-\text{CH}_2-\text{CH}_3$ ,  $-\text{NH}-\text{CH}_2-\text{CH}_2-\text{OH}$ ,  
 $-\text{NH}-\text{CH}_2-\text{CH}_2-\text{OCH}_3$ ,  $-\text{NH}-\text{CH}_2-\text{CH}_2-\text{OH}$ ,  $-\text{NHCOOCH}_3$ ,  $-\text{NHCOC}_2\text{H}_5$ ,  
 $-\text{NHCOCH}_3$ ,  $-\text{NHCO}-\text{C}_6\text{H}_5$ ,  $-\text{NHSO}_2\text{CH}_3$ ,  $-\text{SCH}_3$  or  
 , and

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

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
$R^{10}$  is  $-\text{COOH}$ ,  $-\text{CHO}$ ,  $-\text{COOCH}_3$ ,  $-\text{COOC}_2\text{H}_5$ ,  $-\text{CONH}_2$ ,  
 $-\text{CONHCH}_3$ ,  $-\text{CONHC}_2\text{H}_5$ , , ,

, , ,

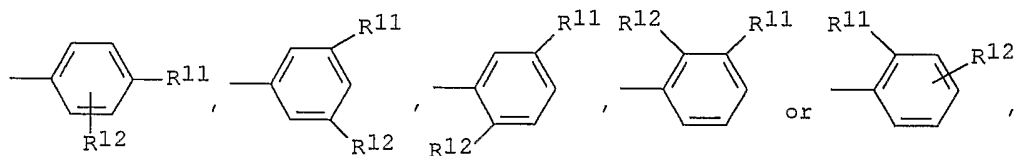
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

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



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







in which  $R^{11}$  is  $-\text{F}$ ,  $-\text{Cl}$  or  $-\text{CH}_3$ , and

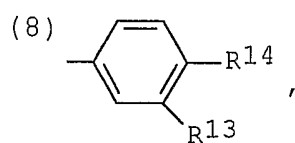
$R^{12}$  is  $-\text{COOH}$ ,  $-\text{CHO}$ ,  $-\text{COOCH}_3$ ,  $-\text{COOC}_2\text{H}_5$ ,  $-\text{CONH}_2$ ,

$-\text{CONHCH}_3$ ,  $-\text{CONHC}_2\text{H}_5$ , , ,

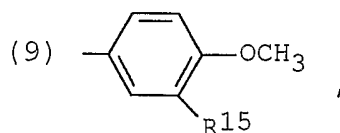
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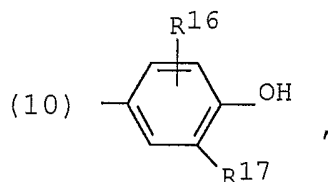
 or ,



in which  $R^{13}$  is  $-Cl$  or  $-CH_3$ ,  
 $R^{14}$  is  $-COOH$  or  $-COOC_2H_5$ , and  
 $X$  is  $-CH_2-$ ,



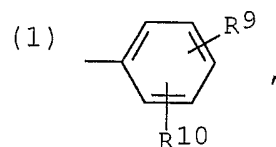
in which  $R^{15}$  is  $-COOH$  or  $-COOC_2H_5$ , and  
 $X$  is  $-CH_2-$ , or





in which  $R^{16}$  is  $-CH_3$  or  $-OCH_3$ , and  
 $R^{17}$  is  $-COOH$ ,  $-COOCH_3$  or  $-COOC_2H_5$ .

3. A compound of claim 2, wherein



Y is









in which  $R^9$  is  $-OH$ , ,  $-CF_3$ ,  $-OCH_2CH_2OH$ ,  
 $-OCH_2COCH_3$ ,  $-OCH_2COOH$ ,  $-OCH_2COOC_2H_5$ ,  $-O-C_6H_5$ ,  
 $-NO_2$ ,  $-NH_2$ ,  $-NHCH_3$ ,  $-NHCH_2CH_2CH_3$ ,  $-NHCH_2CH_2OH$ ,  
 $-NHCH_2CH_2OCH_3$ ,  $-NHCH_2CH_2OH$ ,  $-NHCOOCH_3$ ,  $-NHCOC_2H_5$ ,  
 $-NHCOCH_3$ ,  $-NHCO-C_6H_5$ ,  $-NHSO_2CH_3$ ,  $-SCH_3$  or  
, and







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
$R^{10}$  is  $-\text{COOH}$ ,  $-\text{CHO}$ ,  $-\text{COOCH}_3$ ,  $-\text{COOC}_2\text{H}_5$ ,  $-\text{CONH}_2$ ,  
 $-\text{CONHCH}_3$ ,  $-\text{CONHC}_2\text{H}_5$ ,   $\text{COOH}$ ,   $\text{COOH}$ ,

  $\text{COOCH}_3$ ,   $\text{COOC}_2\text{H}_5$ ,   $\text{COOCH}_3$ ,

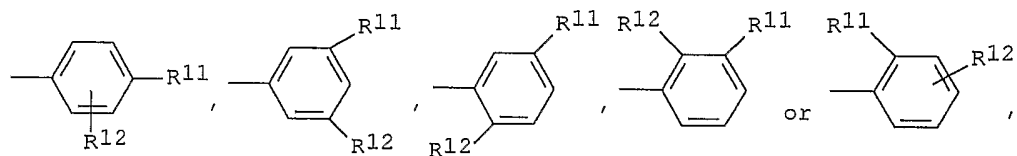
  $\text{COOC}_2\text{H}_5$ ,   $\text{COOH}$ ,   $\text{COOH}$ ,

  $\text{COOCH}_3$ ,   $\text{COOCH}_3$ ,   $\text{COOC}_2\text{H}_5$ ,

  $\text{COOC}_2\text{H}_5$ , ,   $\text{COOH}$ ,   $\text{COOCH}_3$  or



  $\text{COOC}_2\text{H}_5$ , or





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







in which  $R^{11}$  is  $-\text{F}$ ,  $-\text{Cl}$  or  $-\text{CH}_3$ , and

$R^{12}$  is  $-\text{COOH}$ ,  $-\text{CHO}$ ,  $-\text{COOCH}_3$ ,  $-\text{COOC}_2\text{H}_5$ ,  $-\text{CONH}_2$ ,

$-\text{CONHCH}_3$ ,  $-\text{CONHC}_2\text{H}_5$ ,   $\text{COOH}$ ,   $\text{COOH}$ ,

  $\text{COOCH}_3$ ,   $\text{COOCH}_3$ ,   $\text{COOC}_2\text{H}_5$ ,   $\text{COOC}_2\text{H}_5$ ,

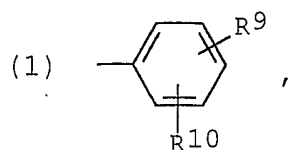
  $\text{COOH}$ ,   $\text{COOH}$ ,   $\text{COOCH}_3$ ,   $\text{COOCH}_3$ ,

  $\text{COOC}_2\text{H}_5$  or   $\text{COOC}_2\text{H}_5$ .

4. A compound of claim 3, wherein

Y is

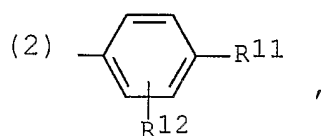
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5 in which  $R^9$  is  $-\text{OH}$ ,  $-\text{OCH}_2\text{CH}_2\text{OH}$ ,  $-\text{OCH}_2\text{OCH}_3$ ,  
 $-\text{OCH}_2\text{COOH}$ ,  $-\text{OCH}_2\text{COOC}_2\text{H}_5$ ,  $-\text{O}-\text{C}_6\text{H}_5$ ,  $-\text{NH}_2$ ,  $-\text{NHCH}_3$ ,  
 $-\text{NHCH}_2\text{CH}_3$ ,  $-\text{NHCH}_2\text{CH}_2\text{OH}$ ,  $-\text{NHCH}_2\text{CH}_2\text{OCH}_3$ ,  $-\text{NHCH}_2\text{CH}_2\text{OH}$ ,  
 10  $-\text{NHCOOCH}_3$ ,  $-\text{NHCOC}_2\text{H}_5$ ,  $-\text{NHCOCH}_3$ ,  $-\text{NHCO}-\text{C}_6\text{H}_5$ ,  
 $-\text{NHSO}_2\text{CH}_3$  or  $-\text{C}_6\text{H}_5$ , and

15  $R^{10}$  is  $-\text{COOH}$ ,  $-\text{COOCH}_3$ ,  $-\text{COOC}_2\text{H}_5$ ,  $-\text{CONH}_2$ ,  
 $-\text{CONHCH}_3$ ,  $-\text{CONHC}_2\text{H}_5$ ,  $-\text{CH}=\text{CHCOOH}$  or  $-\text{CH}_2=\text{CHCOOH}$ ,  
 or

20



in which  $R^{11}$  is  $-\text{CH}_3$ , and  
 25  $R^{12}$  is  $-\text{COOH}$ ,  $-\text{COOCH}_3$ ,  $-\text{COOC}_2\text{H}_5$ ,  $-\text{CONH}_2$ ,  
 $-\text{CONHCH}_3$ ,  $-\text{CONHC}_2\text{H}_5$ ,  $-\text{CH}=\text{CHCOOH}$  or  $-\text{CH}_2=\text{CHCOOH}$ .

5. A compound of claim 4, which is selected from a group  
 30 of

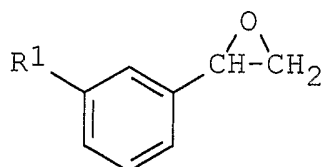
- (1) 2-Amino-5-[[4-[2-[[ (2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]benzoic acid,  
 (2) 5-[[4-[2-[[ (2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-2-
- 35

- (methylamino)benzoic acid,
- (3) 5-[[4-[2-[[ (2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-2-[(methylsulfonyl)amino]benzoic acid,
- 5 (4) 5-[[4-[2-[[ (2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-2-(propionylamino)benzoic acid,
- (5) 5-[[4-[2-[[ (2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-2-[(2-hydroxyethyl)amino]benzoic acid,
- 10 (6) 5-[[4-[2-[[ (2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-2-hydroxy-N-methylbenzamide,
- (7) [4-[[4-[3-[[ (2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-phenoxy]acetic acid,
- 15 (8) 2-Hydroxy-5-[[4-[2-[[ (2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]sulfonyl]benzoic acid,
- (9) 5-[[4-[3-[[ (2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-2-hydroxybenzoic acid,
- 20 (10) 2-[[4-[(2R)-2-[[ (2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-5-propylbenzoic acid,
- 25 (11) 4-[[4-[(2R)-2-[[ (2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-3-biphenylcarboxylic acid, and
- (12) (2Z)-3-[2-[[4-[(2R)-2-[[ (2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-5-methylphenyl]acrylic acid,
- 30 or a pharmaceutically acceptable salt thereof.
6. A process for preparing a compound of claim 1,
- 35 or a salt thereof,

which comprises,

(i) reacting a compound [II] of the formula:

5

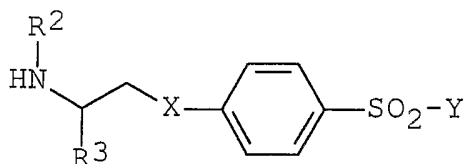


[II]

wherein  $R^1$  is defined in claim 1,

10

with a compound [III] of the formula:

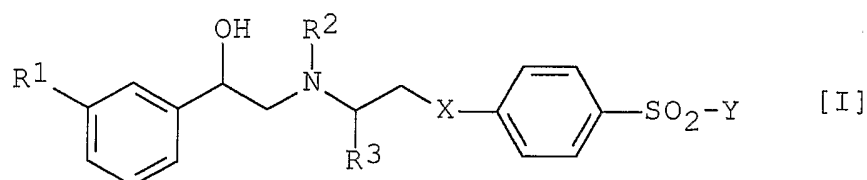


[III]

15

wherein  $R^2$ ,  $R^3$ , X and Y are each as defined in claim 1, or a salt thereof, to give a compound [I] of the formula:

20



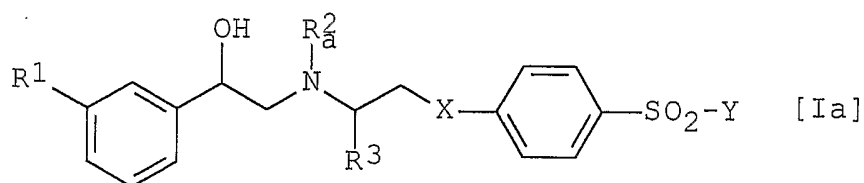
[I]

25

wherein  $R^1$ ,  $R^2$ ,  $R^3$ , X and Y are each as defined in claim 1, or a salt thereof,

(ii) subjecting a compound [Ia] of the formula:

30



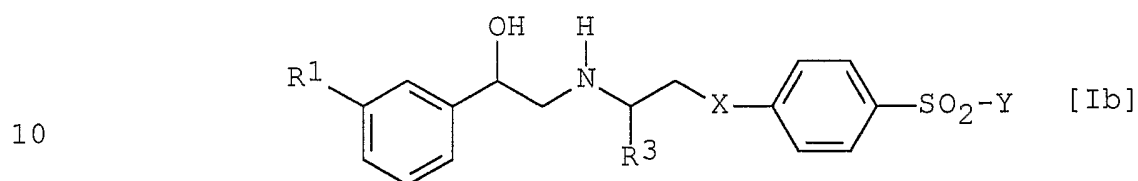
[Ia]

35

204

wherein  $R^1$ ,  $R^3$ , X and Y are each as defined in claim 1,  
and

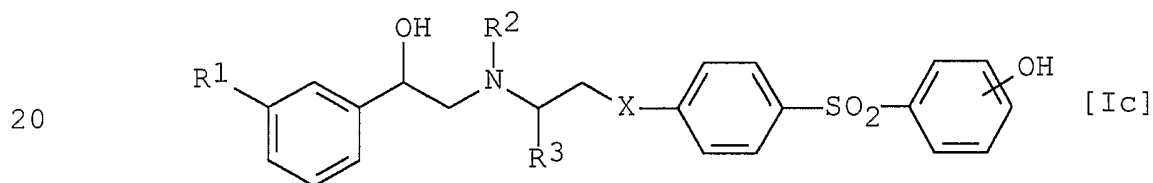
$R_a^2$  is an amino protective group,  
or a salt thereof, to elimination reaction of the amino  
protective group, to give a compound [Ib] of the  
formula:



wherein  $R^1$ ,  $R^3$ , X and Y are each as defined in claim 1,  
or a salt thereof, and

15

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



wherein  $R^1$ ,  $R^2$ ,  $R^3$  and X are each as defined in claim 1,  
or a salt thereof with a compound [IV] of the formula:

25



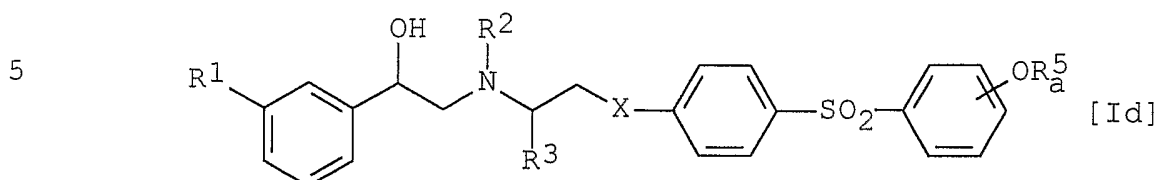
wherein  $R_a^5$  is lower alkyl optionally substituted with  
carboxy or lower alkoxy carbonyl; phenyl  
substituted with lower alkanoyl, carboxy  
or lower alkoxy carbonyl; or pyridyl  
optionally substituted with lower  
alkanoyl, carboxy or lower alkoxy carbonyl,  
and

35

Z is halogen,

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or a salt thereof to give a compound [Id] of the formula:



wherein  $R^1$ ,  $R^2$ ,  $R^3$  and X are each as defined in claim 1,  
10 and

$R_a^5$  is as defined above,  
or a salt thereof.

7. A pharmaceutical composition which comprises, as an  
15 active ingredient, a compound of claim 1 or a  
pharmaceutically acceptable salt thereof in admixture  
with pharmaceutically acceptable carriers or excipients.
8. Use of a compound of claim 1 or a pharmaceutically  
20 acceptable salt thereof for the manufacture of a  
medicament.
9. A compound of claim 1 or a pharmaceutically acceptable  
salt thereof for use as a medicament.
- 25 10. A compound of claim 1 or a pharmaceutically acceptable  
salt thereof for use as selective  $\beta_3$  adrenergic receptor  
agonists.
- 30 11. A method for the prophylactic and/or the 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.

# INTERNATIONAL SEARCH REPORT

Intern:      Application No

PCT/JP 03/14767

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7    A61K31/4412    C07D213/79    C07D213/64    C07D213/80    C07D207/16  
           C07C317/14    A61P13/00

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    C07D    C07C

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

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

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 2002 094770 A (FUJISAWA PHARMACEUTICAL CO., LTD., JAPAN) 28 November 2002 (2002-11-28) cited in the application claims 1,11,12 ---	1-11
Y	WO 02 006250 A (AMERICAN HOME PRODUCTS CORPORATION, USA) 24 January 2002 (2002-01-24) claims 1-14 ---	1-11
Y	WO 02 06229 A (AMERICAN HOME PROD) 24 January 2002 (2002-01-24) claims 1-20 ---	1-11
A	EP 0 089 154 A (BEECHAM GROUP PLC) 21 September 1983 (1983-09-21) the whole document -----	1-11

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \* & \* document member of the same patent family

Date of the actual completion of the international search

1 March 2004

Date of mailing of the international search report

31/03/2004

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) 340-3016

Authorized officer

Bérillon, L

# INTERNATIONAL SEARCH REPORT

In ☐ national application No.  
PCT/JP 03/14767

## 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. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claim 11 is 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.: 1-11 (part)  
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:  
  
see FURTHER INFORMATION sheet PCT/ISA/210
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. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.



## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-11 (part)

Present claims 1-11 relate to compounds defined by reference to a desirable characteristic or property, namely "prodrugs". The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds of formula I or pharmaceutically acceptable salts thereof.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/JP 03/14767

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 2002094770	A	28-11-2002	EP 1389185 A2 WO 02094770 A2	18-02-2004 28-11-2002
WO 02006250	A	24-01-2002	AU 7350101 A WO 0206250 A1 US 2002040023 A1	30-01-2002 24-01-2002 04-04-2002
WO 0206229	A	24-01-2002	AU 8056801 A WO 0206229 A2 US 2003018045 A1 US 2002028832 A1	30-01-2002 24-01-2002 23-01-2003 07-03-2002
EP 0089154	A	21-09-1983	AU 1233883 A EP 0089154 A2 ES 8404323 A1 JP 58167561 A ZA 8301650 A	15-09-1983 21-09-1983 16-07-1984 03-10-1983 30-11-1983