

DESCRIPTION

Method of producing N-phenyl-N'-phenylsulfonyl piperazine derivative

Technical field

[0001]

The present invention relates to a method of producing N-phenyl-N'-phenylsulfonyl piperazine derivative.

Background art

[0002]

N-phenyl-N'-phenylsulfonyl piperazine derivative is known to exhibit various pharmaceutical activities. For example, Patent literature 1 discloses that it has TXA2 receptor antagonistic inhibitory activity and has platelet aggregation activity, Patent literature 2 discloses that it has TXA2 receptor antagonistic inhibitory activity and its applicable diseases include thrombosis, myocardial infarction, arteriosclerosis, and hypertension, Patent literature 3 discloses that it has hydroxysteroid dehydrogenase inhibitory activity and its applicable diseases include type II diabetes mellitus, and osteoporosis, and Patent literature 4 discloses that it has CRTH2 receptor antagonistic inhibitory activity, and its applicable diseases include allergic rhinitis and asthma. Patent literature 5 discloses that it has DP receptor antagonistic inhibitory activity, and its applicable diseases include allergic rhinitis and asthma. However, a multi-stage process is required for producing N-phenyl-N'-phenylsulfonyl piperazine derivative.

[Patent literature 1]

Publication of European Patent Application No.76996 specification

[Patent literature 2]

Japanese Patent Application Laid-open Publication No.5-262751

[Patent literature 3]

International Patent Publication No.2006/105127 pamphlet

[Patent literature 4]

International Patent Publication No.2006/056752 pamphlet

[Patent literature 5]

Disclosure of the Invention

Problem to be solved by the invention

[0003]

The present invention provides an efficient method of producing N-phenyl-N'-phenylsulfonyl piperazine derivative and intermediate thereof.

Means for solving the problem

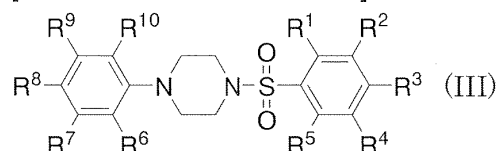
[0004]

The present inventors have found an industrially effective producing method capable of producing N-phenyl-N'-phenylsulfonyl piperazine derivative and intermediate thereof shown below in a simple manner in a short process and/or with good yield.

That is, the present invention provides

1) a method of producing a compound represented by Formula (III):

[Chemical formula 1]

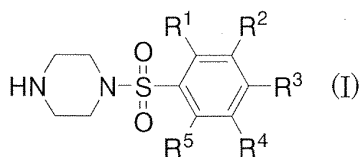


wherein R¹, R², R³, R⁴, and R⁵ each independently represent a hydrogen atom, a halogen atom, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted alkyloxy, optionally substituted alkylthio, acyl, optionally substituted alkyloxycarbonyl, optionally substituted carbamoyl, optionally substituted amino, optionally substituted aryl, optionally substituted heteroaryl, or an optionally substituted non-aromatic heterocyclic group;

R⁶, R⁷, R⁸, R⁹, and R¹⁰ each independently represent a hydrogen atom, a halogen atom, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, hydroxy, optionally substituted alkyloxy, optionally substituted alkylthio, acyl, optionally substituted alkyloxycarbonyl, optionally substituted carbamoyl, optionally substituted amino, optionally substituted aryl, optionally substituted heteroaryl, or an optionally substituted non-aromatic heterocyclic group;

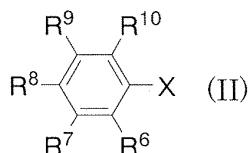
comprising reacting a compound represented by Formula (I):

[Chemical formula 2]



wherein R¹, R², R³, R⁴, and R⁵ are as defined above;
with a compound represented by Formula (II):

[Chemical formula 3]



wherein R⁶, R⁷, R⁸, R⁹, and R¹⁰ are as defined above;
X represents a halogen atom, optionally substituted
alkylsulfonyloxy, or optionally substituted arylsulfonyloxy;
in the presence of a palladium compound, an organic phosphorus
compound, and a base in a solvent.

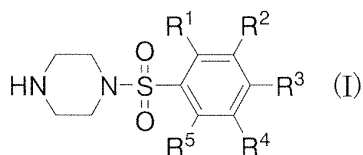
This process may be conducted using a solvent. When X
is a halogen atom, halogen atoms of R⁶, R⁷, R⁸, R⁹, and R¹⁰
each independently are a halogen atom having lower reactivity
than that of X.

Further, the present invention relates to the following
2) to 23).

2) The method according to 1), comprising

Step A of reacting the compound represented by Formula
(I):

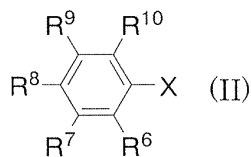
[Chemical formula 4]



wherein R¹, R², R³, R⁴, and R⁵ are as defined in 1);
with the palladium compound, the organic phosphorus compound,
and the base; and

Step B of adding the compound represented by Formula (II):

[Chemical formula 5]

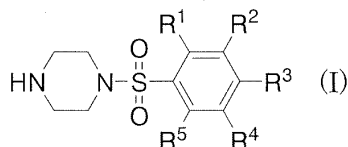


wherein R^6 , R^7 , R^8 , R^9 , R^{10} , and X are as defined in 1); wherein, each Step may be conducted using a solvent. Step A may be conducted at 15 to 30°C for 15 minutes to 2 hours.

3) The method according to 1), comprising:

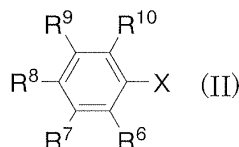
Step C of mixing the palladium compound and the organic phosphorus compound;

Step D of adding the compound represented by Formula (I):
[Chemical formula 6]



wherein R^1 , R^2 , R^3 , R^4 , and R^5 are as defined in 1); and the base to the mixture obtained in Step C; and

Step E of adding the compound represented by Formula (II):
[Chemical formula 7]



wherein R^6 , R^7 , R^8 , R^9 , R^{10} , and X are as defined in 1); to the mixture obtained in Step D.

Here, each Step may be conducted using a solvent. Step C may be conducted at 15 to 30°C for 15 minutes to 2 hours.

4) The method according to any one of 1) to 3), wherein the palladium compound is palladium acetate.

5) The method according to any one of 1) to 4), wherein the organic phosphorus compound is diadamantylbutyl phosphine.

6) The method according to any one of 1), 4) and 5), which is conducted in the presence of sulfinate.

7) The method according to any one of 2), 4) and 5), wherein Step A is conducted in the presence of sulfinate.

8) The method according to any one of 3), 4) and 5), wherein Step D is conducted in the presence of sulfinate.

9) The method according to any one of 6) to 8), wherein the sulfinate is sodium para-toluene sulfinate.

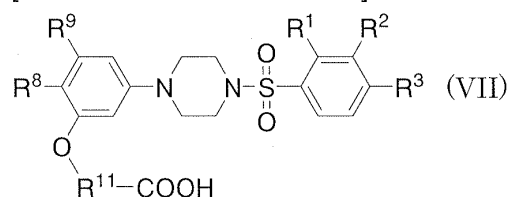
10) The method according to any one of 1) to 9), wherein R^4 , R^5 , R^6 , and R^{10} are hydrogen atoms, R^1 , R^2 , and R^9 each independently are a hydrogen atom, a halogen atom, or alkyl, R^3 is alkyloxy or alkylthio, R^7 is hydroxy or optionally substituted alkyloxy, R^8 is a halogen atom, optionally substituted alkyl, optionally substituted alkyloxy, optionally substituted alkyloxycarbonyl, optionally substituted carbamoyl, optionally substituted amino,

optionally substituted aryl, optionally substituted heteroaryl, or an optionally substituted non-aromatic heterocyclic group, and X is a halogen atom.

11) The method according to any one of 1) to 9), wherein R^1 , R^2 , R^4 , R^5 , R^6 , and R^{10} are hydrogen atoms, R^9 is a hydrogen atom or a halogen atom, R^3 is alkyloxy, R^7 is hydroxy, R^8 is a halogen atom, optionally substituted carbamoyl, optionally substituted amino, optionally substituted aryl, optionally substituted heteroaryl, or an optionally substituted non-aromatic heterocyclic group, and X is a halogen atom.

12) A method of producing a compound represented by Formula (VII):

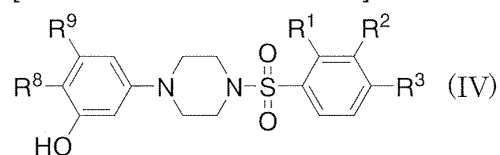
[Chemical formula 8]



wherein R^1 , R^2 , R^3 , R^8 , and R^9 are as defined in 1); R^{11} is alkylene or alkenylene; comprising:

Step F of obtaining a compound represented by Formula (IV):

[Chemical formula 9]



wherein R^1 , R^2 , R^3 , R^8 , and R^9 are as defined in 1); by the production method according to any one of 1) to 11);

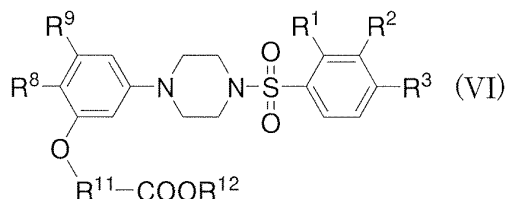
Step G of reacting the compound represented by Formula (IV) with a compound represented by Formula (V):

[Chemical formula 10]



wherein R^{11} is alkylene or alkenylene; R^{12} is a hydrogen atom or alkyl; Y is a halogen atom, optionally substituted alkylsulfonyl, or optionally substituted arylsulfonyl; in the presence of a base, to obtain a compound represented by Formula (VI):

[Chemical formula 11]



wherein R^1 , R^2 , R^3 , R^8 , and R^9 are as defined in 1); R^{11} and R^{12} are as defined above; and

additional Step H of subjecting the compound represented by Formula (VI) to hydrolysis when R^{12} is alkyl.

Here, each Step may be conducted using a solvent.

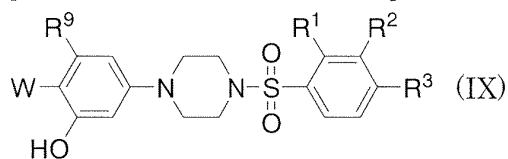
13) The method according to 12), wherein Y is a halogen atom.

14) The method according to 12) or 13), wherein R^1 , R^2 , and R^9 each independently are a hydrogen atom, a halogen atom, or alkyl, R^3 is alkyloxy or alkylthio, R^8 is a halogen atom, optionally substituted alkyl, optionally substituted alkyloxy, optionally substituted alkyloxycarbonyl, optionally substituted carbamoyl, optionally substituted amino, optionally substituted aryl, optionally substituted heteroaryl, or an optionally substituted non-aromatic heterocyclic group, and R^{11} is alkylene.

15) The method according to any one of 12) to 14), wherein R^1 , R^2 , and R^9 each independently are a hydrogen atom, a halogen atom, or alkyl, R^3 is alkyloxy or alkylthio, R^8 is a halogen atom, optionally substituted carbamoyl, optionally substituted amino, optionally substituted aryl, optionally substituted heteroaryl, or an optionally substituted non-aromatic heterocyclic group, and R^{11} is methylene.

16) A method of producing a compound represented by Formula (IX):

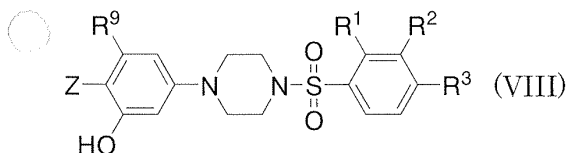
[Chemical formula 12]



wherein R^1 , R^2 , R^3 , and R^9 are as defined in 1); W is optionally substituted aryl or optionally substituted heteroaryl; comprising:

Step I of obtaining a compound represented by Formula (VIII):

[Chemical formula 13]



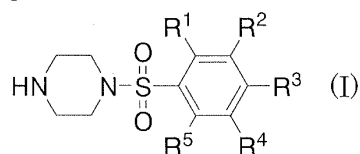
wherein R^1 , R^2 , R^3 , and R^9 are as defined in 1); Z is a halogen atom; by the method according to any one of 1) to 11); and

Step J of reacting the compound represented by Formula (VIII) with an organic boronic acid.

Here, each Step may be conducted using a solvent.

17) A method of producing a compound represented by Formula (I):

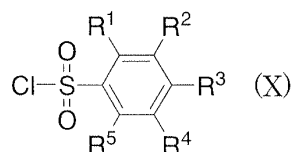
[Chemical formula 14]



wherein R^1 , R^2 , R^3 , R^4 , and R^5 are as defined in 1); comprising:

Step K of adding a compound represented by Formula (X):

[Chemical formula 15]



wherein R^1 , R^2 , R^3 , R^4 , and R^5 are as defined in 1); to a solution of piperazine;

Step L of adding water to the reaction mixture and extracting with an organic solvent; and

Step M of making the organic phase obtained in Step L acidic by adding an acid, and extracting it with water; and

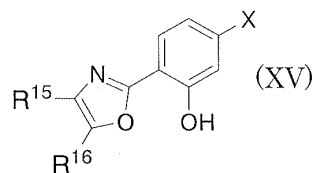
Step N of making the aqueous phase obtained in Step M alkaline by adding a base to cause precipitation of crystals.

When the solution of piperazine is toluene solution, Steps K, L, M, N, and P may be conducted under the following conditions. Step K may be conducted at 45 to 80°C for 1 to 4 hours. Step L may be conducted at 45 to 80°C. Step M may be conducted at 45 to 80°C by using 1 to 4 mol/L of hydrochloric acid as an acid. Step N may be conducted at 45 to 80°C by using 1 to 4 mol/L of sodium hydroxide aqueous solution as a base, to make the reaction alkaline. Further, crystals may be allowed to precipitate at 15 to 30°C.

18) The method according to 17), wherein R^1 , R^2 , R^4 , and R^5 are a hydrogen atom, and R^3 is alkoxy.

19) A method of producing a compound represented by Formula (XV):

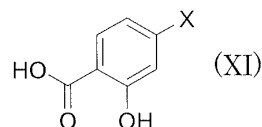
[Chemical formula 16]



wherein X is as defined in 1); R^{15} and R^{16} each independently represent hydrogen atom or alkyl; comprising:

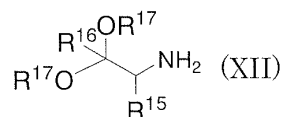
Step P of reacting a compound represented by Formula (XI):

[Chemical formula 17]



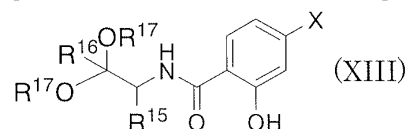
wherein X is as defined in 1); or a reactive derivative thereof with a compound represented by Formula (XII):

[Chemical formula 18]



wherein R^{15} and R^{16} are as defined above; R^{17} is alkyl; to obtain a compound represented by Formula (XIII):

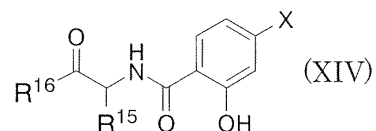
[Chemical formula 19]



wherein X is as defined in 1); R^{15} , R^{16} , and R^{17} are as defined above;

Step Q of reacting the compound represented by Formula (XIII) with an acid, to obtain a compound represented by Formula (XIV):

[Chemical formula 20]



wherein X is as defined in 1); R^{15} and R^{16} are as defined above; and

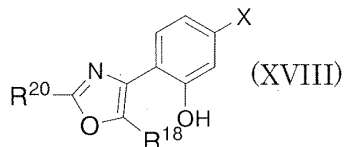
Step R of closing the ring of the compound represented

by Formula (XIV).

Here, each Step may be conducted using a solvent.

20) A method of producing a compound represented by Formula (XVIII):

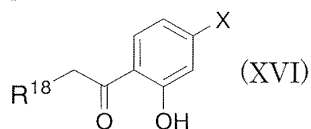
[Chemical formula 21]



wherein X is as defined in 1); R¹⁸ is a hydrogen atom or alkyl; and R²⁰ is a hydrogen atom or alkyl; comprising:

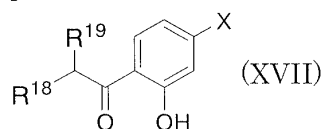
Step S of halogenating a compound represented by Formula (XVI):

[Chemical formula 22]



wherein X is as defined in 1); R¹⁸ is a hydrogen atom or alkyl; to obtain a compound represented by Formula (XVII):

[Chemical formula 23]



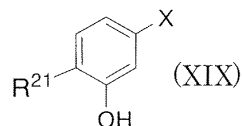
wherein X is as defined in 1); R¹⁸ is as defined above; R¹⁹ is a halogen atom; and

Step T of reacting the compound represented by Formula (XVII) with a compound represented by the formula: R²⁰COONH₄ wherein R²⁰ is as defined above.

Here, each Step may be conducted using a solvent.

21) A compound represented by Formula (XIX):

[Chemical formula 24]



wherein X is as defined in 1); R²¹ is optionally substituted 5-membered heteroaryl; a pharmaceutically acceptable salt thereof, or a solvate thereof.

[0005]

In the following, meanings of various terms are explained. Each term is used in the unified meaning throughout

the specification, and has the same meaning when used alone or in combination with other term.

In the present specification, "halogen atom" means a fluorine atom, a chlorine atom, a bromine atom or an iodine atom. A fluorine atom, a chlorine atom, and a bromine atom are preferred.

In the present specification, "alkyl" includes linear- or branched-chain monovalent hydrocarbons having 1 to 8 carbon atom(s). Examples are methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neo-pentyl, n-hexyl, isohexyl, n-heptyl, n-octyl and the like.

Preferably, C1-C6 alkyl is exemplified. More preferably, C1-C4 alkyl is exemplified. When the number of carbons is particularly specified, it includes "alkyl" having carbon number within the range of the number.

In the present specification, "alkenyl" includes linear- or branched-chain monovalent hydrocarbon groups having 2 to 8 carbon atoms and having one or more than one double bond(s). Examples are vinyl, allyl, 1-propenyl, 2-butenyl, 2-pentenyl, 2-hexenyl, 2-heptenyl, 2-octenyl and the like. Preferably, C2-C6 alkenyl is exemplified. More preferably, C2-C4 alkenyl is exemplified.

In the present specification, "alkynyl" includes linear- or branched-chain monovalent hydrocarbon groups having 2 to 8 carbon atoms and having one or more than one triple bond(s). Examples are ethynyl, 1-propynyl, 2-propynyl, 2-butylnyl, 2-pentylnyl, 2-hexynyl, 2-heptynyl, 2-octynyl and the like. Preferably, C2-C6 alkynyl is exemplified. More preferably, C2-C4 alkynyl is exemplified.

In the present specification, "cycloalkyl" includes cycloalkyls having 3 to 8 carbon atoms. Examples are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and the like. Preferably, C3-C6 cycloalkyl is exemplified.

In the present specification, as "alkyloxy", methyloxy, ethyloxy, n-propyloxy, isopropyloxy, n-butyloxy, isobutyloxy, sec-butyloxy, tert-butyloxy, n-pentyloxy, isopentyloxy, 2-pentyloxy, 3-pentyloxy, n-hexyloxy, isohexyloxy, 2-hexyloxy, 3-hexyloxy, n-heptyloxy, n-octyloxy and the like are exemplified. Preferably, C1-C6 alkyloxy is listed. More preferably, C1-C4 alkyloxy is listed. When the number of carbons is particularly specified, it includes "alkyloxy" having carbon number within the range of the number.

In the present specification, as "alkylthio", methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, isobutylthio, sec-butylthio, tert-butylthio, n-pentylthio, isopentylthio, 2-pentylthio, 3-pentylthio,

n-hexylthio, isohexylthio, 2-hexylthio, 3-hexylthio, n-heptylthio, n-octylthio and the like are exemplified. Preferably, C1-C6 alkylthio is listed. More preferably, C1-C4 alkylthio is listed. When the number of carbons is particularly specified, it includes "alkylthio" having carbon number within the range of the number.

In the present specification, as "alkylsulfonyl", methylsulfonyl, ethylsulfonyl, n-propylsulfonyl, isopropylsulfonyl, n-butylsulfonyl, isobutylsulfonyl, sec-butylsulfonyl, tert-butylsulfonyl, n-pentylsulfonyl, isopentylsulfonyl, 2-pentylsulfonyl, 3-pentylsulfonyl, n-hexylsulfonyl, isohexylsulfonyl, 2-hexylsulfonyl, 3-hexylsulfonyl, n-heptylsulfonyl, n-octylsulfonyl and the like are exemplified. Preferably, C1-C6 alkylsulfonyl is listed. More preferably, C1-C4 alkylsulfonyl is listed.

In the present specification, as "alkyloxycarbonyl", methyloxycarbonyl, ethyloxycarbonyl, n-propyloxycarbonyl, isopropyloxycarbonyl, n-butyloxycarbonyl, tert-butyloxycarbonyl, n-pentyloxycarbonyl and the like are exemplified. Preferably, C1-C4 alkyloxycarbonyl is listed. Particularly preferably, C1-C2 alkyloxycarbonyl is listed.

In the present specification, "acyl" includes alkylcarbonyl whose alkyl moiety is above-described "alkyl" or arylcarbonyl whose aryl moiety is later-described "aryl". Each of "alkyl" and "aryl" may be substituted by a substituent exemplified in later-described "optionally substituted alkyl" and "optionally substituted aryl". Examples are acetyl, propionyl, butyloyl, benzoyl and the like.

In the present specification, "optionally substituted amino" includes amino which may be substituted in one or two position(s) by above-described "alkyl", later-described "aryl", later-described "heteroaryl", above-described "acyl", above-described "alkyloxycarbonyl" and/or above-described "alkylsulfonyl". Examples are amino, methylamino, dimethylamino, ethylamino, diethylamino, ethylmethylamino, benzylamino, acetylamino, benzoylamino, methyloxycarbonylamino, methylsulfonylamino and the like. Preferably, amino, methylamino, dimethylamino, ethylmethylamino, diethylamino, acetylamino, methylsulfonylamino and the like are exemplified.

In the present specification, "optionally substituted carbamoyl" includes optionally substituted aminocarbonyl whose optionally substituted amino moiety is above-described "optionally substituted amino". Examples are carbamoyl, N-methyl carbamoyl, N,N-dimethyl carbamoyl, N-ethyl-N-methyl carbamoyl, N,N-diethyl carbamoyl, N-benzyl carbamoyl, N-acetyl carbamoyl, N-methylsulfonyl carbamoyl and the like. Preferably, carbamoyl, N-methyl carbamoyl, N,N-dimethyl

carbamoyl, N-methylsulfonyl carbamoyl and the like.

In the present specification, "alkylene" means linear- or branched-chain alkylene having 1 to 10 carbon atom(s). Examples are methylene, 1-methyl methylene, 1,1-dimethyl methylene, ethylene, 1-methylethylene, 1-ethylethylene, 1,1-dimethylethylene, 1,2-dimethylethylene, 1,1-diethylethylene, 1,2-diethylethylene, 1-ethyl-2-methylethylene, trimethylene, 1-methyl trimethylene, 2-methyl trimethylene, 1,1-dimethyl trimethylene, 1,2-dimethyl trimethylene, 2,2-dimethyl trimethylene, 1-ethyl trimethylene, 2-ethyl trimethylene, 1,1-diethyl trimethylene, 1,2-diethyl trimethylene, 2,2-diethyl trimethylene, 2-ethyl-2-methyl trimethylene, tetramethylene, 1-methyl tetramethylene, 2-methyl tetramethylene, 1,1-dimethyl tetramethylene, 1,2-dimethyl tetramethylene, 2,2-dimethyl tetramethylene, 2,2-di-n-propyltrimethylene and the like. In particular, linear- or branched-chain alkylene having 2 to 6 carbon atoms is preferred.

In the present specification, "alkenylene" means linear- or branched-chain alkenylene having 2 to 10 carbon atoms, and examples are ethenylene, 1-methyl ethenylene, 1-ethyl ethenylene, 1,2-dimethyl ethenylene, 1,2-diethyl ethenylene, 1-ethyl-2-methyl ethenylene, propenylene, 1-methyl-2-propenylene, 2-methyl-2-propenylene, 1,1-dimethyl-2-propenylene, 1,2-dimethyl-2-propenylene, 1-ethyl-2-propenylene, 2-ethyl-2-propenylene, 1,1-diethyl-2-propenylene, 1,2-diethyl-2-propenylene, 1-butenylene, 2-butenylene, 1-methyl-2-butenylene, 2-methyl-2-butenylene, 1,1-dimethyl-2-butenylene, 1,2-dimethyl-2-butenylene and the like. In particular, linear- or branched-chain alkenylene having 2 to 6 carbon atoms is preferred.

In the present specification, "aryl" includes monocyclic or condensed cyclic aromatic hydrocarbons. This may be condensed at every possible position with above-described "cycloalkyl" or later-described "non-aromatic heterocyclic group". Even in both cases where aryl is a single ring and a condensed ring, binding can occur at every position. Examples are phenyl, 1-naphthyl, 2-naphthyl, anthryl, tetrahydronaphthyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl and the like. Preferably, phenyl, 1-naphthyl, and 2-naphthyl are listed. More preferably, phenyl is listed.

In the present specification, "non-aromatic heterocyclic group" includes a non-aromatic 5 to 7-membered ring containing at least one atom arbitrarily selected from an oxygen atom, a sulfur atom and a nitrogen atom, or a ring of formed by condensation of two or more of such rings. Examples are

pyrrolidinyl (e.g., 1-pyrrolidinyl, 2-pyrrolidinyl), pyrrolinyl (e.g., 3-pyrrolinyl), imidazolidinyl (e.g., 2-imidazolidinyl), imidazolinyl (e.g., imidazolinyl), pyrazolidinyl (e.g., 1-pyrazolidinyl, 2-pyrazolidinyl), pyrazolinyl (e.g., pyrazolinyl), piperidyl (e.g., piperidino, 2-piperidyl), piperazinyl (e.g., 1-piperazinyl), indolinyl (e.g., 1-indolinyl), isoindolinyl (e.g., isoindolinyl), morpholinyl (e.g., morpholino, 3-morpholinyl) and the like.

In the present specification, "heteroaryl" includes 5- to 6-membered aromatic rings containing at least one atom arbitrarily selected from an oxygen atom, a sulfur atom and a nitrogen atom in the ring. This may be condensed at every possible position with above-described "cycloalkyl", above-described "aryl", above-described "non-aromatic heterocyclic group" or other heteroaryl. Even in both cases where heteroaryl is a single ring and a condensed ring, binding can occur at every position. Examples are pyrrolyl (e.g., 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl), furyl (e.g., 2-furyl, 3-furyl), thienyl (e.g., 2-thienyl, 3-thienyl), imidazolyl (e.g., 2-imidazolyl, 4-imidazolyl), pyrazolyl (e.g., 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl), isothiazolyl (e.g., 3-isothiazolyl), isoxazolyl (e.g., 3-isoxazolyl), oxazolyl (e.g., 2-oxazolyl, 4-oxazolyl, 5-oxazolyl), thiazolyl (e.g., 2-thiazolyl, 4-thiazolyl, 5-thiazolyl), pyridyl (e.g., 2-pyridyl, 3-pyridyl, 4-pyridyl), pyrazinyl (e.g., 2-pyrazinyl), pyrimidinyl (e.g., 2-pyrimidinyl, 4-pyrimidinyl), pyridazinyl (e.g., 3-pyridazinyl), tetrazolyl (e.g., 1H-tetrazolyl), oxadiazolyl (e.g., 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,3,4-thiadiazolyl), indolizinyll (e.g., 2-indolizinyll, 6-indolizinyll), isoindolyl (e.g., 2-isoindolyl), indolyl (e.g., 1-indolyl, 2-indolyl, 3-indolyl), indazolyl (e.g., 3-indazolyl), purinyl (e.g., 8-purinyl), quinolizinyll (e.g., 2-quinolizinyll), isoquinolyl (e.g., 3-isoquinolyl), quinolyl (e.g., 2-quinolyl, 5-quinolyl), phthalazinyl (e.g., 1-phthalazinyl), naphthyldinyl (e.g., 2-naphthyldinyl), quinolanyl (e.g., 2-quinolanyl), quinazolinyl (e.g., 2-quinazolinyl), cinnolinyl (e.g., 3-cinnolinyl), pteridinyl (e.g., 2-pteridinyl), carbazolyl (e.g., 2-carbazolyl, 4-carbazolyl), phenanthridinyl (e.g., 2-phenanthridinyl, 3-phenanthridinyl), acridinyl (e.g., 1-acridinyl, 2-acridinyl), dibenzofuranyl (e.g., 1-dibenzofuranyl, 2-dibenzofuranyl), benzimidazolyl (e.g., 2-benzimidazolyl), benzoisoxazolyl (e.g., 3-benzoisoxazolyl), benzoxazolyl (e.g., 2-benzoxazolyl), benzoxadiazolyl (e.g., 4-benzoxadiazolyl), benzoisothiazolyl (e.g., 3-benzoisothiazolyl), benzothiazolyl (e.g., 2-benzothiazolyl), benzofuryl (e.g., 3-benzofuryl),

benzothienyl (e.g., 2-benzothienyl), dibenzothienyl (e.g., 2-dibenzothienyl), benzodioxolyl (e.g., 1,3-benzodioxolyl) and the like.

In the present specification, "5-membered heteroaryl" includes 5-membered aromatic ring containing at least one arbitrarily selected from an oxygen atom, a sulfur atom and a nitrogen atom. Examples are pyrrolyl (e.g., 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl), furyl (e.g., 2-furyl, 3-furyl), thienyl (e.g., 2-thienyl, 3-thienyl), imidazolyl (e.g., 2-imidazolyl, 4-imidazolyl), pyrazolyl (e.g., 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl), isothiazolyl (e.g., 3-isothiazolyl), isoxazolyl (e.g., 3-isoxazolyl), oxazolyl (e.g., 2-oxazolyl, 4-oxazolyl, 5-oxazolyl), thiazolyl (e.g., 2-thiazolyl, 4-thiazolyl, 5-thiazolyl), tetrazolyl (e.g., 1H-tetrazolyl), oxadiazolyl (e.g., 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,3,4-thiadiazolyl) and the like.

In the present specification, as "arylsulfonyl", phenylsulfonyl, naphthylsulfonyl and the like are exemplified. [0006]

In the present specification, as a substituent in "optionally substituted alkyl", "optionally substituted alkyloxy", "optionally substituted alkylthio", "optionally substituted alkylsulfonyl" and "optionally substituted alkyloxycarbonyl", cycloalkyl, hydroxy, alkyloxy which may be substituted by a substituent selected from Substituent group A at one to three position(s), mercapto, alkylthio, a halogen atom, nitro, cyano, carboxy, alkyloxycarbonyl, optionally substituted amino, optionally substituted carbamoyl, acyl, aryl which may be substituted by a substituent selected from Substituent group B at one to three position(s) (e.g., phenyl), heteroaryl which may be substituted by a substituent selected from Substituent group C at one to three position(s) (e.g., pyridyl, furyl, thienyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl), optionally substituted non-aromatic heterocyclic group which may be substituted by a substituent selected from Substituent group C at one to three position(s) (e.g., morpholinyl, pyrrolidinyl, piperazinyl), alkylsulfonyl and the like are exemplified. These may be substituted at one to three position(s) in every possible position.

In the present specification, as a substituent in "optionally substituted alkenyl", "optionally substituted alkynyl" and "optionally substituted cycloalkyl", optionally substituted alkyl which may be substituted by a substituent selected from Substituent group D at one to three position(s), cycloalkyl, hydroxy, alkyloxy which may be substituted by a substituent selected from Substituent group A at one to three position(s), mercapto, alkylthio, a halogen atom, nitro, cyano, carboxy, alkyloxycarbonyl, optionally substituted

amino, optionally substituted carbamoyl, acyl, aryl which may be substituted by a substituent selected from Substituent group B at one to three position(s) (e.g., phenyl), heteroaryl which may be substituted by a substituent selected from Substituent group C at one to three position(s) (e.g., pyridyl, furyl, thienyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl), optionally substituted non-aromatic heterocyclic group which may be substituted by a substituent selected from Substituent group C at one to three position(s) (e.g., morpholinyl, pyrrolidinyl, piperazinyl), alkylsulfonyl and the like are listed. These may be substituted at one or more position(s) in every possible position.

In the present specification, as a substituent in "optionally substituted aryl", "optionally substituted arylsulfonyl", "optionally substituted heteroaryl", "optionally substituted 5-membered heteroaryl", and "optionally substituted non-aromatic heterocyclic group", optionally substituted alkyl which may be substituted by a substituent selected from Substituent group D at one to three position(s), cycloalkyl, alkenyl, alkynyl, hydroxy, alkyloxy which may be substituted by a substituent selected from Substituent group A at one to three position(s), aryloxy which may be substituted by a substituent selected from Substituent group B at one to three position(s) (e.g., phenoxy), mercapto, alkylthio, a halogen atom, nitro, cyano, carboxy, alkyloxycarbonyl, acyl, alkylsulfonyl, optionally substituted amino, optionally substituted carbamoyl, aryl which may be substituted by a substituent selected from Substituent group B at one to three position(s) (e.g., phenyl), heteroaryl which may be substituted by a substituent selected from Substituent group C at one to three position(s) (e.g., pyridyl, furyl, thienyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl), optionally substituted non-aromatic heterocyclic group which may be substituted by a substituent selected from Substituent group C at one to three position(s) (e.g., morpholinyl, pyrrolidinyl, piperazinyl) and the like are exemplified. These may be substituted at one or more position(s) in every possible position.

Substituent group A includes a halogen atom and phenyl which may be substituted by a substituent selected from Substituent group B at 1 to 3 position(s).

Substituent group B includes a halogen atom, alkyl, alkyloxy, cyano and nitro.

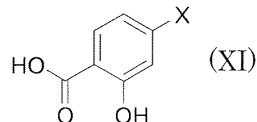
Substituent group C includes a halogen atom and alkyl.

Substituent group D includes a halogen atom and alkyloxy.
[0007]

In the present specification, "its reactive derivative" means halides (e.g., $C(=O)Cl$, $C(=O)Br$), acid anhydrides (e.g.,

mixed acid anhydride with formic acid $C(=O)-O-C(=O)-H$ or mixed acid anhydride with acetic acid $C(=O)-O-C(=O)-CH_3$, active ester (e.g., succinimide ester) corresponding to carboxyl group moiety $C(=O)OH$ of a compound represented by Formula (XI):

[Chemical formula 25]



wherein X is as defined in 1).

[0008]

In the compound represented by General formula (I), preferred Substituent groups for R^1 to R^5 are shown by (Ia) to (If). Compounds of possible combinations of these are preferred.

For each of R^1 , R^2 , R^4 , and R^5 , independently (Ia) a hydrogen atom, a halogen atom, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted alkyloxy, optionally substituted alkylthio, acyl, optionally substituted alkyloxycarbonyl, optionally substituted carbamoyl, optionally substituted amino, optionally substituted aryl, optionally substituted heteroaryl, or optionally substituted non-aromatic heterocyclic group is preferred, and further (Ib) a hydrogen atom, a halogen atom, or alkyl is more preferred, and further (Ic) a hydrogen atom is most preferred.

As R^3 , (Id) a hydrogen atom, a halogen atom, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkyloxy, optionally substituted alkylthio, acyl, optionally substituted alkyloxycarbonyl, optionally substituted carbamoyl, optionally substituted amino, optionally substituted aryl, optionally substituted heteroaryl, or optionally substituted non-aromatic heterocyclic group is preferred, and further, (Ie) optionally substituted alkoxy or optionally substituted alkylthio is more preferred, and further (If) alkoxy is most preferred.

[0009]

Further, in the compound represented by General formula (II), preferred substituent groups for R^6 to R^{10} and X are shown by (Ig) to (Is). Compounds of possible combinations of these are preferred.

As each of R^6 and R^{10} independently, (Ig) a hydrogen atom, a halogen atom, alkyl, or hydroxy is preferred, and (Ih) a hydrogen atom is more preferred.

As R⁷, (Ii) a hydrogen atom, a halogen atom, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, hydroxy, optionally substituted alkyloxy, optionally substituted alkylthio, acyl, optionally substituted alkyloxycarbonyl, optionally substituted carbamoyl, optionally substituted amino, optionally substituted aryl, optionally substituted heteroaryl, or optionally substituted non-aromatic heterocyclic group is preferred, and further (Ij) hydroxy or optionally substituted alkyloxy is more preferred, and further (Ik) hydroxy is most preferred.

As R⁸, (Il) a hydrogen atom, a halogen atom, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, hydroxy, optionally substituted alkyloxy, optionally substituted alkylthio, acyl, optionally substituted alkyloxycarbonyl, optionally substituted carbamoyl, optionally substituted amino, optionally substituted aryl, optionally substituted heteroaryl, or optionally substituted non-aromatic heterocyclic group is preferred, and further, (Im) a halogen atom, optionally substituted alkyl, optionally substituted alkyloxy, optionally substituted alkyloxycarbonyl, optionally substituted carbamoyl, optionally substituted amino, optionally substituted aryl, optionally substituted heteroaryl, or optionally substituted non-aromatic heterocyclic group is preferred, and further, (In) a halogen atom, optionally substituted carbamoyl, optionally substituted amino, optionally substituted aryl, optionally substituted heteroaryl, or an optionally substituted non-aromatic heterocyclic group is more preferred, and further, (Io) a halogen atom, optionally substituted carbamoyl, or optionally substituted heteroaryl is most preferred.

As R⁹, (Ip) a hydrogen atom, a halogen atom, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, hydroxy, optionally substituted alkyloxy, optionally substituted alkylthio, acyl, optionally substituted alkyloxycarbonyl, optionally substituted carbamoyl, optionally substituted amino, optionally substituted aryl, optionally substituted heteroaryl, or an optionally substituted non-aromatic heterocyclic group is preferred, and further (Iq) a hydrogen atom or a halogen atom is more preferred.

As X, (Ir) a halogen atom, optionally substituted alkylsulfonyl, or optionally substituted arylsulfonyl is preferred, and further, (Is) a halogen atom is more preferred.
[0010]

In the compound represented by General formula (III),

preferred substituent groups for R^1 to R^5 and R^6 to R^{10} are the same as the (Ia) to the (Iq). Compounds of possible combinations thereof are preferred.

As each of R^1 , R^2 , R^4 , and R^5 independently, the (Ia) is preferred, and the (Ib) is more preferred, and the (Ic) is most preferred.

As R^3 , the (Id) is preferred, and further the (Ie) is more preferred, and further the (If) is most preferred.

As each of R^6 and R^{10} independently, the (Ig) is preferred, and further, the (Ih) is more preferred.

As R^7 , the (Ii) is preferred, and further the (Ij) is more preferred, and further the (Ik) is most preferred.

As R^8 , the (Il) is preferred, and further the (Im) is more preferred, and further the (In) is further preferred, and further, the (Io) is most preferred.

As R^9 , the (Ip) is preferred, and further, the (Iq) is more preferred.

[0011]

In the compound represented by General formula (IV), preferred substituent groups for R^1 to R^3 and R^8 to R^9 are the same as the (Ia) to the (If) and the (Il) to the (Iq). Compounds of possible combinations thereof are preferred.

As each of R^1 and R^2 independently, the (Ia) is preferred, and further the (Ib) is more preferred, and further the (Ic) is most preferred.

As R^3 , the (Id) is preferred, and further the (Ie) is more preferred, and further the (If) is most preferred.

As R^8 , the (Il) is preferred, and further, the (Im) is more preferred, and further the (In) is further preferred, and the (Io) is most preferred.

As R^9 , the (Ip) is preferred, and further, the (Iq) is more preferred.

[0012]

In the compound represented by General formula (V), preferred substituent groups for R^{11} , R^{12} , and Y are shown by (It) to (Iy). Compounds of possible combinations thereof are preferred.

As R^{11} , (It) alkylene or alkenylene is preferred, and further (Iu) alkylene is more preferred, and (Iv) methylene is most preferred.

As R^{12} , (Iw) a hydrogen atom or alkyl is preferred, and further, (Ix) alkyl is more preferred.

As Y, (Iy) a halogen atom, optionally substituted alkylsulfonyl, or optionally substituted arylsulfonyl is preferred, and further (Iz) a halogen atom is more preferred.

[0013]

In the compound represented by General formula (VI), preferred substituent groups for R^1 to R^3 , R^8 to R^9 , R^{11} , and

R^{12} are the same as (Ia) to (If), (Il) to (Iq), and (It) to (Ix). Compounds of possible combinations thereof are preferred.

As each of R^1 and R^2 independently, (Ia) is preferred, and further, (Ib) is more preferred, and further, (Ic) is most preferred.

As R^3 , (Id) is preferred, and further (Ie) is more preferred, and further (If) is most preferred.

As R^8 , (Il) is preferred, and further (Im) is more preferred, and further (In) is further preferred, and further, (Io) is most preferred.

As R^9 , (Ip) is preferred, and further (Iq) is more preferred.

As R^{11} , (It) is preferred, and further (Iu) is more preferred, and (Iv) is most preferred.

As R^{12} , (Iw) is preferred, and further, (Ix) is more preferred.

[0014]

In the compound represented by General formula (VII), preferred substituent groups for R^1 to R^3 , R^8 to R^9 , and R^{11} are the same as (Ia) to (If), (Il) to (Iq), and (It) to (Iv). Compounds of possible combinations thereof are preferred.

As each of R^1 and R^2 independently, (Ia) is preferred, and further, (Ib) is more preferred, and further (Ic) is most preferred.

As R^3 , (Id) is preferred, and further (Ie) is more preferred, and further (If) is most preferred.

As R^8 , (Il) is preferred, and further, (Im) is more preferred, and further, (In) is further preferred, and further, (Io) is most preferred.

As R^9 , (Ip) is preferred, and further, (Iq) is more preferred.

As R^{11} , (It) is preferred, and further, (Iu) is more preferred, and (Iv) is most preferred.

[0015]

In the compound represented by General formula (VIII), preferred substituent groups for R^1 to R^3 , R^9 , and Z are the same as (Ia) to (If), (Ip) to (Iq), and shown by (IIa). Compounds of possible combinations thereof are preferred.

As each of R^1 and R^2 independently, (Ia) is preferred, and further (Ib) is more preferred, and further (Ic) is most preferred.

As R^3 , (Id) is preferred, and further, (Ie) is more preferred, and further, (If) is most preferred.

As R^9 , (Ip) is preferred, and further, (Iq) is more preferred.

As Z, (IIa) a halogen atom is preferred.

[0016]

In the compound represented by General formula (IX), preferred substituent groups for R^1 to R^3 , R^9 , and W are the same as (Ia) to (If), (Ip) to (Iq), and shown by (IIb) to (IIc). Compounds of possible combinations thereof are preferred.

As each of R^1 and R^2 independently, (Ia) is preferred, and further, (Ib) is more preferred, and further, (Ic) is most preferred.

As R^3 , (Id) is preferred, and further, (Ie) is more preferred, and further, (If) is most preferred.

As R^9 , (Ip) is preferred, and further, (Iq) is more preferred.

As W, (IIb) optionally substituted aryl or optionally substituted heteroaryl is preferred, and further, (IIc) optionally substituted heteroaryl is more preferred.

[0017]

In the compound represented by General formula (X), preferred substituent groups for R^1 to R^5 are the same as (Ia) to (If). Compounds of possible combinations thereof are preferred.

As each of R^1 , R^2 , R^4 , and R^5 independently, (Ia) is preferred, and further, (Ib) is more preferred, and further, (Ic) is most preferred.

As R^3 , (Id) is preferred, and further, (Ie) is more preferred, and further, (If) is most preferred.

[0018]

In the compound represented by General formula (XI), preferred substituent groups for X are shown by (Ir) to (Is). Compounds of possible combinations thereof are preferred.

As X, (Ir) is preferred, and further, (Is) a halogen atom is more preferred.

[0019]

In the compound represented by General formula (XII), preferred substituent groups for R^{15} to R^{17} are shown by (IID) to (IIf). Compounds of possible combinations thereof are preferred.

As each of R^{15} and R^{16} independently, (IID) a hydrogen atom or alkyl is preferred, and further, (IIE) a hydrogen atom is more preferred.

As R^{17} , (IIf) alkyl is preferred.

[0020]

In the compound represented by General formula (XIII), preferred substituent groups for R^{15} to R^{17} and X are the same as (Ir) to (Is) and (IID) to (IIf). Compounds of possible combinations thereof are preferred.

As each of R^{15} and R^{16} independently, (IID) is preferred, and further, (IIE) is more preferred.

As R^{17} , (IIf) is preferred.

As X, (Ir) is preferred, and further, (Is) a halogen atom

is more preferred.

[0021]

In the compound represented by General formula (XIV), preferred substituent groups for R^{15} to R^{16} and X are the same as (Ir) to (Is) and (IIId) to (IIe). Compounds of possible combinations thereof are preferred.

As each of R^{15} and R^{16} independently, (IIId) is preferred, and further, (IIe) is more preferred.

As X, (Ir) is preferred, and further, (Is) a halogen atom is more preferred.

[0022]

In the compound represented by General formula (XV), preferred substituent groups for R^{15} to R^{16} and X are the same as (Ir) to (Is) and (IIId) to (IIe). Compounds of possible combinations thereof are preferred.

As each of R^{15} and R^{16} independently, (IIId) is preferred, and further, (IIe) is more preferred.

As X, (Ir) is preferred, and further, (Is) a halogen atom is more preferred.

[0023]

In the compound represented by General formula (XVI), preferred substituent groups for R^{18} and X are the same as (Ir) to (Is), and shown by (IIg). Compounds of possible combinations thereof are preferred.

As R^{18} , (IIg) a hydrogen atom or alkyl is preferred, and further, (IIh) a hydrogen atom is more preferred.

As X, (Ir) is preferred, and further, (Is) a halogen atom is more preferred.

[0024]

In the compound represented by General formula (XVII), preferred substituent groups for R^{18} , R^{19} , and X are the same as (Ir) to (Is) and (IIg) to (IIh), and shown by (IIIi). Compounds of possible combinations thereof are preferred.

As R^{18} , (IIg) a hydrogen atom or alkyl is preferred, and further, (IIh) a hydrogen atom is more preferred.

As R^{19} , (IIIi) a halogen atom is preferred.

As X, (Ir) is preferred, and further, (Is) a halogen atom is more preferred.

[0025]

Further, in the compound represented by General formula (XVIII), preferred substituent groups for R^{18} , R^{20} , and X are the same as (Ir) to (Is) and (IIg) to (IIh), and shown by (IIj). Compounds of possible combinations thereof are preferred.

As R^{18} , (IIg) a hydrogen atom or alkyl is preferred, and further, (IIh) a hydrogen atom is more preferred.

As R^{20} , (IIj) a hydrogen atom or alkyl is preferred, and further, (IIIi) a hydrogen atom is more preferred.

As X, (Ir) is preferred, and further, (Is) a halogen atom

is more preferred.

[0026]

Further, in the compound represented by General formula (XIX), preferred substituent groups for R^{21} and X are the same as (Ir) to (Is), and shown by (IIk) to (III). Compounds of possible combinations thereof are preferred.

As R^{21} , (IIk) 5-membered heteroaryl is preferred, and further, (III) furyl, thienyl, oxazolyl, pyrazolyl, oxadiazolyl or thiadiazolyl is more preferred.

As X, (Ir) is preferred, and further, (Is) a halogen atom is more preferred.

Effect of the invention

[0027]

The present method is simple, requires short steps, and/or provides high yield, and is useful as an industrial method of N-phenyl-N'-phenylsulfonyl piperazine derivative and intermediates thereof.

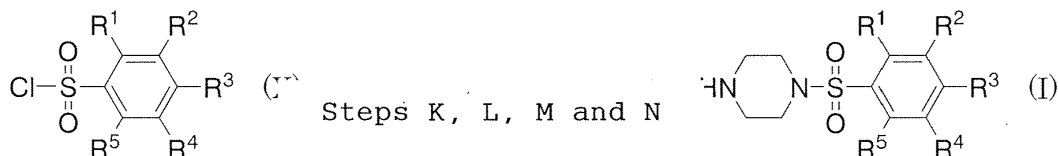
Best mode for carrying out the invention

[0028]

Production method A to Production method G will be illustrated by the following. When the compound has asymmetric center(s), racemates or optically active substances are also included.

Production method A

[Chemical formula 26]



wherein R^1 , R^2 , R^3 , R^4 , and R^5 are as defined in 1).

The starting compound represented by Formula (X) may be used a commercially available product.

Production method A is a method of producing the compound represented by Formula (I) from piperazine and the compound represented by Formula (X) through Step K, Step L, Step M, Step N and Step P.

Step K is a step of adding the compound represented by Formula (X) to a solution of piperazine.

Adding means addition or/and reaction.

Piperazine may be used in an amount of 1.5 to 5 molar equivalents, preferably 2.5 to 3.5 molar equivalents relative to the compound represented by (X).

As a solvent for solution of piperazine, dichloromethane,

chloroform, dioxane, benzene, toluene, hexane, ethyl acetate, tetrahydrofuran, acetonitrile, acetone, and N,N-dimethylformamide may be used alone or in combination. Tetrahydrofuran or toluene is preferred, and toluene is more preferred.

When the compound represented by Formula (X) is added, it may be added at 15°C to solvent reflux temperature, preferably at 45 to 80°C at once or in appropriate parts over 15 minutes to 2 hours, and the mixture is further allowed to react at 15°C to solvent reflux temperature, preferably at 45 to 80°C for 15 minutes to 2 hours.

When a solution containing the compound represented by Formula (X) is added, it may be added dropwise at 15°C to solvent reflux temperature, preferably at 45 to 80°C over 15 minutes to 2 hours, and the mixture is further allowed to react at 15°C to solvent reflux temperature, preferably at 45 to 80°C for 15 minutes to 2 hours.

When the solvent is toluene, it may be added dropwise preferably at 60 to 70°C preferably over 30 minutes to 1 hour and 30 minutes, and the mixture is further allowed to react preferably at 60 to 70°C preferably for 30 minutes to 1 hour and 30 minutes.

Step L is a step of adding water to a reaction liquid and extracting with an organic solvent.

Step L is preferably conducted at 45 to 80°C. When the solvent is toluene, the step is preferably conducted at 55 to 65°C.

As an organic solvent, toluene, ethyl acetate, dichloromethane, chloroform, and hexane may be used. Toluene is preferred.

Step M is a step of making the organic phase obtained in Step L acidic by adding an acid, and extracting it with water.

As the acid, hydrochloric acid, hydrobromic acid, sulfuric acid, or nitric acid may be used. Hydrochloric acid is preferred, 1 to 4 mol/L of hydrochloric acid is more preferred, and 2 mol/L of hydrochloric acid is most preferred.

Step M is preferably conducted at 45 to 80°C. When the solvent is toluene, the step is preferably conducted at 55 to 65°C.

Step N is a step of making the aqueous phase obtained in Step M alkaline by adding a base, and causing precipitation of crystals.

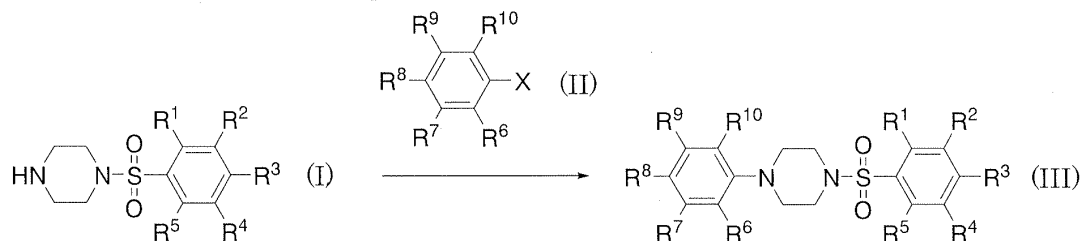
As the base, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, or aqueous solution thereof may be used. Sodium hydroxide aqueous solution is preferred, 1 to 4 mol/L of sodium hydroxide aqueous solution is more preferred, and 2 mol/L of sodium hydroxide aqueous solution is most preferred.

In Step N, it is preferred to make alkaline by adding a base 45 to 80°C. When toluene is used as the solvent, the step is preferred to conduct at 55 to 65°C. It is preferred to cause precipitation of crystals at 15 to 30°C.

[0029]

Production method B

[Chemical formula 27]



wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , and X are as defined in 1).

Production method B is a method of producing a compound represented by Formula (III) by reacting the compound represented by Formula (I) with the compound represented by Formula (II) in a solvent in the presence of a palladium compound, an organic phosphorus compound, and a base.

Also it may be conducted in a solvent, in the presence of a palladium compound, an organic phosphorus compound, a base, and a sulfinate.

The compound represented by Formula (I) obtained in Production method A may be used.

The compound represented by Formula (II) may be used in an amount of 0.5 to 2 molar equivalents, preferably 0.75 to 1.5 molar equivalents, relative to the compound represented by Formula (I).

The palladium compound may be used in an amount of 0.002 to 0.2 molar equivalents, preferably 0.002 to 0.1 molar equivalents, relative to the compound represented by Formula (I).

The organic phosphorus compound may be used in an amount of 0.002 to 0.2 molar equivalents, preferably 0.002 to 0.1 molar equivalents, relative to the compound represented by Formula (I).

The organic phosphorus compound may be used in an amount of 1 to 8 equivalents, preferably 1 to 2 equivalents, relative to the palladium compound.

The base may be used in an amount of 0.8 to 5 molar equivalents, preferably 2 to 3 molar equivalents, relative to the compound represented by Formula (I).

Reaction temperature may be 15°C to solvent reflux temperature.

Reaction time may be 1 to 24 hours.

As the palladium compound, palladium acetate, palladium chloride, tris(dibenzylidene acetone)dipalladium, bis(dibenzylidene acetone)palladium, tetrakis(triphenylphosphine)palladium, [1,1'-bis(diphenylphosphino)ferrocene]dichloro palladium, bis(tri-ortho-tolylphosphine)palladium dichloride, bis(triphenylphosphine)palladium dichloride, acetylacetonato palladium, palladium carbon, dichlorobis(acetonitrile)palladium, bis(benzonitrile)palladium chloride, or (1,3-diisopropyl imidazole-2-ylidene)(3-chloropyridyl)palladium dichloride may be used. Palladium acetate is preferred.

As the solvent, dichloromethane, chloroform, dioxane, benzene, toluene, hexane, ethyl acetate, tetrahydrofuran, acetonitrile, acetone, and N,N-dimethylformamide may be used alone or in combination. Toluene is preferred.

As the organic phosphorus compound, triphenylphosphine, tri(ortho-tolyl)phosphine, 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthine, tri(tert-butyl)phosphine, di(tert-butyl)methylphosphine, diadamantylbutyl phosphine, 1,1'-bis(diphenylphosphino)ferrocene, 1,2-bis(diphenylphosphino)ethane, 1,3-bis(diphenylphosphino)propane, 1,4-bis(diphenylphosphino)butane, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, tricyclohexylphosphine, diphenylcyclohexylphosphine, dicyclohexylphenylphosphine, diphenylphosphinoferrocene, 2-(di-tert-butylphosphino)biphenyl, tri(tert-butyl)phosphonium tetraphenyl borate, or di(tert-butyl)methyl phosphonium tetraphenyl borate may be used. Diadamantylbutyl phosphine, or tri(tert-butyl)phosphine is preferred.

Also bis(tri-tert-butylphosphine)palladium, dichlorobis(triphenylphosphine)palladium, dichlorobis(tricyclohexylphosphine)palladium, or dichlorobis(tri-ortho-tolylphosphine)palladium which is a complex of a palladium compound and the organic phosphorus compound may be used.

As the base, sodium tert-butoxide, sodium tert-pentoxide, cesium carbonate, sodium carbonate, potassium carbonate, and aqueous solutions thereof may be used. Sodium tert-pentoxide is preferred.

As the sulfinato, sodium methane sulfinato, sodium benzene sulfinato, or sodium para-toluene sulfinato may be used. Sodium para-toluene sulfinato is preferred.

As a method of adding the compound represented by Formula

(I), the compound represented by Formula (II), the palladium compound, the organic phosphorus compound, and the base to the solvent, Method a, Method b, and Method c may be used.

Method a is a method of adding all of the compound represented by Formula (I), the compound represented by Formula (II), the palladium compound, the organic phosphorus compound, and the base, adding sulfinate as necessary, and causing reaction at 60°C to solvent reflux temperature.

Method b is a method including Step A of adding the compound represented by Formula (I), the palladium compound, the organic phosphorus compound, and the base, and sulfinate if necessary, and causing reaction at 15 to 30°C for 15 minutes to 2 hours, and then Step B of adding the compound represented by Formula (II) and causing reaction at 60°C to solvent reflux temperature.

Method c is a method including Step C of adding the palladium compound and the organic phosphorus compound to cause reaction at 15 to 30°C for 15 minutes to 2 hours, Step D of adding the compound represented by Formula (I) and the base, and sulfinate if necessary, and then Step B of adding the compound represented by Formula (II) to cause reaction at 60°C to solvent reflux temperature.

Method b and Method c are preferred, and Method c is more preferred.

Method b realizes more stable reaction yield than Method a.

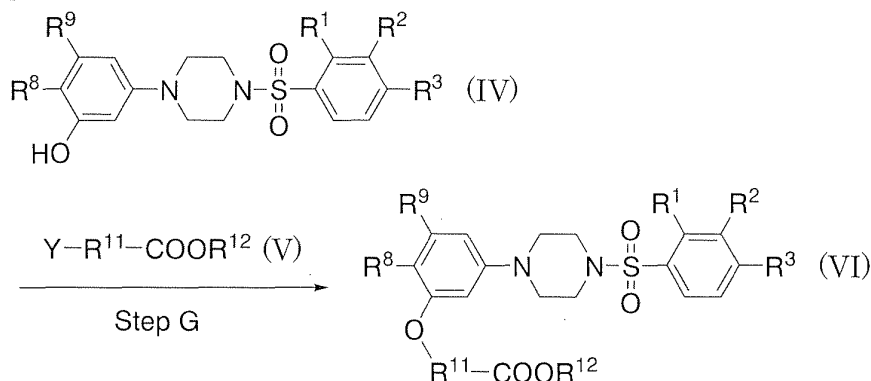
Method c realizes more stable reaction yield in mass production than Method b.

The obtained compound may be isolated and purified by using the generally used method such as silica gel chromatography, recrystallization, or/and distillation. Also, it may be used in the next reaction without being purified.

[0030]

Production method C

[Chemical formula 28]



wherein R¹, R², R³, R⁸, and R⁹ are as defined in 1); R¹¹ and

○ R¹² are as defined in 12).

Production method C is a method of producing the compound represented by Formula (VI) by reacting the compound represented by Formula (IV) obtained in Production method B with the compound represented by Formula (V) in a solvent in the presence of a base.

The compound represented by Formula (V) may be used in an amount of 0.8 to 2 molar equivalents, preferably 1.2 to 1.6 molar equivalents, relative to the compound represented by Formula (IV).

The base may be used in an amount of 1 to 3 molar equivalents, preferably 1.5 to 2.5 molar equivalents, relative to the compound represented by Formula (IV).

Reaction temperature may be 5°C to solvent reflux temperature, preferably 75 to 85°C.

Reaction time is preferably 30 minutes to 24 hours.

If necessary, potassium iodide may be used in an amount of 0.05 to 0.3 molar equivalents, relative to the compound represented by Formula (V).

As the solvent, dichloromethane, chloroform, dioxane, benzene, toluene, hexane, ethyl acetate, tetrahydrofuran, acetonitrile, acetone, N-methylpyrrolidone, and N,N-dimethylformamide may be used alone or in combination. N,N-dimethylformamide is preferable.

As the base, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydroxide, potassium hydroxide, or cesium hydroxide may be used. Potassium carbonate or cesium carbonate is preferred.

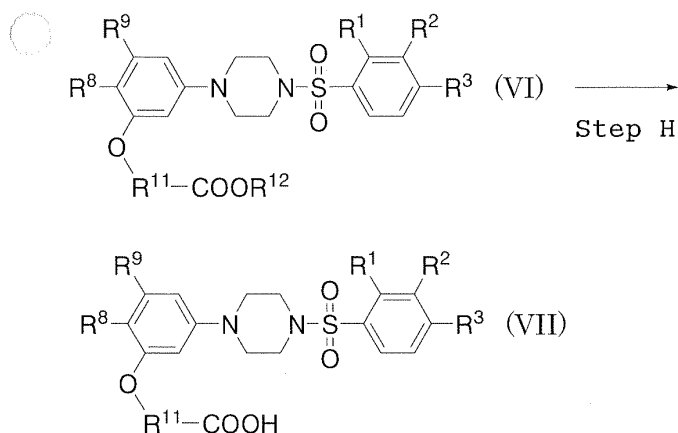
When R¹² is a hydrogen atom, it is not necessary to conduct Production method D, however, when R¹² is alkyl, it is possible to obtain the compound represented by Formula (VI) by hydrolyzing the compound represented by Formula (VI).

The obtained compound may be isolated and purified by using the generally used method such as silica gel chromatography, recrystallization, or/and distillation. Also, it may be used in the next reaction without being purified.

[0031]

Production method D

[Chemical formula 29]



wherein R^1 , R^2 , R^3 , R^8 , and R^9 are as defined in 1); R^{11} and R^{12} are as defined in 12).

Production method D is a method of producing the compound represented by Formula (VI) by hydrolyzing the compound represented by Formula (VI) in a solvent in the presence of a base.

The base may be used in an amount of 1 to 10 molar equivalents, preferably 2 to 4 molar equivalents, relative to the compound represented by Formula (VI).

Reaction temperature may be 5°C to solvent reflux temperature, preferably 55 to 65°C .

Reaction time is preferably 30 minutes to 24 hours.

As the solvent, dioxane, benzene, toluene, hexane, tetrahydrofuran, methanol, ethanol, *N,N*-dimethylformamide and water may be used alone or in combination. Mixed solvent of methanol/tetrahydrofuran/water is preferred.

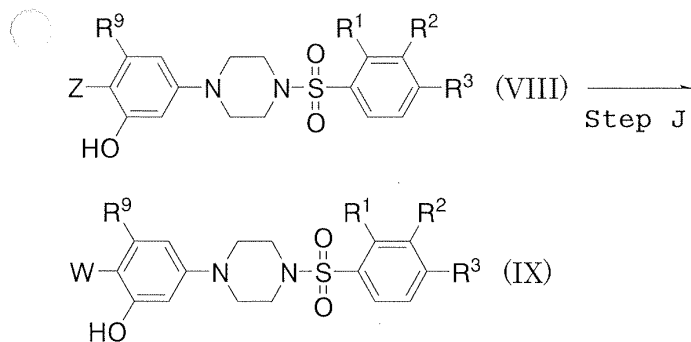
As the base, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydroxide, potassium hydroxide, lithium hydroxide, and aqueous solutions thereof may be used. Sodium hydroxide aqueous solution is preferred.

The obtained compound may be isolated and purified by using the generally used method such as silica gel chromatography, recrystallization, or/and distillation. Also, it may be used in the next reaction without being purified.

[0032]

Production method E

[Chemical formula 30]



wherein R^1 , R^2 , R^3 , R^8 , and R^9 are as defined in 1); R^{11} and R^{12} are as defined in 12),

Production method E is a method of producing the compound represented by Formula (IX) by reacting the compound represented by Formula (VIII) obtained in Production method B with the organic boronic acid in a solvent.

The organic boronic acid may be used in an amount of 0.5 to 3 molar equivalents, preferably 0.8 to 1.5 molar equivalents, relative to the compound represented by Formula (VIII).

Reaction temperature is preferably 30°C to solvent reflux temperature.

Reaction time is preferably 30 minutes to 24 hours.

It may be conducted in the presence of the palladium compound and the organic phosphorus compound.

As the palladium compound, the above-mentioned palladium compound may be used. Palladium acetate is preferred.

As the organic phosphorus compound, the above-mentioned organic phosphorus compound may be used. Triphenylphosphine is preferred.

As a complex of palladium compound and organic phosphorus compound, the complex of palladium compound and organic phosphorus compound as described in the Production method B may be used.

As the organic boronic acid, arylboronic acid, and heteroaryl boronic acid may be used. Furyl boronic acid and thiophene boronic acid are preferred.

As the solvent, dioxane, benzene, toluene, hexane, tetrahydrofuran, methanol, ethanol, and N,N-dimethylformamide may be used alone or in combination. Dioxane is preferred.

As the base, sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, and aqueous solutions thereof may be used. Sodium carbonate aqueous solution is preferred.

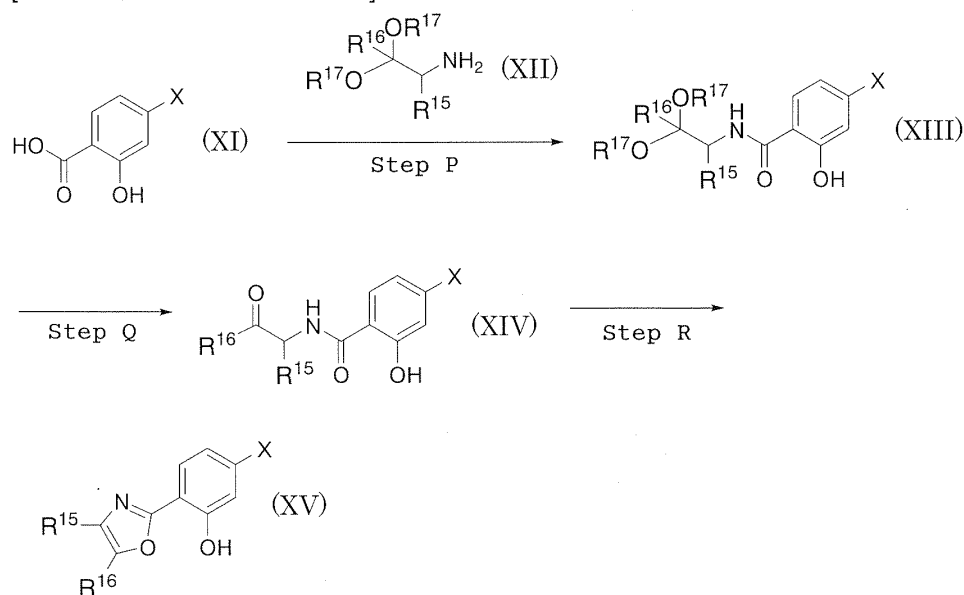
The obtained compound may be isolated and purified by using the generally used method such as silica gel chromatography, recrystallization, or/and distillation.

Also, it may be used in the next reaction without being purified.

[0033]

Production method F

[Chemical formula 31]



wherein X is as defined in 1); R^{15} , R^{16} , and R^{17} are as defined in 19).

Production method F is a method of producing the compound represented by Formula (XV) including Step P of reacting the compound represented by Formula (XI) or its reactive derivative with the compound represented by Formula (XII) in a solvent to obtain the compound represented by Formula (XIII), Step Q of reacting the compound represented by Formula (XIII) obtained in Step P with an acid, to obtain the compound represented by Formula (XIV), and Step R of closing ring of the compound represented by Formula (XIV) obtained in Step Q.

In Step P, the compound represented by Formula (XII) may be used in an amount of 0.5 to 3 molar equivalents, preferably 0.8 to 1.5 molar equivalents, relative to the compound represented by Formula (XI).

As the solvent, dioxane, benzene, toluene, hexane, tetrahydrofuran, and ethyl acetate may be used alone or in combination.

Reaction temperature is preferably 15° C to solvent reflux temperature.

Reaction time is preferably 30 minutes to 24 hours.

When the compound represented by Formula (XI) is used, N,N'-dicyclohexylcarbodiimide may be used as a condensing agent. When the reactive derivative of the compound represented by Formula (XI) is an acid chloride derivative,

it may be reacted with thionyl chloride in a solvent, and then, the obtained compound may be reacted with the compound represented by Formula (XII) in the presence of a base.

As the base, triethylamine is preferred.

In Step Q, the compound represented by Formula (XIII) obtained in Step P may be caused to react with an acid to obtain the compound represented by Formula (XIV).

The acid may be used in an amount of 2 to 50 molar equivalents, relative to the compound represented by Formula (XIII).

Reaction temperature is preferably 30°C to solvent reflux temperature.

Reaction time is preferably 30 minutes to 24 hours.

As the solvent, dioxane, benzene, toluene, hexane, tetrahydrofuran, N,N-dimethylformamide, and acid may be used alone or in combination.

As the acid, hydrochloric acid, hydrogen bromide, sulfuric acid, nitric acid, and para-toluene sulfonic acid may be used.

In Step R, the compound represented by Formula (XV) may be obtained by closing ring of the compound represented by Formula (XIV) obtained in Step Q.

It may be conducted in the presence of hexachloroethane, triphenylphosphine, and base.

Hexachloroethane may be used in an amount of 1 to 5 molar equivalents, relative to the compound represented by Formula (XIV).

As the base, triethylamine is preferred, and may be used in an amount of 2 to 10 molar equivalents, relative to the compound represented by Formula (XIV).

Reaction temperature is preferably 30°C to solvent reflux temperature.

Reaction time is preferably 30 minutes to 24 hours.

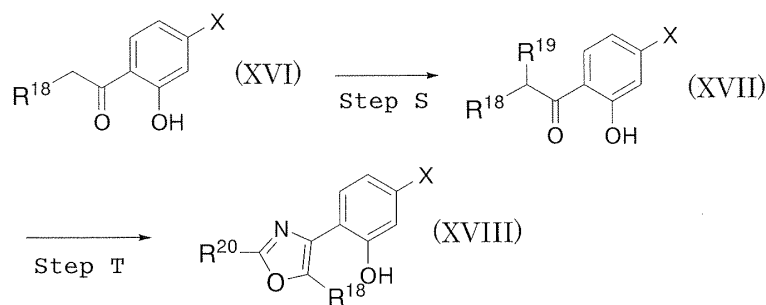
As the solvent, dioxane, benzene, toluene, hexane, tetrahydrofuran, N,N-dimethylformamide, and acetonitrile may be used alone or in combination.

The obtained compound may be isolated and purified by using the generally used method such as silica gel chromatography, recrystallization, or/and distillation. Also, it may be used in the next reaction without being purified.

[0034]

Production method G

[Chemical formula 32]



wherein X is as defined in 1); R¹⁸, R¹⁹, and R²⁰ are as defined in 20).

Production method G is a method of producing the compound represented by Formula (XVIII) including Step S of halogenating the compound represented by Formula (XVI) in a solvent to obtain the compound represented by Formula (XVII), and Step T of reacting the compound represented by Formula (XVII) obtained in Step S with the compound represented by the formula: R²⁰COONH₄.

In Step S, halogen may be used in an amount of 0.5 to 2 molar equivalents, preferably 0.8 to 1.2 molar equivalents, relative to the compound represented by Formula (XVI).

Reaction temperature is preferably 10 to 50°C.

Reaction time is preferably 30 minutes to 24 hours.

As the halogen, chlorine and bromine may be used. Bromine is preferred.

As the solvent, dichloromethane, chloroform, dioxane, benzene, toluene, hexane, tetrahydrofuran, and N,N-dimethylformamide may be used alone or in combination.

In Step T, the compound represented by the formula R²⁰COONH₄ may be used in an amount of 1 to 8 molar equivalents, preferably 1.5 to 6 molar equivalents, relative to the compound represented by Formula (XVII).

Reaction temperature is preferably 30°C to solvent reflux temperature.

Reaction time is preferably 30 minutes to 24 hours.

As the compound represented by the formula: R²⁰COONH₄, ammonium formate or ammonium acetate is preferred.

As the solvent, dioxane, benzene, toluene, hexane, tetrahydrofuran, methanol, ethanol, N,N-dimethylformamide, carboxylic acid represented by the formula: R²⁰COOH, and water may be used alone or in combination. Carboxylic acid represented by the formula: R²⁰COOH is preferred.

The obtained compound may be isolated and purified by using the generally used method such as silica gel chromatography, recrystallization, or/and distillation. Also, it may be used in the next reaction without being purified.

The compounds represented by the above formulas such as

the compound represented by the above Formula (XV) and the compound represented by the above Formula (XVIII) are important intermediates of N-phenyl-N'-phenylsulfonyl piperazine derivative.

X-ray diffraction patterns of crystals of the compounds represented by Formula (I) to Formula (XVIII) generated in the production methods can be obtained by powder X-ray diffraction.

Measuring condition of powder X-ray diffraction includes tube lamp CuK α ray, tube voltage of 40 Kv, and tube current of 40 mA. Crystals are characterized by respective diffraction angle or surface separation ($d\sin\theta = n\lambda$ (n is an integer, d is surface separation (unit: angstrom), θ is diffraction angle (unit: degree))).

[0035]

In the present specification, "solvate" includes, for example, solvate with organic solvent, hydrate and the like. When solvate with organic solvent is formed, it may be coordinated with an arbitrary number of organic solvent molecules. When hydrate is formed, it may be coordinated with an arbitrary number of water molecules. Hydrate is preferred.

By reference to "the present compound", its pharmaceutically acceptable salt, or its solvate is also included. For example, salts with alkaline metal (lithium, sodium, potassium and the like), alkaline earth metal (magnesium, calcium and the like), ammonium, organic base and amino acid, or salts with inorganic acid (hydrochloric acid, hydrogen bromide, phosphoric acid, sulfuric acid and the like), and organic acid (acetic acid, citric acid, maleic acid, fumaric acid, benzenesulfonic acid, para-toluenesulfonic acid and the like) are listed. These salts may be formed by commonly used methods.

The present compound is not limited to a particular isomer, but includes all possible isomers and racemates.

Examples

[0036]

The present invention is illustrated in more detail below by Examples and Test Examples, however, the present invention is not limited thereto.

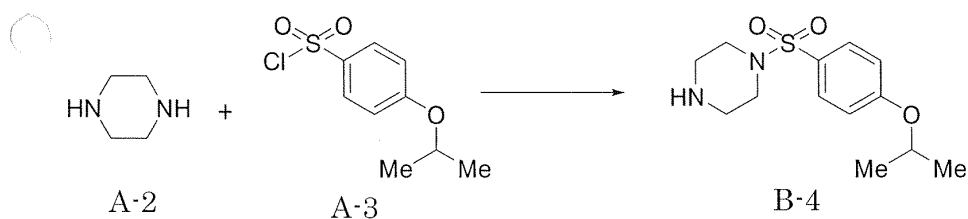
In Examples, the following abbreviations are used.

Me: methyl

DMSO: dimethylsulfoxide

MeOH: methanol

Reference Example 1 Synthesis of Intermediate
4-(isopropoxybenzenesulfonyl)piperazine (B-4)
[Chemical formula 33]



To a solution of piperazine (A-2, 22.7 g, 89.5 mmol) in tetrahydrofuran (180 mL), a solution of 4-isopropoxybenzenesulfonyl chloride (A-3, 21.0 g, 89.5 mmol) in tetrahydrofuran (30 mL) was added dropwise at room temperature over 30 minutes. The reaction liquid was stirred at room temperature for 30 minutes, then added with water (200 mL), extracted with ethyl acetate, and the organic phase was washed with saline. The organic phase was extracted with 2 mol/L of hydrochloric acid (100 mL). After filtering off insoluble substances, the aqueous phase was washed with ethyl acetate, and made into alkaline with 2 mol/L of sodium hydroxide aqueous solution. Precipitated crystals were dissolved in ethyl acetate, and dried over sodium sulfate. The solvent was distilled off under reduced pressure to obtain 4-(isopropoxybenzenesulfonyl)piperazine (B-4, 19.9 g, yield 78%) as white crystals.

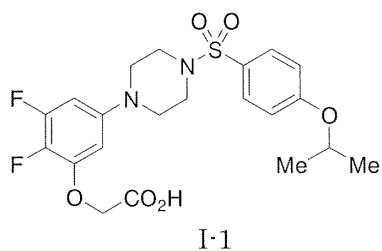
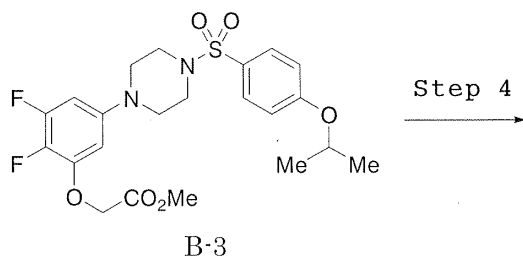
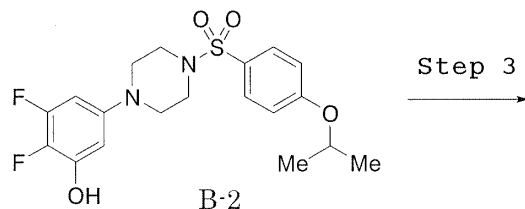
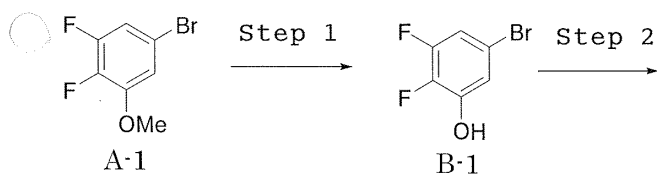
Melting point: 133.6 to 133.7°C

¹H-NMR(CDCl₃) δppm: 1.37 (d, J = 6.0 Hz, 6H), 2.95 (m, 8H), 4.63 (m, 1H), 6.94 (d, J = 8.7 Hz, 2H), 7.65 (d, J = 8.7 Hz, 2H).

Example 1 Synthesis of

{2,3-difluoro-5-[4-(4-isopropoxybenzenesulfonyl)-piperazine-1-yl]-phenoxy}-acetic acid (I-1)

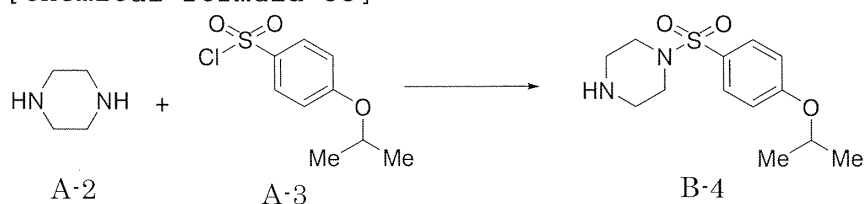
[Chemical formula 34]



Synthesis of Intermediate

N-(4-isopropoxybenzenesulfonyl)piperazine (B-4)

[Chemical formula 35]



To a solution of piperazine (A-2, 44.0 g, 511 mmol) in toluene (280 mL), a solution of 4-isopropoxybenzenesulfonyl chloride (A-3, 40.0 g, 170 mmol) in toluene (126 mL) was added dropwise at 65°C over 1 hour. After stirring the reaction liquid at 65°C for 1 hour, water (196 mL) was added, liquid separation was conducted at 60°C, and then the organic phase was washed with saline. The organic phase was extracted at 60°C

with 2 mol/L of hydrochloric acid (212 mL). The aqueous phase was washed with toluene, and made into alkaline by adding 2 mol/L of sodium hydroxide aqueous solution at 60°C. After cooling to room temperature, the generated precipitate was collected by filtration to obtain 4-(isopropoxybenzenesulfonyl)piperazine (B-4, 44.7 g, yield 92%) as white crystals.

Data of melting point and NMR coincided with those of compound (B-4) obtained in Reference Example 1.

Result of powder X-ray diffraction is shown in Table 1 and Fig. 1.

Diffraction angles of major peaks: $2\theta = 5.0, 10.2, 14.6, 19.0, 23.5$ degrees

[Table 1]

Angle 2-Theta °	d value Angstrom	Intensity %
5.0	17.71	99.3
10.2	8.70	93.6
14.3	6.21	35.0
14.6	6.05	64.4
15.2	5.83	18.2
19.0	4.66	100.0
20.3	4.38	21.2
21.1	4.21	15.4
22.8	3.90	13.0
23.2	3.83	13.2
23.5	3.79	46.2
24.3	3.66	7.3
25.3	3.52	20.7
26.3	3.38	13.7
27.0	3.29	22.3
29.4	3.04	9.3
31.1	2.87	9.0
31.5	2.84	8.4
32.3	2.77	8.7
32.8	2.73	6.6
33.2	2.70	6.8
34.3	2.62	6.1
35.1	2.56	6.7
35.8	2.51	15.4
36.1	2.48	7.2
37.3	2.41	7.0

Step 1 Synthesis of 2,3-difluoro-5-bromophenol (B-1)

A solution of 2,3-difluoro-5-bromoanisole (A-1, 1.15 g) in dichloromethane (5 mL) was added dropwise with 1 mol/L of boron tribromide-methylene chloride solution (7.5 mL) under ice cooling, and stirred for 2 hours under ice cooling and for 2 hours at room temperature. The reaction liquid was poured into ice water, added with concentrated hydrochloric acid and

stirred overnight. The reaction liquid was extracted with ethyl acetate, and the organic phase was extracted with sodium hydroxide aqueous solution. The aqueous phase was made into acidic with diluted hydrochloric acid, and extracted with ethyl acetate. After drying the organic phase over magnesium sulfate, the solvent was distilled off under reduced pressure to obtain 2,3-difluoro-5-bromophenol (B-1, 850 mg, yield 81%) as an oily substance.

$^1\text{H-NMR}(\text{CDCl}_3)\delta\text{ppm}$: 5.36 (d, $J = 3.6\text{ Hz}$, 1H), 6.91 (ddd, $J = 9.3\text{ Hz}$, 6.3 Hz, 2.4 Hz, 1H), 6.97 (ddd, $J = 6.6\text{ Hz}$, 2.4 Hz, 2.4 Hz, 1H).

Step 2 Synthesis of

2,3-difluoro-5-[4-(4-isopropoxybenzenesulfonyl)-piperazine-1-yl]-phenol (B-2)

Under argon gas flow, a suspension of the synthesized intermediate 4-(para-isopropoxybenzenesulfonyl)piperazine (B-4, 1.14 g), palladium acetate (22 mg), sodium para-toluene sulfinate (36 mg), and sodium tert-pentoxide (1.11 g) in toluene (7 mL) was added with diadamantylbutyl phosphine (72 mg) and stirred at room temperature for 30 minutes. Under ice cooling, the reaction suspension was added with 2,3-difluoro-5-bromophenol obtained in Step 1 (B-1, 700 mg) and toluene (3 mL), and refluxed for 2 hours with heating. The reaction liquid was cooled to room temperature, added with 2 mol/L of hydrochloric acid (7 mL), and extracted with toluene. The organic phase was washed with water and saline, and then dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the obtained residue was purified by column chromatography to obtain 2,3-difluoro-5-[4-(4-isopropoxybenzenesulfonyl)-piperazine-1-yl]-phenol (B-2, 1.28 g, yield 93%) as colorless amorphous.

$^1\text{H-NMR}(\text{CDCl}_3)\delta\text{ppm}$: 1.37 (d, $J = 6.0\text{ Hz}$, 6H), 3.14 (m, 8H), 4.63 (qq, $J = 6.0\text{ Hz}$, 6.0 Hz, 1H), 5.48 (brs, 1H), 6.08 - 6.29 (m, 2H), 6.97 (d, $J = 9.3\text{ Hz}$, 2H), 7.69 (d, $J = 9.3\text{ Hz}$, 2H).

Step 3 Synthesis of methyl

{2,3-difluoro-5-[4-(4-isopropoxybenzenesulfonyl)-piperazine-1-yl]-phenoxy}- acetate (B-3)

A solution of

2,3-difluoro-5-[4-(4-isopropoxybenzenesulfonyl)-piperazine-1-yl]-phenol obtained in Step 2 (B-2, 412 mg) in *N,N*-dimethylformamide (5 mL) was added with potassium carbonate (276 mg), potassium iodide (17 mg), and bromomethyl acetate ester (189 μL), and stirred at room temperature for 2 hours. The reaction liquid was diluted with ethyl acetate, washed with diluted hydrochloric acid, water, and saline, and

dried over magnesium sulfate. The solvent was distilled off under reduced pressure, and the obtained residue was purified by column chromatography to obtain methyl {2,3-difluoro-5-[4-(4-isopropoxybenzenesulfonyl)-piperazine-1-yl]-phenoxy}-acetate (B-3, 452 mg, yield 93%) as pale purple solid.

¹H-NMR(CDCl₃)δppm: 1.38 (d, J = 6.0 Hz, 6H), 3.14 (s, 8H), 3.79 (s, 3H), 4.60-4.68 (m, 3H), 6.26 (brs, 1H), 6.30 - 6.37 (m, 1H), 6.98 (d, J = 8.7 Hz, 2H), 7.69 (d, J = 8.7 Hz, 2H).

Step 4 Synthesis of

{2,3-difluoro-5-[4-(4-isopropoxybenzenesulfonyl)-piperazine-1-yl]-phenoxy}-acetic acid (I-1)

A mixed solution of methyl

2,3-difluoro-5-[4-(4-isopropoxybenzenesulfonyl)-piperazine-1-yl]-phenoxy acetate obtained in Step 3 (B-3, 367 mg) in methanol (3 mL)-tetrahydrofuran (3 mL) was added with 2 mol/L of sodium hydroxide aqueous solution (1.14 mL), and stirred at room temperature for 2 hours. The reaction liquid was added with diethylether, and extracted with water. The aqueous phase was made into pH4 with diluted hydrochloric acid, and extracted with ethyl acetate. After drying the organic phase over magnesium sulfate, the solvent was distilled off under reduced pressure to obtain

{2,3-difluoro-5-[4-(4-isopropoxybenzenesulfonyl)-piperazine-1-yl]-phenoxy}-acetic acid (I-1, 265 mg, yield 74%) as colorless crystals.

¹H-NMR(CDCl₃)δppm: 1.38 (d, J = 6.0 Hz, 6H), 3.00 (brs, 1H), 3.15 (s, 8H), 4.64 (qq, J = 6.0 Hz, 6.0 Hz, 1H), 4.71 (s, 2H), 6.27 (brs, 1H), 6.32 - 6.39 (m, 1H), 6.98 (d, J = 8.7 Hz, 2H), 7.69 (d, J = 8.7 Hz, 2H).

Result of powder X-ray diffraction is shown in Table 2 and Fig. 2.

Diffraction angles of major peaks: 2θ = 9.4, 15.9, 16.1, 17.9, 21.0, 21.2 degrees

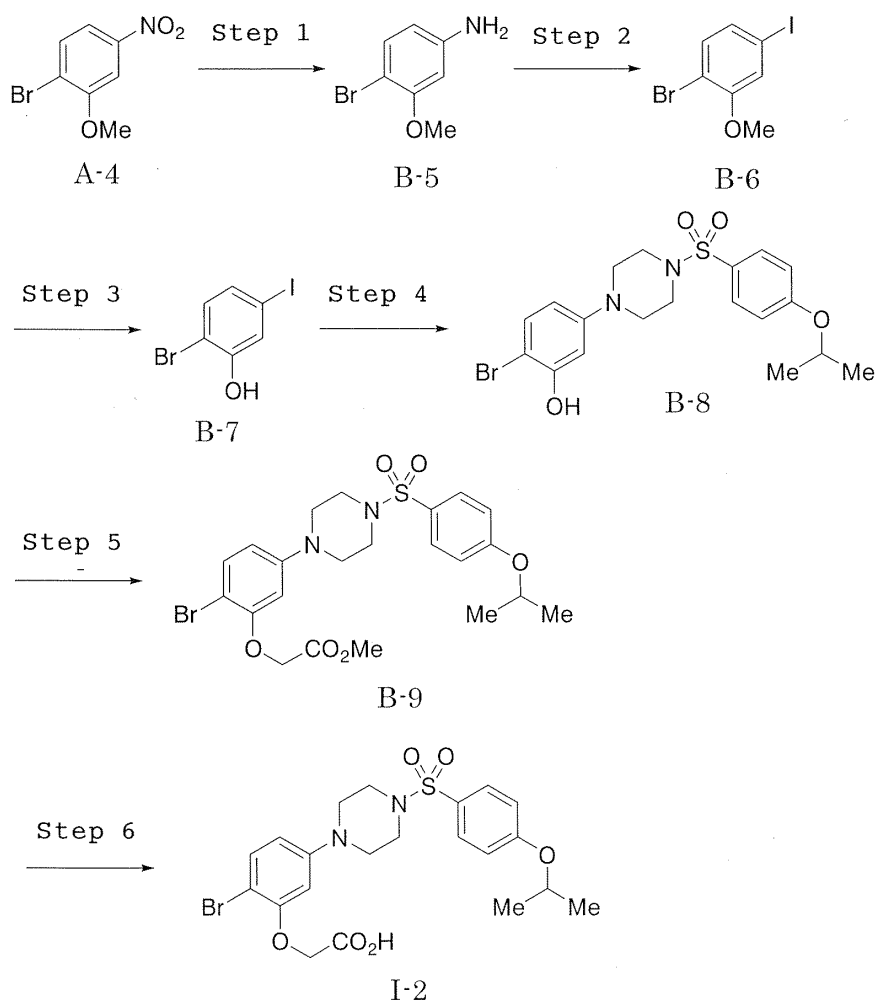
[Table 2]

Angle 2-Theta °	d value Angstrom	Intensity %
9.4	9.45	100.0
11.8	7.47	14.8
14.4	6.16	11.9
15.9	5.57	96.8
16.1	5.49	67.5
17.2	5.15	51.4
17.9	4.96	63.7
18.6	4.77	42.1
19.9	4.45	17.1
20.5	4.32	40.1
21.0	4.23	75.9
21.2	4.18	61.4
21.8	4.07	53.8
22.3	3.98	31.7
22.7	3.92	17.5
23.5	3.78	50.3
24.3	3.65	37.4
25.5	3.49	12.7
26.7	3.34	10.9
27.5	3.25	18.4
28.2	3.16	16.8
29.1	3.07	19.4
30.0	2.98	10.5
30.5	2.93	21.8
30.9	2.89	27.9
31.2	2.86	23.4
31.6	2.83	16.5
32.1	2.78	11.0
33.5	2.67	10.9
34.0	2.64	18.5
34.3	2.61	15.9
34.9	2.57	12.7
35.4	2.53	14.5
36.4	2.47	12.8
36.9	2.44	13.1
39.4	2.29	9.9

Example 2 Synthesis of

{2-bromo-5-[4-(4-isopropoxybenzenesulfonyl)-piperazine-1-yl]-phenoxy}-acetic acid (I-2)

[Chemical formula 36]



Step 1 Synthesis of 2-bromo-5-aminoanisole (B-5)

A solution of 2-bromo-5-nitroanisole (A-4, 11.6 g, 50.0 mmol) in methanol (150 mL) was added with iron (5.59 g, 100 mmol), ammonium chloride (5.35 g, 100 mmol), and water (75.0 mL) and stirred at 100°C for 6 hours. The reaction liquid was filtered through Celite, and the filtrate was diluted with water, and then added with diluted hydrochloric acid to be acidic. After washing with diethylether, the aqueous phase was added with sodium hydroxide aqueous solution to make it alkaline. The aqueous phase was extracted with ethyl acetate, dried over anhydrous magnesium sulfate, and then the solvent was distilled off under reduced pressure to obtain 2-bromo-5-aminoanisole (B-5, 4.20 g, yield 42%) as brown powder.

$^1\text{H-NMR}(\text{CDCl}_3)\delta\text{ppm}$: 3.8 (brs, 2H), 3.84 (s, 3H), 6.19 (dd, $J = 8.7 \text{ Hz}, 2.4 \text{ Hz}, 1\text{H}$), 6.26 (d, $J = 2.4 \text{ Hz}, 1\text{H}$), 7.25 (d, $J = 8.7 \text{ Hz}, 1\text{H}$).

Step 2 Synthesis of 2-bromo-5-iodoanisole (B-6)

2-bromo-5-aminoanisole obtained in Step 1 (B-5, 4.12 g, 20.4 mmol) was added with concentrated hydrochloric acid (32.0 mL), and added dropwise with a solution of nitric acid/sodium (3.37 g, 48.8 mmol) in water (10.0 mL) over 20 minutes under ice cooling. Further, a solution of potassium iodide (9.96 g, 61.0 mmol) in water (10.0 mL) was added dropwise over 20 minutes. The reaction liquid was stirred under ice cooling for 1 hour, and then extracted with diethylether. The organic phase was washed with an aqueous solution of thiosodium sulfate and water, and then dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure to obtain 2-bromo-5-iodoanisole (B-6, 5.00 g, yield 65%).

$^1\text{H-NMR}(\text{CDCl}_3)\delta\text{ppm}$: 3.88 (s, 3H), 7.17 (m, 2H), 7.22 (m, 1H).

Step 3 Synthesis of 2-bromo-5-iodophenol (B-7)

A solution of 2-bromo-5-iodoanisole obtained in Step 2 (B-6, 5.00 g, 16.0 mmol) in methylene chloride (10.0 mL) was added dropwise with 1M boron tribromide-methylene chloride solution (32.0 mL) over 30 minutes under ice cooling. After stirring for 1 hour under ice cooling, and for 3 hours at room temperature, the reaction liquid was poured into ice water, added with concentrated hydrochloric acid, and stirred for 1 hour at room temperature. Following extraction with diethylether, the organic phase was extracted with sodium hydroxide aqueous solution. The aqueous phase was added with diluted hydrochloric acid to make acidic, and extracted with ethyl acetate. The organic phase was washed with water, and then dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure to obtain 2-bromo-5-iodophenol (B-7, 4.30 g, yield 90%) as crystals.

$^1\text{H-NMR}(\text{CDCl}_3)\delta\text{ppm}$: 5.48 (s, 1H), 7.14 (d, $J = 1.8\text{ Hz}$, 1H), 7.15 (s, 1H), 7.37 (d, $J = 1.8\text{ Hz}$, 1H).

Result of powder X-ray diffraction is shown in Table 3 and Fig. 3.

Diffraction angles of major peaks: $2\theta = 17.9, 27.3, 28.6$ degrees [Table 3]

Angle 2-Theta °	d value Angstrom	Intensity %
13.3	6.64	4.2
17.9	4.95	100.0
20.2	4.39	5.0
20.8	4.27	6.4
22.2	4.01	3.4
24.7	3.61	4.5
25.9	3.44	4.1
27.3	3.26	12.8
28.6	3.12	32.7
29.1	3.06	3.4
31.0	2.88	4.1
31.5	2.84	6.7
31.9	2.81	4.7
34.2	2.62	4.3
35.7	2.51	3.1
36.0	2.49	9.2
37.8	2.38	2.0

Step 4 Synthesis of

2-bromo-5-[4-(4-isopropoxybenzenesulfonyl)-piperazine-1-yl]-phenol (B-8)

Under argon gas flow, a suspension of 4-(para-isopropoxybenzenesulfonyl)piperazine obtained in Example 1 (B-4, 1.05 g), palladium acetate (22 mg), sodium para-toluene sulfinat (36 mg), and sodium tert-pentoxide (1.11 g) in toluene (7 mL) was added with diadamantylbutyl phosphine (72 mg), and stirred at room temperature for 30 minutes. Under ice cooling, the reaction liquid was added with 2-bromo-5-iodophenol obtained in Step 3 (B-7, 1.00 g), and toluene (2 mL), and refluxed for 2 hours. The reaction liquid was cooled to room temperature, added with 2 mol/L of hydrochloric acid (7 mL), diluted with ethyl acetate (10 mL), and insoluble substances were filtered off, and the filtrate was extracted with toluene. The organic phase was washed with water and saline, and then dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the obtained residue was purified by column chromatography to obtain

2-bromo-5-[4-(4-isopropoxybenzenesulfonyl)-piperazine-1-yl]-phenol (B-8, 845 mg, yield 56%) as white crystals.

¹H-NMR(CDCl₃)δppm: 1.37 (d, J = 6.0 Hz, 6H), 3.16 (m, 4H), 3.25 (m, 4H), 4.63 (qq, J = 6.0 Hz, 6.0 Hz, 1H), 5.45 (s, 1H), 6.40 (dd, J = 9.0 Hz, 2.4 Hz), 6.58 (d, J = 2.4 Hz, 1H), 6.97 (d, J = 9.0 Hz, 2H), 7.29 (d, J = 9.0 Hz, 1H), 7.69 (d, J = 9.0 Hz, 2H).

Result of powder X-ray diffraction is shown in Table 4 and Fig.

4.

Diffraction angles of major peaks: $2\theta = 6.1, 12.2, 17.5, 19.0, 19.4$ degrees

[Table 4]

Angle 2-Theta °	d value Angstrom	Intensity %
6.1	14.39	16.3
7.4	11.92	8.1
9.9	8.93	8.5
12.2	7.24	15.8
13.7	6.48	7.5
14.3	6.18	7.2
14.9	5.93	13.1
16.1	5.48	8.5
16.9	5.24	12.6
17.5	5.06	21.9
19.0	4.67	21.6
19.4	4.58	100.0
20.4	4.34	10.5
21.2	4.20	12.7
21.4	4.14	8.8
21.9	4.05	7.1
23.2	3.83	4.4
24.5	3.62	8.9
25.4	3.50	9.1
26.1	3.41	5.6
27.0	3.30	7.8
27.5	3.24	6.2
28.1	3.17	8.5
29.0	3.08	8.9
29.7	3.01	6.4
30.4	2.94	11.6
31.7	2.82	11.6
33.5	2.68	7.6
35.9	2.50	5.0
37.3	2.41	5.4

Step 5 Synthesis of methyl

{2-bromo-5-[4-(4-isopropoxybenzenesulfonyl)-piperazine-1-yl]-phenoxy}- acetate (B-9)

A solution of

2-bromo-5-[4-(4-isopropoxybenzenesulfonyl)-piperazine-1-yl]-phenol obtained in Step 4 (B-8, 170 mg, 0.37 mmol) in N,N-dimethylformamide (2.0 mL) was added with potassium carbonate (103 mg, 0.75 mmol), and bromomethyl acetate ester (0.042 mL, 0.45 mmol), and stirred at room temperature for 18 hours. The reaction liquid was poured into water, and extracted with ethyl acetate. The organic phase was washed with diluted hydrochloric acid and water, and then dried over

anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure to obtain methyl {2-bromo-5-[4-(4-isopropoxybenzenesulfonyl)-piperazine-1-yl]-phenoxy}-acetate (B-9, 150 mg, yield 76%) as colorless powder.

¹H-NMR(CDCl₃)δppm: 1.37 (d, J = 6.0 Hz, 6H), 3.13-3.26 (m, 8H), 3.79 (s, 3H), 4.59 - 4.67 (m, 3H), 6.39-6.57 (m, 2H), 6.96 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.7 Hz, 1H), 7.68 (d, J = 8.7 Hz, 2H).

Step 6 Synthesis of

{2-bromo-5-[4-(4-isopropoxybenzenesulfonyl)-piperazine-1-yl]-phenoxy}-acetic acid (I-2)

A solution of methyl

{2-bromo-5-[4-(4-isopropoxybenzenesulfonyl)-piperazine-1-yl]-phenoxy}-acetate obtained in Step 5 (B-9, 150 mg, 0.28mmol) in methanol (2.0 mL)-tetrahydrofuran (2.0 mL) was added with 2 mol/L of sodium hydroxide solution (0.43 mL, 0.85 mmol), and stirred at room temperature for 3 hours. The reaction liquid was poured into water, and washed with diethylether. The aqueous phase was added with diluted hydrochloric acid to make acidic, and extracted with ethyl acetate. The organic phase was washed with water and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The obtained crude crystals were recrystallized from ethyl acetate/hexane to obtain {2-bromo-5-[4-(4-isopropoxybenzenesulfonyl)-piperazine-1-yl]-phenoxy}-acetic acid (I-2, 142 mg, yield 97%) as colorless crystals.

¹H-NMR(DMSO-d₆)δppm: 1.30 (d, J = 6.0 Hz, 6H), 2.95 (brs, 4H), 3.02 (brs, 4H), 4.71 - 4.79 (m, 3H), 6.42 (dd, J = 9.0 Hz, 2.4 Hz, 1H), 6.54 (d, J = 2.4 Hz, 1H), 7.13 (d, J = 9.0 Hz, 2H), 7.32 (d, J = 8.7 Hz, 1H), 7.66 (d, J = 8.7 Hz, 2H).

Result of powder X-ray diffraction is shown in Table 5 and Fig. 5.

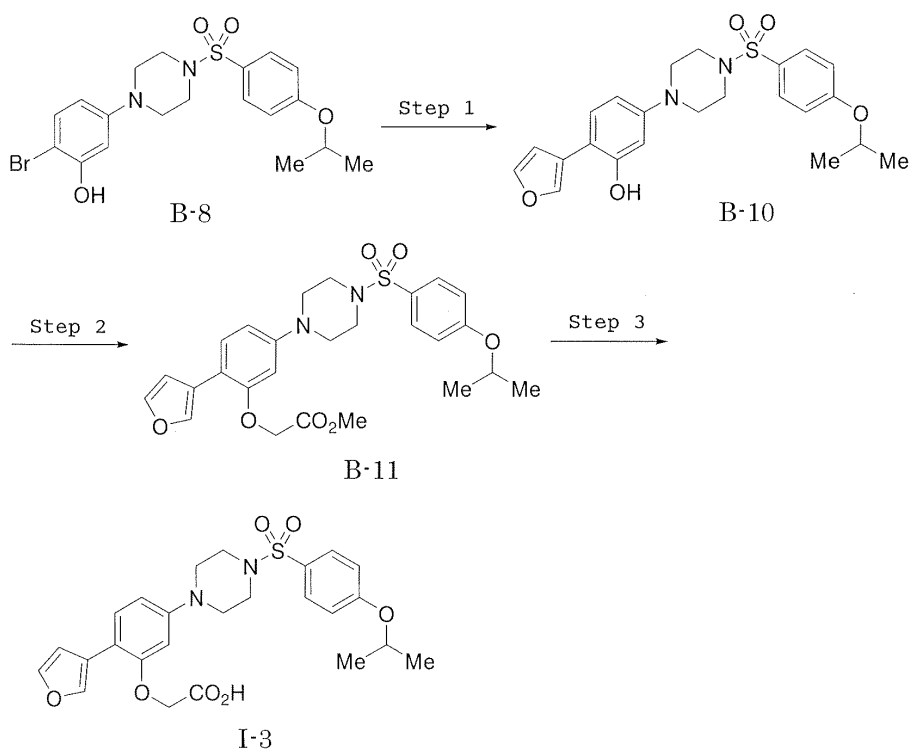
Diffraction angles of major peaks: 2θ = 9.6, 18.2, 19.9, 20.6, 21.6, 22.0 degrees

[Table 5]

Angle 2-Theta °	d value Angstrom	Intensity %
9.6	9.22	96.2
15.5	5.71	41.3
16.0	5.53	47.6
16.2	5.45	42.2
18.2	4.87	73.3
19.9	4.45	66.4
20.6	4.31	100.0
21.3	4.18	38.3
21.6	4.10	50.1
22.0	4.04	78.9
22.6	3.93	21.1
23.1	3.84	27.0
23.7	3.74	31.8
24.5	3.64	33.3
26.1	3.41	27.9
26.6	3.35	24.7
27.0	3.29	28.1
27.9	3.19	39.7
30.4	2.94	26.4
31.0	2.88	41.8
32.7	2.74	32.3
33.4	2.68	23.4
35.0	2.56	26.4
35.5	2.53	30.2
36.0	2.49	23.5
38.3	2.35	22.1
38.9	2.31	20.8

Example 3 Synthesis of
 {2-(3-furyl)-5-[4-(4-isopropoxybenzenesulfonyl)-piperazi
 ne-1-yl]-phenoxy}-acetic acid (I-3)

[Chemical formula 37]



Step 1 Synthesis of
 2-(3-furyl)-5-[4-(4-isopropoxybenzenesulfonyl)-piperazine-1-yl]-phenol (B-10)

A solution of 2-bromo-5-[4-(4-isopropoxybenzenesulfonyl)-piperazine-1-yl]-phenol obtained in Example 2 (B-8, 300 mg), 3-furylboronic acid (111 mg), palladium acetate (5 mg), and triphenylphosphine (23 mg) in 1,4-dioxane (4 mL) was added with 2 mol/L of sodium carbonate aqueous solution (2 mL) under argon gas flow, and refluxed for 6 hours. The reaction liquid was cooled to room temperature, added with ammonium chloride aqueous solution, and extracted with ethyl acetate. The organic phase was washed with water and saline, and dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the obtained residue was purified by column chromatography to obtain 2-(3-furyl)-5-[4-(4-isopropoxybenzenesulfonyl)-piperazine-1-yl]-phenol (B-10, 155 mg, yield 53%) as colorless scale crystals.

$^1\text{H-NMR}$ (DMSO- d_6) δ ppm: 1.37 (d, J = 6.0 Hz, 6H), 3.17 (m, 4H), 3.27 (m, 4H), 4.63 (qq, J = 6.0 Hz, 6.0 Hz, 1H), 6.51 (m, 2H), 6.61 (m, 1H), 6.97 (d, J = 9.0 Hz, 2H), 7.22 (d, J = 9.0 Hz, 1H), 7.50 (dd, J = 1.8 Hz, 1.5 Hz, 1H), 7.69 (d, J = 9.0 Hz, 2H), 7.74 (m, 1H).

Result of powder X-ray diffraction is shown in Table 6 and Fig.

6.

Diffraction angles of major peaks: 2θ = 6.1, 15.2, 16.3, 17.8, 20.5, 21.2, 25.1 degrees

[Table 6]

Angle 2-Theta °	d value Angstrom	Intensity %
6.1	14.44	81.5
7.1	12.47	27.7
8.5	10.44	13.5
10.2	8.62	24.7
14.3	6.21	29.2
15.2	5.83	51.1
16.3	5.45	53.2
16.9	5.24	33.7
17.8	4.98	90.3
18.7	4.75	37.8
19.4	4.57	39.9
20.5	4.33	100.0
21.2	4.19	68.0
22.1	4.02	16.3
22.7	3.91	20.9
24.8	3.59	23.3
25.1	3.54	55.8
26.8	3.32	15.8
28.4	3.14	9.6
29.2	3.05	19.3
29.8	2.99	15.7
30.9	2.90	14.9
32.3	2.77	9.9
35.3	2.54	13.5

Step 2 Synthesis of methyl

{2-(3-furyl)-5-[4-(4-isopropoxybenzenesulfonyl)-piperazine-1-yl]-phenoxy}- acetate (B-11)

A solution of

2-(3-furyl)-5-[4-(4-isopropoxybenzenesulfonyl)-piperazine-1-yl]-phenol obtained in Step 1 (B-10, 140 mg, 0.32 mmol) in N,N-dimethylformamide (2.0 mL) was added with potassium carbonate (87.3 g, 0.63 mmol) and bromomethyl acetate ester (0.036 mL, 0.38 mmol), and stirred at room temperature for 18 hours. The reaction liquid was poured into water, and extracted with ethyl acetate. The organic phase was washed with diluted hydrochloric acid and water, and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure to obtain methyl {2-(3-furyl)-5-[4-(4-isopropoxybenzenesulfonyl)-piperazine-1-yl]-phenoxy}- acetate (B-11, 110 mg, yield 68%) as colorless powder.

¹H-NMR(CDCl₃)δppm: 1.37 (d, J = 6.0 Hz, 6H), 3.23 (brs, 4H), 3.27 (brs, 4H), 3.84 (s, 3H), 4.58-4.68 (m, 3H), 6.50 (brs, 1H), 6.62 (d, J = 8.4 Hz, 1H), 6.77 (s, 1H), 6.97 (d, J = 9.0 Hz, 2H), 7.40-7.46 (m, 2H), 7.71 (d, J = 8.4Hz, 2H), 8.19 (s, 1H).

Step 3

A solution of methyl

{2-(3-furyl)-5-[4-(4-isopropoxybenzenesulfonyl)-piperazine-1-yl]-phenoxy}-acetate obtained in Step 1 (B-11, 100 mg, 0.19 mmol) in methanol (2.0 mL)-tetrahydrofuran (2.0 mL) was added with 2 mol/L of sodium hydroxide aqueous solution (0.29 mL, 0.58 mmol), and stirred at room temperature for 2 hours. The reaction liquid was poured into water, and washed with diethylether. The aqueous phase was added with diluted hydrochloric acid to make acidic, and extracted with ethyl acetate. The organic phase was washed with water, and dried over anhydrous magnesium sulfate. The solvent was concentrated under reduced pressure, and the obtained crude crystals were recrystallized from ethyl acetate/hexane to obtain

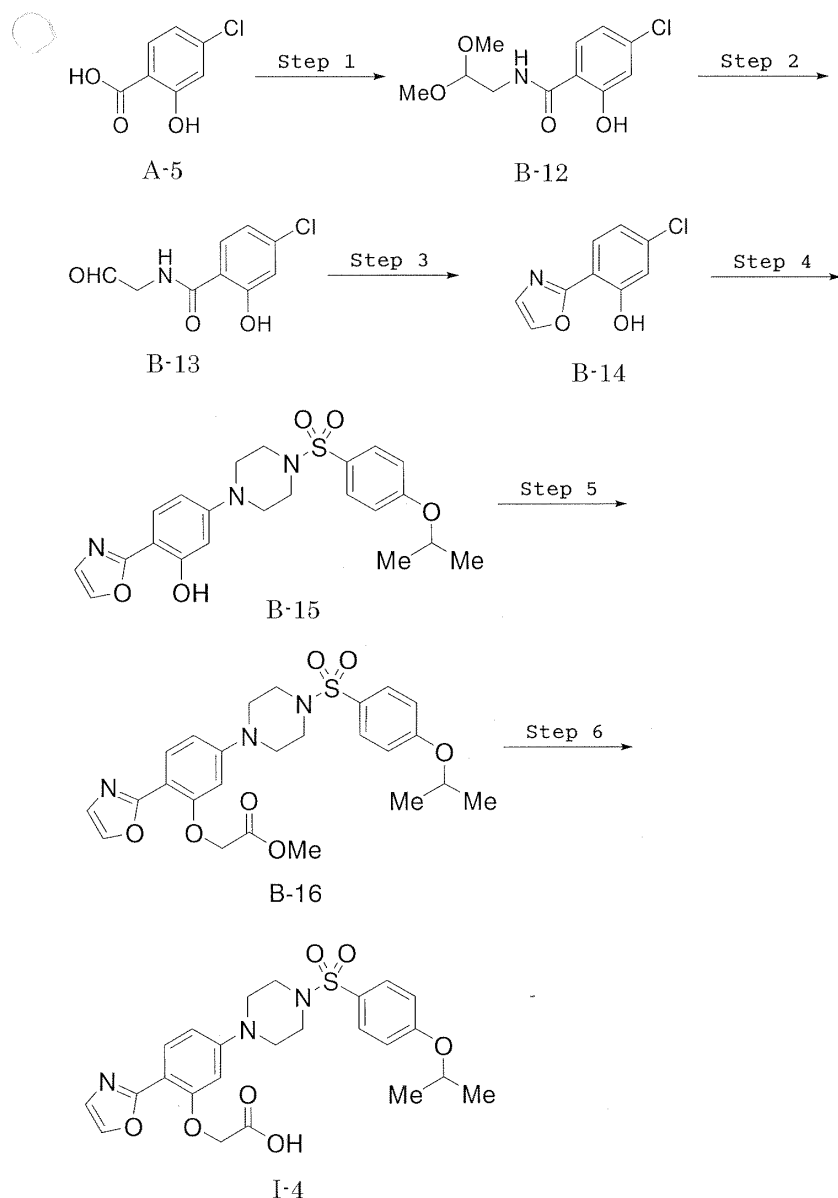
{2-(3-furyl)-5-[4-(4-isopropoxybenzenesulfonyl)-piperazine-1-yl]-phenoxy}-acetic acid (I-3, 85 mg, yield 88%) as colorless powder.

¹H-NMR(DMSO-d₆)δppm: 1.29 (d, J = 6.0 Hz, 6H), 2.97 (brs, 4H), 3.26 (brs, 4H), 4.79 - 4.70 (m, 3H), 6.52 (d, J = 9.0 Hz, 1H), 6.55 (s, 1H), 6.97 (s, 1H), 7.14 (d, J = 9.0 Hz, 2H), 7.44 (d, J = 9.0 Hz, 1H), 7.66 (s, 1H), 7.67 (d, J = 9.0 Hz, 2H), 8.36 (s, 1H).

Example 4 Synthesis of

{5-[4-(4-isopropoxybenzenesulfonyl)-piperazine-1-yl]-2-(2-oxazolyl)-phenoxy}-acetic acid (I-4)

[Chemical formula 38]



Step 1 Synthesis of

4-chloro-N-(2,2-dimethoxyethyl)-2-hydroxybenzamide (B-12)

A suspension of 4-chlorosalicylic acid (A-5, 50.0 g, 290 mmol) in ethyl acetate (200 mL) was added with thionyl chloride (41.4 g, 348 mmol) at room temperature, and refluxed under heating for 3 hours. The reaction liquid was cooled to room temperature, diluted with tetrahydrofuran (50 mL), and added dropwise into a solution of aminoacetaldehyde dimethyl acetal (42.6 g, 406 mmol) and triethylamine (110 mL, 789 mmol) in tetrahydrofuran (250 mL) at room temperature. The reaction liquid was stirred at 40°C for 1 hour, cooled to room temperature, added with water (300 mL), and extracted with

ethyl acetate. The organic phase was washed with 2 mol/L of hydrochloric acid, 10% potassium carbonate aqueous solution, and water. The solvent was concentrated under reduced pressure to obtain a crude product of

4-chloro-N-(2,2-dimethoxyethyl)-2-hydroxybenzamide (B-12, 60.9 g).

$^1\text{H-NMR}(\text{CDCl}_3)\delta\text{ppm}$: 1.28 (d, 6H, $J = 6.6$ Hz), 4.27 (dq, $J = 7.8$ Hz, 6.6 Hz, 6.6 Hz, 1H), 6.02 (brs, 1H), 7.00 (d, $J = 8.4$ Hz, 1H), 7.18 (dd, $J = 8.4$ Hz, 1.5 Hz, 1H), 7.39 (d, $J = 1.5$ Hz, 1H), 12.52 (brs, 1H).

Step 2 Synthesis of

4-chloro-2-hydroxy-N-(2-oxoethyl)benzamide (B-13)

A solution of the crude product obtained in Step 1 (B-12, 30.0 g) in tetrahydrofuran (120 mL) was added with 2 mol/L of hydrochloric acid (116 mL, 231 mmol), and stirred at 60°C for 1 hour and 15 minutes. The reaction liquid was cooled to room temperature, added with water (90 mL), extracted with ethyl acetate, and the organic phase was washed twice with water. The solvent was concentrated under reduced pressure, and the residue was recrystallized with diisopropyl ether to obtain 4-chloro-2-hydroxy-N-(2-oxoethyl)benzamide (B-13, 14.4 g, total yield of Step 1 and Step 2: 47%) as white crystals.

$^1\text{H-NMR}(\text{CDCl}_3)\delta\text{ppm}$: 4.41 (s, 1H), 4.43 (s, 1H), 6.87 (dd, $J = 8.7$ Hz, 2.1 Hz, 1H), 7.00 (brs, 1H), 7.01 (d, $J = 2.1$ Hz, 1H), 7.39 (d, $J = 8.7$ Hz, 1H), 9.78 (s, 1H), 12.13 (brs, 1H).

Step 3 Synthesis of 2-chloro-2-(oxazole-2-yl)phenol (B-14)

A suspension of

4-chloro-2-hydroxy-N-(2-oxoethyl)benzamide obtained in Step 2 (B-13, 1.00 g, 4.68 mmol) and hexachloro ethane (2.22 g, 9.36 mmol) in acetonitrile (10 mL) was added with triphenylphosphine (2.46 g, 9.36 mmol) at room temperature, stirred for 5 minutes, and then added with triethylamine (2.61 mL, 18.7 mmol). The reaction liquid was stirred for 1 hour at room temperature, for 1 hour at 60°C, and further refluxed for 6 hours with heating. The reaction liquid was cooled to room temperature, added with water (10 mL), and then extracted with ethyl acetate. The organic phase was washed with saturated saline and water. The solvent was concentrated under reduced pressure, and the residue was recrystallized from methanol/water to obtain 2-chloro-2-(oxazole-2-yl)phenol (B-14, 779 mg, yield 85%) as white crystals.

$^1\text{H-NMR}(\text{CDCl}_3)\delta\text{ppm}$: 6.94 (ddd, $J = 8.4$ Hz, 2.1 Hz, 0.3 Hz, 1H), 7.09 (d, $J = 2.1$ Hz, 1H), 7.25 (d, $J = 0.9$ Hz, 1H), 7.70 (dd, $J = 0.9$ Hz, 0.3 Hz, 1H), 11.37 (brs, 1H).

Result of powder X-ray diffraction is shown in Table 7 and Fig.

7.

Diffraction angles of major peaks: $2\theta = 11.9, 16.6, 23.9, 27.1$ degrees

[Table 7]

Angle 2-Theta °	d value Angstrom	Intensity %
9.5	9.27	9.8
11.9	7.43	44.8
15.3	5.79	10.8
16.6	5.33	100.0
17.1	5.18	24.6
17.9	4.94	20.4
21.1	4.20	16.3
22.9	3.88	5.0
23.9	3.72	30.9
25.3	3.52	10.1
26.0	3.42	16.2
26.4	3.37	15.4
27.1	3.29	39.4
27.8	3.20	9.8
28.2	3.16	7.2
28.6	3.12	6.6
30.0	2.98	5.0
30.4	2.94	5.5
32.0	2.80	10.8
32.7	2.74	9.5
33.1	2.71	9.3
35.9	2.50	6.0
36.5	2.46	6.0
38.6	2.33	8.0
39.3	2.29	5.8

Step 4 Synthesis of

5-[4-(4-isopropoxybenzenesulfonyl)-piperazine-1-yl]-2-(2-oxazolyl)-phenol (B-15)

Under argon gas flow, a suspension of 4-(para-isopropoxybenzenesulfonyl)piperazine obtained in Example 1 (B-4, 1.12 g), palladium acetate (24 mg), sodium para-toluene sulfinat (39 mg), and sodium tert-pentoxide (1.18 g) in toluene (7 mL) was added with diadamantylbutyl phosphine (77 mg), and stirred at room temperature for 30 minutes. Under ice cooling, the reaction liquid was added with 2-(2-oxazolyl)-5-chlorophenol obtained in Step 3 (B-14, 700 mg), and toluene (3 mL), and refluxed for 3 hours. The reaction liquid was cooled to room temperature, and then added with 2 mol/L of hydrochloric acid (7.5 mL). The generated precipitate was collected by filtration to obtain 5-[4-(4-isopropoxybenzenesulfonyl)-piperazine-1-yl]-2-(2-oxazolyl)-phenol (B-15, 1.27 g, yield 80%) as pale brown

crystals.

$^1\text{H-NMR}(\text{CDCl}_3)\delta\text{ppm}$: 1.37 (d, $J = 6.0\text{ Hz}$, 6H), 3.19 (m, 4H), 3.39 (m, 4H), 4.63 (qq, $J = 6.0\text{ Hz}$, 6.0 Hz, 1H), 6.54 (m, 1H), 6.97 (d, $J = 9.0\text{ Hz}$, 2H), 7.18 (m, 1H), 7.63 (m, 1H), 7.67 - 7.71 (m, 3H).

Result of powder X-ray diffraction is shown in Table 8 and Fig. 8.

Diffraction angles of major peaks: $2\theta = 3.8, 7.6, 15.9, 18.9, 19.2, 24.6, 25.5$ degrees

[Table 8]

Angle 2-Theta °	d value Angstrom	Intensity %
3.8	23.51	72.0
5.0	17.56	8.2
7.6	11.64	100.0
10.3	8.60	8.0
11.5	7.72	21.2
13.6	6.52	16.6
14.0	6.33	18.4
15.4	5.74	19.3
15.9	5.57	53.9
17.1	5.17	27.7
17.6	5.03	11.9
18.9	4.68	52.4
19.2	4.61	57.7
20.4	4.35	11.2
21.2	4.19	13.7
21.8	4.07	33.9
23.4	3.80	27.3
24.6	3.62	70.6
25.0	3.56	36.6
25.5	3.49	62.2
26.1	3.41	12.9
27.0	3.30	15.2
27.4	3.25	14.3
28.5	3.13	22.5
29.5	3.03	16.3
30.0	2.98	10.3
30.8	2.90	12.9
34.6	2.59	10.1
35.5	2.52	8.7
36.4	2.47	15.1

Step 5 Synthesis of methyl

{5-[4-(4-isopropoxybenzenesulfonyl)-piperazine-1-yl]-2-(2-oxazolyl)-phenoxy}- acetate (B-16)

A solution of

5-[4-(4-isopropoxybenzenesulfonyl)-piperazine-1-yl]-2-(2-oxazolyl)-phenol obtained in Step 4 (B-15, 200 mg, 0.45 mmol),

potassium carbonate (93 mg, 0.67 mmol), potassium iodide (15 mg, 0.09 mmol), and bromomethyl acetate ester (0.064 mL, 0.68 mmol) in N,N-dimethylformamide (1.6 mL) was stirred at 90°C for 1 hour. Under ice cooling, the reaction liquid was added with 2 mol/L of hydrochloric acid (0.23 mL), MeOH (5.0 mL), and water (5.0 mL). The obtained crystals were collected by filtration to obtain methyl

{5-[4-(4-isopropoxybenzenesulfonyl)-piperazine-1-yl]-2-(2-oxazolyl)-phenoxy}-acetate (B-16, 212 mg, yield 91%) as white crystals.

¹H-NMR(CDCl₃)δppm: 1.37 (d, J = 6.0 Hz, 6H), 3.14 (m, 4H), 3.43 (m, 4H), 3.79 (s, 3H), 4.63 (m, 1H), 4.75 (s, 2H), 6.38 (d, J = 2.4 Hz, 1H), 6.58 (dd, J = 8.7 Hz, 2.4 Hz, 1H), 6.98 (d, J = 8.7 Hz, 2H), 7.22 (d, 1H), 7.67 - 7.71 (m, 3H), 7.86 (d, J = 9.0 Hz, 1H).

Step 6 Synthesis of

{5-[4-(4-isopropoxybenzenesulfonyl)-piperazine-1-yl]-2-(2-oxazolyl)-phenoxy}-acetic acid (I-4)

A solution of methyl

{5-[4-(4-isopropoxybenzenesulfonyl)-piperazine-1-yl]-2-(2-oxazolyl)-phenoxy}-acetate obtained in Step 5 (B-16, 65 mg, 0.126 mmol), and 4 mol/L of sodium hydroxide aqueous solution (80 μL, 0.315 mmol) in N,N-dimethylformamide (1 mL) was stirred overnight. The reaction liquid was added with 2 mol/L of hydrochloric acid (315 μL), and water (2.0 mL), and stirred under ice cooling for 30 minutes. The generated crystals were collected by filtration to obtain

{5-[4-(4-isopropoxybenzenesulfonyl)-piperazine-1-yl]-2-(2-oxazolyl)-phenoxy}-acetic acid (I-4, 50.6 mg, yield 80%) as white crystals.

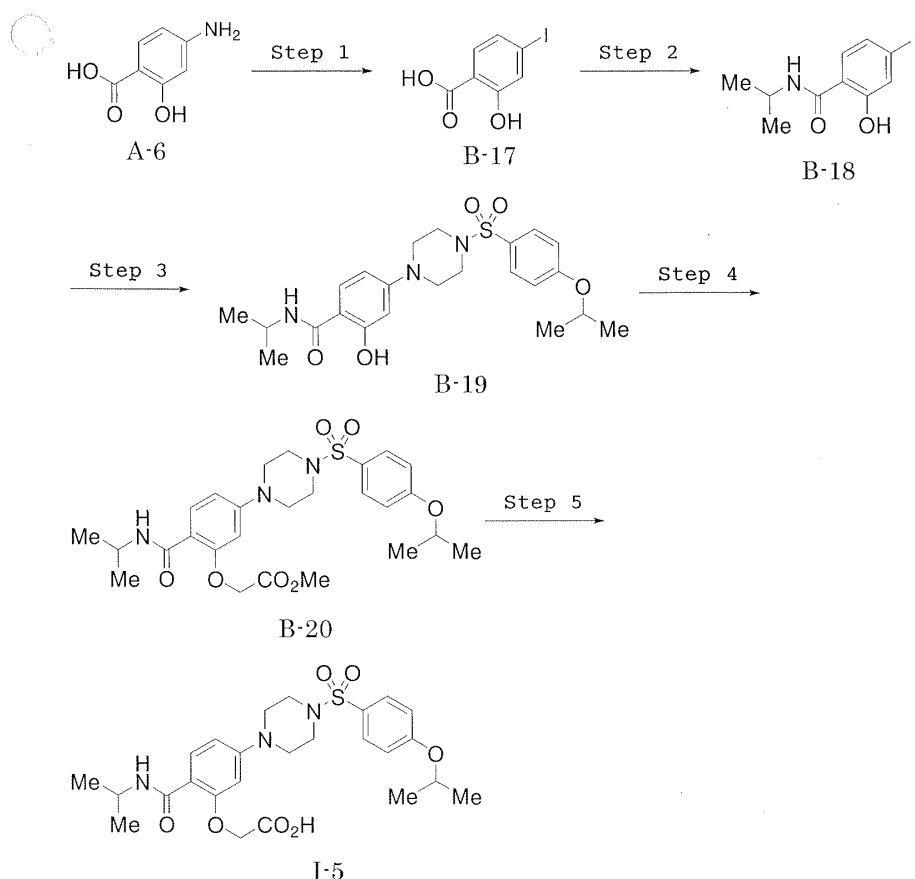
¹H-NMR(CDCl₃)δppm: 1.37 (d, J = 6.0 Hz, 6H), 3.16 (m, 4H), 3.42 (m, 4H), 4.63 (m, 1H), 4.77 (s, 2H), 6.40 (d, J = 2.7 Hz, 1H), 6.62 (dd, J = 9.0 Hz, 2.4 Hz, 1H), 6.98 (d, J = 3.0 Hz, 2H), 7.27 (m, 1H), 7.67 - 7.72 (m, 3H), 7.79 (d, J = 3.0 Hz, 1H). Result of powder X-ray diffraction is shown in Table 9 and Fig. 9.

Diffraction angles of major peaks: 2θ = 4.1, 13.6, 16.7, 20.1, 23.6 degrees

[Table 9]

Angle 2-Theta °	d value Angstrom	Intensity %
4.1	21.44	100.0
8.3	10.68	8.0
11.1	7.96	2.0
12.4	7.11	8.9
13.6	6.49	17.8
14.3	6.19	5.1
15.5	5.71	3.3
16.0	5.54	5.8
16.7	5.31	32.4
17.5	5.07	7.1
18.7	4.75	3.9
20.1	4.42	22.2
20.6	4.31	11.8
21.2	4.18	13.3
22.9	3.88	6.5
23.3	3.81	4.5
23.6	3.76	16.6
24.7	3.61	8.7
25.0	3.56	9.2
25.5	3.49	3.6
26.3	3.39	3.0
26.8	3.33	4.6
27.6	3.23	5.9
28.4	3.14	2.4
29.3	3.05	10.7
29.9	2.99	3.3
30.6	2.92	3.4
32.2	2.78	4.5
34.8	2.58	3.5
35.6	2.52	4.5
36.1	2.48	4.0
39.8	2.26	7.7

Example 5 Synthesis of
 {5-[4-(4-isopropoxybenzenesulfonyl)-piperazine-1-yl]-2-i
 sopropyl carbamoyl-phenoxy}-acetic acid (I-5)
 [Chemical formula 39]



Step 1 Synthesis of 4-iodosalicylic acid (B-17)

A suspension of 4-aminosalicylic acid (A-6, 5.00 g) in concentrated hydrochloric acid (30 mL) was added dropwise with a solution of sodium nitrite salt (4.50 g) in water (12 mL) over 20 minutes under ice cooling. Further, a solution of potassium iodide (13.55 g) in water (12 mL) was added dropwise over 15 minutes, and stirred for 2 hours under ice cooling. The reaction liquid was added with ethyl acetate (60 mL), and insoluble substances were filtered off after stirring. The filtrate was washed with sodium thiosulfate aqueous solution, water, and saline, and then dried over sodium sulfate. The solvent was distilled off under reduced pressure to obtain a crude product of 4-iodosalicylic acid (B-17, 4.97 g).

Step 2 Synthesis of 2-hydroxy-4-iodinated-N-isopropylbenzamide (B-18)

A solution of the crude product obtained in Step 1 (B-17, 4.97 g), WSCD·HCl (5.42 g), and HOBt (2.54 g) in N,N-dimethylformamide (25 mL) was added with isopropylamine (2.0 mL), and stirred at room temperature for 5 hours. The reaction liquid was added with 1 mol/L of hydrochloric acid

(100 mL), and extracted with ethyl acetate. The organic phase was washed with diluted hydrochloric acid, water, and saline, and dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was added with methylene chloride, and insoluble substances were filtered off. The filtrate was concentrated under reduced pressure, and the obtained crude product was purified by column chromatography to obtain

2-hydroxy-4-iodinated-N-isopropyl-benzamide (B-18, 1.67 g, total yield of Step 1 to Step 2: 19%) as colorless crystals. ¹H-NMR(CDCl₃)δppm: 1.28 (d, J = 6.6 Hz, 6H), 4.27 (dqq, J = 7.8 Hz, 6.6 Hz, 6.6 Hz, 1H), 6.02 (brs, 1H), 7.00 (d, J = 8.4 Hz, 1H), 7.18 (dd, J = 8.4 Hz, 1.5 Hz, 1H), 7.39 (d, J = 1.5 Hz, 1H), 12.52 (brs, 1H).

Result of powder X-ray diffraction is shown in Table 10 and Fig. 10.

Diffraction angles of major peaks: 2θ = 9.3, 20.9, 21.6, 24.2 degrees

[Table 10]

Angle 2-Theta °	d value Angstrom	Intensity %
7.3	12.14	24.2
7.7	11.42	20.1
9.3	9.53	41.4
13.8	6.41	23.8
16.2	5.47	33.3
17.2	5.15	28.7
19.2	4.62	26.6
20.9	4.25	100.0
21.6	4.12	41.1
22.9	3.89	18.4
24.2	3.68	42.2
25.4	3.50	20.1
26.2	3.40	25.7
27.1	3.29	21.8
27.7	3.22	27.5
28.7	3.11	20.3
30.5	2.93	30.8
34.2	2.62	28.0

Step 3 Synthesis of

2-hydroxy-4-[4-(4-isopropoxybenzenesulfonyl)-piperazine-1-yl]-N-isopropyl-benzamide (B-19)

Under argon gas flow, a suspension of 4-(para-isopropoxybenzenesulfonyl)piperazine obtained in Example 1 (B-4, 1.49 g), palladium acetate(18 mg), sodium para-toluene sulfinatate (28 mg), and sodium tert-pentoxide (1.16 g) in toluene (7 mL) was added with diadamantylbutyl

phosphine (57 mg), and stirred at room temperature for 30 minutes. Under ice cooling, the reaction liquid was added with 2-hydroxy-4-iodo-N-isopropyl-benzamide obtained in Step 2 (800 mg), and toluene (3 mL), and refluxed for 45 minutes. The reaction liquid was cooled on ice, and added with 2 mol/L of hydrochloric acid (8 mL). The generated precipitate was collected by filtration to obtain 2-hydroxy-4-[4-(4-isopropoxybenzenesulfonyl)-piperazine-1-yl]-N-isopropyl-benzamide (B-19, 1.07 g, yield 88%) as pale brown crystals.

¹H-NMR(CDCl₃)δppm: 1.25 (d, J = 6.6 Hz, 6H), 1.37 (d, J = 6.0 Hz, 6H), 3.15 (m, 4H), 3.58 (m, 4H), 4.24 (dq, J = 7.8 Hz, 6.6 Hz, 6.6 Hz, 1H), 4.63 (q, J = 6.0 Hz, 6.0 Hz, 1H), 5.83 (brd, J = 7.8 Hz, 1H), 6.35 - 6.38 (m, 2H), 6.96 (d, J = 9.0 Hz, 2H), 7.17 (d, J = 9.3 Hz, 1H), 7.68 (d, J = 9.0 Hz, 2H), 12.7 (brs, 1H).

Result of powder X-ray diffraction is shown in Table 11 and Fig. 11.

Diffraction angles of major peaks: 2θ = 4.3, 4.6, 8.7, 11.6, 19.3 degrees

[Table 11]

Angle 2-Theta °	d value Angstrom	Intensity %
4.3	20.47	100.0
4.6	19.03	9.2
8.3	10.70	4.0
8.7	10.16	19.8
9.4	9.43	3.7
11.3	7.81	5.9
12.4	7.15	2.5
13.1	6.78	2.9
14.3	6.19	4.5
14.9	5.93	5.4
16.9	5.25	5.8
17.5	5.06	11.6
18.7	4.74	5.9
19.3	4.60	8.9
20.3	4.37	5.2
21.7	4.10	5.2
22.7	3.91	5.0
23.9	3.72	5.8
25.1	3.55	2.7
25.7	3.46	2.3
26.8	3.33	3.5
28.2	3.16	2.6
29.6	3.01	3.1
30.8	2.90	2.6
32.6	2.75	1.7

Step 4 Synthesis of methyl

{5-[4-(4-isopropoxybenzenesulfonyl)-piperazine-1-yl]-2-isopropyl carbamoyl-phenoxy}- acetate (B-20)

A solution of

2-hydroxy-4-[4-(4-isopropoxybenzenesulfonyl)-piperazine-1-yl]-N-isopropyl-benzamide obtained in Step 3 (B-19, 170 mg, 0.37 mmol), cesium carbonate (180 mg, 0.55 mmol), and bromomethyl acetate ester (0.052 mL, 0.55 mmol) in N,N-dimethylformamide (2 mL) was stirred at room temperature for 3 hours. The reaction liquid was poured into water, and extracted with ethyl acetate. The organic phase was washed with water, diluted hydrochloric acid, and saline. The solvent was concentrated under reduced pressure, and the residue was purified by silica gel chromatography (ethyl acetate/hexane = 1/1) to obtain methyl

{5-[4-(4-isopropoxybenzenesulfonyl)-piperazine-1-yl]-2-isopropyl carbamoyl-phenoxy}- acetate (B-20, 195 mg, yield was quantitative).

¹H-NMR(CDCl₃)δppm: 1.27 (d, J = 6.6 Hz, 6H), 1.37 (d, J = 6.0 Hz, 6H), 3.16 (m, 4H), 3.36 (m, 4H), 3.87 (s, 3H), 4.64 (m, 1H), 4.66 (s, 2H), 6.23 (d, 1H), 6.58 (dd, J = 8.7 Hz, 2.1 Hz, 1H), 6.97 (d, J = 9.0 Hz, 2H), 7.68 (d, J = 9.0 Hz, 2H), 8.12 (d, J = 9.0 Hz, 1H), 8.19 (d, J = 7.5 Hz, 1H).

Step 5 Synthesis of

{5-[4-(4-isopropoxybenzenesulfonyl)-piperazine-1-yl]-2-isopropyl carbamoyl-phenoxy}-acetic acid (I-5)

A solution of methyl

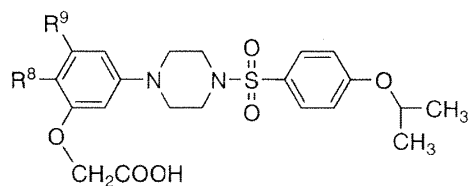
{5-[4-(4-isopropoxybenzenesulfonyl)-piperazine-1-yl]-2-isopropyl carbamoyl-phenoxy}- acetate obtained in Step 4 (B-20, 190 mg, 0.36 mmol), and 4 mol/L of sodium hydroxide aqueous solution (220 μL, 0.89 mmol) in THF(1 mL)-MeOH(1 mL) was stirred overnight. The reaction liquid was added with 2 mol/L of hydrochloric acid (1 mL), and extracted with ethyl acetate. The organic phase was washed with water and saline. The solvent was concentrated under reduced pressure to obtain {5-[4-(4-isopropoxybenzenesulfonyl)-piperazine-1-yl]-2-isopropyl carbamoyl-phenoxy}-acetic acid (I-5, 165 mg, yield 89%).

¹H-NMR(CDCl₃)δppm: 1.24 (d, J = 6.3 Hz, 6H), 1.37 (d, J = 6.0 Hz, 6H), 3.14 (m, 4H), 3.35 (m, 4H), 4.65 (m, 1H), 4.71 (s, 2H), 6.29 (d, J = 2.4 Hz, 1H), 6.53 (dd, J = 8.7 Hz, 2.1 Hz, 1H), 6.97 (d, J = 3.0 Hz, 2H), 7.66-7.72 (m, 3H), 7.84 (d, J = 8.7 Hz, 1H).

[0037]

Using a method similarly to the above, compounds I-6 to I-43 were synthesized. Structural formulas and physical

properties are shown in Tables 14 to 18.
[Table 12]



Compound No.	R ⁸	R ⁹
I-6	Cl	H
I-7	·NH·C(=O)·Me	H
I-8	·NH·C(=O)·(furan-2-yl)	H
I-9	·NH·C(=O)·Ph	H
I-10	·NH·C(=O)·CH ₂ ·OMe	H
I-11	1,3,4-oxadiazol-2-yl	H
I-12	·NH·C(=O)·(pyridin-2-yl)	H
I-13	·NH·C(=O)·(pyridin-3-yl)	H
I-14	·NH·C(=O)·(pyridin-4-yl)	H
I-15	Ph	H
I-16	·NH·C(=O)·(isoxazol-5-yl)	H
I-17	·NH·C(=O)·OMe	H
I-18	·NH·C(=O)·(5-Me-isoxazol-3-yl)	H
I-19	5-Me-1,3,4-oxazol-2-yl	H
I-20	·C(=O)·NH(Ph)	H
I-21	furan-2-yl	H
I-22	·NH·C(=O)·(isopropoxy)	H
I-23	·NH·C(=O)·(isopropylamino)	H
I-24	5-Me-oxazol-2-yl	H
I-25	5-Me-1,3,4-thiadiazol-2-yl	H
I-26	·C(=O)·NH ₂	H
I-27	·C(=O)·NH(Me)	H
I-28	·C(=O)·NH(n-Pr)	H
I-29	oxazol-5-yl	H
I-30	thiadiazol-2-yl	H
I-31	·C(=O)·NH(cyclopropyl)	H
I-32	thiazol-2-yl	H
I-33	pyrazol-1-yl	H
I-34	oxazol-4-yl	H
I-35	·C(=O)·NH·CH ₂ ·(thiophen-2-yl)	H
I-36	·C(=O)·NH·CH ₂ ·(pyridin-2-yl)	H
I-37	·C(=O)·NH·CH ₂ ·(cyclopropyl)	H
I-38	·C(=O)·NH·CH ₂ ·(furan-2-yl)	H
I-39	·C(=O)·NH(thiazol-2-yl)	H
I-40	·C(=O)·NH(1,3,4-thiadiazol-2-yl)	H
I-41	·C(=O)·NH(1-Me-pyrazol-3-yl)	H
I-42	·C(=O)·NH(3-cyclopropylpyrazol-5-yl)	H
I-43	·C(=O)·NMe ₂	H

[Table 13]

Compound No.	¹ H-NMR (solvent) δ
I-6	(CDCl ₃) 1.37 (d, 6H, J = 6.0 Hz), 3.16-3.23 (brs, 8H), 3.73 (brs, 1H), 4.60-4.71 (m, 3H), 6.49-6.54 (m, 2H), 6.98 (d, 2H, J = 9.0 Hz), 7.24 (d, 1H, J = 8.7 Hz), 7.69 (d, 2H, J = 9.0 Hz)
I-7	(DMSO-d ₆) 1.30 (d, J = 6.0 Hz, 6H), 2.02 (s, 3H), 2.96 (brs, 4H), 3.14 (brs, 4H), 4.69 (s, 2H), 4.71-4.79 (m, 1H), 6.45 (dd, J = 2.4, 9.0 Hz, 1H), 6.54 (d, J = 2.4 Hz, 1H), 7.14 (d, J = 8.7 Hz, 2H), 7.65-7.68 (m, 3H), 9.02 (s, 1H)
I-8	(DMSO-d ₆) 1.30 (d, J = 6.0 Hz, 6H), 2.97 (brs, 4H), 3.20 (brs, 4H), 4.71-4.79 (m, 3H), 6.55 (dd, J = 2.4, 8.7 Hz, 1H), 6.68-6.70 (m, 2H), 7.15 (d, J = 8.7 Hz, 2H), 7.23 (dd, J = 0.6, 2.2 Hz, 1H), 7.68 (d, J = 9.0 Hz, 2H), 7.81 (d, J = 8.7 Hz, 1H), 7.89-7.90 (m, 1H), 9.30 (s, 1H)
I-9	(DMSO-d ₆) 1.30 (d, J = 6.0 Hz, 6H), 2.98 (brs, 4H), 3.21 (brs, 4H), 4.72-4.80 (m, 3H), 6.57 (dd, J = 2.4, 8.7 Hz, 1H), 6.71 (d, J = 2.4 Hz, 1H), 7.15 (d, J = 8.7 Hz, 2H), 7.49-7.61 (m, 3H), 7.68 (d, J = 8.7 Hz, 2H), 7.74 (d, J = 8.7 Hz, 1H), 7.95 (d, J = 8.4 Hz, 2H), 9.51 (s, 1H)
I-10	(DMSO-d ₆) 1.30 (d, J = 6.0 Hz, 6H), 2.97 (brs, 4H), 3.16 (brs, 4H), 3.39 (s, 3H), 3.96 (s, 2H), 4.70-4.80 (m, 3H), 6.49 (d, J = 8.4 Hz, 1H), 6.64 (s, 1H), 7.14 (d, J = 8.7 Hz, 2H), 7.67 (d, J = 8.4 Hz, 2H), 7.91 (d, J = 8.7 Hz, 1H), 8.92 (s, 1H)
I-11	(CDCl ₃) 1.37 (d, 6H, J = 6.0 Hz), 3.17 (t, 4H), 3.46 (t, 4H), 4.63 (m, 1H), 4.76 (s, 2H), 6.38 (d, 1H, J = 2.4 Hz), 6.62 (dd, 1H, J = 9.0 Hz, 2.1 Hz), 6.98 (d, 2H), 7.67-7.75 (m, 3H), 8.39 (s, 1H)
I-12	(DMSO-d ₆) 1.30 (d, J = 6.0 Hz, 6H), 2.98 (brs, 4H), 3.20 (brs, 4H), 4.70-4.79 (m, 1H), 4.85 (s, 2H), 6.55 (d, J = 9.0 Hz, 1H), 6.68 (s, 1H), 7.14 (d, J = 8.7 Hz, 2H), 7.64-7.69 (m, 3H), 8.06 (d, J = 9.3 Hz, 1H), 8.16 (d, J = 7.8 Hz, 1H), 8.24 (d, J = 7.8 Hz, 1H), 8.68 (d, J = 5.7 Hz, 1H), 10.40 (s, 1H), 13.05 (brs, 1H)
I-13	(DMSO-d ₆) 1.30 (d, J = 6.0 Hz, 6H), 2.98 (brs, 4H), 3.22 (brs, 4H), 4.72-4.80 (m, 3H), 6.57 (dd, J = 2.1, 8.7 Hz, 1H), 6.68 (d, J = 2.4 Hz, 1H), 7.15 (d, J = 9.0 Hz, 2H), 7.53-7.57 (m, 1H), 7.64-7.70 (m, 3H), 8.29 (d, J = 8.1 Hz, 1H), 8.74 (s, 1H), 9.10 (s, 1H), 9.79 (s, 1H), 13.10 (brs, 1H)
I-14	(DMSO-d ₆) 1.30 (d, J = 6.3 Hz, 6H), 2.98 (brs, 4H), 3.22 (brs, 4H), 4.73-4.80 (m, 3H), 6.57 (dd, J = 2.4, 9.0 Hz, 1H), 6.69 (d, J = 1.8 Hz, 1H), 7.15 (d, J = 9.0 Hz, 2H), 7.65-7.70 (m, 3H), 7.85 (d, J = 5.4 Hz, 2H), 8.76 (brs, 2H), 9.86 (brs, 1H), 13.16 (brs, 1H)
I-15	(DMSO-d ₆) 1.30 (d, J = 6.0 Hz, 6H), 2.99 (brs, 4H), 3.26 (brs, 4H), 4.78 (s, 2H), 4.72-4.79 (m, 1H), 6.55-6.57 (m, 2H), 7.14-7.17 (m, 3H), 7.23 (t, J = 7.2 Hz, 1H), 7.34 (t, J = 7.8 Hz, 2H), 7.51 (d, J = 7.8 Hz, 2H), 7.68 (d, J = 9.0 Hz, 2H)
I-16	(DMSO-d ₆) 1.30 (d, J = 6.0 Hz, 6H), 2.97 (brs, 4H), 3.23 (brs, 4H), 4.70-4.80 (m, 3H), 6.48-6.65 (m, 3H), 7.03-7.16 (m, 3H), 7.65-7.78 (m, 3H), 9.60 (s, 1H), 12.98 (brs, 1H)
I-17	(DMSO-d ₆) 1.30 (d, J = 6.0 Hz, 6H), 2.96 (brs, 4H), 3.15 (brs, 4H), 3.61 (s, 3H), 4.66-4.80 (m, 3H), 6.49 (d, J = 8.1 Hz, 1H), 6.58 (s, 1H), 7.14 (d, J = 9.0 Hz, 2H), 7.41 (s, 1H), 7.67 (d, J = 8.4 Hz, 2H), 8.29 (brs, 1H), 13.00 (brs, 1H)
I-18	(DMSO-d ₆) 1.30 (d, J = 5.4 Hz, 6H), 2.50 (s, 3H), 2.97 (brs, 4H), 3.20 (brs, 4H), 4.65-4.85 (m, 3H), 6.54 (d, J = 7.5 Hz, 1H), 6.66-6.70 (m, 2H), 7.15 (d, J = 8.7 Hz, 2H), 7.68 (d, J = 8.4 Hz, 2H), 7.86 (d, J = 9.0 Hz, 1H), 9.47 (s, 1H), 13.11 (brs, 1H)

[Table 14]

Compound No.	¹ H-NMR (solvent) δ
I-19	(CDCl ₃) 1.37 (d, 6H, J = 6.0 Hz), 2.60 (s, 3H), 3.17 (t, 4H), 3.44 (t, 4H), 4.63 (m, 1H), 4.74 (s, 2H), 6.38 (d, 1H, J = 2.1 Hz), 6.60 (dd, 1H, J = 8.4 Hz, 1.8 Hz), 6.98 (d, 2H, J = 9.0 Hz), 7.67-7.71 (m, 3H)
I-20	(CDCl ₃) 1.37 (d, 6H, J = 6.0 Hz), 3.21 (t, 4H), 3.41 (t, 4H), 4.63 (m, 1H), 4.79 (s, 2H), 6.37 (d, 1H), 6.63 (dd, 1H), 6.99 (d, 2H), 7.09 (t, 1H), 7.32 (t, 1H), 7.69 (d, 1H, 9.0 Hz), 7.79 (d, 2H, J = 8.1 Hz), 8.09 (d, 1H), 9.80 (s, 1H).
I-21	(DMSO-d ₆) 1.29 (d, J = 6.0 Hz, 6H), 2.97 (brs, 4H), 3.29 (brs, 4H), 4.71-4.80 (m, 3H), 6.52-6.57 (m, 3H), 7.11 (d, J = 3.0 Hz, 1H), 7.14 (d, J = 9.0 Hz, 2H), 7.56 (d, J = 9.3 Hz, 1H), 7.61 (d, J = 1.2 Hz, 1H), 7.67 (d, J = 9.0 Hz, 2H)
I-22	(DMSO-d ₆) 1.21 (d, J = 6.3 Hz, 6H), 1.30 (d, J = 6.0 Hz, 6H), 2.96 (brs, 4H), 3.14 (brs, 4H), 4.62 (s, 2H), 4.71-4.85 (m, 2H), 6.48 (d, J = 9.9 Hz, 1H), 6.59 (s, 1H), 7.14 (d, J = 8.7 Hz, 2H), 7.47 (brd, J = 6.6 Hz, 1H), 7.67 (d, J = 8.7 Hz, 2H), 8.26 (brs, 1H)
I-23	(DMSO-d ₆) 1.06 (d, J = 6.6 Hz, 6H), 1.30 (d, J = 6.3 Hz, 6H), 2.96-2.97 (m, 4H), 3.06-3.08 (m, 4H), 3.65-3.76 (m, 1H), 4.71-4.79 (m, 3H), 6.39 (dd, J = 2.4, 8.7 Hz, 1H), 6.50 (d, J = 2.4 Hz, 1H), 6.62 (d, J = 7.5 Hz, 1H), 7.14 (d, J = 9.0 Hz, 2H), 7.52 (s, 1H), 7.67 (d, J = 9.0 Hz, 2H), 7.81 (d, J = 9.0 Hz, 1H), 13.02 (brs, 1H)
I-24	(CDCl ₃) 1.37 (d, 6H, J = 6.0 Hz), 2.43 (s, 3H), 3.16 (br, 4H), 3.45 (br, 4H), 4.63 (m, 1H), 4.85 (s, 2H), 6.43 (br, 1H), 6.57 (br, 1H), 6.96-7.01 (m, 3H), 7.68-7.75 (m, 3H).
I-25	(CDCl ₃) 1.37 (d, 6H, J = 6.0 Hz), 2.79 (s, 3H), 3.16 (t, 4H), 3.43 (t, 4H), 4.63 (m, 1H), 4.82 (s, 2H), 6.41 (d, 1H, J = 2.1 Hz), 6.57 (dd, 1H, J = 8.4 Hz, 2.4 Hz), 6.98 (d, 2H, J = 8.7 Hz), 7.62 (d, 1H, J = 8.4 Hz), 7.69 (d, 2H).
I-26	(DMSO-d ₆) 1.30 (d, 6H, J = 6.0 Hz), 2.95 (t, 4H), 3.38 (t, 4H), 4.74 (m, 1H), 4.79 (s, 2H), 6.50 (d, 1H), 6.55 (dd, 1H, J = 8.7 Hz), 7.13 (d, 2H, J = 9.0 Hz), 7.32 (br, 1H), 7.67 (d, 2H), 7.77 (d, 1H), 8.01 (br, 1H).
I-27	(DMSO-d ₆) 1.29 (d, 6H, J = 6.0 Hz), 2.78 (d, 3H, 4.5 Hz), 2.95 (t, 4H), 3.35 (t, 4H), 4.74 (m, 1H), 4.81 (s, 2H), 6.50 (d, 1H, J = 2.1 Hz), 6.56 (dd, 1H, J = 9.0 Hz, 2.1 Hz), 7.13 (d, 2H, J = 9.0 Hz), 7.67 (d, 2H), 7.75 (d, 1H), 8.54 (d, 1H).
I-28	(DMSO-d ₆) 0.88 (t, 3H, J = 7.2 Hz), 1.29 (d, 6H, J = 6.0 Hz), 1.54 (m, 2H), 2.95 (t, 4H), 3.36 (t, 4H), 4.74 (m, 1H), 4.80 (s, 2H), 6.51 (d, 1H), 6.56 (dd, 1H, J = 8.4 Hz, 2.1 Hz), 7.13 (d, 2H, J = 8.7 Hz), 7.66 (d, 2H), 7.76 (d, 1H), 8.58 (t, 1H).
I-29	(DMSO-d ₆) 1.29 (d, J = 6.0 Hz, 6H), 2.97 (brs, 4H), 3.33 (brs, 4H), 4.70-4.78 (m, 3H), 6.59-6.61 (m, 2H), 7.14 (d, J = 9.0 Hz, 2H), 7.52 (d, J = 9.0 Hz, 1H), 7.67 (d, J = 9.0 Hz, 2H), 7.74 (s, 1H), 8.29 (s, 1H)
I-30	(DMSO-d ₆) 1.29 (d, 6H, J = 6.0 Hz), 2.97 (t, 4H), 3.41 (t, 4H), 4.74 (m, 1H), 4.91 (s, 2H), 6.64 (d, 1H), 6.68 (dd, 1H, J = 9.0 Hz), 7.14 (d, 2H, J = 9.0 Hz), 7.67 (d, 2H), 8.14 (d, 1H), 9.49 (s, 1H).
I-31	(DMSO-d ₆) 0.55 (m, 2H), 0.68 (m, 2H), 1.29 (d, 6H, J = 6.3 Hz), 2.90 (t, 4H), 3.37 (t, 4H), 4.74 (m, 1H), 4.76 (s, 2H), 6.48 (d, 1H, J = 1.8 Hz), 6.56 (dd, 1H, J = 9.0 Hz), 7.13 (d, 2H, J = 8.7 Hz), 7.66 (d, 2H), 7.77 (d, 1H), 8.61 (d, 1H, J = 4.8 Hz).

[Table 15]

Compound No.	¹ H-NMR (solvent) δ
I-32	(DMSO-d ₆) 1.29 (d, 6H, J = 6.0 Hz), 2.97 (t, 4H), 3.38 (t, 4H), 4.74 (m, 1H), 4.93 (s, 2H), 6.61 (d, 1H), 6.64 (dd, 1H, J = 9.3 Hz), 7.14 (d, 2H, J = 9.0 Hz), 7.63-7.69 (m, 3H), 7.83 (d, 1H, J = 3.0 Hz), 8.08 (d, 1H).
I-33	¹ H NMR (DMSO-d ₆) 1.30 (d, J = 6.0 Hz, 6H), 2.97 (brs, 4H), 3.25 (brs, 4H), 4.70-4.80 (m, 3H), 6.41(s, 1H), 6.57 (d, 1H), 6.66 (s, 1H), 7.14 (d, J = 8.7 Hz, 2H), 7.47 (d, J = 8.4 Hz, 1H), 7.61 (s, 1H), 7.67 (d, J = 8.7 Hz, 2H), 8.36 (s, 1H)
I-34	¹ H NMR (DMSO-d ₆) 1.29 (d, J = 6.0 Hz, 6H), 2.96 (brs, 4H), 3.26 (brs, 4H), 4.30 (s, 2H), 4.69-4.77 (m, 1H), 6.50 (s, 1H), 6.53 (d, J = 9.0 Hz, 1H), 7.12 (d, J = 8.7 Hz, 2H), 7.65 (d, J = 9.0 Hz, 2H), 7.78 (d, J = 8.7 Hz, 1H), 8.31 (s, 1H), 9.13 (s, 1H)
I-35	¹ H NMR (CDCl ₃) 1.36 (d, 6H, J = 6.0 Hz), 3.08-3.15 (m, 4H), 3.25-3.35 (m, 4H), 4.58-4.65 (m, 1H), 4.69 (s, 2H), 4.78 (d, 2H, J = 6.0 Hz), 6.24 (s, 1H), 6.52 (d, 1H, J = 8.5 Hz), 6.87-6.91 (m, 1H), 6.96 (d, 2H, J = 8.5 Hz), 6.96-6.98 (m, 1H), 7.14 (d, 1H, J = 8.5 Hz), 7.68 (d, 2H, J = 8.5 Hz), 7.90 (d, 1H, J = 8.5 Hz), 8.30-8.35 (m, 1H).
I-36	¹ H NMR (DMSO-d ₆) 1.30 (d, 6H, J = 6.0 Hz), 3.08-3.15 (m, 4H), 3.25-3.35 (m, 4H), 4.55 (d, 2H, J = 6.0 Hz), 4.74-4.84 (m, 1H), 4.79 (s, 2H), 6.53 (s, 1H), 6.58 (d, 1H, J = 8.5 Hz), 7.14 (d, 2H, J = 8.5 Hz), 7.20-7.24 (m, 1H), 7.32 (d, 1H, J = 8.5 Hz), 7.64 (d, 2H, J = 8.5 Hz), 7.69-7.72 (m, 1H), 7.79 (d, 1H, J = 8.5 Hz), 8.48 (d, 1H, J = 4.5 Hz), 9.30-9.35 (m, 1H).
I-37	¹ H-NMR (CDCl ₃) 8.04 (0.5H, s), 7.85 (1H, d, J = 8.7 Hz), 7.73 (2H, d, J = 8.9 Hz), 7.01 (2H, d, J = 8.9 Hz), 6.64-6.61 (1H, m), 4.78 (2H, s), 4.71-4.63 (1H, m), 4.12-4.04 (1H, m), 3.42-3.32 (6H, m), 3.23 (4H, brs), 1.41 (6H, d, J = 6.0 Hz), 1.26 (6H, d, J = 6.0 Hz), 1.14-1.07 (1H, m), 0.58-0.53 (2H, m), 0.32-0.24 (2H, m).
I-38	¹ H NMR (DMSO-d ₆) 1.29 (d, 6H, J = 6.0 Hz), 3.08-3.15 (m, 4H), 3.25-3.35 (m, 4H), 4.45 (d, 2H, J = 6.0 Hz), 4.74-4.84 (m, 1H), 4.81 (s, 2H), 6.22 (d, 1H, J = 2.3 Hz), 6.32 (d, 1H, J = 2.3 Hz), 6.50 (s, 1H), 6.58 (d, 1H, J = 8.5 Hz), 7.14 (d, 2H, J = 8.5 Hz), 7.52 (d, 1H, J = 2.3 Hz), 7.64 (d, 2H, J = 8.5 Hz), 7.76 (d, 1H, J = 8.5 Hz), 8.90-8.95 (m, 1H).
I-39	¹ H-NMR (DMSO-d ₆) 1.29 (6H, d, J = 6.0 Hz), 2.96 (4H, m), 3.48 (4H, m), 4.74 (1H, tt, J = 6.0, 6.0 Hz), 4.96 (2H, s), 6.60 (1H, d, J = 2.1 Hz), 6.66 (1H, d, J = 2.1, 9.0 Hz), 7.13 (2H, d, J = 9.0 Hz), 7.22 (1H, d, J = 3.6 Hz), 7.47 (1H, d, J = 3.6 Hz), 7.66 (2H, d, J = 9.0 Hz), 7.84 (1H, d, J = 9.0 Hz), 11.56 (1H, brs).
I-40	¹ H-NMR (DMSO-d ₆) 1.28 (6H, d, J = 6.0 Hz), 2.96 (4H, m), 3.50 (4H, m), 4.73 (1H, tt, J = 6.0, 6.0 Hz), 4.96 (2H, s), 6.61 (1H, d, J = 2.1 Hz), 6.67 (1H, dd, J = 2.1, 9.0 Hz), 7.13 (2H, d, J = 9.0 Hz), 7.67 (2H, d, J = 9.0 Hz), 7.84 (1H, d, J = 9.0 Hz), 9.16 (1H, s), 11.88 (1H, brs), 13.5 (1H, br).
I-41	¹ H-NMR (DMSO-d ₆) 1.28 (6H, d, J = 6.0 Hz), 2.96 (4H, m), 3.42 (4H, m), 3.73 (3H, s), 4.74 (1H, tt, J = 6.0, 6.0 Hz), 4.93 (2H, s), 6.54 (1H, d, J = 2.4 Hz), 6.57 (1H, d, J = 2.4 Hz), 6.61 (1H, dd, J = 2.4, 9.0 Hz), 7.13 (2H, d, J = 9.0 Hz), 7.55 (1H, d, J = 2.4 Hz), 7.67 (2H, d, J = 9.0 Hz), 7.81 (1H, d, J = 9.0 Hz), 10.32 (1H, s), 13.35 (1H, brs).

[Table 16]

Compound No.	¹ H-NMR (solvent) δ
I-42	¹ H NMR (DMSO-d ₆) 0.63-0.68 (m, 2H), 0.88-0.92 (m, 2H), 1.30 (d, 6H, J = 6.0 Hz), 1.93-1.96 (m, 1H), 3.08-3.15 (m, 4H), 3.25-3.35 (m, 4H), 4.74-4.84 (m, 1H), 4.90 (s, 2H), 6.18 (s, 1H), 6.53 (s, 1H), 6.58 (d, 1H, J = 8.5 Hz), 7.14 (d, 2H, J = 8.5 Hz), 7.64 (d, 2H, J = 8.5 Hz), 7.79 (d, 1H, J = 8.5 Hz), 9.80-9.85 (m, 1H).
I-43	¹ H-NMR (CDCl ₃) 7.73 (2H, d, J = 9.4 Hz), 7.16 (1H, d, J = 9.1 Hz), 7.02 (2H, d, J = 8.9 Hz), 6.59-6.57 (2H, m), 4.81 (2H, s), 4.72-4.64 (1H, m), 3.40-3.38 (4H, m), 3.22-3.17 (10H, m), 1.42 (6H, d, J = 6.0 Hz).

Industrial applicability

[0038]

An industrially useful production method capable of producing N-phenyl-N'-phenylsulfonyl piperazine derivative and intermediate thereof in a simple manner in a short process and/or with good yield has been found.

Brief description of drawings

[0039]

[Fig. 1] Powder X-ray diffraction pattern and peak values of crystal of compound (B-4) obtained in Example 1. The vertical axis represents intensity, and the horizontal axis represents diffraction angle (2 θ , unit: degree).

[Fig. 2] Powder X-ray diffraction pattern and peak values of crystal of compound (I-1) obtained in Example 1. The vertical axis represents intensity (unit: cps), and the horizontal axis represents diffraction angle (2 θ , unit: degree).

[Fig. 3] Powder X-ray diffraction pattern and peak values of crystal of compound (B-7) obtained in Example 2. The vertical axis represents intensity, and the horizontal axis represents diffraction angle (2 θ , unit: degree).

[Fig. 4] Powder X-ray diffraction pattern and peak values of crystal of compound (B-8) obtained in Example 2. The vertical axis represents intensity, and the horizontal axis represents diffraction angle (2 θ , unit: degree).

[Fig. 5] Powder X-ray diffraction pattern and peak values of crystal of compound (I-2) obtained in Example 2. The vertical axis represents intensity (unit: cps), and the horizontal axis represents diffraction angle (2 θ , unit: degree).

[Fig. 6] Powder X-ray diffraction pattern and peak values of crystal of compound (B-10) obtained in Example 3. The vertical axis represents intensity (unit: cps), and the horizontal axis represents diffraction angle (2 θ , unit: degree).

[Fig. 7] Powder X-ray diffraction pattern and peak values

of crystal of compound (B-13) obtained in Example 4. The vertical axis represents intensity (unit: cps), and the horizontal axis represents diffraction angle (2θ , unit: degree).

[Fig. 8] Powder X-ray diffraction pattern and peak values of crystal of compound (B-14) obtained in Example 4. The vertical axis represents intensity (unit: cps), and the horizontal axis represents diffraction angle (2θ , unit: degree).

[Fig. 9] Powder X-ray diffraction pattern and peak values of crystal of compound (I-4) obtained in Example 4. The vertical axis represents intensity (unit: cps), and the horizontal axis represents diffraction angle (2θ , unit: degree).

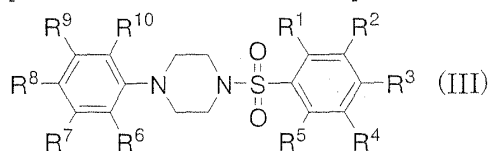
[Fig. 10] Powder X-ray diffraction pattern and peak values of crystal of compound (B-18) obtained in Example 5. The vertical axis represents intensity (unit: cps), and the horizontal axis represents diffraction angle (2θ , unit: degree).

[Fig. 11] Powder X-ray diffraction pattern and peak values of crystal of compound (B-19) obtained in Example 5. The vertical axis represents intensity (unit: cps), and the horizontal axis represents diffraction angle (2θ , unit: degree).

Claims

[Claim 1] A method of producing a compound represented by Formula (III):

[Chemical formula 1]

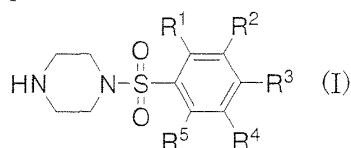


wherein R^1 , R^2 , R^3 , R^4 , and R^5 each independently represent a hydrogen atom, a halogen atom, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted alkyloxy, optionally substituted alkylthio, acyl, optionally substituted alkyloxycarbonyl, optionally substituted carbamoyl, optionally substituted amino, optionally substituted aryl, optionally substituted heteroaryl, or an optionally substituted non-aromatic heterocyclic group;

R^6 , R^7 , R^8 , R^9 , and R^{10} each independently represent a hydrogen atom, a halogen atom, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, hydroxy, optionally substituted alkyloxy, optionally substituted alkylthio, acyl, optionally substituted alkyloxycarbonyl, optionally substituted carbamoyl, optionally substituted amino, optionally substituted aryl, optionally substituted heteroaryl, or an optionally substituted non-aromatic heterocyclic group;

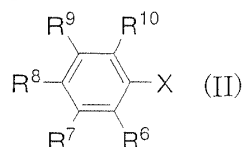
comprising reacting a compound represented by Formula (I):

[Chemical formula 2]



wherein R^1 , R^2 , R^3 , R^4 , and R^5 are as defined above; with a compound represented by Formula (II):

[Chemical formula 3]

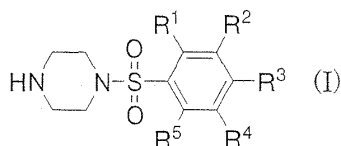


wherein R^6 , R^7 , R^8 , R^9 , and R^{10} are as defined above;
 X represents a halogen atom, optionally substituted
 alkylsulfonyloxy, or optionally substituted arylsulfonyloxy;
 in the presence of a palladium compound, an organic phosphorus
 compound, and a base in a solvent.

[Claim 2] The method according to claim 1, comprising

Step A of reacting the compound represented by Formula
 (I):

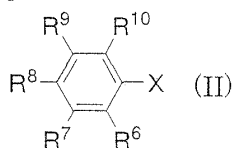
[Chemical formula 4]



wherein R^1 , R^2 , R^3 , R^4 , and R^5 are as defined in claim 1;
 with the palladium compound, the organic phosphorus compound,
 and the base; and

Step B of adding the compound represented by Formula (II):

[Chemical formula 5]



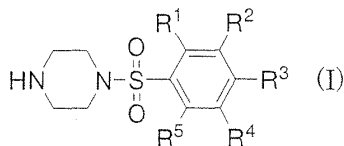
wherein R^6 , R^7 , R^8 , R^9 , R^{10} , and X are as defined in claim 1.

[Claim 3] The method according to claim 1, comprising:

Step C of mixing the palladium compound and the organic
 phosphorus compound;

Step D of adding the compound represented by Formula (I):

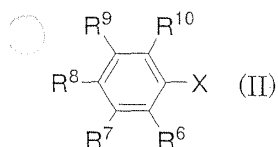
[Chemical formula 6]



wherein R^1 , R^2 , R^3 , R^4 , and R^5 are as defined in claim 1; and
 the base to the mixture obtained in Step C; and

Step E of adding the compound represented by Formula (II):

[Chemical formula 7]



wherein R⁶, R⁷, R⁸, R⁹, R¹⁰, and X are as defined in claim 1; to the mixture obtained in Step D.

[Claim 4] The method according to claim 1, wherein the palladium compound is palladium acetate.

[Claim 5] The method according to claim 1, wherein the organic phosphorus compound is diadamantylbutyl phosphine.

[Claim 6] The method according to claim 1, which is conducted in the presence of sulfinate.

[Claim 7] The method according to claim 2, wherein Step A is conducted in the presence of sulfinate.

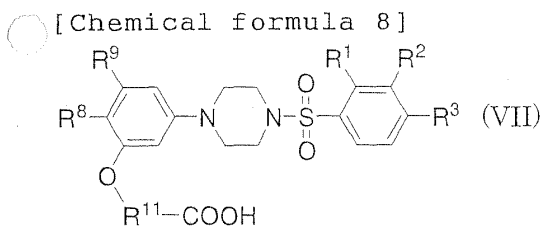
[Claim 8] The method according to claim 3, wherein Step D is conducted in the presence of sulfinate.

[Claim 9] The method according to any one of claims 6 to 8, wherein the sulfinate is sodium para-toluene sulfinate.

[Claim 10] The method according to claim 1, wherein R⁴, R⁵, R⁶, and R¹⁰ are hydrogen atoms, R¹, R², and R⁹ each independently are a hydrogen atom, a halogen atom, or alkyl, R³ is alkyloxy or alkylthio, R⁷ is hydroxy or optionally substituted alkyloxy, R⁸ is a halogen atom, optionally substituted alkyl, optionally substituted alkyloxy, optionally substituted alkyloxycarbonyl, optionally substituted carbamoyl, optionally substituted amino, optionally substituted aryl, optionally substituted heteroaryl, or optionally substituted an non-aromatic heterocyclic group, and X is halogen atom.

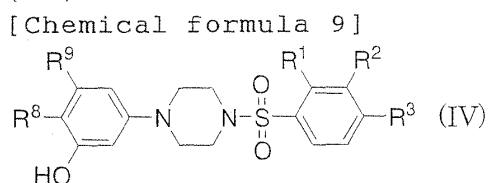
[Claim 11] The method according to claim 1, wherein R¹, R², R⁴, R⁵, R⁶, and R¹⁰ are hydrogen atoms, R⁹ is a hydrogen atom or a halogen atom, R³ is alkyloxy, R⁷ is hydroxy, R⁸ is a halogen atom, optionally substituted carbamoyl, optionally substituted amino, optionally substituted aryl, optionally substituted heteroaryl, or an optionally substituted non-aromatic heterocyclic group, and X is a halogen atom.

[Claim 12] A method of producing a compound represented by Formula (VII):



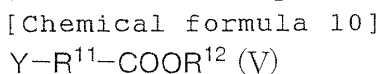
wherein R^1 , R^2 , R^3 , R^8 , and R^9 are as defined in claim 1; R^{11} is alkylene or alkenylene; comprising:

Step F of obtaining a compound represented by Formula (IV):

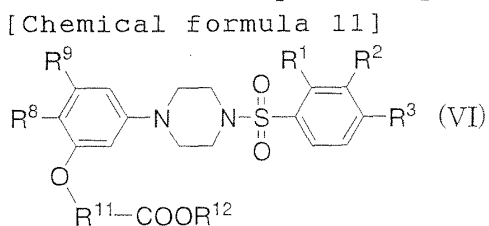


wherein R^1 , R^2 , R^3 , R^8 , and R^9 are as defined in claim 1; by the method according to claim 1;

Step G of reacting the compound represented by Formula (IV) with a compound represented by Formula (V):



wherein R^{11} is defined above; R^{12} is a hydrogen atom or alkyl; Y is a halogen atom, optionally substituted alkylsulfonyl, or optionally substituted arylsulfonyl; in the presence of a base to obtain a compound represented by Formula (VI):



wherein R^1 , R^2 , R^3 , R^8 , and R^9 are as defined in claim 1; R^{11} and R^{12} are as defined above; and

additional Step H of subjecting the compound represented by Formula (VI) to hydrolysis when R^{12} is alkyl.

[Claim 13] The method according to claim 12, wherein Y is halogen atom.

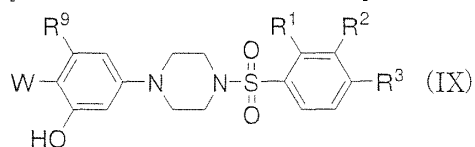
[Claim 14] The method according to claim 12, wherein R^1 , R^2 ,

and R⁹ each independently are a hydrogen atom, a halogen atom, or alkyl, R³ is alkyloxy or alkylthio, R⁸ is a halogen atom, optionally substituted alkyl, optionally substituted alkyloxy, optionally substituted alkyloxycarbonyl, optionally substituted carbamoyl, optionally substituted amino, optionally substituted aryl, optionally substituted heteroaryl, or an optionally substituted non-aromatic heterocyclic group, and R¹¹ is alkylene.

[Claim 15] The method according to claim 12, wherein R¹, R², and R⁹ each independently are a hydrogen atom, a halogen atom, or alkyl, R³ is alkyloxy or alkylthio, R⁸ is a halogen atom, optionally substituted carbamoyl, optionally substituted amino, optionally substituted aryl, optionally substituted heteroaryl, or an optionally substituted non-aromatic heterocyclic group, and R¹¹ is methylene.

[Claim 16] A method of producing a compound represented by Formula (IX):

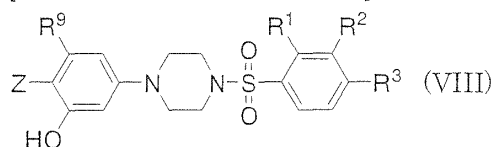
[Chemical formula 12]



wherein R¹, R², R³, and R⁹ are as defined in claim 1; W is optionally substituted aryl or optionally substituted heteroaryl; comprising:

Step I of obtaining a compound represented by Formula (VIII):

[Chemical formula 13]

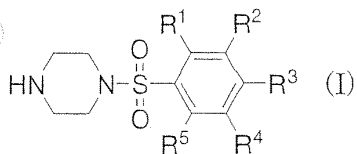


wherein R¹, R², R³, and R⁹ are as defined in claim 1; Z is a halogen atom; by the method according to claim 1; and

Step J of reacting the compound represented by Formula (VIII) with an organic boronic acid.

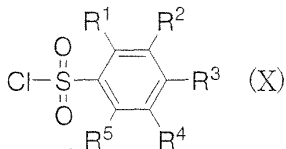
[Claim 17] A method of producing a compound represented by Formula (I):

[Chemical formula 14]



wherein R¹, R², R³, R⁴, and R⁵ are as defined in claim 1; comprising:

Step K of adding a compound represented by Formula (X):
[Chemical formula 15]



wherein R¹, R², R³, R⁴, and R⁵ are as defined in claim 1; to a solution of piperazine;

Step L of adding water to the reaction mixture and extracting it with an organic solvent; and

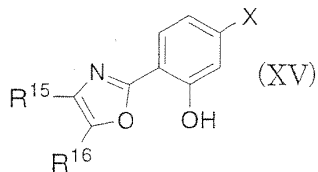
Step M of making the organic phase obtained in Step L acidic by adding an acid, and extracting it with water; and

Step N of making the aqueous phase obtained in Step M alkaline by adding a base to cause precipitation of crystals.

[Claim 18] The method according to claim 17, wherein R¹, R², R⁴, and R⁵ are a hydrogen atom, and R³ is alkoxy.

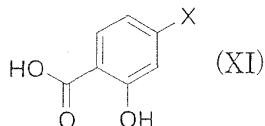
[Claim 19] A method of producing a compound represented by Formula (XV):

[Chemical formula 16]



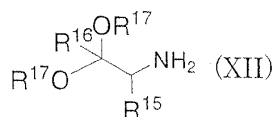
wherein X is as defined in claim 1; R¹⁵ and R¹⁶ each independently represent hydrogen atom or alkyl; comprising:

Step P of reacting a compound represented by Formula (XI):
[Chemical formula 17]



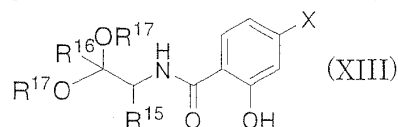
wherein X is as defined in claim 1; with a compound represented by Formula (XII):

[Chemical formula 18]



wherein R^{15} and R^{16} are as defined above; R^{17} is alkyl; to obtain a compound represented by Formula (XIII):

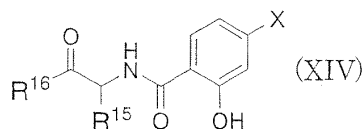
[Chemical formula 19]



wherein X is as defined in claim 1; R^{15} , R^{16} , and R^{17} are as defined above;

Step Q of reacting the compound represented by Formula (XIII) with an acid to obtain a compound represented by Formula (XIV):

[Chemical formula 20]

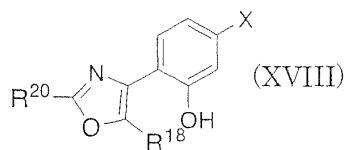


wherein X is as defined in claim 1; R^{15} and R^{16} are as defined above; and

Step R of closing the ring of the compound represented by Formula (XIV).

[Claim 20] A method of producing a compound represented by Formula (XVIII):

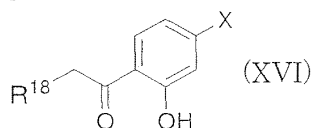
[Chemical formula 21]



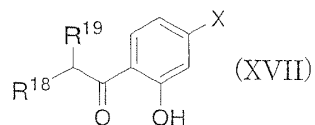
wherein X is as defined in claim 1; R^{18} is a hydrogen atom or alkyl; and R^{20} is a hydrogen atom or alkyl; comprising:

Step S of halogenating a compound represented by Formula (XVI):

[Chemical formula 22]



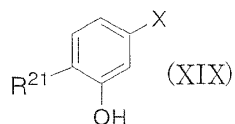
wherein X is as defined in claim 1; R¹⁸ is a hydrogen atom or alkyl; to obtain a compound represented by Formula (XVII):
[Chemical formula 23]



wherein X is as defined in claim 1; R¹⁸ is as defined above; R¹⁹ is a halogen atom; and

Step T of reacting the compound represented by Formula (XVII) with a compound represented by the formula: R²⁰COONH₄ wherein R²⁰ is as defined above.

[Claim 21] A compound represented by Formula (XIX):
[Chemical formula 24]



wherein X is as defined in claim 1; R²¹ is optionally substituted 5-membered heteroaryl; a pharmaceutically acceptable salt thereof, or a solvate thereof.