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DESCRIPTION

2-Iminopyrrolidine Derivatives

Technical Field

5 The present invention relates to novel 2-
iminopyrrolidine derivatives, salts thereof, and
pharmaceutical compositions containing the same and
the like.

Background Art

10 A recent approach for thrombosis have involved
inhibiting thrombin enzyme activity, and compounds
used for this purpose have included heparin, low
molecular weight heparin, hirudin, argatroban, hirulog
and the like. All such compounds inhibit the enzyme
activity of thrombin, and work by inhibiting fibrin
15 blood clot formation without specifically inhibiting
the effect of thrombin on cells. Bleeding tendency is
therefore a common side effect encountered in the
clinic. The role of thrombin in thrombosis is not
limited to its blood clotting activity, as it is
20 believed to also participate in platelet aggregation
at sites of vascular injury occurring as a result of
the activation of platelet thrombin receptor.

Another approach for thrombosis has been the use
of intravenous injection agents such as Abciximab,
25 Eptifibatide and Tirofiban, as GPIIb/IIIa receptor
antagonists. These compounds, while exhibiting



powerful anti-thrombotic effects by suppressing
platelet aggregation induced by various stimulation
such as thrombin, ADP, collagen, PAF or the like, also
produce a bleeding tendency as a side effect similarly
5 to thrombin enzyme activity inhibitors. For this
reason, no such compounds have yet been marketed,
although their development as oral agents continues to
progress.

Restenosis is a vascular hypertrophic response to
10 vascular wall injury induced by invasive treatment
such as coronary angioplasty, and this phenomenon may
be provoked by the direct or indirect effect of
thrombin on cells. Platelets adhere to injured blood
vessels, leading to release of growth factors and
15 eliciting proliferation of smooth muscle cells.
Smooth muscle cells may also be affected indirectly by
the action of thrombin on endothelial cells. Also,
platelet adhesion occurs and procoagulant activity
increases at sites of vascular injury. Smooth muscle
20 cells can undergo further direct stimulation due to
the high local thrombin concentration which is
produced at such sites. While recent studies using
the powerful thrombin inhibitor hirudin have suggested
that thrombin induces cell proliferation during the
25 process of restenosis, it has not yet been determined
whether the thrombin effect is direct or indirect

(Sarembock et al., Circulation 1992, 84:232-243).

Despite the implication of the cellular effects of thrombin in a variety of pathological symptoms, no therapeutically active substance is known which specifically blocks such effects.

The thrombin receptor (PAR1) has recently been cloned (Vu et al., Cell, 1991, 64:1057-1068), opening an important door to development of substances which target cellular thrombin receptors. Detailed examination of the amino acid sequence of this thrombin receptor has revealed a thrombin binding site and hydrolysis site located in the 100 residue amino terminal domain of the receptor. Later research by amino acid mutation in the receptor has established that limited hydrolysis of this portion of the thrombin receptor by thrombin is necessary for receptor activation (Vu et al., Nature, 1991, 353:674-677). A synthetic peptide corresponding to the amino acid sequence newly generated by hydrolysis of the thrombin receptor (the synthetic peptide is known as "thrombin receptor activating peptide", or TRAP) can activate receptors which have not been hydrolyzed by thrombin. This suggests that upon the cleavage of the receptor, the new amino acid sequence generated at the amino terminal (known as the "tethered ligand peptide") functions as the ligand and interacts with

the distal binding site. Further studies of TRAP have confirmed homology of the thrombin receptors present in platelet, endothelial cell, fibroblast and smooth muscle cell (Hung et al., J. Cell. Biol. 1992, 116:827-832, Ngaiza, Jaffe, Biochem. Biophys. Res. Commun. 1991, 179:1656-1661).

Research on the structure activity relationship of TRAP suggests that the pentapeptide Phe-Leu-Leu-Arg-Asn is a weak antagonist for platelet thrombin receptors activated by either thrombin or TRAP (Vassallo. et al., J.Biol.Chem.,1992, 267:6081-6085(1992)). Different approaches to receptor antagonism have also been examined by other groups. One of these approaches has been an attempt to prepare antibodies for the thrombin binding domain of the thrombin receptor. Such antibodies specifically and effectively suppress activation of platelets by thrombin, and act as thrombin receptor antagonists (Hung et al., J. Clin. Invest. 1992, 89:1350-1353).

Another approach has been development of peptide derivatives from TRAP (Steven M.S., J. Med. Chem. 1996, 39:4879-4887; William J.H., Bioorg. Med. Chem. Lett. 1998, 8:1649-1654; David F.M., Bioorg. Med. Chem. Lett. 1999, 9:255-260). Yet another has been development of low molecular weight compounds discovered by high throughput screening using various assay systems such

as receptor binding (Andrew W.S. et al., Bioorg. Med Chem. Lett. 1999, 9:2073-2078; Scherig Plough WO99/26943; Halord S. et al., ACS meeting in Oct. 2001).

5 **Disclosure of the Invention**

Compounds having antagonistic action on thrombin receptors are expected to exhibit excellent effects for therapy or prevention of diseases associated with thrombin, and therefore offer promise for effective
10 therapy or prevention of, for example, thrombosis, vascular restenosis, deep venous thrombosis, pulmonary embolism, cerebral infarction, heart disease, disseminated intravascular coagulation, hypertension, inflammatory diseases, rheumatism, asthma,
15 glomerulonephritis, osteoporosis, neurological disorders, malignant tumors, and the like. It has been ardently desired to provide thrombin receptor antagonists which are satisfactory in numerous aspects including pharmacological activity, thrombin receptor
20 specificity, safety, dosage and oral efficacy.

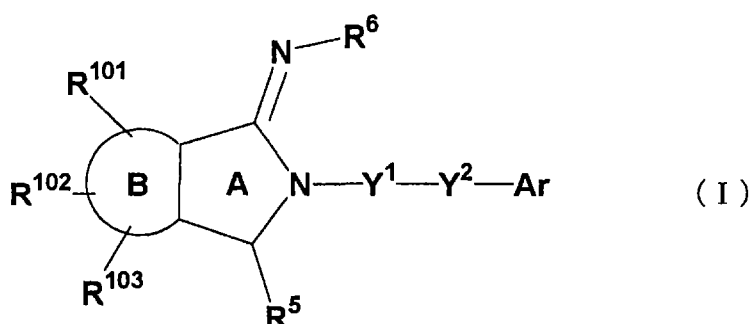
However, the conventional thrombin receptor antagonists have been inadequate in terms of receptor specificity and oral efficacy.

It is therefore an object of the present
25 invention to search for and discover compounds having excellent thrombin receptor inhibiting activity and

being therefore useful as thrombin receptor antagonists.

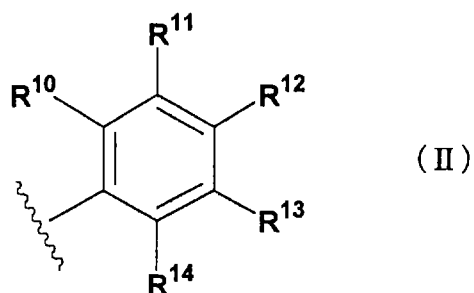
As a result of much vigorous research conducted under the circumstances described above, the present inventors have completed this invention upon successfully synthesizing novel 2-iminopyrrolidine derivatives represented by the following general formula (I), and also upon unexpectedly finding that these compounds or their salts have excellent thrombin receptor inhibiting activity and are useful as thrombin receptor antagonists.

The present invention resides in the following:
<1> a compound represented by the formula:



(wherein ring B represents an optionally substituted (1) aromatic hydrocarbon ring or (2) aromatic heterocycle optionally having 1 or 2 nitrogen; R^{101} , R^{102} and R^{103} are the same or different and each represents (1) hydrogen or (2) a group selected from Substituent Group C below; R^5 represents (1) hydrogen, (2) cyano, (3) halogen or (4) a group selected from Substituent Group A below; R^6 represents (1) hydrogen,

(2) C₁₋₆ alkyl, (3) acyl, (4) carbamoyl, (5) hydroxyl, (6) C₁₋₆ alkoxy, (7) C₁₋₆ alkyloxycarbonyloxy, (8) C₃₋₈ cycloalkyl, (9) C₁₋₆ alkyloxycarbonyl optionally substituted with acyloxy or (10) a C₆₋₁₄ aromatic hydrocarbon ring group or 5- to 14-membered aromatic heterocyclic group (each of the foregoing members being optionally substituted with at least one group selected from Substituent Group E); Y¹ represents a single bond, -(CH₂)_m-, -CR⁸-, -CR⁸R⁹-, -CH₂CO-, -NR⁸-, -SO-, -SO₂-, -CO-, -CONR⁸- or -SO₂NR⁸- [wherein m represents an integer of 1 to 3, and R⁸ and R⁹ are the same or different and each represents hydrogen, halogen, C₁₋₆ alkyl, carboxyl or C₁₋₆ alkoxy carbonyl]; Y² represents a single bond, O, N, -(CH₂)_m-, -CR⁸-, CR⁸R⁹-, -CO-, -SO-, -SO₂- or -C(=N-OR⁸)- [wherein m, R⁸ and R⁹ are as defined above]; Ar represents (1) hydrogen, (2) a group represented by the formula:



[wherein R¹⁰, R¹¹, R¹², R¹³ and R¹⁴ are the same or different and each represents (1) hydrogen, (2) cyano, (3) halogen, (4) nitro or (5) a group selected from Substituent Group B below, and R¹¹ and R¹² or R¹² and R¹³ may bond together to form a 5- to 8-membered

heterocycle optionally having 1 to 4 hetero atoms selected from N, S and O and also optionally substituted with at least one group selected from Substituent Group F] or (3) a 5- to 14-membered aromatic heterocyclic group optionally substituted with at least one group selected from Substituent Group G below.

<Substituent Group A> The group consisting of C₁₋₆ alkyl, alkylidene, C₂₋₆ alkenyl, C₂₋₆ alkynyl, acyl, carboxyl, carbamoyl, C₁₋₆ alkoxycarbonyl, C₁₋₆ alkylaminocarbonyl, hydroxyl, C₁₋₆ alkoxy, C₃₋₈ cycloalkyloxy, amino, C₁₋₆ alkylamino, C₃₋₈ cycloalkylamino, acylamino, sulfonylamino, sulfonyl, sulfamoyl, C₃₋₈ cycloalkyl, a 5- to 14-membered non-aromatic heterocyclic group, a C₆₋₁₄ aromatic hydrocarbon ring group and a 5- to 14-membered aromatic heterocyclic group, each of the foregoing members being optionally substituted with at least one group selected from Substituent Group A' below;

<Substituent Group A'> The group consisting of C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, cyano, acyl, carboxyl, carbamoyl, C₁₋₆ alkoxycarbonyl, C₁₋₆ alkylaminocarbonyl, hydroxyl, C₁₋₆ alkoxy, C₃₋₈ cycloalkyloxy, amino, C₁₋₆ alkylamino, C₃₋₈ cycloalkylamino, acylamino, ureido, ureylene, sulfonylamino, sulfonyl, sulfamoyl, halogen, C₃₋₈ cycloalkyl, a heterocyclic alkyl group, a 5- to

14-membered non-aromatic heterocyclic group, a C₆₋₁₄ aromatic hydrocarbon ring group and a 5- to 14-membered aromatic heterocyclic group, wherein the C₆₋₁₄ aromatic hydrocarbon ring group and the 5- to 14-membered aromatic heterocyclic group may be

substituted with at least one group selected from the group consisting of C₁₋₆ alkyl, cyano, acyl, carboxyl, carbamoyl, C₁₋₆ alkoxy carbonyl, C₁₋₆ alkylaminocarbonyl, hydroxyl, C₁₋₆ alkoxy, C₃₋₈ cycloalkyloxy, nitro, amino, C₁₋₆ alkylamino, C₃₋₈ cycloalkylamino, acylamino, ureido, ureylene, sulfonylamino, sulfonyl, sulfamoyl, halogen and C₃₋₈ cycloalkyl;

<Substituent Group B> The group consisting of C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, acyl, carboxyl, carbamoyl, C₁₋₆ alkoxy carbonyl, C₁₋₆ alkylaminocarbonyl, hydroxyl, C₁₋₆ alkoxy, C₃₋₈ cycloalkyloxy, amino, C₁₋₆ aminoalkyl, C₁₋₆ alkylamino, C₃₋₈ cycloalkylamino, acylamino, ureido, sulfonylamino, sulfonyl, sulfamoyl, C₃₋₈ cycloalkyl, a 5- to 14-membered non-aromatic heterocyclic group, a C₆₋₁₄ aromatic hydrocarbon ring group and a 5- to 14-membered aromatic heterocyclic group, each of the foregoing members being optionally substituted with at least one group selected from Substituent Group B' below;

<Substituent Group B'> The group consisting of C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, oxo, cyano, C₁₋₆

cyanoacyl, C₂₋₇ acyl, C₁₋₆ alkanoyl, benzoyl, aralkanoyl,
 C₁₋₆ alkoxyalkylcarbonyl, C₁₋₆ hydroxyalkylcarbonyl,
 carboxyl, C₁₋₆ carboxyalkyl, C₁₋₆ carboxyalkyloxy,
 carbamoyl, carbamoylalkyloxy, C₁₋₆ alkoxycarbonyl, C₁₋₁₀
 5 alkoxycarbonyl-C₁₋₆ alkyl, C₁₋₁₀ alkoxycarbonyl-C₁₋₆
 alkyloxy, C₁₋₆ monoalkylaminocarbonyl, C₂₋₆
 dialkylaminocarbonyl, hydroxyl, C₁₋₆ alkoxy, C₁₋₁₀
 alkoxyalkyl, C₁₋₁₀ aralkyloxyalkyl, C₁₋₆ hydroxyalkyl,
 C₃₋₈ cycloalkyloxy, amino, C₁₋₆ alkylamino, C₃₋₈
 10 cycloalkylamino, acylamino, ureido, ureylene, C₁₋₆
 alkylsulfonylamino, phenylsulfonylamino, C₁₋₆
 alkylsulfonyl, phenylsulfonyl, C₁₋₆
 monoalkylaminosulfonyl, C₂₋₆ dialkylaminosulfonyl,
 sulfamoyl, halogeno, C₃₋₈ cycloalkyl, a 5- to 14-
 15 membered non-aromatic heterocyclic group, a C₆₋₁₄
 aromatic hydrocarbon ring group, a 5- to 14-membered
 aromatic heterocyclic group, a heterocyclic
 aminocarbonyl group, a heterocyclic aminosulfonyl
 group and isoxazolinyl, wherein the 5- to 14-membered
 20 non-aromatic heterocyclic group, the C₆₋₁₄ aromatic
 hydrocarbon ring group, the 5- to 14-membered aromatic
 heterocyclic group and isoxazolinyl may be
 independently substituted with at least one group
 selected from the group consisting of C₁₋₆ alkyl, oxo,
 25 cyano, acyl, carboxyl, carbamoyl, C₁₋₆ alkoxycarbonyl,
 C₁₋₆ alkylaminocarbonyl, hydroxyl, C₁₋₆ alkoxy, C₃₋₈

cycloalkyloxy, nitro, amino, C₁₋₆ aminoalkyl, C₁₋₆ alkylamino, C₁₋₆ dialkylamino, C₃₋₈ cycloalkylamino, acylamino, ureido, ureylene, alkylsulfonylamino, alkylsulfonyl, sulfamoyl, halogeno and C₃₋₈ cycloalkyl;

5 <Substituent Group C> The group consisting of (1) cyano, (2) halogen and (3) C₁₋₆ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, acyl, carboxyl, carbamoyl, C₁₋₆ alkoxy, C₁₋₆ alkylaminocarbonyl, hydroxyl, C₁₋₆ alkoxy, C₃₋₈ cycloalkyloxy, amino, C₁₋₆ alkylamino, C₃₋₈ cycloalkylamino, acylamino, ureido, sulfonylamino, sulfonyl, sulfamoyl, C₃₋₈ cycloalkyl, a 5- to 14-membered non-aromatic heterocyclic group, a C₆₋₁₄ aromatic hydrocarbon ring group and 5- to 14-membered aromatic heterocyclic group (each of the foregoing members being optionally substituted with at least one group selected from Substituent Group C' below);

15 <Substituent Group C'> The group consisting of C₁₋₆ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, cyano, acyl, carboxyl, carbamoyl, C₁₋₆ alkoxy, C₁₋₆ alkylaminocarbonyl, hydroxyl, C₁₋₆ alkoxy, C₃₋₈ cycloalkyloxy, amino, C₁₋₆ alkylamino, C₃₋₈ cycloalkylamino, acylamino, ureido, ureylene, sulfonylamino, sulfonyl, sulfamoyl, halogeno, C₃₋₈ cycloalkyl, a 5- to 14-membered non-aromatic heterocyclic group, a C₆₋₁₄ aromatic hydrocarbon ring group and a 5- to 14-membered aromatic heterocyclic group;

<Substituent Group E> The group consisting of C₁₋₆ alkyl, cyano, acyl, carboxyl, carbamoyl, C₁₋₆ alkoxy, C₃₋₈ cycloalkyloxy, amino, C₁₋₆ alkylamino, C₃₋₈ cycloalkylamino, acylamino, ureido, ureylene, sulfonylamino, sulfonyl, sulfamoyl, halogen and C₃₋₈ cycloalkyl;

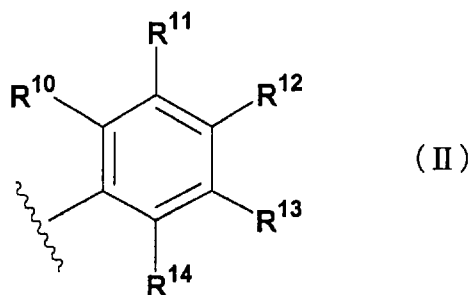
<Substituent Group F> The group consisting of (1) hydrogen, (2) cyano, (3) halogen, (4) oxo and (5) C₁₋₆ alkyl, alkenyl, alkynyl, acyl, C₁₋₆ alkanoyl, carboxyl, carbamoyl, C₁₋₆ alkoxy, C₃₋₈ cycloalkyloxy, amino, imino, C₁₋₆ aminoalkyl, C₁₋₆ alkylamino, C₃₋₈ cycloalkylamino, acylamino, ureido, sulfonylamino, sulfonyl, sulfamoyl, C₃₋₈ cycloalkyl, a 5- to 14-membered non-aromatic heterocyclic group, a C₆₋₁₄ aromatic hydrocarbon ring group and a 5- to 14-membered aromatic heterocyclic group (each of the foregoing members being optionally substituted with at least one group selected from Substituent Group F' below);

<Substituent Group F'> The group consisting of C₁₋₆ alkyl, oxo, cyano, acyl, carboxyl, carbamoyl, C₁₋₆ alkoxy, C₃₋₈ cycloalkyloxy, amino, C₁₋₆ alkylamino, C₃₋₈ cycloalkylamino, acylamino, ureido, ureylene, C₁₋₆

alkylsulfonylamino, C₁₋₆ alkylsulfonyl, sulfamoyl, halogeno, C₃₋₈ cycloalkyl, a 5- to 14-membered non-aromatic heterocyclic group, a C₆₋₁₄ aromatic hydrocarbon ring group and a 5- to 14-membered aromatic heterocyclic group;

<Substituent Group G> The group consisting of C₁₋₆ alkyl, cyano, acyl, carboxyl, carbamoyl, C₁₋₆ alkoxy carbonyl, C₁₋₆ alkylaminocarbonyl, sulfonyl, sulfamoyl, halogeno and C₃₋₈ cycloalkyl.} or a salt thereof;

<2> a compound according to <1> or a salt thereof, wherein ring B represents a further optionally substituted benzene ring or pyridine ring; R¹⁰¹, R¹⁰² and R¹⁰³ are the same or different and each represents a group selected from the group consisting of hydrogen, halogen, C₁₋₆ alkyl, C₁₋₆ alkylaminocarbonyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino and C₃₋₈ cycloalkyl; R⁵ represents a group selected from the group consisting of hydrogen, C₁₋₆ alkyl and C₁₋₆ alkoxy-C₁₋₆ alkyl; R⁶ represents a group selected from the group consisting of hydrogen, C₁₋₆ alkyl and C₁₋₆ alkyloxycarbonyl optionally substituted with acyloxy; Y¹ represents a single bond or -(CH₂)_m- [wherein m represents an integer of 1 to 3]; Y² represents a single bond or -CO-; and Ar represents hydrogen or a group represented by the formula:



[wherein R^{10} , R^{11} , R^{12} , R^{13} and R^{14} are the same or different and each represents a group selected from the group consisting of hydrogen, C_{1-6} alkyl, hydroxyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{3-8} cycloalkylamino, acylamino, a 5- to 14-membered non-aromatic heterocyclic group and C_{1-6} alkyloxycarbonyloxy, and R^{11} and R^{12} or R^{12} and R^{13} may bond together to form a 5- to 8-membered heterocyclic ring (i) optionally having 1 to 4 hetero atoms selected from N, S and O and (ii) optionally substituted with at least one group selected from the group consisting of cyano, oxo, and C_{1-6} alkyl, acyl, C_{1-6} alkanoyl, carboxyl, carbamoyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylaminocarbonyl, hydroxyl, C_{1-6} alkoxy, C_{3-8} cycloalkyloxy, amino, C_{1-6} alkylamino, sulfonyl and a 5- to 14-membered non-aromatic heterocyclic group (each of the foregoing member being optionally substituted with at least one group selected from Substituent Group F" below)

<Substituent Group F"> The group consisting of C_{1-6} alkyl, oxo, cyano, acyl, carboxyl and C_{1-6} alkoxy];
 <3> a compound according to <1> or a salt thereof,
 wherein ring B is an optionally substituted benzene

ring;

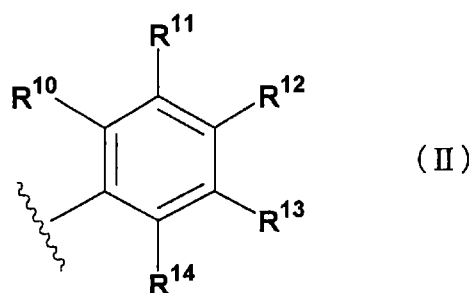
<4> a compound according to <1> or a salt thereof,
wherein Y^1 is $-CH_2-$;

5 <5> a compound according to <1> or a salt thereof,
wherein Y^2 is $-CO-$;

<6> a compound according to <1> or a salt thereof,
wherein Y^1 is $-CH_2-$ and Y^2 is $-CO-$;

10 <7> a compound according to <1> or a salt thereof,
wherein Y^1 is a single bond, Y^2 is a single bond and
Ar is hydrogen;

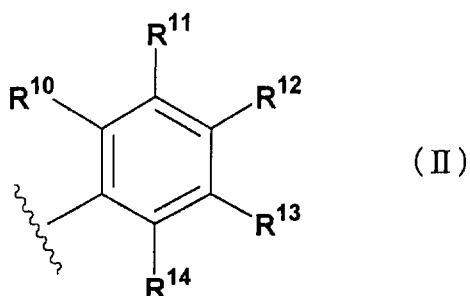
<8> a compound according to <1> or a salt thereof,
wherein Ar is a group represented by the formula:



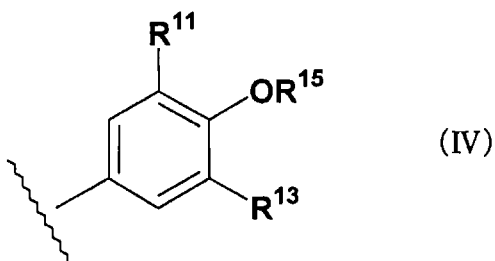
15 [wherein R^{10} , R^{11} , R^{12} , R^{13} and R^{14} are as defined
above];

<9> a compound according to <8> or a salt thereof,
wherein R^{10} and R^{14} are hydrogen;

<10> a compound according to <1> or a salt thereof,
wherein Ar is (1) a group represented by the formula:



[wherein R^{10} , R^{11} , R^{12} , R^{13} and R^{14} are as defined above]
 or (2) a 5- to 14-membered aromatic heterocyclic group
 optionally substituted with at least one group
 5 selected from Substituent Group G above;
 <11> a compound according to <10> or a salt thereof,
 wherein R^{10} and R^{14} are hydrogen;
 <12> a compound according to <1> or a salt thereof,
 wherein Ar is a group represented by the formula:



10 [wherein R^{11} and R^{13} are as defined above, R^{15}
 represents (1) hydrogen or (2) a group selected from
 Substituent Group H below, and R^{11} and R^{15} may bond
 together to form a 5- to 8-membered heterocycle
 15 optionally substituted with at least one group
 selected from Substituent Group F above and optionally
 having 1 or 2 hetero atoms selected from N, S and O.
 <Substituent Group H> The group consisting of C_{1-6}
 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, acyl, C_{1-6}

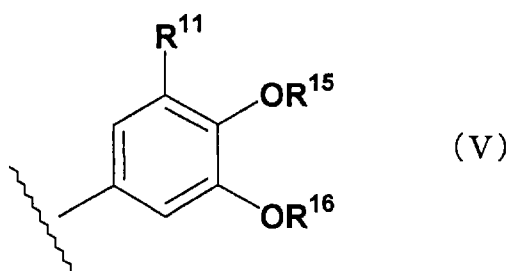
alkoxycarbonyl, aminocarbonyl, C₁₋₆ alkylaminocarbonyl, C₃₋₈ cycloalkyl, C₁₋₆ aminoalkyl, sulfonyl, C₃₋₈ cycloalkylamino, a 5- to 14-membered non-aromatic heterocyclic group, a C₆₋₁₄ aromatic hydrocarbon ring group and a 5- to 14-membered aromatic heterocyclic group, each of the foregoing members being optionally substituted with at least one group selected from Substituent Group H' below;

<Substituent Group H'> The group consisting of C₁₋₆

alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, oxo, cyano, C₁₋₆ cyanoalkyl, C₂₋₇ acyl, C₁₋₆ alkanoyl, benzoyl, aralkanoyl, C₁₋₆ alkoxyalkylcarbonyl, C₁₋₆ hydroxyalkylcarbonyl, carboxyl, C₁₋₆ carboxyalkyl, C₁₋₆ carboxyalkyloxy, carbamoyl, carbamoylalkyloxy, C₁₋₆ alkoxycarbonyl, C₁₋₁₀ alkoxycarbonyl-C₁₋₆ alkyl, C₁₋₁₀ alkoxycarbonyl-C₁₋₆ alkyloxy, C₁₋₆ monoalkylaminocarbonyl, C₂₋₆ dialkylaminocarbonyl, hydroxyl, C₁₋₆ alkoxy, C₁₋₁₀ alkoxyalkyl, C₁₋₁₀ aralkyloxyalkyl, C₁₋₆ hydroxyalkyl, C₃₋₈ cycloalkyloxy, amino, C₁₋₆ alkylamino, C₃₋₈ cycloalkylamino, acylamino, ureido, ureylene, C₁₋₆ alkylsulfonylamino, phenylsulfonylamino, C₁₋₆ alkylsulfonyl, phenylsulfonyl, C₁₋₆ monoalkylaminosulfonyl, C₂₋₆ dialkylaminosulfonyl, sulfamoyl, halogeno, C₃₋₈ cycloalkyl, a 5- to 14-membered non-aromatic heterocyclic group, a C₆₋₁₄ aromatic hydrocarbon ring group, a 5- to 14-membered

aromatic heterocyclic group, a heterocyclic
 aminocarbonyl group, a heterocyclic aminosulfonyl
 group and isoxazolinyl, wherein the 5- to 14-membered
 non-aromatic heterocyclic group, the C₆₋₁₄ aromatic
 5 hydrocarbon ring group, the 5- to 14-membered aromatic
 heterocyclic group and isoxazolinyl may be
 independently substituted with at least one group
 selected from the group consisting of C₁₋₆ alkyl, oxo,
 cyano, acyl, carboxyl, carbamoyl, C₁₋₆ alkoxy, carbonyl,
 10 C₁₋₆ alkylaminocarbonyl, hydroxyl, C₁₋₆ alkoxy, C₃₋₈
 cycloalkyloxy, nitro, amino, C₁₋₆ aminoalkyl, C₁₋₆
 alkylamino, C₁₋₆ dialkylamino, C₃₋₈ cycloalkylamino,
 acylamino, ureido, ureylene, alkylsulfonylamino,
 alkylsulfonyl, sulfamoyl, halogeno and C₃₋₈
 15 cycloalkyl];

<13> a compound according to <1> or a salt thereof,
 wherein Ar is a group represented by the formula:

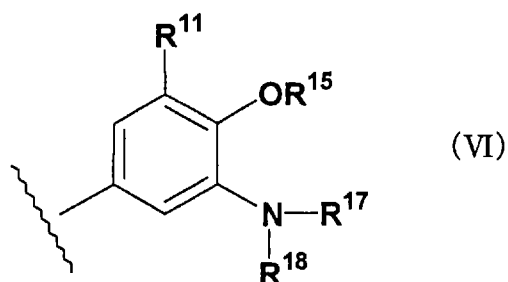


[wherein R¹¹ and R¹⁵ are as defined above, and R¹⁶
 20 represents (1) hydrogen or (2) a group selected from
 Substituent Group H above, and R¹¹ and R¹⁵ or R¹⁵ and
 R¹⁶ may bond together to form a 5- to 6-membered
 heterocycle optionally substituted with at least one

group selected from Substituent Group F above and also optionally having 1 or 2 hetero atoms selected from N, S and O];

<14> a compound according to <1> or a salt thereof,

5 wherein Ar is a group represented by the formula:



[wherein R^{11} and R^{15} are as defined above, and R^{17} and R^{18} are the same or different and each represents (1) hydrogen or (2) a group selected from Substituent Group I below, and R^{11} and R^{15} , R^{15} and R^{17} , R^{15} and R^{18} or R^{17} and R^{18} may bond together to form a 5- to 8-membered heterocycle optionally substituted with at least one group selected from Substituent Group F above and also optionally having 1 or 2 hetero atoms selected from N, S and O.

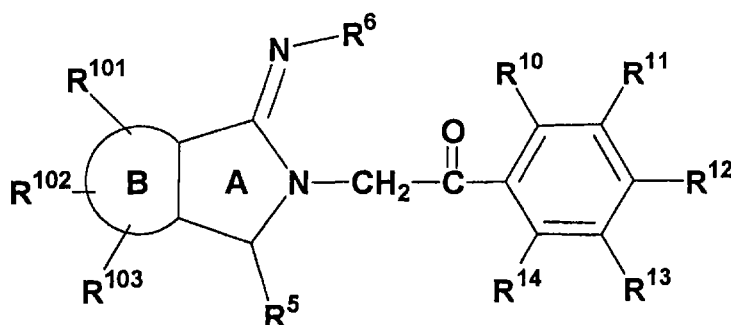
<Substituent Group I> The group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, acyl, carbamoyl, C_{1-6} alkoxy carbonyl, C_{1-6} alkylaminocarbonyl, C_{1-6} aminoalkyl, sulfonyl, sulfamoyl, C_{3-8} cycloalkyl, a 5- to 14-membered non-aromatic heterocyclic group, a C_{6-14} aromatic hydrocarbon ring group and a 5- to 14-membered aromatic heterocyclic group, each of the foregoing members being optionally substituted with at

least one group selected from Substituent Group I'
below;

<Substituent Group I'> The group consisting of C₁₋₆
alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, oxo, cyano, C₁₋₆
5 cyanoalkyl, C₂₋₇ acyl, C₁₋₆ alkanoyl, benzoyl,
aralkanoyl, C₁₋₆ alkoxyalkylcarbonyl, C₁₋₆
hydroxyalkylcarbonyl, carboxyl, C₁₋₆ carboxyalkyl, C₁₋₆
carboxyalkyloxy, carbamoyl, carbamoylalkyloxy, C₁₋₆
alkoxycarbonyl, C₁₋₁₀ alkoxycarbonyl-C₁₋₆ alkyl, C₁₋₁₀
10 alkoxycarbonyl-C₁₋₆ alkyloxy, C₁₋₆
monoalkylaminocarbonyl, C₂₋₆ dialkylaminocarbonyl,
hydroxyl, C₁₋₆ alkoxy, C₁₋₁₀ alkoxyalkyl, C₁₋₁₀
aralkyloxyalkyl, C₁₋₆ hydroxyalkyl, C₃₋₈ cycloalkyloxy,
amino, C₁₋₆ alkylamino, C₃₋₈ cycloalkylamino, acylamino,
15 ureido, ureylene, C₁₋₆ alkylsulfonylamino,
phenylsulfonylamino, C₁₋₆ alkylsulfonyl, phenylsulfonyl,
C₁₋₆ monoalkylaminosulfonyl, C₂₋₆ dialkylaminosulfonyl,
sulfamoyl, halogeno, C₃₋₈ cycloalkyl, a 5- to 14-
membered non-aromatic heterocyclic group, a C₆₋₁₄
20 aromatic hydrocarbon ring group, a 5- to 14-membered
aromatic heterocyclic group, a heterocyclic
aminocarbonyl group, a heterocyclic aminosulfonyl
group and isoxazolinyl, wherein the 5- to 14-membered
non-aromatic heterocyclic group, the C₆₋₁₄ aromatic
25 hydrocarbon ring group, the 5- to 14-membered aromatic
heterocyclic group and isoxazolinyl may be

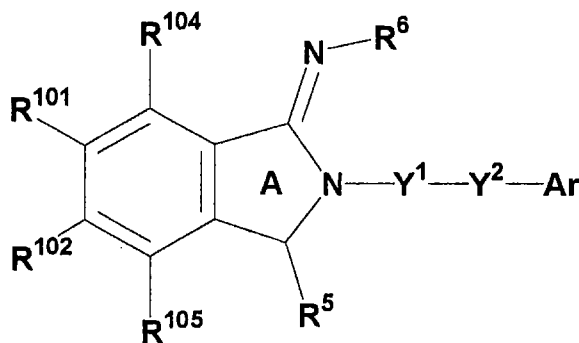
independently substituted with at least one group selected from the group consisting of C₁₋₆ alkyl, oxo, cyano, acyl, carboxyl, carbamoyl, C₁₋₆ alkoxy, C₁₋₆ alkylaminocarbonyl, hydroxyl, C₁₋₆ alkoxy, C₃₋₈ cycloalkyloxy, nitro, amino, C₁₋₆ aminoalkyl, C₁₋₆ alkylamino, C₁₋₆ dialkylamino, C₃₋₈ cycloalkylamino, acylamino, ureido, ureylene, alkylsulfonylamino, alkylsulfonyl, sulfamoyl, halogeno and C₃₋₈ cycloalkyl];

<15> a compound according to <1> or a salt thereof, wherein the compound is represented by the formula:



[wherein the definitions of the symbols are the same as given above];

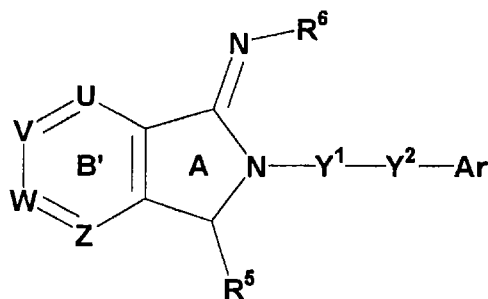
<16> a compound according to <1> or a salt thereof, wherein the compound is represented by the formula:



[wherein R¹⁰⁴ and R¹⁰⁵ are the same or different and

each represents hydrogen, C₁₋₆ alkoxy, C₁₋₆ alkyl or halogen, and R¹⁰¹, R¹⁰², R⁵, R⁶, Y¹, Y² and Ar are as defined above];

<17> a compound according to <1> or a salt thereof, wherein the compound is represented by the formula:



[wherein U represents N or CH, V represents N or CR¹⁰¹, W represents N or CR¹⁰², Z represents N or CR¹⁰⁵, one or two from U, V, W and Z are N, and R¹⁰¹, R¹⁰², R¹⁰⁵, R⁵, R⁶, Y¹, Y² and Ar are as defined above];

<18> a compound according to <16> or <17> or a salt thereof, wherein Y¹ is -CH₂-;

<19> a compound according to <16> or <17> or a salt thereof, wherein Y² is -CO-;

<20> a compound according to <17> or a salt thereof, wherein U is N and V is CR¹⁰¹ [where R¹⁰¹ are as defined above];

<21> a pharmaceutical composition comprising a compound according to <1> or a salt thereof;

<22> a composition according to <21>, wherein the composition is a thrombin receptor antagonist;

<23> a composition according to <21>, wherein the composition is a thrombin receptor PAR1 antagonist;

<24> a composition according to <21>, wherein the composition is a platelet aggregation inhibitor;

<25> a composition according to <21>, wherein the composition is a proliferation inhibitor for smooth muscle cells;

<26> a composition according to <21>, wherein the composition is a proliferation inhibitor for endothelial cells, fibroblasts, nephrocytes, osteosarcoma cells, muscle cells, cancer cells and/or glia cells;

<27> a composition according to <21>, wherein the composition is a therapeutic or preventive agent for thrombosis, vascular restenosis, deep venous thrombosis, pulmonary embolism, cerebral infarction, heart disease, disseminated intravascular coagulation, hypertension, inflammatory disease, rheumatism, asthma, glomerulonephritis, osteoporosis, neurological disease and/or malignant tumor;

<28> use of a compound according to <1> or a salt thereof for the manufacture of a thrombin receptor antagonist;

<29> use according to <28>, wherein the thrombin receptor antagonist is a PAR1 receptor antagonist;

<30> use of a compound according to <1> or a salt thereof for the manufacture of a platelet aggregation inhibitor;

<31> a method of treating a thrombin receptor mediated disease in a patient suffering from the disease, comprising administering to the patient, a therapeutically effective amount of a compound according to <1> or a salt thereof; and
5 <32> a method for treating a proliferative disease of endothelial cells, fibroblasts, nephrocytes, osteosarcoma cells, muscle cells, cancer cells and/or glia cells, in a patient suffering from the disease, comprising administering to the patient, a therapeutically effective amount of a compound according to <1> or a salt thereof.
10

Best Mode for Carrying Out the Invention

The present invention will now be explained in greater detail.
15

Several of the structural formulas given for the compounds of the invention throughout the present specification will represent only a specific isomer for convenience, but the invention is not limited to such specific isomers and encompasses all isomers and isomer mixtures, including geometric isomers, asymmetric carbon-derived optical isomers, stereoisomers and tautomers which are implied by the structures of the compounds, and any isomer or mixture thereof may be used. The compounds of the invention therefore include those having asymmetric carbons in
20
25

their molecules and existing as optically active forms or racemic forms, and all such compounds are encompassed by the invention without restrictions.

There are also no restrictions on any crystalline polymorphism of the compounds, and any crystal forms may be used alone or in mixtures. The compounds of the invention and their salts may also be in the form of anhydrides or solvates such as hydrates, and all such forms are included within the scope of the claims of the present specification. Metabolites of the compounds of the invention produced by degradation in the body, as well as prodrugs of the compounds of the invention and their salts, are also encompassed within the scope of the claims of the present specification.

The symbols and terms used throughout the present specification will now be defined, with a more detailed description of the invention.

The term "and/or" as used throughout the present specification carries the meaning of both "and" and "or".

The term "halogen" used throughout the present specification refers to an atom such as fluorine, chlorine, bromine or iodine, and preferably fluorine, chlorine or bromine.

The term "C₁₋₆ alkyl" used throughout the present specification refers to an alkyl group of 1 to 6

carbons, and as examples of such groups there may be mentioned preferably linear or branched alkyl groups such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, n-pentyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl, 1-ethylpropyl, 2-ethylpropyl, n-hexyl, 1-methyl-2-ethylpropyl, 1-ethyl-2-methylpropyl, 1,1,2-trimethylpropyl, 1-propylpropyl, 1-methylbutyl, 2-methylbutyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethylbutyl, 1,3-dimethylbutyl, 2,3-dimethylbutyl, 2-ethylbutyl, 2-methylpentyl and 3-methylpentyl, and more preferably methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl and n-pentyl.

The term "C₂₋₆ alkenyl" used throughout the present specification refers to an alkenyl group of 2 to 6 carbons, and as preferred examples of such groups there may be mentioned vinyl, allyl, 1-propenyl, 2-propenyl, isopropenyl, 2-methyl-1-propenyl, 3-methyl-1-propenyl, 2-methyl-2-propenyl, 3-methyl-2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1-pentenyl, 1-hexenyl, 1,3-hexanedieryl and 1,6-hexanedieryl.

The term "C₂₋₆ alkynyl" used throughout the present specification refers to an alkynyl group of 2 to 6 carbons, and as preferred examples of such groups there may be mentioned ethynyl, 1-propynyl, 2-propynyl,

1-butynyl, 2-butynyl, 3-butynyl, 3-methyl-1-propynyl,
1-ethynyl-2-propynyl, 2-methyl-3-propynyl, 1-pentynyl,
1-hexynyl, 1,3-hexanediynyl and 1,6-hexanediynyl.

5 The term "C₃₋₈ cycloalkyl" used throughout the
present specification refers to a cycloalkyl group
composed of 3 to 8 carbons, and as examples there may
be mentioned cyclopropyl, cyclobutyl, cyclopentyl,
cyclohexyl, cycloheptyl and cyclooctyl.

10 The term "C₃₋₈ cycloalkenyl" used throughout the
present specification refers to a C₃₋₈ cycloalkenyl
group composed of 3 to 8 carbons, and as examples
there may be mentioned cyclopropen-1-yl, cyclopropen-
3-yl, cyclobuten-1-yl, cyclobuten-3-yl, 1,3-
cyclobutadien-1-yl, cyclopenten-1-yl, cyclopenten-3-yl,
15 cyclopenten-4-yl, 1,3-cyclopentadien-1-yl, 1,3-
cyclopentadien-2-yl, 1,3-cyclopentadien-5-yl,
cyclohexen-1-yl, cyclohexen-3-yl, cyclohexen-4-yl,
1,3-cyclohexadien-1-yl, 1,3-cyclohexadien-2-yl, 1,3-
cyclohexadien-5-yl, 1,4-cyclohexadien-3-yl, 1,4-
20 cyclohexadien-1-yl, cyclohepten-1-yl, cyclohepten-3-yl,
cyclohepten-4-yl, cyclohepten-5-yl, 1,3-cyclohepten-2-
yl, 1,3-cyclohepten-1-yl, 1,3-cycloheptadien-5-yl,
1,3-cycloheptadien-6-yl, 1,4-cycloheptadien-3-yl, 1,4-
cycloheptadien-2-yl, 1,4-cycloheptadien-1-yl, 1,4-
25 cycloheptadien-6-yl, 1,3,5-cycloheptatrien-3-yl,
1,3,5-cycloheptatrien-2-yl, 1,3,5-cycloheptatrien-1-yl,

1,3,5-cycloheptatrien-7-yl, cycloocten-1-yl,
 cycloocten-3-yl, cycloocten-4-yl, cycloocten-5-yl,
 1,3-cyclooctadien-2-yl, 1,3-cyclooctadien-1-yl, 1,3-
 cyclooctadien-5-yl, 1,3-cyclooctadien-6-yl, 1,4-
 5 cyclooctadien-3-yl, 1,4-cyclooctadien-2-yl, 1,4-
 cyclooctadien-1-yl, 1,4-cyclooctadien-6-yl, 1,4-
 cyclooctadien-7-yl, 1,5-cyclooctadien-3-yl, 1,5-
 cyclooctadien-2-yl, 1,3,5-cyclooctatrien-3-yl, 1,3,5-
 cyclooctatrien-2-yl, 1,3,5-cyclooctatrien-1-yl, 1,3,5-
 10 cyclooctatrien-7-yl, 1,3,6-cyclooctatrien-2-yl, 1,3,6-
 cyclooctatrien-1-yl, 1,3,6-cyclooctatrien-5-yl and
 1,3,6-cyclooctatrien-6-yl.

The term "C₁₋₆ alkoxy" used throughout the present
 specification refers to an alkoxy group of 1 to 6
 15 carbons, and as preferred examples there may be
 mentioned methoxy, ethoxy, n-propoxy, iso-propoxy,
 sec-propoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-
 butoxy, n-pentyloxy, iso-pentyloxy, sec-pentyloxy, n-
 hexoxy, iso-hexoxy, 1,1-dimethylpropyloxy, 1,2-
 20 dimethylpropoxy, 2,2-dimethylpropyloxy, 2-ethylpropoxy,
 1-methyl-2-ethylpropoxy, 1-ethyl-2-methylpropoxy,
 1,1,2-trimethylpropoxy, 1,1,2-trimethylpropoxy, 1,1-
 dimethylbutoxy, 1,2-dimethylbutoxy, 2,2-dimethylbutoxy,
 2,3-dimethylbutyloxy, 1,3-dimethylbutyloxy, 2-
 25 ethylbutoxy, 1,3-dimethylbutoxy, 2-methylpentoxy, 3-
 methylpentoxy and hexyloxy.

The term "C₂₋₆ alkenyloxy" used throughout the present specification refers to an alkenyloxy group of 2 to 6 carbons, and as preferred examples there may be mentioned vinyloxy, allyloxy, 1-propenyloxy, 2-propenyloxy, isopropenyloxy, 2-methyl-1-propenyloxy, 3-methyl-1-propenyloxy, 2-methyl-2-propenyloxy, 3-methyl-2-propenyloxy, 1-butenyloxy, 2-butenyloxy, 3-butenyloxy, 1-pentenyloxy, 1-hexenyloxy, 1,3-hexanedienyloxy and 1,6-hexanedienyloxy.

The term "acyl" used throughout the present specification refers to an atomic group derived by removing the OH group from a carboxyl group of a carboxylic acid, and it is preferably a C₂₋₇ acyl group (an atomic group derived by removing the OH group from a carboxyl group of a C₂₋₇ carboxylic acid (more preferably fatty acid)), of which preferred examples include acetyl, propionyl, butyroyl and benzoyl.

The term "C₆₋₁₄ aromatic hydrocarbon ring group" used throughout the present specification refers to an aromatic hydrocarbon ring group composed of 6 to 14 carbons, and includes monocyclic groups as well as fused rings such as bicyclic and tricyclic groups. As specific examples of such groups there may be mentioned phenyl, indenyl, 1-naphthyl, 2-naphthyl, azulenyl, heptalenyl, biphenyl, indacenyl, acenaphthyl, fluorenyl, phenalenyl, phenanthrenyl, anthracenyl,

cyclopentacyclooctenyl and benzocyclooctenyl.

The term "5- to 14-membered aromatic heterocyclic group" used throughout the present specification refers to a monocyclic, bicyclic or tricyclic 5- to 14-membered aromatic heterocyclic group comprising one or more hetero atoms selected from the group consisting of nitrogen, sulfur and oxygen. As specific examples of such groups there may be mentioned (i) nitrogen-containing aromatic heterocyclic groups such as pyrrolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazolyl, tetrazolyl, benzotriazolyl, pyrazolyl, imidazolyl, benzimidazolyl, indolyl, isoindolyl, indolidinyl, purinyl, indazolyl, quinolyl, isoquinolyl, quinolidyl, phthalazyl, naphthylidinyl, quinoxalyl, quinazolinyl, cinnolinyl, pteridinyl, imidazotriazinyl, pyrazinopyridazinyl, acridinyl, phenanthridinyl, carbazolyl, carbazolinyl, perimidinyl, phenanthrolinyl, phenacenyl, imidazopyridinyl, imidazopyrimidinyl, pyrazolopyridinyl, pyrazolopyrimidinyl, etc.; (ii) sulfur-containing aromatic heterocyclic groups such as thienyl, benzothienyl, etc.; (iii) oxygen-containing aromatic heterocyclic groups such as furyl, pyranyl, cyclopentapyranyl, benzofuryl, isobenzofuryl, etc.; and (iv) aromatic heterocyclic groups containing 2 or more different hetero atoms, such as thiazolyl,

isothiazolyl, benzothiazolyl, benzothiadiazolyl,
phenothiazinyl, isoxazolyl, furazanyl, phenoxazinyl,
oxazolyl, isoxazolyl, benzoxazolyl, oxadiazolyl,
pyrazoloxazolyl, imidazothiazolyl, thienofuranyl,
5 fuopyrrolyl, pyridoxazinyl, etc.

The term "5- to 14-membered non-aromatic
heterocyclic group" used throughout the present
specification refers to a monocyclic, bicyclic or
tricyclic 5- to 14-membered non-aromatic heterocyclic
10 group comprising one or more hetero atoms selected
from the group consisting of nitrogen, sulfur and
oxygen. As specific examples of such groups there may
be mentioned pyrrolidyl, pyrrolyl, piperidyl,
piperazyl, imidazolyl, pyrazolidyl, imidazolidyl,
15 morpholyl, tetrahydrofuryl, tetrahydropyranyl,
aziridinyl, oxiranyl and oxathiolanyl. Non-aromatic
heterocyclic groups also include a pyridone ring-
derived group, and a non-aromatic fused ring (for
example, a phthalimide ring-derived group and a
20 succinimide ring-derived group).

The term "5- to 8-membered heterocycle" used
throughout the present specification refers to a 5- to
8-membered aromatic or non-aromatic heterocycle.

The term "aryl" used throughout the present
25 specification refers to an atomic group remaining
after elimination of one hydrogen atom bonded to the

ring of the aromatic hydrocarbon, and there may be mentioned phenyl, tolyl, xylyl, biphenyl, naphthyl, anthoryl and phenanthoryl.

5 The term "alkylidene" used throughout the present specification refers to a divalent group derived by the loss of two hydrogen atoms from the same carbon of an aliphatic hydrocarbon (preferably a C₁₋₆ alkane), and there may be mentioned ethylidene and the like.

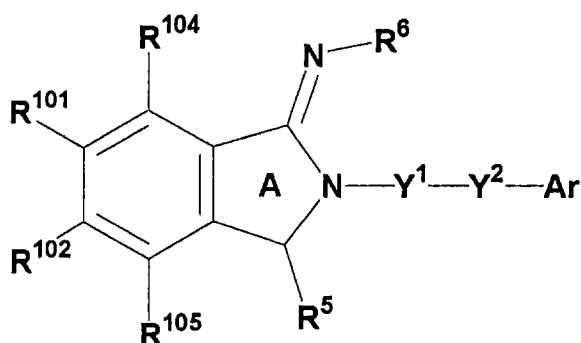
10 The expression "optionally substituted" appearing throughout the present specification has the same meaning as "having one or multiple substituents in any desired combination at substitutable positions".

15 The term "hetero atom" used throughout the present specification refers specifically to oxygen, sulfur, nitrogen, phosphorus, arsenic, antimony, silicon, germanium, tin, lead, boron, mercury and the like, and preferably oxygen, sulfur and nitrogen.

20 Throughout the present specification, the prefix "n-" signifies a normal type or primary substituent, "sec-" signifies a secondary substituent, "t-" signifies a tertiary substituent and "i-" signifies an iso type substituent.

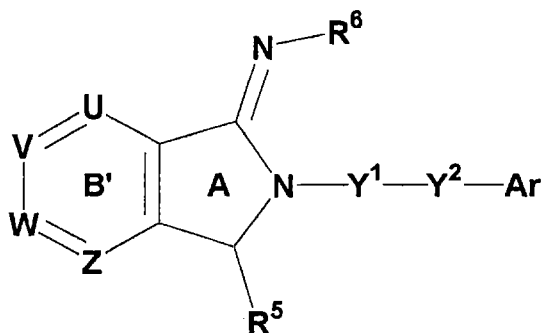
25 The definitions of ring B, R¹⁰¹, R¹⁰², R¹⁰³, R⁵, R⁶, Y¹, Y², and Ar in the compounds of the invention represented by the general formula (I) above are as explained above, but ring B is preferably a benzene

ring or a 6-membered aromatic heterocycle containing 1
or 2 nitrogen atoms, with benzene ring and pyridine
ring being more preferred. Thus, as more preferred
examples among compounds with a benzene ring as ring B
there may be mentioned a compound represented by the
5 formula:



[wherein R^{104} and R^{105} are the same or different and
each represents hydrogen, C_{1-6} alkoxy, C_{1-6} alkyl or
10 halogen; and R^{101} , R^{102} , R^5 , R^6 , Y^1 , Y^2 and Ar have the
same definitions given above].

As more preferred examples among compounds with a
6-membered aromatic heterocycle containing 1 or 2
nitrogen atoms as ring B there may be mentioned a
15 compound represented by the formula:



[wherein U represents N or CH (preferably N); V
represents N or CR^{101} (preferably CR^{101}); W represents N

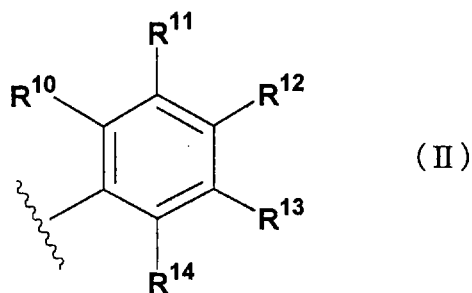
or CR^{102} ; Z represents N or CR^{105} ; one or two atoms selected from U, V, W and Z are N; and R^{101} , R^{102} , R^{105} , R^5 , R^6 , Y^1 , Y^2 and Ar have the same definitions given above].

5 Also, R^{101} , R^{102} and R^{103} are each preferably a group selected from the group consisting of hydrogen, halogen, C_{1-6} alkyl, C_{1-6} alkylaminocarbonyl, C_{1-6} alkoxy, C_{1-6} alkylamino and C_{3-8} cycloalkyl.

10 R^5 is preferably a group selected from the group consisting of hydrogen, C_{1-6} alkyl and C_{1-6} alkoxy- C_{1-6} alkyl, and R^6 is preferably a group selected from the group consisting of hydrogen, C_{1-6} alkyl and C_{1-6} alkyloxycarbonyl optionally substituted with acyloxy.

15 Y^1 preferably represents a single bond or $-(\text{CH}_2)_m-$ [wherein m represents an integer of 1 to 3] and Y^2 preferably represents a single bond or $-\text{CO}-$, there being more preferred (i) a combination that Y^1 is $-\text{CH}_2-$ and Y^2 is $-\text{CO}-$, and (ii) a combination that Y^1 and Y^2 are both single bonds.

20 Ar preferably represents hydrogen or a group represented by the formula:



[wherein R^{10} , R^{11} , R^{12} , R^{13} and R^{14} have the same

definitions given above].

(i) When Y^1 is $-CH_2-$ and Y^2 is $-CO-$, Ar is preferably a group represented by the general formula (II) above, and (ii) when Y^1 and Y^2 are both single bonds, Ar is preferably hydrogen.

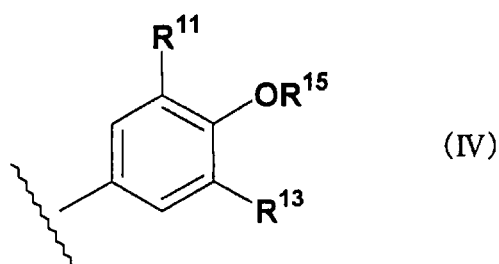
R^{10} , R^{11} , R^{12} , R^{13} and R^{14} are the same or different and are each preferably a group selected from the group consisting of hydrogen, C_{1-6} alkyl, hydroxyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{3-8} cycloalkylamino, acylamino, a 5- to 14-membered non-aromatic heterocyclic group and C_{1-6} alkyloxycarbonyloxy, and especially R^{10} and R^{14} are more preferably hydrogen. Also, R^{11} and R^{12} or R^{12} and R^{13} may bond together to form a 5- to 8-membered heterocyclic ring (i) optionally having 1 to 4 hetero atoms selected from N, S and O and (ii) optionally substituted with at least one group selected from the group consisting of cyano, oxo, and C_{1-6} alkyl, acyl, C_{1-6} alkanoyl, carboxyl, carbamoyl, C_{1-6} alkoxy, C_{1-6} alkoxy, C_{3-8} cycloalkyloxy, amino, C_{1-6} alkylamino, sulfonyl and a 5- to 14-membered non-aromatic heterocyclic group, each optionally substituted with at least one group selected from Substituent Group F" below:

<Substituent Group F"> The group consisting of C_{1-6} alkyl, oxo, cyano, acyl, carboxyl and C_{1-6} alkoxy.

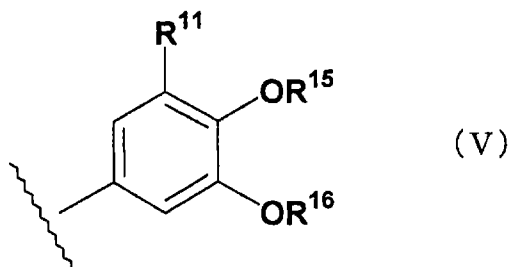
The preferred group for (ii) above is the group

consisting of cyano, oxo, C₁₋₆ alkyl, cyano-C₁₋₆ alkyl, C₁₋₆ acyl, carboxyl, C₁₋₆ alkoxy carbonyl, C₁₋₆ alkylaminocarbonyl, hydroxyl and C₁₋₆ alkoxy.

Thus, as more preferred examples for Ar when
 5 R¹⁰ and R¹⁴ are hydrogen there may be mentioned a group represented by the formula:

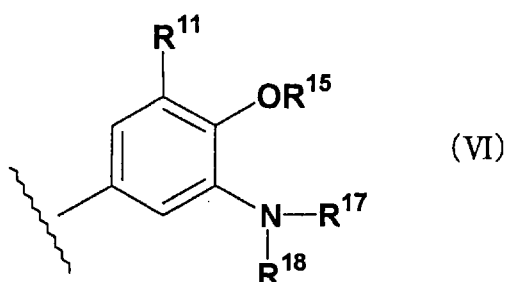


[wherein R¹¹ and R¹³ have the same definitions given above, R¹⁵ represents (1) hydrogen or (2) a group
 10 selected from Substituent Group H above, and R¹¹ and R¹⁵ may bond together to form a 5- to 8-membered heterocycle optionally substituted with at least one group selected from Substituent Group F above and optionally having 1 or 2 hetero atoms selected from N,
 15 S and O];
 a group represented by the formula:



[wherein R¹¹ and R¹⁵ have the same definitions given above, R¹⁶ represents (1) hydrogen or (2) a group

selected from Substituent Group H above, and R^{11} and R^{15} or R^{15} and R^{16} may bond together to form a 5- to 6-membered heterocycle optionally substituted with at least one group selected from Substituent Group F above and optionally having 1 or 2 hetero atoms selected from N, S and O];
 and a group represented by the formula:



[wherein R^{11} and R^{15} have the same definitions given above, R^{17} and R^{18} are the same or different and each represents (1) hydrogen or (2) a group selected from Substituent Group I, and R^{11} and R^{15} , R^{15} and R^{17} , R^{15} and R^{18} or R^{17} and R^{18} may bond together to form a 5- to 8-membered heterocycle optionally substituted with at least one group selected from Substituent Group F above and optionally having 1 or 2 hetero atoms selected from N, S and O].

The term "salt" used throughout the present specification is not particularly restrictive so long as the salt is formed with a compound of the invention and is pharmacologically acceptable, but preferably there may be mentioned hydrogen halide acid salts (for example, hydrofluoride, hydrochloride, hydrobromide

and hydroiodide), inorganic acid salts (for example, sulfate, nitrate, perchlorate, phosphate, carbonate and bicarbonate), organic carboxylate (for example, acetate, trifluoroacetate, oxalate, maleate, tartarate, fumarate and citrate), organosulfonate (for example, methanesulfonate, trifluoromethanesulfonate, ethanesulfonate, benzenesulfonate, toluenesulfonate and camphorsulfonate), amino acid salts (for example, aspartate and glutamate), quaternary amine salts, alkali metal salts (for example, sodium salts and potassium salts) or alkaline earth metal salts (for example, magnesium salts and calcium salts), and more preferred as "pharmacologically acceptable salts" are hydrochloride, oxalate, trifluoroacetate and the like.

The following may be mentioned as specific preferred examples of the compounds of the invention represented by the general formula (I) and their salts explained above.

2-[2-(3,5-di-*tert*-butyl-4-hydroxy-phenyl)-2-oxo-ethyl]-6-ethoxy-3-imino-2,3-dihydro-1H-isoindole-5-carboxylic acid methylamide trifluoroacetate; 2-[2-(3,5-di-*tert*-butyl-4-hydroxy-phenyl)-2-oxo-ethyl]-6-dimethylamino-3-imino-2,3-dihydro-1H-isoindole-5-carboxylic acid methylamide hydrobromide; 1-(3,5-di-*tert*-butyl-4-hydroxy-phenyl)-2-(7-fluoro-1-imino-5,6-dimethoxy-1,3-dihydro-isoindol-2-yl)-ethanone

hydrobromide; 1-(8-*tert*-butyl-4-methyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)-2-(5,6-diethoxy-7-fluoro-1-imino-1,3-dihydro-isoindol-2-yl)-ethanone hydrobromide; 2-[2-(3-*tert*-butyl-4,5-dimethoxy-phenyl)-2-oxo-ethyl]-6-ethoxy-3-imino-2,3-dihydro-1H-isoindole-5-carboxylic acid methylamide hydrobromide; 1-(3,5-di-*tert*-butyl-4-hydroxy-phenyl)-2-(5-ethoxy-7-fluoro-1-imino-6-methoxy-1,3-dihydro-isoindol-2-yl)-ethanone hydrobromide; 2-[2-(3-*tert*-butyl-4-hydroxy-5-isopropoxy-phenyl)-2-oxo-ethyl]-6-ethoxy-3-imino-2,3-dihydro-1H-isoindole-5-carboxylic acid methylamide hydrobromide; 6-[2-(8-*tert*-butyl-4-methyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)-2-oxo-ethyl]-3-ethoxy-7-imino-6,7-dihydro-5H-pyrrolo[3,4-b]pyridine-2-carboxylic acid methylamide hydrochloride; 2-[2-(7-*tert*-butyl-3-methyl-3H-benzimidazol-5-yl)-2-oxo-ethyl]-6-ethoxy-3-imino-2,3-dihydro-1H-isoindole-5-carboxylic acid methylamide hydrobromide; 2-[2-(3-*tert*-butyl-5-dimethylamino-4-hydroxy-phenyl)-2-oxo-ethyl]-6-ethoxy-3-imino-2,3-dihydro-1H-isoindole-5-carboxylic acid methylamide hydrobromide; 5-{2-*tert*-butyl-4-[2-(2-cyclopropyl-7-imino-5,7-dihydro-pyrrolo[3,4-b]pyridin-6-yl)-acetyl]-6-(pyrrolidin-1-yl)-phenoxy}-pentanoic acid trifluoroacetate; 5-{2-*tert*-butyl-4-[2-(7-fluoro-1-imino-5,6-dimethoxy-1,3-dihydro-isoindol-2-yl)-acetyl]-6-(pyrrolidin-1-yl)-

phenoxy}-pentanoic acid trifluoroacetate; 2-[2-(3-
 tert-butyl-5-dimethylamino-4-methoxy-phenyl)-2-oxo-
 ethyl]-6-ethoxy-3-imino-2,3-dihydro-1H-isoindole-5-
 carboxylic acid methylamide hydrobromide; 2-(1-{3-
 5 tert-butyl-5-[2-(7-fluoro-1-imino-5,6-dimethoxy-1,3-
 dihydro-isoindol-2-yl)-acetyl]-2-methoxy-phenyl}-
 pyrrolidin-3-yloxy)-butyric acid trifluoroacetate; 2-
 (1-{3-tert-butyl-5-[2-(7-fluoro-1-imino-5,6-dimethoxy-
 1,3-dihydro-isoindol-2-yl)-acetyl]-2-methoxy-phenyl}-
 10 pyrrolidin-3-yloxy)-butyric acid trifluoroacetate; 1-
 (3-tert-butyl-5-dimethylamino-4-methoxy-phenyl)-2-(7-
 fluoro-1-imino-5,6-dimethoxy-1,3-dihydro-isoindol-2-
 yl)-ethanone hydrobromide; 2-[2-(3-tert-butyl-5-
 dimethylamino-4-methoxy-phenyl)-2-oxo-ethyl]-6-
 15 dimethylamino-3-imino-2,3-dihydro-1H-isoindole-5-
 carboxylic acid methylamide hydrobromide; 6-[2-(3-
 tert-butyl-5-dimethylamino-4-methoxy-phenyl)-2-oxo-
 ethyl]-3-ethoxy-7-imino-6,7-dihydro-5H-pyrrolo[3,4-
 b]pyridine-2-carboxylic acid methylamide
 20 hydrochloride; 2-[2-(3-tert-butyl-5-ethoxy-4-methoxy-
 phenyl)-2-oxo-ethyl]-6-dimethylamino-3-imino-2,3-
 dihydro-1H-isoindole-5-carboxylic acid methylamide
 hydrobromide; 2-[2-(3-tert-butyl-5-ethoxy-4-methoxy-
 phenyl)-2-oxo-ethyl]-6-ethoxy-3-imino-2,3-dihydro-1H-
 25 isoindole-5-carboxylic acid methylamide hydrobromide;
 1-(3-tert-butyl-5-ethoxy-4-methoxy-phenyl)-2-(5,6-

diethoxy-7-fluoro-1-imino-1,3-dihydro-isoindol-2-yl)-
 ethanone hydrobromide; 6-[2-(3-tert-butyl-5-ethoxy-4-
 methoxy-phenyl)-2-oxo-ethyl]-3-ethoxy-7-imino-6,7-
 dihydro-5H-pyrrolo[3,4-b]pyridine-2-carboxylic acid
 5 methylamide trifluoroacetate; {3-tert-butyl-5-[2-(7-
 fluoro-1-imino-5,6-dimethoxy-1,3-dihydro-isoindol-2-
 yl)-acetyl]-2-methoxy-phenoxy}-acetonitrile
 hydrobromide; 4-{3-tert-butyl-5-[2-(7-fluoro-1-imino-
 5,6-dimethoxy-1,3-dihydro-isoindol-2-yl)-acetyl]-2-
 10 methoxy-phenoxy}-butyronitrile hydrobromide; 2-[2-(3-
 tert-butyl-5-cyanomethoxy-4-methoxy-phenyl)-2-oxo-
 ethyl]-6-dimethylamino-3-imino-2,3-dihydro-1H-
 isoindole-5-carboxylic acid methylamide hydrobromide;
 2-{2-[3-tert-butyl-5-(3-cyano-propoxy)-4-methoxy-
 15 phenyl]-2-oxo-ethyl}-6-dimethylamino-3-imino-2,3-
 dihydro-1H-isoindole-5-carboxylic acid methylamide
 hydrobromide; 2-[2-(8-tert-butyl-4-cyanomethyl-3,4-
 dihydro-2H-benzo[1,4]oxazin-6-yl)-2-oxo-ethyl]-6-
 ethoxy-3-imino-2,3-dihydro-1H-isoindole-5-carboxylic
 20 acid methylamide trifluoroacetate; 6-[2-(8-tert-butyl-
 4-cyanomethyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)-2-
 oxo-ethyl]-3-ethoxy-7-imino-6,7-dihydro-5H-
 pyrrolo[3,4-b]pyridine-2-carboxylic acid methylamide
 trifluoroacetate; {8-tert-butyl-6-[2-(7-fluoro-1-
 25 imino-5,6-dimethoxy-1,3-dihydro-isoindol-2-yl)-
 acetyl]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-

acetonitrile trifluoroacetate; {8-*tert*-butyl-6-[2-(5,6-diethoxy-7-fluoro-1-imino-1,3-dihydro-isoindol-2-yl)-acetyl]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-

acetonitrile trifluoroacetate; {8-*tert*-butyl-6-[2-(2-cyclopropyl-7-imino-5,7-dihydro-pyrrolo[3,4-*b*]pyridin-6-yl)-acetyl]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-

acetonitrile trifluoroacetate; 2-[2-(8-*tert*-butyl-4-cyanomethyl-3,4-dihydro-2*H*-benzo[1,4]oxazin-6-yl)-2-oxo-ethyl]-6-dimethylamino-3-imino-2,3-dihydro-1*H*-

isoindole-5-carboxylic acid methylamide

trifluoroacetate; 2-[2-(3-*tert*-butyl-5-cyanomethoxy-4-methoxy-phenyl)-2-oxo-ethyl]-6-ethoxy-3-imino-2,3-dihydro-1*H*-isoindole-5-carboxylic acid methylamide

hydrobromide; 2-{2-[3-*tert*-butyl-5-(3-cyano-propoxy)-4-methoxy-phenyl]-2-oxo-ethyl}-6-ethoxy-3-imino-2,3-dihydro-1*H*-isoindole-5-carboxylic acid methylamide

hydrobromide; 1-(3-*tert*-butyl-5-ethoxy-4-methoxy-phenyl)-2-(7-fluoro-1-imino-5,6-dimethoxy-1,3-dihydro-isoindol-2-yl)-ethanone hydrobromide; 2-[2-(3-*tert*-butyl-4-methoxy-5-morpholino-phenyl)-2-oxo-ethyl]-6-ethoxy-3-imino-2,3-dihydro-1*H*-isoindole-5-carboxylic acid methylamide hydrobromide; 1-(3-*tert*-butyl-4-methoxy-5-morpholino-phenyl)-2-(7-fluoro-1-imino-5,6-dimethoxy-1,3-dihydro-isoindol-2-yl)-ethanone

hydrobromide; 1-(3-*tert*-butyl-4-methoxy-5-morpholino-phenyl)-2-(2-cyclopropyl-7-imino-5,7-dihydro-

pyrrolo[3,4-b]pyridin-6-yl)-ethanone hydrobromide; {3-
 tert-butyl-5-[2-(5,6-diethoxy-7-fluoro-1-imino-1,3-
 dihydro-isoindol-2-yl)-acetyl]-2-methoxy-phenoxy}-
 acetonitrile hydrobromide; 4-{3-tert-butyl-5-[2-(5,6-
 5 diethoxy-7-fluoro-1-imino-1,3-dihydro-isoindol-2-yl)-
 acetyl]-2-methoxy-phenoxy}-butyronitrile hydrobromide;
 4-{3-tert-butyl-5-[2-(2-cyclopropyl-7-imino-5,7-
 dihydro-pyrrolo[3,4-b]pyridin-6-yl)-acetyl]-2-methoxy-
 phenoxy}-butyronitrile hydrobromide; 1-(3-tert-butyl-
 10 5-dimethylamino-4-methoxy-phenyl)-2-(5,6-diethoxy-7-
 fluoro-1-imino-1,3-dihydro-isoindol-2-yl)-ethanone
 hydrobromide; 1-(3-tert-butyl-4-methoxy-5-morpholino-
 phenyl)-2-(5,6-diethoxy-7-fluoro-1-imino-1,3-dihydro-
 isoindol-2-yl)-ethanone hydrobromide; 6-[2-(3-tert-
 15 butyl-4-methoxy-5-morpholino-phenyl)-2-oxo-ethyl]-3-
 ethoxy-7-imino-6,7-dihydro-5H-pyrrolo[3,4-b]pyridine-
 2-carboxylic acid methylamide hydrobromide; 2-tert-
 butyl-4-[2-(5-ethoxy-1-imino-6-methylcarbamoyl-1,3-
 dihydro-isoindol-2-yl)-acetyl]-phenyl methanesulfonate
 20 hydrobromide; 2-tert-butyl-4-[2-(5-dimethylamino-1-
 imino-6-methylcarbamoyl-1,3-dihydro-isoindol-2-yl)-
 acetyl]-phenyl methanesulfonate hydrobromide; 2-tert-
 butyl-4-[2-(3-ethoxy-7-imino-2-methylcarbamoyl-5,7-
 dihydro-pyrrolo[3,4-b]pyridin-6-yl)-acetyl]-phenyl
 25 methanesulfonate hydrobromide; 2-[2-(3-tert-butyl-4-
 cyanomethoxy-5-dimethylamino-phenyl)-2-oxo-ethyl]-6-

dimethylamino-3-imino-2,3-dihydro-1H-isoindole-5-
 carboxylic acid methylamide hydrobromide; 2-[2-(3-
 tert-butyl-4-methoxy-5-(pyrrolidin-1-yl)-phenyl)-2-
 oxo-ethyl]-6-ethoxy-3-imino-2,3-dihydro-1H-isoindole-
 5-carboxylic acid methylamide hydrobromide; 1-(3-tert-
 butyl-4-methoxy-5-(pyrrolidin-1-yl)-phenyl)-2-(5,6-
 diethoxy-7-fluoro-1-imino-1,3-dihydro-isoindol-2-yl)-
 ethanone hydrobromide; 2-[2-(3-tert-butyl-4-methoxy-5-
 (pyrrolidin-1-yl)-phenyl)-2-oxo-ethyl]-6-
 dimethylamino-3-imino-2,3-dihydro-1H-isoindole-5-
 carboxylic acid methylamide hydrobromide; 1-(3-tert-
 butyl-4-methoxy-5-(pyrrolidin-1-yl)-phenyl)-2-(2-
 cyclopropyl-7-imino-5,7-dihydro-pyrrolo[3,4-b]pyridin-
 6-yl)-ethanone hydrobromide; 1-(3-tert-butyl-4-
 methoxy-5-(pyrrolidin-1-yl)-phenyl)-2-(7-fluoro-1-
 imino-5,6-dimethoxy-1,3-dihydro-isoindol-2-yl)-
 ethanone hydrobromide; 2-[2-(3-tert-butyl-5-
 isopropoxy-4-methoxy-phenyl)-2-oxo-ethyl]-6-ethoxy-3-
 imino-2,3-dihydro-1H-isoindole-5-carboxylic acid
 methylamide hydrobromide; 1-(3-tert-butyl-5-
 isopropoxy-4-methoxy-phenyl)-2-(5,6-diethoxy-7-fluoro-
 1-imino-1,3-dihydro-isoindol-2-yl)-ethanone
 hydrobromide; 1-(3-tert-butyl-5-isopropoxy-4-methoxy-
 phenyl)-2-(7-fluoro-1-imino-5,6-dimethoxy-1,3-dihydro-
 isoindol-2-yl)-ethanone hydrobromide; ethyl 2-(8-tert-
 butyl-6-[2-(5-ethoxy-1-imino-6-methylcarbamoyl-1,3-

dihydro-isoindol-2-yl)-acetyl}-2,3-dihydro-
 benzo[1,4]oxazin-4-yl}-propionate hydrochloride; ethyl
 2-(8-tert-butyl-6-[2-(3-ethoxy-7-imino-2-
 methylcarbamoyl-5,7-dihydro-pyrrolo[3,4-b]pyridin-6-
 5 yl)-acetyl]-2,3-dihydro-benzo[1,4]oxazin-4-yl})-
 propionate hydrochloride; 2-[2-(3-dimethylamino-5-
 isopropyl-4-methoxy-phenyl)-2-oxo-ethyl]-6-ethoxy-3-
 imino-2,3-dihydro-1H-isoindole-5-carboxylic acid
 methylamide hydrobromide; 2-(5,6-diethoxy-7-fluoro-1-
 10 imino-1,3-dihydro-isoindol-2-yl)-1-(3-dimethylamino-5-
 isopropyl-4-methoxy-phenyl)-ethanone hydrobromide; 2-
 [2-(3-tert-butyl-4-methoxy-5-methylamino-phenyl)-2-
 oxo-ethyl]-6-ethoxy-3-imino-2,3-dihydro-1H-isoindole-
 5-carboxylic acid methylamide hydrobromide; 6-[2-(3-
 15 tert-butyl-5-isopropoxy-4-methoxy-phenyl)-2-oxo-
 ethyl]-3-ethoxy-7-imino-6,7-dihydro-5H-pyrrolo[3,4-
 b]pyridine-2-carboxylic acid methylamide
 trifluoroacetate; 2-[2-(3-tert-butyl-5-isopropoxy-4-
 methoxy-phenyl)-2-oxo-ethyl]-6-dimethylamino-3-imino-
 20 2,3-dihydro-1H-isoindole-5-carboxylic acid methylamide
 trifluoroacetate; 2-{2-[3-tert-butyl-5-(4-cyano-
 piperidin-1-yl)-4-methoxy-phenyl]-2-oxo-ethyl}-6-
 ethoxy-3-imino-2,3-dihydro-1H-isoindole-5-carboxylic
 acid methylamide hydrobromide; 1-(3-tert-butyl-4-
 25 hydroxy-phenyl)-2-(5,6-diethoxy-7-fluoro-1-imino-1,3-
 dihydro-isoindol-2-yl)-ethanone hydrobromide; 2-(8-

tert-butyl-6-[2-(5-ethoxy-1-imino-6-methylcarbamoyl-
 1,3-dihydro-isoindol-2-yl)-acetyl]-2,3-dihydro-
 benzo[1,4]oxazin-4-yl}-2-methyl-propanoic acid
 hydrochloride; 2-{8-tert-butyl-6-[2-(3-ethoxy-7-imino-
 5 2-methylcarbamoyl-5,7-dihydro-pyrrolo[3,4-b]pyridin-6-
 yl)-acetyl]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-2-
 methyl-propanoic acid hydrochloride; 2-tert-butyl-6-
 dimethylamino-4-[2-(5-ethoxy-1-imino-6-
 methylcarbamoyl-1,3-dihydro-isoindol-2-yl)-acetyl]-
 10 phenyl acetate hydrobromide; 2-{2-[3-tert-butyl-4-
 methoxy-5-(2-oxo-oxazolidin-3-yl)-phenyl]-2-oxo-
 ethyl}-6-ethoxy-3-imino-2,3-dihydro-1H-isoindole-5-
 carboxylic acid methylamide hydrobromide; 2-tert-
 butyl-4-[2-(5,6-diethoxy-7-fluoro-1-imino-1,3-dihydro-
 15 isoindol-2-yl)-acetyl]-phenyl acetate hydrobromide; 2-
 tert-butyl-4-[2-(5-ethoxy-1-imino-6-methylcarbamoyl-
 1,3-dihydro-isoindol-2-yl)-acetyl]-phenyl acetate
 hydrobromide; 1-{3-tert-butyl-5-[2-(5,6-diethoxy-7-
 fluoro-1-imino-1,3-dihydro-isoindol-2-yl)-acetyl]-2-
 20 methoxy-phenyl}-piperidin-4-one hydrobromide; 1-(3-
 tert-butyl-5-dimethylamino-4-methoxy-phenyl)-2-(5-
 ethoxy-7-fluoro-1-imino-6-methoxy-1,3-dihydro-
 isoindol-2-yl)-ethanone hydrobromide; 2-{2-[3-tert-
 butyl-5-(ethyl-methyl-amino)-4-methoxy-phenyl]-2-oxo-
 25 ethyl}-6-ethoxy-3-imino-2,3-dihydro-1H-isoindole-5-
 carboxylic acid methylamide hydrobromide; 6-{2-[3-

tert-butyl-5-(ethyl-methyl-amino)-4-methoxy-phenyl]-2-
 oxo-ethyl]-3-ethoxy-7-imino-6,7-dihydro-5H-
 pyrrolo[3,4-b]pyridine-2-carboxylic acid methylamide
 trifluoroacetate; 2-tert-butyl-4-[2-(5,6-diethoxy-7-
 5 fluoro-1-imino-1,3-dihydro-isoindol-2-yl)-acetyl]-6-
 dimethylamino-phenyl methanesulfonate hydrobromide; 1-
 [3-tert-butyl-5-(4-hydroxy-piperidin-1-yl)-4-methoxy-
 phenyl]-2-(5,6-diethoxy-7-fluoro-1-imino-1,3-dihydro-
 isoindol-2-yl)-ethanone hydrobromide; 6-{2-[3-tert-
 10 butyl-5-(4-hydroxy-piperidin-1-yl)-4-methoxy-phenyl]-
 2-oxo-ethyl]-3-ethoxy-7-imino-6,7-dihydro-5H-
 pyrrolo[3,4-b]pyridine-2-carboxylic acid methylamide
 trifluoroacetate; 1-[3-tert-butyl-5-(4-hydroxy-
 piperidin-1-yl)-4-methoxy-phenyl]-2-(7-fluoro-1-imino-
 15 5,6-dimethoxy-1,3-dihydro-isoindol-2-yl)-ethanone
 hydrobromide; 1-(3-tert-butyl-5-dimethylamino-4-
 hydroxy-phenyl)-2-(5,6-diethoxy-7-fluoro-1-imino-1,3-
 dihydro-isoindol-2-yl)-ethanone hydrobromide; 6-[2-(3-
 tert-butyl-5-dimethylamino-4-ethoxy-phenyl)-2-oxo-
 20 ethyl]-3-ethoxy-7-imino-6,7-dihydro-5H-pyrrolo[3,4-
 b]pyridine-2-carboxylic acid methylamide
 trifluoroacetate; 2-[2-(3-tert-butyl-5-dimethylamino-
 4-methoxy-phenyl)-2-oxo-ethyl]-6-dimethylamino-3-
 imino-2,3-dihydro-1H-isoindole-5-carboxylic acid
 25 methylamide hydrobromide; 1-(3-tert-butyl-4-methoxy-5-
 methylamino-phenyl)-2-(5,6-diethoxy-7-fluoro-1-imino-

1,3-dihydro-isoindol-2-yl)-ethanone hydrobromide; 1-[3-tert-butyl-5-(4-hydroxy-piperidin-1-yl)-4-methoxy-phenyl]-2-(5-ethoxy-7-fluoro-1-imino-6-methoxy-1,3-dihydro-isoindol-2-yl) hydrobromide; 2-(5,6-diethoxy-7-fluoro-1-imino-1,3-dihydro-isoindol-2-yl)-1-[3-dimethylamino-5-(1-fluoro-1-methyl-ethyl)-4-methoxy-phenyl]-ethanone hydrobromide; 1-[3-tert-butyl-5-(3-hydroxy-pyrrolidin-1-yl)-4-methoxy-phenyl]-2-(5,6-diethoxy-7-fluoro-1-imino-1,3-dihydro-isoindol-2-yl)-ethanone trifluoroacetate; 2-[2-(3-tert-butyl-5-ethylamino-4-methoxy-phenyl)-2-oxo-ethyl]-6-ethoxy-3-imino-2,3-dihydro-1H-isoindole-5-carboxylic acid methylamide hydrobromide; 2-[2-(3-tert-butyl-5-ethylamino-4-methoxy-phenyl)-2-oxo-ethyl]-6-ethoxy-3-imino-2,3-dihydro-1H-isoindole-5-carboxylic acid methylamide hydrobromide; 1-(3-tert-butyl-5-ethoxy-4-hydroxy-phenyl)-2-(5,6-diethoxy-7-fluoro-1-imino-1,3-dihydro-isoindol-2-yl)-ethanone hydrobromide; 2-[2-(3-tert-butyl-5-ethoxy-4-hydroxy-phenyl)-2-oxo-ethyl]-6-ethoxy-3-imino-2,3-dihydro-1H-isoindole-5-carboxylic acid methylamide hydrobromide; 2-tert-butyl-4-[2-(5,6-diethoxy-7-fluoro-1-imino-1,3-dihydro-isoindol-2-yl)-acetyl]-6-ethoxy-phenyl ethyl-carbamate hydrobromide; 2-tert-butyl-6-ethoxy-4-[2-(5-ethoxy-1-imino-6-methylcarbamoyl-1,3-dihydro-isoindol-2-yl)-acetyl]-phenyl ethyl-carbamate hydrobromide; 2-tert-butyl-6-

(3-cyano-propoxy)-4-[2-(5,6-diethoxy-7-fluoro-1-imino-1,3-dihydro-isoindol-2-yl)-acetyl]-phenyl
methanesulfonate hydrobromide; 1-(3-tert-butyl-4-methoxy-5-piperazin-1-yl-phenyl)-2-(5,6-diethoxy-7-fluoro-1-imino-1,3-dihydro-isoindol-2-yl)-ethanone
5 dihydrochloride; 2-(2-{3-tert-butyl-4-methoxy-5-[(2-methoxyethyl)-methylamino]-phenyl}-2-oxo-ethyl)-6-dimethylamino-3-imino-2,3-dihydro-1H-isoindole-5-carboxylic acid methylamide hydrobromide; 1-[3-tert-butyl-5-(2-hydroxyethylamino)-4-methoxy-phenyl]-2-(5,6-diethoxy-7-fluoro-1-imino-1,3-dihydro-isoindol-2-yl)-ethanone hydrochloride; 1-{3-tert-butyl-5-[(2-hydroxyethyl)-methylamino]-4-methoxy-phenyl}-2-(5,6-diethoxy-7-fluoro-1-imino-1,3-dihydro-isoindol-2-yl)-ethanone dihydrochloride; 2-{2-[3-tert-butyl-5-(3,4-dihydroxy-pyrrolidin-1-yl)-4-methoxy-phenyl]-2-oxo-ethyl}-6-ethoxy-3-imino-2,3-dihydro-1H-isoindole-5-carboxylic acid methylamide trifluoroacetate; 1-[3-tert-butyl-5-(3-hydroxy-4-methoxy-pyrrolidin-1-yl)-4-methoxy-phenyl]-2-(5,6-diethoxy-7-fluoro-1-imino-1,3-dihydro-isoindol-2-yl)-ethanone trifluoroacetate; {3-tert-butyl-5-[2-(5,6-diethoxy-7-fluoro-1-imino-1,3-dihydro-isoindol-2-yl)-acetyl]-2-methoxy-phenylamino}-acetonitrile hydrobromide; 1-(3-tert-butyl-4-hydroxy-5-morpholino-phenyl)-2-(5,6-diethoxy-7-fluoro-1-imino-1,3-dihydro-isoindol-2-yl)-ethanone hydrochloride; 1-

{3-*tert*-butyl-5-[ethyl-(2-hydroxyethyl)-amino]-4-methoxy-phenyl}-2-(5,6-diethoxy-7-fluoro-1-imino-1,3-dihydro-isoindol-2-yl)-acetyl hydrochloride; (4-{3-*tert*-butyl-5-[2-(5,6-diethoxy-7-fluoro-1-imino-1,3-dihydro-isoindol-2-yl)-acetyl]-2-methoxy-phenyl}-piperazin-1-yl)-acetonitrile hydrobromide; 2-(2-{3-*tert*-butyl-5-[(2-hydroxyethyl)-methylamino]-4-methoxy-phenyl}-2-oxo-ethyl)-6-dimethylamino-3-imino-2,3-dihydro-1H-isoindole-5-carboxylic acid methylamide dihydrochloride; 1-{3-*tert*-butyl-5-[(3-hydroxypropyl)-methylamino]-4-methoxy-phenyl}-2-(5,6-diethoxy-7-fluoro-1-imino-1,3-dihydro-isoindol-2-yl)-ethanone dihydrochloride; 1-{3-*tert*-butyl-5-[(2-hydroxyethyl)-(2-methoxyethyl)-amino]-4-methoxy-phenyl}-2-(5,6-diethoxy-7-fluoro-1-imino-1,3-dihydro-isoindol-2-yl)-ethanone dihydrochloride; 1-[3-*tert*-butyl-5-(3-hydroxy-4-methoxy-pyrrolidin-1-yl)-4-methoxy-phenyl]-2-(5,6-diethoxy-7-fluoro-1-imino-1,3-dihydro-isoindol-2-yl)-ethanone trifluoroacetate; 1-(3-amino-5-*tert*-butyl-4-methoxy-phenyl)-2-(5,6-diethoxy-7-fluoro-1-imino-1,3-dihydro-isoindol-2-yl)-ethanone hydrobromide; 2-[2-(3-*tert*-butyl-5-isopropylamino-4-methoxy-phenyl)-2-oxo-ethyl]-6-ethoxy-3-imino-2,3-dihydro-1H-isoindole-5-carboxylic acid methylamide hydrobromide; 1-[3-(4-acetyl-piperazin-1-yl)-5-*tert*-butyl-4-methoxy-phenyl]-2-(5,6-diethoxy-7-fluoro-1-

imino-1,3-dihydro-isoindol-2-yl)-ethanone
 hydrobromide; 1-[3-tert-butyl-5-(3-hydroxy-4-methoxy-
 pyrrolidin-1-yl)-4-methoxy-phenyl]-2-(5,6-diethoxy-7-
 fluoro-1-imino-1,3-dihydro-isoindol-2-yl)-ethanone
 5 trifluoroacetate; 1-[3-tert-butyl-5-(3,4-dimethoxy-
 pyrrolidin-1-yl)-4-methoxy-phenyl]-2-(5,6-diethoxy-7-
 fluoro-1-imino-1,3-dihydro-isoindol-2-yl)-ethanone
 hydrobromide; (4-{3-tert-butyl-5-[2-(5,6-diethoxy-7-
 fluoro-1-imino-1,3-dihydro-isoindol-2-yl)-acetyl]-2-
 10 methoxy-phenyl}-piperazin-1-yl)-acetic acid
 dihydrochloride; 1-{3-tert-butyl-5-[4-(2-hydroxy-
 acetyl)-piperazin-1-yl]-4-methoxy-phenyl}-2-(5,6-
 diethoxy-7-fluoro-1-imino-1,3-dihydro-isoindol-2-yl)-
 ethanone hydrobromide; 4-{3-tert-butyl-5-[2-(5,6-
 15 diethoxy-7-fluoro-1-imino-1,3-dihydro-isoindol-2-yl)-
 acetyl]-2-methoxy-phenyl}-piperazine-1-carboxylic acid
 ethylamide hydrobromide; ethyl (4-{3-tert-butyl-5-[2-
 (5,6-diethoxy-7-fluoro-1-imino-1,3-dihydro-isoindol-2-
 yl)-acetyl]-2-methoxy-phenyl}-piperazin-1-yl)-acetate
 20 dihydrochloride; 1-{3-tert-butyl-4-methoxy-5-[4-(2-
 methoxy-acetyl)-piperazin-1-yl]-phenyl}-2-(5,6-
 diethoxy-7-fluoro-1-imino-1,3-dihydro-isoindol-2-yl)-
 ethanone hydrobromide; 1-(4-{3-tert-butyl-5-[2-(5,6-
 diethoxy-7-fluoro-1-imino-1,3-dihydro-isoindol-2-yl)-
 25 acetyl]-2-methoxy-phenyl}-piperazin-1-yl)-propan-1-one
 hydrobromide; 1-[3-tert-butyl-5-(3-ethoxy-4-hydroxy-

pyrrolidin-1-yl)-4-methoxy-phenyl]-2-(5,6-diethoxy-7-fluoro-1-imino-1,3-dihydro-isoindol-2-yl)-ethanone trifluoroacetate; 1-(3,5-di-*tert*-butyl-4-hydroxy-phenyl)-2-(7-imino-2-methyl-5,7-dihydro-pyrrolo[3,4-b]pyridin-6-yl)-ethanone hydrochloride; 1-(3,5-di-*tert*-butyl-4-hydroxy-phenyl)-2-(3-ethoxy-7-imino-2,4-dimethyl-5,7-dihydro-pyrrolo[3,4-b]pyridin-6-yl)-ethanone hydrobromide; 2-[2-(3,5-di-*tert*-butyl-4-hydroxy-phenyl)-2-oxo-ethyl]-6-ethoxy-3-imino-2,3-dihydro-1H-isoindole-5-carboxamide hydrobromide; 2-[2-(8-*tert*-butyl-4-methyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)-2-oxo-ethyl]-6-ethoxy-3-imino-2,3-dihydro-1H-isoindole-5-carboxylic acid methylamide hydrobromide; 6-[2-(3,5-di-*tert*-butyl-4-hydroxy-phenyl)-2-oxo-ethyl]-3-ethoxy-7-imino-6,7-dihydro-5H-pyrrolo[3,4-b]pyridine-2-carboxylic acid methylamide hydrochloride; 1-(3,5-di-*tert*-butyl-4-hydroxy-phenyl)-2-(2-ethyl-7-imino-5,7-dihydro-pyrrolo[3,4-b]pyridin-6-yl)-ethanone hydrobromide; 2-(2-cyclopropyl-7-imino-5,7-dihydro-pyrrolo[3,4-b]pyridin-6-yl)-ethanone)-1-(3,5-di-*tert*-butyl-4-hydroxy-phenyl)-ethanone hydrobromide; 2-[2-(8-*tert*-butyl-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)-2-oxo-ethyl]-6-ethoxy-3-imino-2,3-dihydro-1H-isoindole-5-carboxylic acid methylamide hydrobromide; and 1-(3-*tert*-butyl-5-isopropylamino-4-methoxy-phenyl)-2-(5,6-diethoxy-7-fluoro-1-imino-1,3-

dihydro-isoindol-2-yl)-ethanone hydrobromide.

Production processes for compounds of the invention and salts thereof will now be described. Various processes are possible for production of the compounds of the invention represented by the general formula (I) above and their salts, and the synthesis may be carried out by ordinary organic synthesis methods. The following representative production processes will now be presented.

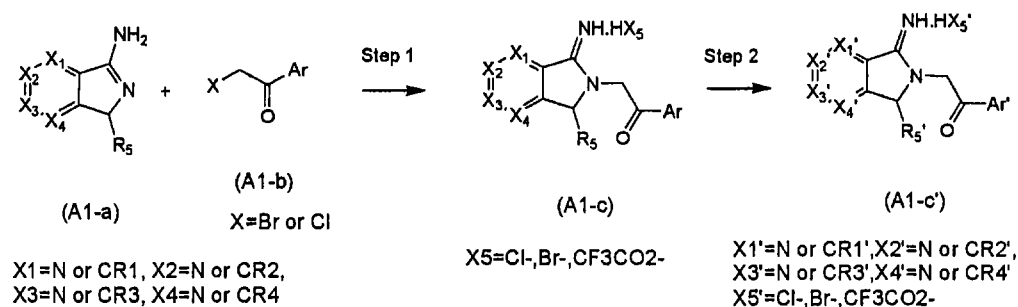
[Representative production processes]

Compounds represented by the general formulas (A1-c) and (A1-c'), which are aromatic or heteroaromatic ring-fused cyclic amidines, may be synthesized from (A1-a) and (A1-b) by the methods described later.

<Production Process A>

A process of synthesizing the aromatic or heteroaromatic ring-fused cyclic amidine compounds (A1-c) and (A1-c'), and compound (A3-b), imino-protected compound (A1-c).

(Scheme A-1)



This scheme is a method of synthesizing (A1-c)

from (A1-a) and (A1-b) by the methods described later.

In the formulas, Ar and Ar' have the same definition as Ar in the compounds represented by formula (I) in claim 1. R1, R2, R3, R4 and R5, and
5 R1', R2', R3', R4' and R5' are defined in Production Process B onward.

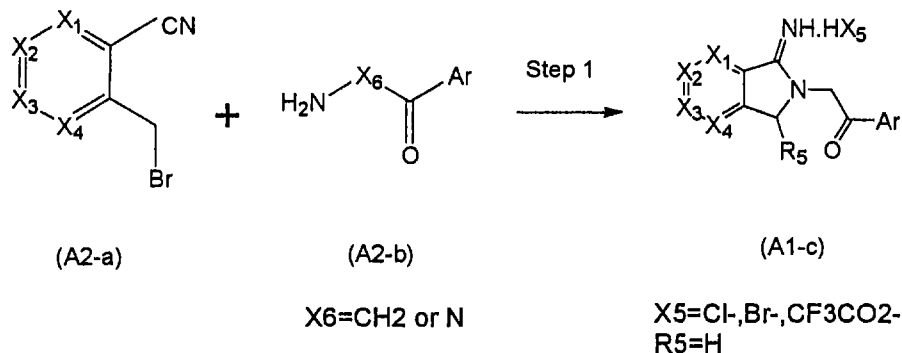
Step 1 is a coupling reaction between compounds (A1-a) and (A1-b). Compound (A1-c) may be obtained from these compounds by dissolving both compounds in
10 dimethylformamide, acetonitrile, an alcohol or the like, and selecting the temperature conditions from room temperature to reflux temperature. As an alternative method, (A1-a) may be reacted with sodium hydride in a solvent such as tetrahydrofuran or
15 dimethylformamide and then reacted with (A1-b) at room temperature or while cooling on ice to obtain a salt free form of (A1-c), which may then be treated with any of various acids. Preferably, it is reacted with a 5 N hydrogen chloride or 5 N hydrogenbromide acetic
20 acid solution in an organic solvent to yield (A1-c) as an ammonium salt.

Step 2 is a step of partial structural modification after Step 1 to yield compound (A1-c'). In this step, in cases where (A1-c) contains a tert-
25 butyl group as the protecting group of carboxyl or a tert-butyloxycarbonyl group as the protecting group of

amino or amide hydrogen, deprotection is accomplished by reaction with 5 N hydrogen chloride in an organic solvent such as ethyl acetate or dioxane, using trifluoroacetic acid, if necessary diluting with dichloromethane, to yield (A1-c'). When (A1-c) contains an alkyl ester, heating to reflux may be accomplished in concentrated hydrochloric acid for hydrolysis to yield (A1-c') as a carboxylic acid. When (A1-c) contains tetrahydropyranyl, methoxymethyl or trialkylsilyl as a hydroxyl-protecting group, it may be deprotected by using 5 N hydrogen chloride in a water-containing organic solvent such as ethyl acetate and dioxane, trifluoroacetic acid or dilute hydrogen chloride in a solvent such as tetrahydrofuran and an alcohol, to yield (A1-c'). When (A1-c) contains benzyl as the protecting group for hydroxyl or carboxyl, or when it contains a double bond, the deprotecting reaction or conversion to a saturated compound may be accomplished by hydrogenation in a solvent such as ethyl acetate or an alcohol, in the presence of a metal catalyst such as palladium hydroxide, to yield (A1-c'). When (A1-c) has carboxyl, it may be converted to an ester under acidic alcohol conditions or to an amide derivative under condensing conditions to yield (A1-c'). When (A1-c) has cyano, it may be converted to a carboxylic acid or

carboxamide under hydrolyzing conditions to yield (A1-c').

(Scheme A-2)



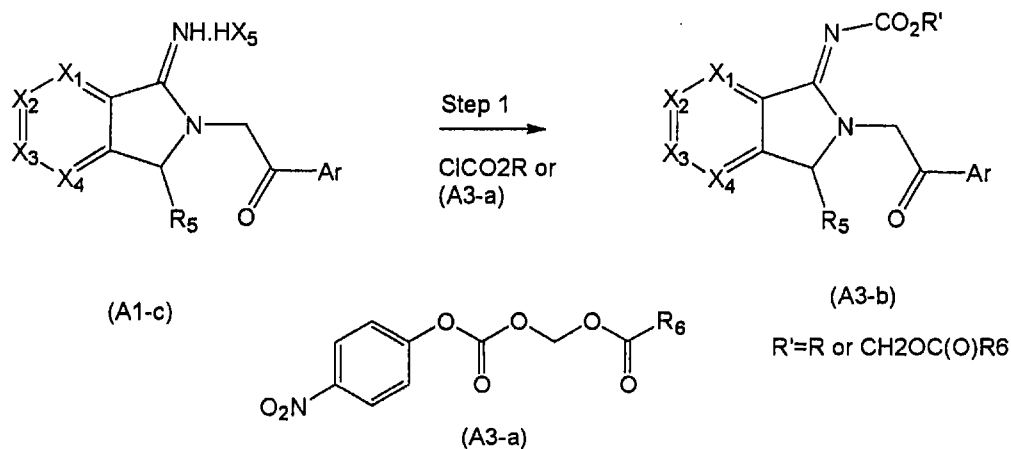
This scheme is a method synthesizing compound (A1-c) from compounds (A2-a) and (A2-b). The compound represented by (A2-a) is one of the intermediates shown in Production Processes B to H, or a compound which can be easily converted from one of the intermediates.

In the formulas, Ar has the same definition as Ar in the compound represented by formula (I) in claim 1. X1, X2, X3 and X4 have the same definitions as X1, X2, X3 and X4 in Scheme A-1.

Step 1 is a reaction for alkylation of the amino group and subsequent ring closure of the secondary amine produced thereby, in an one-pot synthesis. The both compounds are reacted in a dimethylformamide solvent from room temperature to 100°C. However, when the compound represented by (A2-b) is an amine salt, the reaction is conducted in the presence of 1,8-

diazabicyclo[5.4.0]undec-7-ene.

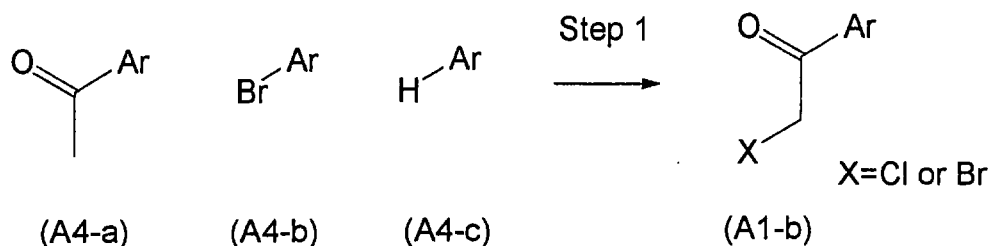
(Scheme A-3)



This scheme is a method of protecting the imino group of compound (A1-c). In the formulas, Ar has the same definition as Ar in the compound represented by formula (I) in claim 1. X1, X2, X3, X4 and R5 have the same definitions as X1, X2, X3, X4 and R5 in Scheme A-1. R represents optionally substituted alkyl or alkenyl, and R6 represents alkyl.

Step 1 is a reaction for introduction of a substituent at the imino group. An alkyl chlorocarbonate or a carbonate having nitrophenol as a leaving group (A3-a), is reacted therewith by reaction in a two-layer system using a base such as a 1 N aqueous sodium hydroxide solution or saturated bicarbonate water, in a solvent such as tetrahydrofuran, to yield (A3-b).

(Scheme A-4)



This scheme is a method of synthesizing a 2-halogeno-1-ethanone derivative represented by (A1-b) in Scheme A-1 from (A4-a), (A4-b) or (A4-c). In the
 5 formulas, Ar has the same definition as Ar in the compound represented by formula (I) in claim 1.

Step 1 is carried out by the following 3 methods corresponding to the starting compounds (A4-a), (A4-b) and (A4-c), respectively.

10 (1) Compound (A4-a) may be treated with a halogenating reagent in the presence of an appropriate solvent to yield (A1-b). Preferably, (A4-a) is continuously treated with *tert*-butyldimethylsilyl trifluoromethanesulfonate, N-bromosuccinimide or N-chlorosuccinimide in tetrahydrofuran in the presence
 15 of triethylamine, to yield (A1-b). More preferably, (A4-a) is treated with tetrabutylammonium tribromide in a solvent mixture of dichloromethane and methanol or in acetic acid to yield (A1-b).

20 (2) After introducing ethanoether as a methyl ketone equivalent at the bromide position of (A4-b) by Stille coupling in an appropriate solvent, the resulting compound may be treated with a halogenating

reagent to yield (A1-b). Preferably, (A4-b) is treated with tributyl(1-ethoxyvinyl)tin, tetrakis(triphenylphosphine)palladium and cesium fluoride in toluene or 1,4-dioxane while heating and ethyl vinyl ether is introduced, and then halogenation is carried out with N-bromosuccinimide or N-chlorosuccinimide to yield (A1-b). Alternatively, introduction of ethyl vinyl ether at the bromide position of (A4-b) may be followed by treatment with preferably 5 N hydrochloric acid-acetone under appropriate acidic conditions to yield (A4-a).

(3) Compound (A4-c) may be treated with a Lewis acid catalyst and Friedel-Crafts acylating reagent in an appropriate solvent to directly yield (A1-b).

Preferably, (A4-c) is treated with bromoacetyl chloride or chloroacetyl chloride in dichloromethane in the presence of aluminum chloride to yield (A1-b).

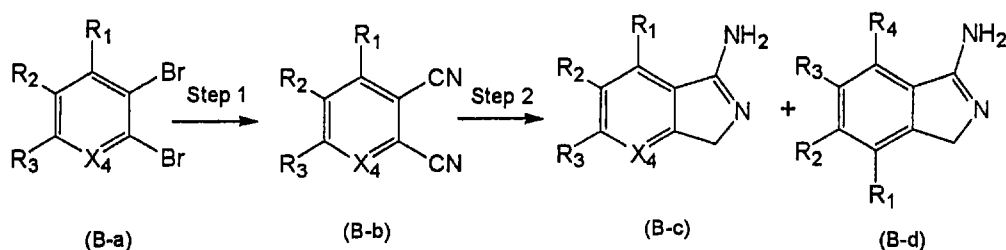
An aromatic or heteroaromatic ring-fused amidine represented by (A1-a) may be synthesized by either Production Process B or C below. Production Process B is a process utilizing a regioselective reduction reaction on a phthalonitrile derivative.

<Production Process B>

A process for synthesis of an aromatic or heteroaromatic ring-fused amidine represented by (A1-a) as the starting material for Scheme A-1 of

Production Process A, utilizing a regioselective reduction reaction on a phthalonitrile derivative.

(Scheme B)



X₄:N or CR₄

5 This scheme is a method of synthesizing
benzamidines derivatives (B-c) and (B-d) from compound
(B-a). The definition of X₄ in the formulas is the
same as X₄ in Scheme A-1 of Production Process A. R₁
and R₄ represent hydrogen, halogeno, optionally
10 substituted alkyl or optionally substituted alkoxy.
R₂ and R₃ represent hydrogen, halogeno, optionally
substituted alkyl, optionally substituted alkenyl,
optionally substituted alkoxy, optionally substituted
amino, optionally substituted carboxyl, optionally
15 substituted aminocarbonyl, optionally substituted
aminosulfonyl, optionally substituted sulfonylamino or
optionally substituted alkanoylamino.

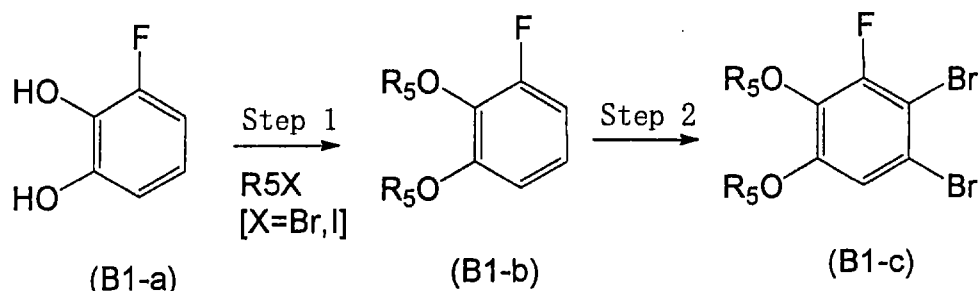
20 Step 1 is a reaction for introduction of a cyano
group. Compound (B-b) may be obtained by heating
compound (B-a) and copper (I) cyanide at 140-160°C in
a solvent such as dimethylformamide, dimethylsulfoxide,
N-methylpiperidone or hexamethylphosphoramide or a
mixture thereof.

Step 2 is a reaction of regioselective reduction of (B-b) and subsequent ring closure of the resulting amine in the system. The reaction conditions may be selected from the following 4 types: 1) hydrogenation reaction using a metal catalyst such as platinum oxide, platinum-carbon or palladium-carbon in a solvent such as ethyl acetate or an alcohol or a mixture thereof, at room temperature and normal pressure, 2) hydride reduction by reaction with diisobutyl aluminum hydride, lithium aluminum hydride or the like on ice or at room temperature in a solvent such as tetrahydrofuran or diethyl ether, 3) reaction with sodium borohydride in the presence of trifluoroacetic acid, 4) reaction with sodium borohydride in the presence of cobalt chloride or the like. Compound (B-d) is also obtained as a result of the substitution on (B-b), but it may be separated and purified by silica gel column chromatography, and both isomers may be used for the reaction represented by Scheme A-1. When a benzylamine derivative is obtained which does not undergo ring closure under reducing reaction conditions, it may be adsorbed onto silica gel and allowed to stand at room temperature from 3 hours to 1 day to yield a cyclic amidine (A1-a).

Compound (B-a) and (B-b) above may also be purchased, or optionally synthesized by any of the

methods from Scheme B-1 to Scheme B-15 described below.

(Scheme B-1)



This scheme is a general synthesis method for a fluorocatechol derivative. In the formulas, R5 represents an optionally substituted alkyl or cycloalkyl.

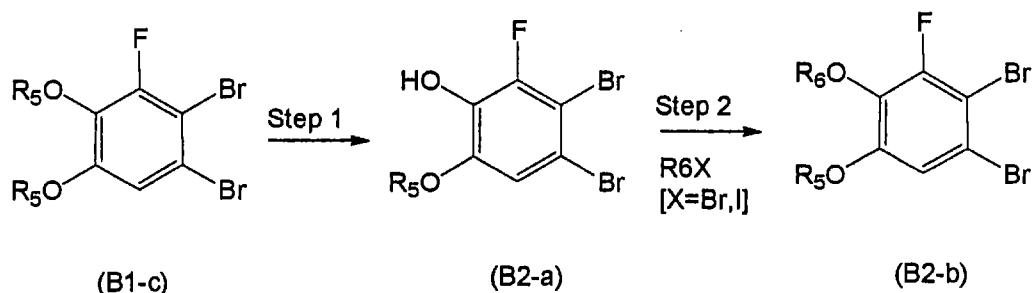
Step 1 is a method for alkylation of the two hydroxyl groups of (B1-a). Compound (B1-b) may be obtained by reaction with an alkyl halide in a solvent such as dimethylformamide, acetonitrile or acetone in the presence of an inorganic base such as potassium carbonate or cesium carbonate, at a temperature from room temperature to reflux temperature.

Step 2 is a step of regiospecific dibromination. Compound (B1-c) may be obtained by a method of reaction with bromine or N-bromosuccinimide in a solvent such as an alcohol or acetonitrile, either while cooling on ice or at room temperature, or by a method of reaction with bromine in an acetic acid solvent in the presence of sodium acetate, from room temperature to 80°C.

Conversion of an alkyl group of compound (B1-c)

may be accomplished by the following method.

(Scheme B-2)



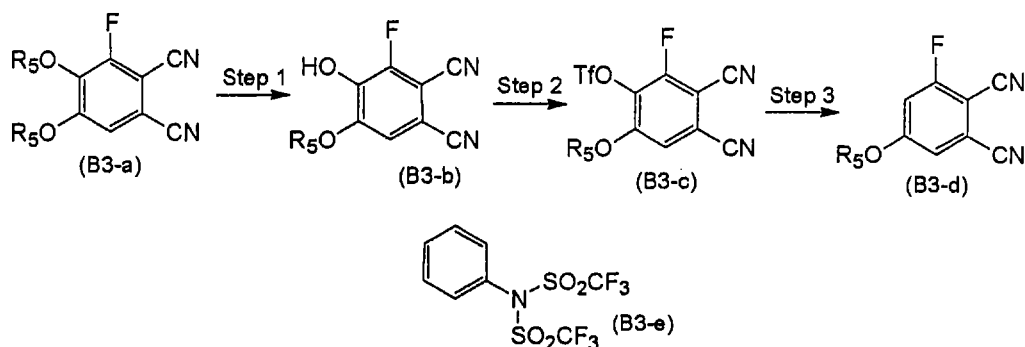
This scheme is a method for synthesis of a fluorocatechol derivative (B2-b) with different substituents. In the formulas, R5 and R6 each represent an optionally substituted alkyl or cycloalkyl.

Step 1 is a step of selective removal of an alkyl group. Compound (B2-a) may be obtained by reaction with two equivalents of aluminum chloride in dichloromethane, from freezing to room temperature.

Step 2 is a step of alkylation, where compound (B2-b) may be obtained similarly to Step 1 of Scheme B-1.

Hydroxyl may then be reductively removed from compound (B2-a).

(Scheme B-3)



This scheme is a method for synthesis of compound (B3-d) from compound (B3-a). In the formulas, R5 represents an optionally substituted alkyl or cycloalkyl.

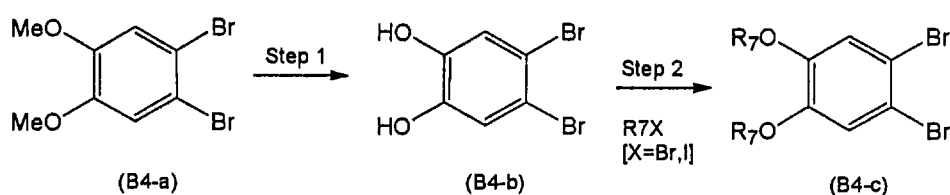
Step 1 is a step of removal of alkyl of the compound represented by (B3-a), which may be synthesized by the method of Scheme B-1. Compound (B3-b) may then be obtained similarly to Step 1 of Scheme B-2.

Step 2 is a step of conversion of hydroxyl to a trifluoromethanesulfonate (triflate). Compound (B3-c) may be obtained by reaction with trifluoromethanesulfonic anhydride in a solvent such as dichloromethane in the presence of a base such as triethylamine or pyridine, or by reaction with compound (B3-e) in the presence of triethylamine or dimethylaminopyridine.

Step 3 is a reaction for reductive removal of the triflate. It may be carried out by heated reaction with a palladium catalyst in dimethylformamide in the presence of formic acid and tributylamine. The

palladium catalyst used may be
 bis(triphenylphosphine)palladium dichloride, and the
 method is preferably ligand substitution with a
 bidentate ligand such as diphenylphosphinopropane or
 the like.

(Scheme B-4)

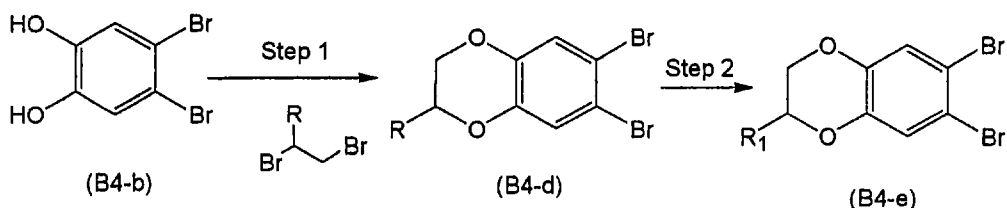


This scheme is a method for synthesis of a
 catechol derivative from a commercially available
 compound (B4-a). In the formulas, R_7 represents an
 optionally substituted alkyl or cycloalkyl group.

Step 1 is a dealkylation step. Compound (B4-a)
 may be reacted with boron tribromide in a solvent such
 as dichloromethane to yield (B4-b).

Step 2 is an alkylation step. Compound (B4-c)
 may be obtained similarly to Step 1 of Scheme B-1.

(Scheme B-4')



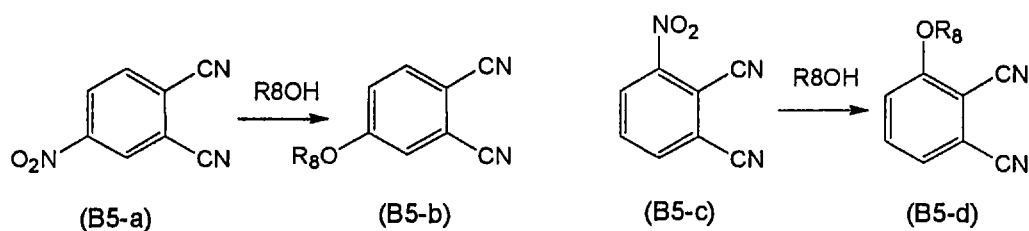
This scheme is a method for synthesis of cyclic
 catechol derivatives (B4-d) and (B4-e). In the
 formulas, R represents hydrogen, alkyl or
 alkyloxycarbonyl. R' represents alkyl optionally

substituted with hydroxyl or alkoxy.

Step 1 is a step of alkylation followed by cyclization, and the reaction conditions may be according to the method of alkylation in Step 1 of Scheme B-1.

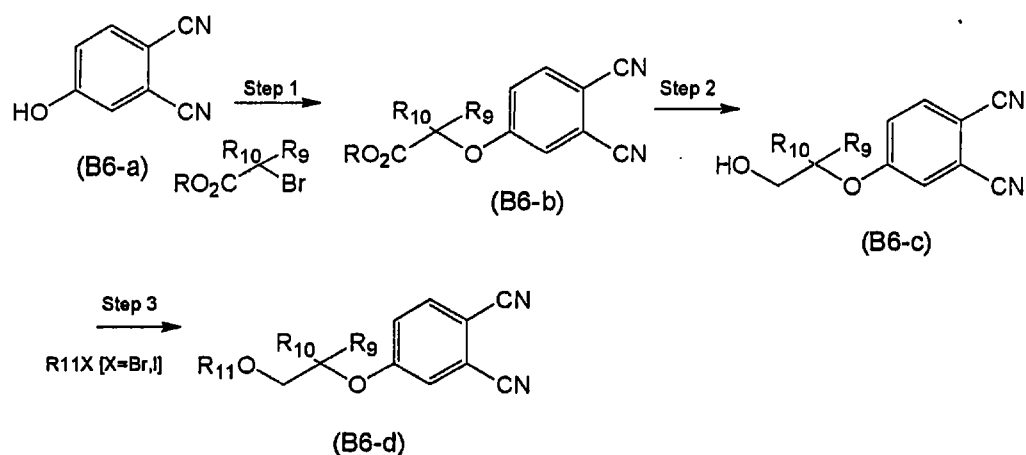
Step 2 is a substitution reaction wherein R of (B4-d) is alkyloxycarbonyl. Compound (B4-e) may be obtained by reduction of the ester group with lithium borohydride or etherification with sodium hydride and an alkylating agent.

(Scheme B-5)



This scheme is a method for synthesis of a monosubstituted alkoxy derivative using a 3- or 4-nitrophthalonitrile substitution reaction, as described in C.C. Leznoff et al., Can. J. Chem., 72, 1990(1994). In the formulas, R8 represents optionally substituted alkyl or cycloalkyl.

(Scheme B-6)



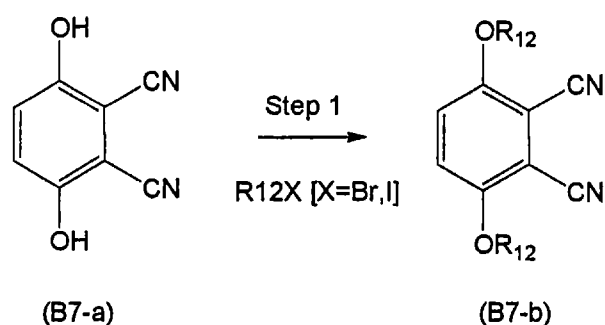
This scheme is a method for synthesis of monosubstituted alkoxy derivatives (B6-b), (B6-c) and (B6-d). In the formulas, R represents alkyl, R₉ and R₁₀ represent hydrogen or optionally substituted alkyl, and R₁₁ represents optionally substituted alkyl.

Step 1 is a reaction for alkylation of compound (B6-a). Compound (B6-b) may be obtained similarly to Step 1 of Scheme B-1, using an α -bromoester as the alkylating agent.

Step 2 is a reaction for reduction of an ester. Compound (B6-c) may be obtained by reaction with lithium borohydride in a tetrahydrofuran solution of (B6-b) [R = Et or Me] while cooling on ice.

Step 3 is a step of ether synthesis by alkylation. Compound (B6-d) may be obtained by reaction with sodium hydride in a solvent such as tetrahydrofuran or dimethylformamide, followed by reaction with an alkyl halide.

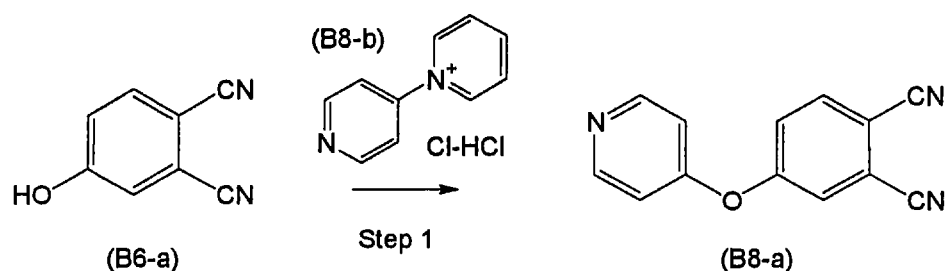
(Scheme B-7)



This scheme is a method for synthesis of a para-substituted dialkoxy derivative (B7-b) by alkylation similarly to Step 1 of Scheme B-1. In the formulas,

5 R12 represents optionally substituted alkyl or cycloalkyl.

(Scheme B-8)



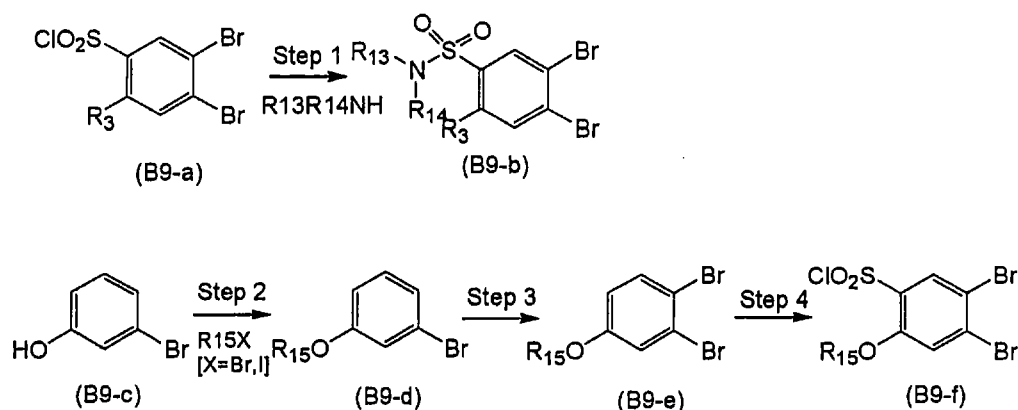
This scheme is a method for synthesis of a 4-pyridinol derivative (B8-a).

10

Step 1 accomplishes etherification at the 4 position of the pyridine. Compound (B8-a) may be obtained by reaction with compound (B8-b) while heating to reflux in an alcohol solvent, in the presence of aqueous sodium hydroxide.

15

(Scheme B-9)



This scheme is a method for synthesis of a substituted sulfonamide derivative (B9-b). In the formulas, R³ represents hydrogen or optionally substituted alkoxy, and R¹³ and R¹⁴ represent hydrogen or optionally substituted alkyl. R¹³ and R¹⁴ may also form a ring with the N. R¹⁵ represents optionally substituted alkyl.

Step 1 is a step of amidation. Compound (B9-b) may be obtained by reaction with aqueous ammonia or an aqueous alkylamine solution, or an organic solvent solution, in a solvent such as tetrahydrofuran or dimethylformamide.

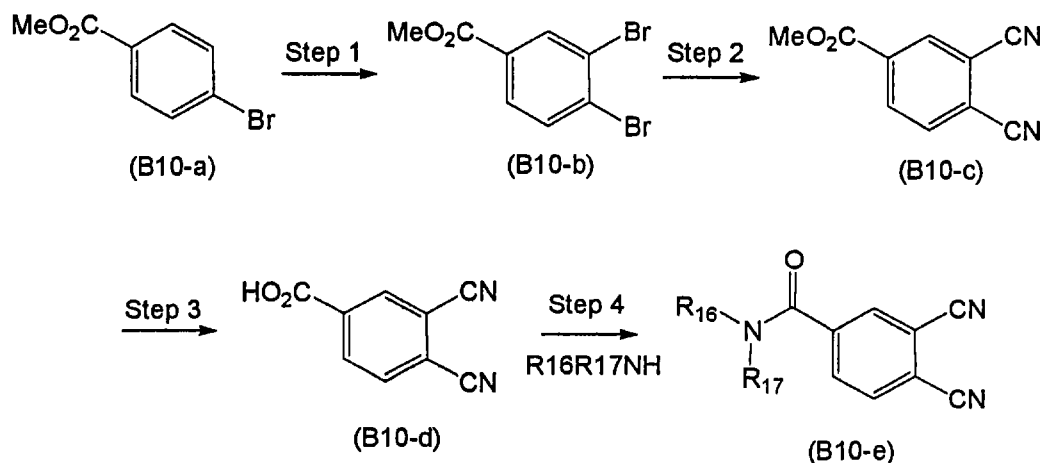
Synthesis of compound (B9-f), corresponding to compound (B9-a) wherein R³ is alkoxy, may be carried out in the following manner.

Step 2 is a step of alkylation, which may be carried out similarly to Step 1 of Scheme B-1.

Step 3 is a step of regioselective bromination, which may be carried out similarly to Step 2 of Scheme B-1.

Step 4 is a reaction for introduction of a chlorosulfonyl group. Compound (B9-f) may be obtained by reaction with chlorosulfonic acid in a solvent such as dichloromethane.

5 (Scheme B-10)



This scheme is a production method for a monosubstituted carboxamide derivative (B10-e) or ester (B10-c). In the formulas, R16 and R17 represent hydrogen or optionally substituted alkyl. R16 and R17 may also form a ring with the N.

Step 1 is a regioselective bromination reaction. Compound (B10-b) may be obtained by reaction with N-bromosuccinimide in concentrated sulfuric acid at room temperature.

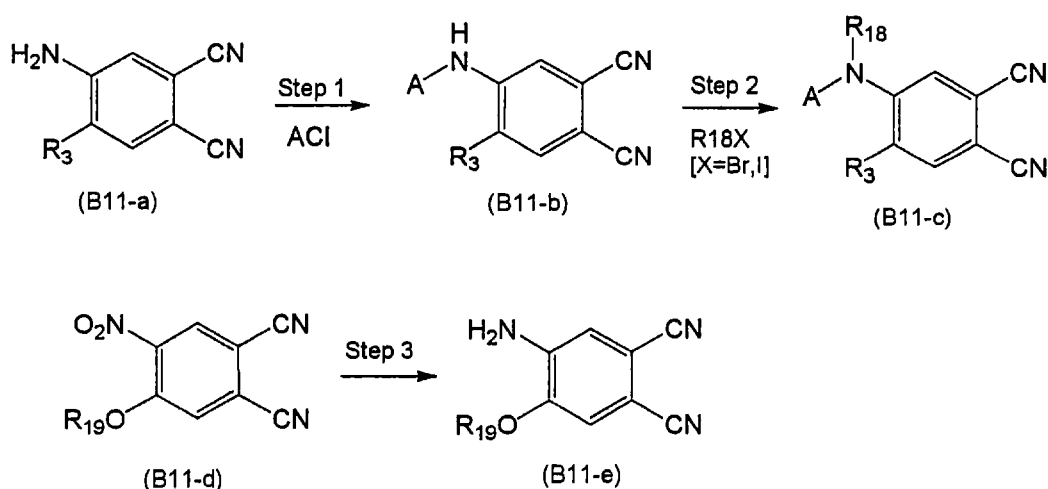
Step 2 is a step of dinitration similarly to Step 1 of Scheme B.

Step 3 is a step of synthesizing a carboxylic acid from an ester with cyano. Compound (B10-d) may be obtained by reaction with lithium iodide in a

dimethylformamide solvent.

Step 4 is a step of amidation. Compound (B10-e) may be obtained by any of the following 3 methods. 1) A method of reaction with an alkyl chlorocarbonate in a solvent such as tetrahydrofuran, ethyl acetate or dichloromethane, in the presence of a base such as triethylamine, to produce a mixed acid anhydride in the reaction system, followed by reaction with an organic solvent solution or aqueous solution of an amine. 2) A method of reaction with an amine together with a condensation agent such as dicyclohexylcarbodiimide or a water-soluble carbodiimide, in a solvent such as tetrahydrofuran, acetonitrile or dichloromethane, in the presence of hydroxybenzotriazole. 3) A method of activation of the carboxyl group with triethylamine and diethyl cyanophosphonate and reaction with an amine.

(Scheme B-11)



This scheme is a synthesis method for aniline derivatives (B11-b) and (B11-c). In the formulas, A represents alkanoyl, alkylsulfonyl, optionally substituted aminocarbonyl or alkoxycarbonyl. R3 represents hydrogen or optionally substituted alkoxy, and R18 and R19 represent optionally substituted alkyl or cycloalkyl.

Step 1 is a step of introducing a substituent at the amino group. Compound (B11-b) may be obtained by reaction with an acid chloride, alkyl chlorocarbonate or alkylsulfonyl chloride in a solvent such as tetrahydrofuran, ethyl acetate or dichloromethane or in the absence of a solvent, and in the presence of a base such as pyridine, or alternatively for synthesis of a urea derivative, by reaction with triphosgene in the presence of a base such as triethylamine or dimethylaminopyridine followed by reaction with an organic solvent solution or aqueous solution of an amine.

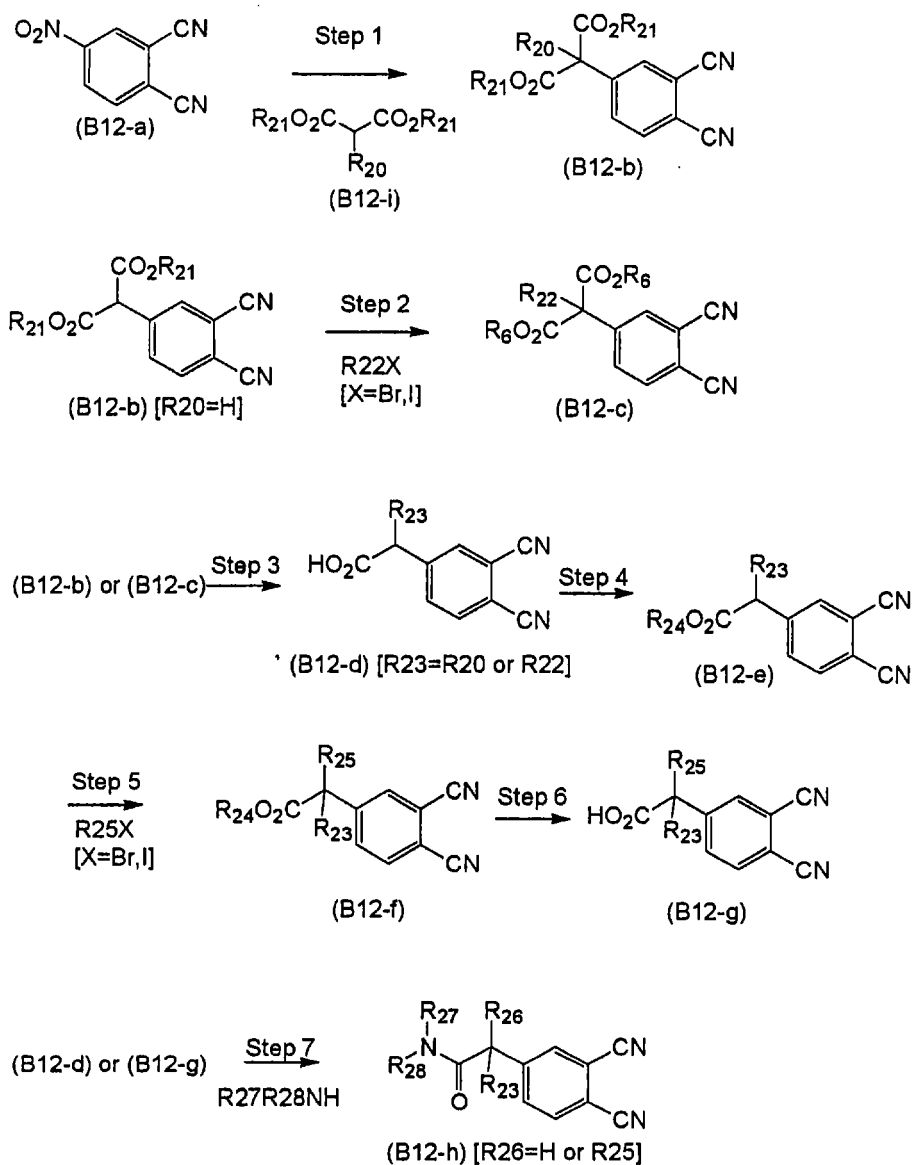
Step 2 is a step of N-alkylation reaction. This may be accomplished by reaction with an alkyl halide in a dimethylsulfoxide solvent, in the presence of sodium hydroxide powder. Alternatively, compound (B11-c) may be obtained by reaction with sodium hydride in a solvent such as tetrahydrofuran or dimethylformamide, followed by reaction with an alkyl

halide.

Compound (B11-a) wherein R3 is an alkoxy group may be synthesized in the following manner using compound (B11-d) which can be synthesized by the method described in C.C. Leznoff et al., Can. J. Chem., 73, 435(1995).

Step 3 is a step of reduction of the nitro group to yield an aniline. Compound (B11-e) may be obtained by adding iron powder in an alcohol solvent in the presence of ammonium chloride powder, and heating to reflux.

(Scheme B-12)



This scheme is a method for synthesis of phenylacetic acid derivatives (B12-e, f, h). In the formulas, R20 represents hydrogen, optionally substituted alkyl or alkoxy. R21 and R24 represent alkyl, and R22 and R25 represent optionally substituted alkyl. R23 represents R20 or R22, and R26 represents hydrogen or R25. R27 and R28 represent hydrogen or optionally substituted alkyl.

Step 1 is a step of substitution reaction at the nitro group of compound (B12-a) with a malonate derivative. When R20 in compound (B12-i) is hydrogen, compound (B12-b) may be obtained under the conditions described in M.P. Roze et al., Zh. Org. Khim, 28, 827(1992), or when R20 is a group other than hydrogen, it may be obtained by a method of using sodium hydride in dimethylformamide on the corresponding malonate to generate an anion, followed by reaction with compound (B12-a). When R20 is H, an alkyl group may also be introduced in other way.

Step 2 is a step of alkylation on the malonate α -carbon. Compound (B12-c) may be obtained by using sodium hydride in dimethylformamide to generate an anion, followed by reaction with an alkyl halide.

Step 3 is a step of decarboxylation of compound (B12-b) or (B12-c). When R6 is ethyl or methyl, compound (B12-d) may be obtained by reaction with aqueous lithium hydroxide in a solvent mixture of tetrahydrofuran and alcohol for hydrolysis, followed by heating to reflux for decarboxylation. When R6 is *tert*-butyl, the dicarboxylic acid obtained by treatment with trifluoroacetic acid may be heated to reflux in xylene for decarboxylation.

Step 4 is a step of esterification. When R24 is methyl, this may be accomplished by reaction with

trimethylsilyldiazomethane in an acetonitrile and alcohol solvent. When R24 is *tert*-butyl, it may be accomplished by reaction with di-*tert*-butyl dicarbonate in *tert*-butyl alcohol in the presence of
5 dimethylaminopyridine, or by reaction with dimethylformamide di-*tert*-butylacetal.

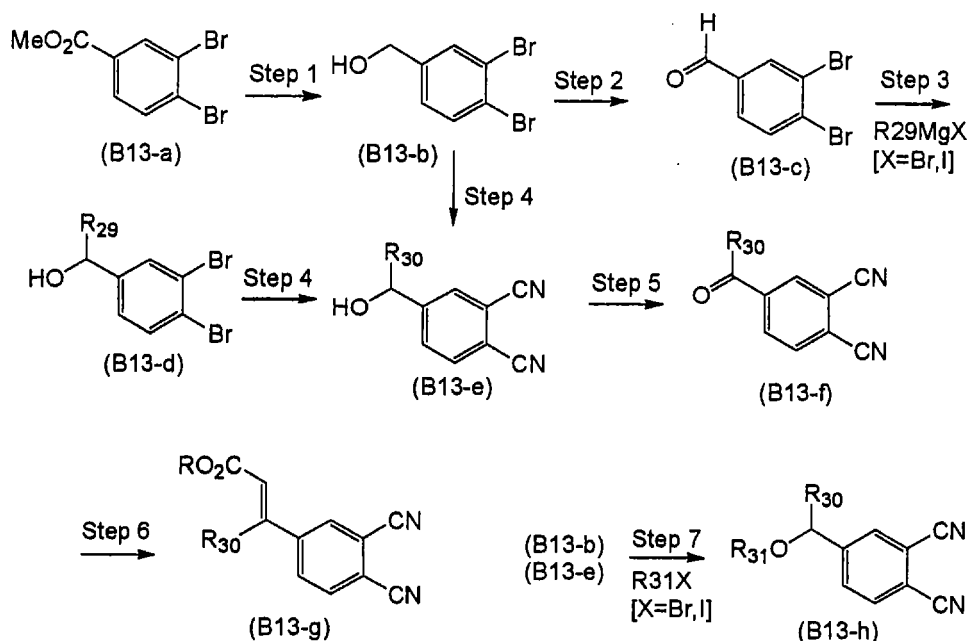
Compounds (B12-f) and (B12-h) having quaternary carbons may also be synthesized.

Step 5 is a step of alkylation of compound (B12-
10 e) [R24 = *t*Bu], wherein compound (B12-f) may be obtained similarly to Step 2 above.

Step 6 is a step of conversion to a carboxyl group. Compound (B12-g) may be obtained by dissolution at room temperature in trifluoroacetic
15 acid diluted with an organic solvent such as dichloromethane.

Step 7 is a step of obtaining compound (B12-h) according to the method of Scheme B-10, Step 4, under conditions for amidation of compound (B12-d) or (B12-
20 g).

(Scheme B-13)



This scheme is a method for synthesis of compounds (B13-e), (B13-g) and (B13-h) from compound (B13-a). In the formulas, R_{29} and R_{31} represent optionally substituted alkyl, R_{30} represents hydrogen or R_{29} , and R represents lower alkyl.

Step 1 is a step of reduction of ester. Compound (B13-b) may be obtained by reaction with lithium borohydride in tetrahydrofuran while cooling on ice.

Step 2 is a step of obtaining compound (B13-c) by Swern oxidation.

Step 3 is a step of introducing an alkyl group. Compound (B13-d) may be obtained by using a Grignard reagent in a solvent such as tetrahydrofuran. The obtained compound (B13-b) or (B13-d) may be converted to a dinitrile (B13-e) by conducting Step 4 using the conditions for Scheme B, Step 1. Conversion to a

styrene derivative is also possible.

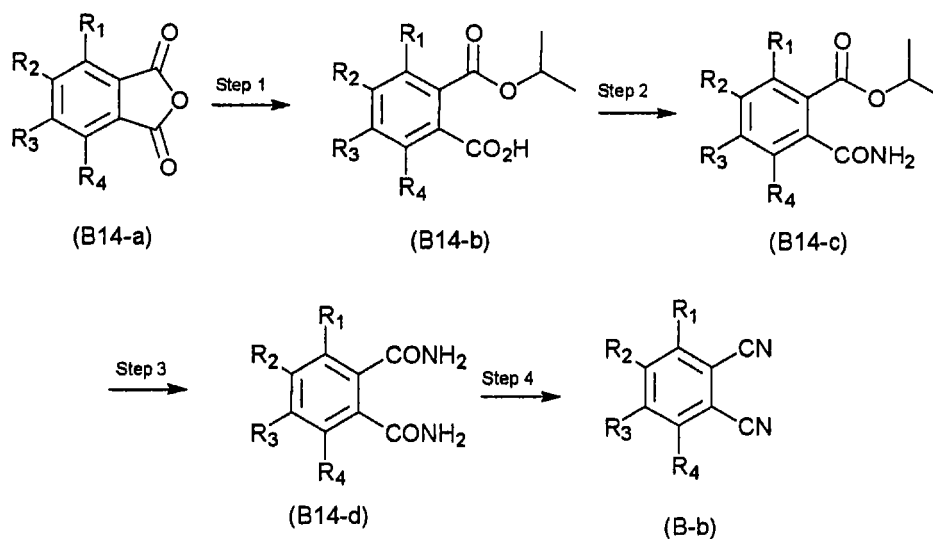
Step 5 is a step of obtaining compound (B13-f) through oxidation of the hydroxyl group by Swern oxidation.

5 Step 6 is a step of conversion to a conjugated ester. Compound (B13-g) may be obtained by Horner-Emmons reaction or Wittig reaction. Conversion from (B13-e) to an alkoxy derivative is also possible.

10 Step 7 is a step of alkylation of the hydroxyl group, wherein compound (B13-h) may be obtained similarly to Scheme B-6, Step 3.

A compound represented by (B-b) in Scheme B may also be synthesized from readily available phthalic anhydride by the method described in D. Wohrle et al.,
15 Synthesis, 194(1993), R.D. George et al., J. Heterocyclic. Chem., 32, 495(1995) or by the method shown in the following Scheme B-14.

(Scheme B-14)



This scheme is a method for synthesis of compound (B-b) using phthalic anhydride as the starting material. R1, R2, R3 and R4 have the same definitions as in Scheme B.

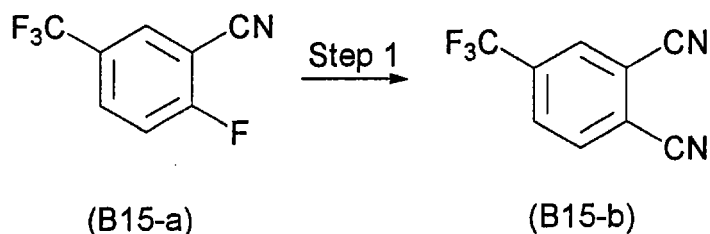
5 Step 1 is a step of synthesizing a phthalic acid monoester. Compound (B14-b) may be obtained by heating to reflux in isopropanol.

10 Step 2 is a step of conversion to a carboxamide, wherein compound (B14-c) may be obtained by the method described in Scheme B-10, Step 4.

 Step 3 is a step of obtaining a carboxamide from the ester. Compound (B14-d) may be obtained by heating to reflux in an ammonia-saturated alcohol solvent.

15 Step 4 is a step of synthesizing a nitrile by dehydration of the carboxamide. A compound represented by (B-b) may be obtained by reaction with trifluoroacetic anhydride in a solvent such as tetrahydrofuran in the presence of pyridine, while
20 cooling on ice.

(Scheme B-15)



This scheme is a method for converting compound

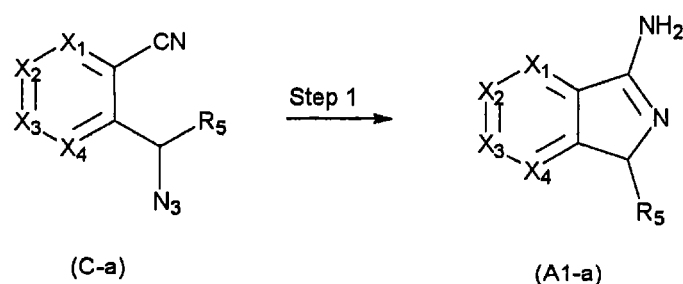
(B15-a) to a dinitrile in a single step to synthesize a trifluoromethyl-substituted derivative (B15-b).

Step 1 is a step of introducing a cyano group. Compound (B15-b) may be obtained by heating a dimethylformamide solution of compound (B15-a) at 110°C in the presence of sodium cyanide.

The compounds represented by (A1-a) in Production Process A, Scheme A-1 may also be synthesized by the following Production Process C via reduction of an azide group.

<Production Process C>

(Scheme C)



X1=N or CR1, X2=N or CR2,
X3=N or CR3, X4=N or CR4

This is a process for synthesizing a compound represented by (A1-a) in Production Process A, Scheme A-1 by reduction of the azide group.

In the formulas, R5 represents hydrogen or optionally substituted alkyl.

Step 1 is a step of reducing the azide group of compound (C-a) and synthesizing a cyclic amidine by ring closure of the resulting amine, and compound (A1-

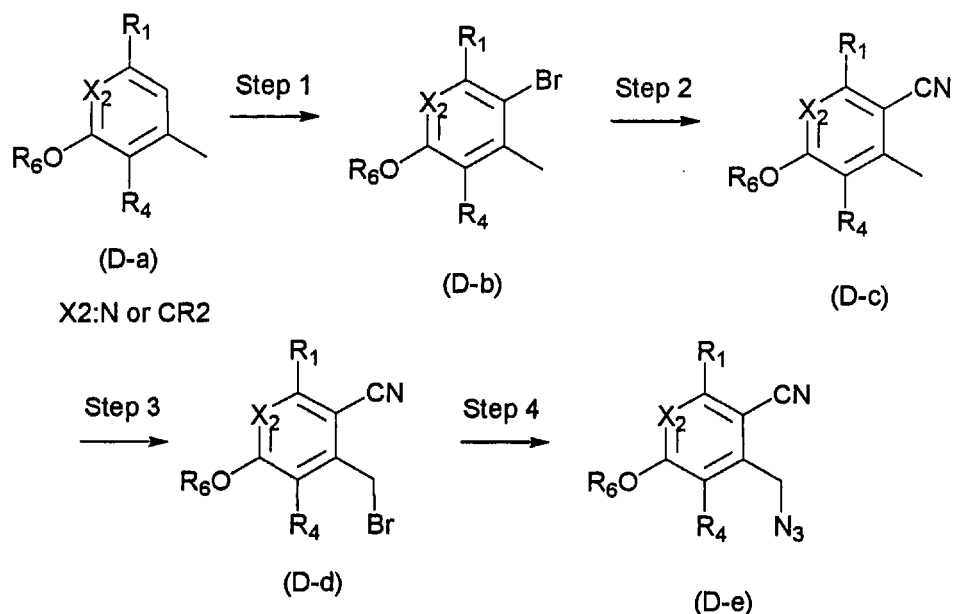
a) may be obtained by either of the following two methods. 1) A reaction using an organophosphorus reagent such as triphenylphosphine or triethylphosphine in a hydrous tetrahydrofuran solvent, or 2) a hydrogenation reaction using a metal catalyst such as palladium-carbon in ethyl acetate, alcohol or a mixture thereof.

A benzylamine derivative may be obtained under reducing reaction conditions without promoting ring closure, by adsorption on silica gel and standing at room temperature from 3 hours to 1 day, to yield a cyclic amidine (A1-a).

A compound represented by (C-a) may be synthesized by selecting any of Production Processes D to H below, which differ mainly in the method of introducing the cyano group and azide group.

<Production Process D>

(Scheme D)



This scheme is a method for synthesis of compound (D-e) from compound (D-a). In the formulas, R1 represents hydrogen, halogeno, optionally substituted alkyl or alkoxy. R2 represents hydrogen, optionally substituted alkyl, optionally substituted alkoxy or optionally substituted amino. R4 represents hydrogen, halogeno or optionally substituted alkoxy. R6 represents optionally substituted alkyl.

Step 1 is a step of regioselective bromination, wherein compound (D-b) may be obtained by the same method as in Scheme B-1, Step 2.

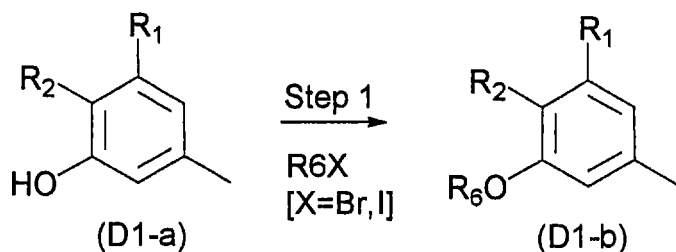
Step 2 is a step of cyanation and may be selected from either of the following two methods. 1) A method of heating together with sodium cyanide, potassium cyanide, zinc cyanide or the like in a solvent such as acetonitrile, propionitrile, valeronitrile or dimethylformamide, in the presence of a palladium

catalyst and copper (I) iodide. The palladium catalyst used may be tetrakis(triphenylphosphine)palladium, bis(triphenylphosphine)palladium dichloride, or the like. 2) A method of using copper (I) cyanide as explained in Scheme B, Step 1. Compound (D-c) is preferably obtained by method 1).

Step 3 is a step of introducing a bromo group by radical reaction. Compound (D-d) may be obtained by heating to reflux together with N-bromosuccinimide in a solvent such as carbon tetrachloride or chlorobenzene, in the presence of azoisobutyronitrile or benzoyl peroxide.

Step 4 is a step of introducing an azide group. Compound (D-e) may be obtained by reaction with sodium azide in a dimethylformamide solvent at room temperature while cooling on ice. In Scheme D, the compounds represented by (D-a) to (D-c) may be synthesized by the methods of the following Schemes D-1 to D-4, for example.

(Scheme D-1)

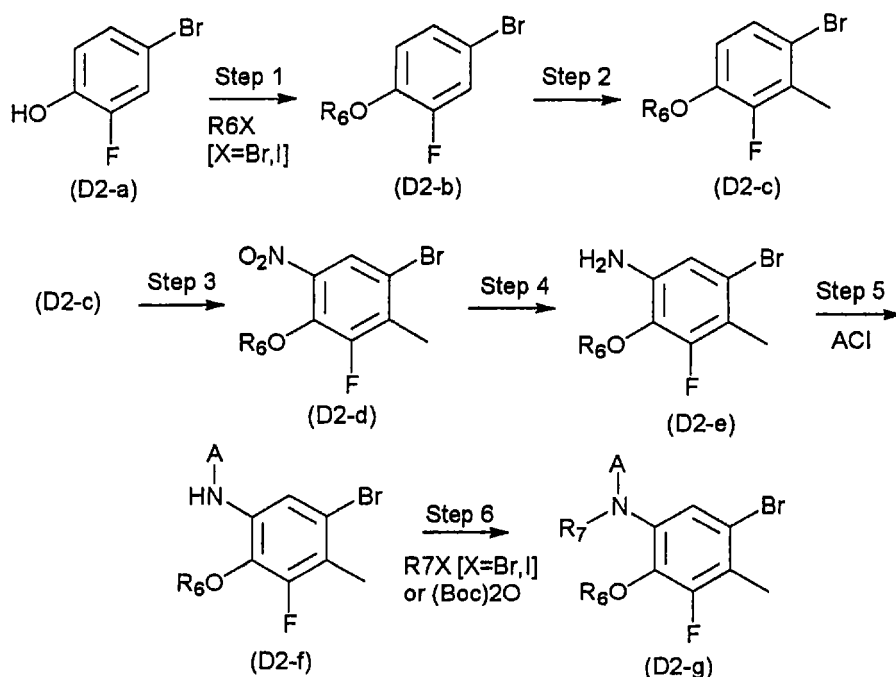


This scheme is a synthesis method employed when

the phenol derivative represented by (D1-a) is available. In the formulas, R1, R2 and R6 have same definitions as in Scheme D.

Step 1 is a step of alkylating compound (D1-a), wherein compound (D1-b) may be obtained by the same method as in Scheme B-1, Step 1.

(Scheme D-2)



This scheme is a synthesis method employed when R4 is fluorine in a compound represented by (D-a) or (D-b). In the formulas, A represents optionally substituted alkanoyl, alkylsulfonyl, aminocarbonyl or alkoxy carbonyl. R7 represents hydrogen, optionally substituted alkyl or *tert*-butyloxycarbonyl. R6 has the same definition as in Scheme D.

Step 1 is a step of alkylating the phenol, wherein compound (D2-b) may be obtained by the same

method as in Scheme B-1, Step 1.

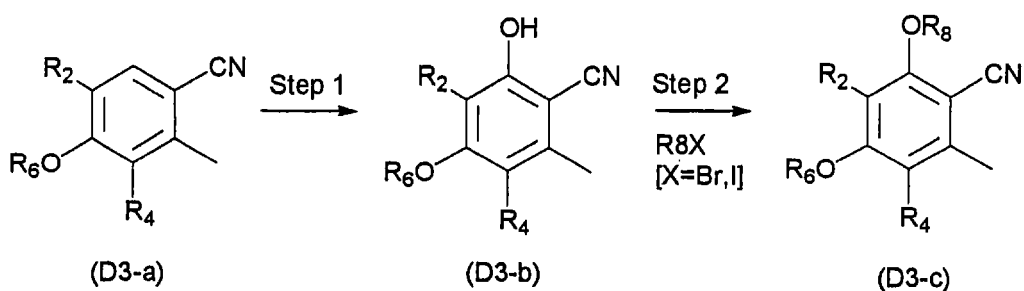
Step 2 is a step of introducing a methyl group. Compound (D2-c) may be synthesized by reaction with a strong base such as lithium diisopropylamide in a solvent such as tetrahydrofuran or diethyl ether for lithiation, followed by reaction with methyl iodide. An aniline derivative may also be synthesized from compound (D2-c).

Step 3 is a step of nitration, wherein compound (D2-d) may be obtained by the method described in C.C. Leznoff et al., Can. J. Chem., 73, 435(1995).

The synthesis method for compounds (D2-f) and (D2-g) shown in Steps 4 to 6 may be carried out by the same method as in Scheme B-11. When a *tert*-butoxycarbonyl group is to be introduced as a protecting group for R7 in compound (D2-f), this may be accomplished by reaction with di-*tert*-butyl dicarbonate in a solvent such as acetonitrile, in the presence of dimethylaminopyridine.

When R1 is alkoxy in a compound represented by (D-c), the synthesis may be conducted, for example, by the following Scheme D-3 via lithiation at the ortho position relative to the nitrile group.

(Scheme D-3)

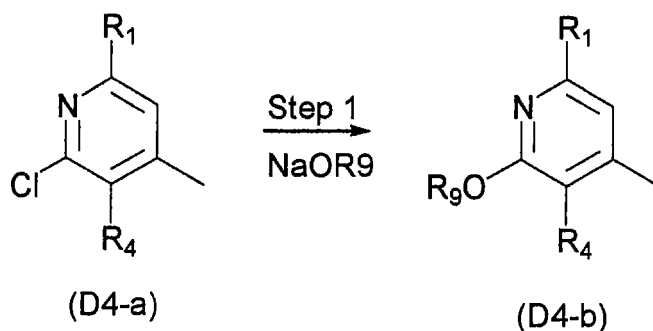


Compound (D3-a) is a compound represented by (D-
c) [R1 = H] which may be synthesized by the method of
Scheme D. In the formulas, R8 represents optionally
substituted alkyl.

Step 1 is a step of introducing a phenolic
hydroxyl group. Compound (D3-a) may be reacted with a
strong base such as lithium diisopropylamide in a
solvent such as tetrahydrofuran or diethyl ether for
lithiation, and then reacted with a trialkyl borate
for introduction of borane. Compound (D3-b) may also
be obtained by oxidation using alkaline hydrogen
peroxide.

Step 2 is a step of alkylation of the phenol,
wherein compound (D3-c) may be obtained by the same
method as in Scheme B-1, Step 1.

(Scheme D-4)



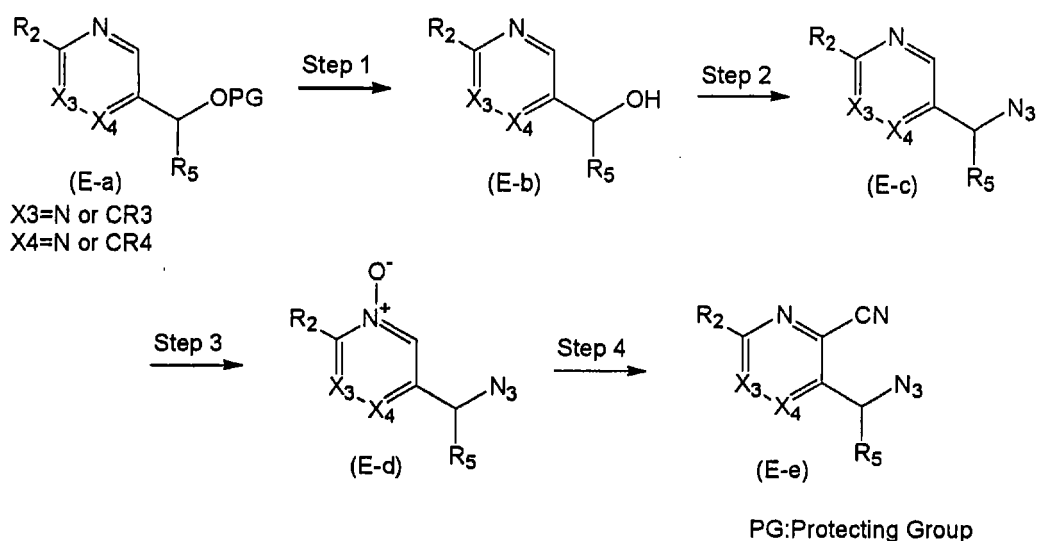
This scheme is a synthesis method for a compound represented by (D-a) wherein X2 is nitrogen, using a 2-chloropyridine derivative as a pyridine derivative for the starting material. In the formulas, R1 and R4 have the same definitions as in Scheme D. R9 represents optionally substituted alkyl.

Step 1 is a step of introducing an alkoxy group at the 2-position of the pyridine. Compound (D4-b) may be obtained using a sodium alkoxide prepared using sodium hydride in the corresponding alcohol solvent, employing conditions from reflux to 120°C with a sealed tube.

Synthesis of a compound represented by (C-a) in Production Process C, Scheme C, wherein X1 is nitrogen, such as a pyridine, pyrazine or pyrimidine derivative, may be carried out by the methods shown in Production Process E to E-2 below.

<Production Process E>

(Scheme E)



This scheme is a synthesis method for a pyridine derivative (E-e). In the formulas, R2 represents hydrogen, halogeno, optionally substituted alkyl, cycloalkyl, optionally substituted alkylaminocarbonyl, carboxyl, alkoxycarbonyl, optionally substituted carbamoyl, an optionally substituted aromatic heterocyclic group or an optionally substituted non-aromatic heterocyclic group. R3 represents hydrogen, carboxyl, alkoxycarbonyl, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkylaminocarbonyl or carbamoyl. R4 and R5 represent hydrogen or optionally substituted alkyl.

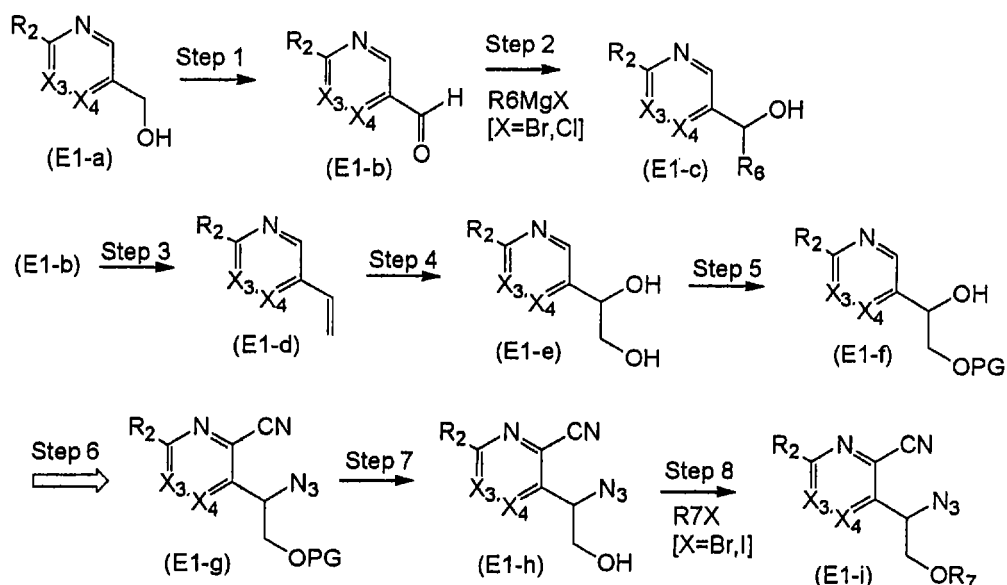
Step 1 is a step of removing the silyl group serving as the hydroxyl-protecting group in a compound represented by (E-a). This may be accomplished by reaction with tetrabutylammonium fluoride or tris(dimethylamino)sulfonium difluorotrimethylsilicate in a tetrahydrofuran solvent either at room

temperature or while cooling on ice. The tetrabutylammonium fluoride may also be used in the copresence of acetic acid in order to trap the generated anions.

5 Step 2 is a step of azidation, wherein compound (E-c) may be obtained by selecting either the method described in A.S. Thompson et al., J. Org. Chem., 58, 5886(1993), or by a two-step process involving reaction with mesyl chloride in a solvent such as
10 dichloromethane in the presence of a base such as triethylamine to synthesize a mesylate or chloride, followed by reaction with sodium azide in a solvent such as dimethylformamide.

15 Step 3 is a step of oxidation of the pyridine nitrogen atom. Compound (E-d) may be obtained by oxidation using a peracid such as m-chloroperbenzoic acid in a solvent such as dichloromethane.

20 Step 4 is a step of introducing a cyano group. Compound (E-e) may be obtained by applying the conditions described in W.K. Fife, J. Org. Chem., 48, 1375(1983).
(Scheme E-1)



This scheme is a synthesis method for introduction of the substituent R5 in a compound represented by (E-b). In the formulas, R2 has the same definition as in Scheme E. R6 represents lower alkyl and R7 represents hydrogen or optionally substituted alkyl.

Step 1 is a step of oxidation of the hydroxyl group of compound (E1-a). Compound (E1-b) may be obtained by heating to reflux together with manganese dioxide, using chloroform as the solvent.

Step 2 is a step of introducing an alkyl group, wherein a compound represented by (E1-c) may be obtained by reaction with a Grignard reagent in a solvent such as tetrahydrofuran or diethyl ether under conditions from freezing to room temperature. A hydroxymethyl group (E1-f) or alkoxymethyl group (E1-j) may also be introduced.

Step 3 is a step of introducing methylene into compound (E1-b), wherein compound (E1-d) may be obtained by Wittig reaction using an ylide prepared from methyltriphenylphosphonium bromide and butyllithium.

Step 4 is a step of dihydroxylation of compound (E1-d). Compound (E1-e) may be obtained by reaction with a catalytic amount of osmium tetroxide in an acetone/water mixed solvent, in the presence of N-methylmorpholine N-oxide.

Step 5 is a step of protecting the hydroxyl group with a silyl group. For a *tert*-butyldimethylsilyl group, reaction may be conducted with *tert*-butyldimethylsilyl chloride in a solvent such as dichloromethane, in the presence of triethylamine and dimethylaminopyridine, or for introduction of a *tert*-butyldiphenylsilyl group, reaction may be conducted with *tert*-butyldiphenylsilyl chloride in dimethylformamide, in the presence of imidazole, to yield compound (E1-f). Compound (E1-f) may be converted to compound (E1-g) by the conversion method of Steps 2 to 4 of Scheme E.

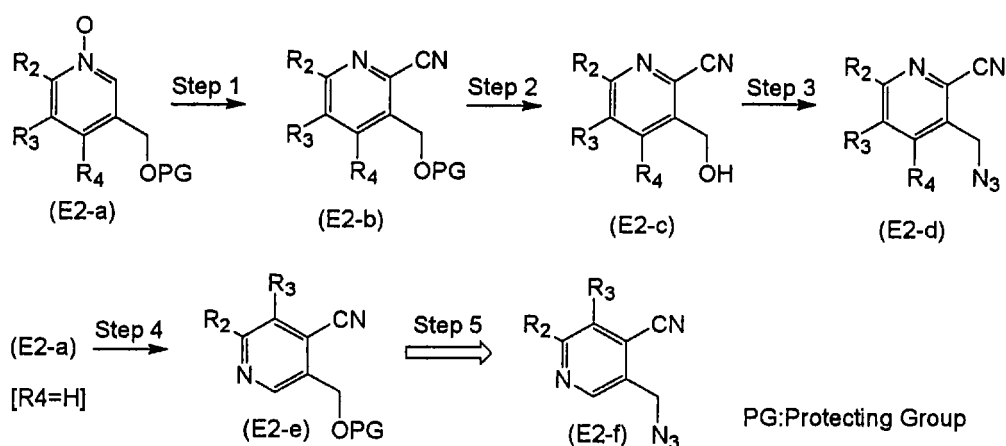
Step 7 is a step of removing the silyl group serving as the hydroxyl-protecting group, wherein compound (E1-h) may be obtained by similarly to Scheme E, Step 1. An alkyl group or alkoxycarbonylmethyl

group may also be introduced into compound (E1-h).

Step 8 is a step of alkylation. Compound (E1-i) may be obtained by reaction with sodium hydride in a solvent such as dimethylformamide or tetrahydrofuran, followed by reaction with an alkyl halide.

<Production Process E-2>

(Scheme E-2)



This scheme is a synthesis method for the pyridine derivatives (E2-d) and (E2-f). In the formulas, R2, R3 and R4 have the same definitions as in Scheme E.

Step 1 is a step of introducing a nitrile group, wherein compound (E2-b) may be obtained by the method shown in Scheme E, Step 4.

Step 2 is a step of removing the silyl protecting group, wherein compound (E2-c) may be obtained by the method shown in Scheme E, Step 1. Particularly preferred is a method of reacting tris(dimethylamino)sulfonium difluorotrimethylsilicate

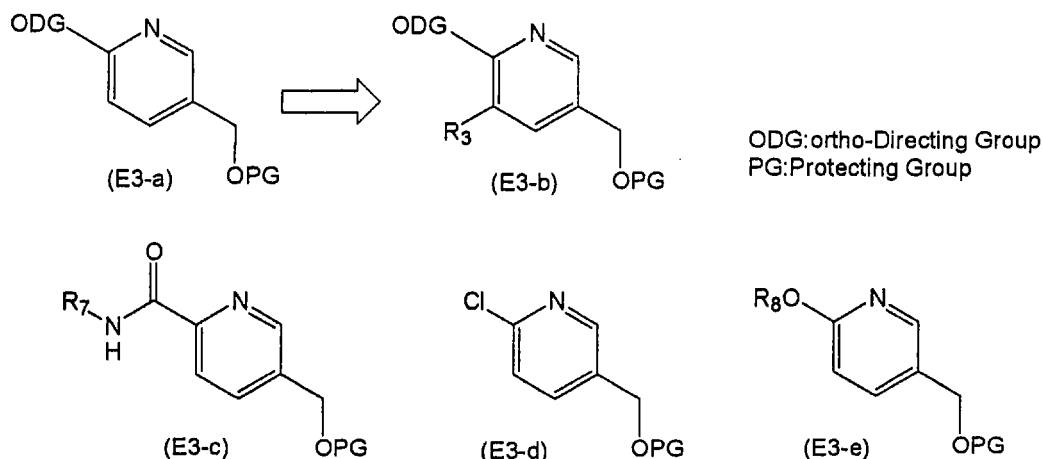
in the presence of acetic acid.

Step 3 is a step of azidation, wherein compound (E2-d) may be obtained by the method of Scheme E, Step 2. A compound (E2-a) wherein R4 = H may be utilized to synthesize a pyridine derivative wherein X3 is nitrogen in a compound represented by (C-a) of Scheme C.

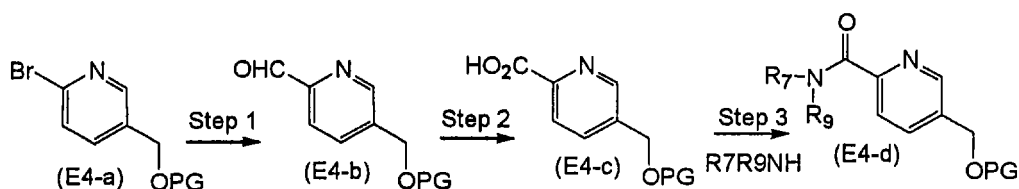
Step 4 is a step of nitrilation at the 4-position of the pyridine N-oxide, wherein compound (E2-e) may be synthesized by O-methylation with dimethylsulfuric acid without a solvent, followed by reaction with potassium cyanide in an ethanol/water mixed solvent. Compound (E2-e) may also be converted to compound (E2-f) by the method of Scheme E-2, Steps 2 and 3.

Each of the intermediates represented by the general formulas in Schemes E to E-2 may also be synthesized by the methods shown in the following Schemes E-3 to E-21. Synthesis of an R2 or R3 disubstituted derivative may be accomplished by introduction of a functional group by ortho metalation of compound (E3-a). Here, any of compounds (E3-c) to (E3-e) may be used as compounds represented by (E3-a), and they may be synthesized by the methods of Schemes E-4 to E-6 below.

(Scheme E-3)



(Scheme E-4)



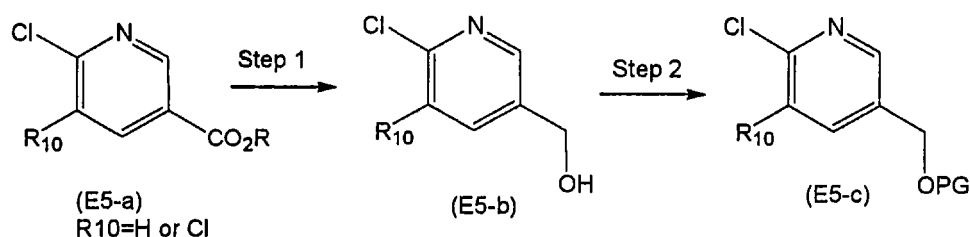
These schemes are synthesis methods for 2-substituted pyridine derivatives (E3-c), (E3-d), (E3-e) and (E4-d). In the formulas, R7, R8 and R9 represent hydrogen or optionally substituted alkyl.

Step 1 is a step of converting the bromo group to a formyl group in compound (E4-a) synthesized by the method described in J.W. Ellingboe et al., J. Med. Chem., 37, 542 (1994). Compound (E4-b) may be obtained by halogen-metal exchange lithiation using butyllithium at -78°C in a solvent such as tetrahydrofuran or diethyl ether, followed by reaction with N-formylmorpholine or dimethylformamide.

Step 2 is a step of converting compound (E4-b) to a carboxylic acid by oxidation. Compound (E4-c) may be obtained by reaction with sodium hypochlorite as an

oxidizing agent at room temperature in a *tert*-butanol/water mixed solvent in the presence of sodium dihydrogenphosphate and 2-methyl-2-butene as a peroxide scavenger.

5 Step 3 is a step of amidation, wherein compound (E4-d) may be obtained similarly to Scheme B-10, Step 4. Compound (E3-c) is compound (E4-d) where R₉ = H, and compound (E4-d) itself is converted to the final target compound as a monosubstituted derivative of
10 compound (E-a) in Scheme E, by Production Process A. (Scheme E-5)



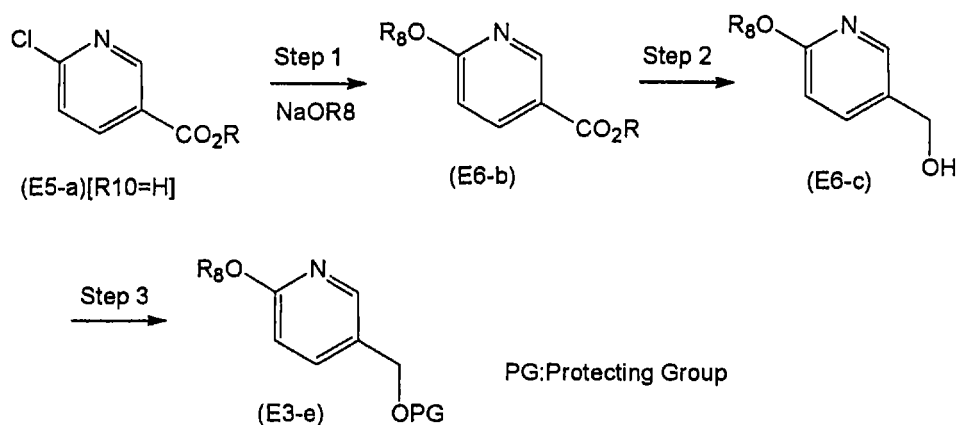
This scheme is a synthesis method for a 2-chloropyridine derivative (E5-c). In the formulas, R
15 represents lower alkyl.

Step 1 is a step of synthesizing an alcohol by reduction of a commercially available ester (E5-a). The reduction may be accomplished using sodium borohydride in an alcohol solvent under conditions
20 from room temperature to reflux.

Step 2 is a step of protecting the hydroxyl group with a silyl group, wherein compound (E5-c) may be obtained similarly to Scheme E-1, Step 5. Compound

(E3-d) is compound (E5-c) where R10 = H, and compound (E5-c) itself is converted to the final target compound as a monosubstituted derivative of compound (E-a) in Scheme E, by Production Process A.

5 (Scheme E-6)



This scheme is a synthesis method for a 2-alkoxypyridine derivative (E3-e). In the formulas, R and R8 represent optionally substituted alkyl.

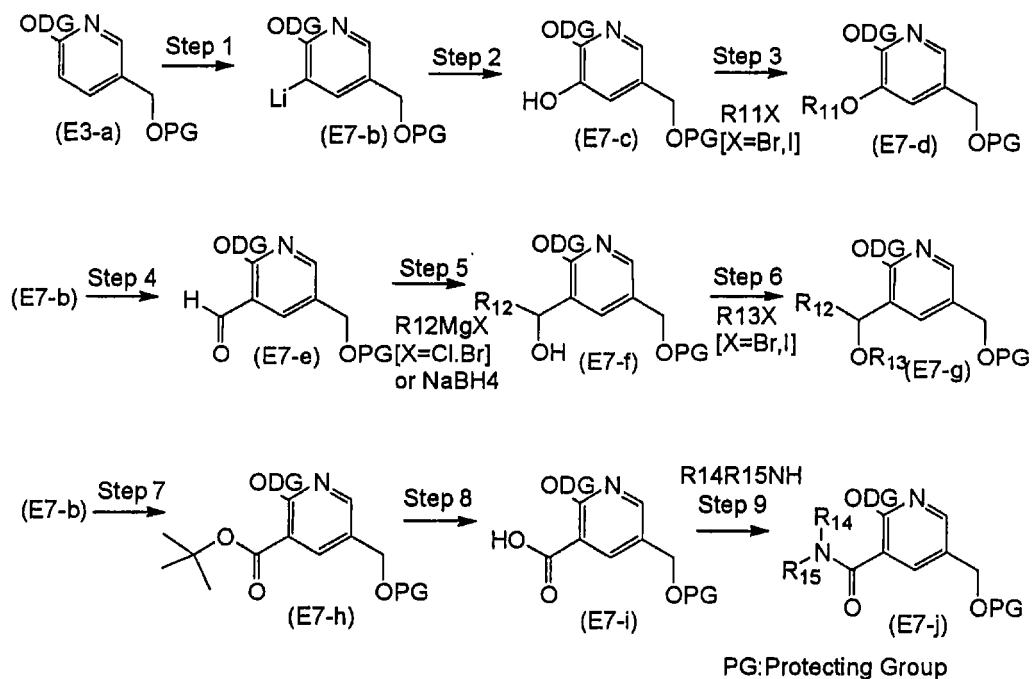
10 Step 1 is a step of introducing an alkoxy group, wherein compound (E6-b) may be obtained similarly to Scheme D-4, Step 1.

Step 2 is a step of reduction of the ester. Compound (E6-c) may be obtained by reaction with
15 lithium aluminum hydride in a solvent such as tetrahydrofuran while cooling on ice.

Step 3 is a step of protecting the hydroxyl group with a silyl group, wherein compound (E3-e) may be obtained similarly to Scheme E-1, Step 5. Compound
20 (E3-e) itself may be utilized as a monosubstituted derivative of compound (E-a) in Scheme E.

The following is a method of introducing substituent R3 in compound (E3-a).

(Scheme E-7)



This scheme is a synthesis method for substituent introduction to compound (E3-a) via ortho-lithiation. In the formulas, R11 and R13 represent optionally substituted alkyl, R12 represents hydrogen or lower alkyl, and R14 and R15 represent hydrogen or optionally substituted alkyl.

Step 1 is a step of ortho-lithiation utilizing an ODG. Intermediate (E7-b) may be obtained *in situ* by using phenyllithium in a tetrahydrofuran solvent, in the presence of 1) butyllithium as a base and 2) a catalytic amount of diisopropylamine. Compound (E7-b) may then be reacted with any of various electrophilic reagents for introduction of substituents.

Step 2 is a step of introducing a hydroxyl group. Compound (E7-c) may be obtained by reaction of compound (E7-b) with trimethylborate, followed by oxidation using alkaline aqueous hydrogen peroxide.

5 Step 3 is a step of alkylation of the phenolic hydroxyl group, wherein compound (E7-d) may be obtained by the method of Scheme B-1, Step 1.

Step 4 is a step of introducing a formyl group. Compound (E7-e) may be obtained by reaction of
10 compound (E7-b) with dimethylformamide or N-formylmorpholine at -70°C .

Step 5 is a step of alkylation and reduction to synthesize an alcohol (E7-f). A compound wherein R12 is alkyl may be synthesized by reaction with a
15 Grignard reagent in tetrahydrofuran, and reduction when R12 is hydrogen may be accomplished using sodium borohydride in an alcohol solvent.

Step 6 is a step of alkylation of the hydroxyl group, wherein compound (E7-g) may be obtained by the
20 method of Scheme B-6, Step 3. When R13 is a tetrahydropyranyl (THP) group introduced as a protecting group, compound (E7-g) [R13 = THP] may be obtained by reaction with dihydropyran in a solvent such as dichloromethane using a catalytic amount of p-
25 toluenesulfonic acid or camphorsulfonic acid as the acid. A carboxyl ester or carboxamide group may also

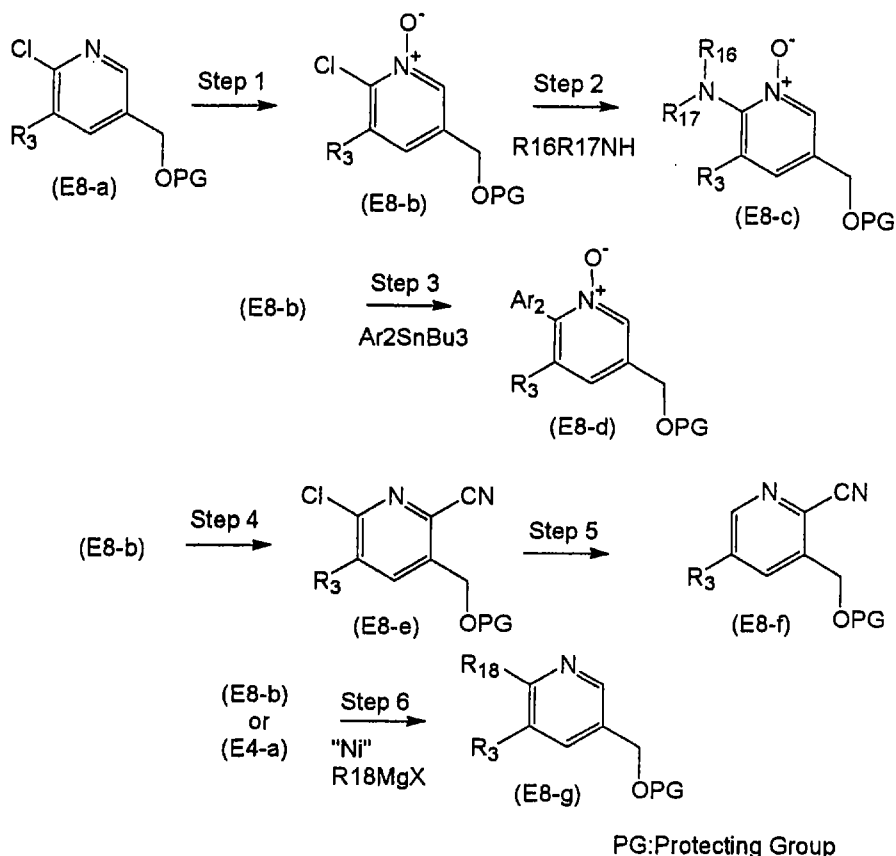
be introduced.

Step 7 is a step of introducing a *tert*-butoxycarbonyl group. Compound (E7-h) may be obtained by reaction of compound (E7-b) with di-*tert*-butyl dicarbonate at -70°C.

Step 8 is a step of removing the *tert*-butyl group. Compound (E7-i) may be obtained by dissolution in trifluoroacetic acid diluted with an organic solvent such as dichloromethane, and reaction at room temperature.

Step 9 is a step of amidation, wherein compound (E7-j) may be obtained by the method described in Scheme B-10, Step 4.

Compound (E8-a), a compound represented by (E3-b) wherein the ODG is chloride, may be converted in the manner shown in Scheme E-8 below.
(Scheme E-8)



This scheme is a synthesis method for compounds (E8-c), (E8-d), (E8-f) and (E8-g). In the formulas, R₃ has the same definition as in Scheme (E3-b). R₁₆, R₁₇ and R₁₈ represent optionally substituted alkyl or optionally substituted cycloalkyl, and R₁₆ and R₁₇ may optionally form a ring together with the N. Ar₂ represents an aromatic heterocyclic group.

Step 1 is a step of oxidation of the pyridine nitrogen atom, wherein compound (E8-b) may be obtained by the method of Scheme E, Step 3.

Step 2 is a step of introducing an amino group by substitution. Compound (E8-c) may be obtained by reaction in an alcohol solvent in the presence of an

amine, under conditions from room temperature to reflux.

Step 3 is a step of introducing a heteroaromatic ring by Stille reaction. Compound (E8-d) may be
5 obtained by heating to reflux together with a tin reagent in a solvent such as toluene or xylene, in the presence of a palladium catalyst. The palladium catalyst is preferably tetrakis(triphenylphosphine)palladium.

10 A pyridine 5-unsubstituted derivative may also be synthesized by the following method.

Step 4 is a step of nitrilation in the same manner as Scheme E, Step 4, to yield compound (E8-e).

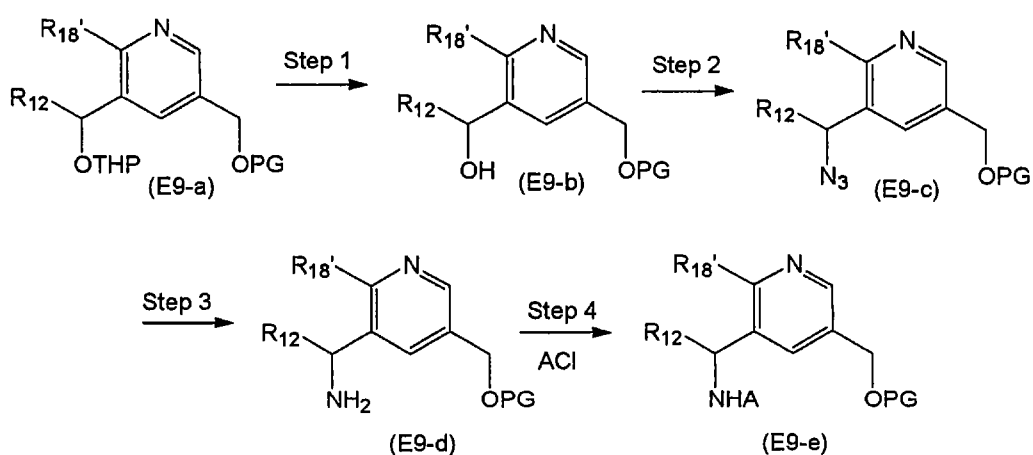
Step 5 is a step of reductive removal of the
15 chloro group. Compound (E8-f) may be obtained by heating to reflux in an acetonitrile solvent in the presence of a palladium catalyst and ammonium formate. The palladium catalyst is preferably tetrakis(triphenylphosphine)palladium. An alkyl group
20 may also be introduced at the pyridine 5-position.

Step 6 is a step of alkylation. Compound (E8-g) may be obtained by reaction of (E8-a) or (E4-a: R3 = H) with a Grignard reagent in a solvent such as tetrahydrofuran or diethyl ether, in the presence of a
25 nickel catalyst under conditions from freezing to room temperature. The nickel catalyst is preferably [1,2-

bis(diphenylphosphino)ferrocenyl]nickel(II) chloride, but another bidentate phosphine ligand such as 1,3-bis(diphenylphosphino)propane may also be used.

The side chain of a compound represented by (E9-a) may also be converted. Here, compounds represented by (E9-a) include compounds represented by (E7-g) wherein R13 is a THP group, and compounds represented by (E7-g) [R13 = THP] which have been subjected to a conversion shown in Scheme E-8.

(Scheme E-9)



PG:Protecting Group

This scheme is a synthesis method for compound (E9-e) having a substituted amino group. In the formulas, A has the same definition as in Scheme B-11 and R12 has the same definition as in Scheme E-7. R18' represents R18, Ar2, hydrogen, optionally substituted alkoxy or optionally substituted amino (wherein R18 and Ar2 have the same definitions as in Scheme E-8).

Step 1 is a step of removing the THP group serving as the hydroxyl-protecting group. Compound (E9-b) may be obtained by reaction in an alcohol solvent in the presence of a catalytic amount of p-toluenesulfonic acid as an acid.

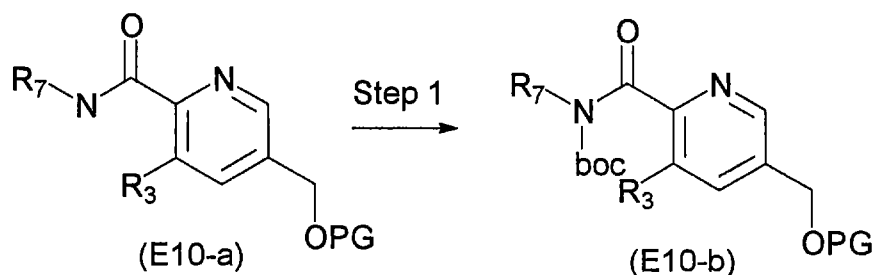
Step 2 is a step of azidation of the hydroxyl group, wherein compound (E9-c) may be obtained similarly to Scheme E, Step 2.

Step 3 is a step of reduction of the azide group, wherein compound (E9-d) may be obtained under the same conditions as in Scheme C, Step 1.

Step 4 is a step of introducing a substituent at the amino group, wherein compound (E9-e) may be obtained similarly to Scheme B-11, Step 1.

In the case of a compound represented by (E3-b), wherein the ODG is a carboxamide derivative, the reaction is preferably followed by protection of the amide hydrogen with a Boc group in the manner shown below.

(Scheme E-10)



PG:Protecting Group

This scheme is a synthesis method for compound

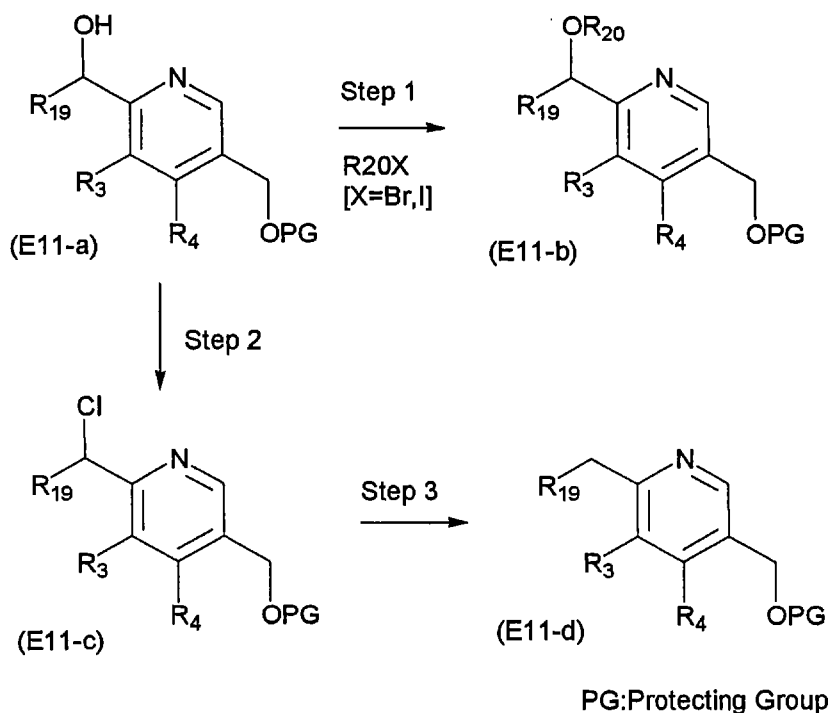
(E10-b). In the formulas, R3 and R7 have the same definitions as in Scheme E-3.

Step 1 is a step of introducing a Boc group at the amide nitrogen atom as a protecting group.

5 Compound (E10-b) may be obtained by reaction with di-*tert*-butyl dicarbonate in a solvent such as acetonitrile in the presence of dimethylaminopyridine.

A compound represented by (E-a) in Scheme E, wherein R2 is substituted methyl or alkyl, may be synthesized by the following method.

(Scheme E-11)



This scheme is a synthesis method for (E11-b) and (E11-d). In the formulas, R₁₉ represents optionally substituted alkyl or cycloalkyl. R₂₀ represents optionally substituted alkyl. R₃ and R₄ have the same

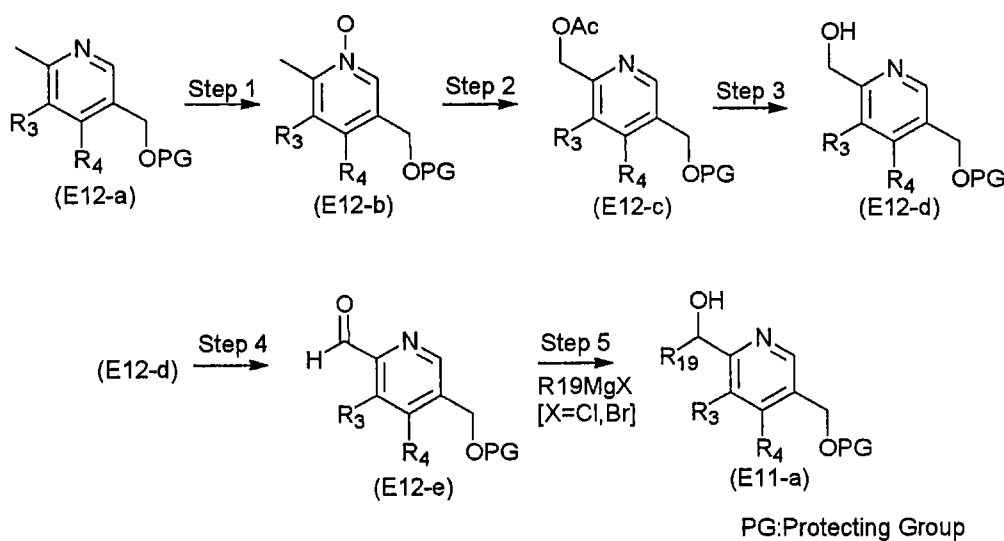
definitions as in Scheme E.

Step 1 is a step of alkylation of the hydroxyl group of compound (E11-a), corresponding to compound (E12-d) or (E12-f) which may be synthesized by the method shown in Scheme E-12 below, to yield compound (E11-b) by the method of Scheme B-6, Step 3.

Step 2 is a step of converting the hydroxyl group to a chloro group. Compound (E11-c) may be obtained by reaction with thionyl chloride in a solvent such as dichloromethane at room temperature, followed by treatment under basic conditions.

Step 3 is a step of removing the chloro group by reduction. Compound (E11-d) may be obtained by hydrogenation in an alcohol solvent at room temperature and normal pressure in the presence of a metal catalyst such as palladium-carbon.

(Scheme E-12)



This scheme is a synthesis method for compound

(E11-a). In the formulas, R3 and R4 have the same definitions as in Scheme E. R19 has the same definition as in Scheme E-11.

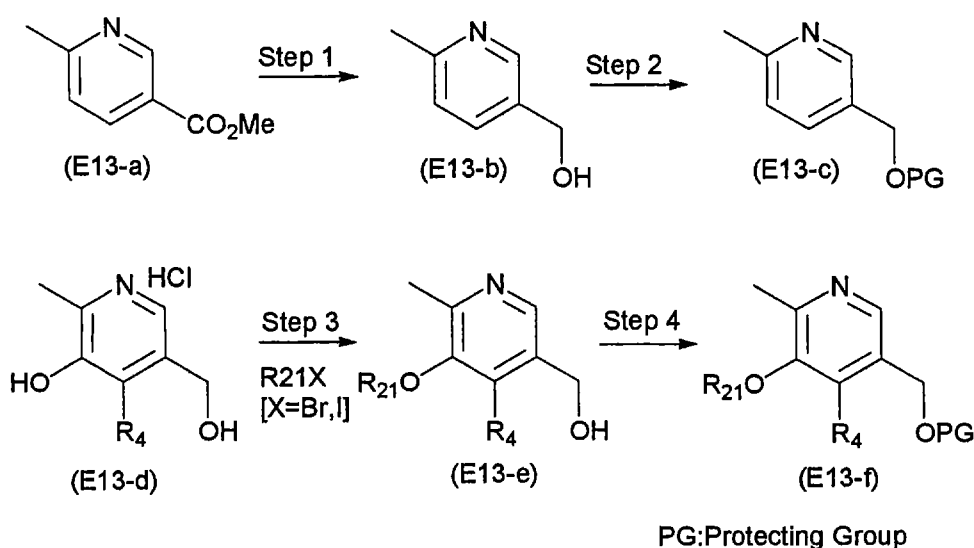
5 Step 1 is a step of oxidation of the pyridine nitrogen atom of compound (E12-a), wherein compound (E12-b) may be obtained similarly to Scheme E, Step 3.

Steps 2 and 3 accomplish introduction of a hydroxyl group at the methyl group by rearrangement. An acetate (E12-c) may be obtained by heating compound
10 (E12-b) from 120°C to 140°C in acetic anhydride. This may then be reacted with sodium methoxide or potassium carbonate in an alcohol solvent to yield compound (E12-d).

15 An alkyl group may also be introduced into compound (E12-d).

Step 4 is a step of obtaining an aldehyde by oxidation of the hydroxyl group. Compound (E12-e) may be obtained by heating to reflux together with manganese dioxide in a chloroform solvent.

20 Step 5 is a step of alkylation. Compound (E12-f) may be obtained by reaction with a Grignard reagent in a solvent such as tetrahydrofuran or diethyl ether. (Scheme E-13)



This scheme is a synthesis method for a compound represented by (E12-a). In the formulas, R₄ has the same definition as in Scheme E. R₂₁ represents optionally substituted alkyl or cycloalkyl.

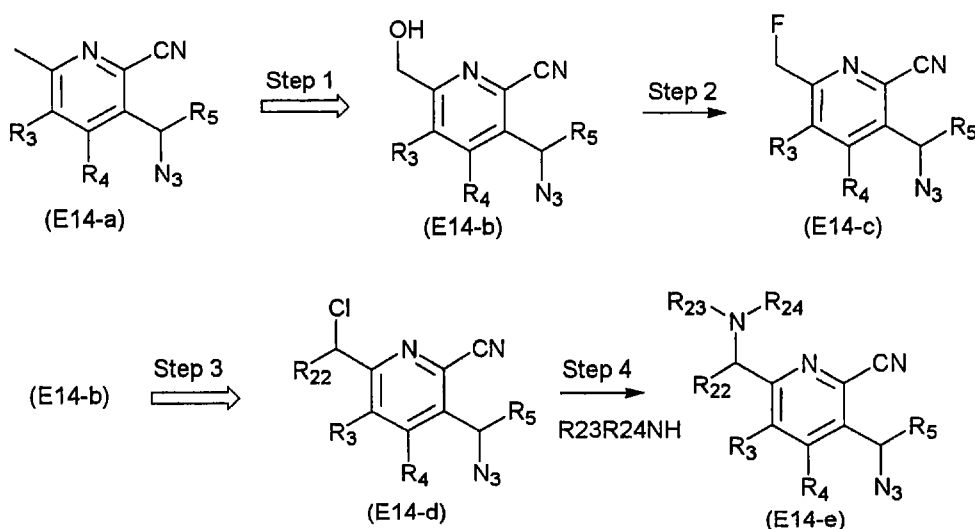
Step 1 is a step of reducing the commercially available compound (E13-a), wherein compound (E13-b) may be obtained similarly to Scheme E-5, Step 1.

Step 2 is a step of protecting the hydroxyl group with a silyl group, wherein compound (E13-c) may be obtained similarly to Scheme E-1, Step 5. Also, a compound represented by (E12-a) wherein R₃ is alkoxy may be synthesized in the following manner.

Step 3 is a step of selectively alkylating the phenolic hydroxyl group of compound (E13-d) either obtained commercially or synthesized by the method described in Y. Morisawa et al., J. Med. Chem., 17, 1235(1974). Compound (E13-e) may be obtained by stirring in dimethylformamide together with 2

equivalents of sodium hydride at room temperature for 3 hours to 1 day to produce a sufficient amount of phenoxy anion, followed by reaction with an alkyl halide.

5 Step 4 is a step of protecting the hydroxyl group with a silyl group, and it may be carried out according to the method in Scheme E-1, Step 5.
(Scheme E-14)



10 This scheme is a synthesis method for compounds (E14-b), (E14-c) and (E14-e) utilizing a compound represented by (E-e) in Scheme E wherein R₂ is methyl. In the formulas, R₃ and R₄ have the same definitions as in Scheme E. R₂₂ has the same definition as R₁₉ in
15 Scheme E-13, or represents hydrogen. R₂₃ and R₂₄ represent hydrogen or optionally substituted alkyl.

Step 1 is a step of introducing a hydroxyl group at the methyl group, wherein compound (E14-b) may be obtained utilizing the same conversion as the method

shown in Scheme E-12.

Step 2 is a step of fluorination. Compound (E14-c) may be obtained by reaction with diethylaminosulfur trifluoride in dichloromethane or 1,2-dichloroethane, under conditions from -70°C to room temperature.

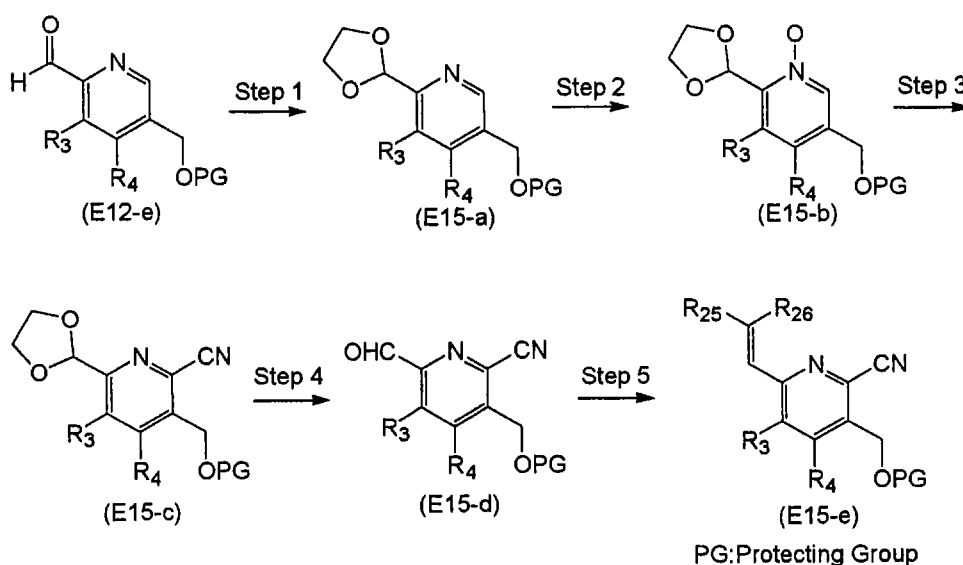
Steps 3 and 4 accomplish introduction of an amino group.

Step 3 is a step of introduction of an alkyl group and conversion to a halogeno group, wherein compound (E14-d) may be obtained similarly to the series of steps shown in Scheme E-12 and E-11 for obtaining compound (E11-c).

Step 4 is a step of introducing an amino group. Compound (E14-e) may be obtained by reaction with an alkylamine hydrochloride in a solvent such as acetonitrile in the presence of sodium carbonate.

Of the compounds represented by (E-a) in Scheme E or (E2-b) in Scheme E-2, those wherein R₂ is a substituent via a double bond may be synthesized by the methods of Scheme E-15 and E-16.

(Scheme E-15)



This scheme is a synthesis method for compound (E15-e). In the formulas, R3 and R4 have the same definitions as in Scheme E. R25 and R26 represent hydrogen or optionally substituted alkyl.

Step 1 is a step of protecting the formyl group of compound (E12-a). Compound (E15-a) may be obtained by heating to reflux in a toluene/ethylene glycol mixed solvent in the presence of a p-toluenesulfonic acid catalyst while removing the water using a Dean-Stark trap.

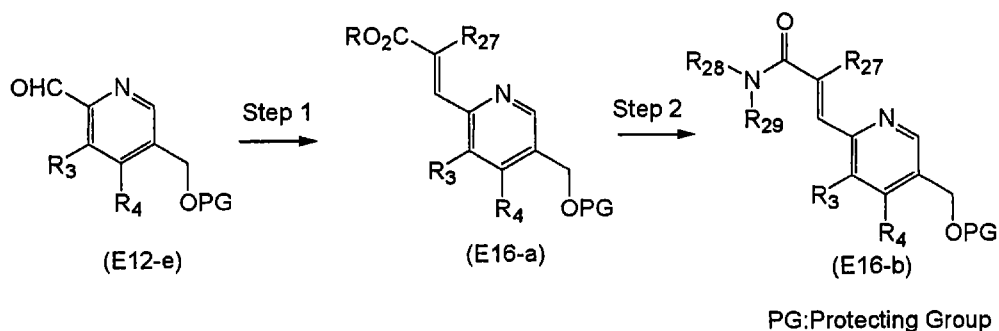
Steps 2 and 3 accomplish conversion in the same manner as Scheme E, Steps 3 and 4 to yield compound (E15-c).

Step 4 is a step of removing the formyl-protecting group. Compound (E15-d) may be obtained by heating at 80°C in 80% aqueous acetic acid.

Step 5 is a step of carbon-carbon bond formation, wherein compound (E15-e) may be obtained by Wittig

reaction or Horner-Emmons reaction.

(Scheme E-16)

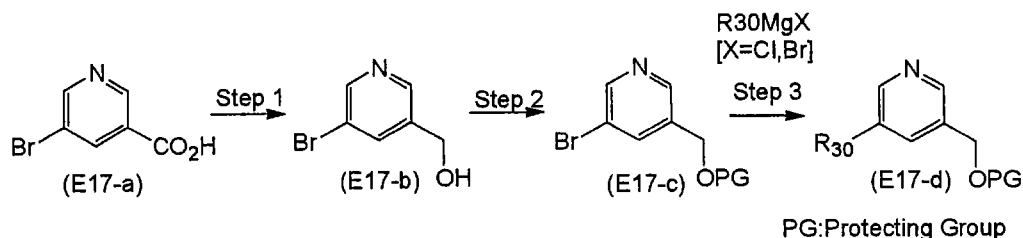


This scheme is a method for synthesis of an
 5 unsaturated ester and unsaturated amide. In the
 formulas, R₃ and R₄ have the same definitions as in
 Scheme E. R₂₇ represents hydrogen or lower alkyl, and
 R₂₈ and R₂₉ represent hydrogen or optionally
 substituted alkyl.

10 Step 1 is a step of carbon-carbon bond formation,
 wherein compound (16E-a) may be obtained by Wittig
 reaction or Horner-Emmons reaction.

Step 2 is a step of amidation of the ester.
 Compound (E16-b) may be obtained by reaction with an
 15 amine hydrochloride in the presence of
 trimethylaluminum.

(Scheme E-17)



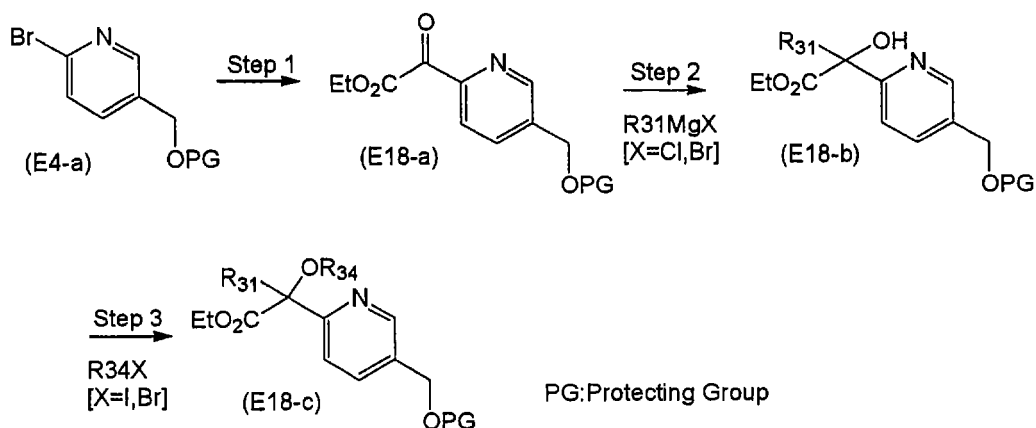
This scheme is a synthesis method for a

substituted pyridine (E17-d) which is a compound represented by (E-a) wherein R3 is alkyl. In the formulas, R30 represents optionally substituted alkyl or cycloalkyl.

Step 1 is a step of reducing the carboxyl group. Compound (E17-b) may be obtained by using an alkylchlorocarbonate in a solvent such as tetrahydrofuran in the presence of triethylamine to produce a mixed acid anhydride in the system, and then reducing it with sodium borohydride to yield compound (E17-b).

Step 2 is a step of protecting the hydroxyl group with a silyl group, wherein compound (E17-c) may be obtained similarly to Scheme E-1, Step 5.

Step 3 is a step of alkylation using a nickel catalyst, wherein compound (E17-d) may be obtained by the same method for alkyl group introduction at the pyridine α -carbon as shown in Scheme E-8, Step 6. (Scheme E-18)



This scheme is a method for synthesis of a

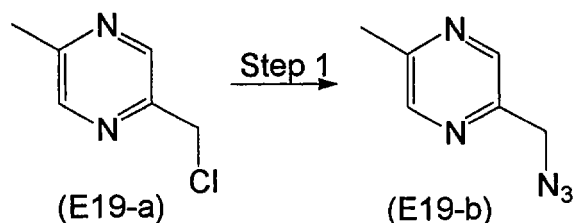
pyridinium methylcarboxylate derivative from compound (E4-a) mentioned above. In the formulas, R31 and R34 represent optionally substituted alkyl.

Step 1 is a step of carbon-carbon bond formation of compound (E4-a) using a halogen-metal exchange method. Compound (E18-a) may be obtained by lithiation with butyllithium followed by treatment with diethyl oxalate.

Step 2 is a step of introducing an alkyl group using a Grignard reagent.

Step 3 is a step of alkylating the hydroxyl group, wherein compound (E18-c) may be obtained by the method of Scheme B-6, Step 3.

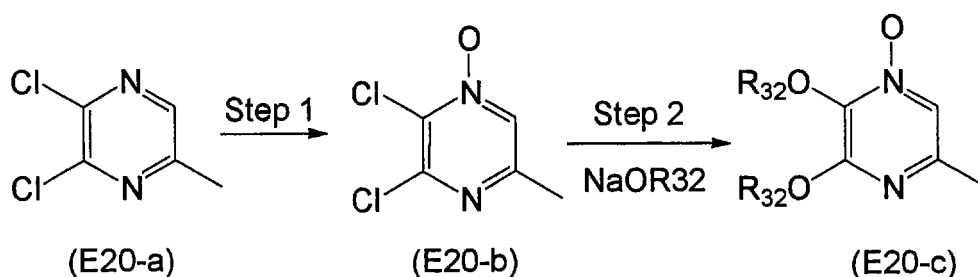
(Scheme E-19)



This scheme is a synthesis method for a pyrazine derivative (E19-b).

Step 1 is a step of azidating compound (E19-a) synthesized by the method described in I. Iovel et al., Oppi Briefs, 23, 188(1991), wherein compound (E19-b) may be obtained by the method of Scheme D, Step 4.

(Scheme E-20)

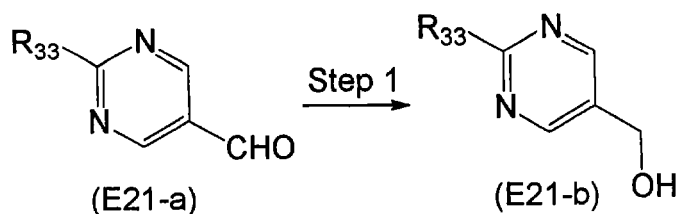


This scheme is a synthesis method for a dialkoxy-substituted pyrazine derivative (E20-c). In the formulas, R₃₂ represents optionally substituted alkyl.

Step 1 is a step of regioselective oxidation of the nitrogen atom of compound (E20-a) synthesized by the method described in J. Adachi et al., J. Org. Chem., 37, 221(1972). Compound (E20-b) may be obtained by oxidation with potassium peroxodisulfate in sulfuric acid.

Step 2 is a step of substitution of the halogeno groups with alkoxy groups. Compound (E20-c) may be obtained by reaction with a sodium alkoxide prepared with sodium hydride in the corresponding alcohol solvent.

(Scheme E-21)



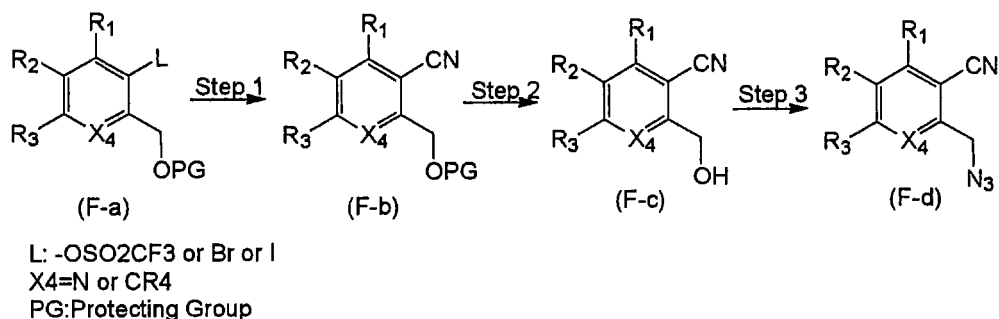
This scheme is a synthesis method for a pyrimidine derivative (E21-b). In the formulas, R₃₃ represents one of the substituents (alkyl, alkoxy,

alkylamino) mentioned in the following publications.

Step 1 is a step of synthesizing an alcohol by reduction of an aldehyde (E21-a) synthesized by the method described in J.T. Gupton, J. Heterocyclic Chem., 28, 1281(1991). Compound (E21-b) may be obtained by reaction with sodium borohydride in an alcohol solvent.

<Production Process F>

(Scheme F)



This scheme is a synthesis method for compound (F-d). In the formulas, R₁ represents hydrogen, halogeno or optionally substituted alkoxy. R₂ represents hydrogen, optionally substituted alkyl, alkoxycarbonyl, carbamoyl or optionally substituted alkylaminocarbonyl. R₃ represents hydrogen, halogeno, optionally substituted alkoxy or alkylamino. R₄ represents hydrogen, halogeno or optionally substituted alkoxy.

Step 1 is a step of introduction of a nitrile group. Compound (F-b) may be obtained according to the method of Scheme D, Step 2.

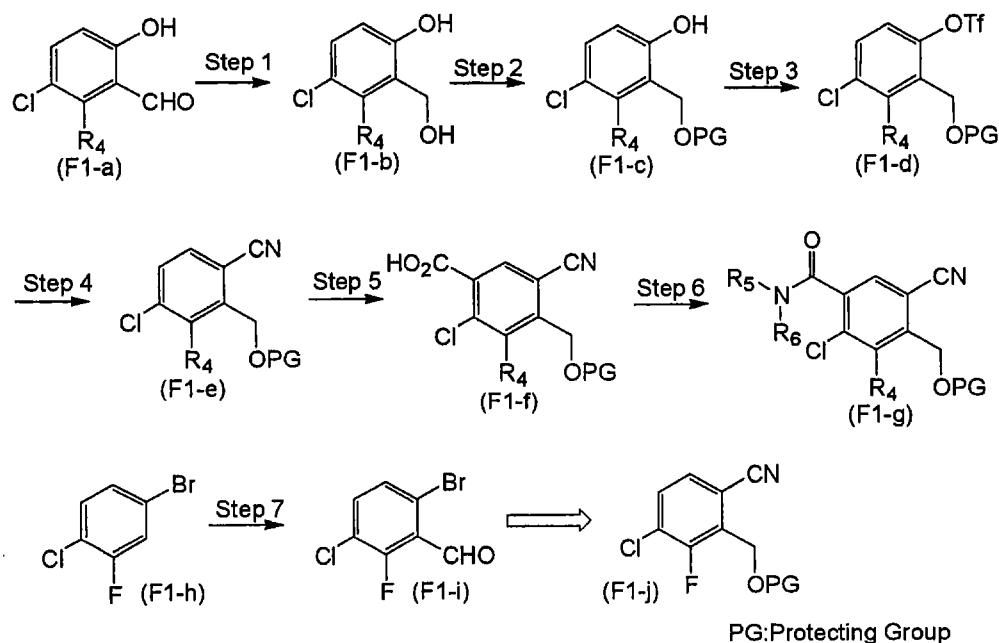
Step 2 is a step of removing the silyl group

serving as a protecting group, wherein compound (F-c) may be obtained according to the method of Scheme E, Step 1.

Step 3 is a step of azidation, wherein compound (F-d) may be obtained according to the method of Scheme E, Step 2.

Compounds represented by (F-a) to (F-c) in Scheme F may also be synthesized, for example, using the methods of Schemes F-1 to F-8 below.

(Scheme F-1)



This scheme is a synthesis method for (F1-e), (F1-g) and (F1-j) in which are compounds represented by (F-b) wherein R3 = Cl. In the formulas, R4 has the same definition as in Scheme F. R5 and R6 represent hydrogen or optionally substituted alkyl.

Step 1 is a step of synthesizing an alcohol by

reduction of the aldehyde (F1-a). Compound (F1-b) may be obtained by reaction with sodium borohydride in an alcohol or dichloromethane solvent.

5 Step 2 is a step of protecting the hydroxyl group with a silyl group, wherein compound (F1-c) may be obtained similarly to Scheme E-1, Step 5.

10 Step 3 is conversion of the phenolic hydroxyl group to a triflate. Compound (F1-d) may be obtained similarly to Scheme B-3, Step 2. Compound (F1-d) may also be converted to a carboxamide derivative.

Step 4 is a step of nitrilation based on the route shown in Scheme F.

15 Step 5 is a step of introducing a carboxyl group via ortho-lithiation. Compound (F1-f) may be obtained by lithiation using lithium diisopropylamide in a solvent such as tetrahydrofuran at -78°C , followed by reaction with carbon dioxide.

20 Step 6 is a step of amidation, wherein compound (F1-g) may be obtained similarly to Scheme B-10, Step 4.

A compound represented by compound (F1-e) wherein $\text{R}_4 = \text{F}$ may be synthesized from a commercially available compound (F1-h) in the following manner.

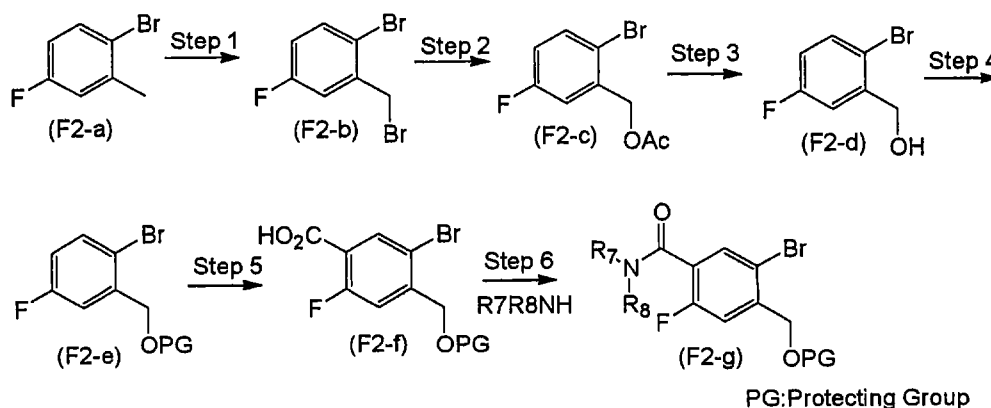
25 Step 7 is a step of introducing a formyl group, wherein compound (F1-i) may be obtained by lithiation using lithium diisopropylamide in a solvent such as

tetrahydrofuran at -78°C , followed by reaction with N-formylmorpholine.

Step 8 is a step of conversion in the same manner as Scheme F-1 (excluding Step 3) to obtain compound (F1-j).

A compound represented by (F-a) wherein $\text{R}_3 = \text{F}$ may be synthesized by a method similar to the one described above.

(Scheme F-2)



This scheme is a synthesis method for compounds (F2-e) and (F2-g) as compounds represented by (F-a). In the formulas, R_7 and R_8 represent hydrogen or optionally substituted alkyl, or R_7 and R_8 may optionally form a ring together with N.

Step 1 is a step of introducing a bromo group by radical reaction, wherein compound (F2-b) may be obtained similarly to Scheme D, Step 3.

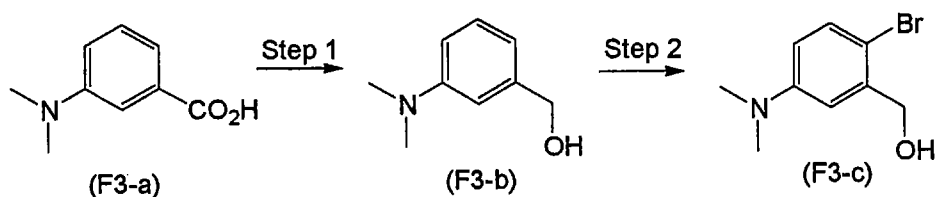
Steps 2 and 3 accomplish conversion of the bromo group to a hydroxyl group. The acetate (F2-c) may be synthesized by reaction with potassium acetate in a

solvent such as dimethylformamide. Compound (F2-d) may then be obtained by methanolysis using potassium carbonate in methanol.

Step 4 is a step of protecting the hydroxyl group with a silyl group. Compound (F2-e) may be obtained similarly to Scheme E-1, Step 5.

Steps 5 and 6 accomplish introduction and amidation of a carboxyl group, wherein compound (F2-g) may be obtained similarly to Scheme F-1, Steps 5 and 6 above.

(Scheme F-3)

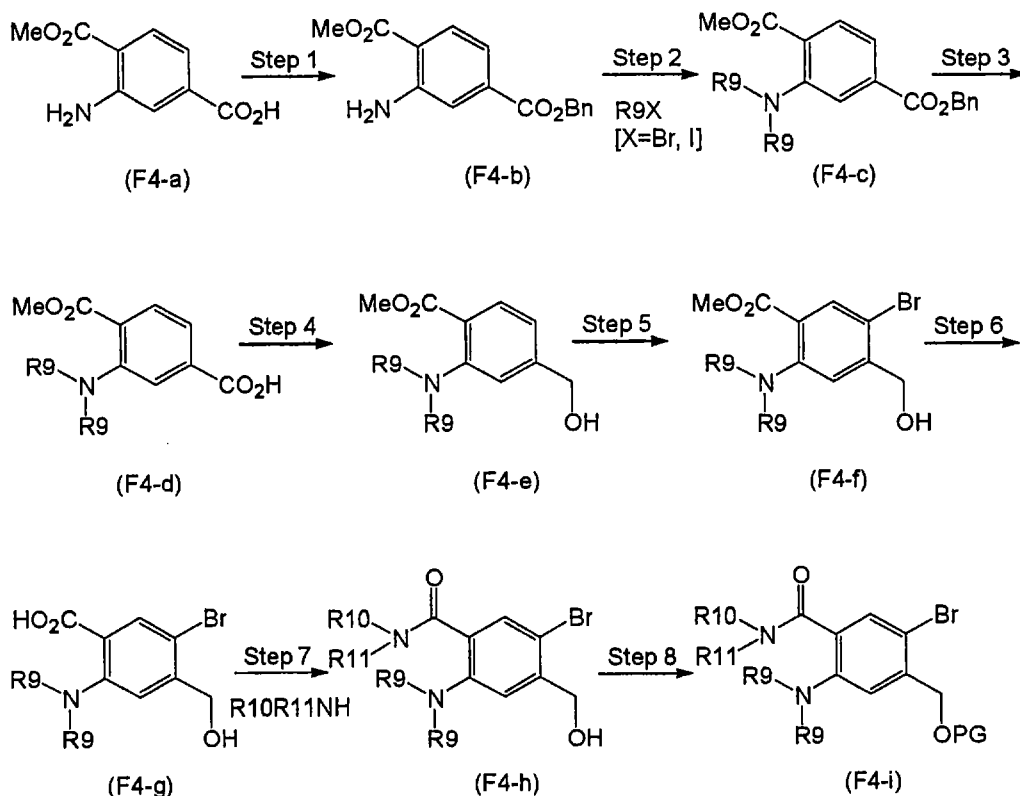


This scheme is a synthesis method for compound (F3-c).

Step 1 is a step of reducing the carboxyl group, wherein compound (F3-b) may be obtained similarly to Scheme E-17, Step 1.

Step 2 is a step of regioselective bromination. Compound (F3-c) may be obtained by reaction with benzyltrimethylammonium tribromide in a dichloromethane/alcohol mixed solvent at room temperature in the presence of potassium carbonate.

(Scheme F-4)



PG:Protecting Group

This scheme is a synthesis method for compound (F4-h). In the formulas, R9, R10 and R11 represent hydrogen or optionally substituted alkyl.

5 Step 1 is a step of benzylesterification of compound (F4-a). Compound (F4-b) may be obtained by reaction with benzyl bromide in dimethylformamide at room temperature, in the presence of potassium carbonate.

10 Step 2 is a step of dialkylation of the amino group. Compound (F4-c) may be obtained by a method of reaction with an alkyl halide in dimethylformamide in the presence of potassium carbonate, or when R9 is methyl, by a method of reaction with formalin while

heating to reflux in a formic acid solvent.

Step 3 is a step of debenzylation. Compound (F4-d) may be obtained by hydrogenation in tetrahydrofuran in the presence of palladium hydroxide-carbon.

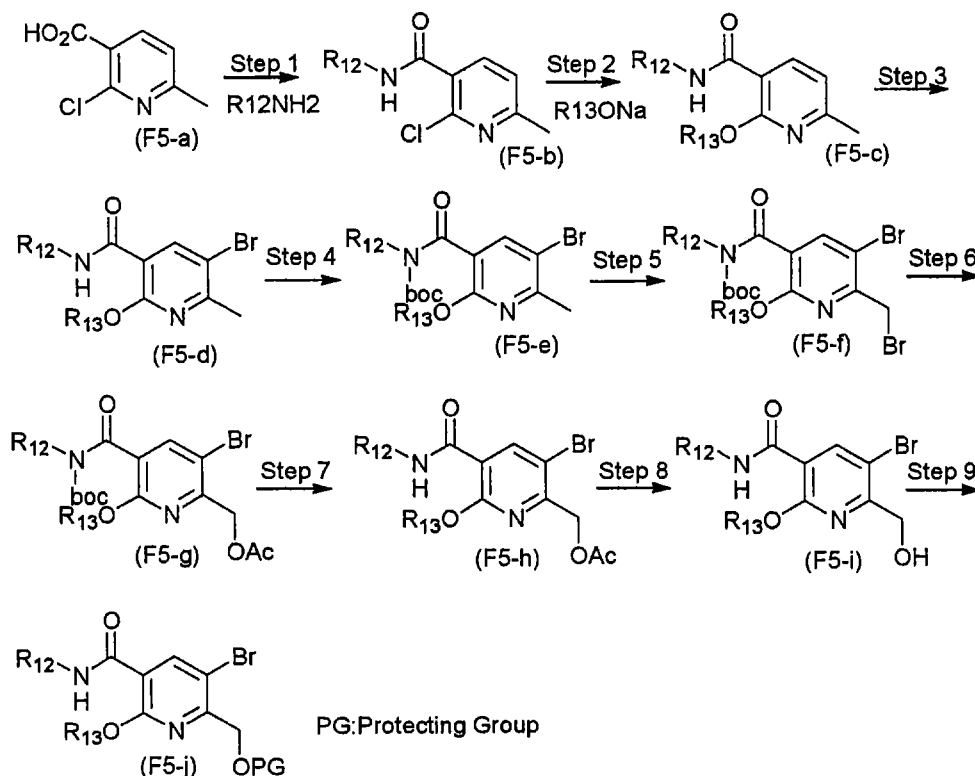
5 Steps 4 and 5 can yield compound (F4-f) by the same method as in Scheme F-3. However, Step 4 is conducted at a temperature of -40°C to -20°C .

Step 6 is a step of hydrolysis of the ester. Compound (F4-g) may be obtained by reaction with a 1 N
10 aqueous sodium hydroxide solution while heating to reflux in a tetrahydrofuran/alcohol mixed solvent.

Step 7 is a step of amidation wherein compound (F4-h) may be obtained similarly to Scheme B-10, Step 4, but a condensing agent such as dicyclohexyl
15 carbodiimide is preferably used.

Step 8 is a step of protecting the hydroxyl group with a silyl group, wherein compound (F4-i) may be obtained by the same method as in Scheme E-1, Step 5.

A pyridine derivative represented by (F-a)
20 wherein X4 is nitrogen may be synthesized by the method shown in the following Scheme F-5.
(Scheme F-5)



This scheme is a synthesis method for a pyridine derivative (F5-j). In the formulas, R12 represents optionally substituted alkyl, and R13 represents lower alkyl.

Step 1 is a step of amidation, wherein compound (F5-b) may be obtained similarly to Scheme B-10, Step 4.

Step 2 is a step of substitution of the halogeno group at the pyridine 2-position. Compound (F5-c) may be obtained by generating a sodium alkoxide from sodium hydride in the corresponding alcohol solvent.

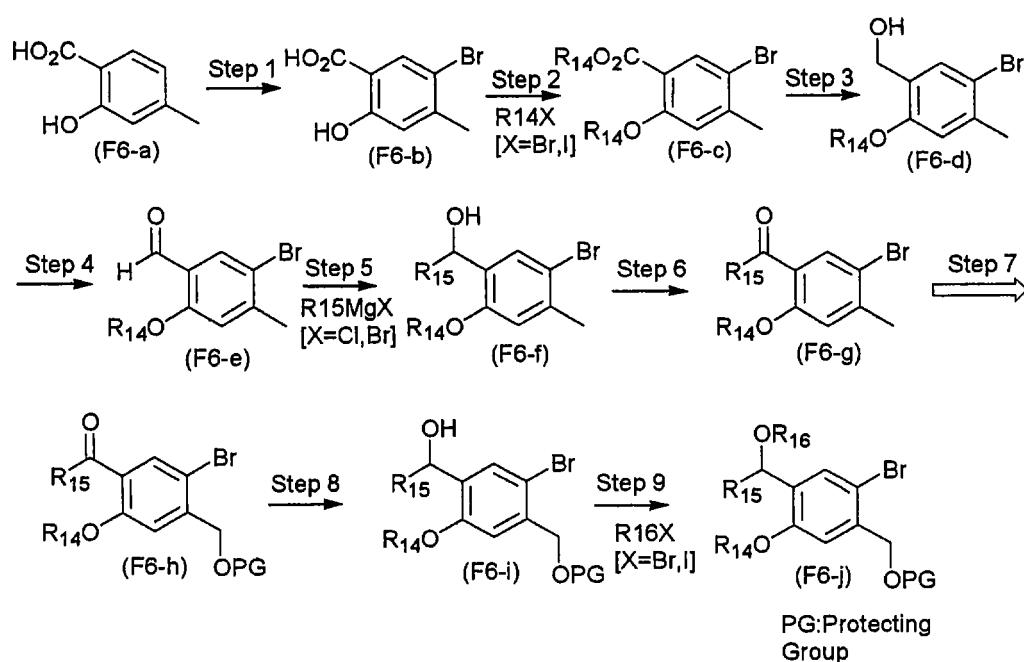
Step 3 is a step of bromination, wherein compound (F5-d) may be obtained similarly to Scheme B-1, Step 2.

Step 4 is a step of protecting the amide with a

tert-butyloxycarbonyl group, wherein compound (F5-e) may be obtained similarly to Scheme E-10.

Steps 5 to 9 may be carried out by conversion in the same manner as for synthesis of compounds (F2-a) to (F2-f) in Scheme F-2 above, but Step 7 is also included for removal of the *tert*-butyloxycarbonyl group serving as the amide-protecting group. The reaction is conducted at room temperature together with trifluoroacetic acid diluted with dichloromethane.

(Scheme F-6)



This scheme is a synthesis method for an alkoxyalkyl (F6-j) or alkylketone (F6-h) derivative. In the formulas, R14, R15 and R16 each represent optionally substituted alkyl.

Step 1 is a step of regioselective bromination, wherein compound (F6-b) may be synthesized by reaction

with bromine in an alcohol or acetonitrile solvent.

Step 2 is a single step of esterification and etherification. Compound (F6-c) may be obtained by reaction with an alkyl halide in a solvent such as dimethylformamide in the presence of potassium carbonate.

Step 3 is a step of synthesizing an alcohol by reduction of the ester, wherein compound (F6-d) may be obtained similarly to Scheme B-13, Step 1.

Step 4 is a step of synthesizing an aldehyde by oxidation, wherein compound (F6-e) may be obtained by Swern oxidation.

Step 5 is a step of introducing an alkyl group. Compound (F6-f) may be obtained by reaction with a Grignard reagent in a solvent such as tetrahydrofuran or diethyl ether.

Step 6 is a step of synthesizing a ketone by oxidation, wherein compound (F6-g) may be obtained by Swern oxidation.

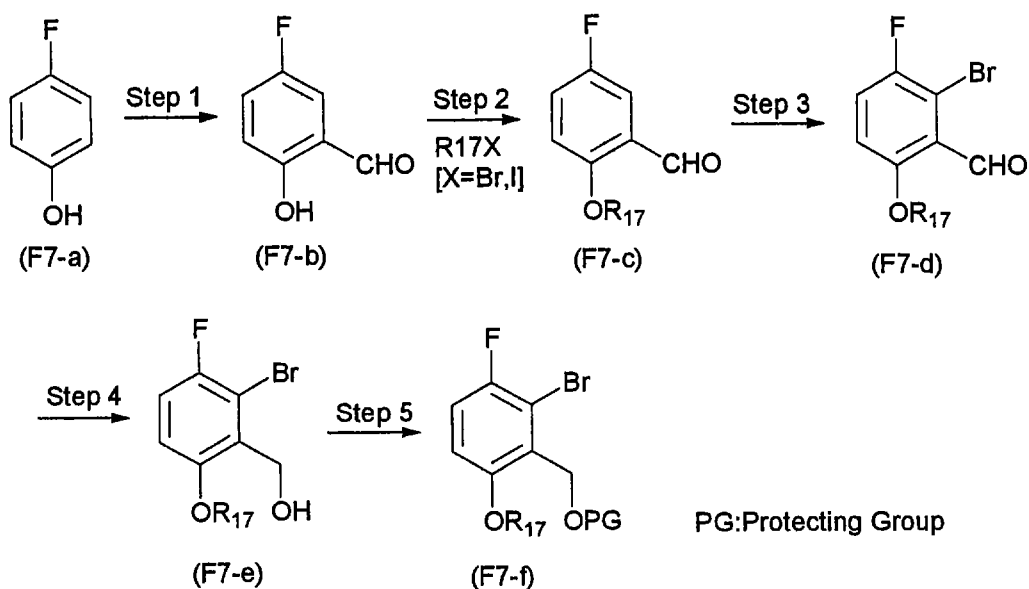
Step 7 is a step of obtaining compound (F6-h) by the same conversion method as Steps (F2-a) to (F2-e) in Scheme F-2 above. Compound (F6-h) may also be converted to (F6-j) having an alkoxyalkyl group.

Step 8 is a step of reduction, wherein compound (F6-i) may be obtained similarly to Scheme B-13, Step 1.

Step 9 is a step of alkylating the hydroxyl group, wherein compound (F6-j) may be obtained according to the method of Scheme B-6, Step 3.

Compounds (F7-f) and (F8-b) which are compounds represented by (F-a) wherein R4 or R1 is an alkoxy group may be synthesized by the methods shown in the following Schemes F-7 and F-8, respectively.

(Scheme F-7)



This scheme is a synthesis method for compound (F7-f). In the formulas, R17 represents optionally substituted alkyl.

Step 1 is a step of introducing a formyl group at the ortho position relative to the hydroxyl group. Compound (F7-b) may be obtained by reaction with tetramethylenetetramine in trifluoroacetic acid, followed by acid hydrolysis using aqueous sulfuric acid.

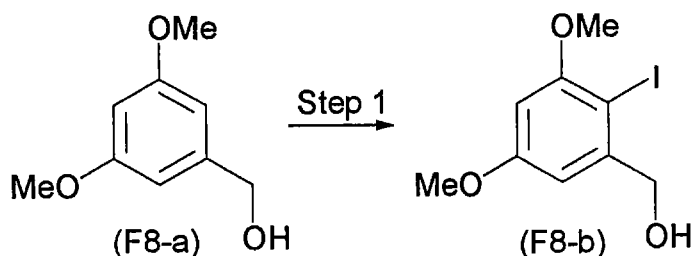
Step 2 is a step of alkylating the hydroxyl group, wherein compound (F7-c) may be obtained similarly to Scheme B-1, Step 1.

Step 3 is a step of bromination, wherein compound (F7-d) may be obtained by lithiation using butyllithium in the presence of N,N',N'-trimethylethylenediamine, followed by reaction with 1,2-dibromotetrafluoroethane.

Step 4 is a step of reducing the formyl group, and it may be accomplished using sodium borohydride in the same manner as above.

Step 5 is a step of protecting the hydroxyl group, wherein compound (E7-f) may be obtained by the same method as in Scheme E-1, Step 5.

(Scheme F-8)



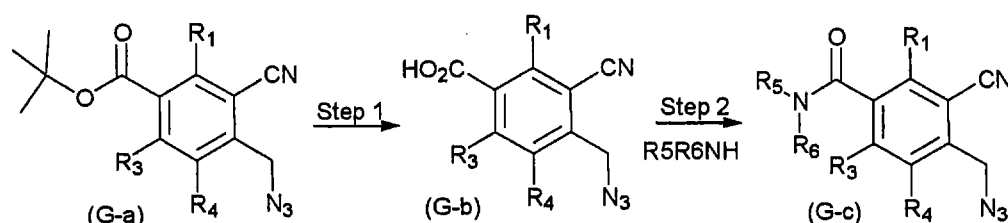
This scheme is a synthesis method for compound (F8-b). Step 1 is a step of regioselective iodination. Compound (F8-b) may be obtained by reaction with iodine in chloroform at room temperature in the presence of mercury trifluoroacetate. A compound represented by (F-d) may be synthesized from compound (F8-b) by conducting the reactions shown in Scheme F,

Step 1 and Step 3 without protection of the hydroxyl group.

Synthesis of carboxamide derivatives may be carried out by the methods shown in Production Process G and Production Process H below.

<Production Process G>

(Scheme G)



This scheme is synthesis method for a carboxamide (G-c). In the formulas, R₁ represents hydrogen or optionally substituted alkoxy, and R₃ represents optionally substituted alkoxy. R₄ represents hydrogen or halogeno, and R₅ and R₆ represent hydrogen or optionally substituted alkyl.

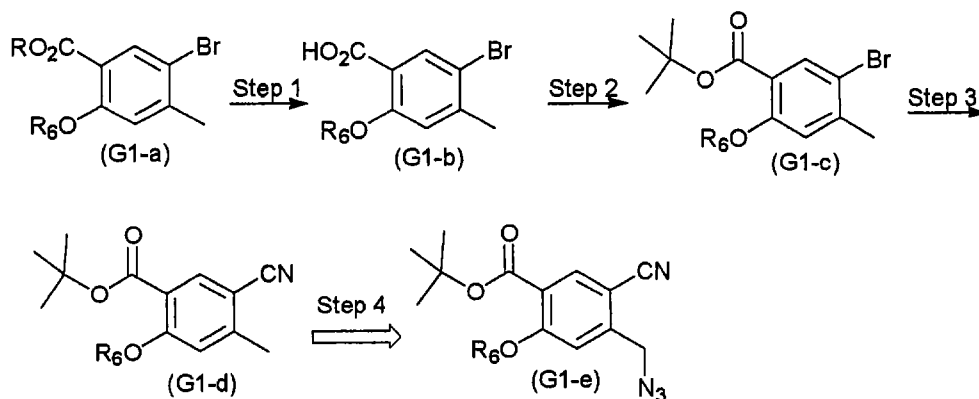
Step 1 is a step of removing the tert-butyl group. Compound (G-b) may be obtained by dissolution in trifluoroacetic acid diluted with an organic solvent such as dichloromethane and reaction at room temperature.

Step 2 is a step of amidation, wherein compound (G-c) may be obtained similarly to Scheme B-10, Step 4.

A compound represented by (G-a) may be synthesized by the method shown in Schemes G-1 to G-3.

The compound represented by (G-a) may itself be converted to a compound represented by (A1-c) by the method shown in Scheme C.

(Scheme G-1)



This is a synthesis method for compound (G1-e). In the formulas, R6 represents optionally substituted alkyl.

Step 1 is a step of hydrolysis of the ester of compound (G1-a) which may be synthesized by the method shown in Scheme F-6. Compound (G1-b) may be obtained by reaction with lithium hydroxide and aqueous sodium hydroxide in an alcohol solvent.

10

Step 2 is a step of *tert*-butylesterification. Di-*tert*-butyl dicarbonate is reacted therewith in *tert*-butyl alcohol, in the presence of dimethylaminopyridine. Alternatively, compound (G1-c) may be obtained by heating together with dimethylformamide *tert*-butylacetal in a solvent such as benzene or toluene.

15

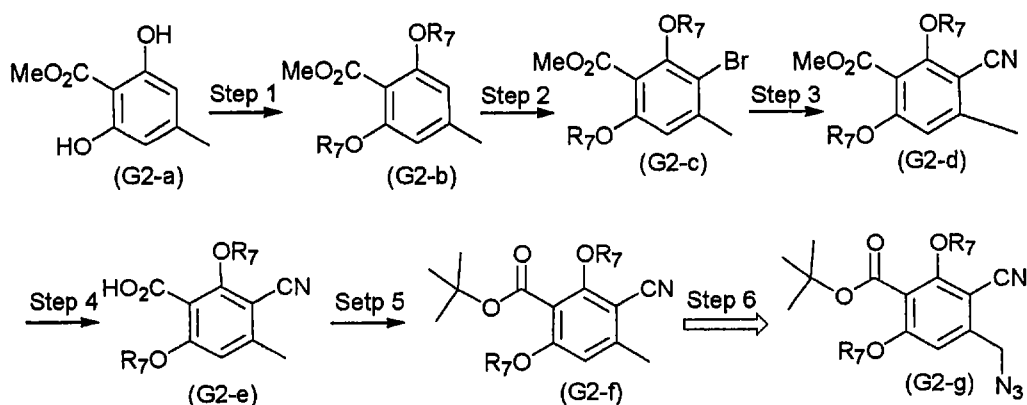
20

Step 3 is a step of nitrilation, wherein compound

(G1-d) may be obtained similarly to Scheme D, Step 2.

Step 4 may be carried out by conversion in the same manner as Steps 3 and 4 in Scheme D to yield compound (G1-e).

5 (Scheme G-2)



This scheme is a synthesis method for a dialkoxy derivative (G2-g). In the formulas, R₇ represents optionally substituted alkyl.

10 Step 1 is a step of alkylating the hydroxyl group, wherein compound (G2-b) may be obtained similarly to Scheme B-1, Step 1.

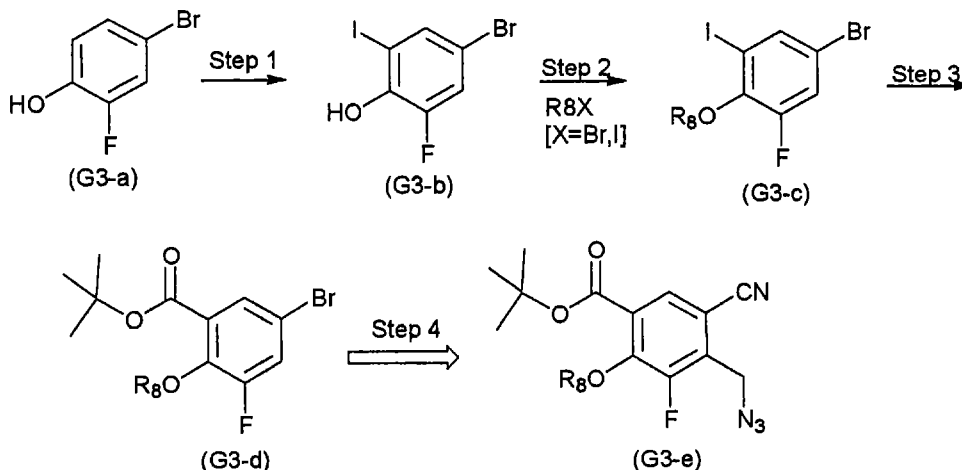
Steps 2 and 3 may be carried out by the same conversion method as in Steps 2 and 3 of Scheme D to
15 yield compound (G2-d).

Step 4 is a step of hydrolyzing the ester, wherein compound (G2-e) may be obtained by reaction with aqueous lithium hydroxide in an alcohol solvent.

20 Step 5 is a step of *tert*-butylesterification, wherein compound (G2-f) may be obtained similarly to Scheme G1, Step 2.

Step 6 may be carried out by conversion in the same manner as Steps 3 and 4 in Scheme D to yield compound (G2-g).

(Scheme G-3)



This scheme is a synthesis method for a fluorine-containing compound (G3-e). In the formulas, R₈ represents optionally substituted alkyl.

Step 1 is a step of regioselective iodination. Compound (G3-b) may be obtained by reaction with N-iodosuccinimide in dimethylformamide at room temperature.

Step 2 is a method of alkylating the hydroxyl group, wherein compound (G3-c) may be obtained similarly to Scheme B-1, Step 1.

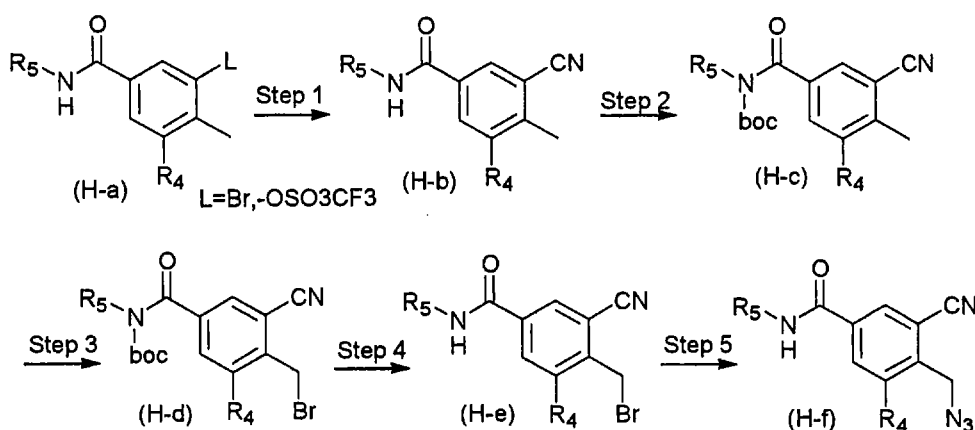
Step 3 is a step of introducing a tert-butoxycarbonyl group by iodine-metal exchange. Compound (G3-d) may be obtained by conversion to a magnesium reagent according to the method described in Knochel et al., Angew. Chem., Int. Ed. Engl., 37,

1701(1998), followed by reaction with di-tert-butyl dicarbonate.

The conversion shown in Step 4 may be carried out by the series of steps for conversion shown in Scheme F-1 to obtain (G3-e).

<Production Process H>

(Scheme H)



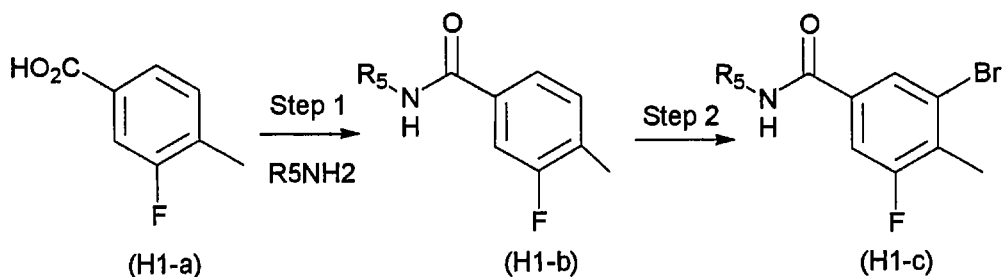
This scheme is a synthesis method for a carboxamide derivative (H-f). In the formulas, R₄ represents halogeno or optionally substituted alkoxy, and R₅ represents optionally substituted alkyl.

In this scheme, Steps 1, 3 and 5 may be carried out in the same manner as Steps 2, 3 and 4 shown in Scheme C-1, and compound (H-f) may be obtained by adding steps of protecting (Step 2) and deprotecting (Step 4) the amide. The protection and deprotection of the amide may be carried out by the method shown in Scheme F-5.

The compounds shown in Scheme H may be synthesized by the methods shown in the following

Schemes H-1 and H-2.

(Scheme H-1)

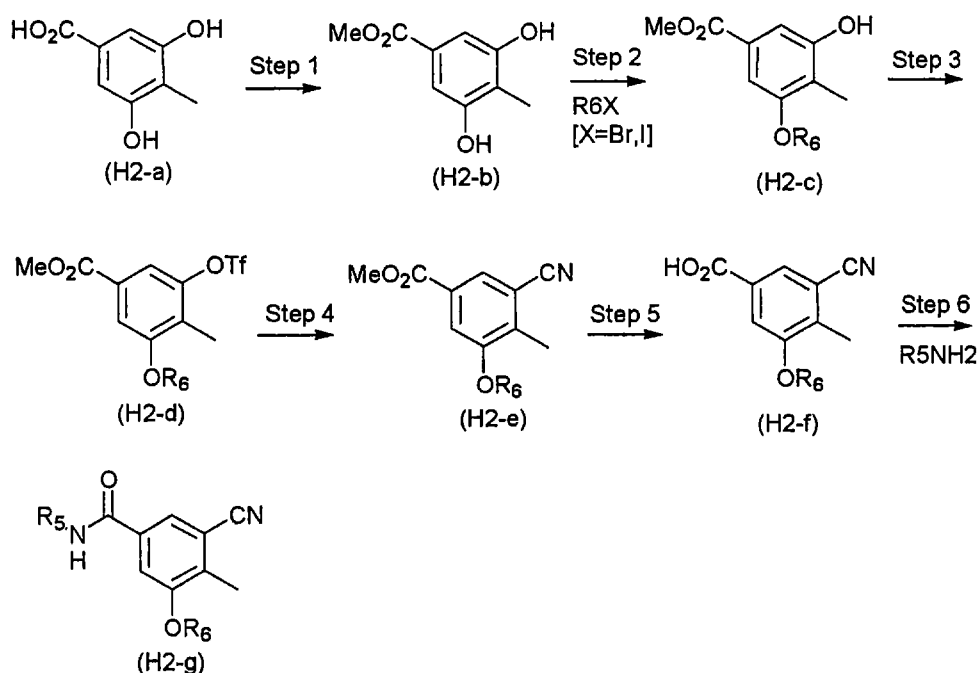


5 This scheme is a synthesis method for a fluorine-containing compound (H1-c). In the formulas, R₅ represents optionally substituted alkyl.

Step 1 is a step of amidation, wherein compound (H1-b) may be obtained by the same method as in Scheme B-10, Step 4.

10 Step 2 is a step of regioselective bromination, wherein compound (H1-c) may be obtained similarly to Scheme B-10, Step 1.

(Scheme H-2)



This scheme is a synthesis method for an alkoxy-containing compound (H2-g). In the formulas, R₆ represents optionally substituted alkyl.

5 Step 1 is a step of esterification. Compound (H2-b) may be obtained by heating to reflux in methanol in the presence of a catalytic amount of concentrated sulfuric acid.

10 Step 2 is a step of monoalkylation. Compound (H2-c) may be obtained by reaction with an alkyl halide in dimethylformamide in the presence of 5 N aqueous sodium hydroxide.

15 Steps 3 and 4 accomplish nitrilation via a triflate, wherein compound (H2-e) may be obtained by the method shown in Scheme F-1.

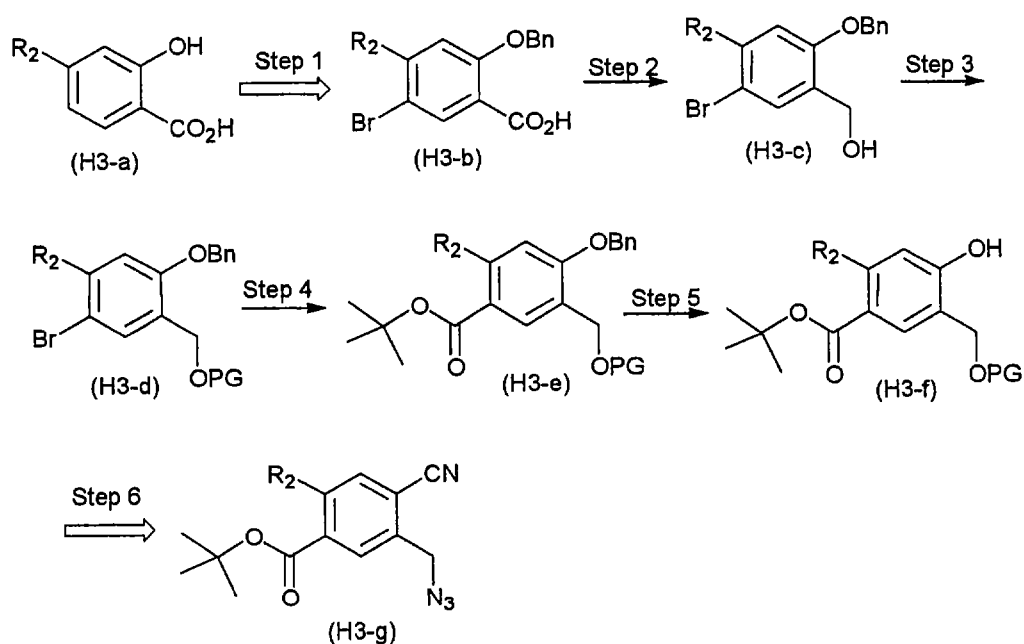
 Step 5 is a step of hydrolyzing the ester, wherein compound (H2-f) may be obtained by reaction

with aqueous sodium hydroxide in an alcohol solvent or a tetrahydrofuran/alcohol mixed solvent.

Step 6 is a step of amidation, wherein compound (H2-g) may be obtained similarly to Scheme B-10, Step 4.

<Production Process H-3>

(Scheme H-3)



This scheme is a synthesis method for a derivative of a compound represented by (C-a) wherein R_3 is carboxamide. In the formulas, R_2 represents hydrogen, optionally substituted alkyl or alkoxy.

Step 1 is a step of conversion from a readily available salicylic acid derivative (H3-a) to compound (H3-b), and it may be conducted by the same method used for synthesis of compound (G1-b) [R_6 = benzyl] in Scheme G-1.

Step 2 is a step of synthesizing an alcohol by reduction of the carboxyl group, wherein compound (H3-c) may be obtained similarly to Scheme E-4, Step 2.

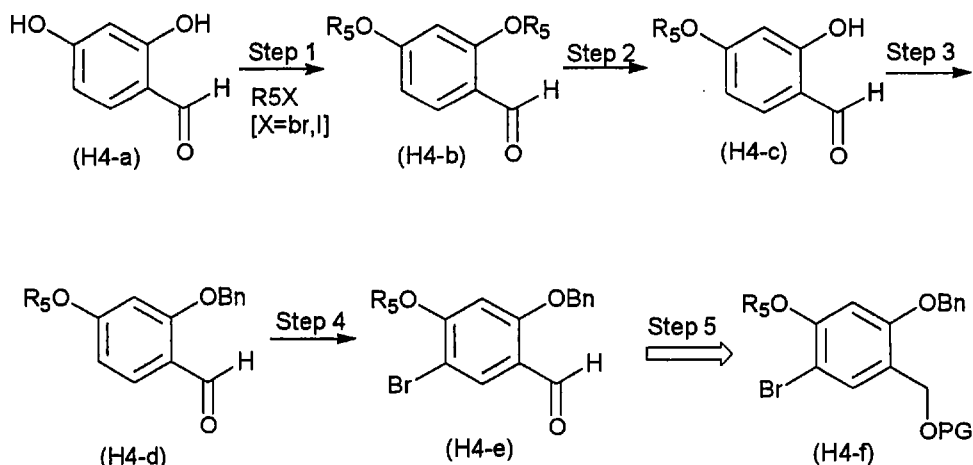
5 Step 3 is a step of protecting the hydroxyl group, wherein compound (E3-d) may be obtained similarly to Scheme E-1, Step 5.

Step 4 is a step of introducing a *tert*-butoxycarbonyl group by halogen-metal exchange. Compound (H3-e) may be obtained by lithiation with
10 butyllithium followed by reaction with di-*tert*-butyl dicarbonate.

Step 5 is a step of removing the benzyl-protecting group. Compound (H3-f) may be obtained by hydrogenation in the presence of palladium-carbon.

15 The conversion of Step 6 may be carried out by the same series of reactions as shown in Production Process F to yield compound (H3-g).

Conversion to an amide derivative of compound (H3-g) may be accomplished by the same method shown in
20 Production Process G. Here, the compound represented by (H3-g) as an intermediate may itself be converted to a compound represented by (A1-a) shown in Scheme C.
(Scheme H-4)



This scheme is a synthesis method for compound (H4-f) which is a compound represented by (H3-d) wherein R2 is alkoxy. In the formulas, R5 represents optionally substituted alkyl.

Step 1 is a step of alkylation of the two hydroxyl groups (R5 represents lower alkyl except benzyl), wherein compound (H4-b) may be obtained similarly to Scheme B-1, Step 1.

Step 2 is a step of regioselective dealkylation. Compound (H4-c) may be obtained by reaction with two equivalents of aluminum chloride in a solvent such as dichloromethane from freezing to room temperature.

Step 3 is a step of introducing benzyl as a protecting group for the hydroxyl group. Compound (H4-e) may be obtained by reaction with benzyl bromide in dimethylformamide in the presence of potassium carbonate.

Step 4 is a step of regioselective bromination, wherein compound (H4-e) may be synthesized by reaction

with bromine in an alcohol or acetonitrile solvent.

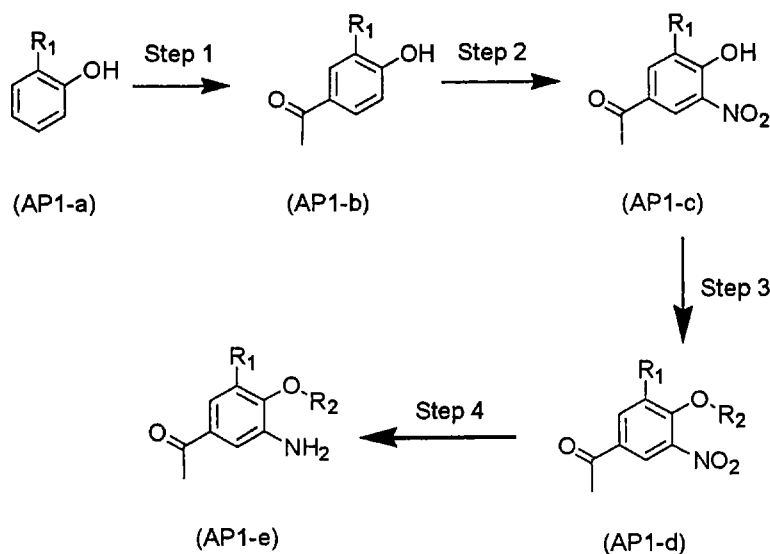
The conversion of Step 5 may be conducted in the same manner as Steps 1 and 2 of Scheme F-1 to obtain compound (H4-f).

5 General synthesis methods for the starting materials used in Scheme A-4 of Production Process A will now be described.

<Production Process AP>

10 This is a process for synthesis of intermediates (AP1-c), (AP1-d), (AP1-e), (AP2-b), (AP2-c) and (AP2-d) as common starting materials for synthesis of aminophenol derivatives.

(Scheme AP-1)



15 This scheme is a method for synthesis of compound (AP1-e) from compound (AP1-a). In the formulas, R1 represents hydrogen, optionally substituted alkyl, optionally substituted cycloalkyl or optionally substituted alkoxy. R2 has the same definition as R6

and R7 in Production Process M0.

Step 1 is a step of Friedel-Crafts acylation. Compound (AP1-b) may be obtained by reacting compound (AP1-a) with acetyl chloride in a solvent such as dichloromethane or toluene, in the presence of a Lewis acid such as aluminum chloride, zinc chloride or tin (II) chloride, at -70°C to room temperature.

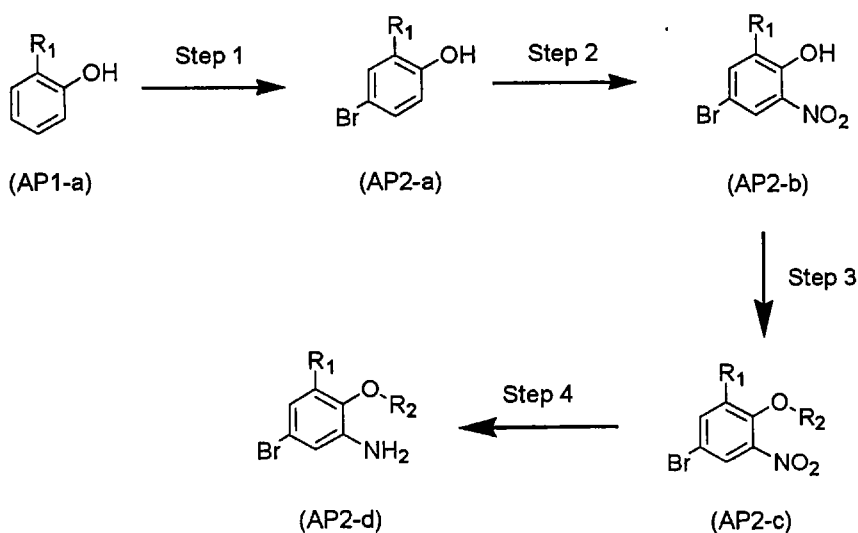
Step 2 is a step of nitration. Compound (AP1-c) may be obtained by reaction with fuming nitric acid or concentrated nitric acid in a solvent such as toluene, hexane, ether or acetic anhydride. Alternatively, the reaction may be conducted by generating nitric acid from sodium nitrate and hydrochloric acid.

Step 3 is a step of introducing a substituent R2 having any of various structures at the hydroxyl group of compound (AP1-c). Compound (AP1-d) may be obtained by reaction with a halide, mesylate or tosylate in a solvent such as dimethylformamide, acetonitrile, tetrahydrofuran, dichloromethane or acetone, in the presence of a base such as potassium carbonate, cesium carbonate, sodium hydrogencarbonate, trialkylamine, a pyridine derivative or sodium hydride. In the formulas, R2 has the same definition as R6 in Step 1 of Production Process M0.

Step 4 is a step of reducing the nitro group. Compound (AP1-e) may be obtained by reaction in a

solvent such as tetrahydrofuran, ethyl acetate, methanol or ethanol under a hydrogen atmosphere, in the presence of a catalyst such as palladium-carbon. Alternatively, compound (AP1-e) may be obtained by
 5 conducting the reaction in a solvent such as hydrous methanol or hydrous ethanol in the presence of ammonium chloride, with addition of iron at the reflux temperature of the solvent.

(Scheme AP-2)



This scheme is a method for synthesis of (AP2-d) from (AP1-a). In the formulas, R1 represents hydrogen, optionally substituted alkyl, optionally substituted cycloalkyl or optionally substituted alkoxy.

15 Step 1 is a step of brominating the para-position relative to the phenolic hydroxyl group. Reaction with bromine is conducted in a solvent such as methanol, ethanol or chloroform. Alternatively, compound (AP2-a) may be obtained by reaction with N-

bromosuccinimide in a solvent such as acetonitrile or dimethylformamide.

Step 2 is a step of nitration. Compound (AP2-b) may be obtained by reaction with fuming nitric acid or concentrated nitric acid in a solvent such as toluene, hexane, ether or acetic anhydride. Alternatively, the reaction may be conducted by generating nitric acid from sodium nitrate and hydrochloric acid.

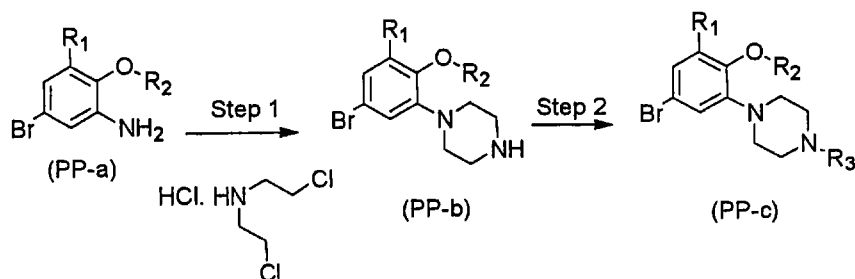
Step 3 is a step of introducing a substituent R₂ with any of various structures at the hydroxyl group of compound (AP2-b). Compound (AP2-c) may be obtained by reaction with a halide, mesylate or tosylate in a solvent such as dimethylformamide, acetonitrile, tetrahydrofuran, dichloromethane or acetone, in the presence of a base such as potassium carbonate, cesium carbonate, sodium hydrogencarbonate, trialkylamine, a pyridine derivative or sodium hydride. In the formulas, R₂ has the same definition as R₆ in Step 1 of Production Process M0.

Step 4 is a step of reducing the nitro group. Compound (AP2-d) may also be obtained by conducting the reaction in a solvent such as hydrous methanol or hydrous ethanol in the presence of ammonium chloride, with addition of iron at the reflux temperature of the solvent.

The following Production Processes PP to BOL are

general production processes for aminophenol derivatives using compounds synthesized by Production Process AP as the starting materials.

<Production Process PP>



Production Process PP is a general synthesis method for a piperazine derivative.

Step 1 is a step of treating the amino group of compound (PP-a) with bischloroethylamine hydrochloride to form a piperazine ring. Preferably, compound (PP-a) is reacted with bischloroethylamine hydrochloride in 1,2-dichlorobenzene while heating to reflux, and the reaction is conducted while removing the generated hydrogen chloride gas to yield compound (PP-b).

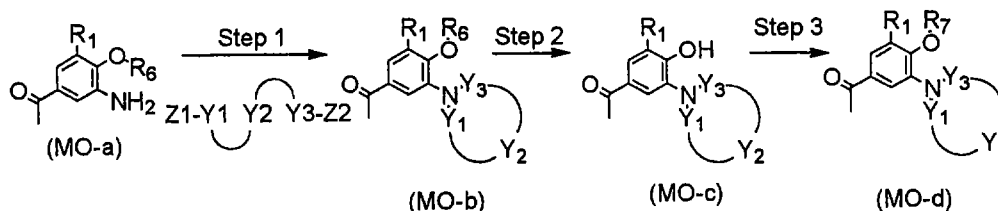
In the formulas, R1 represents hydrogen, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted alkoxy or optionally substituted alkylamino. R2 represents hydrogen or optionally substituted alkyl.

The formulas in Production Process PP show only a piperazine group, but any 5- to 8-membered ring containing more than one nitrogen atom may be formed, without any restriction to piperazine.

Step 2 is a step of introducing substituent R3 at the secondary amine position of the piperazine of compound (PP-b). Compound (PP-b) may be reacted with reagent R3-X1 (X1 = halogen) in an appropriate solvent such as dichloromethane or tetrahydrofuran, in the presence of an inorganic base such as potassium carbonate or sodium hydrogencarbonate or in the presence of an organic base such as trialkylamine or a pyridine derivative to yield compound (PP-c) having R3 introduced therein. R3 of reagent R3-X1 represents optionally substituted alkyl, optionally substituted alkyl having cyano on the end or a branch, alkyl having protected or substituted carboxylic acid on the end or a branch, alkyl having protected or substituted hydroxyl on the end or a branch, alkyl having protected or substituted amino on the end or a branch, optionally substituted sulfonyl, optionally substituted acyl, or optionally substituted carbamoyl. The reagent used to introduce substituent R3 into compound (PP-b) may be, instead of R3-X1 mentioned above, di-t-butyl dicarbonate or optionally substituted isocyanate. Compound (PP-b) may be subjected to reductive amination using an optionally substituted aldehyde or ketone and sodium triacetoxymethylborohydride or sodium cyanoborohydride for introduction of substituent R3.

Compound (PP-c) obtained by this Production Process is converted to the final target compound by Production Process A.

<Production Process MO>



Production Process MO is a general production process for a heterocyclic amino derivative.

Step 1 is a step of treating the amino group of compound (MO-a) with a reagent represented by Z1-Y1-Y2-Y3-Z2 to form a nitrogen-containing ring.

Compound (MO-b) may be obtained by reacting compound (MO-a) with reagent Z1-Y1-Y2-Y3-Z2 in an appropriate solvent such as dimethylformamide, tetrahydrofuran or dichloromethane, in the presence of an inorganic base such as potassium carbonate, sodium hydrogencarbonate or cesium carbonate or in the presence of an organic base such as trialkylamine or a pyridine derivative.

Z1 and Z2 in the reagent Z1-Y1-Y2-Y3-Z2 represent leaving groups such as halogen or sulfonate. Y1 and Y3 represent methylene optionally substituted with alkyl, alkoxy or the like, carbonyl, carboxyl, sulfonyl or amide. Elements to form the main chain at the portion represented by -Y2- include carbon, oxygen,

nitrogen and sulfur. There are no particular restrictions on the length of the chain. Where possible, the element forming the -Y2- main chain may also have as a substituent an optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkoxyalkyl, optionally substituted hydroxyalkyl, hydroxy, carbonyl, optionally protected or substituted carboxyl, optionally protected or substituted carboxyalkyl, optionally protected or substituted amine or optionally protected or substituted aminoalkyl. An oxo group may also be present on the -Y2- main chain and form a carbonyl, sulfonyl or sulfinyl group together with carbon or sulfur on the main chain.

In the formulas, R1 has the same definition as R1 in Step 1 of Production Process PP. R6 represents an optionally substituted alkyl, a protecting group for hydroxyl, such as methoxymethyl, tetrahydropyranyl or trialkylsilyl, or alternatively alkyl having cyano at the end or a branch, alkyl having protected or substituted carboxylic acid on the end or a branch, arylalkyl having protected or substituted carboxylic acid on the end or a branch, alkyl having a protected or substituted hydroxyl group on the end or a branch, arylalkyl having protected or substituted hydroxyl on the end or a branch, alkyl having protected or

substituted amino on the end or a branch, arylalkyl having protected or substituted amino on the end or a branch, optionally substituted sulfonyl, optionally substituted acyl or optionally substituted carbamoyl.

5 Step 2 is a step of deprotection when R6 of compound (MO-b) is a protecting group for the phenolic hydroxyl group. For example, compound (MO-c) wherein R6 is methoxymethyl may be obtained by treating compound (MO-b) with an acidic mixed solvent such as 5
10 N hydrochloric acid/acetone or 10% aqueous perchloric acid/tetrahydrofuran.

Step 3 is a step of introducing a new substituent R7 at the phenolic hydroxyl group of compound (MO-c).

15 R7 has the same definition as R6 in Step 1 of Production Process MO.

Compound (MO-d) wherein X2 of reagent R7-X2 described below is a leaving group such as halogen or sulfonate may be synthesized in the following manner. The compound (MO-d) may be obtained by reacting
20 compound (MO-c) with reagent R7-X2 in an appropriate solvent such as dimethylformamide, acetonitrile, diethyl ether, tetrahydrofuran or dichloromethane, in the presence of an inorganic base such as potassium carbonate, sodium hydrogencarbonate or cesium
25 carbonate or in the presence of an organic base such as trialkylamine or a pyridine derivative, or in the

presence of sodium hydride.

Compound (MO-d) wherein R7 is methyl may be obtained at a high yield by reacting compound (MO-c) with diazomethane in diethyl ether or with
5 trimethylsilyldiazomethane in acetonitrile-diisopropylethylamine-methanol.

Compound (MO-d) wherein X2 in reagent R7-X2 is hydroxyl may be obtained by reacting compound (MO-c) with reagent R7-X2 by the publicly known Mitsunobu
10 reaction in an appropriate solvent such as tetrahydrofuran or toluene.

In Production Process MO, R6 and R7 may sometimes undergo conversion to a structure which is not defined herein by a method easily predictable by a person
15 skilled in the art at an appropriate stage after introduction. Likewise, the -N-Y1-Y2-Y3(-N) portion obtained by cyclization in Step 1 may also undergo conversion to a structure which is not defined herein. (Conversion of the -N-Y1-Y2-Y3(-N) portion is
20 described in some of the following Production Process examples).

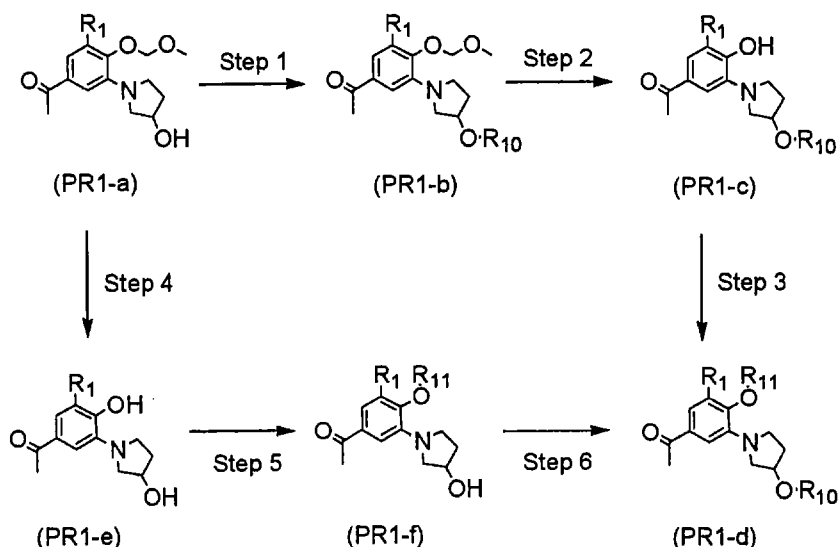
Compounds (MO-b), (MO-c) and (MO-d) obtained in this Production Process are converted to the final target compounds by Production Process A.

25 <Production Process PR>

Production Process PR is a general synthesis

method for pyrrolidine derivatives.

(Scheme PR-1)



Scheme PR-1 is one production process whereby the
 5 -N-Y1-Y2-Y3(-N) portion obtained by cyclization in
 Step 1 of Production Process MO may undergo additional
 structural conversion. In the formulas, R1 has the
 same definition as R1 in Step 1 of Production Process
 PP. R10 and R11 have the same definitions as R6 and
 10 R7 in Production Process MO. Although only
 methoxymethyl is mentioned as a protecting group for
 the phenolic hydroxyl groups of compounds (PR1-a) and
 (PR1-b), there is no limitation to methoxymethyl.

Step 1 is a step of introducing a substituent R10
 15 at the hydroxyl group of compound (PR1-a). The
 reaction is conducted using reagent R10-X3 in an
 appropriate alkaline hydrous organic solvent, in the
 presence of a phase transfer catalyst. Preferably,
 compound (PR1-b) is obtained by reaction of reagent

R10-X3 with compound (PR1-a) in a mixture of 50% aqueous sodium hydroxide and toluene in the presence of tetrabutylammonium bromide. Here, X3 is a leaving group such as a halogen or sulfonate.

5 Step 2 is a step of treating compound (PR1-b) in the same manner as Step 2 of Production Process MO to yield compound (PR1-c).

 Step 3 is a step of introducing a new substituent R11 at the phenolic hydroxyl group of compound (PR1-c).
10 Compound (PR1-c) may be treated in the same manner as for introduction of R7 in Step 3 of Production Process MO to yield compound (PR1-d) having R11 introduced therein.

 Step 4 is a step of treating compound (PR1-a) in
15 the same manner as Step 2 of Production Process MO to yield compound (PR1-e).

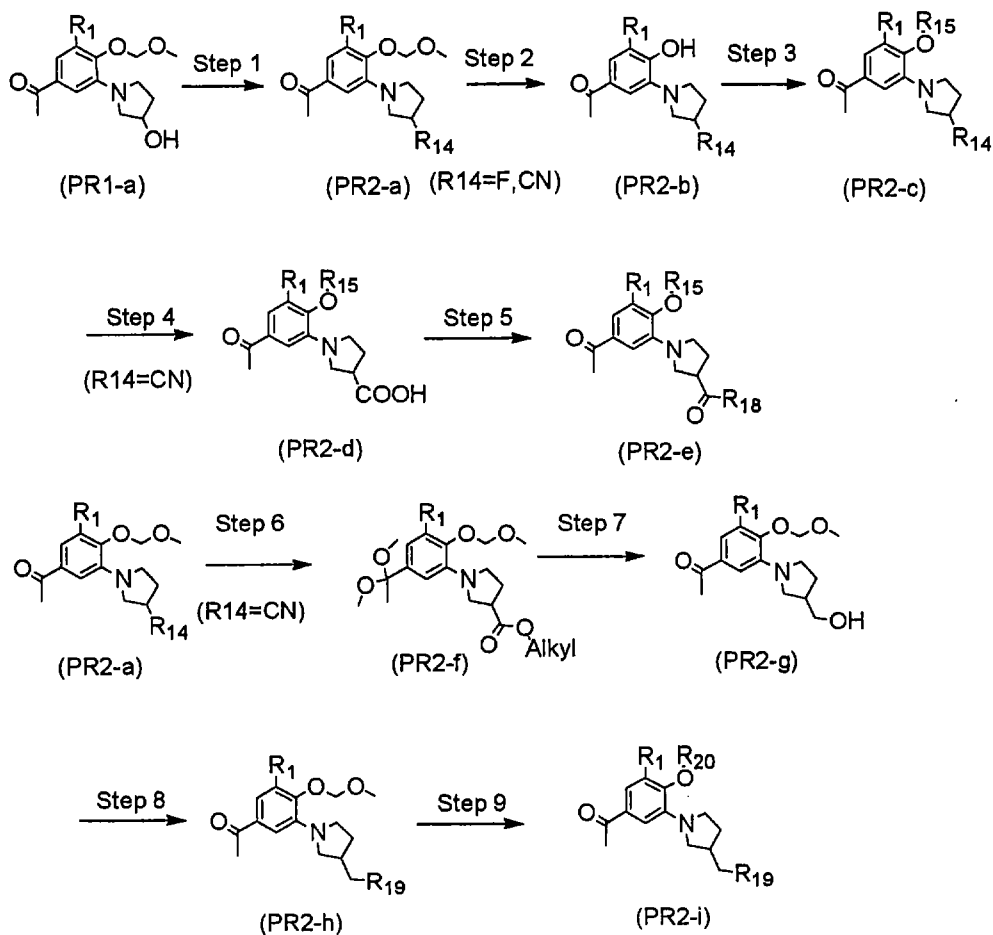
 Step 5 is a step of selectively introducing substituent R11 only at the phenolic hydroxyl group of compound (PR1-e). Utilizing the difference in
20 reactivity between the two hydroxyl groups of compound (PR1-e), treatment may be carried out in the same manner as for introduction of R7 in Step 3 of Production Process MO to yield compound (PR1-f) having R11 introduced therein.

25 Step 6 is a step of treating compound (PR1-f) in the same manner as Step 1 of this Scheme PR-1 to yield

compound (PR1-d).

Compounds (PR1-b) and (PR1-d) obtained in this Scheme PR-1 are converted to the final target compounds by Production Process A.

5 (Scheme PR-2)



Scheme PR-2 is one production process whereby the -N-Y1-Y2-Y3(-N) portion obtained by cyclization in Step 1 of Production Process MO may undergo additional structural conversion. In the formulas, R₁ has the same definition as R₁ in Step 1 of Production Process PP. R₁₅ and R₂₀ have the same definitions as R₆ and R₇ in Production Process MO.

Step 1 is a step of replacing the hydroxyl group of compound (PR1-a) with a substituent R14 (F or CN). When R14 is fluoro, compound (PR1-a) may be treated with diethylaminosulfur trifluoride (DAST) in
5 dichloromethane to yield compound (PR2-a: R14 = F). When R14 is cyano, the hydroxyl group of compound (PR1-a) may first be converted to a leaving group with an acyl chloride reagent such as methanesulfonyl chloride in an appropriate solvent such as
10 dichloromethane, in the presence of a base such as triethylamine. A hydrogen cyanide salt may then be reacted with this intermediate to introduce a cyano group. Preferably, the intermediate is added to dimethylformamide and reacted with sodium cyanide in
15 the presence of tetrabutylammonium iodide to yield compound (PR2-a: R14 = CN).

Step 2 is a step of treating compound (PR2-a) (R14 = F or CN) in the same manner as Step 2 of Production Process M0 to yield compound (PR2-b) (R14 = F or CN).

20 Step 3 is a step of introducing substituent R15 at the phenolic hydroxyl group of compound (PR2-b) (R14 = F or CN). Compound (PR2-b) may be treated in the same manner as for introduction of R7 in Step 3 of Production Process M0 to yield compound (PR2-c) (R14 =
25 F or CN) having R15 introduced therein.

Step 4 is a step of converting compound (PR2-c)

wherein R14 = CN to compound (PR2-d) wherein the cyano group is converted to a carboxyl group by alkali hydrolysis. Preferably, compound (PR2-c) wherein R14 = CN may be reacted by heating to reflux in a mixed solvent of aqueous sodium hydroxide and ethanol to yield compound (PR2-d).

Step 5 is a step of esterifying or amidating the carboxylic acid group of compound (PR2-d) for introduction of a substituent R18 by common methods.

The carboxylic acid group of compound (PR2-d) may be converted to an active species by a common method such as an acid mixing method using a chloroformic acid ester or an acid chloride method using oxalyl chloride, and then reacted with an alcohol or amine for conversion to (PR2-e). Alternatively, (PR2-d) may be esterified by reaction with the corresponding alkyl halide reagent in the presence of an appropriate base or by reaction with di-*tert*-butyl dicarbonate in *tert*-butyl alcohol in the presence of dimethylaminopyridine. Compound (PR2-d) may also be subjected to dehydration reaction using an alcohol or amine and a peptide-forming condensing agent, for conversion to compound (PR2-e). The synthesis may also be carried out by other suitable known reactions. R18 represents amino or alkoxy.

Step 6 is a step of subjecting compound (PR2-a:

R14 = CN) to alkali hydrolysis in the same manner as Step 4 followed by treatment in the same manner as the esterification in Step 5, and then ketal protection of the carbonyl group of the acetophenone. After

5 converting compound (PR2-a: R14 = CN) to a carboxylic acid ester, it may be reacted with a ketalizing reagent such as methyl orthoformate under acidic conditions to yield compound (PR2-f). Preferably, the methyl orthoformate is reacted with the carbonyl group
10 in methanol in the presence of an acid catalyst such as camphorsulfonic acid or p-toluenesulfonic acid and Molecular Sieve 3A, to yield compound (PR2-f).

Step 7 is a step of reducing the ester group of compound (PR2-f) for conversion to a hydroxymethyl
15 group, and then selectively deprotecting only the ketal protection of the acetophenone carbonyl group. First, compound (PR2-f) is reacted with an ester-reducing reagent such as lithium aluminum hydride in an appropriate solvent such as tetrahydrofuran or
20 diethyl ether, for conversion to a hydroxymethyl group. Next, under mildly acidic conditions, preferably under conditions with an acetic acid-tetrahydrofuran-water (4:1:1) mixed acid solvent, the ketal protecting group for the carbonyl group is selectively deprotected
25 while leaving the methoxymethyl group for the phenolic hydroxyl, to yield compound (PR2-g).

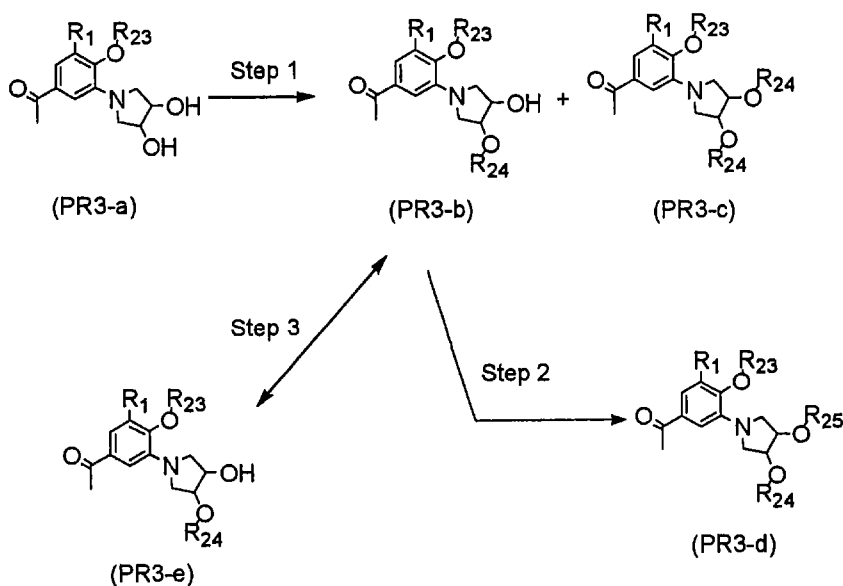
Step 8 is a step of converting the hydroxyl group of compound (PR2-g) to substituent R19 (cyano or various alkoxy).

5 When R19 is cyano, treatment is carried out in the same manner as for conversion in Step 1 when R14 is cyano, to yield compound (PR2-h) wherein the hydroxymethyl group of compound (PR2-g) is converted to cyanomethyl, in which case R19 represents cyano. When R19 is an alkoxy group, compound (PR2-g) is
10 treated in the same manner as Step 1 of Scheme PR-1 to yield compound (PR2-h) for conversion to the alkoxy group, in which case R19 has the same definition as OR10 in Scheme PR-1.

15 Step 9 is a step of deprotecting the methoxymethyl group serving as the protecting group for the phenolic hydroxyl of compound (PR2-h), and then introducing a substituent R20. First, compound (PR2-h) is treated in the same manner as Step 2 of Production Process M0 to remove the methoxymethyl
20 group. It is then treated in the same manner as for introduction of R7 in Step 3 of Production Process M0 to yield compound (PR2-i) having R20 introduced therein.

25 Compounds (PR2-c), (PR2-e) and (PR2-i) obtained in this Scheme PR-2 are converted to the final target compounds by Production Process A.

(Scheme PR-3)



Scheme PR-3 is one production process whereby the -N-Y1-Y2-Y3(-N) portion obtained by cyclization in Step 1 of Production Process M0 may undergo additional structural conversion. In the formulas, R_1 has the same definition as R_1 in Step 1 of Production Process PP. R_{23} , R_{24} and R_{25} have the same definitions as R_6 and R_7 in Production Process M0.

Step 1 is a step of treating compound (PR3-a) in the same manner as Step 1 of Scheme PR-1 to yield compound (PR3-b) having one substituent R_{24} introduced therein and compound (PR3-c) having two substituents R_{24} introduced therein. Alternatively, when R_{24} is a methoxymethyl group or the like, an excess of methoxymethyl chloride may be reacted with compound (PR3-a) in the presence of diisopropylethylamine to yield compounds (PR3-b) and (PR3-c). Compounds (PR3-

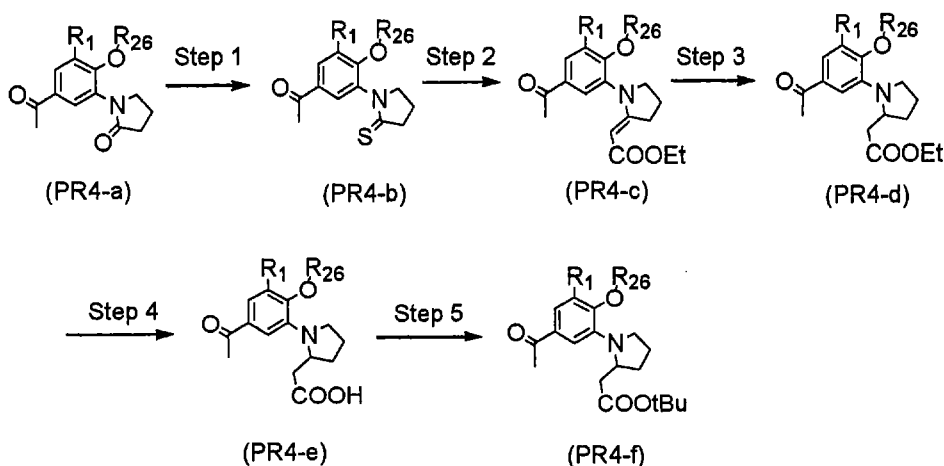
b) and (PR3-c) may be separated by silica gel column chromatography.

Step 2 is a step of treating compound (PR3-b) in the same manner as Step 1 to yield compound (PR3-d) having a newly introduced substituent R25.

Step 3 is a step of stereoinversion of the hydroxyl group of compound (PR3-b) to yield compound (PR3-e). Compound (PR3-b) is reacted with m-nitrobenzenesulfonyl chloride in dichloromethane in the presence of triethylamine and dimethylaminopyridine. It is then treated with cesium acetate while heating in dimethylsulfoxide to yield a hydroxyl-inverted acetate. This is treated with potassium carbonate in methanol to yield the hydroxyl-inverted compound (PR3-e).

Compounds (PR3-b), (PR3-c) and (PR3-d) obtained in Scheme PR-3 are converted to the final target compounds by Production Process A. Compound (PR3-e) may also be treated in the same manner as Step 2 of this Scheme and then converted to the final target compound by Production Process A.

(Scheme PR-4)



Scheme PR-4 is one production process whereby the -N-Y1-Y2-Y3(-N) portion obtained by cyclization in Step 1 of Production Process MO may undergo additional structural conversion. In the formulas, R1 has the same definition as R1 in Step 1 of Production Process PP. R26 has the same definition as R6 and R7 in Production Process MO.

Step 1 is a step of treating compound (PR4-a) with Lawesson's reagent while heating in a 1,4-dioxane solvent to yield a thioamide (PR4-b).

Step 2 is a step of treating compound (PR4-b) with ethyl O-trifluoromethanesulfonylhydroxyacetate, triphenylphosphine and triethylamine to yield compound (PR4-c).

Step 3 is a step of reacting compound (PR4-c) with sodium triacetoxyborohydride in 1,2-dichloroethane in the presence of acetic acid for reduction of the enamine to yield compound (PR4-d).

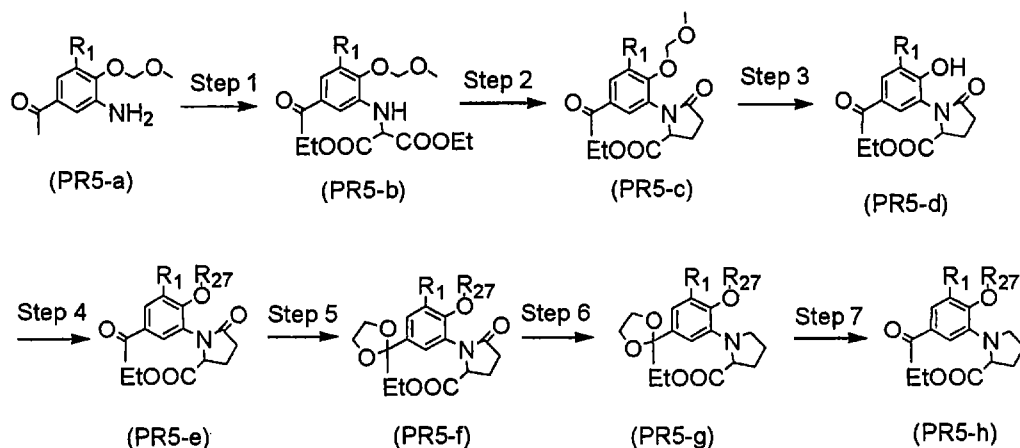
Step 4 is a step of converting compound (PR4-d)

to a carboxylic acid derivative (PR4-e) under appropriate conditions such that substituent R26 is not affected. Generally, it is treated with aqueous sodium hydroxide or aqueous lithium hydroxide in an alcohol or an alcohol-tetrahydrofuran mixed solvent for alkali hydrolysis to yield compound (PR4-e).

Step 5 is a step of treating compound (PR4-e) with di-*tert*-butyl dicarbonate in *tert*-butanol in the presence of dimethylaminopyridine to yield the *tert*-butylesterified compound (PR4-f).

Compounds (PR4-c), (PR4-d) and (PR4-f) obtained in this Scheme (PR-4) are converted to the final target compounds by Production Process A.

(Scheme PR-5)



Scheme PR-5 is one production process whereby the -N-Y1-Y2-Y3(-N) portion obtained by cyclization in Step 1 of Production Process MO may undergo additional structural conversion. In the formulas, R1 has the same definition as R1 in Step 1 of Production Process

PP. R27 has the same definition as R6 and R7 in
Production Process M0.

Step 1 is a step of treating compound (PR5-a)
with a catalytic amount of rhodium (II) acetate dimer
5 and the known reagent diethyl diazomalonate while
heating in a toluene solvent, to yield compound (PR5-
b).

Step 2 is a step of treating compound (PR5-b)
with equivalents of sodium ethoxide and ethyl acrylate
10 while heating in ethanol to yield the cyclized
compound (PR5-c).

Step 3 is a step of treating compound (PR5-c)
with 5 N hydrochloric acid while heating in ethanol to
yield compound (PR5-d) having the methoxymethyl
15 protecting group removed.

Step 4 is a step of converting compound (PR5-d)
to compound (PR5-e) having a newly introduced
substituent R27. Compound (PR5-e) may be obtained by
treatment in the same manner as for introduction of R7
20 in Step 3 of Production Process M0.

Step 5 is a step of treating compound (PR5-e)
with 1,2-bis(trimethylsiloxy)ethane and
triethylsilyltriflate in dichloromethane to yield
compound (PR5-f) wherein the acetyl carbonyl of
25 compound (PR5-e) is ketal-protected.

Step 6 is a step of reducing the lactam carbonyl

of compound (PR5-f) for conversion to methylene.

Compound (PR5-f) may be reacted with

tris(triphenylphosphine)rhodium(I) carbonyl hydride

and diphenylsilane in an appropriate solvent such as

5 tetrahydrofuran to yield compound (PR5-g).

Step 7 is a step of reacting compound (PR5-g) in

5% hydrochloric acid-tetrahydrofuran to yield the

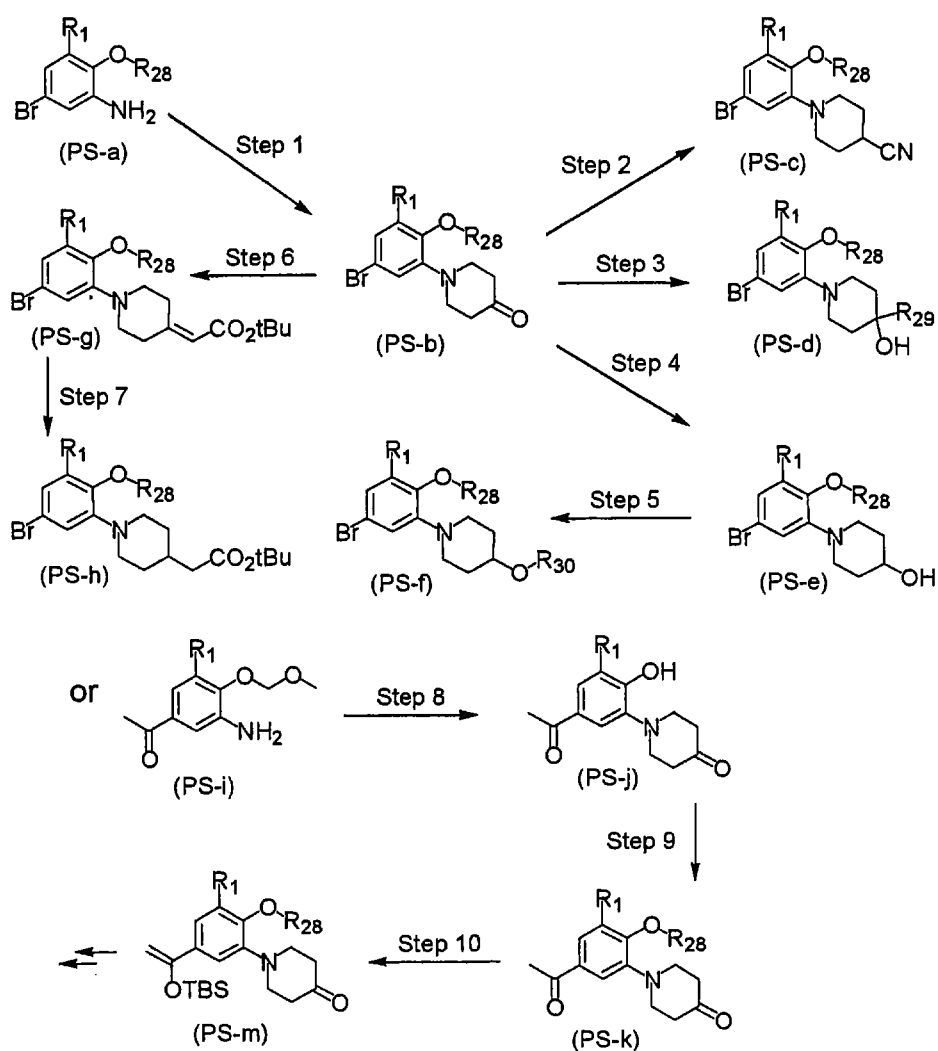
ketal-deprotected compound (PR5-h).

Compounds (PR5-d), (PR5-e) and (PR5-h) obtained in

10 Scheme PR-5 are converted to the final target compound

by Production Process A.

<Production Process PS>



This Production Process PS is a general synthesis method for a piperidine derivative. In the formulas, R₁ has the same definition as R₁ in Step 1 of Production Process PP. R₂₈ and R₃₀ have the same definitions as R₆ and R₇ in Production Process MO.

Step 1 is a step of reacting compound (PS-a) with formaldehyde to produce an imine, and then subjecting it to hetero Diels-Alder reaction with a diene having an enol ether structure to form an oxopiperidine ring. Preferably, Compound (PS-a) is reacted with 37%

formalin in dichloromethane in the presence of magnesium sulfate to produce an imine, and the reaction mixture is filtered with celite. After adding 2-trimethylsilyloxy-1,3-butadiene and toluene to the filtrate and cooling to -70°C , a 1 M hexane solution of diethylaluminum chloride is added dropwise and the temperature is raised. After completion of the reaction, it is exchanged with a tetrahydrofuran solution and treatment is carried out with 1 N hydrochloric acid to yield compound (PS-b) having the silylenol ether converted to a ketone.

Step 2 is a step of treating compound (PS-b) with p-toluenesulfonylmethyl isocyanide (TosMIC) in dimethoxyethane-tert-butanol in the presence of tert-butoxypotassium, to yield compound (PS-c) having the oxo group converted to cyano.

Step 3 is a step of reacting the carbonyl group of compound (PS-b) with any of various organometallic reagents to yield a tertiary alcohol (PS-d) having an added substituent R29. For example, compound (PS-b) may be reacted with methylmagnesium bromide in diethyl ether to yield compound (PS-d) having an added methyl group. R29 represents alkyl, alkenyl or alkynyl.

Step 4 is a step of treating compound (PS-b) with a reducing agent for conversion to an alcohol compound (PS-e). Any of various reducing agents may be used,

but treatment with sodium borohydride in a methanol-dichloromethane mixed solvent is preferred to yield compound (PS-e).

5 Step 5 is a step of treating compound (PS-e) in the same manner as Step 1 of Scheme PR-1 of Production Process PR to yield compound (PS-f) having a newly introduced substituent R30 at the hydroxyl group. Substituent R30 has the same definition as R6 and R7 in Production Process MO.

10 Step 6 is a step of Horner-Emmons reaction at the carbonyl group of compound (PS-b) to yield the carbon-carbon bond formed unsaturated ester (PS-g). After treating a *tert*-butyl diethylphosphonoacetate with sodium hydride in 1,2-dimethoxyethane, compound (PS-b)
15 dissolved in 1,2-dimethoxyethane is added to yield Compound (PS-g).

20 Step 7 is a step of 1,4-reduction of the unsaturated ester. Compound (PS-g) may be treated with sodium borohydride in a dichloromethane-methanol mixed solvent in the presence of a catalytic amount of nickel (II) chloride·6 hydrate, or reacted with magnesium in methanol for selective 1,4-reduction of the unsaturated ester to yield compound (PS-h).

25 A piperidine derivative may also be synthesized by the following Steps 8 to 10.

Step 8 is a step of treating compound (PS-i) in

the same manner as Step 1 to yield compound (PS-j), with simultaneous formation of a oxopiperidine ring and deprotection of the methoxymethyl group serving as the phenolic hydroxyl-protecting group.

5 Step 9 is a step of treating compound (PS-j) in the same manner as for introduction of R7 in Step 3 of Production Process MO, to yield compound (PS-k) substituted with substituent R28.

10 Step 10 is a step of selectively protecting the carbonyl group of the acetophenone of compound (PS-k). After adding compound (PS-k) to tetrahydrofuran, adding triethylamine and cooling to -70°C, the mixture is treated with *tert*-butyldimethylsilyl trifluoromethanesulfonate. The state of the reaction
15 is periodically examined by thin-layer column chromatography, and the temperature is gradually raised if necessary. Water may be added at low temperature to stop the reaction to yield compound (PS-m).

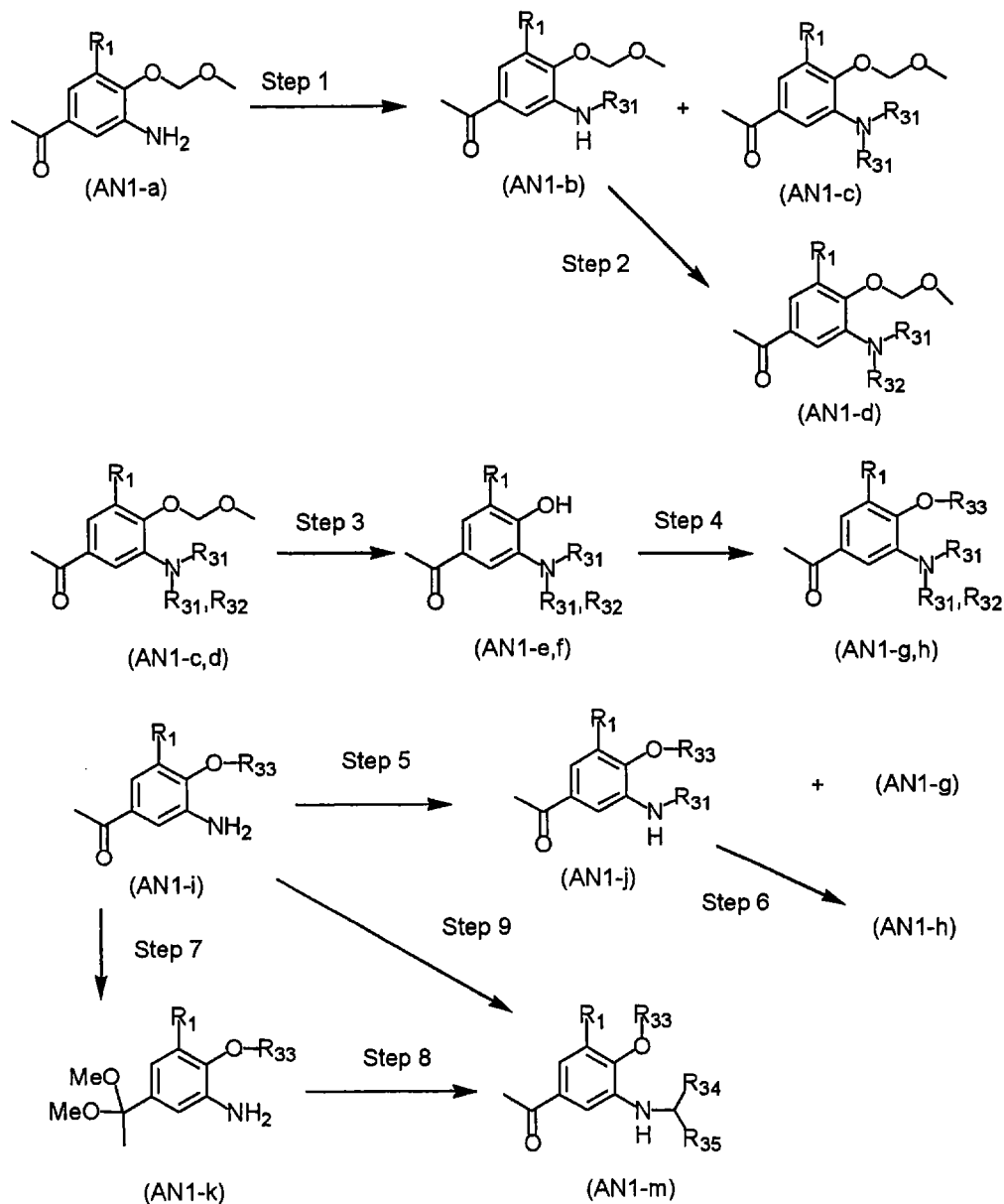
20 Finally, Compound (PS-m) may be treated in the same manner as in Steps 2, 3 and 4. Alternatively, it may be converted directly to an acyl bromide according to Production Process A for conversion to the final target compound.

25 Compounds (PS-b), (PS-c), (PS-d), (PS-e), (PS-f), (PS-g), (PS-h), (PS-j) and (PS-k) obtained in this

Production Process are converted to the final target compounds by Production Process A.

<Production Process AN>

(Scheme AN-1)



5

This scheme is a general synthesis for an aniline derivative. In the formulas, R1 has the same definition as in Step 1 of Production Process PP. R31, R32 and R33 have the same definitions as R6 and R7 in

Production Process M0.

Step 1 is a step of introducing one or two substituents R31 at the amino group of compound (AN1-a). Compound (AN1-a) may be treated in approximately the same manner as for introduction of R7 at the hydroxyl group in Step 3 of Production Process M0 to yield compounds (AN1-b) and (AN1-c). When R31 is bonded to the aniline amino group as simple alkyl and not via acyl or sulfonyl (for example, when R31-I or R31-Br is used as the reagent), a prolonged reaction with heating may be necessary to introduce the substituent R31. Incidentally, compounds (AN1-b) and (AN1-c) may be easily separated and purified by silica gel column chromatography.

Step 2 is a step of treating compound (AN1-b) in the same manner as Step 1 to yield compound (AN1-d) having a newly introduced substituent R32.

Step 3 is a step of treating compounds (AN1-c) and (AN1-d) in the same manner as Step 2 of Production Process M0 to yield the respective compounds (AN1-e) and (AN1-f).

Step 4 is a step of treating compounds (AN1-e) and (AN1-f) in the same manner as for introduction of R7 in Step 3 of Production Process M0 to yield the respective compounds (AN1-g) and (AN1-h).

Step 5 is a step of using compound (AN1-i) as the

starting material for treatment in the same manner as Step 1 to yield compound (AN1-j) having substituents R31 and R33. Compound (AN1-g) can also be obtained by this method.

5 Step 6 is a step of treating compound (AN1-j) in the same manner as Step 2 to yield compound (AN1-h).

Step 7 is a step of treating compound (AN1-i) in the same manner as the ketalizing step of Step 6 in Scheme PR-2, to yield compound (AN1-k).

10 Step 8 is a step of using an aldehyde or ketone (represented by R34-(C=O)-R35) and a reducing agent for reductive amination to yield compound (AN1-m).

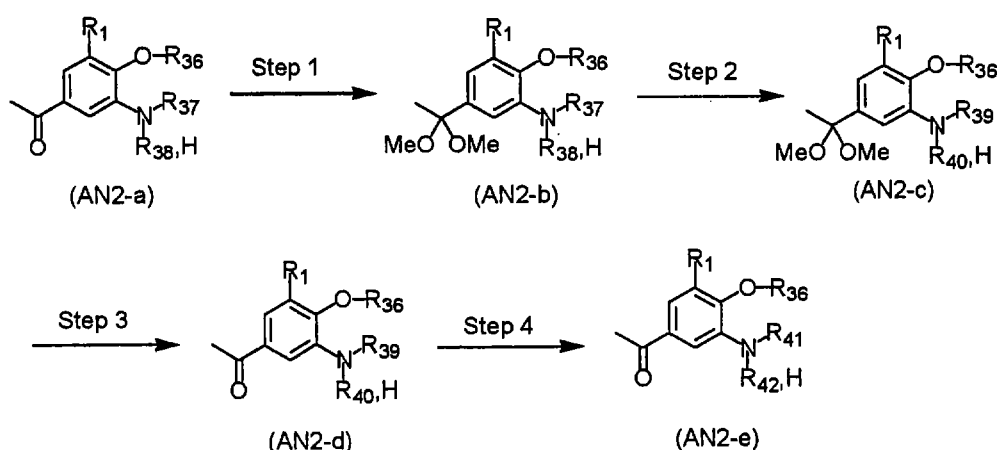
Compound (AN1-k) may be reacted with sodium cyanoborohydride in a methanol-acetic acid mixed
15 solvent or reacted with sodium triacetoxyborohydride in a 1,2-dichloroethane-acetic acid mixed solvent, to directly yield compound (AN1-m) having the ketal protecting group also deprotected. Either or both R34 and R35 may be hydrogen, or R34 and R35 may together
20 form a ring.

Step 9 is a step of using an aldehyde or ketone (represented by R34-(C=O)-R35) and a reducing agent for reductive amination to yield compound (AN1-m), without ketal protection of compound (AN1-i). In most
25 cases, reaction is conducted with sodium triacetoxyborohydride in a 1,2-dichloroethane-acetic

acid mixed solvent.

Compounds (AN1-b), (AN1-c), (AN1-d), (AN1-e),
(AN1-f), (AN1-g), (AN1-h), (AN1-j) and (AN1-m)
obtained in this Scheme AN-1 are converted to the
final target compounds by Production Process A.

(Scheme AN-2)



Scheme AN-2 is a general synthesis method for
further structural conversion of the substituents on
the aniline nitrogen of the intermediate synthesized
in Scheme AN-1. In the formulas, R_1 has the same
definition as R_1 in Step 1 of Production Process 1.
 R_{36} has the same definition as R_6 and R_7 in Production
Process M0. Either or both R_{37} and R_{38} may form an
amide bond with the aniline nitrogen, or the
substituents may have ester structures. One of the
substituents on the aniline nitrogen of the starting
material (AN2-a) may be hydrogen.

Step 1 is a step of treating compound (AN2-a) in
the same manner as the ketalizing reaction step of

Step 6 in Scheme PR-2 of Production Process PR, to yield compound (AN2-b) having the carbonyl group protected.

5 Step 2 is a step of treating compound (AN2-b) with a reducing agent for conversion of an amide group to methyleneamino (from -N-CO- to -N-CH₂-), or of an ester to an alcohol (from -CO-O- to -CH₂-OH, from -O-CO- to -OH). Preferably, compound (AN2-b) may be treated with lithium aluminum hydride in diethyl ether
10 to yield compound (AN2-c). Substituents R39 and R40 are defined as the structures after this conversion of R37 and R38.

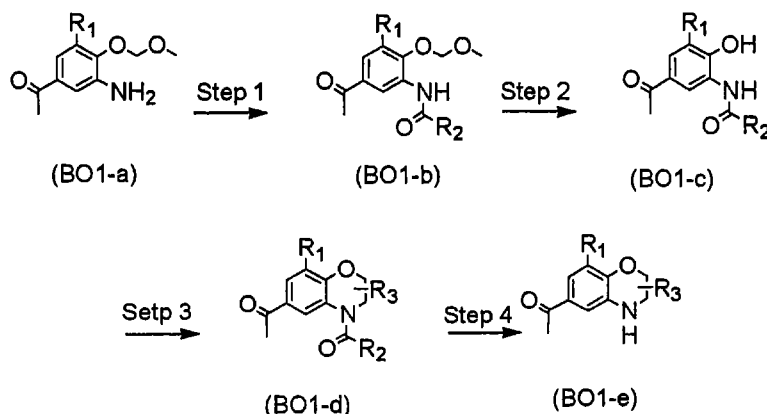
Step 3 is a step of treating compound (AN2-c) in the same manner as the ketal deprotection step of Step
15 7 in Scheme PR-2, to yield compound (AN2-d).

Step 4 is a step carried out only when compound (AN2-d) has a hydroxyl group on substituent R39 or R40, and here a new substituent is introduced at the hydroxyl group to yield compound (AN2-e) by conversion
20 to substituents R41 and R42.

The reaction of this step is conducted in the same manner as Step 1 in Scheme PR-1 of Production Process PR. Compounds (AN2-d) and (AN2-e) obtained in this Scheme (AN-2) are converted to the final target
25 compounds by Production Process A.
<Production Process B0>

The following Schemes BO-1, 2, 3 and 4 of Production Process BO are general synthesis methods for benzoxazine derivatives.

(Scheme BO-1)



In the formulas, R1 has the same definition as R1 in Step 1 of Production Process PP. R2 represents hydrogen, optionally substituted alkyl or the like. R3 represents hydrogen, halogeno, oxo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted acyl, optionally substituted carboxyl or optionally substituted carbamoyl.

Step 1 is a step of acylating the amino group. Compound (BO1-b) may be obtained either by reaction with an acyl chloride at room temperature in a solvent such as tetrahydrofuran, methylene chloride or acetonitrile in the presence of a base such as pyridine or triethylamine, or by reaction with an acid anhydride in a pyridine solution.

Step 2 is a step of deprotecting the methoxymethyl group protecting the alcohol. Compound

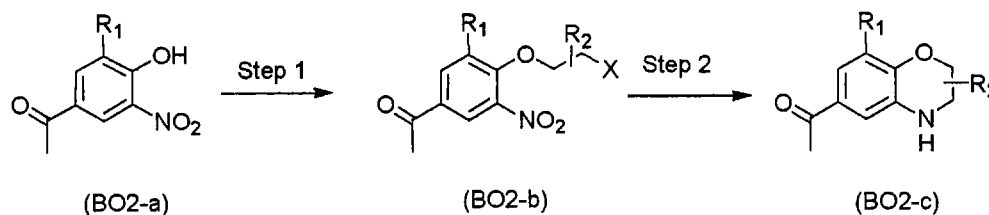
(BO1-c) may be obtained by reaction with dilute aqueous hydrochloric acid and 10% aqueous perchloric acid in a solvent such as tetrahydrofuran or acetone at room temperature.

5 Step 3 is a step of alkylating the hydroxyl and amino groups. Compound (BO1-d) may be obtained by reaction with a dihalide, dimesylate or ditosylate in a dimethylformamide solution in the presence of a base such as potassium carbonate, cesium carbonate or
10 sodium hydride, while heating from room temperature to 150°C.

 Step 4 is a step of deacylation. Compound (BO1-e) may be obtained either by reaction with an aqueous sodium hydroxide solution in a solvent such as
15 methanol, ethanol or tetrahydrofuran, at room temperature to the reflux temperature of the solvent, or by reaction in an aqueous hydrochloric acid solution at room temperature to the reflux temperature of the solvent.

20 Compounds (BO1-d) and (BO1-e) obtained in this Scheme BO-1 are converted to the final target compounds by Production Process A.

(Scheme BO-2)



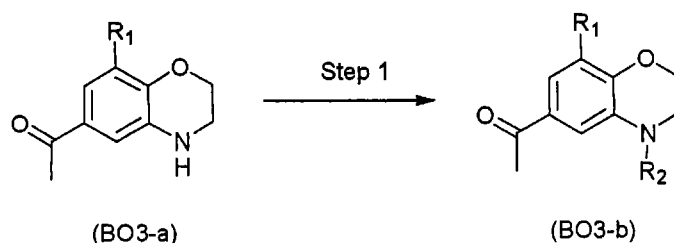
In the formulas, R1 has the same definition as R1 in Step 1 of Production Process PP. R2 has the same definition as R3 in Scheme BO-1.

Step 1 is a step of alkylating the hydroxyl group. Compound (BO2-b) may be obtained by reaction with a dihalide, dimesylate or ditosylate in a dimethylformamide solution while heating from room temperature to 150°C.

Step 2 is a step of forming an oxazine ring. Reaction is conducted with a dihalide, dimesylate or ditosylate in a dimethylformamide solution in the presence of a base such as potassium carbonate, cesium carbonate or sodium hydride, while heating from room temperature to 150°C. Reaction is then conducted at room temperature in an ethanol or methanol solution in the presence of a catalytic amount of palladium-carbon in a hydrogen atmosphere to yield compound (BO2-c).

Compound (BO2-c) obtained in this Scheme BO-2 is converted to the final target compound by Production Process A.

(Scheme BO-3)



In the formulas, R1 represents hydrogen,

optionally substituted alkyl, optionally substituted cycloalkyl or optionally substituted alkoxy. R₂ represents hydrogen, optionally substituted alkyl, alkyl having cyano at the end or a branch, optionally substituted alkoxy, optionally substituted arylalkyl, optionally substituted acyl, optionally substituted sulfonyl, optionally substituted carbamoyl or optionally substituted carboxyl.

Step 1 is a step of alkylating, acylating, substituted carbamoylating or urethanating the amino group, by any of the following methods 1 to 4.

1. Compound (B03-b) may be obtained by reaction with a halide, mesylate or tosylate in a dimethylformamide solution in the presence of a base such as potassium carbonate, cesium carbonate or sodium hydride, while heating from room temperature to 150°C.

2. Compound (B03-b) may be obtained either by reaction with an acyl chloride, sulfonyl chloride or isocyanate at room temperature in a solvent such as tetrahydrofuran, methylene chloride or acetonitrile, in the presence of a base such as pyridine or triethylamine, or by reaction with an acid anhydride in a pyridine solution.

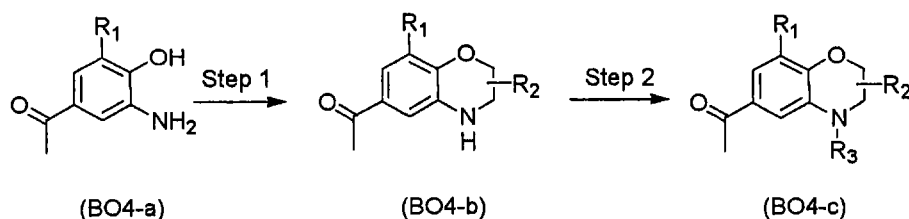
3. Compound (B03-b) may be obtained by reaction with ethyl N-(1-cyano)iminoformate in a methanol or

ethanol solvent in the presence of a catalytic amount of 4-dimethylaminopyridine, at room temperature to the reflux temperature of the solvent.

4. Compound (BO3-b) may be obtained by reaction with trimethyl orthoformate or triethyl orthoformate in a methanol or ethanol solvent in the presence of a catalytic amount of p-toluenesulfonic acid or camphorsulfonic acid, ketal protection of the acetyl group and introduction of different substituents by methods 1 to 3 above, followed by deprotection under acidic conditions.

Compound (BO3-b) obtained in this Scheme BO-3 is converted to the final target compound by Production Process A.

(Scheme BO-4)



In the formulas, R1 has the same definition as R1 in Step 1 of Production Process PP. R2 has the same definition as R3 in Scheme BO-1. R3 has the same definition as R2 in Scheme BO-3.

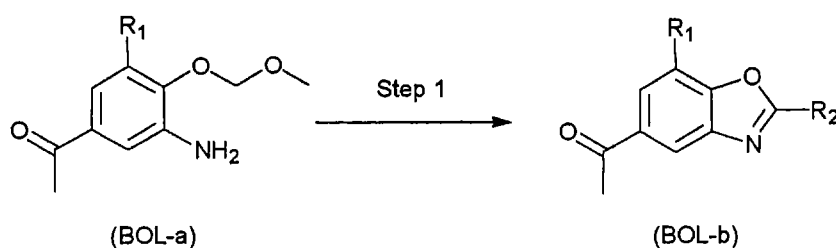
Step 1 is a step of alkylation. Compound (BO4-b) may be obtained by the method described in Tawada, H., Sugiyama, Y., Ikeda, H., Yamamoto, Y., Meguro, K; Chem.

Pharm. Bull., 38(5), 1238-1245(1990), or by reaction with allyl bromide, maleic anhydride or the like in a solvent such as methanol, ethanol or toluene in the presence of a base such as potassium carbonate, cesium carbonate or sodium hydrogencarbonate at room temperature to the reflux temperature of the solvent, followed by reaction in a methanol or ethanol solvent in the presence of a base such as potassium carbonate or triethylamine, at room temperature to the reflux temperature of the solvent.

Step 2 is a step of alkylating, acylating, substituted carbamoylating or urethanating the amino group. Compound (B04-c) may be obtained by treatment in the same manner as Step 1 of Scheme B0-3.

Compounds (B04-b) and (B04-c) obtained in Scheme B0-4 are converted to the final target compound by Production Process A.

<Production Process BOL>



Production Process BOL is a general synthesis method for a benzoxazole derivative. In the formulas, R1 has the same definition as R1 in Step 1 of Production Process PP. R2 represents hydrogen,

optionally substituted alkyl or optionally substituted alkoxy.

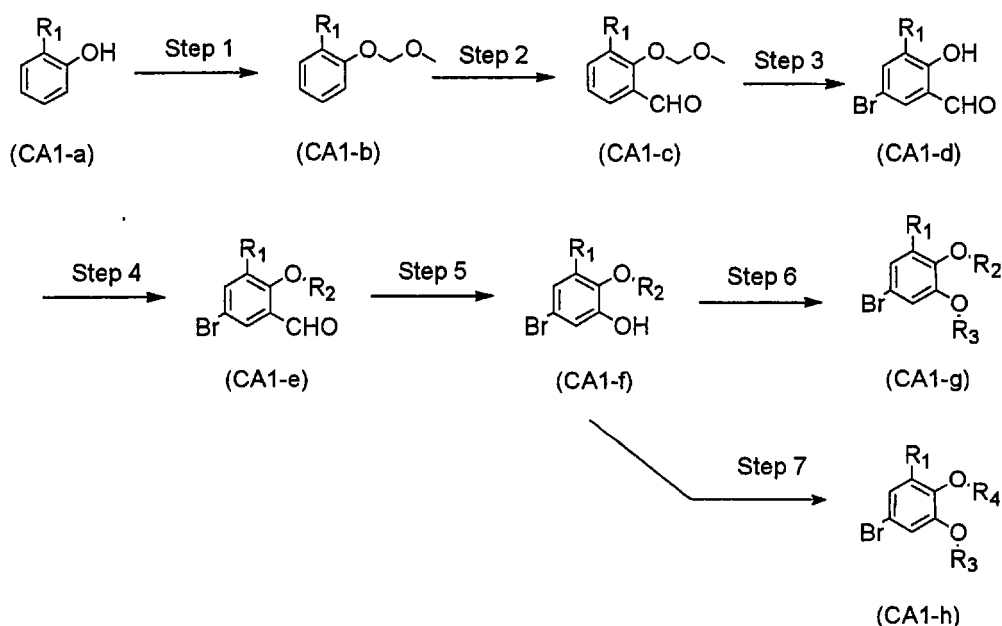
Step 1 is a step of forming an oxazole ring. Compound (BOL-b) may be obtained by reaction with an acid chloride in a solvent such as tetrahydrofuran, methylene chloride or acetonitrile in the presence of a base such as triethylamine, followed by reaction with dilute aqueous hydrochloric acid or p-toluenesulfonic acid in a solvent such as ethanol, methanol, tetrahydrofuran or methyl ethyl ketone.

The benzoxazoleethanone derivative (BOL-b) obtained in Production Process BOL is converted to the final compound by Production Process A.

<Production Process CA>

Schemes CA-1, 2 and 3 below in Production Process CA are general synthesis methods for catechol derivatives.

(Scheme CA-1)



In the formulas, R1 has the same definition as R1 in Step 1 of Production Process PP. R2, R3 and R4 have the same definitions as R6 and R7 in Production Process MO.

Step 1 is a step of methoxymethylating the hydroxyl group of compound (CA1-a). Compound (CA1-b) is obtained by reaction of compound (CA1-a) and sodium hydride in dimethylformamide at room temperature, followed by reaction with methoxymethyl chloride (MOM-Cl).

Step 2 is a step of introducing a formyl group by ortholithiation utilizing the substituent effect of the methoxymethyl group of compound (CA1-b). The orthoformylated compound (CA1-c) is obtained by treatment of compound (CA1-b) with n-butyllithium in a diethyl ether solvent while cooling on ice in the

presence of tetramethylethylenediamine, followed by treatment with a formylating agent such as dimethylformamide or N-formylmorpholine.

Step 3 is a step of brominating the para-position relative to the methoxymethyl group of compound (CA1-c). Compound (CA1-d) is obtained by reaction of compound (CA1-c) with bromine in methanol at room temperature, and removal of the methoxymethyl group by the hydrogen bromide generated in the system.

Step 4 is a step of introducing any of various substituents at the hydroxyl group of compound (CA1-d). Compound (CA1-e) is obtained by the same method as for introduction of R7 in Step 3 of Production Process M0.

Step 5 is a step of oxidative conversion of the formyl group to a hydroxyl group. Compound (CA1-f) is obtained by reacting compound (CA1-e) with m-chloroperbenzoic acid in dichloromethane at room temperature or with heating, and then hydrolyzing the purified ester using potassium carbonate in methanol.

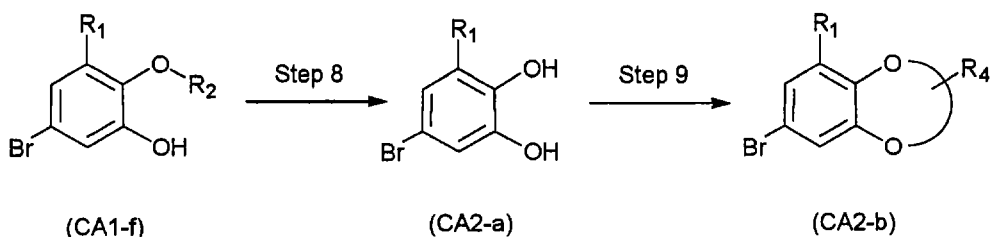
Step 6 is a step of obtaining compound (CA1-g) having substituent R3 introduced therein by the same method as in Step 4 of Scheme CA-1.

Step 7 is a step of conversion to substituent R4 when R2 is a hydroxyl-protecting group. Compound (CA1-h) is obtained in the same manner as the continuous treatment in Steps 2 and 3 of Production

Process MO.

Compounds (CA1-g) and (CA1-h) obtained in this Scheme CA-1 are converted to the final target compound by Production Process A.

5 (Scheme CA-2)



Scheme CA-2 is a general synthesis method for a cyclic catechol derivative. In the formulas, R1 has the same definition as R1 in Step 1 of Production Process PP. R2 and R4 have the same definitions as R6 and R7 in Production Process MO.

10

Step 8 is a step of conversion to a catechol when R2 is a removable hydroxyl-protecting group. When R2 is methoxymethyl, a diol (catechol) (CA2-a) is obtained by treating compound (CA1-f) with 6 N hydrochloric acid.

15

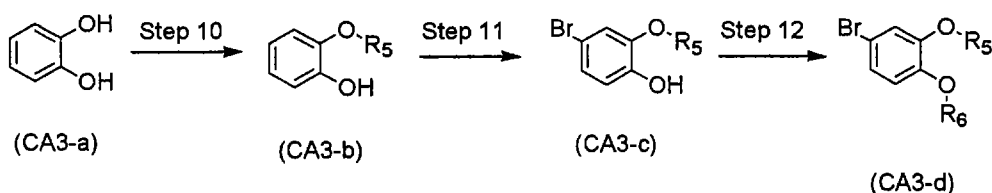
Step 9 is a step of cyclizing the catechol by alkylation. Compound (CA2-a) is reacted with a 1,2-dibromoethyl derivative in a solvent such as dimethylformamide, acetonitrile or acetone in the presence of a base such as potassium carbonate, cesium carbonate or sodium hydride, to yield a fused dioxane ring (CA2-b). Compound (CA2-a) may also be treated

20

with acetone in the presence of phosphorus pentaoxide to yield a 5-membered cyclic product (CA2-b) as an acetonide.

Compound (CA2-b) obtained in this Scheme CA-2 is converted to the final target compound by Production Process A.

(Scheme CA-3)



Scheme CA-3 is a general synthesis method for a disubstituted catechol derivative. In the formulas, R5 and R6 have the same definitions as R6 and R7 in Production Process MO.

Step 10 is a step of obtaining compound (CA3-b) by the same method as in Step 4 of Scheme CA-1 using the catechol (CA3-a) as the starting material.

Step 11 is a step of treating compound (CA3-b) by the same method as in Step 3 of Scheme CA-1 to yield compound (CA3-c) which is selectively brominated at the para-position relative to the non-substituted hydroxyl group.

Step 12 is a step of obtaining compound (CA3-d) having R6 introduced by the same method as in Step 4 of Scheme CA-1.

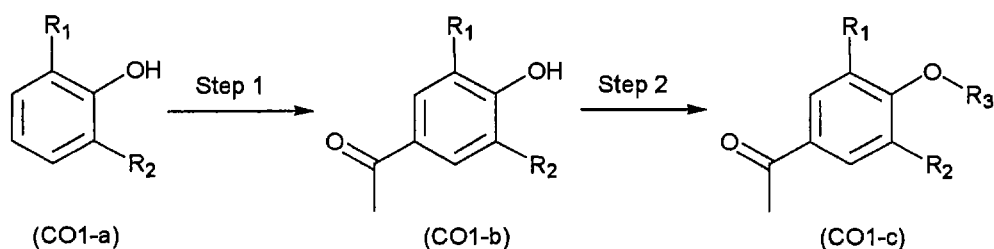
Compound (CA3-d) obtained by Scheme CA-3 is

converted to the final target compound by Production Process A.

<Production Process CO>

Schemes CO-1, CO-2, CO-3, CO-4, CO-5, CO-6, CO-7, CO-8 and CO-9 in Production Process CO are general synthesis methods for phenol and phenoxy derivatives.

(Scheme CO-1)



In the formulas of Scheme CO-1, R1 and R2 have the same definition as R1 in Step 1 of Production Process PP. R3 has the same definition as R6 and R7 in Production Process MO.

Step 1 is a step of Friedel-Crafts acylation. Compound (CO1-b) is obtained by reaction with acetyl chloride in a methylene chloride or toluene solvent in the presence of a Lewis acid such as aluminum chloride, zinc chloride or tin (II) chloride, at -70°C to room temperature.

Step 2 is a step of alkylation, carbonation, sulfonation or the like.

1. Compound (CO1-c) may be obtained by reaction with a halide, mesylate or tosylate in a dimethylformamide solution in the presence of a base

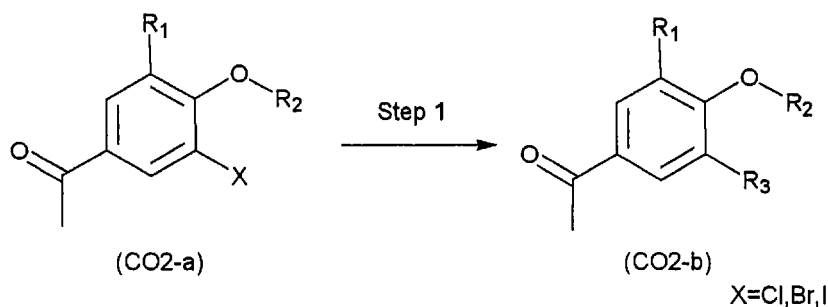
such as potassium carbonate, cesium carbonate or sodium hydride, while heating from room temperature to 150°C.

2. Compound (CO1-c) may be obtained either by reaction with an acyl chloride, sulfonyl chloride or isocyanate in a solvent such as tetrahydrofuran, methylene chloride or acetonitrile in the presence of a base such as pyridine or triethylamine, at -15°C to room temperature, or by reaction with an acid anhydride in a pyridine solution.

3. Compound (CO1-c) may also be obtained by reaction with phenyl chloroformate in a solvent such as tetrahydrofuran, methylene chloride or acetonitrile in the presence of a base such as pyridine or triethylamine, followed by reaction with an amine.

Compounds (CO1-b) and (CO1-c) obtained in this Scheme CO-1 are converted to the final target compounds by Production Process A. Compound (CO1-a) may also be used in the conversion of compound (A4-c) in Scheme A-4 of Production Process A.

(Scheme CO-2)



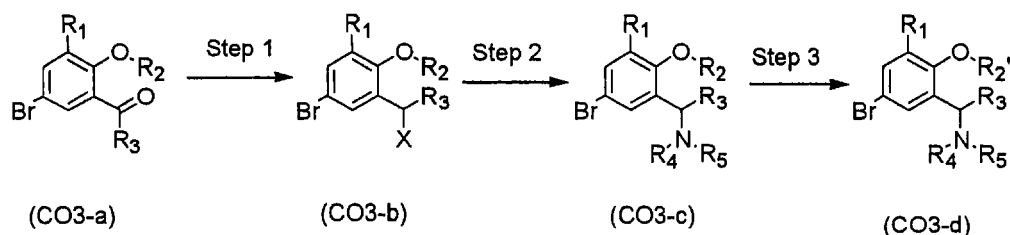
Scheme CO-2 is a general synthesis method for an

aromatic-substituted benzene derivative. In the formulas, R1 has the same definition as R1 in Step 1 of Production Process PP. R2 has the same definition as R6 and R7 in Production Process MO. R3 represents an aromatic ring.

Step 1 is a step of introducing an aromatic substituent using the Stille coupling method. Compound (CO2-b) is obtained by reaction with aromatic-substituted tributyltin in a solvent such as toluene or xylene under a nitrogen atmosphere in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium, at the reflux temperature of the solvent.

Compound (CO2-b) obtained in this Scheme CO-2 is converted to the final target compound by Production Process A.

(Scheme CO-3)



Scheme CO-3 is a general synthesis method for a benzylamine derivative. In the formulas, R1 and R3 have the same definition as R1 in Step 1 of Production Process PP. R2 and R2' have the same definitions as R6 and R7 in Production Process MO. R4 and R5 have

the same definition as R2 in Scheme BO-3. R4 and R5 may also form a ring together. X represents hydroxyl or a sulfonate.

5 Step 1 is a step of introducing an alkyl halide. Compound (CO3-b) is obtained by reaction with sodium borohydride in a methanol or ethanol solvent, followed by reaction with methanesulfonyl chloride in dimethylformamide, in the presence of a base such as pyridine or triethylamine.

10 Step 2 is a step of amination.

1. Compound (CO3-c) may be obtained by reaction with an amine in a methanol, ethanol, acetonitrile or tetrahydrofuran solvent.

15 2. Compound (CO3-c) may be obtained by reaction with an amine in a dimethylformamide solvent in the presence of a base such as potassium carbonate or sodium hydride.

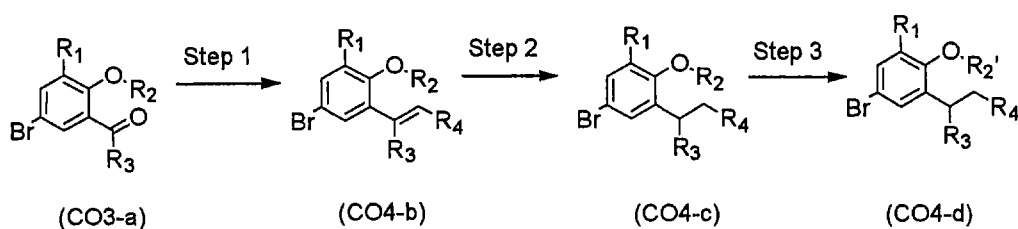
20 3. When X is hydroxyl, compound (CO3-c) may be obtained by reaction with diphenylphosphoryl azide in a toluene solvent in the presence of a base such as 1,8-diazabicyclo[5.4.0]undec-7-ene to yield an azide, followed by reaction with a trialkylphosphine or triphenylphosphine in a tetrahydrofuran-water solvent.

25 Step 3 is a step of converting R2 to substituent R2' when R2 is a hydroxyl-protecting group. Compound (CO3-d) is obtained in the same manner as the

continuous treatment in Steps 2 and 3 of Production Process MO.

Compounds (CO3-c) and (CO3-d) obtained in this Scheme CO-3 are converted to the final target compounds by Production Process A.

(Scheme CO-4)



Scheme CO-4 is a general synthesis method for phenol and phenoxy derivatives by Wittig reaction. In the formulas, R₁ has the same definition as R₁ in Production Process PP. R₂ and R₂' have the same definitions as R₆ and R₇ in Production Process MO. R₃ represents hydrogen or lower alkyl. R₄ represents optionally substituted alkyl, optionally substituted carboxyl, cyano or the like.

Step 1 is a step of alkylation utilizing a Wittig reaction. Reaction is conducted with a phosphorane derivative in a methylene chloride or tetrahydrofuran solvent. Alternatively, compound (CO4-b) may be obtained by reaction with a phosphonium salt or phosphonate in a tetrahydrofuran or dimethylformamide solvent in the presence of a base such as potassium *tert*-butoxide or sodium hydride.

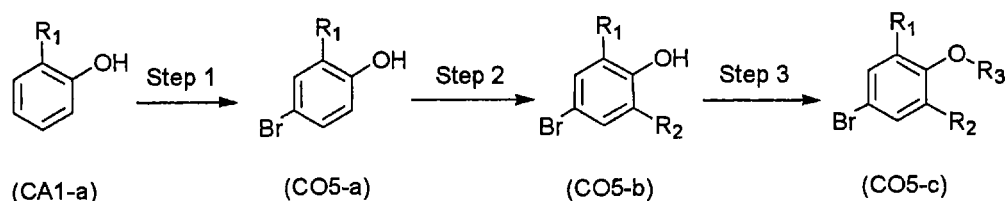
Step 2 is a step of reducing the olefin.

Compound (CO4-c) may be obtained by reaction in ethyl acetate, tetrahydrofuran or methanol under a hydrogen atmosphere in the presence of palladium-carbon, or by
 5 reaction with magnesium in methanol.

Step 3 is a step of conversion to substituent R2' when R2 is a hydroxyl-protecting group. Compound (CO4-d) is obtained in the same manner as the continuous treatment in Steps 2 and 3 of Production
 10 Process MO.

Compounds (CO4-b), (CO4-c) and (CO4-d) obtained in this Scheme CO-4 are converted to the final target compounds by Production Process A.

(Scheme CO-5)



Scheme CO-5 is a general synthesis method for phenol and phenoxy derivatives utilizing a Friedel-Crafts reaction. In the formulas, R1 has the same definition as R1 in Step 1 of Production Process PP. R2 represents hydrogen, optionally substituted alkyl or optionally substituted cycloalkyl. R3 has the same
 20 definition as R6 and R7 in Production Process MO.

Step 1 is a step of bromination at the phenyl para-position. Reaction may be conducted with bromine

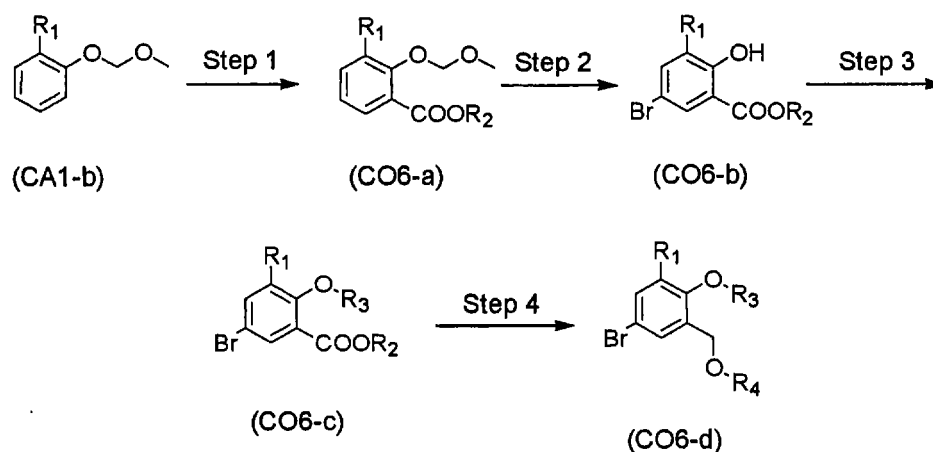
in a methanol or ethanol solvent or with N-bromosuccinimide in an acetonitrile solvent to yield Compound (CO5-a).

Step 2 is a step of alkylation by Friedel-Crafts reaction. Compound (CO5-b) is obtained by reaction with an alkyl mesylate in a benzene or dichloroethane solvent in the presence of scandium triflate, by the method described in H. Katsuki et al., Synthesis 603(1999).

Step 3 is a step of introducing a substituent R3 at the hydroxyl group. Compound (CO5-c) is obtained by treatment in the same manner as for introduction of R7 in Step 3 of Production Process MO.

Compounds (CO5-b) and (CO5-c) obtained in Scheme CO-5 are converted to the final target compounds by Production Process A.

(Scheme CO-6)



Scheme CO-6 is a general synthesis method for carboxylic acid derivatives and benzyl alcohol

derivatives. In the formulas, R1 has the same definition as R1 in Step 1 of Production Process PP. R2 represents optionally substituted alkyl and R3 and R4 have the same definitions as R6 and R7 in
5 Production Process MO.

Step 1 is a step of introducing a carboxyl group by ortholithiation utilizing the substituent effect of the methoxymethyl group of compound (CA1-b). Compound (CO6-a) is obtained by treating compound (CA1-b) with
10 n-butyllithium in a diethyl ether solvent in the presence of tetramethylethylenediamine while cooling on ice, and then reacting it with an alkyl dicarbonate.

Step 2 is a step of deprotection of the methoxymethyl group serving as the alcohol-protecting group. Compound (CO6-b) is obtained by reaction with
15 dilute aqueous hydrochloric acid and 10% aqueous perchloric acid in a tetrahydrofuran or acetone solvent at room temperature.

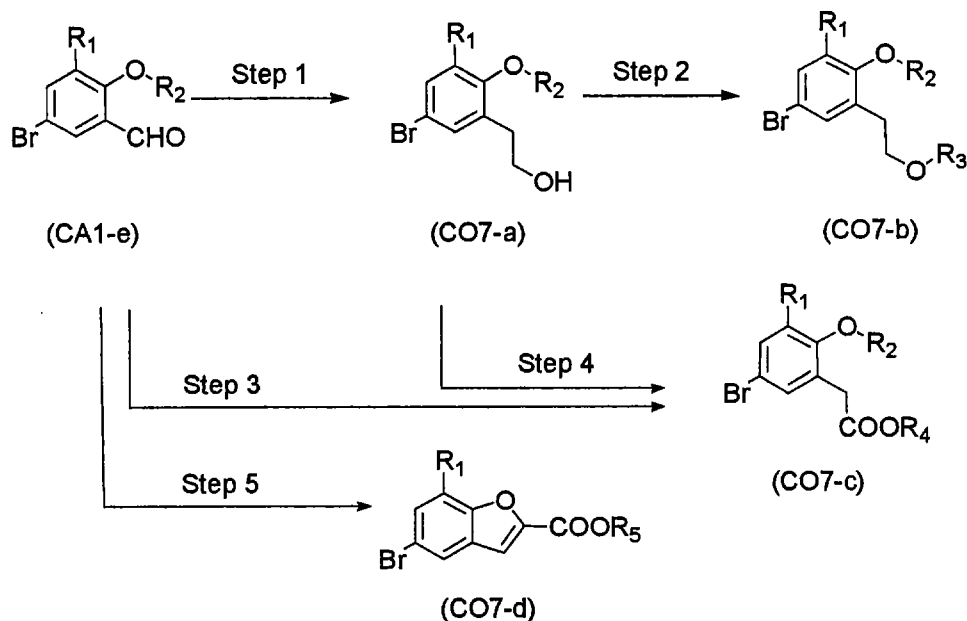
Step 3 is a step of introducing a substituent R3 at the hydroxyl group. Compound (CO6-c) is obtained
20 by treatment in the same manner as for introduction of R7 in Step 3 of Production Process MO.

Step 4 is a step of reduction and alkylation of the carboxyl group. Compound (CO6-d) is obtained by
25 reaction with lithium aluminum hydride in a diethyl ether or tetrahydrofuran solvent while cooling on ice,

followed by the same method as in Step 3.

Compounds (CO6-b), (CO6-c) and (CO6-d) obtained in this Scheme CO-6 are converted to the final target compounds by Production Process A.

5 (Scheme CO-7)



Scheme CO-7 is a general synthesis method for phenethyl alcohol derivatives, phenylacetic acid derivatives and benzofuran derivatives. In the formulas, R1 has the same definition as R1 in Step 1 of Production Process PP. R2 and R3 have the same definitions as R6 and R7 in Production Process MO. R4 and R5 represent optionally substituted alkyl.

Step 1 is a step of introducing a hydroxyl group by Wittig reaction followed by hydroboration reaction. The reaction is conducted with methyltriphenylphosphonium bromide in a

tetrahydrofuran solvent in the presence of potassium *tert*-butoxide. Reaction is then conducted with borane-tetrahydrofuran in a tetrahydrofuran solvent and with 30% aqueous hydrogen peroxide to yield compound (C07-a).

Step 2 is a step of introducing a substituent R3 at the hydroxyl group. Compound (C07-b) is obtained by treatment in the same manner as for introduction of R7 in Step 3 of Production Process MO.

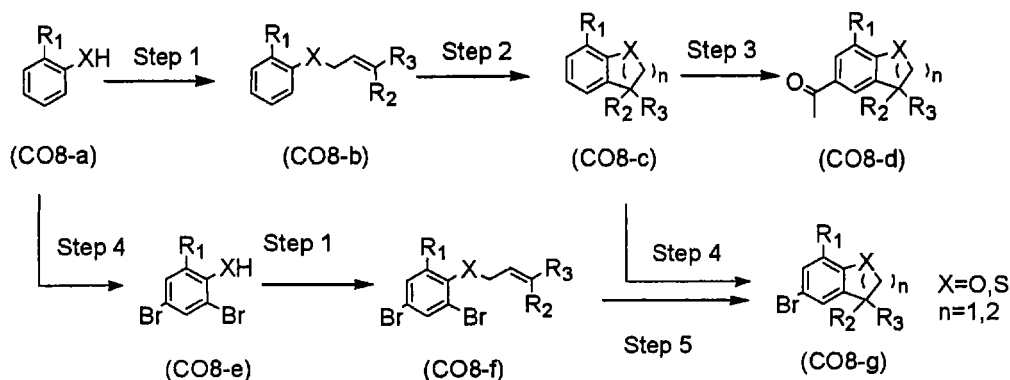
Step 3 is a step of carbon-carbon bond formation. Compound (C07-c) is obtained by reaction with methylmethylthiomethyl sulfoxide in a tetrahydrofuran solvent in the presence of Triton B, at the reflux temperature of the solvent, followed by reaction with dilute aqueous hydrochloric acid in a methanol or ethanol solvent.

Step 4 is a step of oxidation. Compound (C07-c) is obtained by the method described in Mangzho Zhao et al., *Tetrahedron Lett.* 39, 5323(1998) or the method described in Ryoji Noyori et al., *J. Am. Chem. Soc.*, 119, 12386(1997).

Step 5 is a step of forming a furan ring when R2 is hydrogen. Compound (C07-d) is obtained by reaction with a bromoacetic acid ester in a dimethylformamide solvent in the presence of potassium carbonate, at the reflux temperature of the solvent.

Compounds (CO7-a), (CO7-b), (CO7-c) and (CO7-d) obtained in this Scheme CO-7 are converted to the final target compounds by Production Process A.

(Scheme CO-8)



5

Scheme CO-8 is a general synthesis method for a 2,3-dihydrobenzofuran derivative or 2,3-dihydrobenzothiophene derivative. In the formulas, R1 has the same definition as R1 in Step 1 of Production Process PP. R2 and R3 represent hydrogen, optionally substituted alkyl or optionally substituted alkoxy.

10

Step 1 is a step of alkylation of the hydroxyl group. Compound (CO8-b) is obtained by reaction with an allyl halide, allyl mesylate or allyl tosylate in a solvent such as dimethylformamide, acetonitrile or acetone, in the presence of sodium iodide and in the presence of a base such as potassium carbonate, cesium carbonate or sodium hydride, according to the method described in J.M. Janusz et al., J. Med. Chem. 41, 1112(1998).

15

20

Step 2 is a step of forming a furan or thiophene

ring. Compound (CO8-c) is obtained by the method described in J.M. Janusz et al., J. Med. Chem. 41, 1112(1998), or by reaction at 210°C in magnesium chloride.

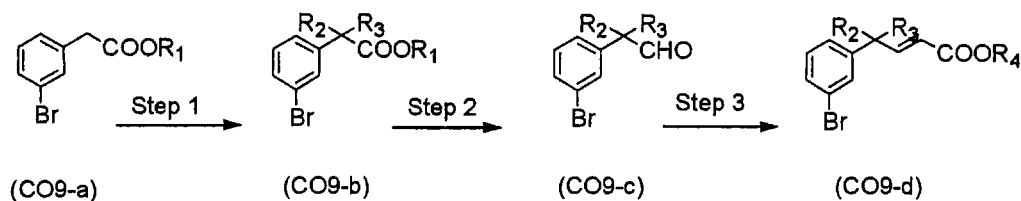
5 Step 3 is a step of Friedel-Crafts acylation. Compound (CO8-d) is obtained by reaction with acetyl chloride in a methylene chloride or toluene solvent in the presence of a Lewis acid such as aluminum chloride, zinc chloride or tin (II) chloride, at -70°C to room
10 temperature.

 Step 4 is a step of bromination by reaction with bromine in a methanol or ethanol solvent.

 Alternatively, compounds (CO8-e) and (CO8-g) are obtained by reaction with N-bromosuccinimide in an
15 acetonitrile or dimethylformamide solvent.

 Step 5 is a step of forming a furan or thiophene ring. Compound (CO8-g) is obtained by reaction with sodium borohydride at 75°C in a dimethylacetamide solvent in the presence of
20 cyclopentadienyldichlorotitanium, by the method described in J. Schwartz et al., J. Org. Chem. 59, 940(1994).

 Compounds (CO8-d) and (CO8-g) obtained in this Scheme CO-8 are converted to the final target
25 compounds by Production Process A.
 (Scheme CO-9)



Scheme CO-9 is a general synthesis method for a carboxylic acid derivative. In the formulas, R1, R2, R3 and R4 represent hydrogen or optionally substituted alkyl.

Step 1 is a step of alkylation. Compound (CO9-b) is obtained by reaction with an alkyl halide, mesylate or tosylate in a tetrahydrofuran or dimethylformamide solvent, in the presence of potassium *tert*-butoxide or sodium hydride.

Step 2 is a step of reduction. Compound (CO9-c) is obtained by reaction with diisobutylaluminum hydride in a tetrahydrofuran solvent.

Step 3 is a step of carbon-carbon bond formation utilizing a Wittig reaction. The reaction is conducted with a phosphorane derivative in a methylene chloride or tetrahydrofuran solvent. Alternatively, compound (CO9-d) is obtained by reaction with either a phosphonium salt or phosphonate in a tetrahydrofuran or dimethylformamide solvent in the presence of a base such as potassium *tert*-butoxide or sodium hydride.

Compounds (CO9-b) and (CO9-d) obtained in this Scheme CO-9 are converted to the final target compounds by Production Process A.

Representative production processes for compounds according to the invention and salts thereof have been described above, but the starting compounds and reagents used for production of the compounds of the invention may also form salts or hydrates, and these are not particularly restricted so long as the reaction is not inhibited. When compound (I) of the invention is obtained as a free compound, a common method may be used to convert it to a salt which compound (I) may form. The different isomers (for example, geometric isomers, optical isomers based on asymmetric carbon, stereoisomers, tautomers or the like) obtained for compound (I) according to the invention may be purified and isolated using common separation means such as recrystallization, diastereomer salt methods, enzymatic resolution methods and chromatography methods (for example, thin-layer chromatography, column chromatography, gas chromatography, etc.).

The compounds of the invention represented by formula (I) and salts thereof exhibit excellent thrombin receptor antagonism and especially selective antagonism against PAR1 thrombin receptors. The compounds of the invention and their salts also exhibit excellent inhibition against platelet aggregation and smooth muscle cell proliferation, with

high oral efficacy. The compounds of the invention and salts thereof can therefore inhibit the cellular response to thrombin which includes platelet aggregation, without inhibiting the catalytic activity of thrombin which converts fibrinogen to fibrin, and can also inhibit vascular smooth muscle proliferation occurring as a result of damage to vascular walls by coronary angioplasty and the like, through selective inhibition of PAR1.

Thus, the compounds of the invention and salts thereof may be used to obtain pharmaceutical compositions (formulations) as (i) thrombin receptor antagonists (especially PAR1 thrombin receptor antagonists), (ii) platelet aggregation inhibitors, (iii) smooth muscle cell proliferation inhibitors, (iv) endothelial cell, fibroblast, nephrocyte, osteosarcoma cell, muscle cell, cancer cell and/or glia cell proliferation inhibitors and (v) therapeutic or preventive agents for thrombosis, vascular restenosis, deep venous thrombosis, pulmonary embolism, cerebral infarction, heart disease, disseminated intravascular coagulation, hypertension, inflammatory diseases, rheumatism, asthma, glomerulonephritis, osteoporosis, neurological disease and/or malignant tumor.

The compounds of the invention and their salts

may be administered for treatment of patients
suffering from diseases associated with thrombin
receptors, and for treatment of patients suffering
from proliferative diseases of, for example,
5 endothelial cell, fibroblast, nephrocyte, osteosarcoma
cell, muscle cell, cancer cell and/or glia cell.

A compound of the invention represented by
formula (I) above, a salt thereof or a hydrate of the
foregoing may be formulated by a common method. As
10 preferred dosage forms there may be mentioned tablets,
powders, fine particles, granules, coated tablets,
capsules, syrups, lozenges, inhalants, suppositories,
injections, ointments, eye salves, eye drops, nasal
drops, ear drops, paps, lotions and the like. For the
15 formulation there may be employed any commonly used
excipients, binders, disintegrators, lubricants,
coloring agents, corrective coatings, and if necessary,
stabilizers, emulsifiers, absorbefaciants, surfactants,
pH adjustors, preservatives, antioxidants, or the like,
20 in combination with various components that are
ordinarily used as materials for pharmaceutical
formulations.

As such components there may be mentioned (1)
animal and vegetable oils such as soybean oil, beef
25 tallow and synthetic glycerides; (2) hydrocarbons such
as liquid paraffin, squalane and solid paraffin; (3)

ester oils such as octyldodecyl myristate and
isopropyl myristate; (4) higher alcohols such as
cetostearyl alcohol and behenyl alcohol; (5) silicone
resins; (6) silicone oils; (7) surfactants such as
5 polyoxyethylene fatty acid esters, sorbitan fatty acid
esters, glycerin fatty acid esters, polyoxyethylene
sorbitan fatty acid esters, polyoxyethylene
hydrogenated castor oil and
polyoxyethylene/polyoxypropylene block copolymer; (8)
10 water-soluble polymers such as hydroxyethylcellulose,
polyacrylic acid, carboxyvinyl polymer, polyethylene
glycol, polyvinylpyrrolidone and methylcellulose; (9)
lower alcohols such as ethanol and isopropanol; (10)
polyhydric alcohols such as glycerin, propylene glycol,
15 dipropylene glycol and sorbitol; (11) sugars such as
glucose and sucrose; (12) inorganic powders such as
silicic anhydride, magnesium aluminum silicate and
aluminum silicate; (13) purified water, and the like.

Examples of (1) excipients which may be used
20 include lactose, corn starch, white soft sugar,
glucose, mannitol, sorbit, crystalline cellulose and
silicon dioxide; examples of (2) binders which may be
used include polyvinyl alcohol, polyvinyl ether,
methylcellulose, ethylcellulose, gum arabic,
25 tragacanth, gelatin, shellac, hydroxypropylcellulose,
hydroxypropylmethylcellulose, polyvinylpyrrolidone,

polypropylene glycol/polyoxyethylene block polymer,
meglumine, calcium citrate, dextrin and pectin;
examples of (3) disintegrators which may be used
include starch, agar, gelatin powder, crystalline
5 cellulose, calcium carbonate, sodium hydrogencarbonate,
calcium citrate, dextrin, pectin and calcium
carboxymethylcellulose; examples of (4) lubricants
which may be used include magnesium stearate, talc,
polyethylene glycol, silica and hydrogenated vegetable
10 oils; examples of (5) coloring agents which may be
used include any of those approved for addition to
drugs; examples of (6) corrective coatings which may
be used include cocoa powder, menthol, aromatic
powders, mentha oil, borneol and powdered cinnamon;
15 and examples of (7) antioxidants which may be used
include those approved for addition to drugs, such as
ascorbic acid, α -tocopherol and the like.

(i) An oral formulation may be prepared by
combining a compound of the invention or its salt with
20 an excipient, if necessary adding a binder,
disintegrator, lubricant, coloring agent, corrective
coating or the like, and forming a powder, fine
particles, granules, tablets, coated tablets, capsules,
etc. by a common method. (ii) Tablets or granules may,
25 of course, also be coated with a sugar coating,
gelatin coating or other type of suitable coating if

necessary. (iii) In the case of a liquid formulation such as syrup, injection, eye drops or the like, a common method may be used for formulation with a pH adjustor, solubilizer, isotonizing agent or the like, as well as a solubilizing aid, stabilizer, buffering agent, suspending agent, antioxidant, etc. if necessary. In the case of a liquid formulation, it may also be lyophilized, and an injection may be administered intravenously, subcutaneously or intramuscularly. As preferred examples of suspending agents there may be mentioned methylcellulose, polysorbate 80, hydroxyethylcellulose, gum arabic, tragacanth powder, sodium carboxymethylcellulose, polyoxyethylene sorbitan monolaurate and the like; as preferred examples of solubilizing aids there may be mentioned polyoxyethylene hydrogenated castor oil, polysorbate 80, nicotinamide, polyoxyethylene sorbitan monolaurate and the like; as preferred examples of stabilizing agents there may be mentioned sodium sulfite, sodium metasulfite, ether and the like; and as preferred examples of preservatives there may be mentioned methyl p-oxybenzoate, ethyl p-oxybenzoate, sorbic acid, phenol, cresol, chlorocresol, and the like. (iv) There are no particular restrictions on the method of preparing an external application, and any common method may be employed. The base materials

used may be any raw materials commonly employed in drugs, quasi drugs, cosmetics and the like, and as examples there may be mentioned raw materials such as animal and vegetable oils, mineral oils, ester oils, waxes, higher alcohols, fatty acids, silicone oils, surfactants, phospholipids, alcohols, polyhydric alcohols, water-soluble polymers, clay minerals, purified water and the like, with addition of pH adjustors, antioxidants, chelating agents, antiseptics and fungicides, coloring agents, aromas and the like if necessary. Also, there may be included differentiation-inducing components, or other components such as circulation promoters, microbicides, antiphlogistic agents, cell activators, vitamins, amino acids, humectants, keratolytic agents and the like, as necessary.

Although the dosage of a drug according to the invention will differ depending on the patient's severity of symptoms, age, gender and body weight, the dosage form and type of salt, drug sensitivity, the specific type of disease, etc., it will generally be from about 30 μg to 1000 mg, preferably from 100 μg to 500 mg and more preferably from 100 μg to 100 mg per day for adults in the case of oral administration or about 1-3000 $\mu\text{g}/\text{kg}$ and preferably 3-1000 $\mu\text{g}/\text{kg}$ per day for adults in the case of injection, administered once

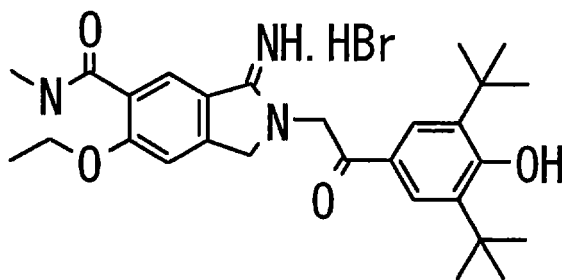
or divided over several times a day.

Examples

Preferred embodiments of the compounds of the invention represented by formula (I) above and salts thereof will now be explained, with the understanding that the following examples and test examples are only representative and are not intended to be restrictive on the compounds of the invention or salts thereof in any way. It will be apparent to those skilled in the art that the present invention can be carried out with various modifications added beyond these examples, and such modifications are also encompassed within the claims of the present specification.

<Example 1>

2-[2-(3,5-Di-tert-butyl-4-hydroxyphenyl)-2-oxo-ethyl]-6-ethoxy-3-imino-2,3-dihydro-1H-isoindole-5-carboxylic acid methylamide hydrobromide



(Step 1) 5-Bromo-2-hydroxy-4-methylbenzoic acid

