



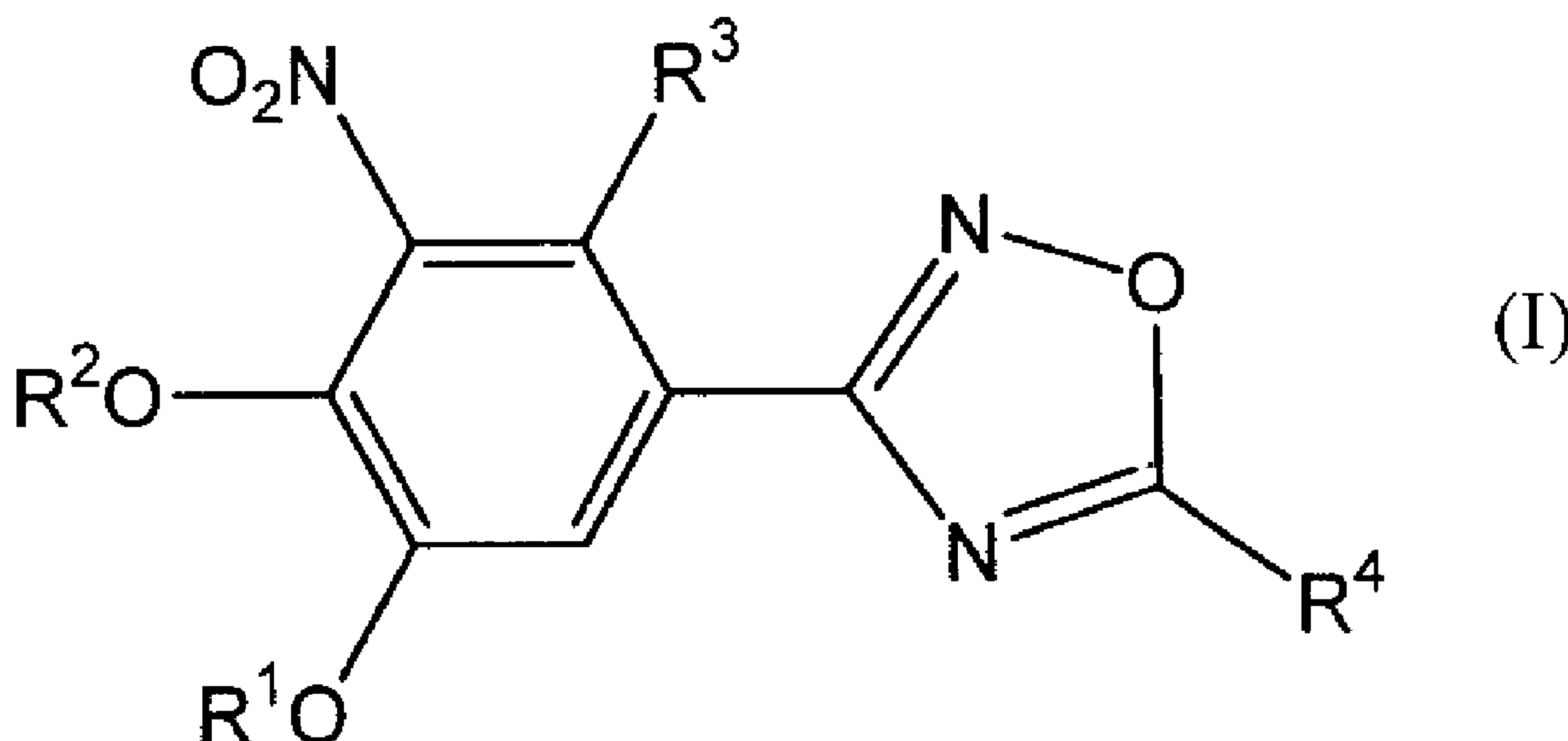
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(54) Title: NOVEL CATECHOL DERIVATIVE, PHARMACEUTICAL COMPOSITION CONTAINING THE SAME, USE OF
THE CATECHOL DERIVATIVE, AND USE OF THE PHARMACEUTICAL COMPOSITION



(57) Abrégé/Abstract:

The present invention provides compounds represented by general formula (I): (see formula I) or pharmaceutical acceptable salts thereof, wherein R^1 and R^2 are each hydrogen, lower acyl, lower alkoxy-carbonyl or the like; R^3 is halo-lower alkyl, lower acyl, halo-lower alkyl-carbonyl, cycloalkyl-carbonyl, optionally substituted aryl-carbonyl, lower alkoxy-carbonyl or the like; R^4 is lower alkyl, halo-lower alkyl, cycloalkyl, lower alkoxy-lower alkyl or the like, which exhibit potent COMT inhibitory activities. The present invention also provides pharmaceutical compositions containing said compound, and uses thereof.

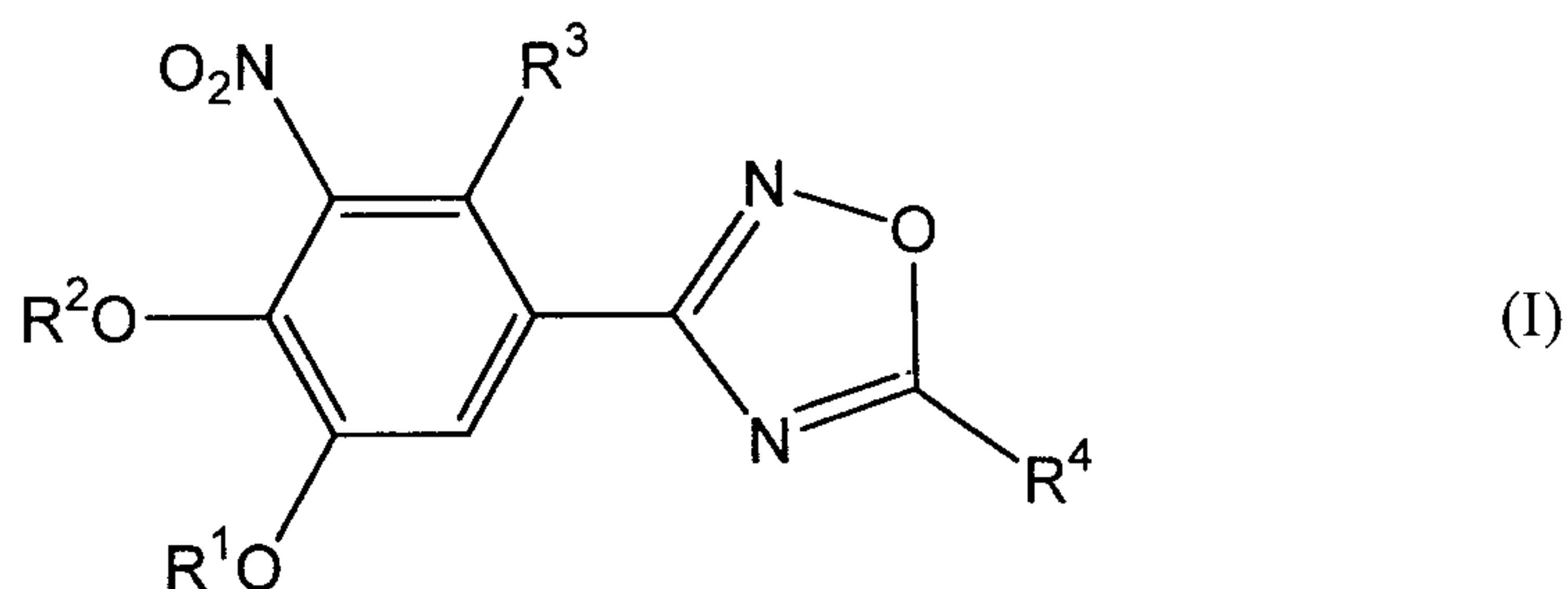
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ABSTRACT

The present invention provides compounds represented by general formula (I):



or pharmaceutical acceptable salts thereof, wherein R^1 and R^2
5 are each hydrogen, lower acyl, lower alkoxycarbonyl or the like;
 R^3 is halo-lower alkyl, lower acyl, halo-lower alkylcarbonyl,
cycloalkylcarbonyl, optionally substituted arylcarbonyl, lower
alkoxycarbonyl or the like; R^4 is lower alkyl, halo-lower alkyl,
cycloalkyl, lower alkoxy-lower alkyl or the like, which exhibit
10 potent COMT inhibitory activities. The present invention also
provides pharmaceutical compositions containing said compound,
and uses thereof.

DESCRIPTION

NOVEL CATECHOL DERIVATIVE, PHARMACEUTICAL COMPOSITION
CONTAINING THE SAME, USE OF THE CATECHOL DERIVATIVE, AND USE
OF THE PHARMACEUTICAL COMPOSITION

5 **TECHNICAL FIELD**

[0001]

The present invention relates to novel catechol derivatives, which exhibit catechol-O-methyltransferase inhibitory activities, pharmaceutical compositions containing
10 the same, and their uses.

BACKGROUND ART

[0002]

Parkinson's disease is a progressive neurodegenerative disease which usually affects elderly patients. The number of
15 parkinsonian patients is growing with progressive aging of society. Parkinson's disease is characterized by impairment in coordinated motor function such as rest tremor, rigidity, akinesia, postural instability and the like. It is thought that Parkinson's disease results from deficiency of dopamine in the
20 striatum, which is caused by degeneration of dopamine neuron in the substantia nigra. For that reasons, L-dopa or dopamine receptor stimulants are used for the treatment of Parkinson's disease.

[0003]

25 L-dopa is a precursor of dopamine, and is metabolized to dopamine which exerts its efficacy in the brain. Since L-dopa has a very short serum half-life, L-dopa is administered usually

in combination with a peripheral aromatic L-amino acid decarboxylase inhibitor and/or a catechol-O-methyltransferase inhibitor, which inhibit the metabolism of L-dopa in the body. Catechol-O-methyltransferase (hereinafter referred to as

5 "COMT") is an enzyme that catalyze the transfer of the methyl group of S-adenosyl-L-methionine to catechol substrates. The inhibition of the COMT enzyme slows down the metabolism of L-dopa to 3-O-methyl-L-dopa, which results in the significant increase in serum half-life of L-dopa and the amount of L-dopa crossing

10 the blood-brain-barrier. In this way, a COMT inhibitor, when administered in combination with L-dopa, increases the bioavailability of L-dopa and prolongs its effects (see Non Patent Literature 1).

[0004]

15 COMT inhibitors are also expected to be useful for treating or preventing hypertension since COMT inhibitors exhibit urinary sodium excretion promoting activities (see Non Patent Literature 2). COMT inhibitors are also expected to be useful for treating or preventing depression (see Non Patent Literature 3).

20 [0005]

A variety of COMT inhibitors have been reported recently. Among them, tolcapone (3,4-dihydroxy-4'-methyl-5-nitro-benzophenone, Patent Literature 1) and entacapone ((E)-2-cyano-N,N-diethyl-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide,

25 Patent Literature 2) are the most potent COMT inhibitors known to date. Tolcapone or entacapone are clinically administered to patients for treating Parkinson's disease. However, it has

been reported that tolcapone causes severe liver function damage, and can only be used in parkinsonian patients strictly with regular monitoring of liver function (see Non Patent Literature 4). On the other hand, entacapone has less potent efficacy than tolcapone, and has a problem to have a very limited duration of effect (see Non Patent Literature 5). Accordingly, there is still a need for novel COMT inhibitors with potent COMT inhibitory activities and a desirable safety profile.

[0006]

Patent Literature 1 discloses 5-(3-methyl-1,2,4-oxadiazol-5-yl)-3-nitropyrocatechol as an [1,2,4]oxadiazole derivative having COMT inhibitory activities (see example 75 in Patent Literature 1). However, the binding position of the 1,2,4-oxadiazole ring to nitro catechol moiety in the compounds of Patent Literature 1 is different from those in compounds of the present invention.

Citation List

[Patent Literature]

1. Publication of Unexamined Application of European Patent Specification No.237929
2. Publication of Unexamined Application of British Patent Specification No.2200109

[Non Patent Literature]

1. Nutt J.G. et al, "Lancet", 1998, vol.351, No.9111, p.1221-1222
2. Eklof A.C. et al, "Kidney Int.", 1997, vol.52, No.3, p.742-747

3. Moreau J.L. et al, "Behav. Pharmacol.", 1994, vol.5, No.3,
p.344-350
4. Benabou R. et al, "Expert Opin. Drug Saf.", 2003, vol.2,
No.3, p.263-267
5. Forsberg M. et al, "J. Pharmacol. Exp. Ther.", 2003, vol.304,
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6. Koga K. et al, "Eur. J. Pharmacol.", 2000, vol.408, p.249-255

DISCLOSURE OF THE INVENTION

[0007]

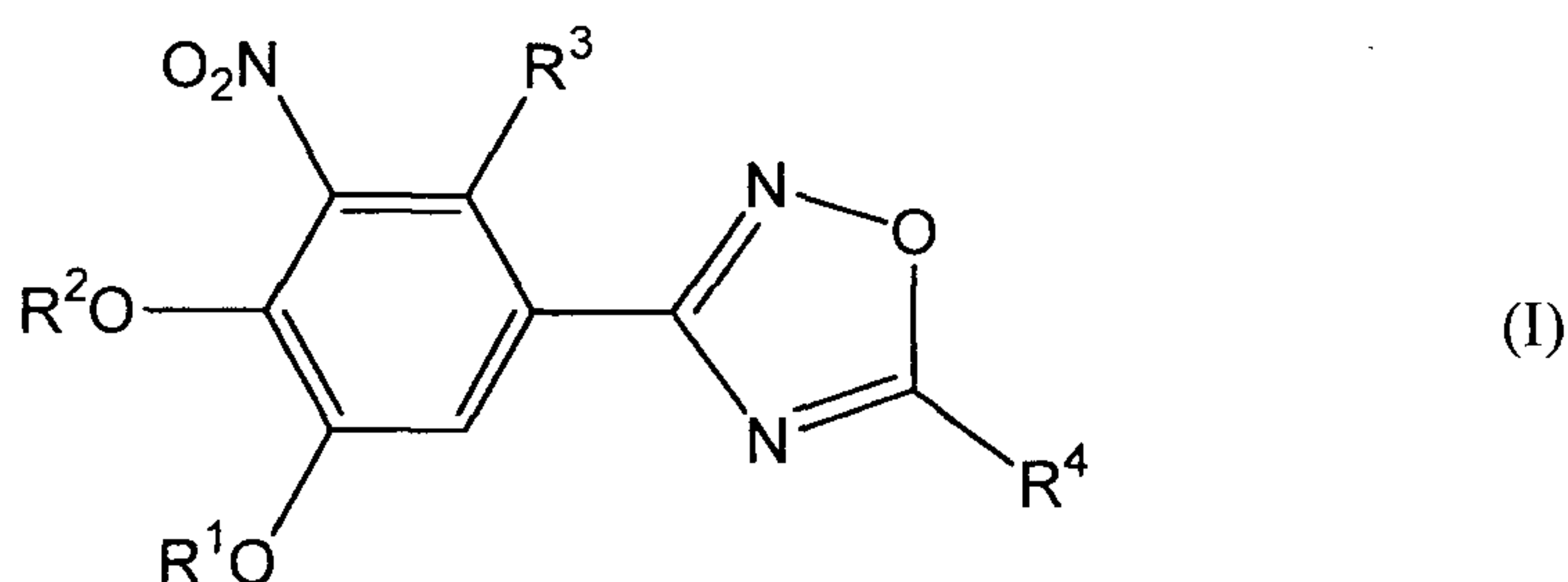
10 An object of the present invention is to provide a novel compound having potent COMT inhibitory activities, and more preferably possessing a desirable safety profile.

[0008]

The inventors of the present invention diligently worked
15 to achieve the foregoing object and found that catechol derivatives represented by general formula (I) show excellent COMT inhibitory activities and possess high safety. Based on these findings, the present invention has been accomplished.

[0009]

20 The present invention therefore provides a compound represented by general formula (I):



or a pharmaceutically acceptable salt thereof,

wherein

R^1 and R^2 are each independently a hydrogen atom, a (C₁₋₆ alkyl)-CO- group, a (C₁₋₆ alkoxy)-C(O)- group, an aralkylcarbonyl group or -C(O)NR¹¹R¹², or R^1 and R^2 are joined
5 together to form -C(O)- or a C₁₋₆ alkylene group;

R^3 is:

- a) a halo C₁₋₆ alkyl group,
- b) a (C₁₋₆ alkyl)-CO- group,
- c) a (halo-C₁₋₆ alkyl)-C(O)- group,
- 10 d) a cycloalkylcarbonyl group,
- e) an arylcarbonyl group, wherein the ring of the arylcarbonyl group is unsubstituted or substituted with 1 to 5 substituents, said substituent is independently a halogen atom, a C₁₋₆ alkyl group, a halo-C₁₋₆ alkyl group, a C₁₋₆
15 alkoxy group, a cycloalkyl C₁₋₆ alkoxy group, a hydroxy group, a (C₁₋₆ alkoxy)-C(O)- group, -C(O)NR¹¹R¹² or a cyano group,
- f) a heteroarylcarbonyl group, wherein the ring of the heteroarylcarbonyl group is unsubstituted or substituted
20 with 1 to 3 substituents, said substituent is independently a halogen atom, a C₁₋₆ alkyl group, a halo-C₁₋₆ alkyl group or a C₁₋₆ alkoxy group,
- g) an aralkylcarbonyl group, wherein the ring of the aralkylcarbonyl group is unsubstituted or substituted with 1
25 to 5 substituents, said substituent is independently a halogen atom, a C₁₋₆ alkyl group, a halo-C₁₋₆ alkyl group or a C₁₋₆ alkoxy group,
- h) an (aryloxy-C₁₋₆ alkyl)-C(O)-group, wherein the ring of the (aryloxy-C₁₋₆ alkyl)-C(O)-group is unsubstituted or
30 substituted with 1 to 5 substituents, said substituent is

independently a halogen atom, a C₁₋₆ alkyl group, a halo-C₁₋₆ alkyl group or a C₁₋₆ alkoxy group,

i) a (C₁₋₆ alkoxy)-C(O)- group,

j) a cycloalkyloxycarbonyl group,

5 k) a (C₁₋₆ alkoxy-C₁₋₆ alkoxy)-C(O)- group,

l) a carboxy group,

m) a cyano group,

n) -C(O)NR¹¹R¹²,

o) -C(O)C(O)NR¹¹R¹²,

10 p) a C₁₋₆ alkylsulfonyl group,

q) -SO₂NR¹¹R¹² or

r) a heteroaryl group, wherein the ring of the heteroaryl group is unsubstituted or substituted with 1 to 3 substituents, said substituent is independently a halogen

15 atom, a C₁₋₆ alkyl group, a halo-C₁₋₆ alkyl group or a C₁₋₆ alkoxy group;

R⁴ is:

a) a C₁₋₆ alkyl group,

b) a halo-C₁₋₆ alkyl group,

20 c) a cycloalkyl group,

d) a heterocycloalkyl group,

e) a C₁₋₆ alkoxy- C₁₋₆ alkyl group,

f) an aryloxy-C₁₋₆ alkyl group,

g) a (C₁₋₆ alkoxy)-C(O)- C₁₋₆ alkyl group or

25 h) a hydroxy C₁₋₆ alkyl group; and

R¹¹ and R¹² are each independently a hydrogen atom, a C₁₋₆ alkyl group, a cycloalkyl group, a bridged cyclic hydrocarbon group, a phenyl group or an aralkyl group, or R¹¹ and R¹², together with the nitrogen atom to which they are
30 bonded, form a cyclic amino group.

[0010]

In another aspect, the present invention provides a pharmaceutical composition which comprises, as an active ingredient, a compound of general formula (I) or a
5 pharmaceutically acceptable salt thereof.

[0011]

In still another aspect, the present invention provides a catechol-O-methyltransferase inhibitor which comprises, as an active ingredient, a compound of general formula (I) or a
10 pharmaceutically acceptable salt thereof.

[0012]

In still another aspect, the present invention provides a pharmaceutical combination which comprises a compound of general formula (I) or a pharmaceutically acceptable salt
15 thereof and at least one selected from L-dopa or an aromatic L-amino acid decarboxylase inhibitor.

[0013]

In still another aspect, the present invention provides a therapeutic or prophylactic agent for Parkinson's disease, depression or hypertension, which comprises, s an active
20 ingredient, a compound of general formula (I) or a pharmaceutically acceptable salt thereof.

[0014]

In still another aspect, the present invention provides a use of a compound represented by general formula (I) or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating or preventing Parkinson's disease, depression or hypertension.

[0015]

In still another aspect, the present invention provides a method for treating or preventing Parkinson's disease, depression or hypertension, which comprises administering an effective amount of a compound represented by general formula (I) or a pharmaceutically acceptable salt thereof.

[0016]

The invention is described using the terms defined below unless otherwise specified.

[0017]

The term "lower" herein denotes residues with 1 to 6 carbon atoms unless otherwise specified.

[0018]

The term "halogen atom" refers to a fluorine, chlorine, bromine or iodine atom.

[0019]

The term "lower alkyl group" refers to a straight chained or branched C₁₋₆ alkyl group such as a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, tert-pentyl, 1-methylbutyl, 2-methylbutyl, 1,2-dimethylpropyl, hexyl, isohexyl group and the like. Preferred lower alkyl groups for R⁴, R¹¹ and R¹² are

a C₁₋₄ alkyl group, and more preferably a methyl group.

[0020]

The term "halo-lower alkyl group" refers to a C₁₋₆ alkyl group substituted with the same or different 1 to 3 halogen atoms
5 such as a fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl group and the like, preferably a difluoromethyl or trifluoromethyl group.

[0021]

The term "hydroxy-lower alkyl group" refers to a hydroxy-
10 C₁₋₆ alkyl group such as a hydroxymethyl, 1-hydroxyethyl, 1-hydroxy-1,1-dimethylmethyl, 2-hydroxyethyl, 2-hydroxy-2-methylpropyl, 3-hydroxypropyl group and the like.

[0022]

The term "lower alkoxy group" refers to a straight chained
15 or branched C₁₋₆ alkoxy group such as a methoxy, ethoxy, propoxy, isopropoxy, butoxy isobutoxy, sec-butoxy, tert-butoxy, pentyloxy, hexyloxy group and the like.

[0023]

The term "cycloalkyl group" refers to a 3- to 7-membered
20 saturated cyclic hydrocarbon such as a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl group.

[0024]

The term "heterocycloalkyl group" refers to a 4- to
7-membered saturated heterocyclic group which contains -NH-,
25 -O- or -S- as a member of the ring and is bonded via a carbon atom. Examples of heterocycloalkyl groups include a tetrahydrofuryl, tetrahydrothienyl, tetrahydropyranyl,

pyrrolidin-2-yl, pyrrolidin-3-yl, piperidin-2-yl,
piperidin-3-yl, piperidin-4-yl group and the like.

[0025]

The term "bridged cyclic hydrocarbon group" refers to a
5 5- to 7-membered bridged saturated cyclic hydrocarbon having 7
to 10 carbon atoms such as a bicyclo[2.2.1]heptan-2-yl,
adamantan-1-yl group and the like.

[0026]

The term "aryl group" refers to a C₆₋₁₀ aromatic hydrocarbon
10 group such as a phenyl, 1-naphtyl and 2-naphthyl group,
preferably a phenyl group.

[0027]

The term "aralkyl group" refers to an aryl-C₁₋₆ alkyl group
such as a benzyl, phenethyl, 1-phenylethyl, 3-phenylpropyl,
15 4-phenylbutyl, naphthylmethyl group and the like.

[0028]

The term "cycloalkyl-lower alkoxy group" refers to a
cycloalkyl-C₁₋₆ alkoxy group such as a cyclopropylmethoxy,
cyclopentylmethoxy, cyclohexylmethoxy group and the like.

20 [0029]

The term "heteroaryl group" refers to a 5- or 6-membered
monocyclic aromatic heterocycle having 1 to 5 carbon atoms and
1 to 4 heteroatoms selected independently from the group
consisting of an oxygen, nitrogen and sulfur atom, or a 8- to
25 10-membered bicyclic aromatic heterocycle having 1 to 9 carbon
atoms and 1 to 4 heteroatoms selected independently from the
group consisting of an oxygen, nitrogen and sulfur atom, provided

that said heterocycles do not include adjacent oxygen and/or sulfur atoms. Examples of monocyclic heteroaryl groups include pyrrolyl, furyl, thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, 1,2,4-oxadiazolyl, tetrazolyl, thiazolyl, isothiazolyl, 1,2,3-thiadiazolyl, triazolyl, pyridyl, pyrazinyl, pyrimidyl and pyridazinyl, preferably pyridyl, thiazoryl or 1,2,4-oxadiazolyl. Examples of bicyclic heteroaryl groups include indolyl, indazolyl, benzofuranyl, benzothienyl, benzothiazolyl, quinolyl, isoquinolyl, phthalazinyl, benzimidazolyl, benzoxazolyl and the like. The heterocycles include all position isomers such as 2-pyridyl, 3-pyridyl or 4-pyridyl.

[0030]

The term "lower alkoxy-lower alkyl group" refers to a C₁₋₆ alkoxy-C₁₋₆ alkyl group such as a methoxymethyl, 2-methoxyethyl, ethoxymethyl, 2-ethoxyethyl group and the like, preferably a methoxymethyl or 2-ethoxyethyl group.

[0031]

The term "aryloxy-lower alkyl group" refers to an aryloxy-C₁₋₆ alkyl group such as a phenoxymethyl, 1-phenoxyethyl, 2-phenoxyethyl, 1-methyl-1-phenoxyethyl, 3-phenoxypropyl, naphthyloxymethyl group and the like.

[0032]

The term "lower acyl group" refers to a (C₁₋₆ alkyl)-CO-group such as an acetyl, propionyl, butyryl, isobutyryl, pivaloyl, valeryl, isovaleryl group and the like.

[0033]

The term "halo-lower alkylcarbonyl group" refers to a (halo-C₁₋₆ alkyl)-C(O)- group such as trifluoroacetyl, trichloroacetyl group and the like.

[0034]

5 The term "cycloalkylcarbonyl group" refers to a (cycloalkyl)-C(O)- group such as a cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl group and the like.

[0035]

10 The term "arylcarbonyl group" refers to a (aryl)-C(O)- group such as a benzoyl group and the like.

Examples of "arylcarbonyl group, wherein the ring of the arylcarbonyl group is unsubstituted or substituted with 1 to 5 substituents selected from the group consisting of a halogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a cycloalkyl-lower alkoxy group, a hydroxy group, 15 a lower alkoxy carbonyl group, -C(O)NR¹¹R¹² and a cyano group" for R³ include a benzoyl, 2-fluorobenzoyl, 3-fluorobenzoyl, 4-fluorobenzoyl, 2,4-difluorobenzoyl, 4-chlorobenzoyl, 20 2-methylbenzoyl, 3-methylbenzoyl, 4-methylbenzoyl, 2-methoxybenzoyl, 3-methoxybenzoyl, 4-methoxybenzoyl, 4-hydroxybenzoyl, 4-cyanobenzoyl, 4-methoxycarbonylbenzoyl, 4-ethoxycarbonylbenzoyl, 4-cyclopropylmethylbenzoyl group and the like, preferably a benzoyl, 2-fluorobenzoyl or 25 4-hydroxybenzoyl group, and more preferably a benzoyl group.

[0036]

The term "heteroarylcarbonyl group" refers to a

(heteroaryl)-C(O)- group such as a 2-furylcarbonyl, 2-thienylcarbonyl, 2-oxazolylcarbonyl, 2-thiazolylcarbonyl, 5-isoxazolylcarbonyl, 2-pyridylcarbonyl, 3-pyridylcarbonyl, 4-pyridylcarbonyl group and the like.

5 [0037]

The term "aralkylcarbonyl group" refers to an (aralkyl)-C(O)- group such as a benzylcarbonyl, 2-phenylethylcarbonyl group and the like.

[0038]

10 The term "aryloxy-lower alkylcarbonyl group" refers to a (aryloxy-C₁₋₆ alkyl)-C(O)- group such as a phenoxymethylcarbonyl group and the like.

[0039]

The term "lower alkoxy carbonyl group" refers to a (C₁₋₆ alkoxy)-C(O)- group such as a methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, pentyloxy carbonyl, hexyloxy carbonyl group and the like.

[0040]

20 The term "cycloalkyloxy carbonyl group" refers to a (cycloalkyl)-O-C(O)- group such as a cyclopentyloxy carbonyl, cyclohexyloxy carbonyl group and the like.

[0041]

Ther term "lower alkoxy-lower alkoxy carbonyl group" refers to a (C₁₋₆ alkoxy-C₁₋₆ alkoxy)-C(O)- group such as 2-methoxyethoxycarbonyl, 2-ethoxyethoxycarbonyl, 3-methoxypropoxycarbonyl group and the like.

[0042]

The term "lower alkoxy carbonyl-lower alkyl group" refers to a (C₁₋₆ alkoxy)-C(O)-C₁₋₆ alkyl group such as a methoxycarbonylmethyl, ethoxycarbonylmethyl, 2-(ethoxy-carbonyl)ethyl group and the like.

[0043]

The term "lower alkylsulfonyl group" refers to a (C₁₋₆ alkyl)-SO₂- group such as a methanesulfonyl, ethanesulfonyl, propanesulfonyl, butanesulfonyl, pentanesulfonyl, hexanesulfonyl group and the like, preferable a methanesulfonyl group.

[0044]

The term "cyclic amino group" refers to a 5- to 7-membered saturated cyclic amine which may contain -NH-, -O- or -S- as a member of the ring. Examples of cyclic amino groups include a 1-pyrrolidyl, piperidino, piperazino, morpholino, thiomorpholino group. The cyclic amino group may be optionally substituted with one or two alkyl group.

20 [0045]

The term "lower alkylene group" refers to a bivalent saturated C₁₋₆ hydrocarbon chain, which may be straight chained or branched. Examples of lower alkylene groups include -CH₂-, -CH₂CH₂-, -CH(CH₃)-, -CH(CH₃)CH₂-, -CH₂CH(CH₃)-, -C(CH₃)₂- and the like, preferably -CH(CH₃)- or -C(CH₃)₂-.

[0046]

In the case where a compound represented by general formula

(I) contains one or more asymmetric carbons, then all stereoisomers in the R- or S-configuration at each of asymmetric carbons and their mixture are contemplated within the scope of the present invention. In such cases, racemic compounds, racemic
5 mixtures, individual enantiomers and mixtures of diastereomers are also contemplated within the scope of the present invention.

In the case where a compound represented by general formula (I) exists in one or more geometrical isomers, then all geometrical isomers are also contemplated within the scope of
10 the present invention.

In the case where a compound represented by general formula (I) exists in one or more atrop-isomers, then all atrop-isomers are also contemplated within the scope of the present invention.

A compound represented by general formula (I) may form
15 a solvate with a pharmaceutically acceptable solvent such as water, ethanol and the like.

[0047]

Compounds represented by general formula (I) may exist in the form of salts. Examples of such salts include acid addition
20 salts formed with mineral acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, phosphoric acid and the like; acid addition salts formed with organic acids such as formic acid, acetic acid, trifluoroacetic acid, methanesulfonic acid, benzenesulfonic acid,
25 p-toluenesulfonic acid, propionic acid, citric acid, succinic acid, tartaric acid, fumaric acid, butyric acid, oxalic acid, malonic acid, maleic acid, lactic acid, malic acid, carbonic

acid, glutamic acid, aspartic acid and the like; basic salts formed with inorganic bases such as lithium, sodium, potassium, calcium, magnesium and the like; basic salts formed with organic bases such as triethylamine, piperidine, morpholine, lysine and
5 the like.

[0048]

In an embodiment of a compound represented by general formula (I) of the present invention,

preferably R^1 and R^2 are each independently a hydrogen
10 atom, a lower acyl group, a lower alkoxy carbonyl group or $-C(O)NR^{11}R^{12}$, or R^1 and R^2 are joined together to form $-C(O)-$, and more preferably R^1 and R^2 are a hydrogen atom;

R^3 is preferably:

- a) a halo-lower alkyl group,
- 15 b) a lower acyl group,
- c) a halo-lower alkyl carbonyl group,
- d) a cycloalkyl carbonyl group,
- e) an aryl carbonyl group, wherein the ring of the aryl carbonyl group is unsubstituted or substituted with 1 to 5 substituents
20 selected from the group consisting of a halogen atom, a lower alkyl group, a halo-lower alkyl group and a lower alkoxy group,
- f) a heteroaryl carbonyl group, wherein the ring of the heteroaryl carbonyl group is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of a halogen
25 atom, a lower alkyl group, a halo-lower alkyl group and a lower alkoxy group,
- g) an aralkyl carbonyl group, wherein the ring of the

aralkylcarbonyl group is unsubstituted or substituted with 1 to 5 substituents selected from the group consisting of a halogen atom, a lower alkyl group, a halo-lower alkyl group and a lower alkoxy group,

5 h) an aryloxy-lower alkylcarbonyl group, wherein the ring of the aryloxy-lower alkylcarbonyl group is unsubstituted or substituted with 1 to 5 substituents selected from the group consisting of a halogen atom, a lower alkyl group, a halo-lower alkyl group and a lower alkoxy group,

10 i) a lower alkoxycarbonyl group,

j) a cycloalkyloxycarbonyl group,

k) a lower alkoxy-lower alkoxycarbonyl group,

l) a carboxy group,

m) a cyano group,

15 n) $-C(O)NR^{11}R^{12}$,

o) $-C(O)C(O)NR^{11}R^{12}$,

p) a lower alkylsulfonyl group,

q) $-SO_2NR^{11}R^{12}$ or

r) a heteroaryl group, wherein the ring of the heteroaryl group
20 is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of a halogen atom, a lower alkyl group, a halo-lower alkyl group and a lower alkoxy group,

more preferably R^3 is:

a) a lower acyl group,

25 b) a halo-lower alkylcarbonyl group,

c) a cycloalkylcarbonyl group,

d) an arylcarbonyl group, wherein the ring of the arylcarbonyl

group is unsubstituted or substituted with 1 to 5 substituents selected from the group consisting of a halogen atom, a lower alkyl group, a halo-lower alkyl group and a lower alkoxy group,

5 e) a heteroarylcarbonyl group, wherein the ring of the heteroarylcarbonyl group is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of a halogen atom, a lower alkyl group, a halo-lower alkyl group and a lower alkoxy group,

10 f) an aralkylcarbonyl group, wherein the ring of the aralkylcarbonyl group is unsubstituted or substituted with 1 to 5 substituents selected from the group consisting of a halogen atom, a lower alkyl group, a halo-lower alkyl group and a lower alkoxy group,

15 g) an aryloxy-lower alkylcarbonyl group, wherein the ring of the aryloxy-lower alkylcarbonyl group is unsubstituted or substituted with 1 to 5 substituents selected from the group consisting of a halogen atom, a lower alkyl group, a halo-lower alkyl group and a lower alkoxy group,

h) a lower alkoxycarbonyl group,

20 i) a cycloalkyloxycarbonyl group,

j) a lower alkoxy-lower alkoxycarbonyl group,

k) $-C(O)C(O)NR^{11}R^{12}$ or

l) a lower alkylsulfonyl group,

even more preferably R^3 is:

25 a) a lower acyl group,

b) a cycloalkylcarbonyl group,

c) an arylcarbonyl group, wherein the ring of the arylcarbonyl

group is unsubstituted or substituted with 1 to 5 substituents selected from the group consisting of a halogen atom, a lower alkyl group, a halo-lower alkyl group and a lower alkoxy group,

d) a lower alkoxycarbonyl group,

5 e) a cycloalkyloxycarbonyl group,

f) a lower alkoxy-lower alkoxycarbonyl group or

g) $-C(O)C(O)NR^{11}R^{12}$, and

especially preferably R^3 is:

a) a lower acyl group,

10 b) a cycloalkylcarbonyl group,

c) an arylcarbonyl group, wherein the ring of the arylcarbonyl group is unsubstituted or substituted with 1 to 5 substituents selected from the group consisting of a halogen atom, a lower alkyl group, a halo-lower alkyl group and a lower alkoxy group,

15 d) a lower alkoxycarbonyl group or

e) $-C(O)C(O)NR^{11}R^{12}$;

R^4 is preferably:

a) a lower alkyl group,

b) a halo-lower alkyl group,

20 c) a cycloalkyl group,

d) a heterocycloalkyl group,

e) a lower alkoxy-lower alkyl group,

f) an aryloxy-lower alkyl group or

g) a lower alkoxycarbonyl-lower alkyl group, and

25 more preferably R^4 is:

a) a lower alkyl group,

b) a cycloalkyl group,

c) a lower alkoxy-lower alkyl group or

d) a lower alkoxycarbonyl-lower alkyl group; or

preferably R^{11} and R^{12} are each independently a hydrogen atom, a lower alkyl group, a cycloalkyl group, a bridged cyclic hydrocarbon group or a phenyl group.

[0049]

In a preferable embodiment of the present invention,

R^1 and R^2 are each independently a hydrogen atom, a lower acyl group, a lower alkoxycarbonyl group or $-C(O)NR^{11}R^{12}$, or R^1 and R^2 are joined together to form $-C(O)-$;

R^3 is:

a) a halo-lower alkyl group,

b) a lower acyl group,

c) a halo-lower alkylcarbonyl group,

d) a cycloalkylcarbonyl group,

e) an arylcarbonyl group, wherein the ring of the arylcarbonyl group is unsubstituted or substituted with 1 to 5 substituents selected from the group consisting of a halogen atom, a lower alkyl group, a halo-lower alkyl group and a lower alkoxy group,

f) a heteroarylcarbonyl group, wherein the ring of the heteroarylcarbonyl group is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of a halogen atom, a lower alkyl group, a halo-lower alkyl group and a lower alkoxy group,

g) an aralkylcarbonyl group, wherein the ring of the aralkylcarbonyl group is unsubstituted or substituted with 1 to 5 substituents selected from the group consisting of a halogen

atom, a lower alkyl group, a halo-lower alkyl group and a lower alkoxy group,

h) an aryloxy-lower alkylcarbonyl group, wherein the ring of the aryloxy-lower alkylcarbonyl group is unsubstituted or substituted with 1 to 5 substituents selected from the group consisting of a halogen atom, a lower alkyl group, a halo-lower alkyl group and a lower alkoxy group,

i) a lower alkoxy carbonyl group,

j) a cycloalkyloxy carbonyl group,

10 k) a lower alkoxy-lower alkoxy carbonyl group,

l) a carboxy group,

m) a cyano group,

n) $-C(O)NR^{11}R^{12}$,

o) $-C(O)C(O)NR^{11}R^{12}$,

15 p) a lower alkylsulfonyl group,

q) $-SO_2NR^{11}R^{12}$ or

r) a heteroaryl group, wherein the ring of the heteroaryl group is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of a halogen atom, a lower alkyl group, a halo-lower alkyl group and a lower alkoxy group;

R^4 is:

a) a lower alkyl group,

b) a halo-lower alkyl group,

c) a cycloalkyl group,

25 d) a heterocycloalkyl group,

e) a lower alkoxy-lower alkyl group,

f) an aryloxy-lower alkyl group or

g) a lower alkoxy carbonyl-lower alkyl group; and

R^{11} and R^{12} are each independently a hydrogen atom, a lower alkyl group, a cycloalkyl group, a bridged cyclic hydrocarbon group, a phenyl group or an aralkyl group, or R^{11} and R^{12} , together
5 with the nitrogen atom to which they are bonded, form a cyclic amino group.

[0050]

In a more preferable embodiment of the present invention,

R^1 and R^2 are a hydrogen atom,

10 R^3 is:

- a) a halo-lower alkyl group,
- b) a lower acyl group,
- c) a halo-lower alkyl carbonyl group,
- d) a cycloalkyl carbonyl group,

15 e) an aryl carbonyl group, wherein the ring of the aryl carbonyl group is unsubstituted or substituted with 1 to 5 substituents selected from the group consisting of a halogen atom, a lower alkyl group, a halo-lower alkyl group and a lower alkoxy group,

f) a heteroaryl carbonyl group, wherein the ring of the
20 heteroaryl carbonyl group is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of a halogen atom, a lower alkyl group, a halo-lower alkyl group and a lower alkoxy group,

g) an aralkyl carbonyl group, wherein the ring of the
25 aralkyl carbonyl group is unsubstituted or substituted with 1 to 5 substituents selected from the group consisting of a halogen atom, a lower alkyl group, a halo-lower alkyl group and a lower

alkoxy group,

h) an aryloxy-lower alkylcarbonyl group, wherein the ring of the aryloxy-lower alkylcarbonyl group is unsubstituted or substituted with 1 to 5 substituents selected from the group
5 consisting of a halogen atom, a lower alkyl group, a halo-lower alkyl group and a lower alkoxy group,

i) a lower alkoxycarbonyl group,

j) a cycloalkyloxycarbonyl group,

k) a lower alkoxy-lower alkoxycarbonyl group,

10 l) a carboxy group,

m) a cyano group,

n) $-C(O)NR^{11}R^{12}$,

o) $-C(O)C(O)NR^{11}R^{12}$,

p) a lower alkylsulfonyl group,

15 q) $-SO_2NR^{11}R^{12}$ or

r) a heteroaryl group, wherein the ring of the heteroaryl group is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of a halogen atom, a lower alkyl group, a halo-lower alkyl group and a lower alkoxy group;

20 R^4 is:

a) a lower alkyl group,

b) a halo-lower alkyl group,

c) a cycloalkyl group,

d) a heterocycloalkyl group,

25 e) a lower alkoxy-lower alkyl group,

f) an aryloxy-lower alkyl group or

g) a lower alkoxycarbonyl-lower alkyl group; and

R^{11} and R^{12} are each independently a hydrogen atom, a lower alkyl group, a cycloalkyl group, a bridged cyclic hydrocarbon group, a phenyl group or an aralkyl group, or R^{11} and R^{12} , together with the nitrogen atom to which they are bonded, form a cyclic
5 amino group.

[0051]

In an even more preferable embodiment of the present invention,

R^1 and R^2 are a hydrogen atom,

10 R^3 is:

a) a lower acyl group,

b) a halo-lower alkylcarbonyl group,

c) a cycloalkylcarbonyl group,

d) an arylcarbonyl group, wherein the ring of the arylcarbonyl
15 group is unsubstituted or substituted with 1 to 5 substituents selected from the group consisting of a halogen atom, a lower alkyl group, a halo-lower alkyl group and a lower alkoxy group,
e) a heteroarylcarbonyl group, wherein the ring of the heteroarylcarbonyl group is unsubstituted or substituted with
20 1 to 3 substituents selected from the group consisting of a halogen atom, a lower alkyl group, a halo-lower alkyl group and a lower alkoxy group,

f) an aralkylcarbonyl group, wherein the ring of the aralkylcarbonyl group is unsubstituted or substituted with 1
25 to 5 substituents selected from the group consisting of a halogen atom, a lower alkyl group, a halo-lower alkyl group and a lower alkoxy group,

g) an aryloxy-lower alkylcarbonyl group, wherein the ring of the aryloxy-lower alkylcarbonyl group is unsubstituted or substituted with 1 to 5 substituents selected from the group consisting of a halogen atom, a lower alkyl group, a halo-lower alkyl group and a lower alkoxy group,

h) a lower alkoxy carbonyl group,

i) a cycloalkyloxy carbonyl group,

j) a lower alkoxy-lower alkoxy carbonyl group,

k) $-C(O)C(O)NR^{11}R^{12}$ or

l) a heteroaryl group, wherein the ring of the heteroaryl group is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of a halogen atom, a lower alkyl group, a halo-lower alkyl group and a lower alkoxy group;

R4 is:

a) a lower alkyl group,

b) a halo-lower alkyl group,

c) a cycloalkyl group,

d) a heterocycloalkyl group,

e) a lower alkoxy-lower alkyl group,

f) an aryloxy-lower alkyl group or

g) a lower alkoxy carbonyl-lower alkyl group; and

R^{11} and R^{12} are each independently a hydrogen atom, a lower alkyl group, a cycloalkyl group, a bridged cyclic hydrocarbon group, a phenyl group or an aralkyl group, or R^{11} and R^{12} , together with the nitrogen atom to which they are bonded, form a cyclic amino group.

[0052]

In another even more preferable embodiment of the present invention,

R^1 and R^2 are a hydrogen atom,

R^3 is:

5 a) a lower acyl group,

b) a halo-lower alkylcarbonyl group,

c) a cycloalkylcarbonyl group,

d) an arylcarbonyl group, wherein the ring of the arylcarbonyl group is unsubstituted or substituted with 1 to 5 substituents selected from the group consisting of a halogen atom, a lower alkyl group, a halo-lower alkyl group and a lower alkoxy group,

10 e) a heteroarylcarbonyl group, wherein the ring of the heteroarylcarbonyl group is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of a halogen atom, a lower alkyl group, a halo-lower alkyl group and a lower alkoxy group,

15 f) an aralkylcarbonyl group, wherein the ring of the aralkylcarbonyl group is unsubstituted or substituted with 1 to 5 substituents selected from the group consisting of a halogen atom, a lower alkyl group, a halo-lower alkyl group and a lower alkoxy group,

20 g) an aryloxy-lower alkylcarbonyl group, wherein the ring of the aryloxy-lower alkylcarbonyl group is unsubstituted or substituted with 1 to 5 substituents selected from the group consisting of a halogen atom, a lower alkyl group, a halo-lower alkyl group and a lower alkoxy group,

25 h) a lower alkoxycarbonyl group,

i) a cycloalkyloxycarbonyl group,

j) a lower alkoxy-lower alkoxy carbonyl group,

k) $-C(O)C(O)NR^{11}R^{12}$ or

l) a heteroaryl group, wherein the ring of the heteroaryl group
5 is unsubstituted or substituted with 1 to 3 substituents selected
from the group consisting of a halogen atom, a lower alkyl group,
a halo-lower alkyl group and a lower alkoxy group; and

R4 is:

a) a lower alkyl group,

10 b) a cycloalkyl group,

c) a lower alkoxy-lower alkyl group, or

d) a lower alkoxy carbonyl-lower alkyl group.

[0053]

In another even more preferable embodiment of the present
15 invention,

R^1 and R^2 are a hydrogen atom,

R^3 is:

a) a lower acyl group,

b) a cycloalkyl carbonyl group,

20 c) an aryl carbonyl group, wherein the ring of the aryl carbonyl
group is unsubstituted or substituted with 1 to 5 substituents
selected from the group consisting of a halogen atom, a lower
alkyl group, a halo-lower alkyl group and a lower alkoxy group,

d) a lower alkoxy carbonyl group,

25 e) a cycloalkyloxycarbonyl group,

f) a lower alkoxy-lower alkoxy carbonyl group, or

g) $-C(O)C(O)NR^{11}R^{12}$; and

R4 is:

- a) a lower alkyl group,
- b) a cycloalkyl group,
- c) a lower alkoxy-lower alkyl group, or
- 5 d) a lower alkoxycarbonyl-lower alkyl group.

[0054]

In an especially preferable embodiment of the present invention,

R^1 and R^2 are a hydrogen atom,

10 R^3 is:

- a) a lower acyl group,
- b) a cycloalkylcarbonyl group,
- c) an arylcarbonyl group, wherein the ring of the arylcarbonyl group is unsubstituted or substituted with 1 to 5 substituents
- 15 selected from the group consisting of a halogen atom, a lower alkyl group, a halo-lower alkyl group and a lower alkoxy group,
- d) a lower alkoxycarbonyl group, or
- e) $-C(O)C(O)NR^{11}R^{12}$; and

R4 is:

- 20 a) a lower alkyl group,
- b) a cycloalkyl group,
- c) a lower alkoxy-lower alkyl group, or
- d) a lower alkoxycarbonyl-lower alkyl group.

[0055]

25 Specific examples of preferred embodiments of the present invention are compounds selected from the group consisting of:

[3,4-dihydroxy-6-(5-methyl-[1,2,4]oxadiazol-3-yl)-2-

nitrophenyl]phenylmethanone;

1-[3,4-dihydroxy-6-(5-methyl-[1,2,4]oxadiazol-3-yl)-2-nitrophenyl]ethanone;

5 methyl 3,4-dihydroxy-6-(5-methyl-[1,2,4]oxadiazol-3-yl)-2-nitrobenzoate;

N-cyclohexyl-2-[3,4-dihydroxy-6-(5-methyl-[1,2,4]oxadiazol-3-yl)-2-nitrophenyl]-2-oxoacetamide;

N-cyclohexyl-2-[3,4-dihydroxy-6-(5-methyl-[1,2,4]oxadiazol-3-yl)-2-nitrophenyl]-N-methyl-2-oxoacetamide;

10 1-{6-[5-(2-ethoxyethyl)-[1,2,4]oxadiazol-3-yl]-3,4-dihydroxy-2-nitrophenyl}ethanone; and

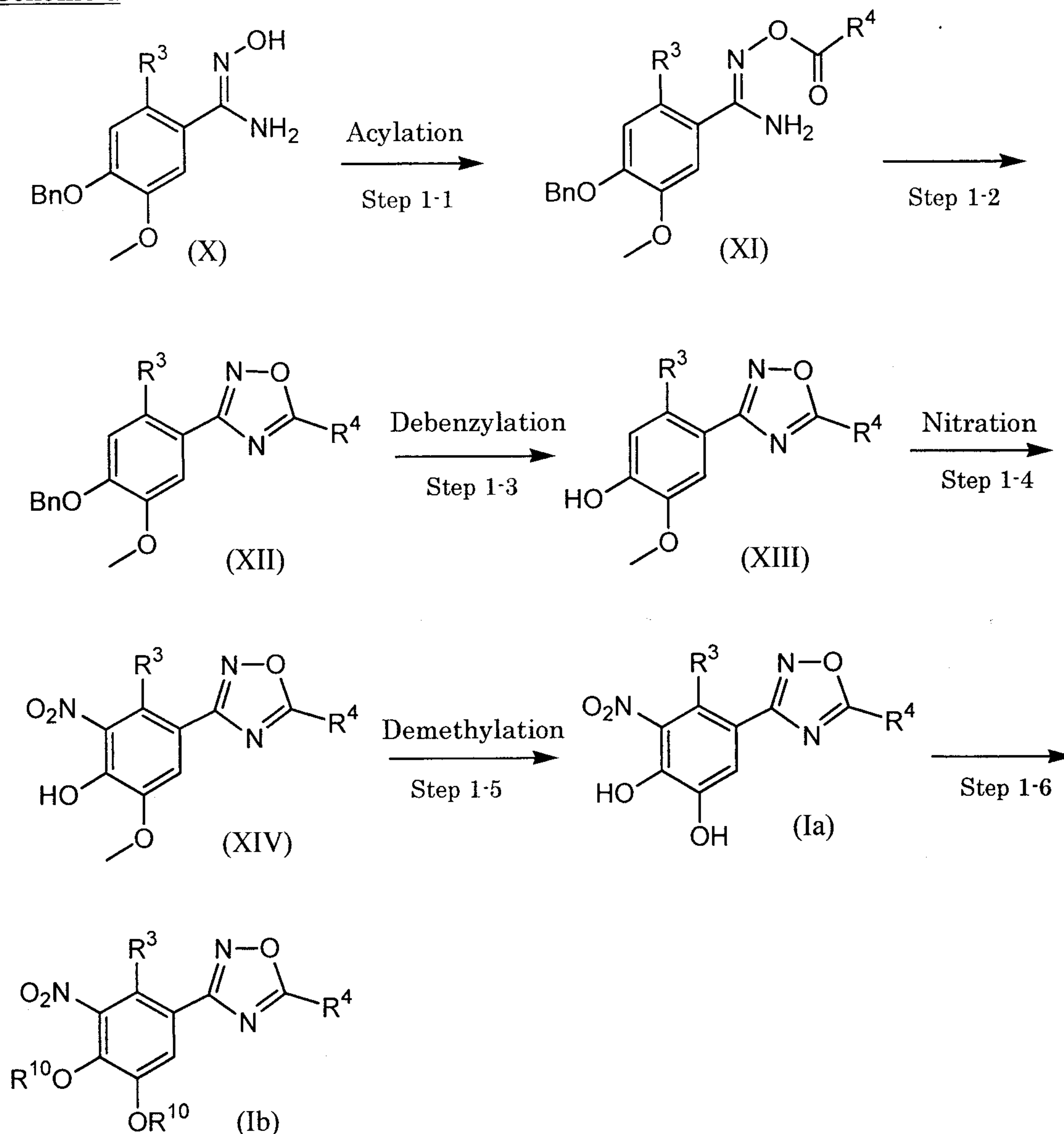
cyclohexyl-[3,4-dihydroxy-6-(5-methyl-[1,2,4]oxadiazol-3-yl)-2-nitrophenyl]methanone.

[0056]

15 Compound represented by general formula (I) can be prepared by the methods as illustrated in schemes 1 to 5.

[0057]

Scheme 1



wherein R³ and R⁴ are as defined above, R¹⁰ is a lower acyl or lower alkoxycarbonyl group or -CONR¹¹R¹², and Bn is a benzyl group.

5 [0058]

Step 1-1

Acylation of amidoxime (X) with an acylating reagent in the presence of a base in an inert solvent or in a base-solvent provides acylamidoxime derivative (XI). The acylating reagents

employed in the acylation reaction include acid halide, acid anhydride, mixed acid anhydride, benzotriazol-1-yl ester, 4-nitrophenyl ester, 2,5-dioxapyrrolidine ester or the like. The bases include triethylamine, pyridine, N,N-diisopropylethylamine or the like. The inert solvents include tetrahydrofuran, methylene chloride or the like. The acylation reaction is carried out ordinarily at -20°C to reflux temperature. The reaction time varies depending on the starting materials employed, the solvent, the reaction temperature or the like, but is usually 15 minutes to 24 hours.

Alternatively, the acylamidoxime derivative (XI) can be prepared by condensing amidoxime (X) with carboxylic acid in the presence of a condensing reagent such as dicyclohexylcarbodiimide, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, ethyl cyanophosphate, diphenylphosphoryl azide or the like. The condensing reaction is carried out ordinarily at -20°C to reflux temperature. The reaction time varies depending on the starting materials employed, the solvent, the reaction temperature or the like, but is usually 15 minutes to 24 hours.

[0059]

Step 1-2

Cyclization of acylamidoxime derivative (XI) in the presence of a base such as pyridine, tetrabutylammonium fluoride or the like in an inert solvent such as tetrahydrofuran or the like provides oxadiazole derivative (XII). The reaction is carried out ordinarily at 0°C to 120°C. The reaction time varies

depending on the starting materials employed, the solvent, the reaction temperature or the like, but is usually 15 minutes to 12 hours.

Alternatively, the oxadiazole derivative (XII) can be
5 prepared by cyclizing acylamidoxime derivative (XI) in a base such as pyridine or the like. The cyclization is carried out ordinarily at 20°C to reflux temperature. The reaction time varies depending on the starting materials employed, the solvent, the reaction temperature or the like, but is usually 15 minutes
10 to 24 hours.

[0060]

Step 1-3

The benzyl group of oxadiazole derivative (XII) is removed in the presence of a metal catalyst such as palladium carbon, platinum oxide or the like under an atmosphere of hydrogen in
15 an inert solvent such as ethanol, N,N-dimethylformamide, tetrahydrofuran or the like to afford phenol derivative (XIII). The reaction is carried out ordinarily at room temperature to 80°C. The reaction time varies depending on the starting
20 materials employed, the solvent, the reaction temperature or the like, but is usually 30 minutes to 12 hours.

Alternatively, the debenzylation reaction can be carried out by treating oxadiazole derivative (XII) with an acid or Lewis acid such as hydrogen bromide, aluminum chloride, titanium
25 tetrachloride or the like in an inert solvent such as methylene chloride, toluene or the like. The reaction is carried out ordinarily at 0°C to 80°C. The reaction time varies depending

on the starting materials employed, the solvent, the reaction temperature or the like, but is usually 15 minutes to 24 hours.

[0061]

Step 1-4

- 5 Nitration of phenol derivative (XIII) with a nitrating reagent in an inert solvent provides nitrophenol derivative (XIV). The inert solvents employed in the reaction include methylene chloride, 1,2-dichloroethane, ethyl acetate, acetic acid, tetrahydrofuran, acetic anhydride or the like. The nitrating
- 10 reagents include nitric acid, fuming nitric acid, nitronium tetrafluoroborate or the like. The reaction is carried out ordinarily at -40°C to 80°C . The reaction time varies depending on the starting materials employed, the solvent, the reaction temperature or the like, but is usually 5 minutes to 12 hours.
- 15 The nitration reaction can also be carried out, if desired, by adding an additive such as sulfuric acid or the like.

[0062]

Step 1-5

- 20 Demethylation of nitrophenol derivative (XIV) with a demethylation reagent in an inert solvent provides compound (Ia). The inert solvents employed in the reaction include ethyl acetate, pyridine, 1,4-dioxane or the like. The demethylation reagents include aluminum chloride-pyridine, boron tribromide or the like. The reaction is carried out ordinarily at -20°C to 120°C . The
- 25 reaction time varies depending on the starting materials employed, the solvent, the reaction temperature or the like, but is usually 1 hour to 24 hours.

Alternatively, the demethylation can be carried out by treating nitrophenol derivative (XIV) with hydrobromic acid or hydroiodic acid in a solvent of acetic acid. The reaction is carried out ordinarily at 20°C to reflux temperature. The reaction time
5 varies depending on the starting materials employed, the reaction temperature or the like, but is usually 1 hour to 24 hours.
[0063]

Step 1-6

Acylation of compound (Ia) with an acylating reagent
10 provides compound (Ib). Such acylation reactions are well known to those ordinarily skilled in the art, and can be carried out according to procedures as described in T.W. Green and P.G.H. Wuts, "Protective Groups in Organic Synthesis" the fourth edition.

15 [0064]

Scheme 2

Scheme 2 illustrates the synthesis of compound (Ic) from compound (XV) through a series of steps:

- Step 2-1 (iodination):** Compound (XV) (3-benzyloxy-4-methoxybenzaldehyde) is iodinated to form compound (XVI) (3-benzyloxy-4-methoxy-2-iodobenzaldehyde).
- Step 2-2:** Compound (XVI) is converted to compound (XVII) (3-benzyloxy-4-methoxy-2-iodobenzaldehyde oxime).
- Step 2-3:** Compound (XVII) is converted to compound (XVIII) (3-benzyloxy-4-methoxy-2-iodobenzaldehyde oxime).
- Step 2-4 (acylation):** Compound (XVIII) is acylated to form compound (XIX) (3-benzyloxy-4-methoxy-2-iodobenzaldehyde oxime, acylated).
- Step 2-5:** Compound (XIX) is converted to compound (XX) (3-benzyloxy-4-methoxy-2-iodobenzaldehyde oxime, acylated).
- Step 2-6:** Compound (XX) is converted to compound (XXI) (3-benzyloxy-4-methoxy-2-iodobenzaldehyde oxime, acylated).
- Step 2-7:** Compound (XXI) is converted to compound (XXII) (3-benzyloxy-4-methoxy-2-iodobenzaldehyde oxime, acylated).
- Step 2-8:** Compound (XXII) is converted to compound (XXIII) (3-benzyloxy-4-methoxy-2-iodobenzaldehyde oxime, acylated).
- Step 2-9:** Compound (XXIII) is converted to compound (XXIV) (3-benzyloxy-4-methoxy-2-iodobenzaldehyde oxime, acylated).
- Step 2-10 (oxidation):** Compound (XXIV) is oxidized to form compound (XXV) (3-benzyloxy-4-methoxy-2-iodobenzaldehyde oxime, acylated).
- Final Step:** Compound (XXV) is converted to compound (Ic) (3-benzyloxy-4-methoxy-2-iodobenzaldehyde oxime, acylated).

wherein R⁴ and Bn are as defined above, R²⁰ represents aryl, lower alkyl, halo-lower alkyl, cycloalkyl, heteroaryl or aralkyl, and

X represents chloro, bromo or $-N(CH_3)OCH_3$.

[0065]

Step 2-1

Iodination of aldehyde derivative (XV) with an
5 iodinating reagent such as iodine, N-iodosuccinimide or iodine
monochloride in an inert solvent such as methylene chloride,
methanol, acetic acid or the like provides iodobenzaldehyde (XVI).
The reaction is carried out ordinarily at 20°C to reflux
temperature. The reaction time varies depending on the starting
10 materials employed, the reaction temperature or the like, but
is usually 15 minutes to 24 hours.

The iodination can be also carried out, if desired, by
adding an additive such as trifluoroacetic acid, silver
trifluoroacetate or the like.

15 [0066]

Step 2-2

Oximation of iodobenzaldehyde (XVI) with hydroxylamine
in an inert solvent such as ethanol, N,N-dimethylformamide,
tetrahydrofuran or the like provides oxime derivative (XVII).
20 The reaction is carried out ordinarily at 20°C to reflux
temperature. The reaction time varies depending on the starting
materials employed, the reaction temperature or the like, but
is usually 15 minutes to 24 hours. The reaction can also be carried
out, if desired, by adding an additive such as sodium acetate,
25 sodium hydroxide or the like.

[0067]

Step 2-3

Chlorination of oxime derivative (XVII) with a chlorinating reagent such as N-chlorosuccinimide in an inert solvent such as N,N-dimethylformamide, tetrahydrofuran or the like provides a N-hydroxybenzimidoyl chloride derivative. The
5 reaction is carried out at 0°C to 80°C. The reaction time varies depending on the starting materials employed, the reaction temperature or the like, but is usually 5 minutes to 24 hours.

The N-hydroxybenzimidoyl chloride derivative is treated with an aminating reagent such as aqueous ammonia or the like
10 in an inert solvent such as N,N-dimethylformamide, tetrahydrofuran or the like to afford amidoxime derivative (XVIII). The reaction is carried out at 0°C to 30°C. The reaction time varies depending on the starting materials employed, the reaction temperature or the like, but is usually 15 minutes to
15 24 hours.

[0068]

Step 2-4

Acylation of amidoxime derivative (XVIII) according to the procedures as described in Step 1-1 provides acylamidoxime
20 derivative (XIX).

[0069]

Step 2-5

Cyclization of acylamidoxime derivative (XIX) according to the procedures as described in Step 1-2 provides oxadiazole
25 derivative (XX).

[0070]

Step 2-6

Oxadiazole derivative (XX) is treated with an organic magnesium reagent in an inert solvent, followed by reaction with aldehyde (XXI) to afford benzylalcohol derivative (XXII). The inert solvents employed in the reaction include tetrahydrofuran or the like. The organic magnesium reagents include isopropyl magnesium chloride or the like. The reaction is carried out ordinarily at -78°C to 10°C . The reaction time varies depending on the starting materials employed, the solvent, the reaction temperature or the like, but is usually 15 minutes to 2 hours.

10 [0071]

Step 2-7

Oxadiazole derivative (XX) is treated with an organic magnesium reagent in an inert solvent, followed by reaction with N,N-dimethylformamide (DMF) to afford aldehyde derivative (XXIII). The inert solvents employed in the reaction include tetrahydrofuran or the like. The organic magnesium reagents include isopropyl magnesium chloride or the like. The reaction is carried out ordinarily at -78°C to 10°C . The reaction time varies depending on the starting materials employed, the solvent, the reaction temperature or the like, but is usually 15 minutes to 2 hours.

[0072]

Step 2-8

Aldehyde derivative (XXIII) is treated with an organic magnesium reagent (XXIV) or an organic lithium reagent (XXV) in an inert solvent such as tetrahydrofuran or the like to afford benzylalcohol derivative (XXII). The reaction is carried out

ordinarily at -78°C to 10°C . The reaction time varies depending on the starting materials employed, the solvent, the reaction temperature or the like, but is usually 15 minutes to 2 hours.
[0073]

5 Step 2-9.

Oxadiazole derivative (XX) is treated with an organic magnesium reagent in an inert solvent, followed by reaction with acid anhydride (XXVI), acid halide or N-methoxy-N-methyl-amide(XXVII) to afford ketone derivative (XXVIII). The inert
10 solvents employed in the reaction include tetrahydrofuran or the like. The organic magnesium reagents include isopropyl magnesium chloride or the like. The reaction is carried out ordinarily at -78°C to 50°C . The reaction time varies depending on the starting materials employed, the solvent, the reaction
15 temperature or the like, but is usually 15 minutes to 2 hours.
[0074]

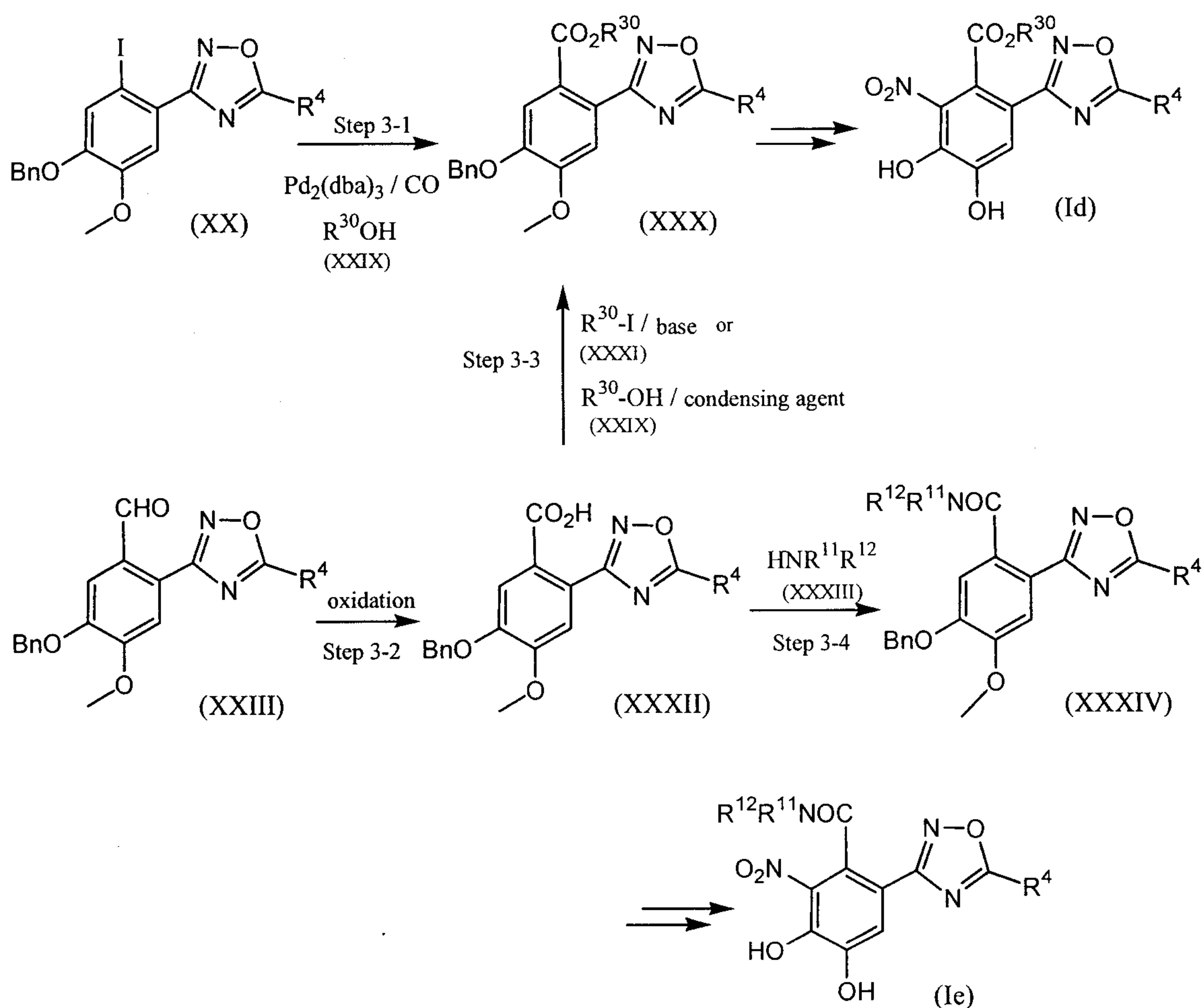
Step 2-10

Oxidation of benzylalcohol derivative (XXII) with an oxidizing agent in a suitable solvent provides ketone derivative
20 (XXVIII). The solvents employed in the reaction include methylene chloride, acetonitrile or the like. The oxidizing agents include manganese dioxide, sulfur trioxide-pyridine complex-dimethylsulfoxide, 4-methylmorpholine-N-oxide or the like. The reaction is carried out ordinarily at 0°C to 30°C .
25 The reaction time varies depending on the starting materials employed, the solvent, the oxidizing agent, the reaction temperature or the like, but is usually 15 minutes to 3 days.

[0075]

Thereafter, compound (Ic) can be prepared from ketone derivative (XXVIII) according to the procedures as described in Step 1-3 to Step 1-5.

5 [0076]

Scheme 3

wherein R⁴, R¹¹, R¹² and Bn are as defined above, R³⁰ represents lower alkyl, cycloalkyl or lower alkoxy-lower alkyl.

[0077]

10 Step 3-1

Condensation of compound (XX) with alcohol (XXIX) under an atmosphere of carbon monoxide in the presence of a base, a

palladium catalyst and a phosphine ligand in an inert solvent provides ester derivative (XXX). The inert solvents employed in the reaction include N,N-dimethylformamide, 1,4-dioxane, 1,2-dimethoxyethane, tetrahydrofuran, toluene or the like. The
5 bases include triethylamine, N,N-diisopropylethylamine or the like. The palladium catalysts include tris(dibenzylideneacetone)dipalladium(0), palladium acetate or the like. The phosphine ligands include 1,1'-bis(diphenylphosphino) ferrocene, triphenylphosphine or the like. The reaction is carried out
10 ordinarily at 80°C to 110°C. The reaction time varies depending on the starting materials employed, the solvent, the reaction temperature or the like, but is usually 1 hour to 24 hours.
[0078]

Step 3-2

15 Oxidation of aldehyde derivative (XXIII) with an oxidizing agent in an inert solvent provides carboxylic acid derivative (XXXII). The solvents employed in the reaction include methylene chloride, acetonitrile, water, methanol or the like. The oxidizing agents include potassium permanganate, manganese
20 dioxide, sodium chlorite-hydrogen peroxide, sodium chlorite-dimethylsulfoxide or the like. The reaction is carried out ordinarily at 0°C to 80°C. The reaction time varies depending on the starting materials employed, the solvent, the oxidizing agent, the reaction temperature or the like, but is usually 15
25 minutes to 3 days. The reaction can be carried out, if desired, by adding an additive such as sodium hydrogen phosphate, sulfuric acid or the like.

[0079]

Step 3-3

Carboxylic acid derivative (XXXII) is treated with alkyl halide (XXXI) in the presence of a base in an inert solvent provides ester derivative (XXX). The inert solvents employed in the reaction include 1,4-dioxane, N,N-dimethylformamide, 1,2-dimethoxyethane, tetrahydrofuran or the like. The bases include sodium tert-butoxide, potassium tert-butoxide, potassium carbonate or the like. The reaction is carried out ordinarily at 0°C to 100°C. The reaction time varies depending on the starting materials employed, the solvent, the reaction temperature or the like, but is usually 5 minutes to 24 hours.

The ester derivative (XXX) can be prepared by condensing carboxylic acid derivative (XXXII) with alcohol (XXIX) in the presence of a condensing agent such as dicyclohexylcarbodiimide, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, diethyl cyanophosphate, diphenylphosphoryl azide or the like in an inert solvent such as methylene chloride, N,N-dimethylformamide or the like. The reaction can be carried out, if desired, by adding a base such as triethylamine or the like.

[0080]

Step 3-4

Carboxylic acid derivative (XXXII) is treated with amine (XXXIII) in the presence of a condensing agent such as dicyclohexylcarbodiimide, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, diethyl cyanophosphate,

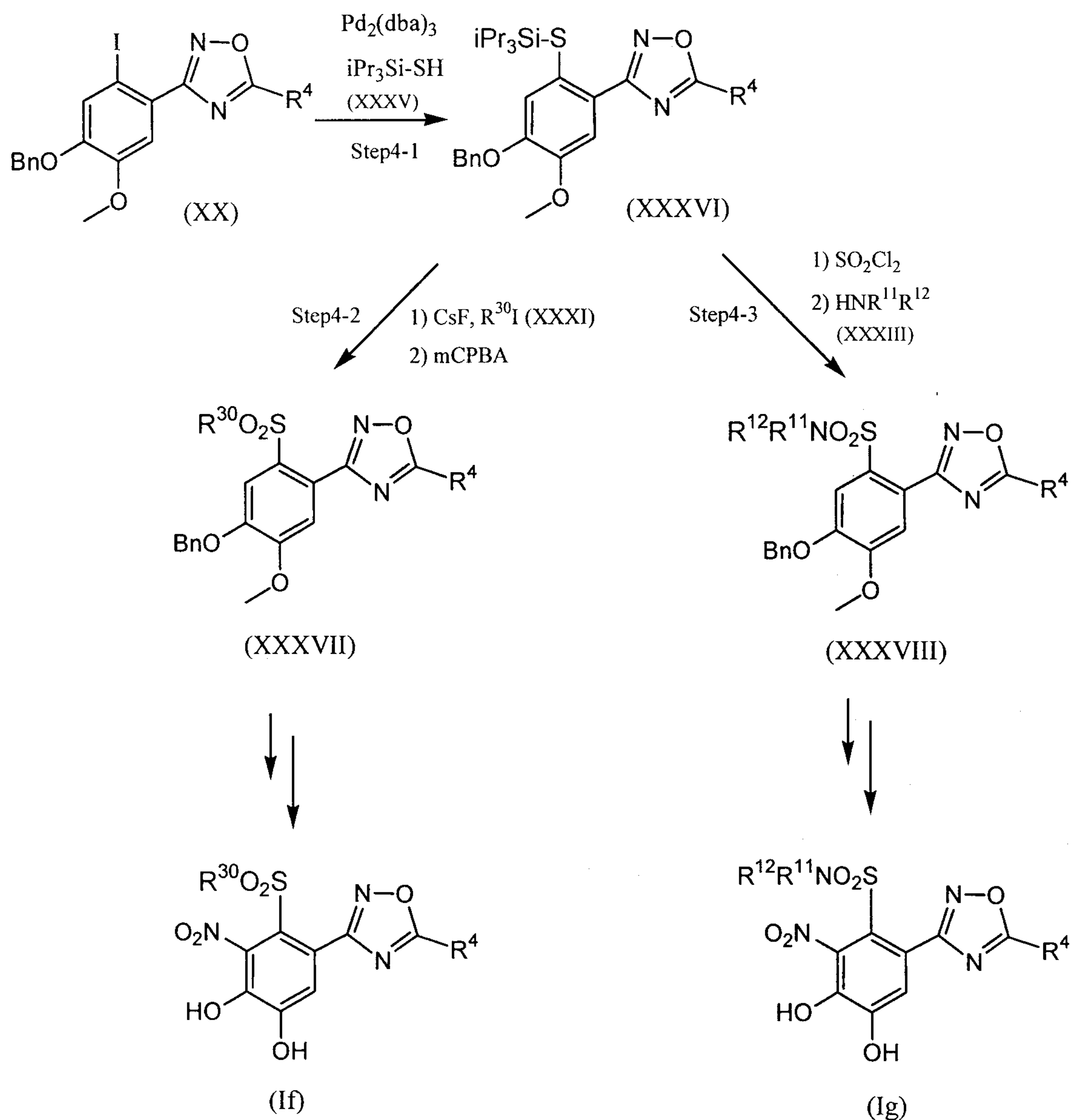
diphenylphosphorylazide or the like in an inert solvent such as methylene chloride, N,N-dimethylformamide, tetrahydrofuran or the like to afford amide derivative (XXXIV). The reaction is carried out ordinarily at -20°C to reflux temperature. The
5 reaction time varies depending on the starting materials employed, the solvent, the reaction temperature or the like, but is usually 15 minutes to 24 hours. The reaction can be carried out, if desired, by adding an additive such as triethylamine or the like.

10 [0081]

Thereafter, compound (Id) can be prepared from compound (XXX) according to the procedures as described in Step 1-3 to Step 1-5. Compound (Ie) can be prepared from compound (XXXIV) according to the procedures as described in Step 1-3 to Step
15 1-5.

[0082]

Scheme 4



wherein R⁴, R¹¹, R¹², R³⁰ and Bn are as defined above.

[0083]

Step 4-1

- 5 Condensation of compound (XX) with triisopropylsilanethiol (XXXV) in the presence of a base, a palladium catalyst and a phosphine ligand in an inert solvent provides triisopropylsilyl phenyl thioether (XXXVI). The inert solvents employed in the reaction include toluene,

N,N-dimethylformamide, 1,4-dioxane, 1,2-dimethoxymethane or the like. The bases include sodium hexamethyldisilazide, lithium hexamethyldisilazide, potassium tert-butoxide or the like. The palladium catalysts include tris(dibenzylidene-
5 acetone)dipalladium(0), tetrakis(triphenylphosphine)palladium(0), palladium acetate or the like. The phosphine ligands include (oxydi-2,1-phenylene)bis(diphenylphosphine) or the like. The reaction is carried out ordinarily at 60°C to 110°C. The reaction time varies depending on the starting
10 materials employed, the solvent, the reaction temperature or the like, but is usually 1 hour to 24 hours.

[0084]

Step 4-2

The triisopropylsilyl group of triisopropylsilyl phenyl
15 thioether derivative (XXXVI) is converted to the corresponding alkyl group (R^{30}) by treatment of alkyl halide (XXXI) in the presence of a base such as cesium fluoride, tetrabutylammonium fluoride or the like in an inert solvent such as 1,4-dioxane, N,N-dimethylformamide, 1,2-dimethoxyethane, tetrahydrofuran
20 or the like to afford an alkyl phenyl thioether derivative. The reaction is carried out ordinarily at 0°C to 100°C. The reaction time varies depending on the starting materials employed, the solvent, the reaction temperature or the like, but is usually 5 minutes to 24 hours.

25 Oxidation of the alkyl phenyl thioether derivative with an oxidizing agent in a suitable solvent provides sulfone derivative (XXXVII). The solvents employed in the reaction

include methylene chloride, acetone, acetic acid, water or the like. The oxidizing agents include m-chloroperbenzoic acid, oxone (registered mark), hydrogen peroxide solution, sodium perborate or the like. The reaction is carried out ordinarily
5 at 0°C to 80°C. The reaction time varies depending on the starting materials employed, the solvent, the reaction temperature or the like, but is usually 5 minutes to 24 hours.

[0085]

Step 4-3

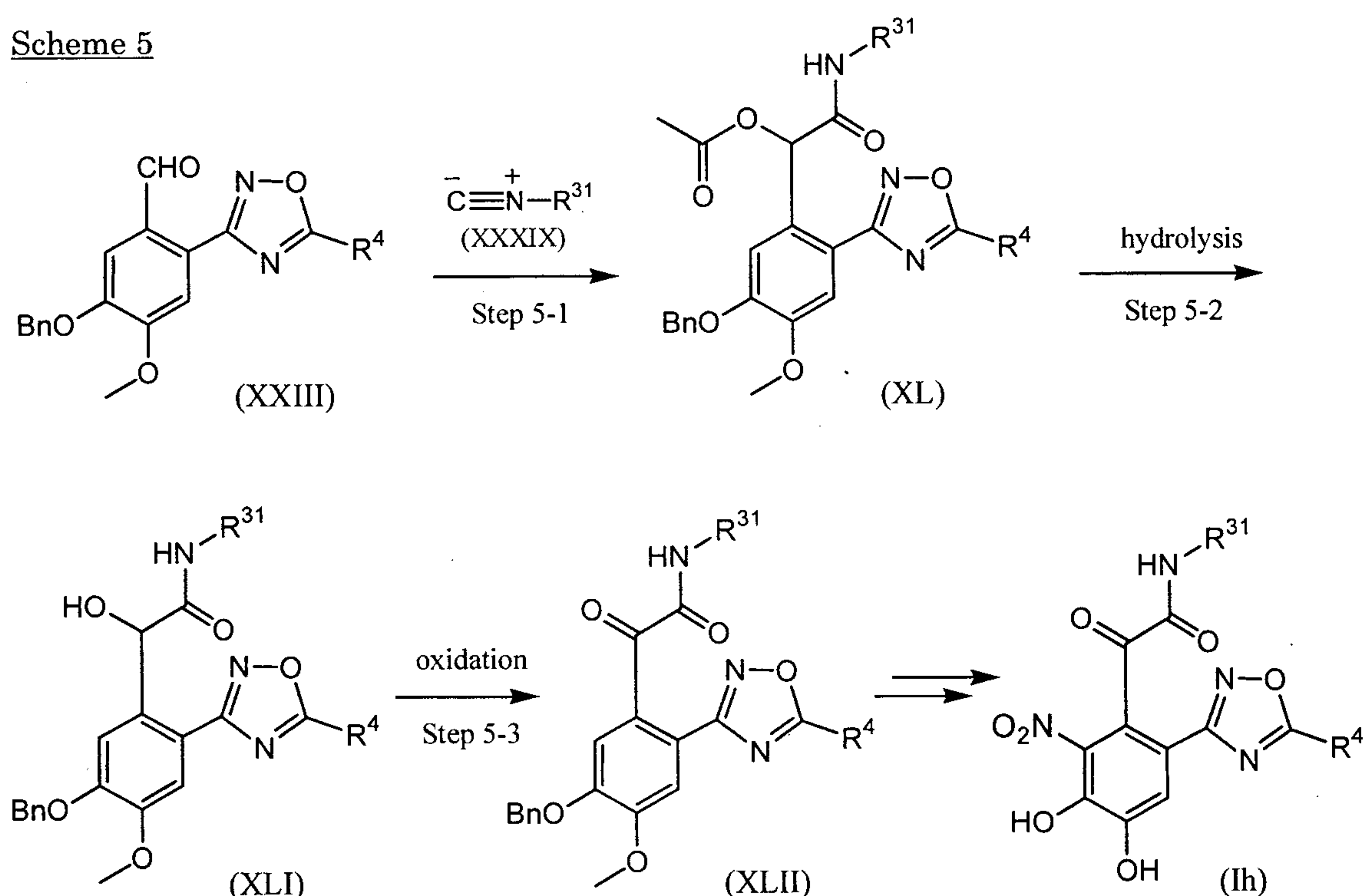
10 Triisopropylsilyl phenyl thioether derivative (XXXVI) is treated with sulfuryl chloride in the presence of a nitrate such as potassium nitrate, sodium nitrate, silver nitrate or the like in an inert solvent such as acetonitrile, N,N-dimethylformamide or the like to afford a sulfonyl chloride derivative. The reaction
15 is carried out ordinarily at 0°C to 40°C. The reaction time varies depending on the starting materials employed, the solvent, the reaction temperature or the like, but is usually 5 minutes to 5 hours.

Condensation of the sulfonyl chloride derivative with
20 amine (XXXIII) in the presence of a base such as triethylamine, N,N-diisopropylethylamine or the like in an inert solvent such as tetrahydrofuran, N,N-dimethylformamide, ethyl acetate, methylene chloride or the like provides sulfonamide derivative (XXXVIII). The reaction is carried out ordinarily at 0°C to 40°C.
25 The reaction time varies depending on the starting materials employed, the solvent, the reaction temperature or the like, but is usually 5 minutes to 5 hours.

[0086]

Thereafter, compound (If) can be prepared from compound (XXXVII) according to the procedures as described in Step 1-3 to Step 1-5. Compound (Ig) can be prepared from compound (XXXVIII) according to the procedures as described in Step 1-3 to Step 1-5.

[0087]

Scheme 5

wherein R⁴, R¹¹, R¹² and Bn are as defined above, and R³¹ represents lower alkyl or cycloalkyl.

[0088]

Step 5-1

Condensation of aldehyde derivative (XXIII) with isocyanide (XXXIX) in the presence of acetic acid in an inert solvent such as acetonitrile, methylene chloride, diethyl ether or the like provides ester derivative (XL). The reaction is

carried out ordinarily at 20°C to 100°C. The reaction time varies depending on the starting materials employed, the solvent, the reaction temperature or the like, but is usually 5 minutes to 24 hours. The reaction can also be carried out, if desired, by
5 adding an additive such as titanium tetrachloride or the like.
[0089]

Step 5-2

Hydrolysis of ester derivative (XL) in the presence of a base such as sodium hydroxide, potassium hydroxide, lithium
10 hydroxide or the like in an inert solvent such as tetrahydrofuran, methanol, ethanol, water or the like provides alcohol derivative (XLI). The reaction is carried out ordinarily at 20°C to 100°C. The reaction time varies depending on the starting materials employed, the solvent, the reaction temperature or the like,
15 but is usually 5 minutes to 24 hours.
[0090]

Step 5-3

Oxidation of alcohol derivative (XLI) according to the procedures as described in Step 2-10 provides ketone derivative
20 (XLII).
[0091]

Thereafter, compound (Ih) can be prepared from compound (XLII) according to the procedures as described in Step 1-3 to Step 1-5.

25 [0092]

The forementioned schemes are exemplary for preparing compounds represented by general formula (I) of the present

invention and synthetic intermediates thereof. Those ordinarily skilled in the art will appreciate that various changes or modifications of the forementioned schemes may be made without departing from the scope of the invention.

5 [0093]

Compounds represented by general formula (I) of the present invention and intermediates for preparing the compounds of the present invention can be isolated or purified, if required, according to conventional isolation or purification techniques well known to those skilled in the art, such as solvent extraction, crystallization, recrystallization, chromatography, preparative high performance liquid chromatography or the like.

[0094]

Compounds of general formula (I) exhibit excellent COMT inhibitory activities, and are useful as a therapeutic or prophylactic agent for Parkinson's disease. Compounds of general formula (I) are preferably used in combination with L-dopa. Compounds of general formula (I) may be used in combination with L-dopa and an aromatic L-amino acid decarboxylase inhibitor.

20 Examples of aromatic L-amino acid decarboxylase inhibitors which may be used in combination with COMT inhibitors of the present invention, include carbidopa, benserazide or the like.

COMT inhibitors of the present invention can be used, if required, in combination with anti-Parkinson drugs other than L-dopa. Such anti-Parkinson drugs include droxidopa, melevodopa, threodops; dopamine D₂ receptor agonists such as cabergoline, bromocriptine mesylate, terguride, talipexole hydrochloride,

25

ropinirole hydrochloride, pergolide mesylate, pramipexole hydrochloride, rotigotine and the like; anticholinergic agents such as profenamine, trihexyphenidyl hydrochloride, mazaticol hydrochloride, biperiden, piroheptine hydrochloride, methixene hydrochloride and the like; adenosine A_{2A} receptor antagonists such as istradefylline and the like; NMDA antagonists such as budipine and the like; monoamine oxidase B inhibitors such as selegiline hydrochloride, rasagiline mesylate, safinamide mesylate and the like; zonisamide; amantadine hydrochloride and the like.

[0095]

Compounds of of the present invention are useful as a therapeutic or prophylactic agent for depression. Compounds of of the present invention are useful as a therapeutic agent for hypertension since compounds of of the present invention exhibit urinary sodium excretion promoting activities.

[0096]

Pharmaceutical compositions comprising a compound of general formula (I) or a pharmaceutically acceptable salt thereof can be administered in various dosage forms depending on their usages. Exemplary dosage forms include powders, granules, fine granules, dry syrups, tablets, capsules, injections, liquids, ointments, suppositories, poultices and the like, which are administered orally or parenterally.

[0097]

Pharmaceutical compositions can be formulated by admixing, diluting or dissolving with appropriate pharmaceutical carriers

such as excipients, disintegrators, binders, lubricants, diluents, buffers, isotonic agents, preservatives, wetting agents, emulsifying agents, dispersing agents, stabilizing agents, solubilizing agents and the like, according to a
5 conventional formulation procedure depending upon their dosage forms.

[0098]

The dosage of a compound represented by general formula (I) or a pharmaceutically acceptable salt thereof is
10 appropriately determined depending on the age, sex or body weight of the individual patient, the severity of the disease, the condition to be treated and the like. A typical dosage for oral administration is in the range of from about 10 mg to about 3000 mg per day per adult human. A typical dosage for parenteral
15 administration is in the range of from about 5 mg to about 1000 mg per day per adult human. The dosages may be administered in single or divided doses, for example one to several times daily.

[0099]

A pharmaceutical combination comprising a compound
20 represented by general formula (I) or a pharmaceutically acceptable salt thereof, and at least one selected from L-dopa and an aromatic L-amino acid decarboxylase inhibitor, can be administered as a single pharmaceutical composition comprising all of active ingredients, or as separately formulated
25 pharmaceutical compositions each of which comprises a single active ingredient. Where separately formulated pharmaceutical compositions are used, the compositions may be administered

separately, concurrently or at different intervals. Alternatively, where separately formulated pharmaceutical compositions are used, the compositions may be mixed together with an appropriate diluent, and administered simultaneously.

5 [0100]

In a pharmaceutical combination comprising a compound represented by general formula (I) or a pharmaceutically acceptable salt thereof, and at least one selected from L-dopa and an aromatic L-amino acid decarboxylase inhibitor,
10 the dosage of each active ingredient may be appropriately determined depending on the age, sex or body weight of the individual patient, the severity of the disease, administration time, dosage form, administration method, combination of active ingredients and the like.

15 **Advantageous Effects of Invention**

[0101]

Compounds of the present invention exhibit potent COMT inhibitory activities. Moreover, compounds of the present invention have a desirable safety profile since compounds of
20 the present invention have extremely slight hepatotoxicity. Accordingly, compounds of the present invention are useful as a therapeutic or prophylactic agent for Parkinson's disease, depression or hypertension. Especially, compounds of the present invention are useful as a therapeutic or prophylactic
25 agent for Parkinson's disease since use of compounds of the present invention in combination with L-dopa increases the bioavailability of L-dopa remarkably.

BEST MODE FOR CARRYING OUT THE INVENTION

[0102]

The following reference examples, examples and test examples illustrate the invention in further detail. It is to be understood, however, that they are not to be construed as limiting the scope of the invention in any way.

[0103]

Reference example 1-1

4-Benzyloxy-2-iodo-5-methoxybenzaldehyde

To a mixture of 4-benzyloxy-3-methoxybenzaldehyde (10g), silver trifluoroacetate (11.4g) and methylene chloride (105mL) was added iodine (13.1g) at room temperature. After stirring for 2 hours, the mixture was passed through a layer of Celite (registered mark). The filtrate was washed with an aqueous solution of sodium hydrogen sulfite and brine successively, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was triturated with methanol: water = 4:1 to give the title compound (13.2g).

¹H-NMR (CDCl₃) δ ppm: 3.91 (3H, s), 5.19 (2H, s), 7.30-7.50 (7H, m), 9.86 (1H, s)

[0104]

Reference example 1-2

5-Benzyloxy-2-iodo-4-methoxybenzaldehyde

The title compound was prepared in a manner similar to those as described in Reference example 1-1 using 3-benzyloxy-4-methoxybenzaldehyde instead of 4-benzyloxy-3-methoxybenzaldehyde.

¹H-NMR (CDCl₃) δ ppm: 3.95 (3H, s), 5.16 (2H, s), 7.29-7.47 (6H, m),
7.48 (1H, s), 9.84 (1H, s)

[0105]

Reference example 2-1

5 4-Benzyloxy-2-iodo-5-methoxybenzaldehyde oxime

A mixture of 4-benzyloxy-2-iodo-5-methoxybenzaldehyde
(Reference example 1-1) (12.2g), hydroxylamine hydrochloride
(2.54g), sodium acetate (6g) and ethanol (170mL) was stirred at
70°C for 1.5 hours. The mixture was concentrated under reduced
10 pressure. Water was added to the residue, and the mixture was
stirred at room temperature for 30 minutes. The solid was
collected by filtration to give the title compound (12.8g).

¹H-NMR (CDCl₃) δ ppm: 3.88 (3H, s), 5.13 (2H, s), 7.19 (1H, s), 7.29 (1H,
s), 7.30-7.50 (6H, m), 8.30 (1H, s)

15 [0106]

Reference examples 2-2 to 2-3 were prepared in a manner
similar to those as described in Reference example 2-1 using
the corresponding aldehydes instead of 4-benzyloxy-2-iodo-
5-methoxybenzaldehyde. These were illustrated in table 1.

20 [0107]

Table1

Reference example	Structure	Reference example	Structure
2-1		2-3	
2-2			

[0108]

The physical data of reference example 2-3 was shown below.

[0109]

5 Reference example 2-3

$^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 3.88 (3H, s), 5.13 (2H, s), 7.25 (1H, s), 7.29-7.45 (6H, m), 8.28 (1H, s)

[0110]

Reference example 3-1

10 4-Benzyloxy-N-hydroxy-2-iodo-5-methoxybenzamidine

To a mixture of 4-benzyloxy-2-iodo-5-methoxybenzaldehyde oxime (reference example 2-1) (12.8g) and N,N-dimethylformamide (110mL) was added N-chlorosuccinimide (4.9g) at room temperature. After stirring at room temperature for 20 minutes, water and ethyl acetate were added to the mixture under ice-bath cooling. The separated organic layer was dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give 4-benzyloxy-N-hydroxy-2-iodo-5-methoxy-

benzimidoylchloride.

To a mixture of 4-benzyloxy-N-hydroxy-2-iodo-5-methoxy-benzimidoylchloride and N,N-dimethylformamide (110mL) was added a 28% ammonia in water (12mL) under ice-bath cooling. After
5 stirring for 3 hours under ice-bath cooling, water and ethyl acetate were added to the mixture. The separated organic layer was washed with water and brine successively, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was triturated with hexane: diethyl
10 ether=1:4 to give the title compound (9.3g).

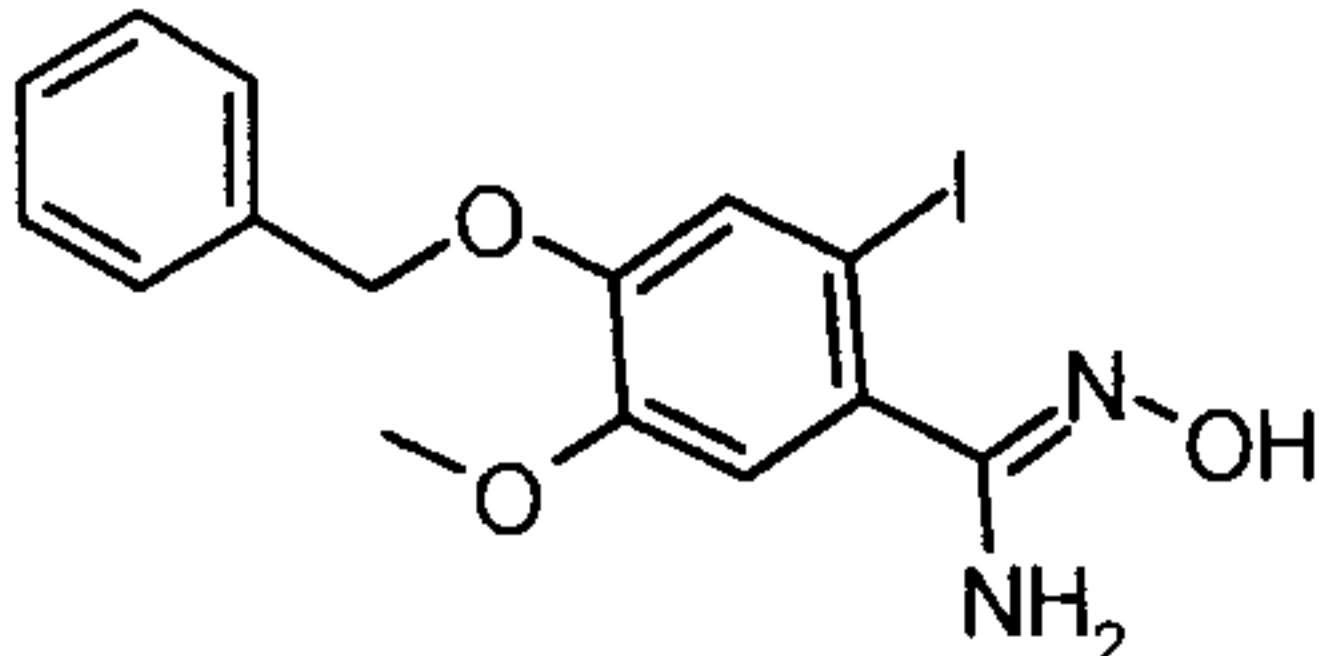
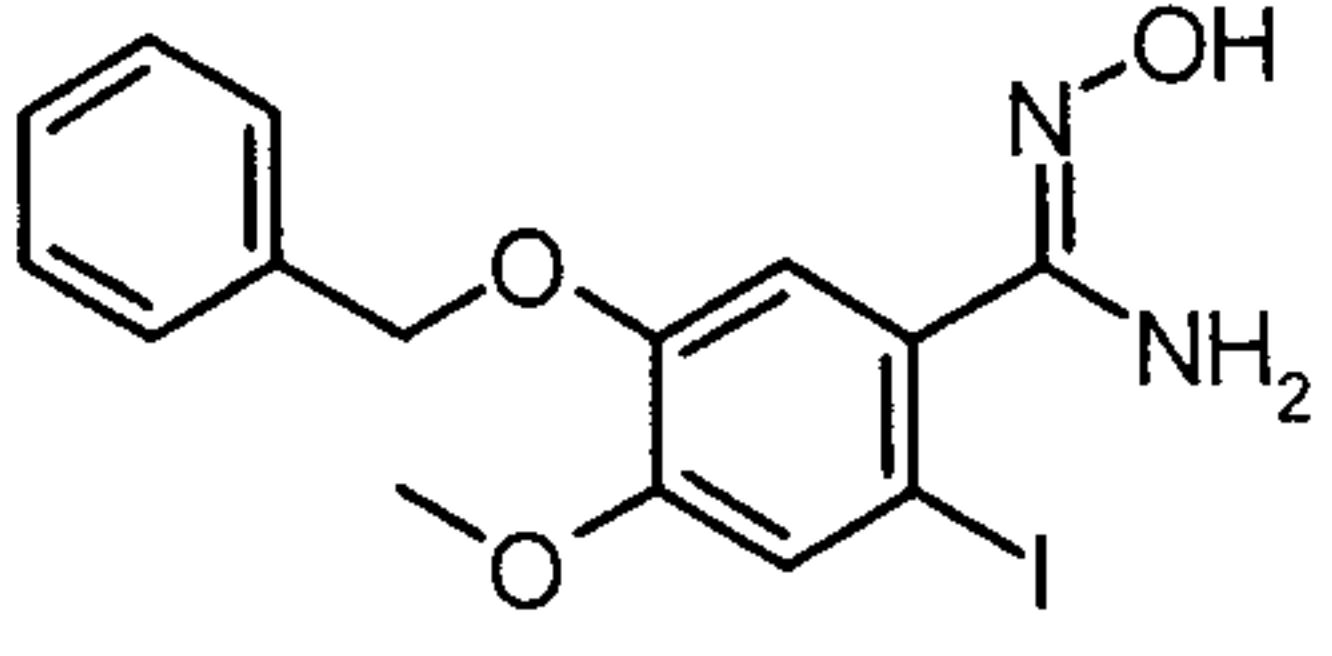
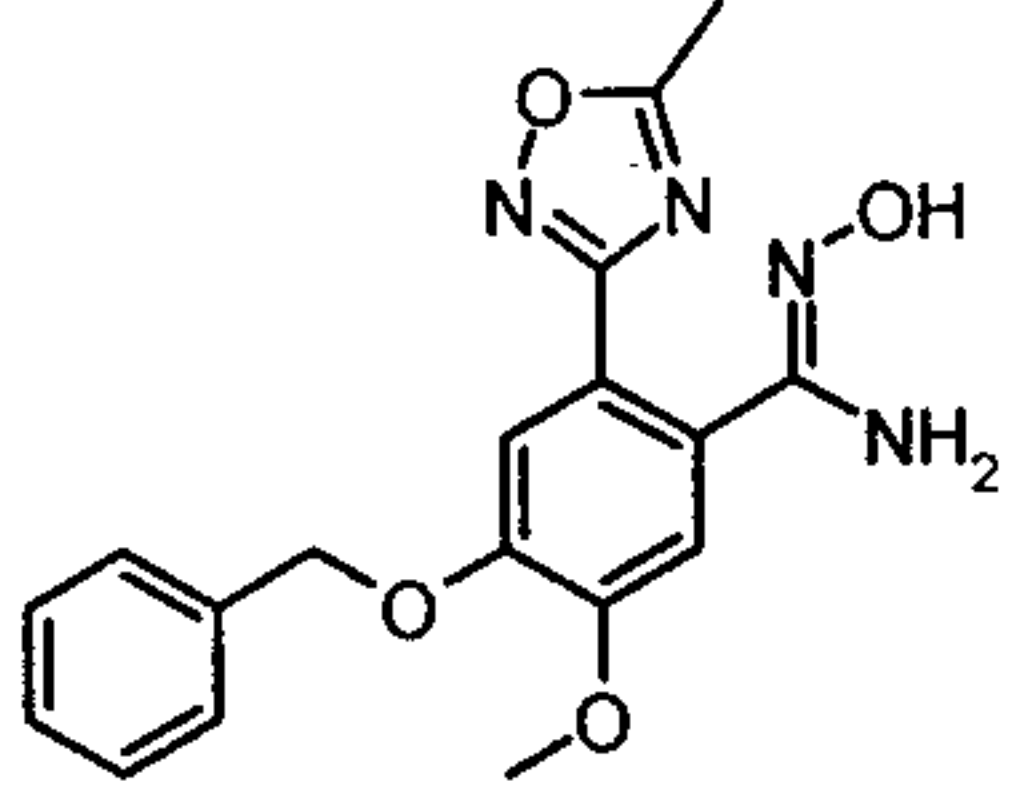
¹H-NMR (DMSO-d₆) δ ppm: 3.77 (3H, s), 5.12 (2H, s), 5.65 (2H, br s), 6.91 (1H, s), 7.30-7.50 (6H, m), 9.35 (1H, s)

[0111]

Reference examples 3-2 to 3-3 were prepared in a manner
15 similar to those as described in Reference example 3-1 using the corresponding oximes instead of 4-benzyloxy-2-iodo-5-methoxybenzaldehyde oxime. These were illustrated in table 2.

[0112]

Table 2

Reference example	Structure	Reference example	Structure
3-1		3-3	
3-2			

[0113]

The physical data of reference example 3-3 was shown below.

[0114]

5 Reference example 3-3

$^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 3.87 (3H, s), 5.09 (2H, s), 7.00 (1H, s), 7.27-7.50 (5H, m)

[0115]

Reference example 4-1

10 3-(4-Benzyloxy-2-iodo-5-methoxyphenyl)-5-methyl-[1,2,4]oxadiazole

To a mixture of 4-benzyloxy-N-hydroxy-2-iodo-5-methoxybenzimidine (reference example 3-1) (35g), triethylamine (31mL) and tetrahydrofuran (31mL) was added acetyl chloride (8.2mL) under ice-bath cooling. The mixture was stirred at the same temperature for 1 hour. Insoluble materials were removed by filtration. To the filtrate was added tetrabutylammonium fluoride (1mol/L tetrahydrofuran solution, 89mL). After

stirring at the same temperature for 2 hours, water and ethylacetate were added to the mixture. The separated organic layer was washed with 1mol/L hydrochloric acid, a 1mol/L aqueous solution of sodium hydroxide, an aqueous solution of sodium bicarbonate and brine successively, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was triturated with methanol to give the title compound (31.5g).

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 2.67 (3H, s), 3.90 (3H, s), 5.16 (2H, s), 7.28 (1H, s), 7.30-7.50 (6H, m)

[0116]

Reference example 4-2

3-(5-Benzyloxy-2-iodo-4-methoxyphenyl)-5-methyl-[1,2,4]oxadiazole

To a mixture of 5-benzyloxy-N-hydroxy-2-iodo-4-methoxybenzamidine (reference example 3-3) (20g) and pyridine (115mL) was added acetyl chloride (3.8mL) under ice-bath cooling. After stirring at the same temperature for 3 hours, the mixture was stirred and heated at 120°C for 3 hours. After cooling to room temperature, the mixture was concentrated under reduced pressure. To the residue were added ethyl acetate and 2mol/L hydrochloric acid. The separated organic layer was washed with 2mol/L hydrochloric acid and brine successively, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: 15%-50% ethyl acetate/hexane, gradient elution) to give the title compound (17.0g).

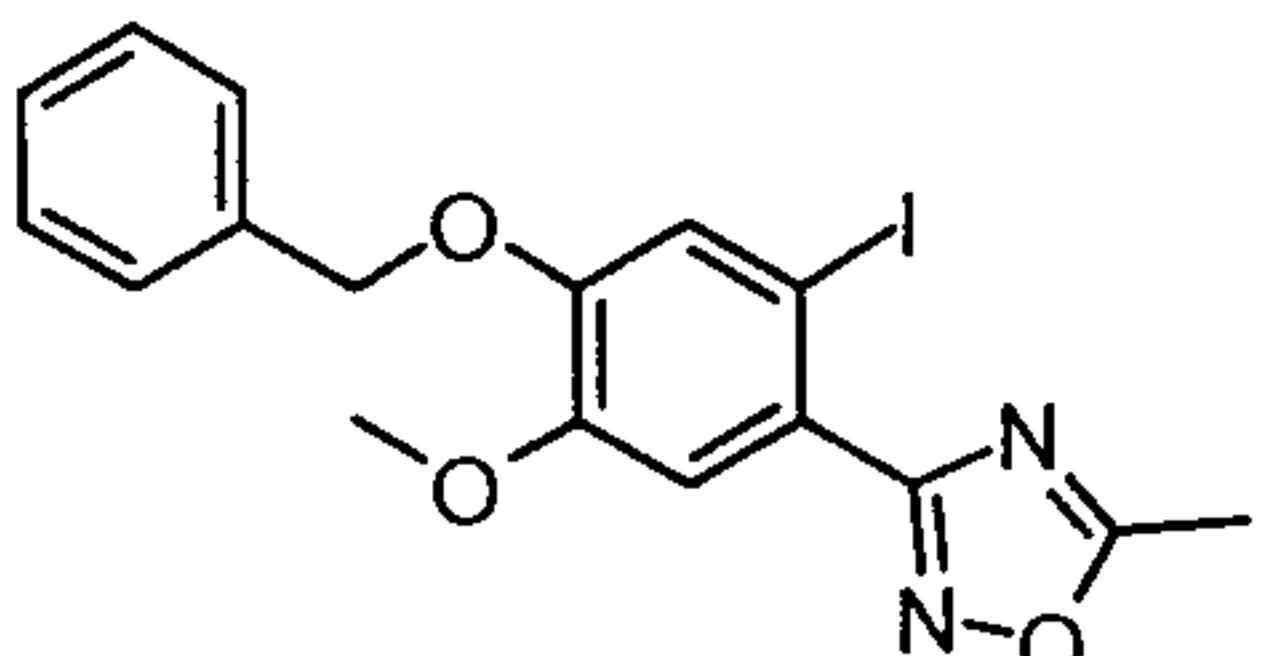
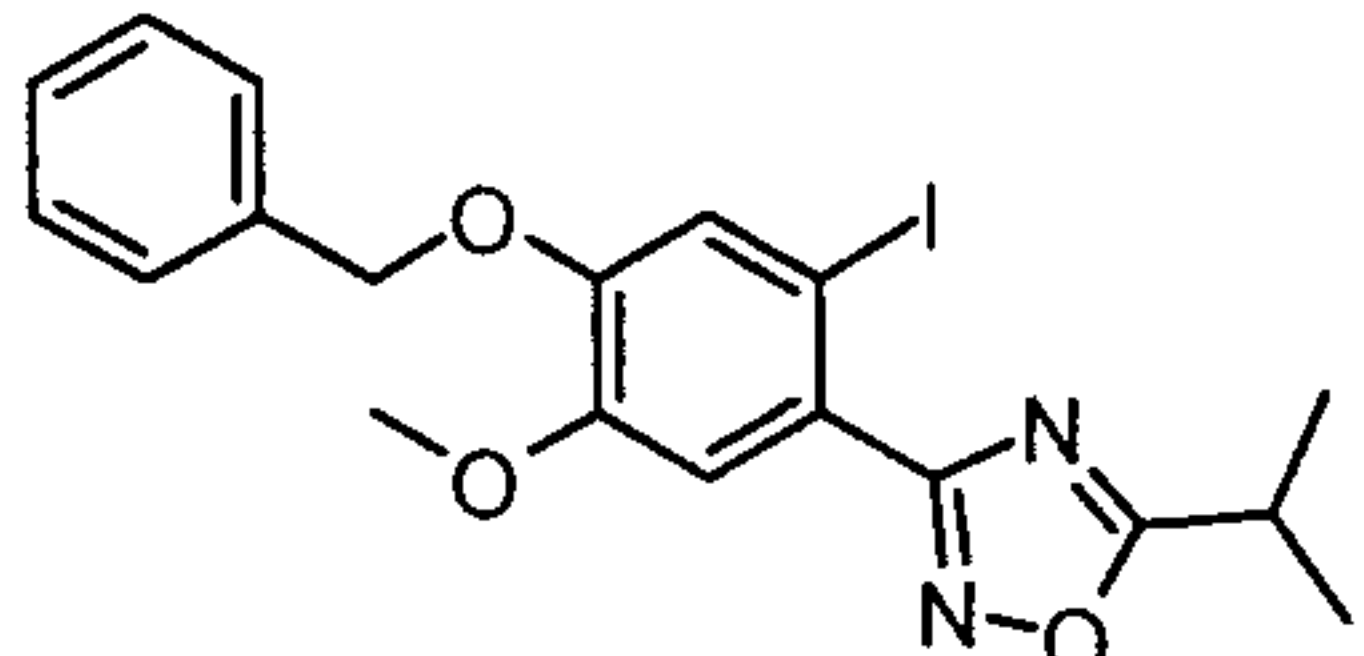
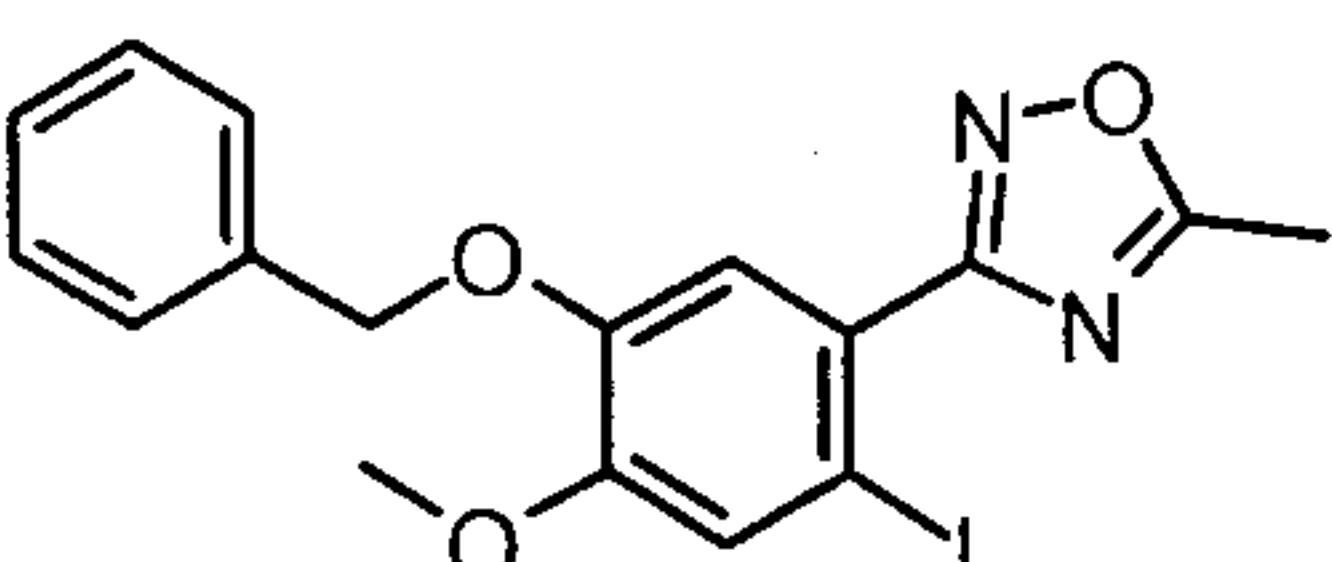
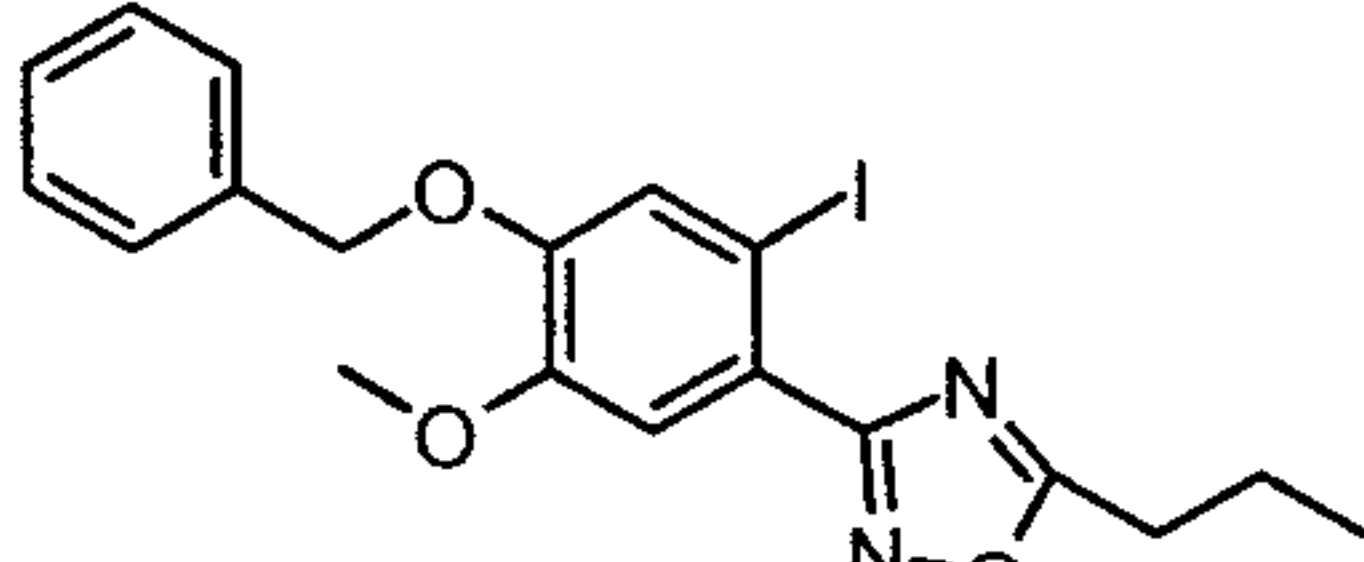
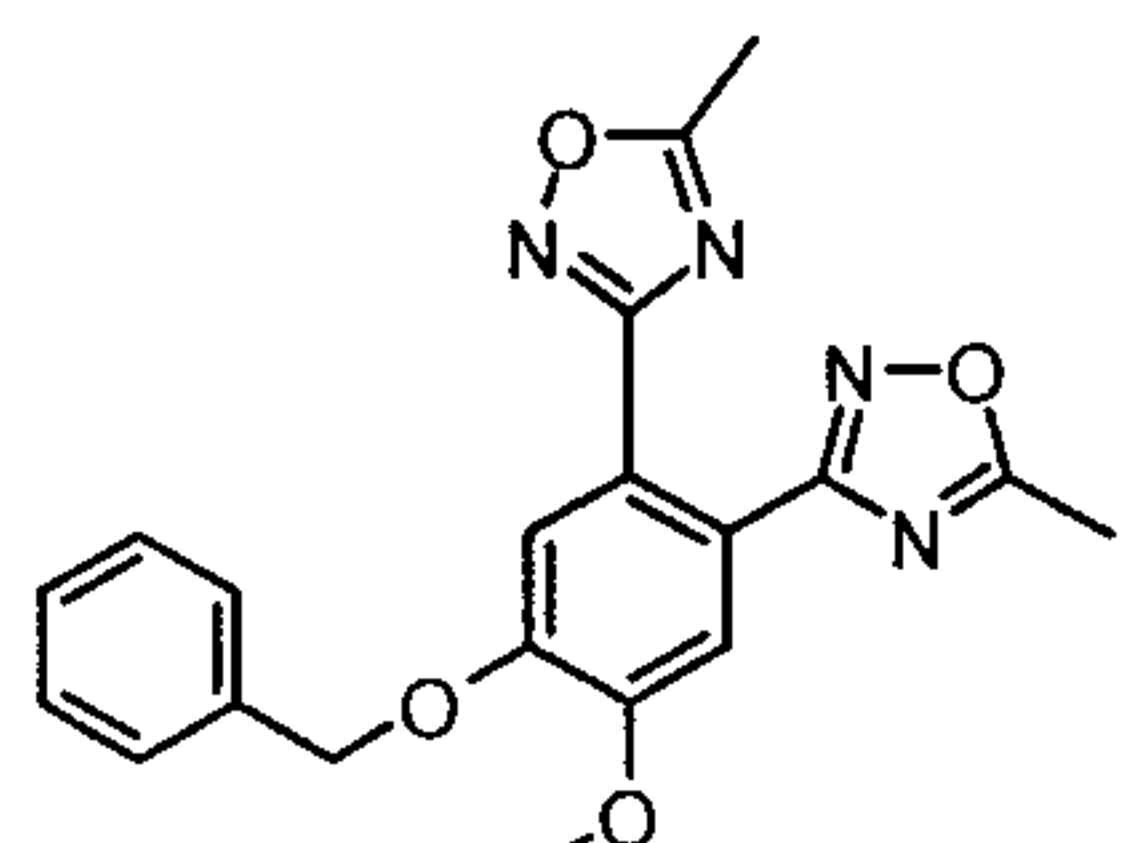
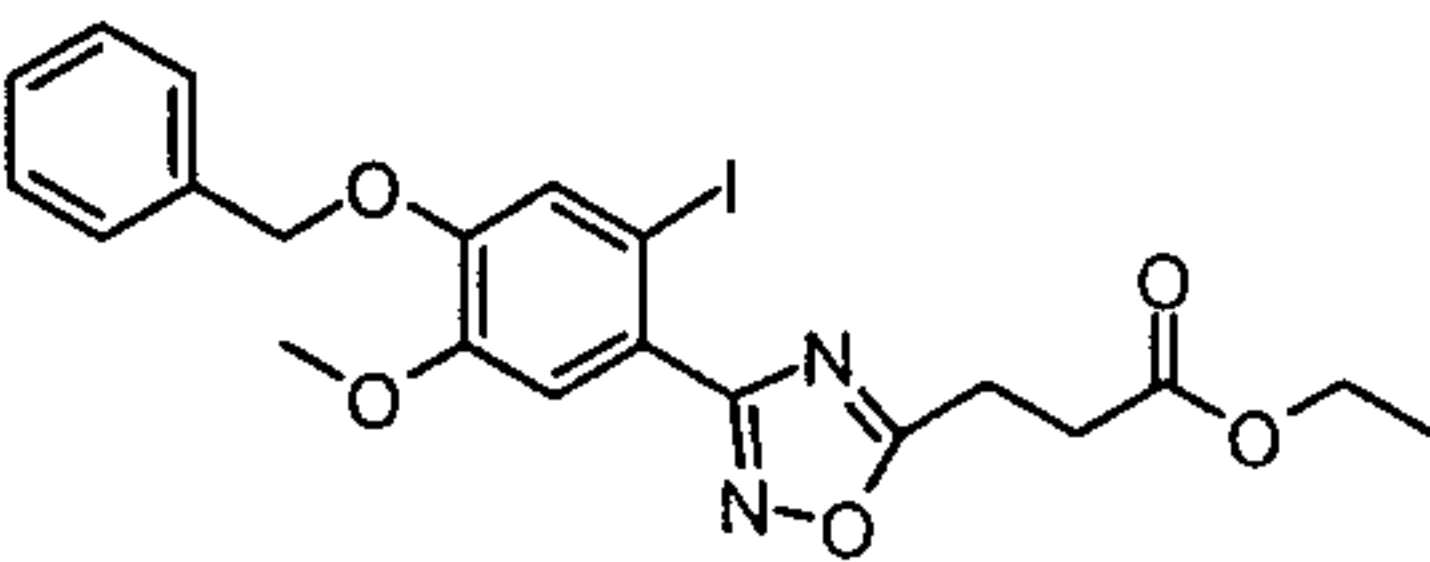
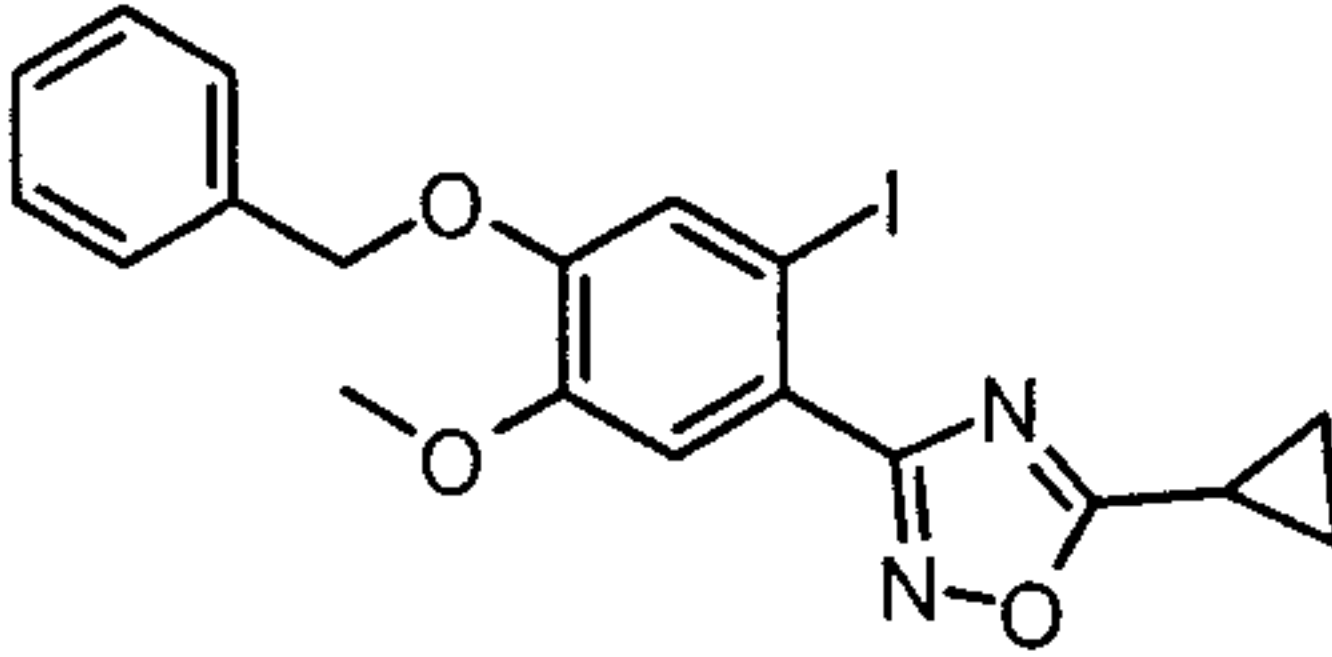
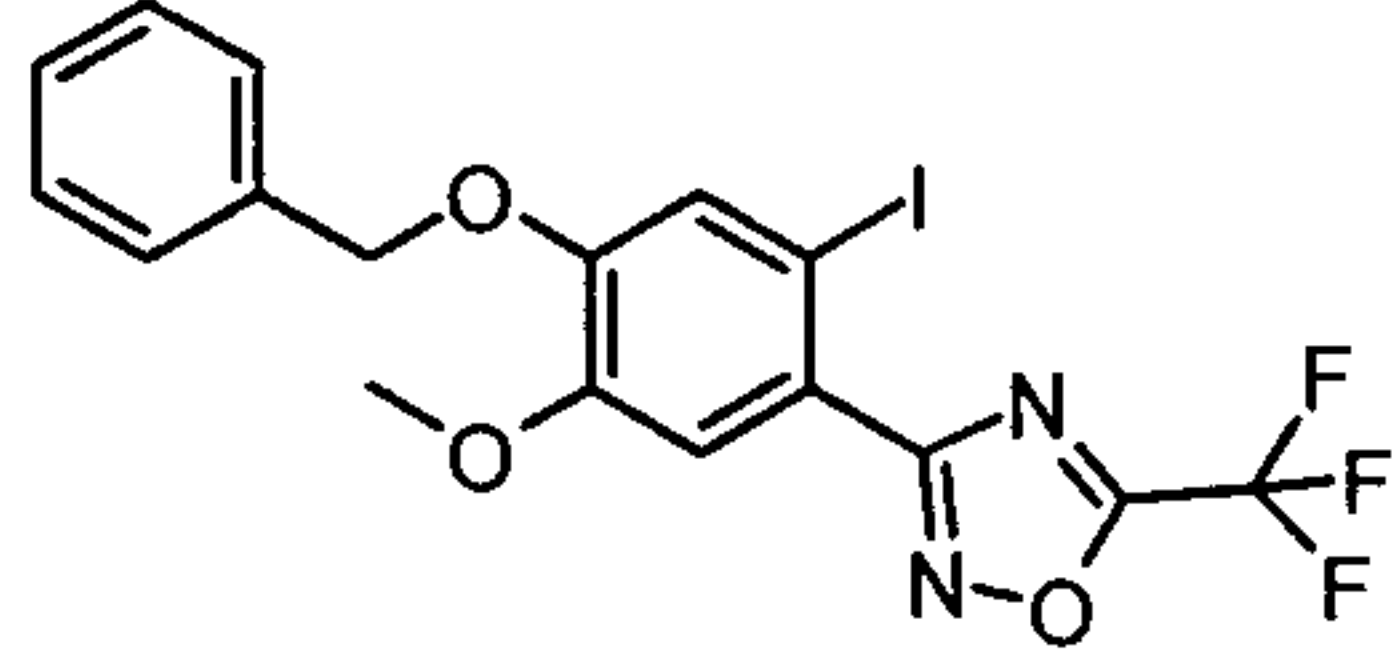
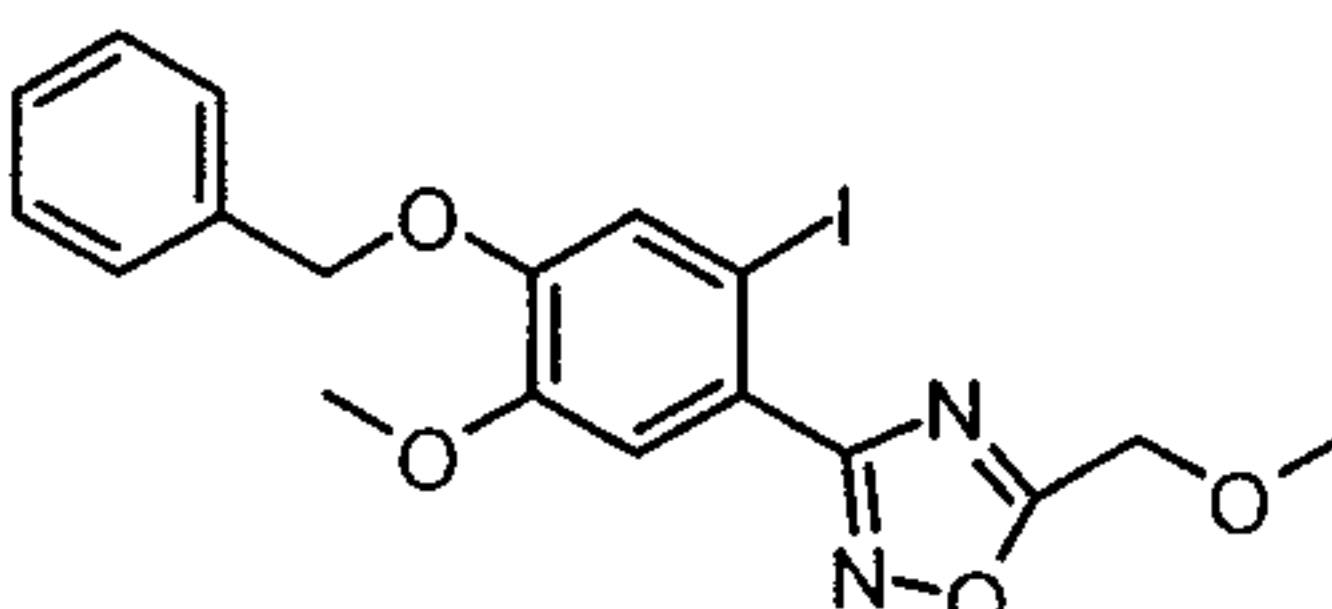
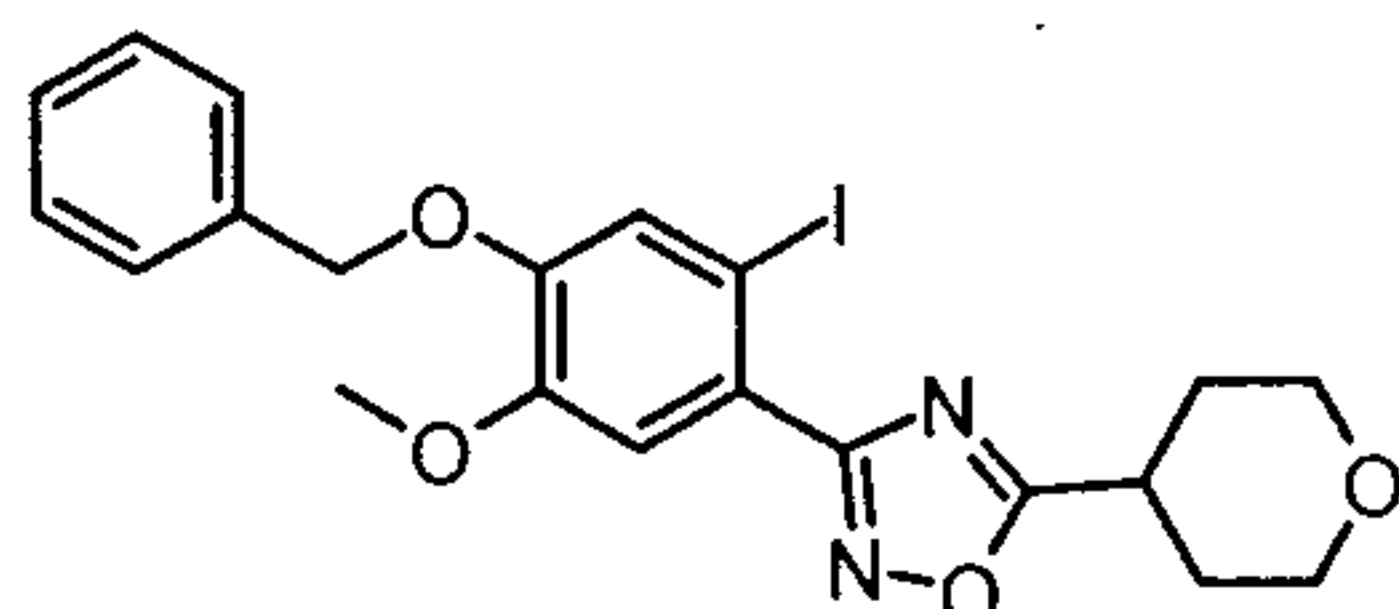
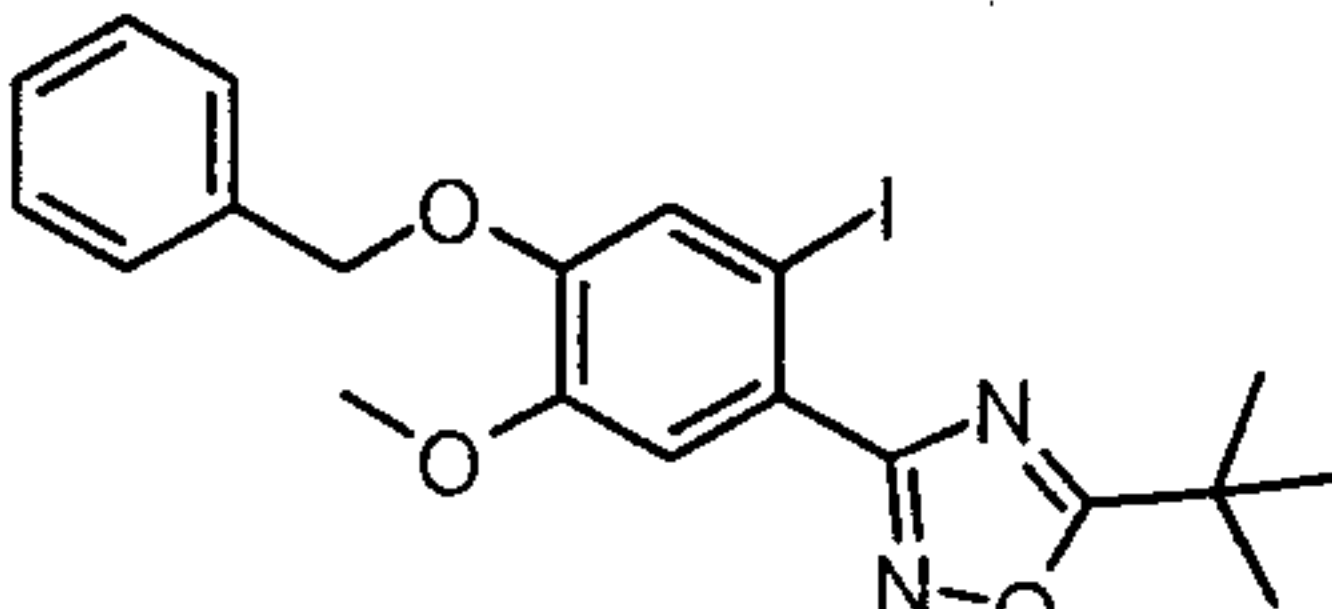
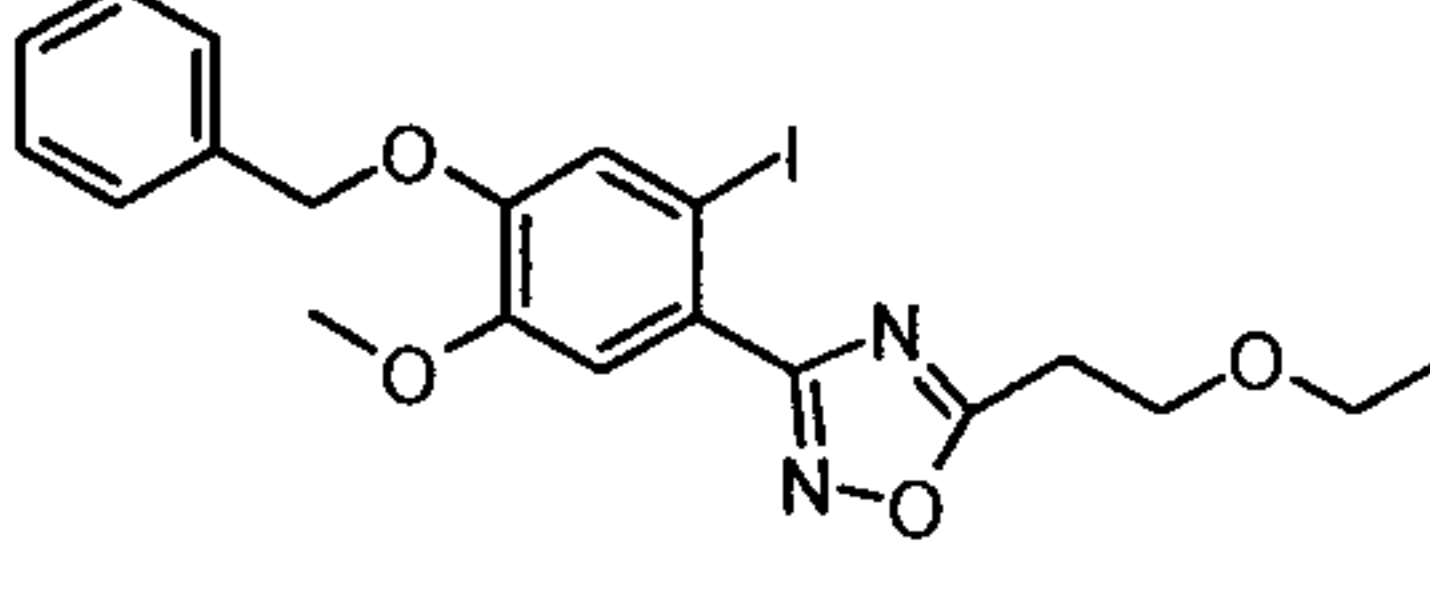
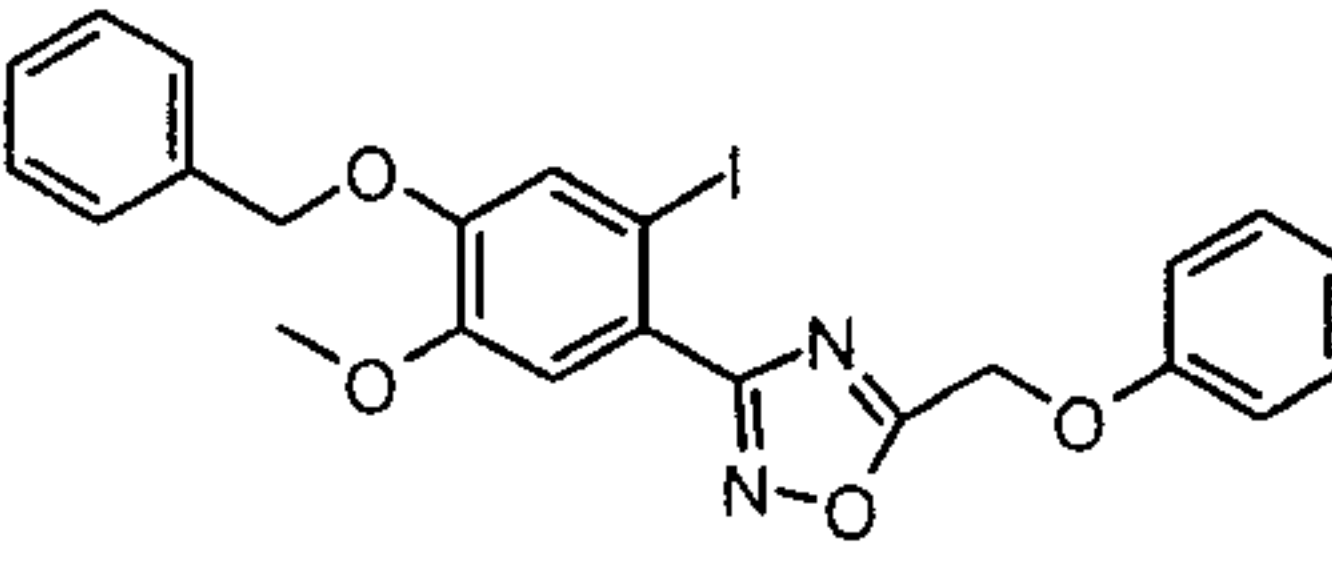
$^1\text{H-NMR}$ (CDCl_3) δ ppm: 2.66 (3H, s), 3.91 (3H, s), 5.14 (2H, s),
7.25-7.50 (7H, m)

[0117]

Reference examples 4-3 to 4-13 were prepared in a manner
5 similar to those as described in Reference example 4-1 using
the corresponding amidines and acid chlorides or acid anhydrides
instead of 4-benzyloxy-N-hydroxy-2-iodo-5-methoxybenzamidine
and acetyl chloride. These were illustrated in table 3.

[0118]

Table 3

Reference example	Structure	Reference example	Structure
4-1		4-8	
4-2		4-9	
4-3		4-10	
4-4		4-11	
4-5		4-12	
4-6		4-13	
4-7			

[0119]

The physical data of reference examples 4-3 to 4-13 were shown below.

[0120]

5 Reference example 4-3

$^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 2.59 (3H, s), 2.60 (3H, s), 3.97 (3H, s), 5.22 (2H, s), 7.25-7.50 (7H, m)

[0121]

Reference example 4-4

10 $^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 1.23-1.28 (2H, m), 1.30-1.34 (2H, m), 2.24-2.30 (1H, m), 3.89 (3H, s), 5.15 (2H, s), 7.25 (1H, s), 7.31-7.45 (6H, m)

[0122]

Reference example 4-5

15 $^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 3.57 (3H, s), 3.90 (3H, s), 4.77 (2H, s), 5.17 (2H, s), 7.32 (1H, s), 7.33-7.46 (5H, m), 7.47 (1H, s)

[0123]

Reference example 4-6

20 $^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 1.51 (9H, s), 3.91 (3H, s), 5.16 (2H, s), 7.29 (1H, s), 7.31-7.45 (6H, m)

[0124]

Reference example 4-7

$^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 3.90 (3H, s), 5.17 (2H, s), 5.37 (2H, s), 7.00-7.10 (3H, m), 7.25-7.50 (9H, m)

25 [0125]

Reference example 4-8

$^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 1.40-1.50 (6H, m), 3.20-3.40 (1H, m), 3.90 (3H, s), 5.16 (2H, s), 7.29 (1H, s), 7.30-7.50 (6H, m)

[0126]

Reference example 4-9

$^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 1.00-1.10 (3H, m), 1.80-2.00 (2H, m),
2.90-3.00 (2H, m), 3.90 (3H, s), 5.16 (2H, s), 7.28 (1H, s),
7.30-7.50 (6H, m)

5 [0127]

Reference example 4-10

$^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 1.27 (3H, t, $J=7.2\text{Hz}$), 2.94 (2H, t, $J=7.4\text{Hz}$),
3.28 (2H, t, $J=7.4\text{Hz}$), 3.90 (3H, s), 4.19 (2H, q, $J=7.2\text{Hz}$), 5.16 (2H,
s), 7.20-7.50 (7H, m)

10 [0128]

Reference example 4-11

$^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 3.92 (3H, s), 5.18 (2H, s), 7.33-7.46 (6H,
m), 7.50 (1H, s)

[0129]

15 Reference example 4-12

$^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 2.05-2.15 (4H, m), 3.24-3.34 (1H, m),
3.54-3.64 (2H, m), 3.90 (3H, s), 4.03-4.10 (2H, m), 5.16 (2H, s),
7.30 (1H, s), 7.31-7.48 (6H, m)

[0130]

20 Reference example 4-13

$^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 1.20 (3H, t, $J=6.8\text{Hz}$), 3.24 (2H, t, $J=6.7\text{Hz}$),
3.56 (2H, q, $J=6.8\text{Hz}$), 3.85-4.00 (5H, m), 5.16 (2H, s), 7.30 (1H,
s), 7.30-7.50 (6H, m)

[0131]

25 Reference example 5-1

5-Benzyloxy-4-methoxy-2-(5-methyl-[1,2,4]oxadiazol-3-yl)
benzoic acid

To a mixture of 5-benzyloxy-4-methoxy-2-(5-methyl-
[1,2,4]oxadiazol-3-yl)benzaldehyde (reference example 15-1)
30 (5.38g), dimethyl sulfoxide (5.89mL), concentrated sulfuric

acid(0.506mL), water(8mL) and acetonitrile(41mL) was added a mixture of sodium chlorite(2.25g) and water(10mL). After stirring at room temperature for 30 minutes, water was added to the mixture. The solid was collected by filtration to give
5 the title compound (3.58g).

$^1\text{H-NMR}(\text{CDCl}_3)\delta\text{ppm}$: 2.67(3H, s), 3.95(3H, s), 5.23(2H, s), 7.19(1H, s), 7.30-7.50(5H, m), 7.68(1H, s)

[0132]

Reference example 6-1

10 [5-Benzyloxy-4-methoxy-2-(5-methyl-[1,2,4]oxadiazol-3-yl)phenyl]phenylmethanol

To a mixture of 5-benzyloxy-4-methoxy-2-(5-methyl-[1,2,4]oxadiazol-3-yl)benzaldehyde(reference example 15-1) (450mg) and tetrahydrofuran(5.6mL) was added dropwise
15 phenylmagnesium bromide(1.08mol/L tetrahydrofuran solution, 1.4mL) in an ice salt bath. After stirring at the same temperature for 30 minutes, an aqueous solution of ammonium chloride, 2mol/L hydrochloric acid and ethyl acetate were added to the mixture. The separated organic layer was dried over anhydrous magnesium
20 sulfate, and concentrated under reduced pressure to give the title compound (564mg).

$^1\text{H-NMR}(\text{CDCl}_3)\delta\text{ppm}$: 2.64(3H, s), 3.94(3H, s), 4.60-4.70(1H, m), 4.90-5.10(2H, m), 6.10-6.20(1H, m), 6.72(1H, s), 7.20-7.40(10H, m), 7.49(1H, s)

25 [0133]

Reference examples 6-2 to 6-7 were prepared in a manner similar to those as described in Reference example 6-1 using

the corresponding aldehydes and organomagnesium instead of 5-benzyloxy-4-methoxy-2-(5-methyl-[1,2,4]oxadiazol-3-yl) benzaldehyde and phenylmagnesium bromide. These were illustrated in table 4.

5 [0134]

Table4

Reference example	Structure	Reference example	Structure
6-1		6-5	
6-2		6-6	
6-3		6-7	
6-4			

[0135]

The physical data of reference examples 6-2 to 6-4 and 6-6 to 6-7 were shown below.

10 [0136]

Reference example 6-2

$^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 1.40-1.50 (3H, m), 2.67 (3H, s), 3.76 (1H, br s), 3.94 (3H, s), 5.20-5.30 (3H, m), 7.20 (1H, s), 7.30-7.50 (6H, m)

[0137]

5 Reference example 6-3

$^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 2.35 (3H, s), 2.63 (3H, s), 3.94 (3H, s), 4.50-4.60 (1H, m), 4.90-5.10 (2H, m), 6.10-6.20 (1H, m), 6.76 (1H, s), 7.00-7.30 (9H, m), 7.48 (1H, br s)

[0138]

10 Reference example 6-4

$^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 0.76-1.18 (7H, m), 1.51-1.72 (3H, m), 1.95-1.99 (1H, m), 2.65 (3H, s), 3.20 (1H, d, $J=5.5\text{Hz}$), 3.94 (3H, s), 4.76-5.81 (1H, m), 5.20-5.30 (2H, m), 7.07 (1H, s), 7.27-7.45 (6H, m)

15 [0139]

Reference example 6-6

$^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 1.40-1.50 (9H, m), 3.20-3.40 (1H, m), 3.94 (3H, s), 3.95-4.10 (1H, m), 5.00-5.20 (1H, m), 5.20-5.30 (2H, m), 7.19 (1H, s), 7.30-7.50 (6H, m)

20 [0140]

Reference example 6-7

$^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 1.00-1.10 (3H, m), 1.40-1.50 (3H, m), 1.80-2.00 (2H, m), 2.90-3.00 (2H, m), 3.90-4.00 (4H, m), 5.10-5.30 (3H, m), 7.19 (1H, s), 7.20-7.50 (6H, m)

25 [0141]

Reference example 7-1

1-[5-Benzyloxy-4-methoxy-2-(5-methyl-[1,2,4]oxadiazol-3-yl)]

phenyl]-2-methylpropan-1-ol

A mixture of 3-(4-benzyloxy-2-iodo-5-methoxyphenyl)-5-methyl-[1,2,4]oxadiazole (reference example 4-1) (844mg) and tetrahydrofuran (6mL) was cooled in an ice salt bath under an argon atmosphere. Isopropylmagnesium chloride (2.0mol/L tetrahydrofuran solution, 1.2mL) was added, and the mixture was stirred under ice-salt-bath cooling for 10 minutes. After an addition of isobutyraldehyde (0.55mL), the mixture was stirred in an ice salt bath for 10 minutes, and at room temperature for 30 minutes. Water and 2mol/L hydrochloric acid were added to the mixture, and the mixture was extracted with ethyl acetate. The separated organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: 15%-35% ethyl acetate/hexane, gradient elution) to give the title compound (533mg).

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 0.63 (3H, d, $J=6.7\text{Hz}$), 0.98 (3H, d, $J=6.7\text{Hz}$), 1.87-1.96 (1H, m), 2.66 (3H, s), 3.36 (1H, d, $J=5.5\text{Hz}$), 3.94 (3H, s), 4.69-4.72 (1H, m), 5.21 (1H, d, $J=12.3\text{Hz}$), 5.27 (1H, d, $J=12.3\text{Hz}$), 7.10 (1H, s), 7.28-7.39 (3H, m), 7.44-7.46 (3H, m) [0142]

Reference examples 7-2 to 7-8 were prepared in a manner similar to those as described in Reference example 7-1 using the corresponding iodobenzenes and aldehydes or N,N-dimethylformamide instead of 3-(4-benzyloxy-2-iodo-5-methoxyphenyl)-5-methyl-[1,2,4]oxadiazole and isobutyraldehyde. These were illustrated in table 5.

[0143]

Table 5

Reference example	Structure	Reference example	Structure
7-1		7-5	
7-2		7-6	
7-3		7-7	
7-4		7-8	

[0144]

The physical data of reference examples 7-2 to 7-3 and
 5 7-5 to 7-8 were shown below.

[0145]

Reference example 7-2

¹H-NMR (CDCl₃) δ ppm : 2.66 (3H, s), 3.93 (3H, s), 4.95-5.15 (2H, m),
 5.60 (1H, d, J=4.4Hz), 6.50-6.60 (1H, m), 6.79 (1H, s),
 10 7.10-7.40 (7H, m), 7.47 (1H, s), 7.50-7.65 (1H, m), 8.45-8.55 (1H,
 m)

[0146]

Reference example 7-3

MS(ESI, m/z):391(M+Na)+

[0147]

5 Reference example 7-5

$^1\text{H-NMR}$ (CDCl_3) δ ppm : 1.92-2.01(1H, m), 2.07-2.17(1H, m),
2.57-2.66(4H, m), 2.73-2.81(1H, m), 3.68(1H, d, J=5.0Hz),
3.94(3H, s), 5.01-5.06(1H, m), 5.17-5.26(2H, m), 7.12-7.46(12H,
m)

10 [0148]

Reference example 7-6

$^1\text{H-NMR}$ (CDCl_3) δ ppm : 0.73(9H, s), 2.25(1H, bs), 2.64(3H, s),
3.94(3H, s), 5.21(1H, d, J=12.6Hz), 5.29(1H, d, J=12.6Hz),
5.45(1H, bs), 7.21(1H, s), 7.28-7.31(1H, m), 7.33-7.38(3H, m),
15 7.44-7.46(2H, m)

[0149]

Reference example 7-7

$^1\text{H-NMR}$ (CDCl_3) δ ppm:2.61(3H, s), 3.93(3H, s), 4.57(1H, d, J=5.2Hz),
4.99-5.10(4H, m), 6.13(1H, d, J=5.2Hz), 6.77(1H, s), 6.88(2H,
20 d, J=8.7Hz), 7.18(2H, d, J=8.7Hz), 7.23-7.47(10H, m), 7.48(1H,
s)

[0150]

Reference example 7-8

$^1\text{H-NMR}$ (CDCl_3) δ ppm:0.33-0.39(2H, m), 0.62-0.69(2H, m),
25 1.22-1.35(1H, m), 2.64(3H, s), 3.80(2H, d, J=7.0Hz), 3.94(3H,
s), 4.56(1H, d, J=5.5Hz), 4.99-5.11(2H, m), 6.11(1H, d, J=5.5Hz),
6.77(1H, s), 6.81(2H, d, J=8.6Hz), 7.16(2H, d, J=8.6Hz),

7.25-7.34 (5H, m), 7.48 (1H, s)

[0151]

Reference example 8-1

5-Benzyloxy-4-methoxy-2-(5-methyl-[1,2,4]oxadiazol-3-yl)

5 benzonitrile

A mixture of 3-(4-benzyloxy-2-iodo-5-methoxy-phenyl)-5-methyl-[1,2,4]oxadiazole (reference example 4-1) (500mg), cuprous cyanide (424mg), tris(dibenzylidene-acetone)dipalladium (0) (271mg), tetraethylammonium cyanide
10 (222mg), 1,1'-bis(diphenylphosphino)ferrocene (525mg) and 1,4-dioxane (12mL) was stirred at 105°C under an argon atmosphere for 2.5 hours. After cooling to room temperature, the mixture was passed through a layer of Celite (registered mark). The filtrate was concentrated under reduced pressure. The residue
15 was purified by silica gel column chromatography (eluent: 25%-50% ethyl acetate/hexane, gradient elution) to give the title compound (231mg).

¹H-NMR (CDCl₃) δ ppm: 2.69 (3H, s), 4.01 (3H, s), 5.21 (2H, s), 7.24 (1H, s), 7.30-7.50 (5H, m), 7.57 (1H, s)

20 [0152]

Reference example 9-1

1-[5-Benzyloxy-4-methoxy-2-(5-methyl-[1,2,4]oxadiazol-3-yl)phenyl]-2-phenylethanone

A mixture of 5-benzyloxy-4-methoxy-2-(5-methyl-[1,2,4]oxadiazol-3-yl)benzoic acid (reference example 5-1)
25 (817mg), thionyl chloride (0.53mL), N,N-dimethylformamide (1 drop) and toluene (10mL) was stirred at 80°C for 30 minutes.

The mixture was concentrated under reduced pressure. Toluene was added to the residue, and the mixture was concentrated under reduced pressure to give 5-benzyloxy-4-methoxy-2-(5-methyl-[1,2,4]oxadiazol-3-yl)benzoyl chloride.

- 5 A mixture of 5-benzyloxy-4-methoxy-2-(5-methyl-[1,2,4]oxadiazol-3-yl)benzoyl chloride, benzylzinc bromide (0.5mol/L, tetrahydrofuran solution, 4.4mL), dichlorobis-(triphenylphosphine)palladium(II) (153mg) and toluene (6mL) was stirred at room temperature under an argon atmosphere for 5 hours.
- 10 Ethyl acetate and 2mol/L hydrochloric acid were added to the mixture. The separated organic layer was washed with water, an aqueous solution of sodium bicarbonate and brine successively, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column
- 15 chromatography (eluent: 5%-20% ethyl acetate/hexane, gradient elution) to give the title compound (307mg).

¹H-NMR (CDCl₃) δ ppm: 1.84 (3H, s), 3.29 (1H, d, J=14.2Hz), 3.42 (1H, d, J=14.2Hz), 3.91 (3H, s), 5.19-5.25 (2H, m), 7.11 (1H, s), 7.15-7.20 (3H, m), 7.26-7.28 (2H, m), 7.30 (1H, s), 7.32-7.45 (5H, m)

20 m)

[0153]

Reference example 10-1

5-Benzyloxy-4-methoxy-2-(5-methyl-[1,2,4]oxadiazol-3-yl)-N-phenylbenzamide

- 25 To a mixture of 5-benzyloxy-4-methoxy-2-(5-methyl-[1,2,4]oxadiazol-3-yl)benzoic acid (reference example 5-1) (500mg), benzotriazol-1-yloxytripyrrolidinephosphonium

hexafluorophosphate (1.15g), 1-hydroxybenzotriazole(20mg),
methylene chloride(3mL) and N,N-dimethylformamide(3mL) were
added aniline(0.2mL) and triethylamine(0.62mL). After stirring
at room temperature for 4 hours, ethyl acetate and 2mol/L
5 hydrochloric acid were added to the mixture. The separated
organic layer was washed with a 2mol/L aqueous solution of sodium
hydroxide, an aqueous solution of sodium bicarbonate and brine
successively, dried over anhydrous magnesium sulfate, and
concentrated under reduced pressure. The residue was triturated
10 with methanol to give the title compound (449mg).

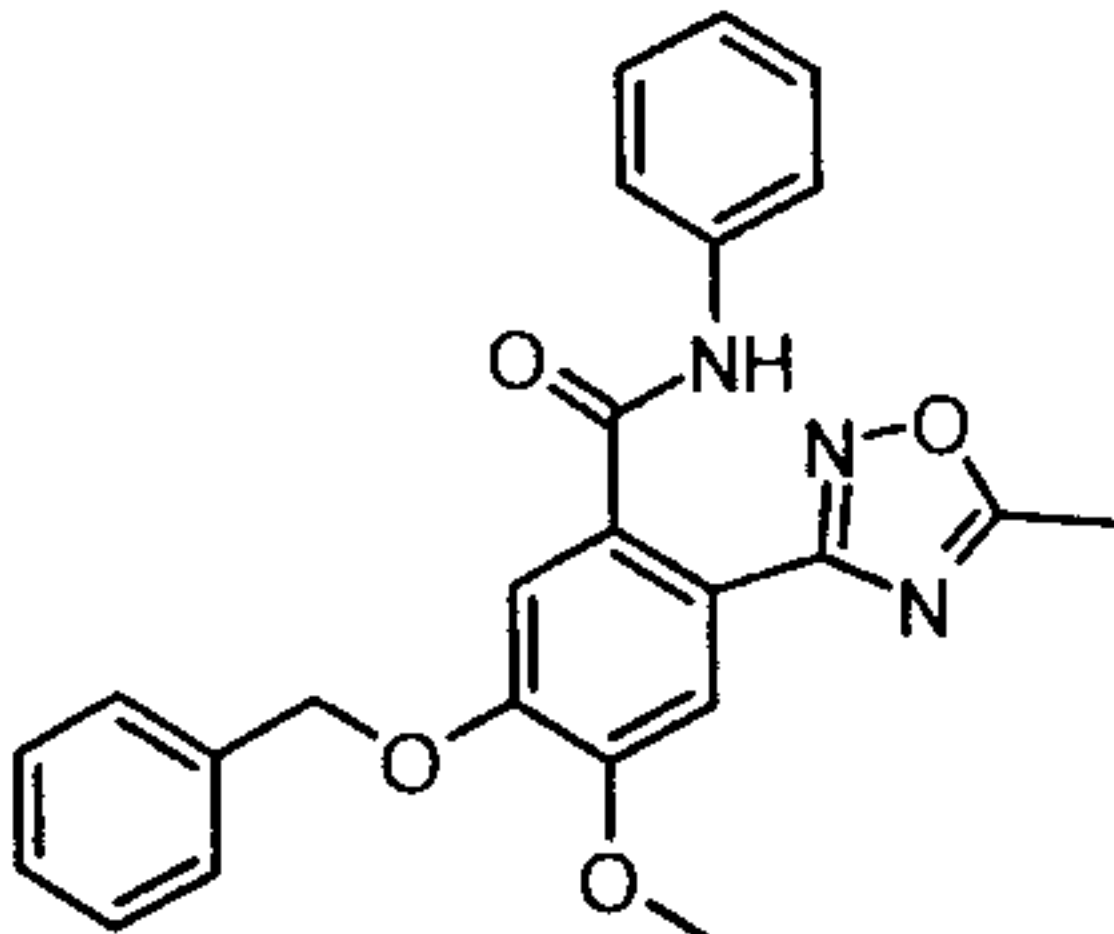
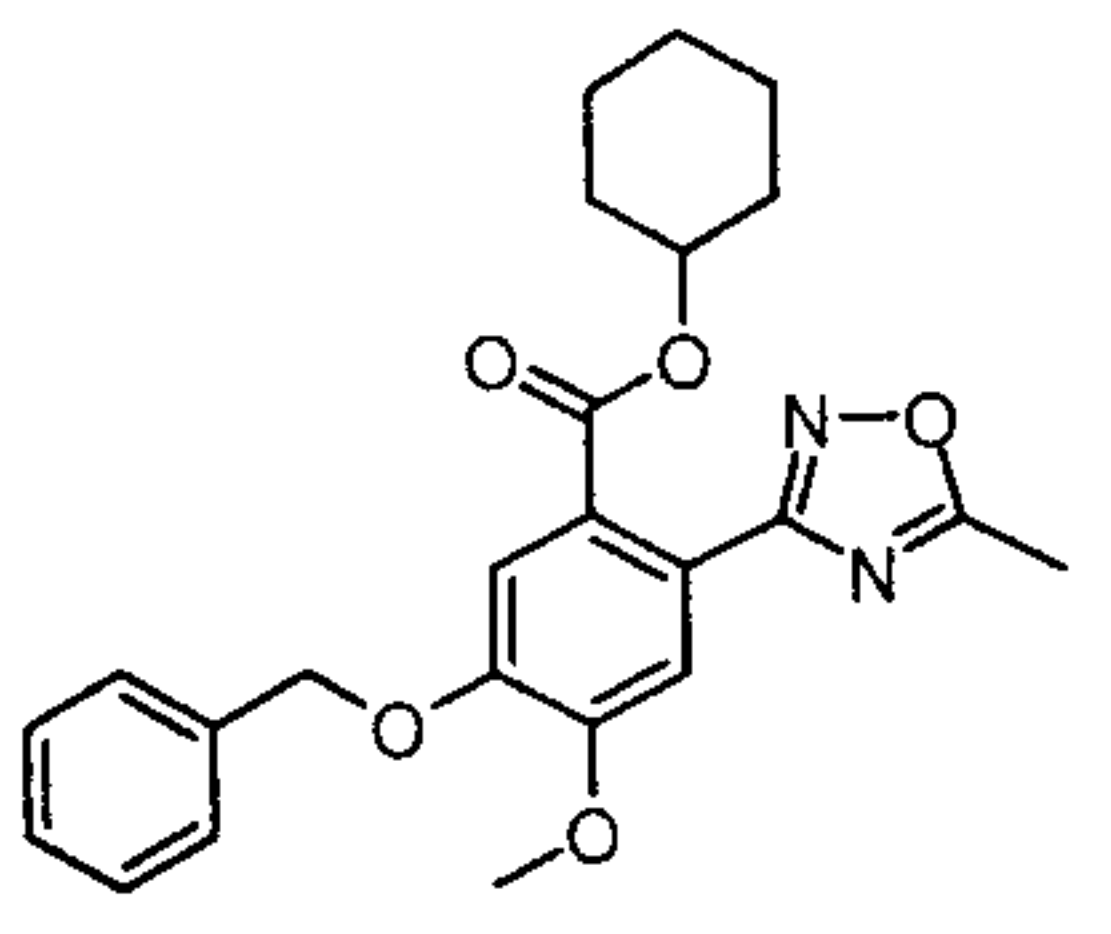
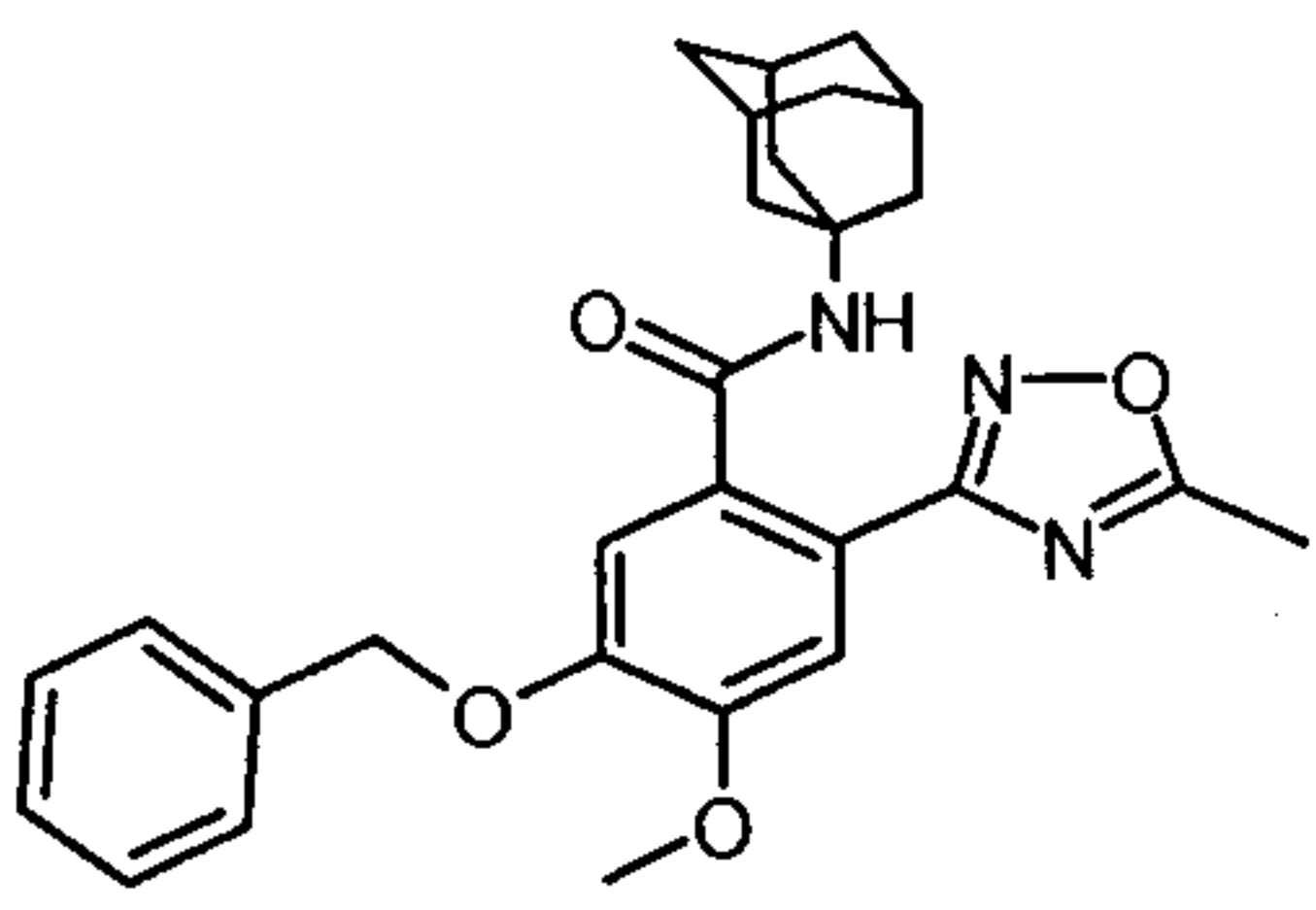
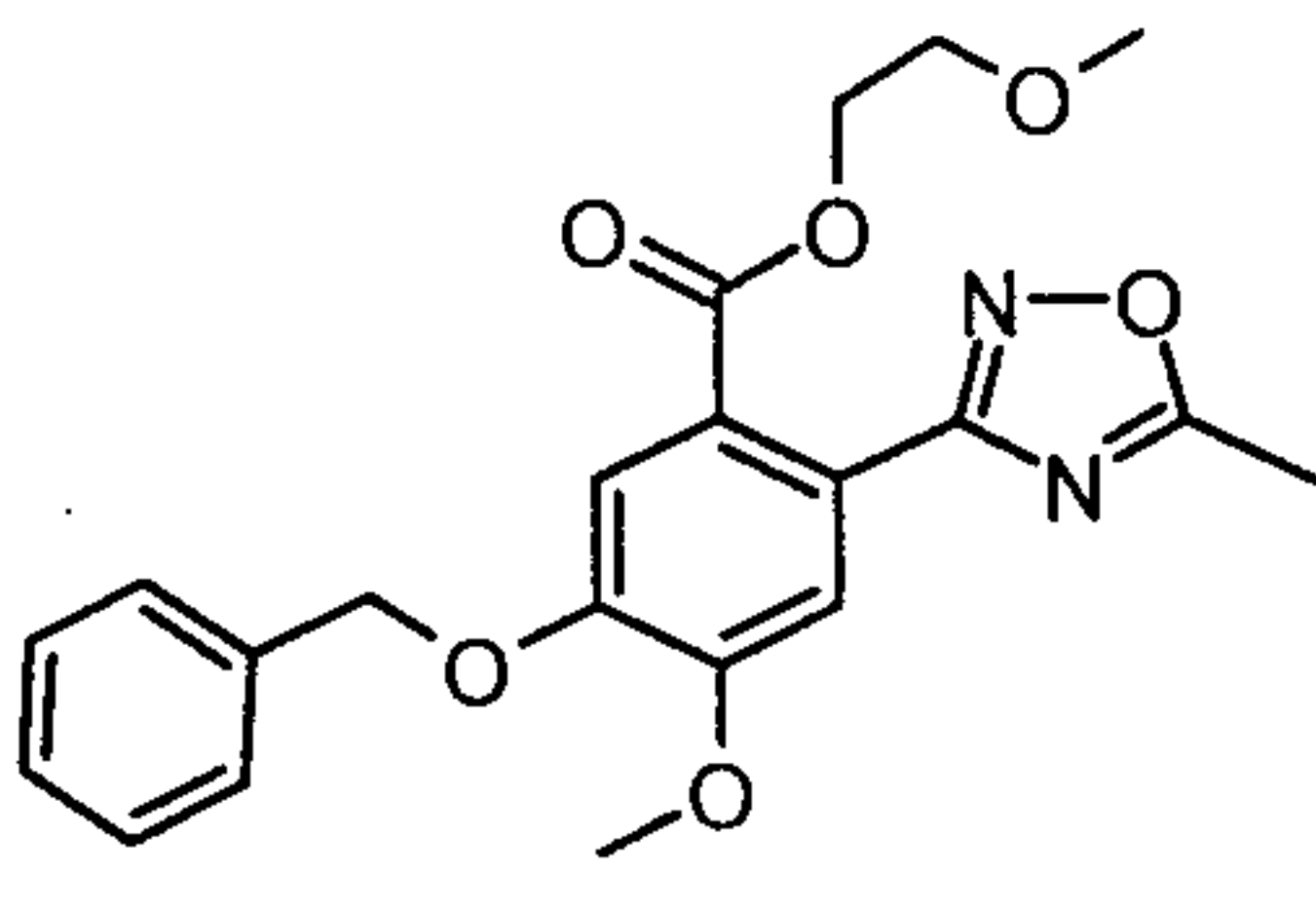
$^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 2.58(3H, s), 3.96(3H, s), 5.22(2H, s),
7.11-7.14(1H, m), 7.31-7.56(11H, m), 8.03(1H, br)

[0154]

Reference examples 10-2 to 10-4 were prepared in a manner
15 similar to those as described in Reference example 10-1 using
the corresponding amines or alcohols instead of aniline. These
were illustrated in table 6.

[0155]

Table6

Reference example	Structure	Reference example	Structure
10-1		10-3	
10-2		10-4	

[0156]

The physical data of reference examples 10-2 and 10-4 were shown below.

5 [0157]

Reference example 10-2

$^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 1.70 (6H, br s), 2.00-2.20 (9H, m), 2.63 (3H, s), 3.93 (3H, s), 5.20 (2H, s), 5.53 (1H, br s), 7.14 (1H, br s), 7.28 (1H, br s), 7.30-7.50 (5H, m)

10 [0158]

Reference example 10-4

$^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 2.63 (3H, s), 3.32 (3H, s), 3.50-3.60 (2H, m), 3.94 (3H, s), 4.20-4.40 (2H, m), 5.22 (2H, s), 7.14 (1H, s), 7.30-7.50 (6H, m)

15 [0159]

Reference example 11-1

Isopropyl 5-benzyloxy-4-methoxy-2-(5-methyl-[1,2,4]oxadiazol-3-yl)benzoate

A mixture of 5-benzyloxy-4-methoxy-2-(5-methyl-[1,2,4]oxadiazol-3-yl)benzoic acid(reference example 5-1) (308mg), 2-iodopropane(0.225mL), potassium carbonate (312mg) and N,N-dimethylformamide(2.6mL) was stirred at 60°C for 2.5
5 hours. After cooling to room temperature, water and ethyl acetate were added to the mixture. The separated organic layer was washed with water, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give the title compound (342mg).

10 ¹H-NMR(CDCl₃)δ ppm:1.10-1.25(6H, m), 2.64(3H, s), 3.93(3H, s), 5.00-5.20(1H, m), 5.23(2H, s), 7.10(1H, s), 7.33-7.50(6H, m) [0160]

Reference example 11-2

Ethyl 5-benzyloxy-4-methoxy-2-(5-methyl-[1,2,4]oxadiazol-
15 3-yl)benzoate

The title compound was prepared in a manner similar to those as described in Reference example 11-1 using iodoethane instead of 2-iodopropane.

¹H-NMR(CDCl₃)δ ppm:1.10-1.30(3H, m), 2.64(3H, s), 3.94(3H, s),
20 4.20-4.30(2H, m), 5.22(2H, s), 7.13(1H, s), 7.30-7.50(6H, m) [0161]

Reference example 12-1

Acetic acid [5-benzyloxy-4-methoxy-2-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]tert-butylcarbamoylemethyl ester

25 A mixture of 5-benzyloxy-4-methoxy-2-(5-methyl-[1,2,4]oxadiazol-3-yl)benzaldehyde(Reference example 15-1) (453mg), tert-butyl isocyanide(465mg), acetic acid(0.32mL) and

acetonitrile(8mL) was stirred at 70°C for 13 hours. After cooling to room temperature, ethyl acetate and water were added to the mixture. The separated organic layer was washed with water, an aqueous solution of sodium bicarbonate, and brine successively,
5 dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography(eluent: 15%-50% ethyl acetate/hexane, gradient elution) to give the title compound(604mg).

¹H-NMR(CDCl₃)δppm:1.26(9H, s), 2.06(3H, s), 2.69(3H, s), 3.95(3H, s),
10 5.21-5.30(2H, m), 6.38(1H, s), 7.27-7.50(8H, m)
[0162]

Reference example 12-2

Acetic acid [5-benzyloxy-4-methoxy-2-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]cyclohexylcarbamoylmethyl ester

15 The title compound was prepared in a manner similar to those as described in Reference example 12-1 using cyclohexyl isocyanide instead of tert-butyl isocyanide.

¹H-NMR(CDCl₃)δ ppm:0.95-1.43(5H, m), 1.48-1.71(4H, m),
1.93-1.99(1H, m), 2.07(3H, s), 2.70(3H, s), 3.67-3.76(1H, m),
20 3.94(3H, s), 5.20-5.30(2H, m), 6.48(1H, s), 7.28-7.50(8H, m)
[0163]

Reference example 13-1

2-[5-Benzyloxy-4-methoxy-2-(5-methyl-[1,2,4]oxadiazol-3-yl)phenyl]N-tert-butyl-2-hydroxyacetamide

25 A mixture of acetic acid [5-benzyloxy-4-methoxy-2-(5-methyl-[1,2,4]oxadiazol-3-yl)phenyl]-tert-butylcarbamoylmethyl ester(Reference example 12-1)(604mg), a 5mol/L aqueous

solution of sodium hydroxide (1mL) and methanol (8mL) was stirred at room temperature for 1.5 hours. Ethyl acetate and water were added to the mixture. The separated organic layer was washed with water, an aqueous solution of sodium bicarbonate
5 successively, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give the title compound (552mg).

MS (ESI, m/z): 426 (M+1)

[0164]

10 Reference example 13-2

2-[5-Benzyloxy-4-methoxy-2-(5-methyl-[1,2,4]oxadiazol-3-yl)phenyl]N-cyclohexyl-2-hydroxyacetamide

The title compound was prepared in a manner similar to those as described in Reference example 13-1 using acetic acid

15 [5-benzyloxy-4-methoxy-2-(5-methyl-[1,2,4]oxadiazol-3-yl)phenyl]cyclohexylcarbamoylemethyl ester (reference example 12-2) instead of acetic acid [5-benzyloxy-4-methoxy-2-(5-methyl-[1,2,4]oxadiazol-3-yl)phenyl]tert-butylcarbamoylemethyl ester.

20 ¹H-NMR (CDCl₃) δ ppm: 0.97-1.48 (5H, m), 1.54-1.95 (5H, m), 2.69 (3H, s), 3.71-3.80 (1H, m), 3.93 (3H, s), 4.84 (1H, d, J=5.5Hz), 5.18 (2H, s), 5.51 (1H, d, J=5.5Hz), 7.16 (1H, s), 7.29-7.47 (6H, m), 7.67 (1H, d, J=7.6Hz)

[0165]

25 Reference example 14-1

[5-Benzyloxy-4-methoxy-2-(5-methyl-[1,2,4]oxadiazol-3-yl)phenyl]phenylmethanone

A mixture of [5-benzyloxy-4-methoxy-2-(5-methyl-[1,2,4]oxadiazol-3-yl)phenyl]phenylmethanol (reference example 6-1) (526mg), manganese dioxide (1.18g) and methylene chloride (6.8mL) was stirred at room temperature overnight. After
5 addition of manganese dioxide (1.18g), the mixture was stirred for 7.5 hours, and manganese dioxide (0.59g) was added, and the mixture was stirred overnight. The mixture was passed through a layer of Celite (registered mark). The filtrate was concentrated under reduced pressure to give the title compound (526mg).

10 $^1\text{H-NMR}$ (CDCl_3) δ ppm: 2.42 (3H, s), 4.01 (3H, s), 5.18 (2H, s), 7.06 (1H, s), 7.30-7.50 (9H, m), 7.60-7.70 (2H, m)

[0166]

Reference example 14-2

1-[5-Benzyloxy-4-methoxy-2-(5-methyl-[1,2,4]oxadiazol-3-yl)
15 phenyl]ethanone

To a mixture of 1-[5-benzyloxy-4-methoxy-2-(5-methyl-[1,2,4]oxadiazol-3-yl)phenyl]ethanol (reference example 6-2) (467mg), triethylamine (0.956mL) and dimethyl sulfoxide (6mL) was added a mixture of pyridine sulfur trioxide
20 complex (655mg) and dimethyl sulfoxide (2mL). After stirring at room temperature for 2 hours, water and ethyl acetate were added to the mixture. The separated organic layer was washed with 2mol/L hydrochloric acid and brine successively, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The
25 residue was purified by silica gel column chromatography (eluent: 25% - 34% ethyl acetate/hexane, gradient elution) to give the title compound (365mg).

¹H-NMR (CDCl₃) δ ppm: 2.38 (3H, s), 2.64 (3H, s), 3.96 (3H, s), 5.22 (2H, s), 7.13 (1H, s), 7.28 (1H, s), 7.30-7.50 (5H, m)

[0167]

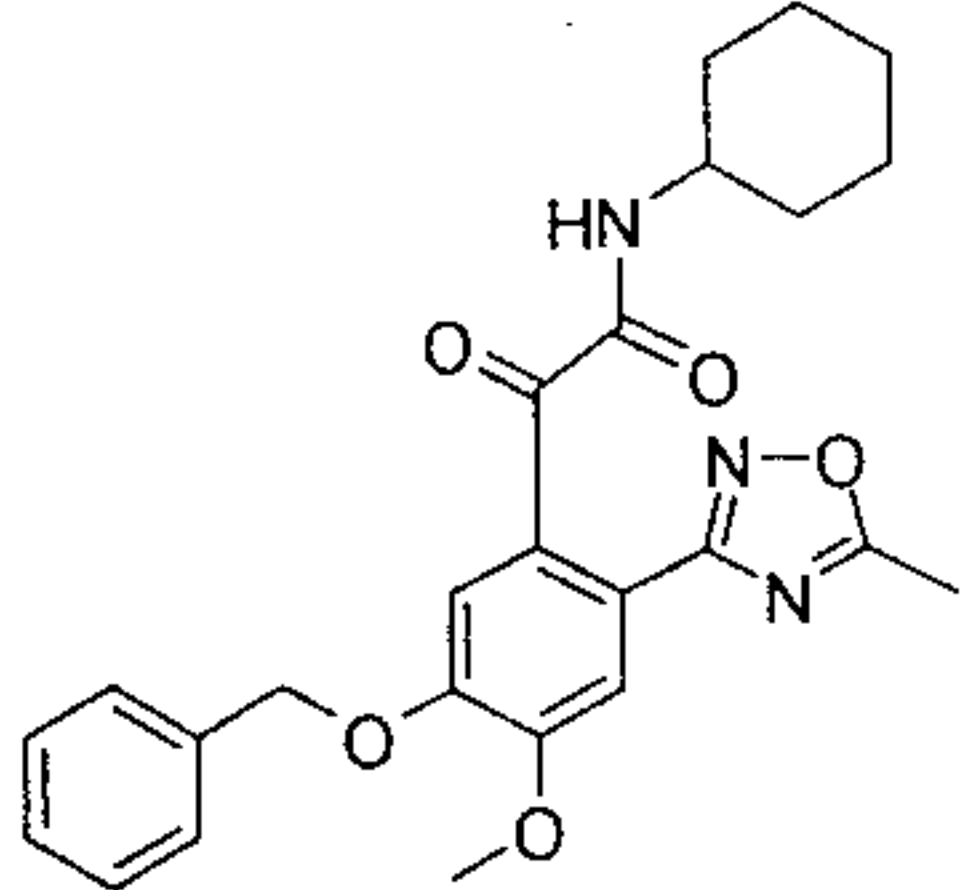
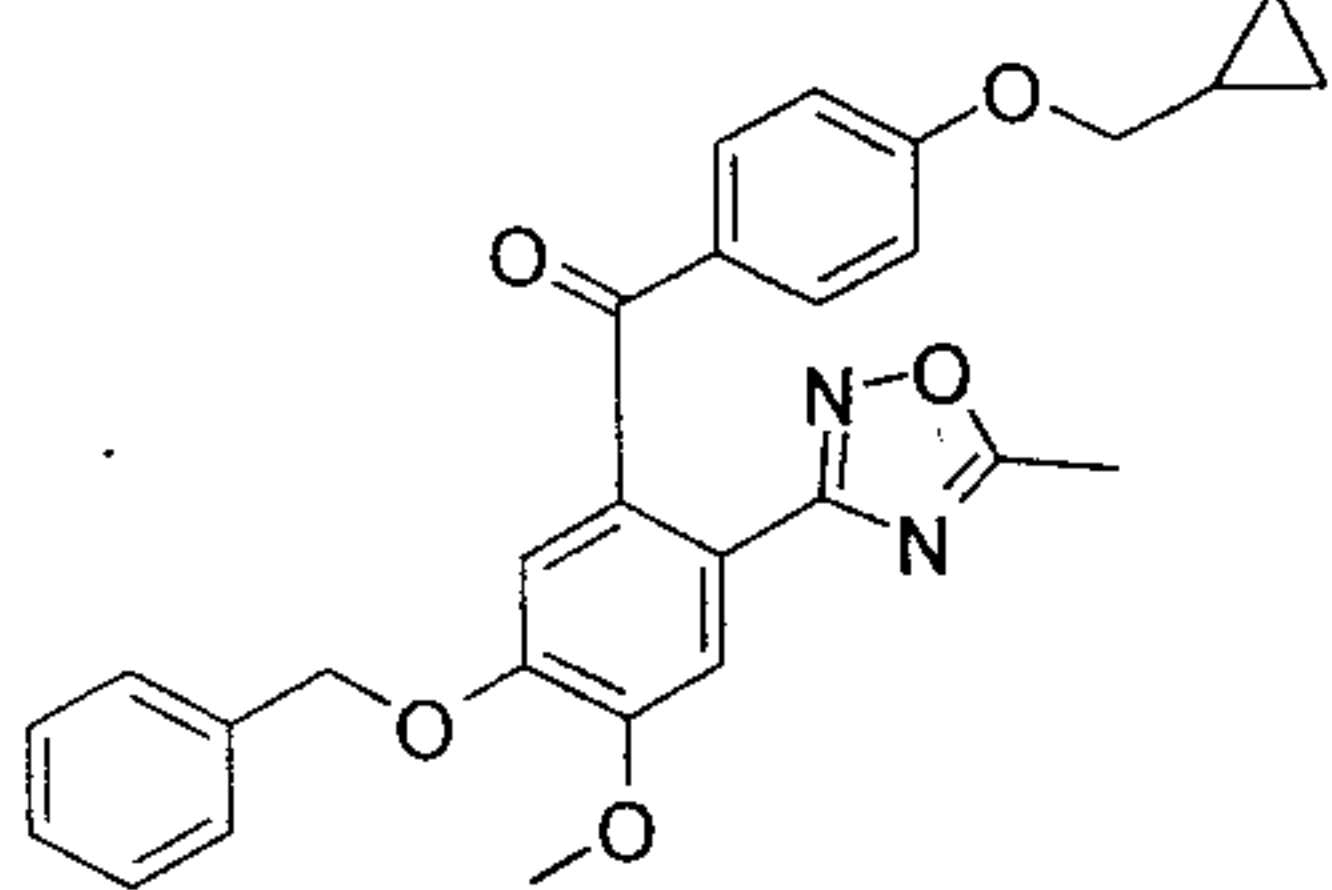
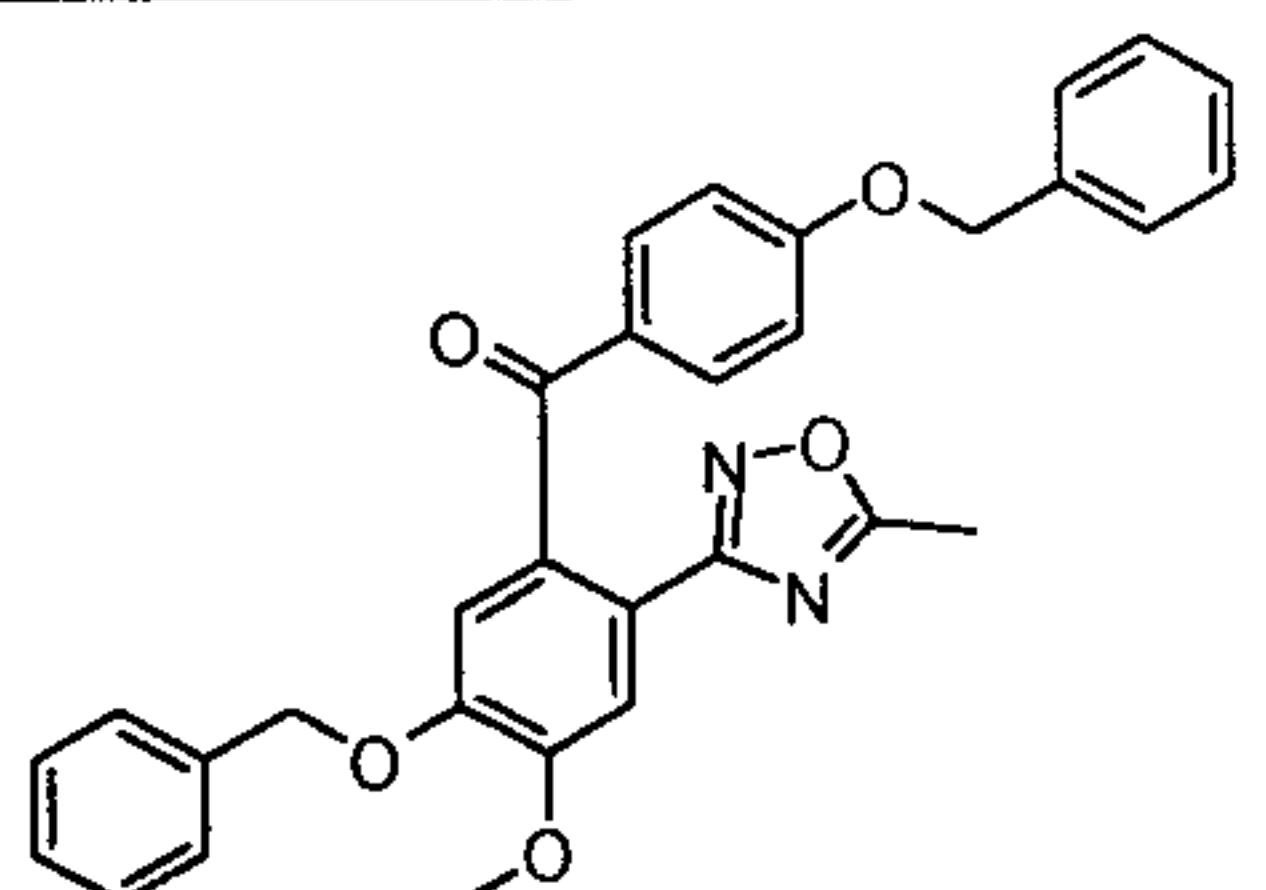
Reference examples 14-3 to 14-7 were prepared in a manner
5 similar to those as described in Reference example 14-1 or
Reference example 14-2 using the corresponding alcohols instead
of [5-benzyloxy-4-methoxy-2-(5-methyl-[1,2,4]oxadiazole-
3-yl)phenyl]phenylmethanol or 1-[5-benzyloxy-4-methoxy-2-
(5-methyl-[1,2,4]oxadiazol-3-yl)phenyl]ethanol. These were
10 illustrated in table 7.

[0168]

Table 7

Reference example	Structure	Reference example	Structure
14-1		14-8	
14-2		14-9	
14-3		14-10	
14-4		14-11	
14-5		14-12	
14-6		14-13	
14-7		14-14	

(continued)

Reference example	Structure	Reference example	Structure
14-15		14-17	
14-16			

[0169]

The physical data of reference examples 14-3 to 14-17 were shown below.

5 [0170]

Reference example 14-3

$^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 1.06 (6H, d, $J=6.8\text{Hz}$), 2.62 (3H, s), 2.79-2.86 (1H, m), 3.97 (3H, s), 5.22 (2H, s), 6.92 (1H, s), 7.29-7.44 (6H, m)

10 [0171]

Reference example 14-4

$^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 1.32 (9H, s), 2.60 (3H, s), 3.99 (3H, s), 5.19 (2H, s), 6.94 (1H, br), 7.18 (1H, s), 7.31-7.47 (6H, m)

[0172]

15 Reference example 14-5

$^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 2.37 (3H, s), 2.44 (3H, s), 4.01 (3H, s), 5.30 (2H, s), 7.03 (1H, s), 7.10-7.70 (10H, m)

[0173]

Reference example 14-6

$^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 2.38 (3H, s), 4.01 (3H, s), 5.21 (2H, s),
7.20-7.55 (8H, m), 7.75-7.85 (1H, m), 8.05-8.20 (1H, m),
8.35-8.50 (1H, m)

[0174]

5 Reference example 14-7

MS (ESI, m/z): 407 (M+1)

[0175]

Reference example 14-8

$^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 0.89-0.93 (2H, m), 1.18-1.22 (2H, m),
10 2.00-2.06 (1H, m), 2.63 (3H, s), 3.96 (3H, s), 5.22 (2H, s), 7.19 (1H,
s), 7.29 (1H, s), 7.30-7.47 (5H, m)

[0176]

Reference example 14-9

$^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 2.45 (3H, s), 3.99 (3H, s), 5.18 (2H, s),
15 6.96-7.01 (1H, m), 7.08-7.12 (1H, m), 7.14 (1H, s), 7.31-7.45 (7H,
m), 7.52-7.57 (1H, m)

[0177]

Reference example 14-10

$^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 2.45 (3H, s), 4.01 (3H, s), 5.22 (2H, s),
20 7.25-7.50 (6H, m), 7.51 (1H, s), 7.55-7.65 (1H, m), 7.75-7.85 (1H,
m)

[0178]

Reference example 14-11

$^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 2.62 (3H, s), 2.93-3.02 (4H, m), 3.95 (3H, s),
25 5.14 (2H, s), 6.92 (1H, s), 7.13-7.44 (11H, m)

[0179]

Reference example 14-12

^1H -NMR(CDCl_3) δ ppm: 1.11 (9H, s), 2.59 (3H, s), 3.98 (3H, s), 5.22 (2H, s), 6.67 (1H, s), 7.28–7.43 (5H, m), 7.54 (1H, s)

[0180]

Reference example 14-13

5 ^1H -NMR(CDCl_3) δ ppm: 1.40–1.50 (6H, m), 2.36 (3H, s), 3.20–3.40 (1H, m), 3.97 (3H, s), 5.22 (2H, s), 7.13 (1H, s), 7.29 (1H, s), 7.30–7.50 (5H, m)

[0181]

Reference example 14-14

10 ^1H -NMR(CDCl_3) δ ppm: 1.00–1.10 (3H, m), 1.80–2.00 (2H, m), 2.36 (3H, s), 2.80–3.00 (2H, m), 3.96 (3H, s), 5.22 (2H, s), 7.13 (1H, s), 7.29 (1H, s), 7.30–7.50 (5H, m)

[0182]

Reference example 14-15

15 ^1H -NMR(CDCl_3) δ ppm: 1.15–1.41 (5H, m), 1.60–1.88 (5H, m), 2.60 (3H, s), 3.58–3.67 (1H, m), 4.00 (3H, s), 5.19 (2H, s), 6.95 (1H, d, $J=8.6\text{Hz}$), 7.21 (1H, s), 7.30–7.48 (6H, m)

[0183]

Reference example 14-16

20 ^1H -NMR(CDCl_3) δ ppm: 2.44 (3H, s), 4.00 (3H, s), 5.10 (2H, s), 5.17 (2H, s), 6.89 (2H, d, $J=9.0\text{Hz}$), 7.01 (1H, s), 7.27–7.44 (10H, m), 7.48 (1H, s), 7.66 (2H, d, $J=9.0\text{Hz}$)

[0184]

Reference example 14-17

25 ^1H -NMR(CDCl_3) δ ppm: 0.33–0.39 (2H, m), 0.62–0.70 (2H, m), 1.22–1.33 (1H, m), 2.46 (3H, s), 3.83 (2H, d, $J=6.9\text{Hz}$), 4.01 (3H, s), 5.17 (2H, s), 6.81 (2H, d, $J=9.0\text{Hz}$), 7.02 (1H, s), 7.28–7.44 (5H, m)

m), 7.49(1H, s), 7.66(2H, d, J=9.0Hz)

[0185]

Reference example 15-1

5-Benzyloxy-4-methoxy-2-(5-methyl-[1,2,4]oxadiazol-3-yl)

5 benzaldehyde

A mixture of 3-(4-benzyloxy-2-iodo-5-methoxyphenyl)-
5-methyl-[1,2,4]oxadiazole(reference example 4-1) (3.52g) and
tetrahydrofuran(35mL) was cooled in an ice salt bath under an
argon atmosphere. Isopropylmagnesium chloride(2.0mol/L
10 tetrahydrofuran solution, 5mL) was added. After stirring under
ice-bath cooling for 1 hour, N,N-dimethylformamide(1.28mL) was
added to the mixture. After stirring at room temperature
overnight, water, 2mol/L hydrochloric acid and ethyl acetate
were added successively to the mixture. The separated organic
15 layer was dried over anhydrous magnesium sulfate, and
concentrated under reduced pressure. The residue was purified
by silica gel column chromatography (eluent: 25%-34% ethyl
acetate/hexane, gradient elution) to give the title
compound(1.83g).

20 ¹H-NMR(CDCl₃)δ ppm:2.69(3H, s), 4.02(3H, s), 5.25(2H, s),
7.30-7.50(6H, m), 7.67(1H, s), 10.58(1H, s)

[0186]

Reference examples 15-2 to 15-14 were prepared in a manner
similar to those as described in Reference Example 15-1 using
25 the corresponding halobenzenes and N,N-dimethylformamide, acid
anhydrides, acid chlorides or N-methoxy-N-methylamides instead
of 3-(4-benzyloxy-2-iodo-5-methoxyphenyl)-5-methyl-[1,2,4]-

oxadiazole and N,N-dimethylformamide. These were illustrated in table 8.

[0187]

Table 8

Reference example	Structure	Reference example	Structure
15-1		15-8	
15-2		15-9	
15-3		15-10	
15-4		15-11	
15-5		15-12	
15-6		15-13	
15-7		15-14	

[0188]

The physical data of reference examples 15-2 to 15-14 were shown below.

[0189]

5 Reference example 15-2

$^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 2.68 (3H, s), 3.99 (3H, s), 2.27 (2H, s), 7.30-7.50 (5H, m), 7.56 (1H, s), 7.62 (1H, s), 10.61 (1H, s)

[0190]

Reference example 15-3

10 $^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 2.50 (3H, s), 4.03 (3H, s), 5.23 (2H, s), 6.67 (1H, d, $J=1.7\text{Hz}$), 7.21 (1H, s), 7.30-7.50 (5H, m), 7.51 (1H, s), 8.23 (1H, d, $J=1.7\text{Hz}$)

[0191]

Reference example 15-4

15 $^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 2.63 (3H, s), 4.00 (3H, s), 5.21 (2H, s), 7.12 (1H, s), 7.25-7.55 (6H, m)

[0192]

Reference example 15-5

MS (ESI, m/z): 431 (M+1)

20 [0193]

Reference example 15-6

$^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 2.35 (3H, s), 3.96 (3H, s), 5.23 (2H, s), 5.34 (2H, s), 6.95-7.10 (3H, m), 7.14 (1H, s), 7.20-7.60 (8H, m)

[0194]

25 Reference example 15-7

$^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 1.40-1.50 (6H, m), 3.20-3.40 (1H, m), 4.02 (3H, s), 5.25 (2H, s), 7.30-7.50 (6H, m), 7.67 (1H, s), 10.59 (1H, s)

[0195]

Reference example 15-8

^1H -NMR(CDCl_3) δ ppm:1.00-1.10(3H, m), 1.90-2.00(2H, m),
2.90-3.00(2H, m), 4.02(3H, s), 5.25(2H, s), 7.30-7.50(6H, m),
5 7.67(1H, s), 10.59(1H, s)

[0196]

Reference example 15-9

^1H -NMR(CDCl_3) δ ppm:1.27(3H, t, $J=7.1\text{Hz}$), 2.35(3H, s), 2.90(2H,
t, $J=7.2\text{Hz}$), 3.24(2H, t, $J=7.2\text{Hz}$), 3.96(3H, s), 4.18(2H, q,
10 $J=7.1\text{Hz}$), 5.21(2H, s), 7.11(1H, s), 7.29(1H, s), 7.25-7.50(5H,
m)

[0197]

Reference example 15-10

^1H -NMR(CDCl_3) δ ppm:2.44(3H, s), 3.98(3H, s), 5.25(2H, s), 7.21(1H,
15 s), 7.25(1H, s), 7.30-7.50(5H, m)

[0198]

Reference example 15-11

^1H -NMR(CDCl_3) δ ppm:1.95-2.15(4H, m), 2.37(3H, s), 3.19-3.30(1H,
m), 3.52-3.62(2H, m), 3.97(3H, s), 4.00-4.08(2H, m), 5.22(2H,
20 s), 7.13(1H, s), 7.29(1H, s), 7.30-7.50(5H, m)

[0199]

Reference example 15-12

^1H -NMR(CDCl_3) δ ppm:1.19(3H, d, $J=7.0\text{Hz}$), 2.36(3H, s), 3.21(2H,
t, $J=6.6\text{Hz}$), 3.54(2H, q, $J=7.0\text{Hz}$), 3.89(2H, t, $J=6.6\text{Hz}$), 3.96(3H,
25 s), 5.22(2H, s), 7.13(1H, s), 7.29(1H, s), 7.30-7.50(5H, m)

[0200]

Reference example 15-13

¹H-NMR (CDCl₃) δ ppm: 2.42 (3H, s), 3.93 (3H, s), 4.02 (3H, s), 5.19 (2H, s), 7.06 (1H, s), 7.30-7.44 (5H, m), 7.49 (1H, s), 7.71 (2H, d, J=8.6Hz), 7.98 (2H, d, J=8.6Hz)

[0201]

5 Reference example 15-14

¹H-NMR (CDCl₃) δ ppm: 2.44 (3H, s), 4.02 (3H, s), 5.20 (2H, s), 7.04 (1H, s), 7.30-7.46 (5H, m), 7.50 (1H, s), 7.61 (2H, d, J=8.8Hz), 7.73 (2H, d, J=8.8Hz)

[0202]

10 Reference example 16-1

Methyl 5-benzyloxy-4-methoxy-2-(5-methyl-[1,2,4]oxadiazol-3-yl)benzoate

A mixture of tris(dibenzylideneacetone)dipalladium(0) (163mg), 1,1'-bis(diphenylphosphino)ferrocene (394mg) and
15 N,N-dimethylformamide (10mL) was stirred under an argon atmosphere for 10 minutes. 3-(4-Benzyloxy-2-iodo-5-methoxy-phenyl)-5-methyl-[1,2,4]oxadiazole (reference example 4-1) (1.5g), methanol (15mL) and triethylamine (1.5mL) were added to the mixture. After displacement to a carbon monoxide atmosphere,
20 the mixture was stirred at 90°C for 16 hours. After cooling to room temperature, ethyl acetate and 2mol/L hydrochloric acid were added to the mixture. The separated organic layer was washed with water, a 2mol/L aqueous solution of sodium hydroxide, an aqueous solution of sodium bicarbonate and brine successively,
25 dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: 15%-30% ethyl acetate/hexane, gradient

elution) to give the title compound(1.1g).

$^1\text{H-NMR}(\text{CDCl}_3)\delta\text{ppm}: 2.65(3\text{H}, \text{s}), 3.77(3\text{H}, \text{s}), 3.94(3\text{H}, \text{s}), 5.21(2\text{H}, \text{s}), 7.16(1\text{H}, \text{s}), 7.31-7.47(6\text{H}, \text{m})$

[0203]

5 Reference examples 16-2 to 16-4 were prepared in a manner similar to those as described in Reference Example 16-1 using the corresponding iodobenzenes instead of 3-(4-benzyloxy-2-iodo-5-methoxyphenyl)-5-methyl-[1,2,4]oxadiazole. These were illustrated in table 9.

10 [0204]

Table 9

Reference example	Structure	Reference example	Structure
16-1		16-3	
16-2		16-4	

[0205]

The physical data of reference examples 16-2 to 16-4 were shown below.

15 [0206]

Reference example 16-2

$^1\text{H-NMR}(\text{CDCl}_3)\delta\text{ppm}: 1.22-1.30(4\text{H}, \text{m}), 2.21-2.27(1\text{H}, \text{m}), 3.76(3\text{H}, \text{s}), 3.94(3\text{H}, \text{s}), 5.21(2\text{H}, \text{s}), 7.15(1\text{H}, \text{s}), 7.31-7.46(6\text{H}, \text{m})$

[0207]

Reference example 16-3

$^1\text{H-NMR}(\text{CDCl}_3)\delta\text{ppm}$: 3.56 (3H, s), 3.77 (3H, s), 3.95 (3H, s), 4.76 (2H, s), 5.22 (2H, s), 7.17 (1H, s), 7.32-7.47 (5H, m), 7.49 (1H, s)
[0208]

5 Reference example 16-4

$^1\text{H-NMR}(\text{CDCl}_3)\delta\text{ppm}$: 1.49 (9H, s), 3.73 (3H, s), 3.95 (3H, s), 5.21 (2H, s), 7.18 (1H, s), 7.30-7.46 (6H, m)
[0209]

Reference example 17-1

10 3-(4-Benzyloxy-5-methoxy-2-trifluoromethylphenyl)-5-methyl-[1,2,4]oxadiazole

A mixture of 3-(4-benzyloxy-2-iodo-5-methoxyphenyl)-5-methyl-[1,2,4]oxadiazole (reference example 4-1), methyl fluorosulfonyldifluoroacetate (0.59 mL), copper(I) iodide
15 (88 mg) and N,N-dimethylformamide (8 mL) was stirred at 90°C for 3.5 hours. After cooling to room temperature, ethyl acetate was added to the mixture. The mixture was passed through a layer of Celite (registered mark). The filtrate was washed with an aqueous solution of sodium hydroxide, an aqueous solution of
20 sodium bicarbonate and brine successively, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: 10%-40% ethyl acetate/hexane, gradient elution) to give the title compound (522 mg).

25 $^1\text{H-NMR}(\text{CDCl}_3)\delta\text{ppm}$: 2.67 (3H, s), 3.95 (3H, s), 5.22 (2H, s), 7.25 (1H, s), 7.31 (1H, s), 7.32-7.47 (5H, m)
[0210]

Reference example 18-1

2-[5-Benzyloxy-4-methoxy-2-(5-methyl-[1,2,4]oxadiazol-3-yl)phenyl]N-cyclohexyl-N-methyl-2-oxoacetamide

To a mixture of 2-[5-benzyloxy-4-methoxy-2-(5-methyl-[1,2,4]oxadiazol-3-yl)phenyl]N-cyclohexyl-2-oxoacetamide (reference example 14-15) (860mg) and N,N-dimethylformamide (6mL) was added sodium hydride (60%, 92mg). After stirring at room temperature for 20 minutes, iodomethane (0.48mL) was added to the mixture. After stirring at room temperature for 8 hours, the mixture was poured into a mixture of 2mol/L hydrochloric acid and ice-water. Ethyl acetate was added to the mixture. The separated organic layer was washed with water, an aqueous solution of sodium bicarbonate and brine successively, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: 0%-50% ethyl acetate/hexane, gradient elution) to give the title compound (605mg).

MS (ESI, m/z): 464 (M+1)

[0211]

Reference example 19-1

5-Methanesulfonyl-2-methoxy-4-(5-methyl-[1,2,4]oxadiazol-3-yl)phenol

A mixture of 3-(4-benzyloxy-2-iodo-5-methoxyphenyl)-5-methyl-[1,2,4]oxadiazole (reference example 4-1) (0.7g), triisopropylsilanethiol (0.391mL), tris(dibenzylideneacetone)dipalladium (0) (152mg), (oxydi-2,1-phenylene)bis(diphenylphosphine) (90mg), sodium bis(trimethylsilyl)amide

(1.0mol/L tetrahydrofuran solution, 0.39mL) and toluene (20mL) was stirred at 80°C under argon atmosphere for 2 hours. After cooling to room temperature, Florisil (registered mark) (1g) was added to the mixture. After stirring for 10 minutes, the mixture
5 was passed through a layer of Celite (registered mark). The filtrate was concentrated under reduced pressure to give 3-(4-benzyloxy-5-methoxy-2-triisopropylsilanylsulfanylphenyl)-5-methyl-[1,2,4]oxadiazole.

A mixture of 3-(4-benzyloxy -5-methoxy-2-triisopropyl-
10 silanylsulfanylphenyl)-5-methyl-[1,2,4]oxadiazole, iodomethane (0.155mL), cesium fluoride (756mg) and N,N-dimethylformamide (20mL) was stirred at room temperature for 30 minutes. Water and ethyl acetate were added to the mixture. The separated organic layer was washed with water, dried over
15 anhydrous magnesium sulfate, and concentrated under reduced pressure to give 3-(4-benzyloxy -5-methoxy-2-methylsulfanylphenyl)-5-methyl-[1,2,4]oxadiazole.

A mixture of 3-(4-benzyloxy -5-methoxy-2-methylsulfanylphenyl)-5-methyl-[1,2,4]oxadiazole, m-chloroperbenzoic acid
20 (60%, 1.43g) and methylene chloride (30mL) was stirred overnight. An aqueous solution of sodium hydrogen sulfite and methylene chloride were added to the mixture. The separated organic layer was washed with a 2mol/L aqueous solution of sodium hydroxide and brine successively, dried over anhydrous magnesium sulfate,
25 and concentrated under reduced pressure to give 3-(4-benzyloxy -2-methanesulfonyl-5-methoxyphenyl)-5-methyl-[1,2,4]oxadiazole.

To a mixture of 3-(4-benzyloxy -2-methanesulfonyl-5-methoxyphenyl)-5-methyl-[1,2,4]oxadiazole and methylene chloride (20mL) was added titanium(IV) chloride (0.472g). After stirring at room temperature for 15 minutes, 2mol/L hydrochloric acid and methylene chloride were added to the mixture. The separated organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: 10%-100% ethyl acetate/hexane, gradient elution) to give the title compound (112mg).

¹H-NMR (CDCl₃) δ ppm: 2.67 (3H, s), 3.42 (3H, s), 3.99 (3H, s), 7.18 (1H, s), 7.76 (1H, s)

[0212]

Reference example 20-1

5-Hydroxy-4-methoxy-N,N-dimethyl-2-(5-methyl-[1,2,4]oxadiazol-3-yl)benzenesulfonamide

A mixture of 3-(4-benzyloxy-2-iodo-5-methoxyphenyl)-5-methyl-[1,2,4]oxadiazole (reference example 4-1) (0.7g), triisopropylsilanethiol (0.391mL), tris(dibenzylideneacetone)dipalladium (0) (152mg), (oxydi-2,1-phenylene)bis-(diphenylphosphine) (90mg), sodium bis(trimethylsilyl)amide (1.0mol/L tetrahydrofuran solution, 0.39mL) and toluene (20mL) was stirred at 80°C for 2 hours under an argon atmosphere. After cooling to room temperature, Florisil (registered mark) (1g) was added to the mixture. After stirring for 10 minutes, the mixture was passed through a layer of Celite (registered mark). The filtrate was concentrated under reduced pressure to give 3-(4-benzyloxy -5-methoxy-2-triisopropylsilanylsulfanyl-

phenyl)-5-methyl-[1,2,4]oxadiazole.

To a mixture of 3-(4-benzyloxy-5-methoxy-2-triisopropyl-silanylsulfanylphenyl)-5-methyl-[1,2,4]oxadiazole, sodium nitrate (352mg) and acetonitrile (16mL) was added sulfur
5 chloride (0.336mL) under ice-bath cooling. After stirring at room temperature for 1 hour, the mixture was poured into ice-water. Ethyl acetate was added to the mixture. The separated organic layer was dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give 5-benzyloxy-4-
10 methoxy-2-(5-methyl-[1,2,4]oxadiazol-3-yl)benzenesulfonyl chloride.

To a mixture of 5-benzyloxy-4-methoxy-2-(5-methyl-[1,2,4]oxadiazol-3-yl)benzenesulfonylchloride, dimethyl-amine hydrochloride (203mg) and tetrahydrofuran (20mL) was added
15 triethylamine (0.693mL) under ice-bath cooling. After stirring at room temperature overnight, 2mol/L hydrochloric acid was added to the mixture. The separated organic layer was washed with 2mol/L hydrochloric acid and brine successively, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to
20 give 5-benzyloxy-4-methoxy-N,N-dimethyl-2-(5-methyl-[1,2,4]oxadiazol-3-yl)benzenesulfonamide.

To a mixture of 5-benzyloxy-4-methoxy-N,N-dimethyl-2-(5-methyl-[1,2,4]oxadiazol-3-yl)benzenesulfonamide and methylene chloride (20mL) was added titanium(IV) chloride
25 (0.472g) under ice-bath cooling. After stirring at room temperature overnight, 2mol/L hydrochloric acid and methylene chloride were added to the mixture. The separated organic layer

was washed with 2mol/L hydrochloric acid and brine successively,
and concentrated under reduced pressure. The residue was purified
by silica gel column chromatography (eluent: 10%-100% ethyl
acetate/hexane, gradient elution) to give the title compound
5 (121mg).

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 2.66 (3H, s), 2.78 (6H, s), 3.95 (3H, s), 6.95 (1H,
s), 7.50 (1H, s)

[0213]

Reference example 21-1

10 [5-Hydroxy-4-methoxy-2-(5-methyl-[1,2,4]oxadiazol-3-yl)
phenyl]phenylmethanone

To a mixture of [5-benzyloxy-4-methoxy-2-(5-methyl-
[1,2,4]oxadiazol-3-yl)phenyl]phenylmethanone (reference
example 14-1) (526mg) and methylene chloride (22mL) was added
15 titanium(IV) chloride (0.288mL) at room temperature. After
stirring for 30 minutes, 2mol/L hydrochloric acid and ethyl
acetate were added to the mixture at room temperature. The
separated organic layer was dried over anhydrous magnesium
sulfate, and concentrated under reduced pressure. The residue
20 was purified by silica gel column chromatography (eluent: 50%-67%
ethyl acetate/hexane, gradient elution) to give the title
compound (383mg).

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 2.44 (3H, s), 4.03 (3H, s), 5.93 (1H, s), 7.07 (1H,
s), 7.30-7.80 (6H, m)

25 [0214]

Reference examples 21-2 to 21-45 were prepared in a manner
similar to those as described in Reference example 21-1 using

the corresponding benzyl ethers instead of [5-benzyloxy-4-methoxy-2-(5-methyl-[1,2,4]oxadiazol-3-yl)phenyl]phenylmethanone. These were illustrated in table 10.

[0215]

Table 10

Reference example	Structure	Reference example	Structure
21-1		21-8	
21-2		21-9	
21-3		21-10	
21-4		21-11	
21-5		21-12	
21-6		21-13	
21-7		21-14	

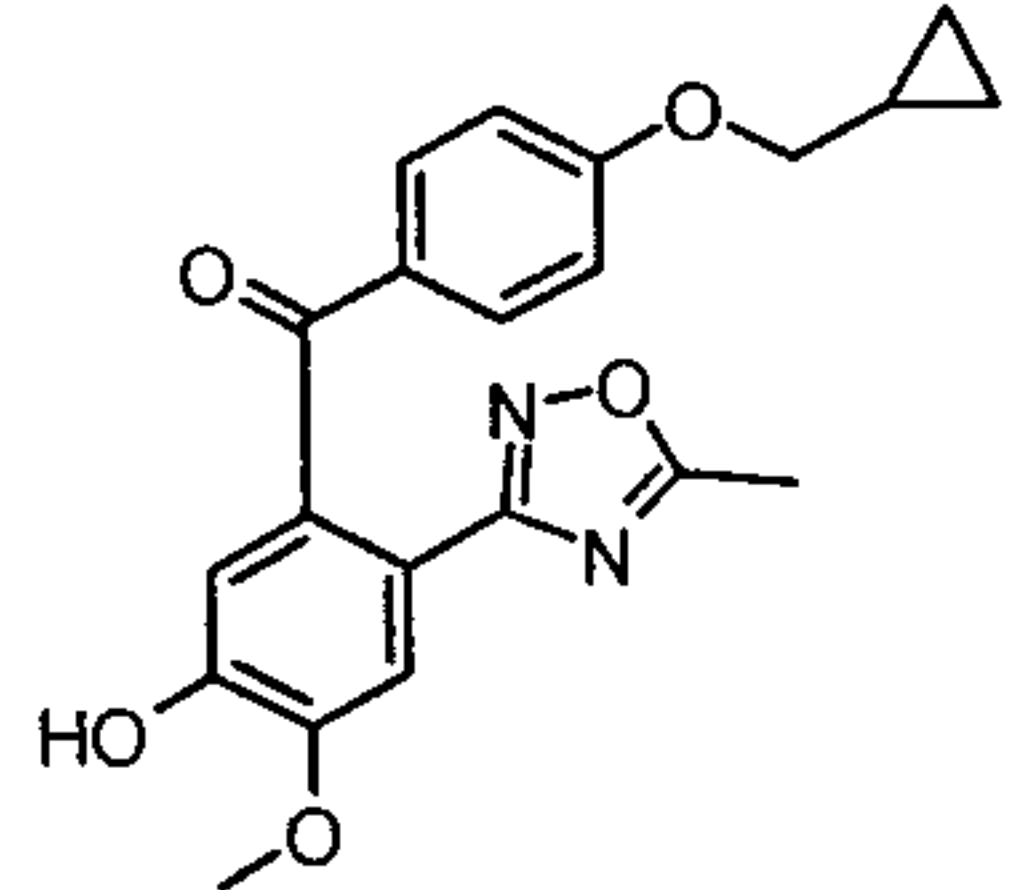
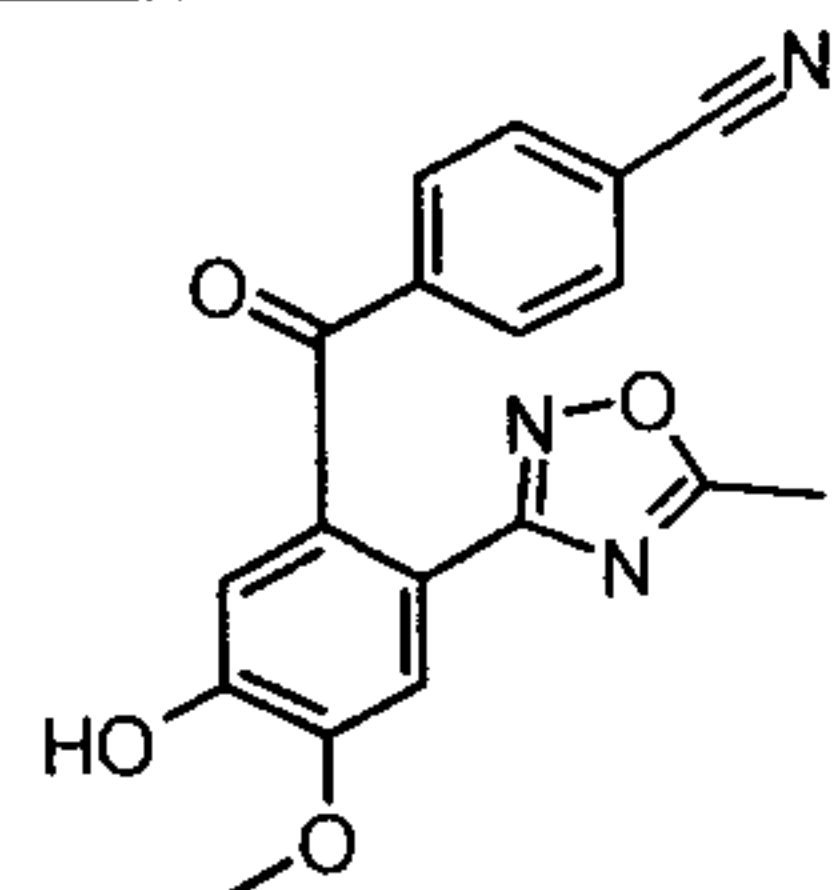
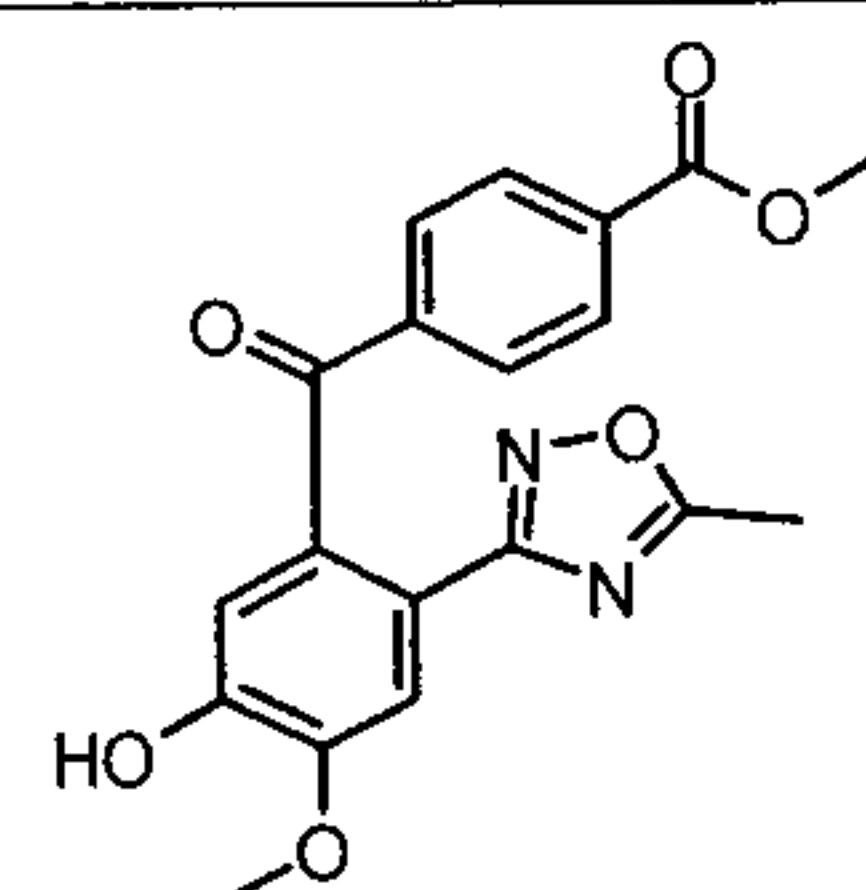
(continued)

Reference example	Structure	Reference example	Structure
21-15		21-22	
21-16		21-23	
21-17		21-24	
21-18		21-25	
21-19		21-26	
21-20		21-27	
21-21		21-28	

(continued)

Reference example	Structure	Reference example	Structure
21-29		21-36	
21-30		21-37	
21-31		21-38	
21-32		21-39	
21-33		21-40	
21-34		21-41	
21-35		21-42	

(continued)

Reference example	Structure	Reference example	Structure
21-43		21-45	
21-44			

[0216]

The physical data of reference examples 21-2 to 21-35 and 21-37 to 21-45 were shown below.

5 [0217]

Reference example 21-2

$^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 2.48 (3H, s), 2.63 (3H, s), 3.98 (3H, s), 5.90 (1H, s), 7.17 (1H, s)

[0218]

10 Reference example 21-3

$^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 1.16 (6H, d, $J=7.0\text{Hz}$), 2.62 (3H, s), 2.90-3.00 (1H, m), 3.99 (3H, s), 5.91 (1H, s), 7.01 (1H, s), 7.38 (1H, s)

[0219]

15 Reference example 21-4

$^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 2.67 (3H, s), 3.98 (3H, s), 5.90 (1H, s), 7.24 (1H, s), 7.36 (1H, s)

[0220]

Reference example 21-5

$^1\text{H-NMR}(\text{CDCl}_3)\delta\text{ppm}: 2.64(3\text{H}, \text{s}), 3.80(3\text{H}, \text{s}), 3.97(3\text{H}, \text{s}), 5.85(1\text{H}, \text{s}), 7.17(1\text{H}, \text{s}), 7.44(1\text{H}, \text{s})$

[0221]

Reference example 21-6

5 $^1\text{H-NMR}(\text{CDCl}_3)\delta\text{ppm}: 2.59(3\text{H}, \text{s}), 2.60(3\text{H}, \text{s}), 4.00(3\text{H}, \text{s}), 5.88(1\text{H}, \text{s}), 7.34(1\text{H}, \text{s}), 7.39(1\text{H}, \text{s})$

[0222]

Reference example 21-7

10 $^1\text{H-NMR}(\text{CDCl}_3)\delta\text{ppm}: 1.21-1.29(4\text{H}, \text{m}), 2.21-2.27(1\text{H}, \text{m}), 3.78(3\text{H}, \text{s}), 3.96(3\text{H}, \text{s}), 5.83(1\text{H}, \text{s}), 7.16(1\text{H}, \text{s}), 7.42(1\text{H}, \text{s})$

[0223]

Reference example 21-8

$^1\text{H-NMR}(\text{CDCl}_3)\delta\text{ppm}: 2.69(3\text{H}, \text{s}), 4.04(3\text{H}, \text{s}), 5.96(1\text{H}, \text{s}), 7.33(1\text{H}, \text{s}), 7.57(1\text{H}, \text{s})$

15 [0224]

Reference example 21-9

$^1\text{H-NMR}(\text{CDCl}_3)\delta\text{ppm}: 3.55(3\text{H}, \text{s}), 3.79(3\text{H}, \text{s}), 3.97(3\text{H}, \text{s}), 4.74(2\text{H}, \text{s}), 5.87(1\text{H}, \text{s}), 7.18(1\text{H}, \text{s}), 7.46(1\text{H}, \text{s})$

[0225]

20 Reference example 21-10

$^1\text{H-NMR}(\text{CDCl}_3)\delta\text{ppm}: 1.49(9\text{H}, \text{s}), 3.76(3\text{H}, \text{s}), 3.98(3\text{H}, \text{s}), 5.84(1\text{H}, \text{s}), 7.19(1\text{H}, \text{s}), 7.42(1\text{H}, \text{s})$

[0226]

Reference example 21-11

25 $^1\text{H-NMR}(\text{CDCl}_3)\delta\text{ppm}: 1.20-1.26(6\text{H}, \text{m}), 2.64(3\text{H}, \text{s}), 3.96(3\text{H}, \text{s}), 5.00-5.20(1\text{H}, \text{m}), 5.86(1\text{H}, \text{s}), 7.11(1\text{H}, \text{s}), 7.46(1\text{H}, \text{s})$

[0227]

Reference example 21-12

$^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 1.30-1.90 (10H, m), 2.63 (3H, s), 3.96 (3H, s),
4.80-5.00 (1H, m), 5.83 (1H, s), 7.10 (1H, s), 7.48 (1H, s)
[0228]

5 Reference example 21-13

$^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 2.63 (3H, s), 3.35 (3H, s), 3.50-3.60 (2H, m),
3.96 (3H, s), 4.30-4.40 (2H, m), 5.89 (1H, s), 7.14 (1H, s), 7.48 (1H,
s)
[0229]

10 Reference example 21-14

$^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 1.20-1.30 (3H, m), 2.64 (3H, s), 3.96 (3H, s),
4.20-4.30 (2H, m), 5.84 (1H, s), 7.14 (1H, s), 7.47 (1H, s)
[0230]

Reference example 21-15

15 $^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 1.21 (9H, s), 2.60 (3H, s), 3.90 (3H, s), 7.04 (1H,
s), 7.30 (1H, s), 7.98 (1H, br), 10.10 (1H, s).
[0231]

Reference example 21-16

MS (ESI, m/z): 249 (M-1)

20 [0232]

Reference example 21-17

$^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 2.39 (3H, s), 2.47 (3H, s), 4.08 (3H, s),
7.10-7.30 (2H, m), 7.60-7.70 (2H, m), 7.79 (1H, s), 10.70 (1H, br
s)

25 [0233]

Reference example 21-18

$^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 2.57 (3H, s), 3.87 (3H, s), 7.02 (1H, s),

7.04-7.07 (1H, m), 7.28-7.32 (2H, m), 7.35 (1H, s), 7.61-7.63 (2H, m), 10.01 (1H, s), 10.23 (1H, br)

[0234]

Reference example 21-19

5 $^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 2.39 (3H, s), 4.03 (3H, s), 5.94 (1H, brs), 7.12 (1H, s), 7.25-7.40 (1H, m), 7.49 (1H, s), 7.75-7.90 (1H, m), 8.10-8.20 (1H, m), 8.40-8.55 (1H, m)

[0235]

Reference example 21-20

10 $^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 1.16-1.24 (3H, m), 1.40-1.48 (2H, m), 1.63-1.93 (5H, m), 2.61 (3H, s), 2.63-2.71 (1H, m), 3.98 (3H, s), 5.88 (1H, s), 7.00 (1H, s), 7.38 (1H, s)

[0236]

Reference example 21-21

15 $^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 1.11-1.14 (2H, m), 1.43-1.46 (2H, m), 2.09-2.15 (1H, m), 2.64 (3H, s), 4.04 (3H, s), 7.64 (1H, s), 10.26 (1H, s)

[0237]

Reference example 21-22

20 $^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 2.47 (3H, s), 4.02 (3H, s), 5.90 (1H, s), 7.00-7.05 (1H, m), 7.12 (1H, s), 7.12-7.17 (1H, m), 7.39 (1H, s), 7.42-7.48 (1H, m), 7.63-7.67 (1H, m)

[0238]

Reference example 21-23

25 $^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 2.45 (3H, s), 4.03 (3H, s), 5.94 (1H, s), 7.31 (1H, s), 7.51 (1H, s), 7.62 (1H, d, $J=3.0\text{Hz}$), 7.84 (1H, d, $J=3.0\text{Hz}$)

[0239]

Reference example 21-24

$^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 2.50 (3H, s), 4.05 (3H, s), 5.99 (1H, brs), 6.80 (1H, d, $J=2.0\text{Hz}$), 7.22 (1H, s), 7.52 (1H, s), 8.26 (1H, d, $J=2.0\text{Hz}$)

5 [0240]

Reference example 21-25

$^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 1.85 (3H, s), 3.28 (1H, d, $J=14.2\text{Hz}$), 3.43 (1H, d, $J=14.2\text{Hz}$), 3.95 (3H, s), 6.07 (1H, s), 7.10 (1H, s), 7.13-7.21 (3H, m), 7.26-7.29 (2H, m), 7.32 (1H, s)

10 [0241]

Reference example 21-26

$^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 2.61 (3H, s), 3.02-3.08 (4H, m), 3.98 (3H, s), 5.88 (1H, s), 7.03 (1H, s), 7.16-7.20 (3H, m), 7.25-7.29 (2H, m), 7.33 (1H, s)

15 [0242]

Reference example 21-27

$^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 1.25 (9H, s), 2.60 (3H, s), 3.98 (3H, s), 5.93 (1H, s), 6.82 (1H, s), 7.53 (1H, s)

[0243]

20 Reference example 21-28

$^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 2.62 (3H, s), 4.03 (3H, s), 5.99 (1H, s), 7.15-7.20 (1H, m), 7.47 (1H, s)

[0244]

Reference example 21-29

25 $^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 1.70 (6H, br s), 2.08 (9H, br s), 2.62 (3H, s), 3.95 (3H, s), 5.53 (1H, br s), 7.10 (1H, br s), 7.29 (1H, br s)

[0245]

Reference example 21-30

$^1\text{H-NMR}(\text{CDCl}_3)\delta\text{ppm}: 2.50(3\text{H}, \text{s}), 4.00(3\text{H}, \text{s}), 4.96(2\text{H}, \text{s}), 5.92(1\text{H}, \text{s}), 6.83-6.96(3\text{H}, \text{m}), 7.12(1\text{H}, \text{s}), 7.21-7.26(2\text{H}, \text{m}), 7.41(1\text{H}, \text{s})$

5 [0246]

Reference example 21-31

$^1\text{H-NMR}(\text{CDCl}_3)\delta\text{ppm}: 2.46(3\text{H}, \text{s}), 3.98(3\text{H}, \text{s}), 5.33(2\text{H}, \text{s}), 5.91(1\text{H}, \text{s}), 6.95-7.10(3\text{H}, \text{m}), 7.19(1\text{H}, \text{s}), 7.27(1\text{H}, \text{s}), 7.25-7.40(2\text{H}, \text{m})$

10 [0247]

Reference example 21-32

$^1\text{H-NMR}(\text{CDCl}_3)\delta\text{ppm}: 1.40-1.50(6\text{H}, \text{m}), 2.46(3\text{H}, \text{s}), 3.20-3.40(1\text{H}, \text{m}), 3.98(3\text{H}, \text{s}), 5.93(1\text{H}, \text{s}), 7.15(1\text{H}, \text{s}), 7.28(1\text{H}, \text{s})$

[0248]

15 Reference example 21-33

$^1\text{H-NMR}(\text{CDCl}_3)\delta\text{ppm}: 1.00-1.10(3\text{H}, \text{m}), 1.80-2.00(2\text{H}, \text{m}), 2.46(3\text{H}, \text{s}), 2.80-3.00(2\text{H}, \text{m}), 3.98(3\text{H}, \text{s}), 5.92(1\text{H}, \text{s}), 7.16(1\text{H}, \text{s}), 7.27(1\text{H}, \text{s})$

[0249]

20 Reference example 21-34

$^1\text{H-NMR}(\text{CDCl}_3)\delta\text{ppm}: 1.27(3\text{H}, \text{t}, J=7.2\text{Hz}), 2.45(3\text{H}, \text{s}), 2.90(2\text{H}, \text{t}, J=7.4\text{Hz}), 3.24(2\text{H}, \text{t}, J=7.4\text{Hz}), 3.98(3\text{H}, \text{s}), 4.18(2\text{H}, \text{q}, J=7.2\text{Hz}), 5.89(1\text{H}, \text{s}), 7.14(1\text{H}, \text{s}), 7.27(1\text{H}, \text{s})$

[0250]

25 Reference example 21-35

$^1\text{H-NMR}(\text{CDCl}_3)\delta\text{ppm}: 2.54(3\text{H}, \text{s}), 4.00(3\text{H}, \text{s}), 5.97(1\text{H}, \text{s}), 7.23(1\text{H}, \text{s}), 7.29(1\text{H}, \text{s})$

[0251]

Reference example 21-37

$^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 1.19 (3H, t, $J=7.0\text{Hz}$), 2.45 (3H, s), 3.20 (2H, t, $J=6.7\text{Hz}$), 3.54 (2H, q, $J=7.0\text{Hz}$), 3.89 (2H, t, $J=6.7\text{Hz}$), 3.98 (3H, s), 5.91 (1H, s), 7.16 (1H, s), 7.28 (1H, s)

[0252]

Reference example 21-38

$^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 2.66 (3H, s), 2.78 (6H, s), 3.95 (3H, s), 6.95 (1H, s), 7.50 (1H, s)

10 [0253]

Reference example 21-39

$^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 2.67 (3H, s), 3.42 (3H, s), 3.99 (3H, s), 7.18 (1H, s), 7.76 (1H, s)

[0254]

15 Reference example 21-40

$^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 1.17-1.41 (5H, m), 1.59-1.91 (5H, m), 2.59 (3H, s), 3.59-3.68 (1H, m), 4.02 (3H, s), 5.94 (1H, br), 6.97 (1H, d, $J=8.3\text{Hz}$), 7.16 (1H, s), 7.48 (1H, s)

[0255]

20 Reference example 21-41

MS (ESI, m/z): 372 (M-1)

[0256]

Reference example 21-42

$^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 2.45 (3H, s), 4.01 (3H, s), 5.09 (2H, s), 6.13 (1H, s), 6.92 (2H, d, $J=8.9\text{Hz}$), 7.02 (1H, s), 7.30-7.43 (5H, m), 7.47 (1H, s), 7.74 (2H, d, $J=8.9\text{Hz}$)

[0257]

Reference example 21-43

¹H-NMR(CDCl₃)δ ppm:0.31-0.39(2H, m), 0.61-0.69(2H, m),
1.21-1.31(1H, m), 2.46(3H, s), 3.83(2H, d, J=6.9Hz), 4.01(3H,
s), 6.11(1H, s), 6.84(2H, d, J=8.8Hz), 7.02(1H, s), 7.48(1H,
5 s), 7.73(2H, d, J=8.9Hz)

[0258]

Reference example 21-44

¹H-NMR(CDCl₃)δ ppm:2.42(3H, s), 3.93(3H, s), 4.04(3H, s), 7.07(1H,
s), 7.49(1H, s), 7.80(2H, d, J=8.5Hz), 8.02(2H, d, J=8.5Hz)
10 [0259]

Reference example 21-45

¹H-NMR(CDCl₃)δ ppm:2.45(3H, s), 3.93(3H, s), 6.95(1H, s), 7.45(1H,
s), 7.73(2H, d, J=8.4Hz), 7.91(2H, d, J=8.4Hz)
[0260]

15 Reference example 22-1

[3-Hydroxy-4-methoxy-6-(5-methyl-[1,2,4]oxadiazol-3-yl)-2-
nitrophenyl]phenylmethanone

To a mixture of [5-hydroxy-4-methoxy-2-(5-methyl-
[1,2,4]oxadiazol-3-yl)phenyl]phenylmethanone(reference
20 example 21-1)(383mg) and methylene chloride(10mL) was added
fuming nitric acid(68μL) at room temperature, and the mixture
was stirred for 20 minutes. The separated organic layer was washed
with water, a saturated aqueous solution of sodium chloride,
and dried over anhydrous sodium sulfate. The residue was
25 triturated with hexane:methylene chloride=4:1 to give the title
compound(377mg).

¹H-NMR(CDCl₃)δ ppm:2.46(3H, s), 4.09(3H, s), 7.30-7.90(6H, m),

10.72(1H, s)

[0261]

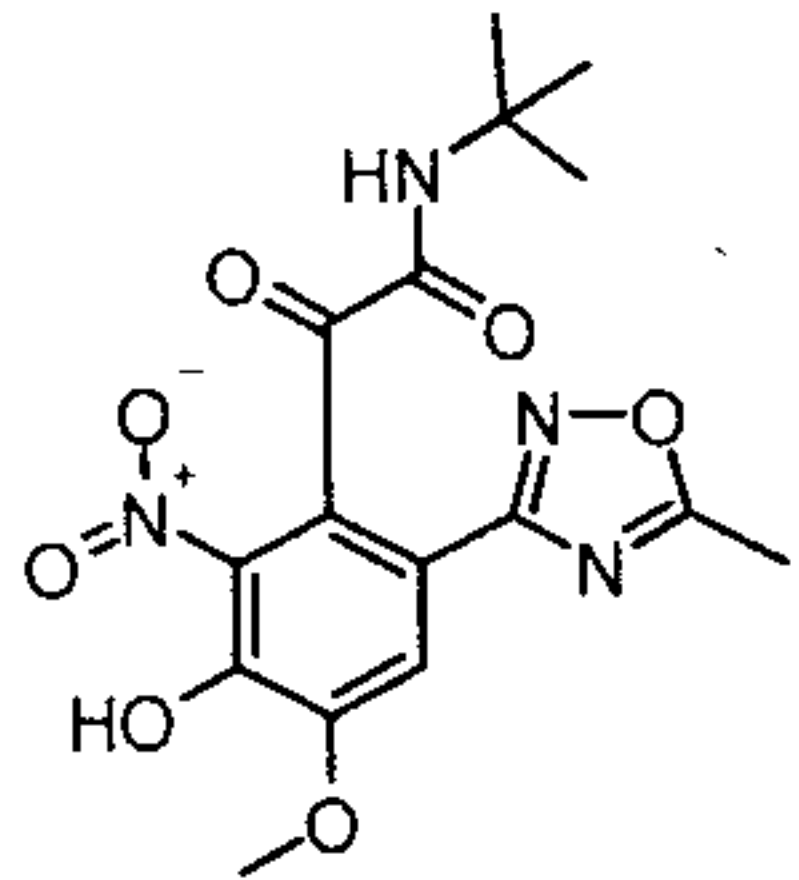
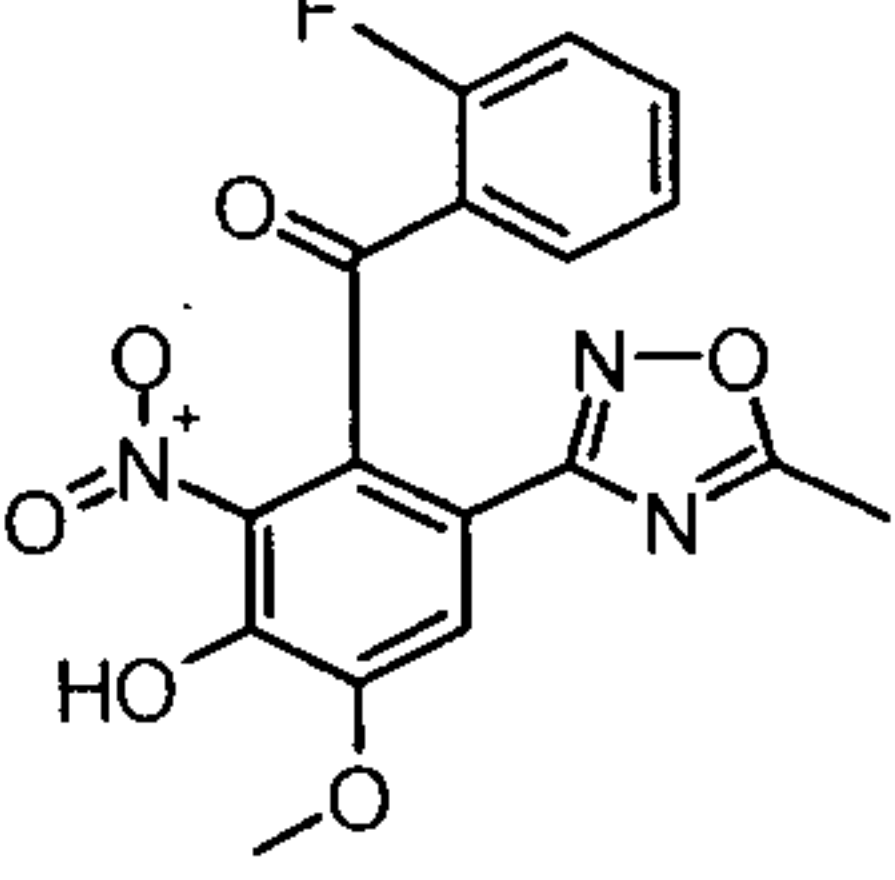
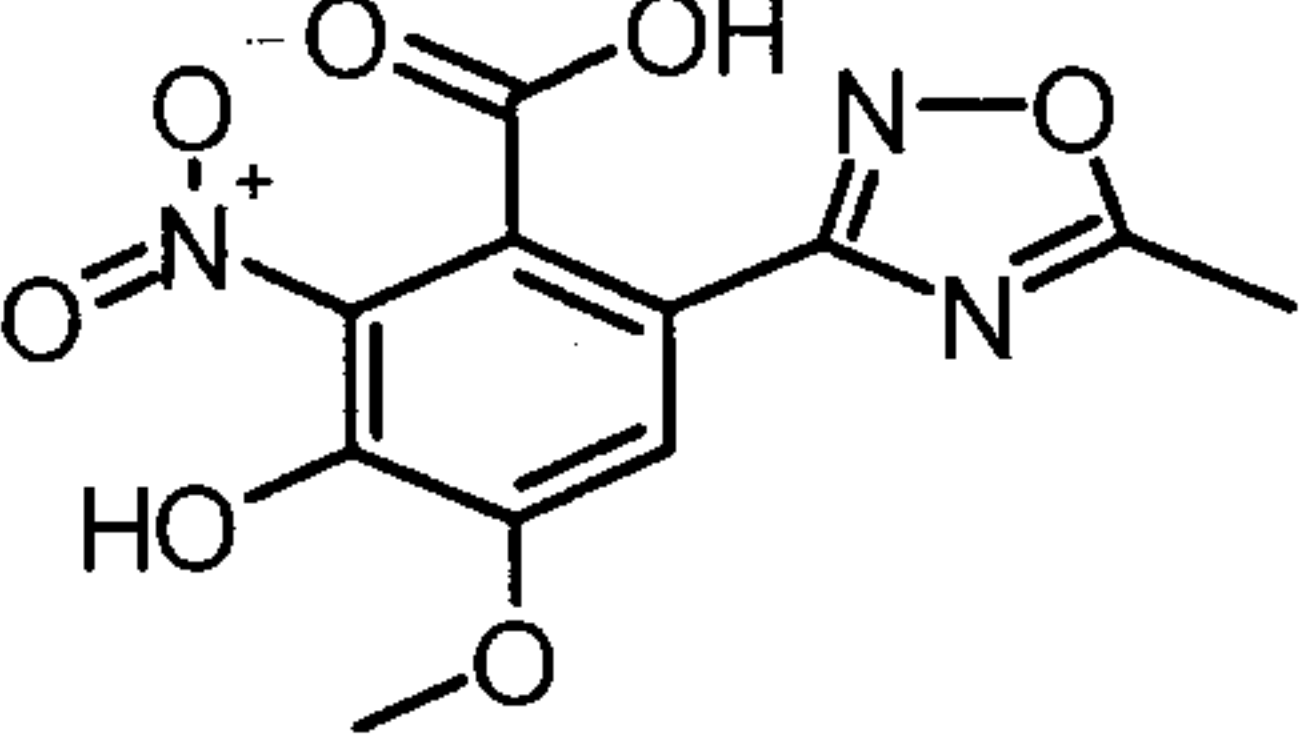
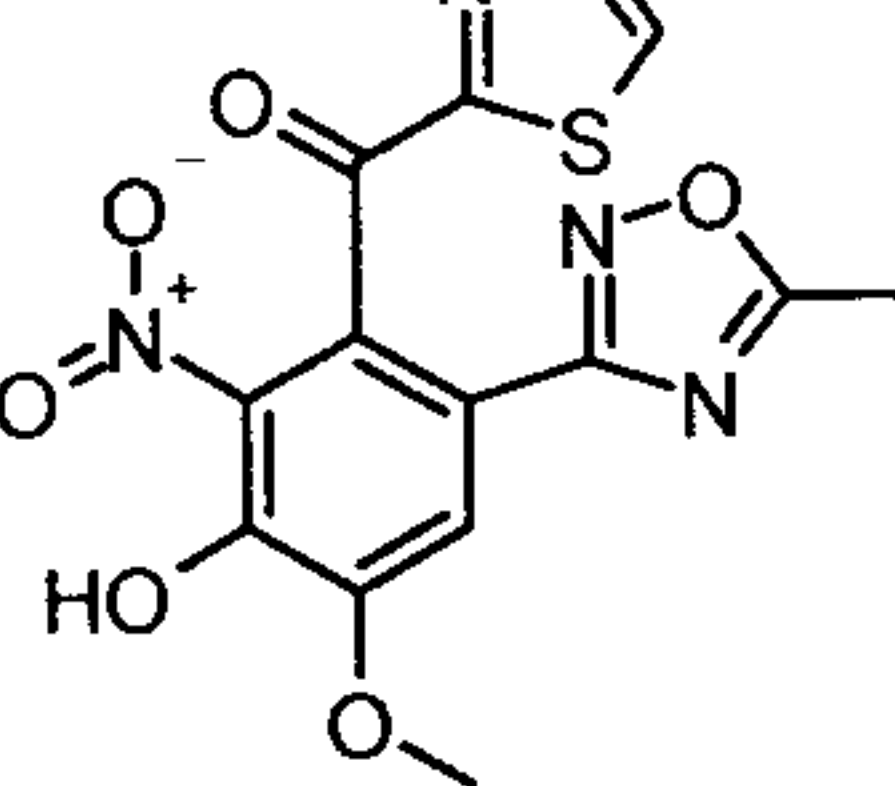
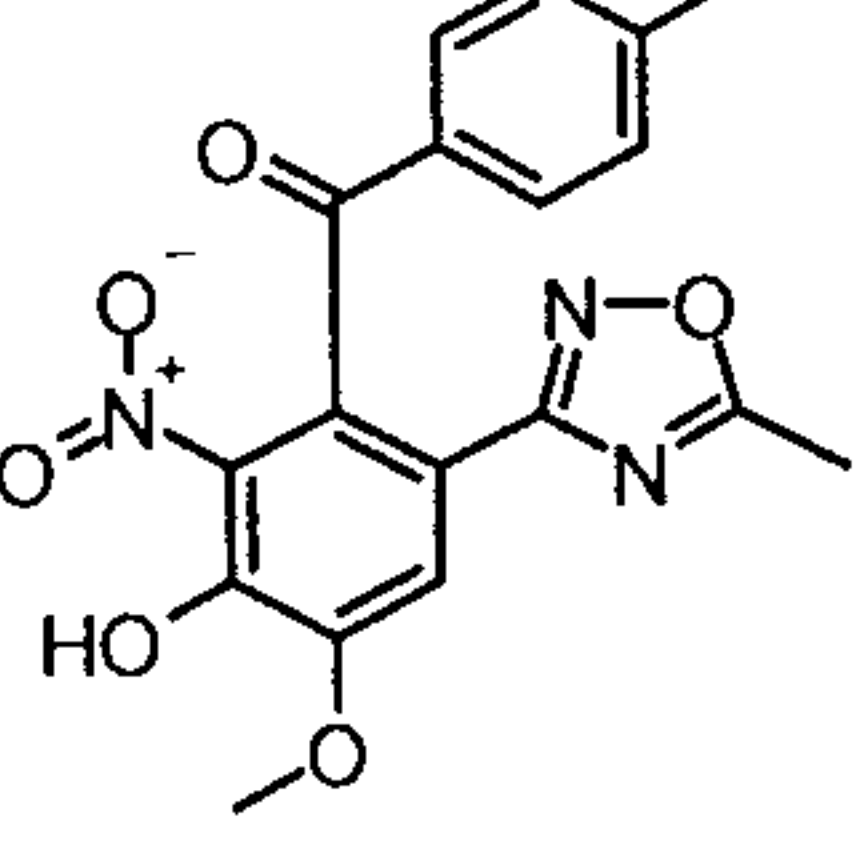
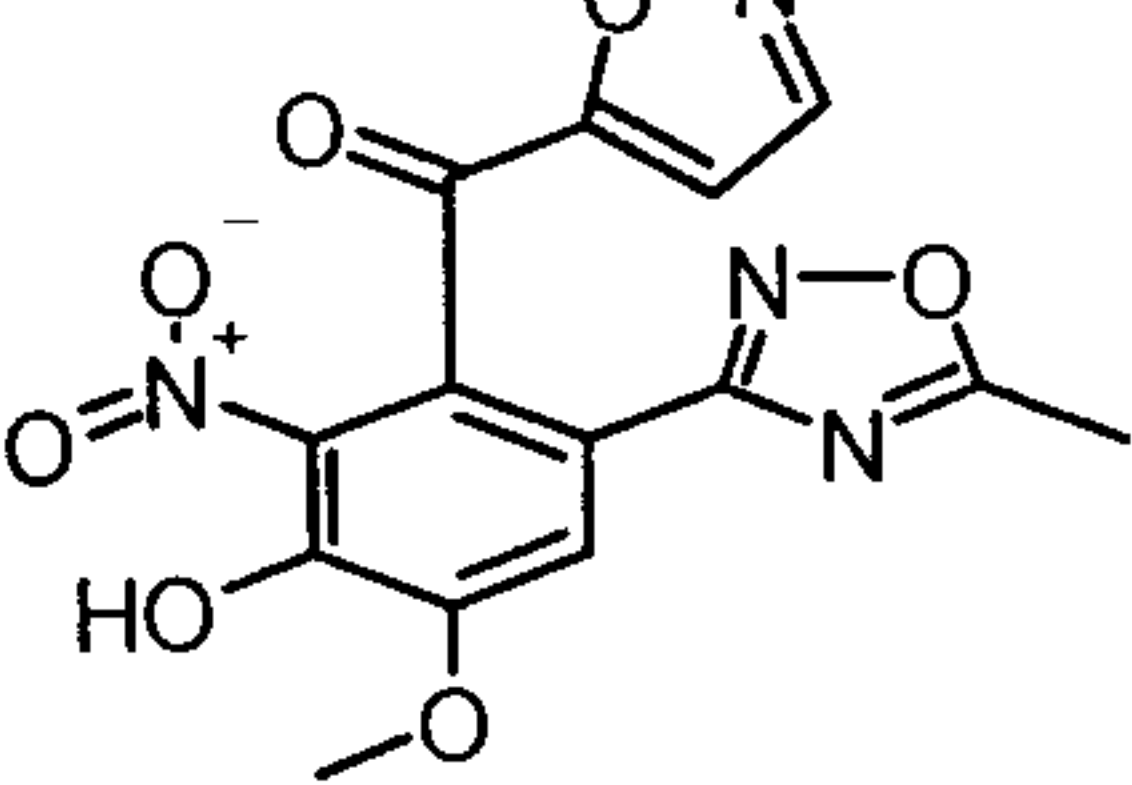
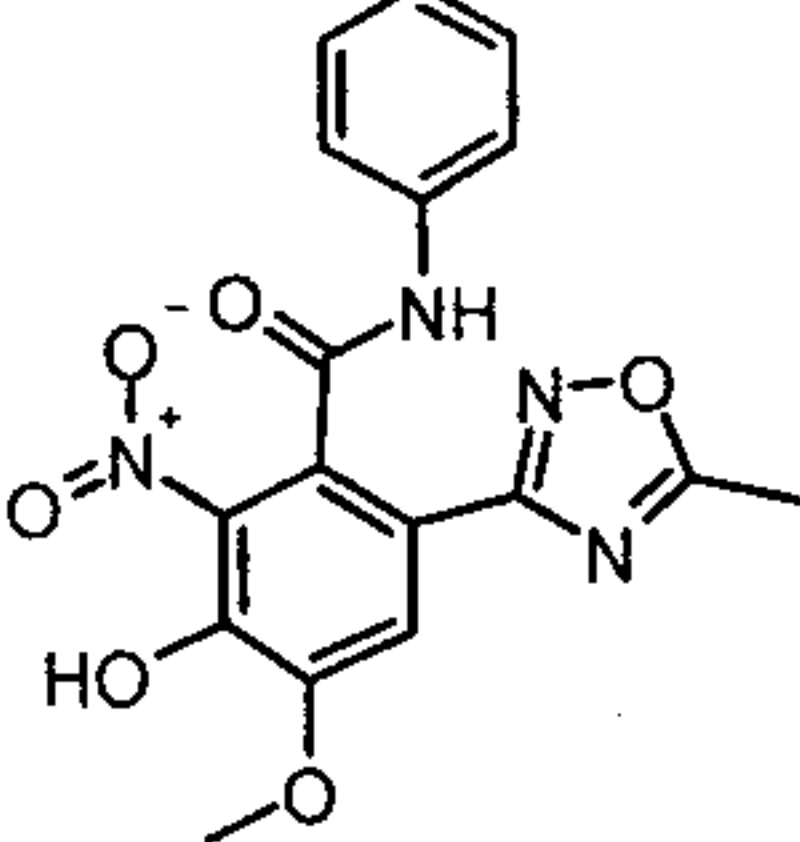
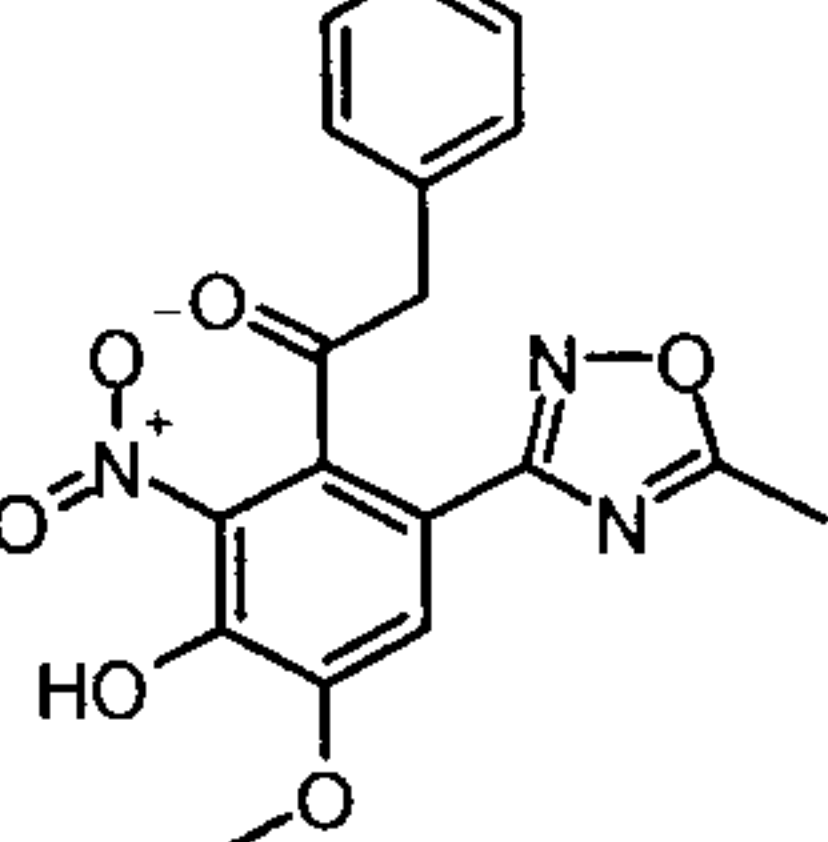
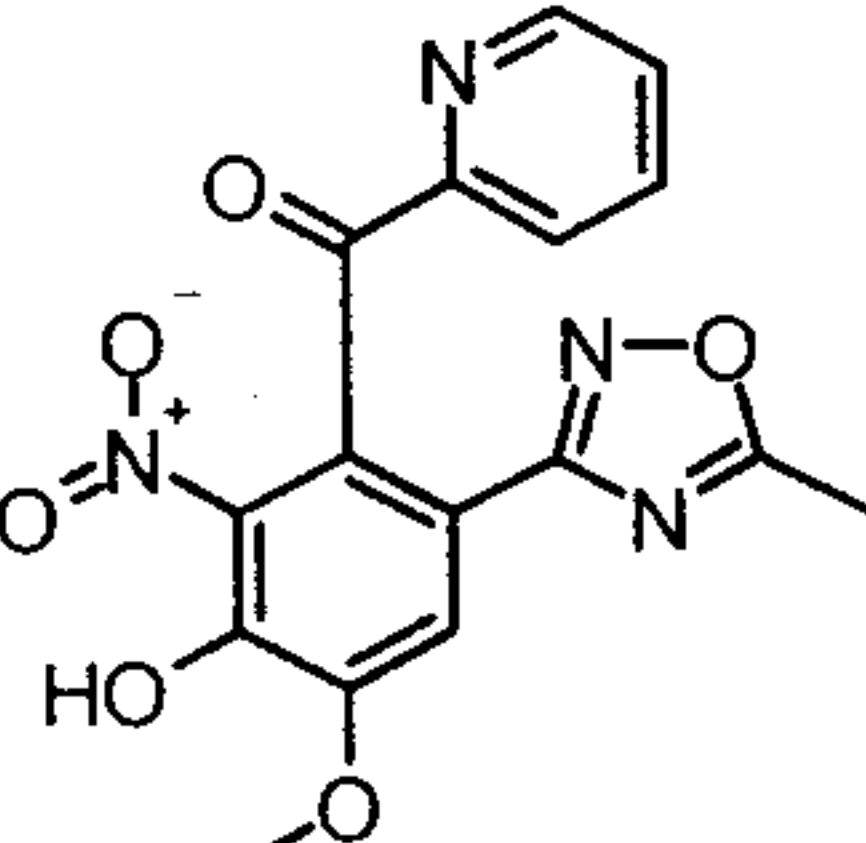
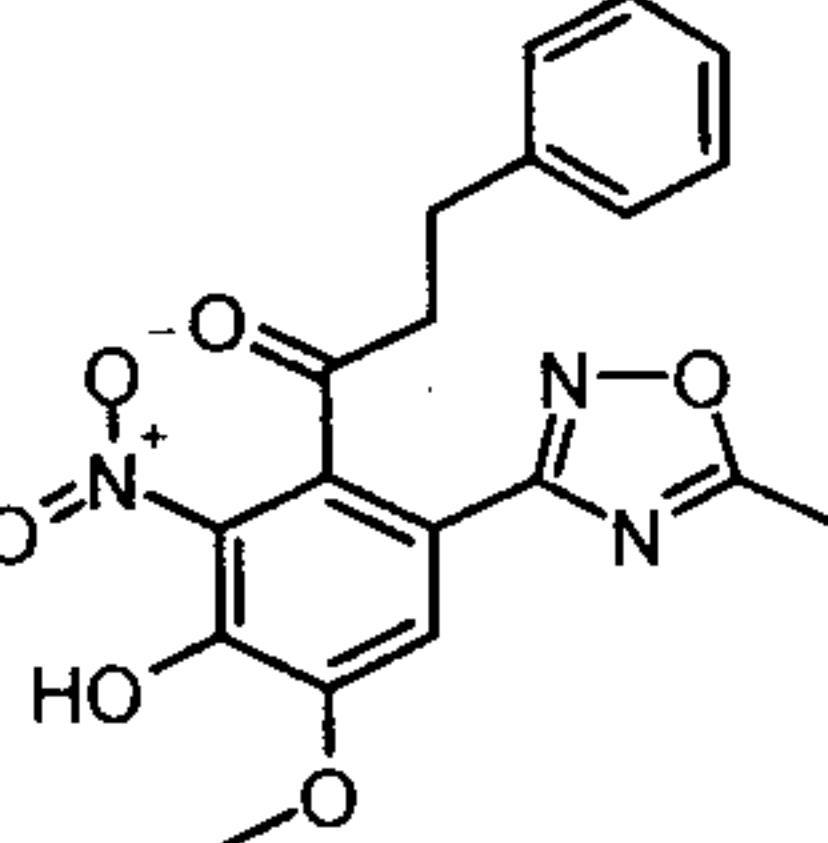
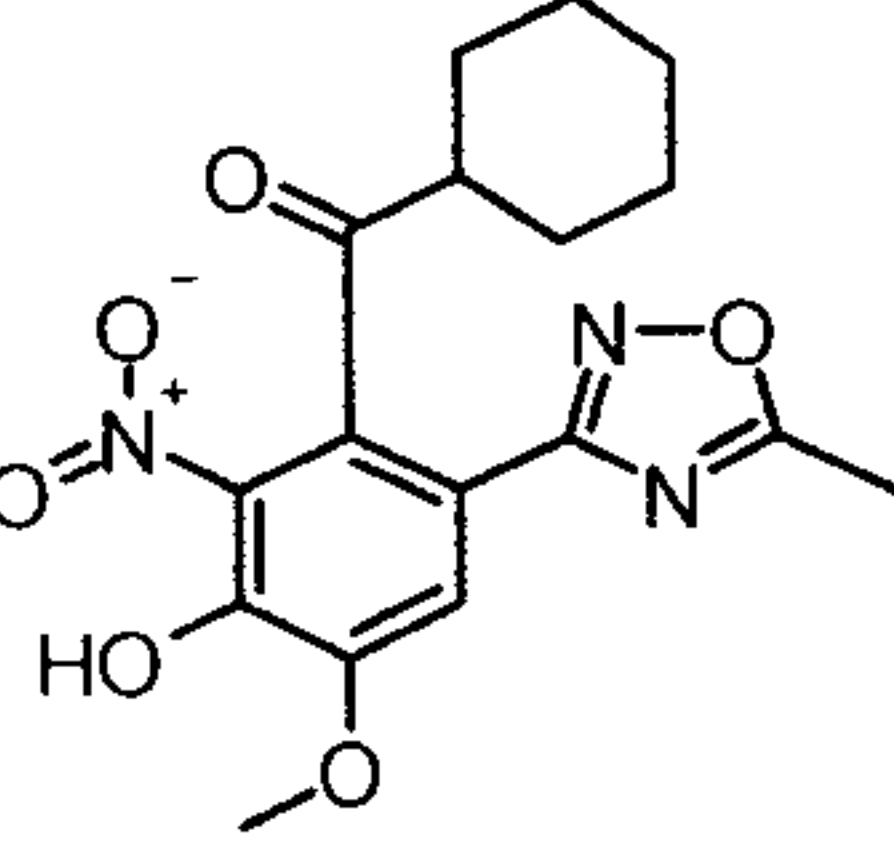
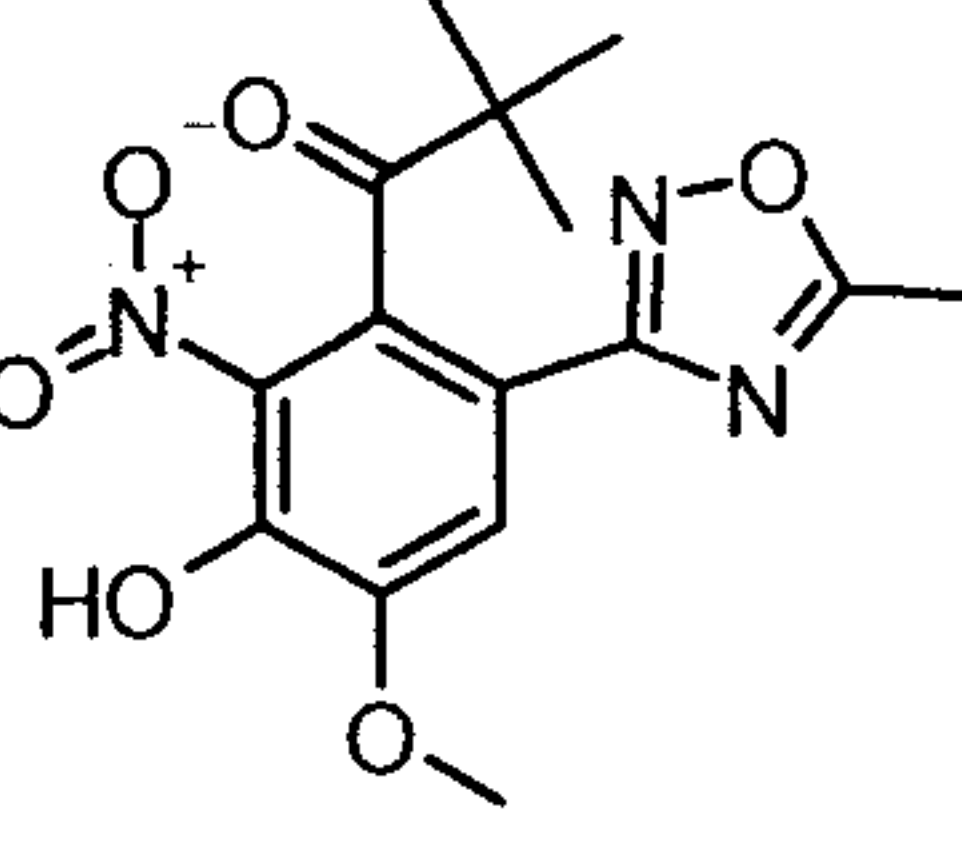
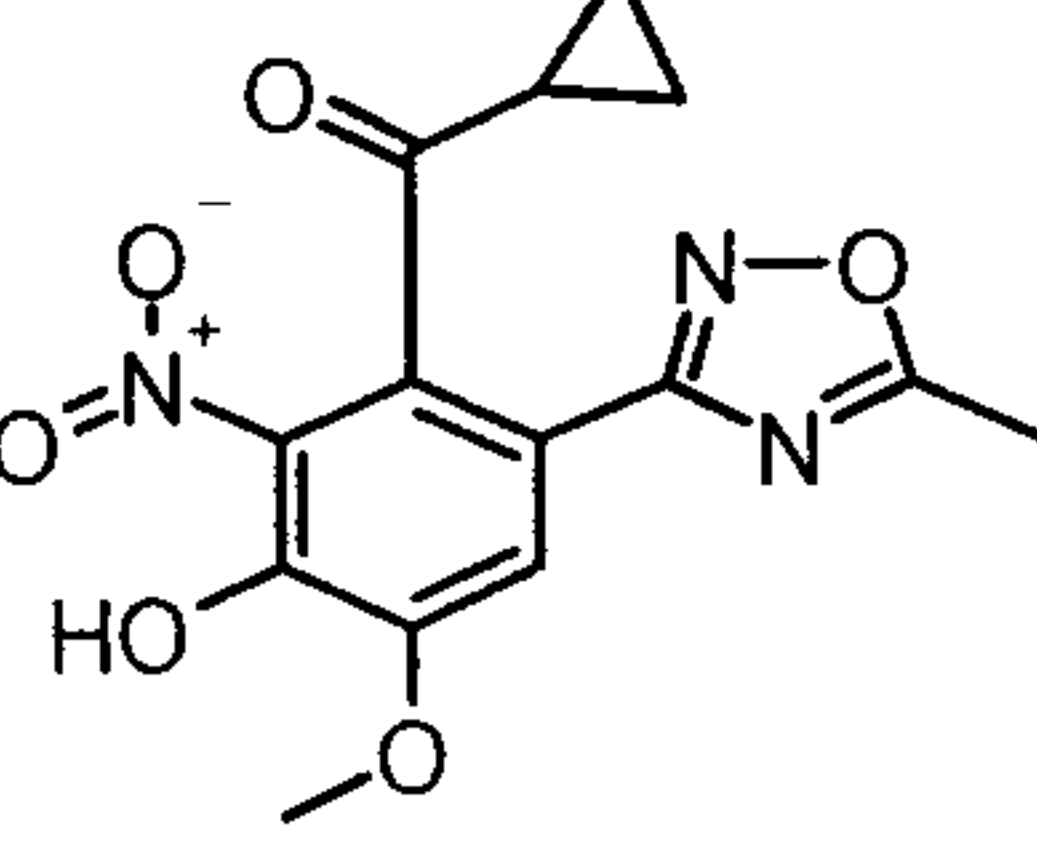
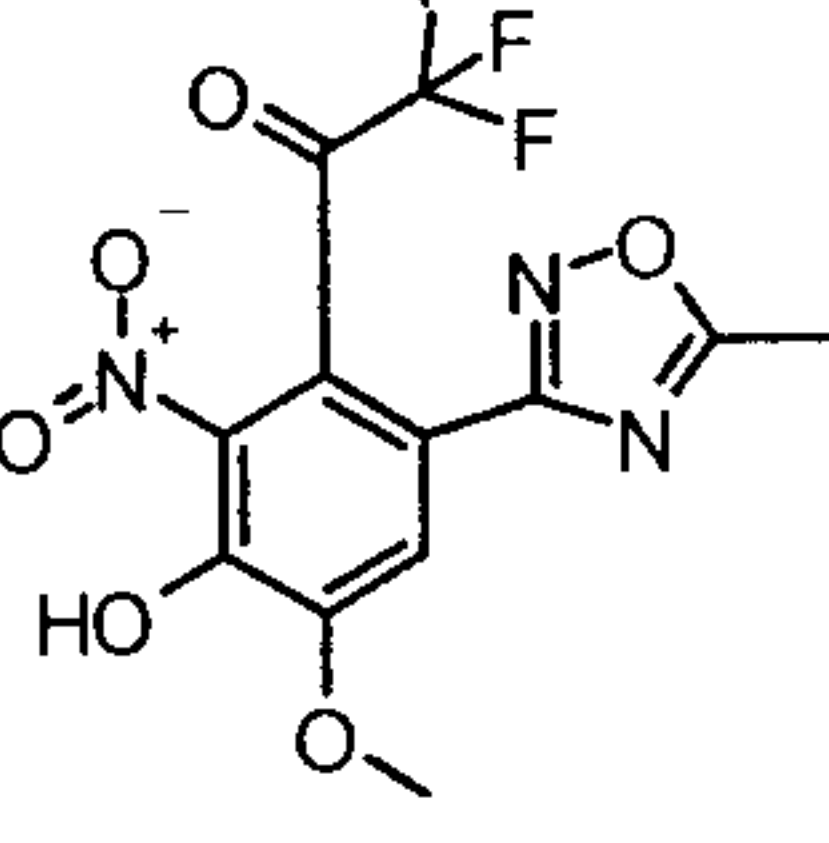
Reference examples 22-2 to 22-45 were prepared in a manner similar to those as described in Reference example 22-1 using
5 the corresponding phenols instead of [5-hydroxy-4-methoxy-2-(5-methyl-[1,2,4]oxadiazol-3-yl)phenyl]phenylmethanone. These were illustrated in table 11.

[0262]

Table 11

Reference example	Structure	Reference example	Structure
22-1		22-8	
22-2		22-9	
22-3		22-10	
22-4		22-11	
22-5		22-12	
22-6		22-13	
22-7		22-14	

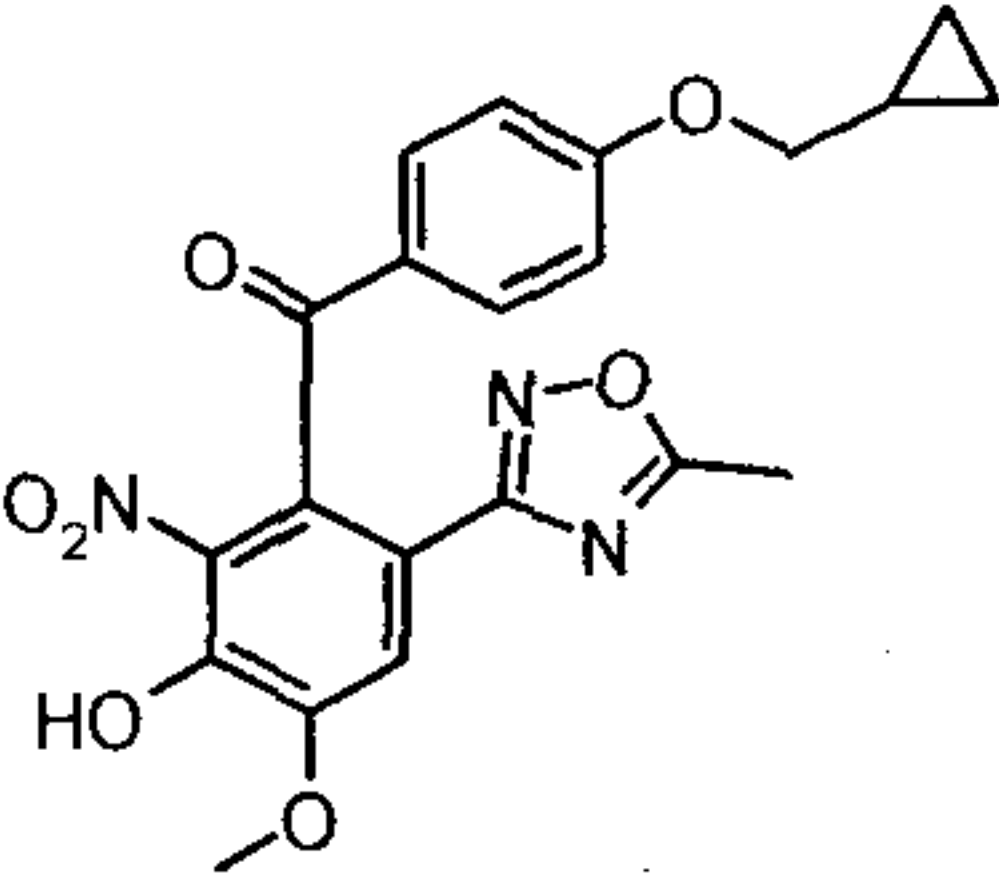
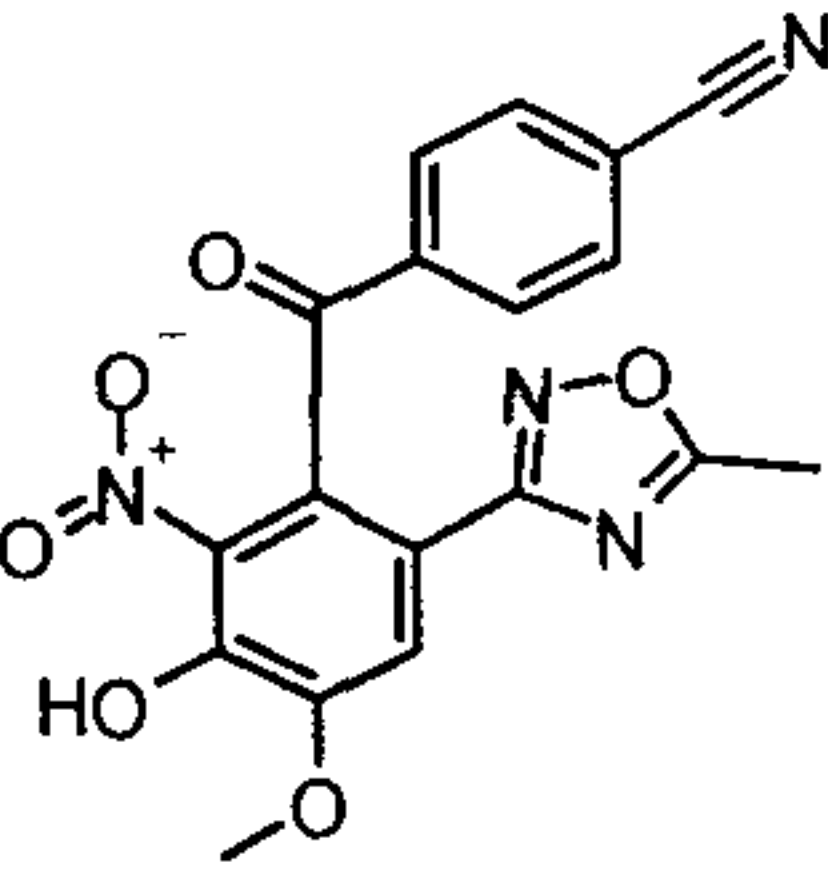
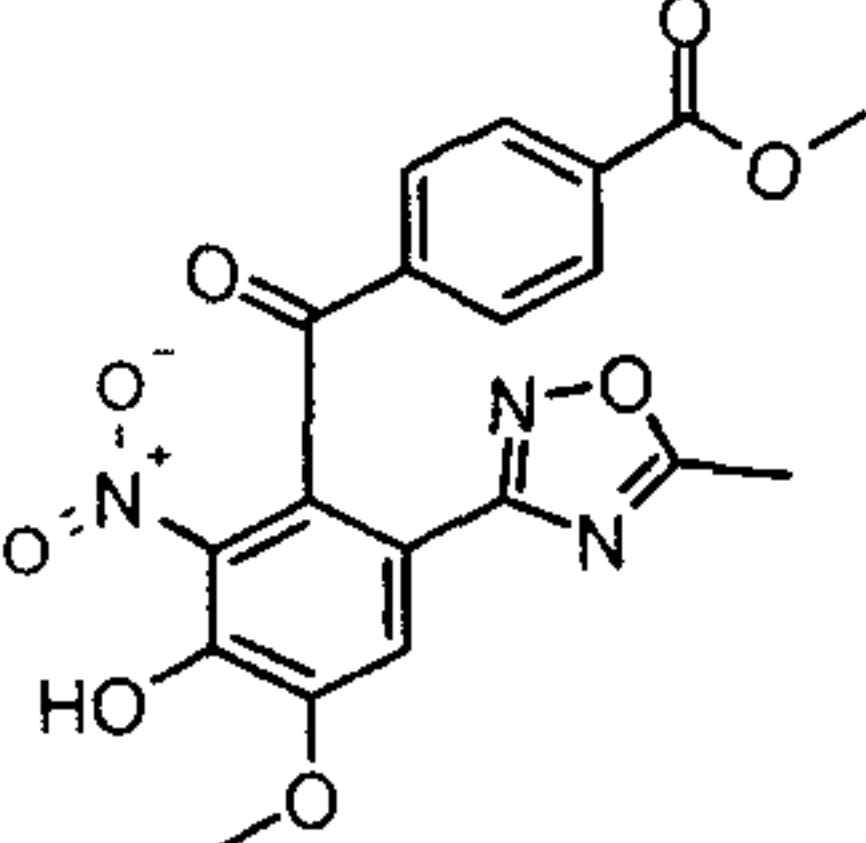
(continued)

Reference example	Structure	Reference example	Structure
22-15		22-22	
22-16		22-23	
22-17		22-24	
22-18		22-25	
22-19		22-26	
22-20		22-27	
22-21		22-28	

(continued)

Reference example	Structure	Reference example	Structure
22-29		22-36	
22-30		22-37	
22-31		22-38	
22-32		22-39	
22-33		22-40	
22-34		22-41	
22-35		22-42	

(continued)

Reference example	Structure	Reference example	Structure
22-43		22-45	
22-44			

[0263]

The physical data of reference examples 22-2 to 22-20, 22-22 to 22-32, 22-34, 22-35 and 22-37 to 22-45 were shown below.

5 [0264]

Reference example 22-2

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 2.64 (3H, s), 2.68 (3H, s), 4.04 (3H, s), 7.75 (1H, s)

[0265]

10 Reference example 22-3

$^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 1.01 (6H, d, $J=6.8\text{Hz}$), 2.57-2.64 (1H, m), 2.67 (3H, s), 4.00 (3H, s), 7.54 (1H, s), 11.47 (1H, br s)

[0266]

Reference example 22-4

15 $^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 2.70 (3H, s), 3.99 (3H, s), 7.43 (1H, s), 11.82 (1H, br)

[0267]

Reference example 22-5

MS (ESI, m/z): 308 (M-1)

[0268]

Reference example 22-6

$^1\text{H-NMR}(\text{DMSO-}d_6)\delta$ ppm: 2.59 (3H, s), 2.62 (3H, s), 4.03 (3H, s),
7.62 (1H, s)

5 [0269]

Reference example 22-7

$^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 1.12-1.15 (2H, m), 1.28-1.32 (2H, m),
2.38-2.43 (1H, m), 3.68 (3H, s), 3.99 (3H, s), 7.50 (1H, s), 11.54 (1H,
br)

10 [0270]

Reference example 22-8

$^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 2.72 (3H, s), 4.10 (3H, s), 7.67 (1H, s), 9.99 (1H,
br s)

[0271]

15 Reference example 22-9

$^1\text{H-NMR}(\text{DMSO-}d_6)\delta$ ppm: 3.42 (3H, s), 3.69 (3H, s), 4.01 (3H, s),
4.83 (2H, s), 7.55 (1H, s), 11.66 (1H, br)

[0272]

Reference example 22-10

20 $^1\text{H-NMR}(\text{DMSO-}d_6)\delta$ ppm: 1.42 (9H, s), 3.68 (3H, s), 4.00 (3H, s),
7.51 (1H, s), 11.58 (1H, br)

[0273]

Reference example 22-11

$^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 1.30-1.40 (6H, m), 2.64 (3H, s), 4.04 (3H, s),
25 5.30-5.40 (1H, m), 7.71 (1H, s), 10.54 (1H, s)

[0274]

Reference example 22-12

$^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 1.00-2.10 (10H, m), 2.63 (3H, s), 4.03 (3H, s),
5.10-5.20 (1H, m), 7.71 (1H, s), 10.51 (1H, br s)

[0275]

Reference example 22-13

5 $^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 2.64 (3H, s), 3.38 (3H, s), 3.70-3.80 (2H, m),
4.04 (3H, s), 4.50-4.60 (2H, s), 7.74 (1H, s), 10.65 (1H, br s)

[0276]

Reference example 22-14

$^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 1.30-1.40 (3H, m), 2.64 (3H, s), 4.04 (3H, s),
10 4.40-4.50 (2H, m), 7.73 (1H, s), 10.58 (1H, s)

[0277]

Reference example 22-15

$^1\text{H-NMR}(\text{DMSO-d}_6)\delta$ ppm: 1.25 (9H, s), 2.62 (3H, s), 4.02 (3H, s),
7.59 (1H, s), 8.00 (1H, br), 11.53 (1H, br)

15 [0278]

Reference example 22-16

$^1\text{H-NMR}(\text{DMSO-d}_6)\delta$ ppm: 2.66 (3H, s), 3.97 (3H, s), 7.43 (1H, s)

[0279]

Reference example 22-18

20 MS (ESI, m/z): 369 (M-1)

[0280]

Reference example 22-19

$^1\text{H-NMR}(\text{DMSO-d}_6)\delta$ ppm: 2.45 (3H, s), 4.03 (3H, s), 7.50-7.70 (2H,
m), 7.95-8.15 (2H, m), 8.40-8.50 (1H, m), 11.00-11.70 (1H, br)

25 [0281]

Reference example 22-20

MS (ESI, m/z): 362 (M+1)

[0282]

Reference example 22-22

$^1\text{H-NMR(DMSO-d}_6\text{)}\delta$ ppm: 2.48 (3H, s), 4.03 (3H, s), 7.20-7.28 (2H, m), 7.60 (1H, s), 7.61-7.65 (2H, m), 11.59 (1H, br s)

5 [0283]

Reference example 22-23

$^1\text{H-NMR(DMSO-d}_6\text{)}\delta$ ppm: 2.49 (3H, s), 4.05 (3H, s), 7.65 (1H, s), 7.94 (1H, d, $J=3.0\text{Hz}$), 8.22 (1H, d, $J=3.0\text{Hz}$), 11.00-12.00 (1H, br)

[0284]

10 Reference example 22-24

$^1\text{H-NMR(DMSO-d}_6\text{)}\delta$ ppm: 2.53 (3H, s), 4.05 (3H, s), 7.16 (1H, d, $J=2.2\text{Hz}$), 7.68 (1H, s), 8.76 (1H, d, $J=2.2\text{Hz}$)

[0285]

Reference example 22-25

15 $^1\text{H-NMR(DMSO-d}_6\text{)}\delta$ ppm: 1.77 (3H, s), 3.97 (3H, s), 7.16-7.24 (5H, m), 7.57 (1H, s), 11.67 (1H, br)

[0286]

Reference example 22-26

20 $^1\text{H-NMR(DMSO-d}_6\text{)}\delta$ ppm: 2.66 (3H, s), 2.88-2.95 (4H, m), 3.97 (3H, s), 7.15-7.28 (5H, m), 7.61 (1H, s), 11.56 (1H, br)

[0287]

Reference example 22-27

$^1\text{H-NMR(DMSO-d}_6\text{)}\delta$ ppm: 1.00 (9H, s), 2.67 (3H, s), 3.99 (3H, s), 7.54 (1H, s), 11.49 (1H, brs)

25 [0288]

Reference example 22-28

$^1\text{H-NMR(DMSO-d}_6\text{)}\delta$ ppm: 2.68 (3H, s), 4.06 (3H, s), 7.68 (1H, s)

[0289]

Reference example 22-29

$^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 1.70 (6H, br s), 2.05-2.20 (9H, m), 2.65 (3H, s), 4.01 (3H, s), 5.39 (1H, br s), 7.53 (1H, s), 9.86 (1H, br s)

5 [0290]

Reference example 22-30

$^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 2.58 (3H, s), 4.06 (3H, s), 5.10 (2H, s), 6.78-6.81 (2H, m), 6.93-6.97 (1H, m), 7.21-7.25 (2H, m), 7.76 (1H, s), 10.85 (1H, s)

10 [0291]

Reference example 22-31

$^1\text{H-NMR}(\text{DMSO-d}_6)\delta$ ppm: 2.30 (3H, s), 4.00 (3H, s), 5.60 (2H, s), 6.95-7.15 (3H, m), 7.25-7.40 (2H, m), 7.60 (1H, s)

[0292]

15 Reference example 22-32

$^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 1.40-1.50 (6H, m), 2.70 (3H, s), 3.20-3.30 (1H, m), 4.05 (3H, s), 7.77 (1H, s), 10.73 (1H, br s)

[0293]

Reference example 22-34

20 $^1\text{H-NMR}(\text{DMSO-d}_6)\delta$ ppm: 1.18 (3H, t, $J=7.1\text{Hz}$), 2.32 (3H, s), 2.88 (2H, t, $J=6.8\text{Hz}$), 3.24 (2H, t, $J=6.8\text{Hz}$), 3.99 (3H, s), 4.08 (2H, q, $J=7.1\text{Hz}$), 7.56 (1H, s), 11.00-12.00 (1H, br)

[0294]

Reference example 22-35

25 $^1\text{H-NMR}(\text{DMSO-d}_6)\delta$ ppm: 2.43 (3H, s), 4.01 (3H, s), 7.62 (1H, s), 11.05-12.50 (1H, br)

[0295]

Reference example 22-37

^1H -NMR (DMSO- d_6) δ ppm: 1.07 (3H, t, $J=7.0\text{Hz}$), 2.34 (3H, s), 3.25 (2H, t, $J=6.1\text{Hz}$), 3.46 (2H, q, $J=7.0\text{Hz}$), 3.80 (2H, t, $J=6.1\text{Hz}$), 3.99 (3H, s), 7.57 (1H, s), 11.40-11.70 (1H, br)

5 [0296]

Reference example 22-38

^1H -NMR (CDCl_3) δ ppm: 2.69 (3H, s), 2.81 (6H, s), 3.99 (3H, s), 6.96 (1H, s)

[0297]

10 Reference example 22-39

^1H -NMR (CDCl_3) δ ppm: 2.69 (3H, s), 3.55 (3H, s), 4.04 (3H, s), 7.15 (1H, s)

[0298]

Reference example 22-40

15 ^1H -NMR (DMSO- d_6) δ ppm: 1.03-1.73 (10H, m), 2.61 (3H, s), 3.39-3.50 (1H, m), 4.03 (3H, s), 7.59 (1H, s), 8.66 (1H, d, $J=8.6\text{Hz}$), 11.56 (1H, br)

[0299]

Reference example 22-41

20 ^1H -NMR (CDCl_3) δ ppm: 1.07-2.01 (10H, m), 2.59-2.60 (3H, m), 2.94-3.36 (3H, m), 4.03-4.04 (3H, m), 4.25-4.80 (1H, m), 7.75-7.80 (1H, m), 10.87 (1H, br)

[0300]

Reference example 22-42

25 ^1H -NMR (CDCl_3) δ ppm: 2.48 (3H, s), 4.08 (3H, s), 5.09 (2H, s), 6.95 (2H, d, $J=9.0\text{Hz}$), 7.31-7.44 (5H, m), 7.63-7.80 (3H, m)

[0301]

Reference example 22-43

$^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 0.32-0.39 (2H, m), 0.63-0.71 (2H, m), 1.22-1.32 (1H, m), 2.48 (3H, s), 3.84 (2H, d, $J=6.9\text{Hz}$), 4.08 (3H, s), 6.86 (2H, d, $J=9.1\text{Hz}$), 7.60-7.79 (3H, m)

5 [0302]

Reference example 22-44

$^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 2.45 (3H, s), 3.93 (3H, s), 4.10 (3H, s), 7.82-7.88 (3H, m), 8.07 (2H, d, $J=8.8\text{Hz}$)

[0303]

10 Reference example 22-45

$^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 2.47 (3H, s), 4.09 (3H, s), 7.69-7.95 (5H, m)

[0304]

Reference example 23-1

[3-Hydroxy-4-methoxy-6-(5-methyl-[1,2,4]oxadiazol-3-yl)-2-

15 nitrophenyl]-(4-hydroxyphenyl)methanone

A mixture of (4-benzyloxyphenyl)-[3-hydroxy-4-methoxy-6-(5-methyl-[1,2,4]oxadiazol-3-yl)-2-nitrophenyl]methanone (reference example 22-42) (395mg) and a 25%hydrogen bromide-acetic acid solution(10mL) was stirred at 45°C for 2 hours.

20 The mixture was concentrated under reduced pressure to give the title compound (310mg).

$^1\text{H-NMR}(\text{CDCl}_3)\delta$ ppm: 2.48 (3H, s), 4.06 (3H, s), 6.81 (2H, d, $J=8.8\text{Hz}$), 7.53-7.68 (2H, m), 7.71 (1H, s)

[0305]

25 Example 1-1

[3,4-Dihydroxy-6-(5-methyl-[1,2,4]oxadiazol-3-yl)-2-nitrophenyl]phenylmethanone (compound 1-1)

To a mixture of [3-hydroxy-4-methoxy-6-(5-methyl-[1,2,4]oxadiazol-3-yl)-2-nitrophenyl]phenylmethanone (reference example 22-1) (377mg) and ethyl acetate (10.6mL) were added aluminum chloride (361mg) and pyridine (0.387mL). The mixture was refluxed for 2.5 hours. After cooling to room temperature, 1mol/L hydrochloric acid was added to the mixture. The separated organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was triturated with hexane:methylene chloride=4:1 to give the title compound (317mg) as an amorphous. ¹H-NMR (DMSO-d₆) δ ppm: 2.43 (3H, s), 7.40-7.70 (6H, m), 11.28 (2H, brs)

MS (ESI, m/z) : 342 (M+1)

[0306]

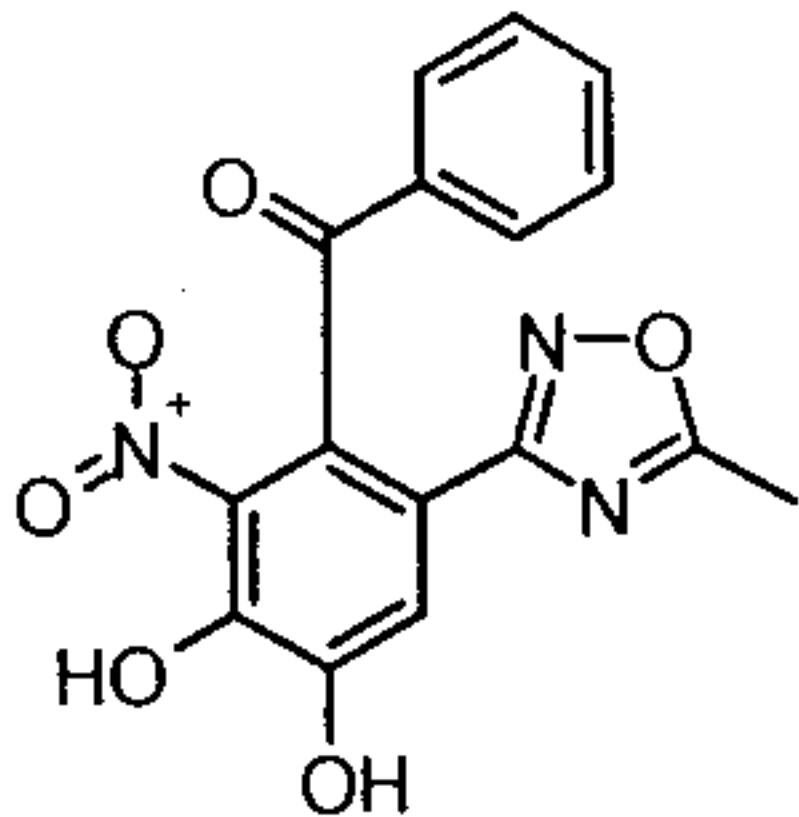
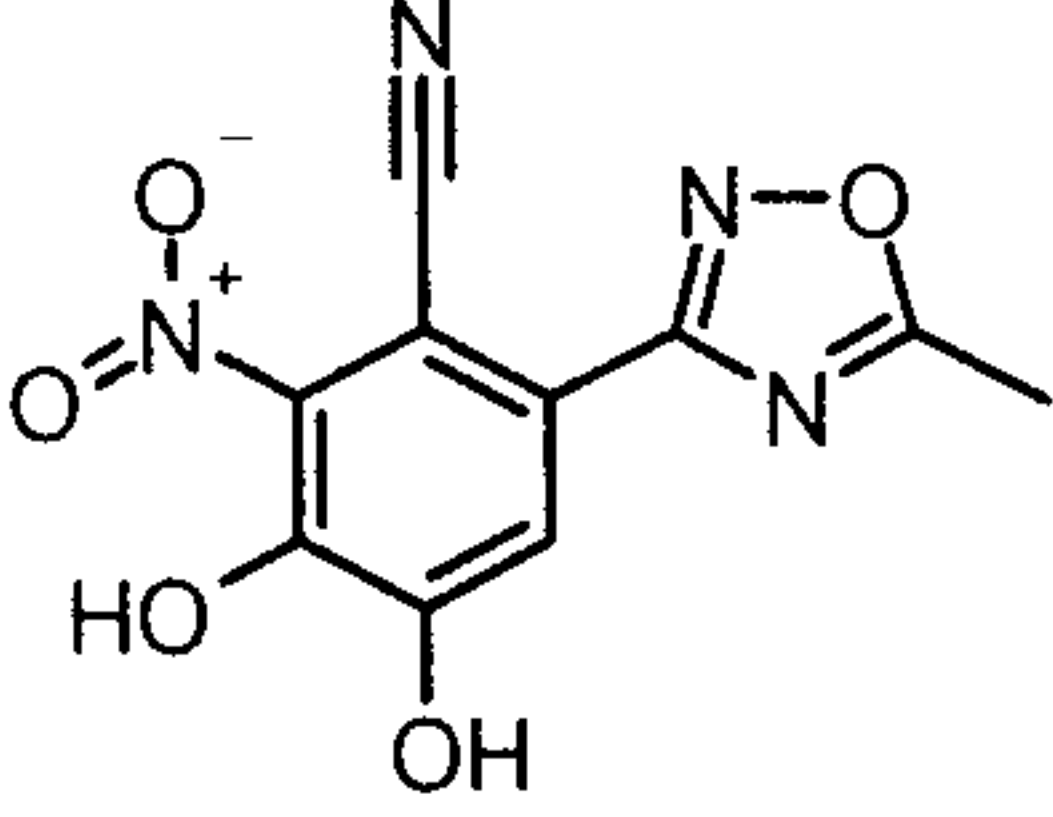
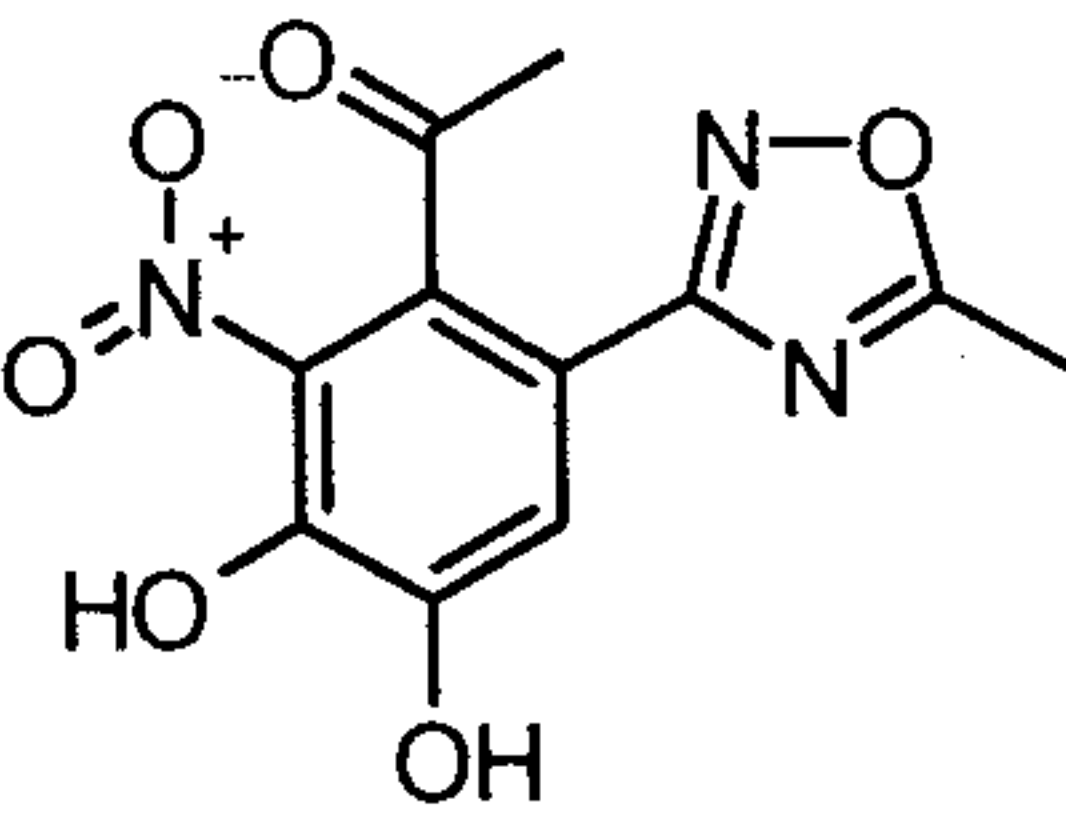
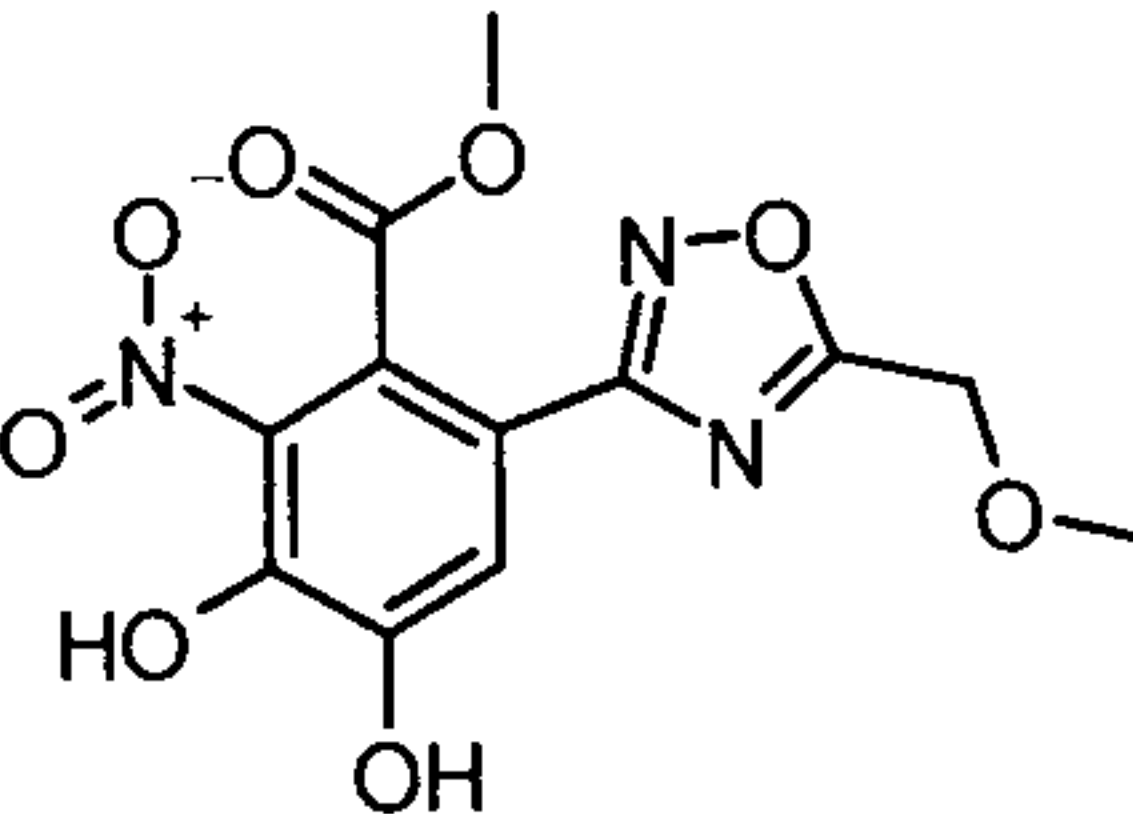
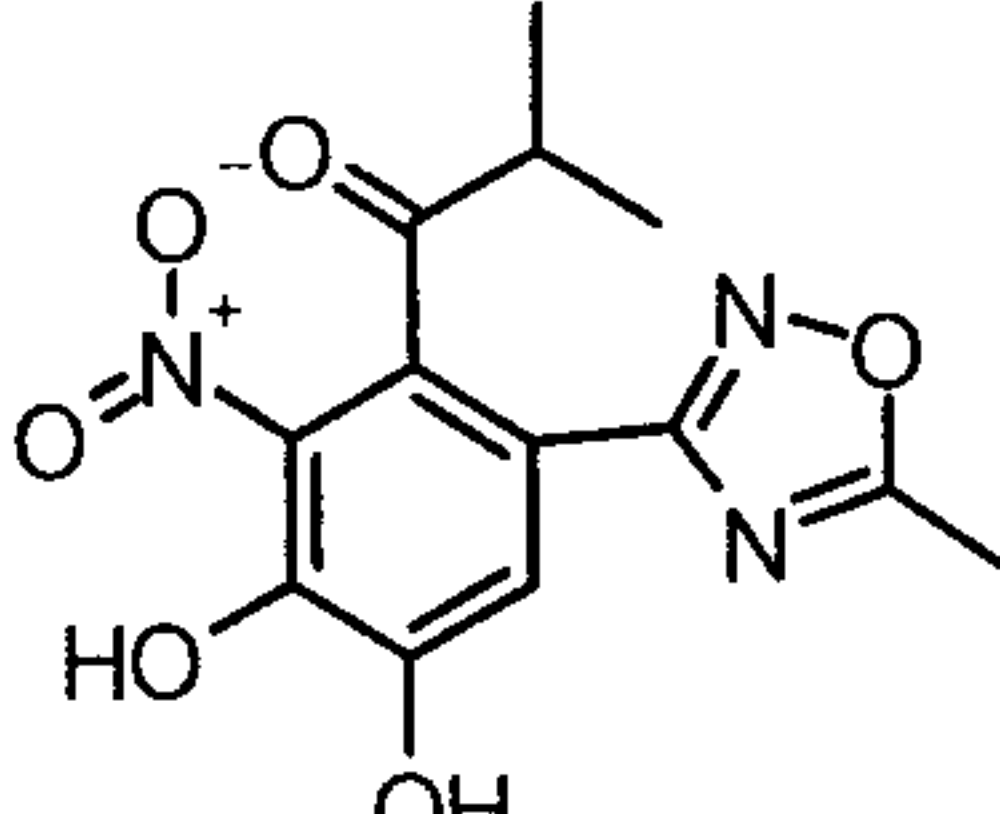
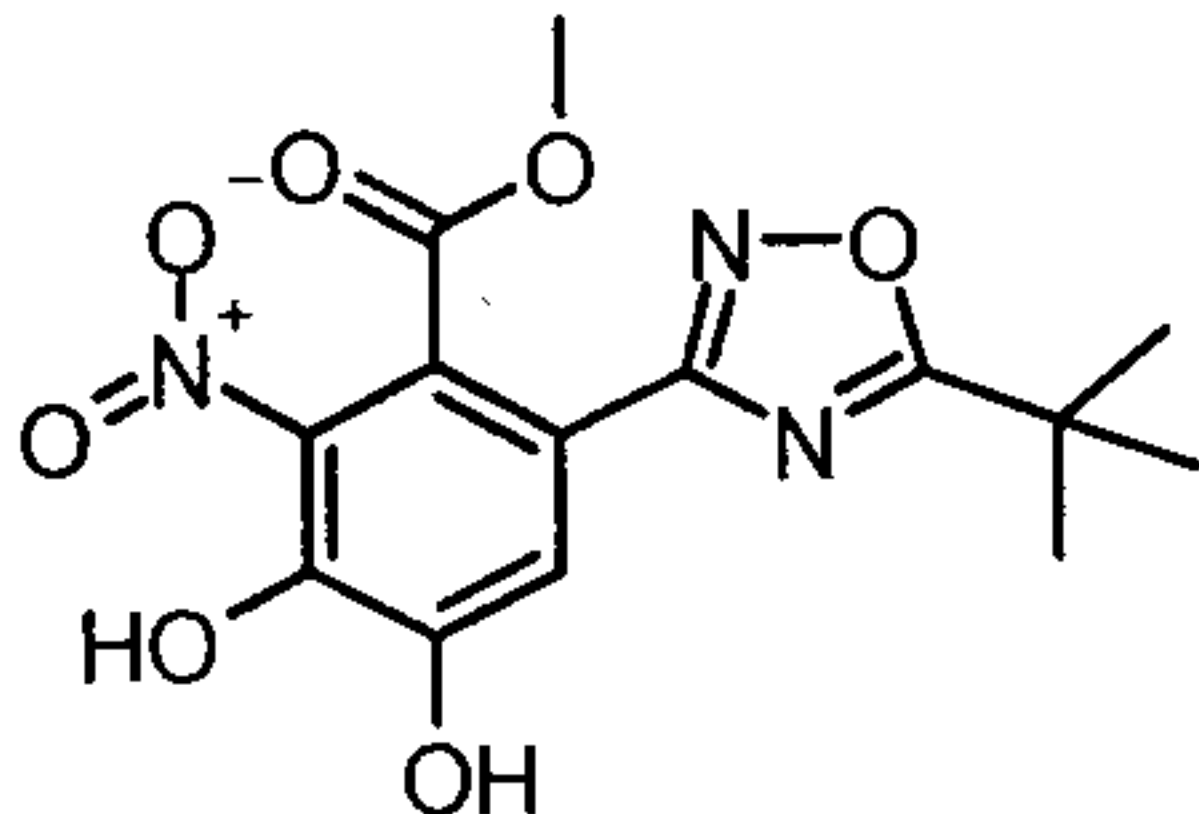
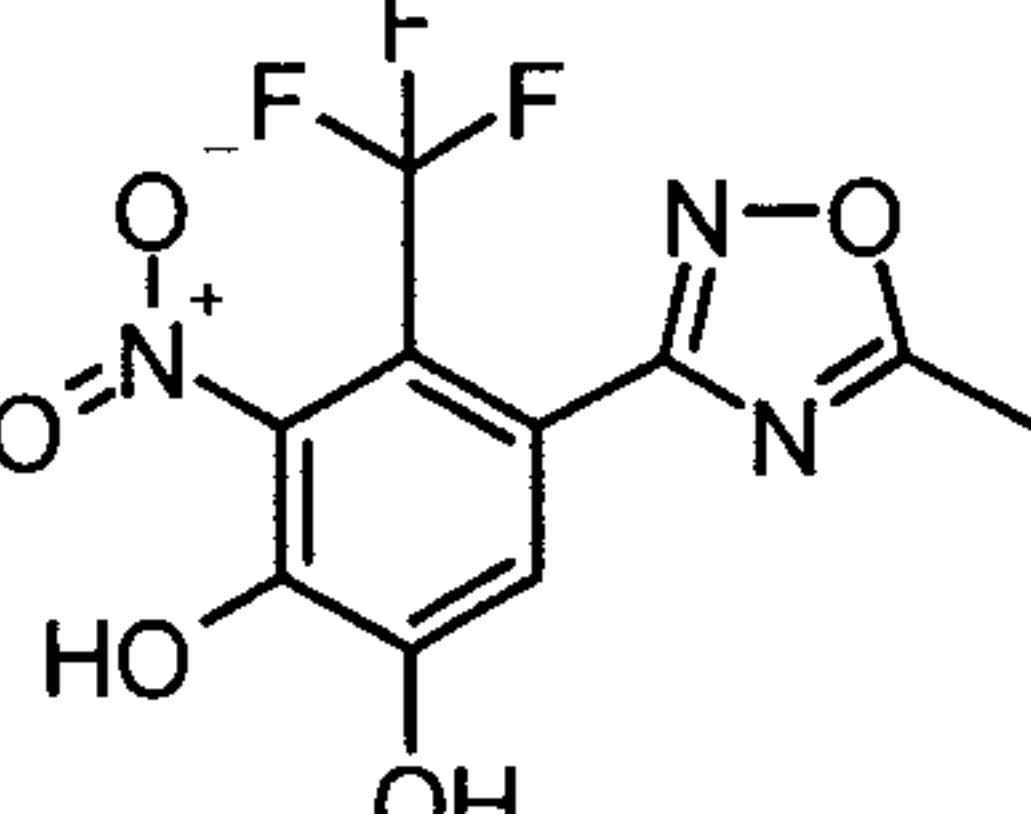
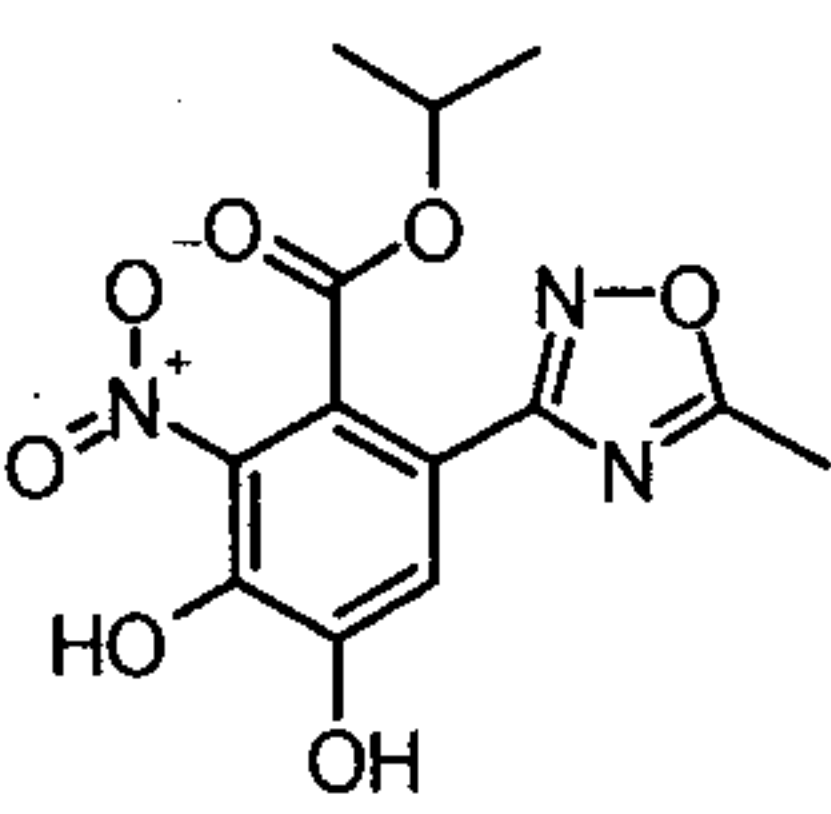
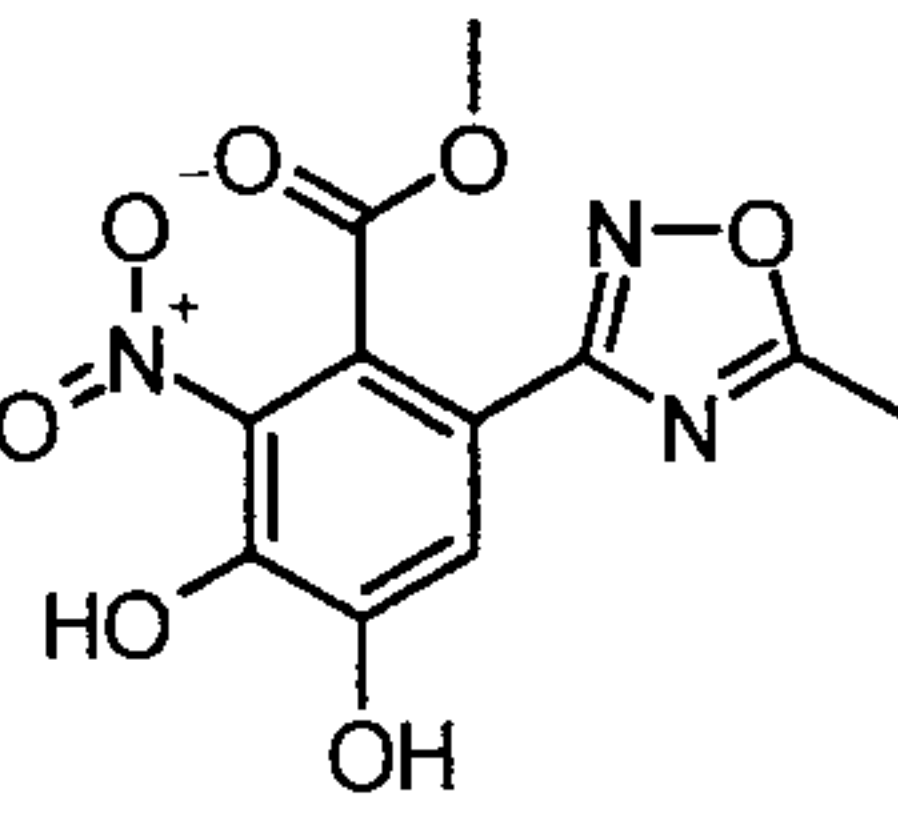
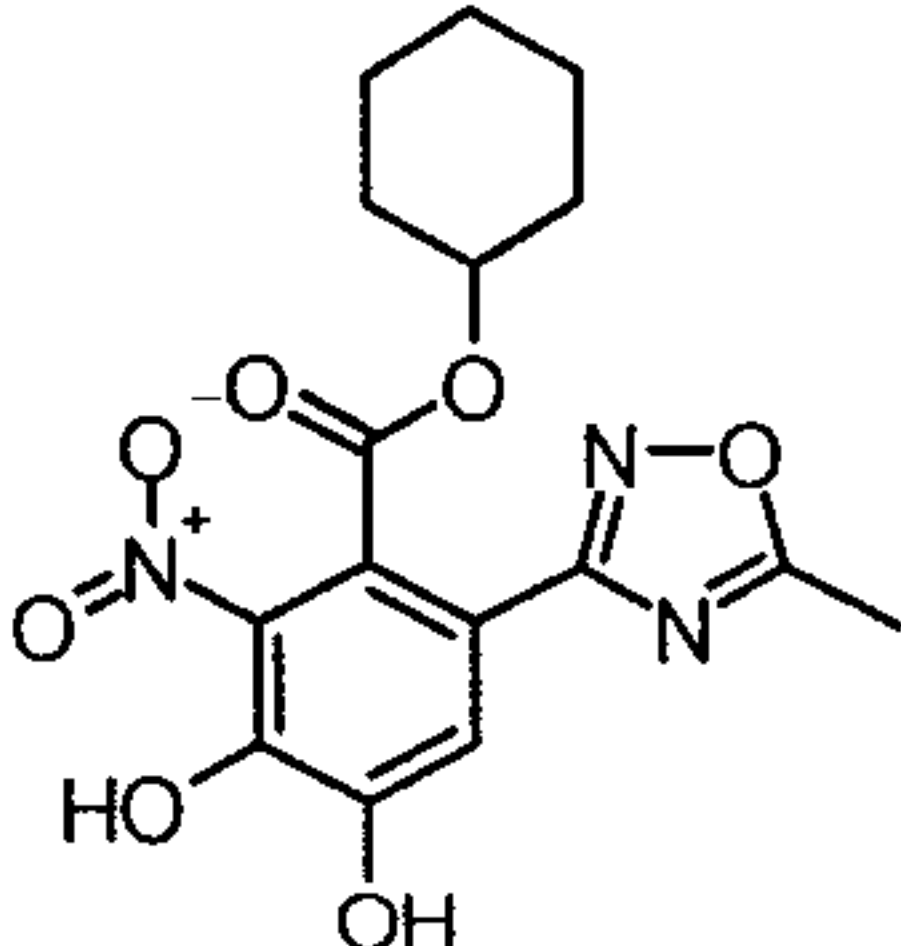
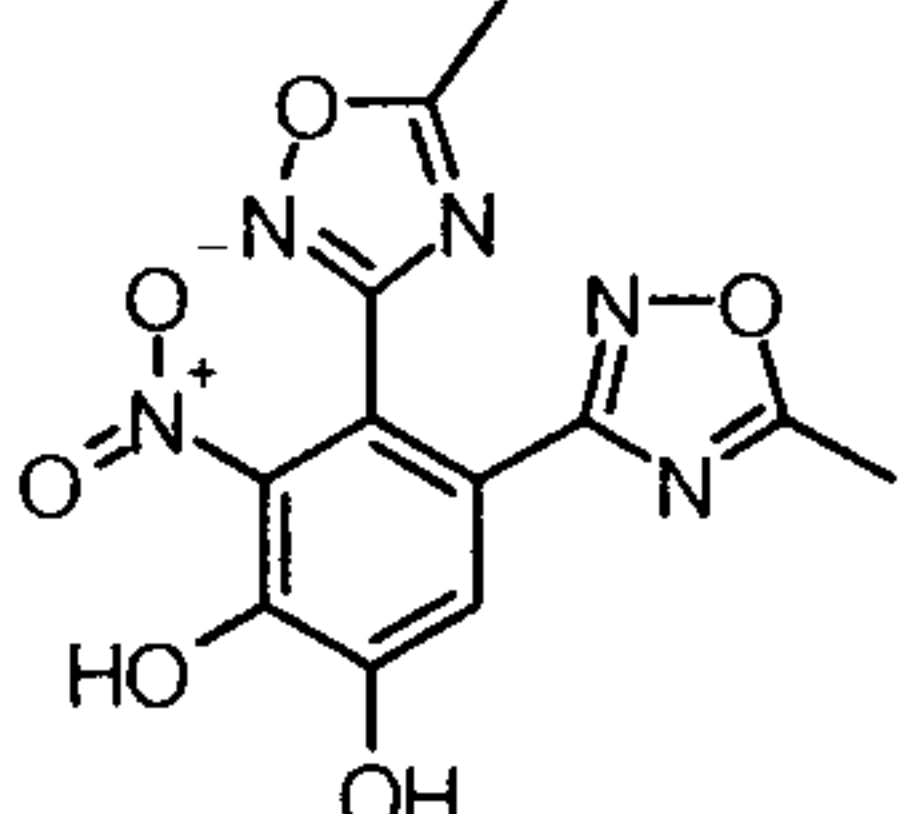
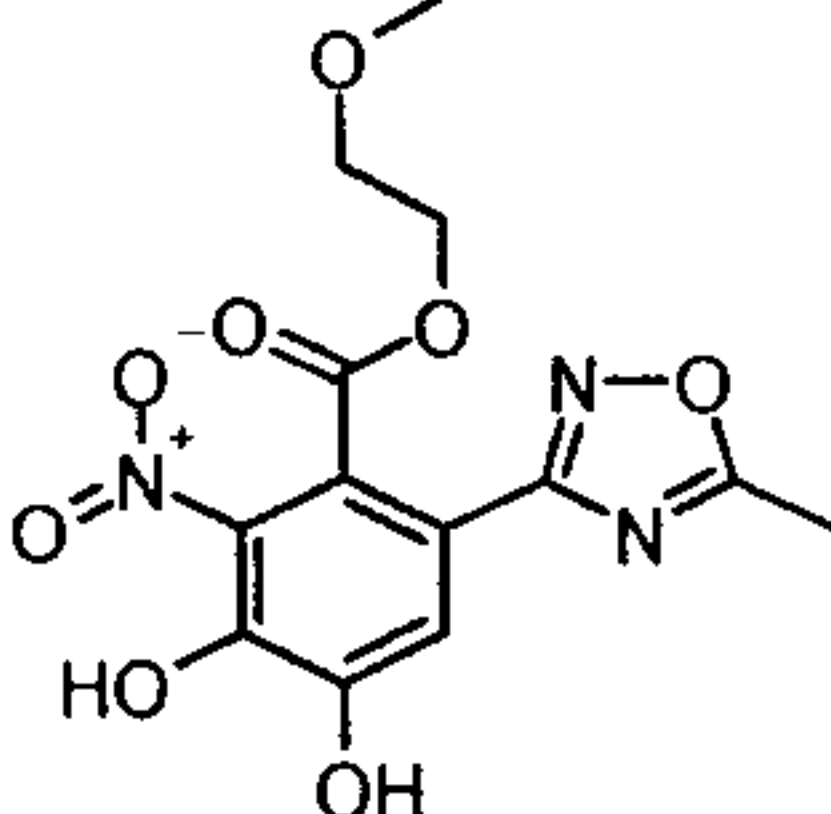
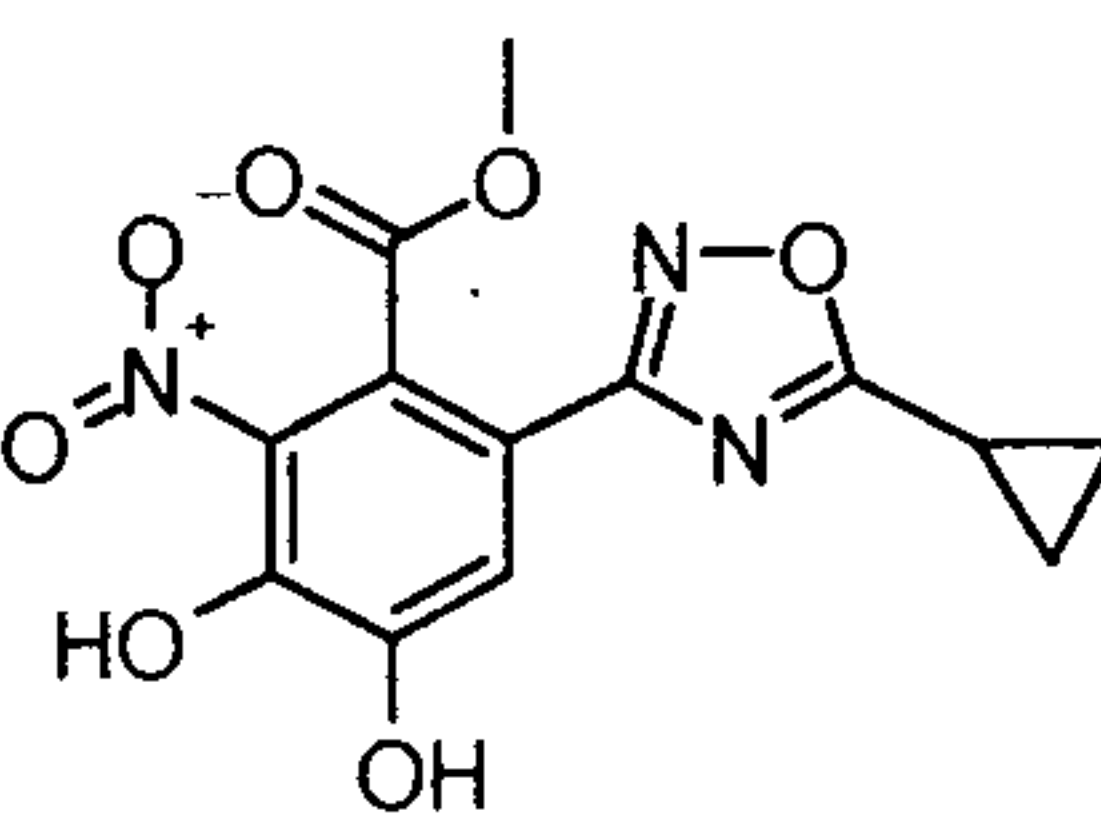
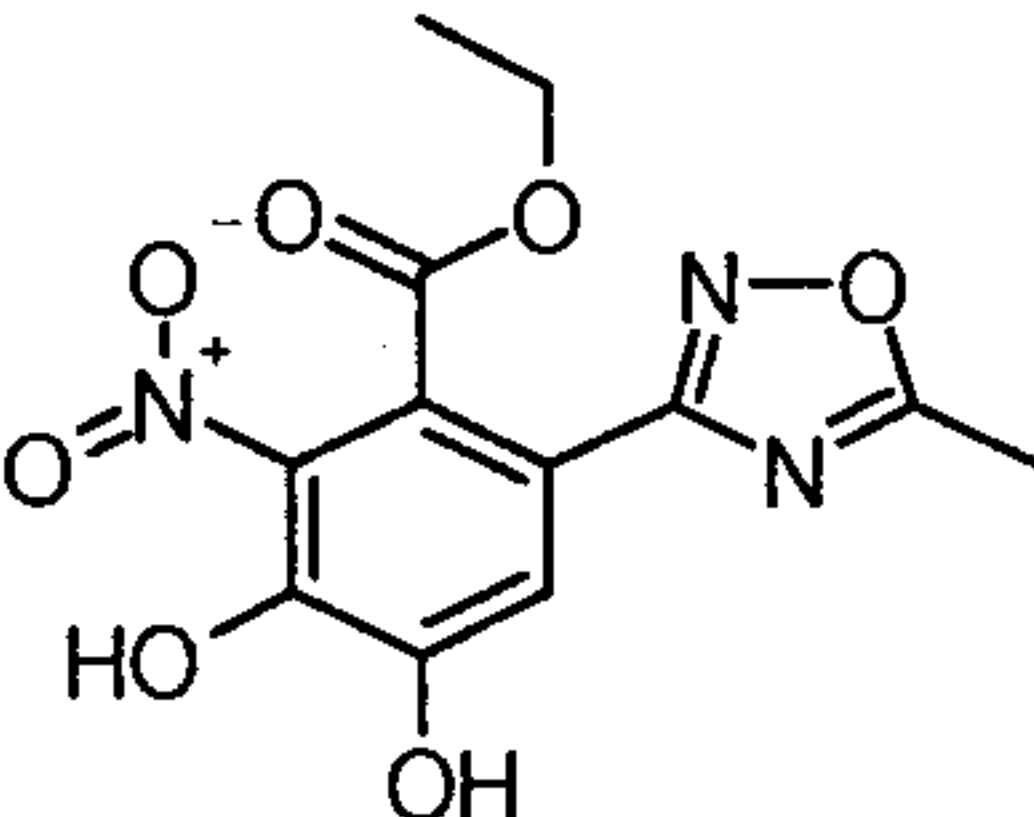
Compounds 1-2 to 1-45 were prepared in a manner similar to those as described in Example 1-1 using the corresponding 3-nitrobenzene-1-methoxy-2-ols instead of

[3-hydroxy-4-methoxy-6-(5-methyl-[1,2,4]oxadiazol-3-yl)-2-nitrophenyl]phenylmethanone. These were illustrated in table

12.

[0307]

Table 12

Compound No.	Structure	Compound No.	Structure
1-1		1-8	
1-2		1-9	
1-3		1-10	
1-4		1-11	
1-5		1-12	
1-6		1-13	
1-7		1-14	

(continued)

Compound No.	Structure	Compound No.	Structure
1-15		1-22	
1-16		1-23	
1-17		1-24	
1-18		1-25	
1-19		1-26	
1-20		1-27	
1-21		1-28	

(continued)

Compound No.	Structure	Compound No.	Structure
1-29		1-36	
1-30		1-37	
1-31		1-38	
1-32		1-39	
1-33		1-40	
1-34		1-41	
1-35		1-42	

(continued)

Compound No.	Structure	Compound No.	Structure
1-43		1-45	
1-44			

[0308]

The physical data of compounds 1-2 to 1-45 were shown below.

[0309]

5 Compound 1-2

$^1\text{H-NMR}$ (DMSO- d_6) δ ppm: 2.34 (3H, s), 2.65 (3H, s), 7.52 (1H, s), 11.17 (1H, br s)

[0310]

Compound 1-3

10 $^1\text{H-NMR}$ (DMSO- d_6) δ ppm: 1.00 (6H, d, $J=6.8\text{Hz}$), 2.56-2.63 (1H, m), 2.64 (3H, s), 7.46 (1H, s), 11.18 (2H, br s)

[0311]

Compound 1-4

$^1\text{H-NMR}$ (DMSO- d_6) δ ppm: 2.68 (3H, s), 7.21 (1H, s), 11.57 (2H, br)

15 [0312]

Compound 1-5

$^1\text{H-NMR}$ (DMSO- d_6) δ ppm: 2.64 (3H, s), 3.67 (3H, s), 7.42 (1H, s), 11.29 (2H, br)

[0313]

Compound 1-6

^1H -NMR (DMSO- d_6) δ ppm: 2.56 (3H, s), 2.61 (3H, s), 7.54 (1H, s),
11.38 (2H, br s)

5 [0314]

Compound 1-7

^1H -NMR (DMSO- d_6) δ ppm: 1.10-1.14 (2H, m), 1.26-1.31 (2H, m),
2.35-2.42 (1H, m), 3.66 (3H, s), 7.40 (1H, s), 11.27 (2H, br)

[0315]

10 Compound 1-8

^1H -NMR (DMSO- d_6) δ ppm: 2.70 (3H, s), 7.61 (1H, s)

[0316]

Compound 1-9

^1H -NMR (DMSO- d_6) δ ppm: 3.41 (3H, s), 3.67 (3H, s), 4.81 (2H, s),
15 7.44 (1H, s), 11.38 (2H, br)

[0317]

Compound 1-10

^1H -NMR (DMSO- d_6) δ ppm: 1.41 (9H, s), 3.67 (3H, s), 7.45 (1H, s),
11.33 (2H, br)

20 [0318]

Compound 1-11

^1H -NMR (DMSO- d_6) δ ppm: 1.10-1.20 (6H, m), 2.63 (3H, s),
4.90-5.00 (1H, m), 7.63 (1H, s), 11.27 (2H, br s)

[0319]

25 Compound 1-12

^1H -NMR (DMSO- d_6) δ ppm: 1.20-1.80 (10H, m), 2.62 (3H, s),
4.70-4.80 (1H, m), 7.36 (1H, s), 11.26 (2H, br s)

[0320]

Compound 1-13

$^1\text{H-NMR}$ (DMSO- d_6) δ ppm: 2.62 (3H, s), 3.18 (3H, s), 3.40-3.50 (2H, m), 4.10-4.20 (2H, m), 7.38 (1H, s), 11.16 (1H, br s)

5 [0321]

Compound 1-14

$^1\text{H-NMR}$ (DMSO- d_6) δ ppm: 1.00-1.20 (3H, m), 2.64 (3H, s), 4.10-4.20 (2H, m), 7.38 (1H, s), 11.25 (1H, br s)

[0322]

10 Compound 1-15

$^1\text{H-NMR}$ (DMSO- d_6) δ ppm: 1.24 (9H, s), 2.60 (3H, s), 7.50 (1H, s), 7.97 (1H, br), 11.32 (2H, br)

[0323]

Compound 1-16

15 $^1\text{H-NMR}$ (DMSO- d_6) δ ppm: 2.63 (3H, s), 7.31 (1H, s)

[0324]

Compound 1-17

$^1\text{H-NMR}$ (DMSO- d_6) δ ppm: 2.33 (3H, s), 2.45 (3H, s), 7.20-7.30 (2H, m), 7.50-7.60 (3H, m), 11.22 (1H, br s)

20 [0325]

Compound 1-18

$^1\text{H-NMR}$ (DMSO- d_6) δ ppm: 2.55 (3H, s), 7.05-7.10 (1H, m), 7.27-7.32 (2H, m), 7.46-7.49 (2H, m), 7.55 (1H, s), 10.41 (1H, s), 10.98 (1H, br), 11.08 (1H, br)

25 [0326]

Compound 1-19

$^1\text{H-NMR}$ (DMSO- d_6) δ ppm: 2.42 (3H, s), 7.50-7.65 (2H, m),

7.95-8.15 (2H, m), 8.40-8.50 (1H, m), 10.50-11.50 (2H, m)

[0327]

Compound 1-20

¹H-NMR (DMSO-d₆) δ ppm: 1.02-1.78 (10H, m), 2.22-2.30 (1H, m),
5 2.65 (3H, s), 7.46 (1H, s), 11.11 (1H, br)

[0328]

Compound 1-21

¹H-NMR (DMSO-d₆) δ ppm: 0.91-0.99 (4H, m), 1.91-1.98 (1H, m),
2.64 (3H, s), 7.43 (1H, s), 11.18 (2H, br)

10 [0329]

Compound 1-22

¹H-NMR (DMSO-d₆) δ ppm: 2.45 (3H, s), 7.19-7.27 (2H, m), 7.51 (1H,
s), 7.58-7.64 (2H, m), 11.27 (1H, br s)

[0330]

15 Compound 1-23

¹H-NMR (DMSO-d₆) δ ppm: 2.46 (3H, s), 7.56 (1H, s), 7.93 (1H, d,
J=3.0Hz), 8.20 (1H, d, J=3.0Hz), 10.50-12.00 (2H, br)

[0331]

Compound 1-24

20 ¹H-NMR (DMSO-d₆) δ ppm: 7.13 (1H, d, J=2.0Hz), 7.62 (1H, s), 8.74 (1H,
d, J=2.0Hz)

[0332]

Compound 1-25

¹H-NMR (DMSO-d₆) δ ppm: 1.75 (3H, s), 3.25-3.33 (2H, m), 7.13 (1H,
25 s), 7.14-7.23 (5H, m), 11.52 (1H, br)

[0333]

Compound 1-26

$^1\text{H-NMR}$ (DMSO- d_6) δ ppm: 2.64 (3H, s), 2.87-2.93 (4H, m),
7.14-7.28 (5H, m), 7.55 (1H, s), 11.17 (2H, br)

[0334]

Compound 1-27

5 $^1\text{H-NMR}$ (DMSO- d_6) δ ppm: 1.00 (9H, s), 2.65 (3H, s), 7.47 (1H, s),
11.11 (2H, br s)

[0335]

Compound 1-28

$^1\text{H-NMR}$ (DMSO- d_6) δ ppm: 2.66 (3H, s), 7.59 (1H, s)

10 [0336]

Compound 1-29

$^1\text{H-NMR}$ (DMSO- d_6) δ ppm: 1.60 (6H, br s), 1.89 (6H, br s), 1.99 (3H,
br s), 2.62 (3H, s), 7.40 (1H, s), 7.81 (1H, s), 10.69 (1H, br
s), 10.81 (1H, br s)

15 [0337]

Compound 1-30

$^1\text{H-NMR}$ (DMSO- d_6) δ ppm: 2.56 (3H, s), 4.94 (2H, s), 6.84-6.96 (3H,
m), 7.23-7.27 (2H, m), 7.58 (1H, s), 11.30 (2H, br)

[0338]

20 Compound 1-31

$^1\text{H-NMR}$ (DMSO- d_6) δ ppm: 2.29 (3H, s), 5.59 (2H, s), 6.95-7.15 (3H,
m), 7.30-7.40 (2H, m), 7.54 (1H, s), 10.00-12.00 (2H, br)

[0339]

Compound 1-32

25 $^1\text{H-NMR}$ (DMSO- d_6) δ ppm: 1.30-1.40 (6H, m), 2.35 (3H, s), 7.56 (1H,
s), 11.17 (2H, br s)

[0340]

Compound 1-33

$^1\text{H-NMR}$ (DMSO- d_6) δ ppm: 0.90-1.00 (3H, m), 1.70-1.90 (2H, m), 2.34 (3H, s), 2.90-3.00 (2H, m), 7.54 (1H, s), 11.18 (2H, br s)
[0341]

5 Compound 1-34

$^1\text{H-NMR}$ (DMSO- d_6) δ ppm: 1.10-1.25 (3H, m), 2.31 (3H, s), 2.86 (2H, t, $J=6.8\text{Hz}$), 3.22 (2H, t, $J=6.8\text{Hz}$), 4.00-4.15 (2H, m), 7.50 (1H, s), 10.50-11.50 (2H, br)
[0342]

10 Compound 1-35

$^1\text{H-NMR}$ (DMSO- d_6) δ ppm: 2.41 (3H, s), 7.57 (1H, s), 10.50-12.00 (2H, br)
[0343]

Compound 1-36

15 MS (ESI, m/z): 348 (M-1)

[0344]

Compound 1-37

$^1\text{H-NMR}$ (DMSO- d_6) δ ppm: 1.07 (3H, t, $J=7.0\text{Hz}$), 2.33 (3H, s), 3.23 (2H, t, $J=6.2\text{Hz}$), 3.45 (2H, q, $J=7.0\text{Hz}$), 3.79 (2H, t, $J=6.2\text{Hz}$), 7.52 (1H, s), 10.80-11.80 (2H, br)
[0345]

Compound 1-38

$^1\text{H-NMR}$ (DMSO- d_6) δ ppm: 2.63 (6H, s), 6.95 (1H, s)
[0346]

25 Compound 1-39

$^1\text{H-NMR}$ (DMSO- d_6) δ ppm: 2.68 (3H, s), 3.46 (3H, s), 7.11 (1H, s)
[0347]

Compound 1-40

$^1\text{H-NMR}$ (DMSO- d_6) δ ppm: 1.02-1.72 (10H, m), 2.59 (3H, s), 3.37-3.48 (1H, m), 7.51 (1H, s), 8.61 (1H, d, $J=8.5\text{Hz}$), 11.32 (2H, br)

5 [0348]

Compound 1-41

$^1\text{H-NMR}$ (DMSO- d_6) δ ppm: 1.03-1.89 (10H, m), 2.60-2.65 (3H, m), 2.60-3.05 (3H, m), 3.83-3.94 (1H, m), 7.40-7.45 (1H, m), 11.30 (2H, br)

10 [0349]

Compound 1-42

$^1\text{H-NMR}$ (DMSO- d_6) δ ppm: 2.47 (3H, s), 6.74 (2H, d, $J=9.1\text{Hz}$), 7.48 (2H, d, $J=8.2\text{Hz}$), 7.54 (1H, s)

[0350]

15 Compound 1-43

$^1\text{H-NMR}$ (DMSO- d_6) δ ppm: 0.29-0.38 (2H, m), 0.53-0.63 (2H, m), 1.19-1.29 (1H, m), 2.47 (3H, s), 3.86-3.92 (2H, m), 6.90-6.97 (3H, m), 7.51 (2H, d, $J=8.8\text{Hz}$)

[0351]

20 Compound 1-44

$^1\text{H-NMR}$ (DMSO- d_6) δ ppm: 2.43 (3H, s), 3.86 (3H, s), 7.60 (1H, s), 7.76 (2H, d, $J=8.7\text{Hz}$), 7.99 (2H, d, $J=8.7\text{Hz}$)

[0352]

Compound 1-45

25 $^1\text{H-NMR}$ (DMSO- d_6) δ ppm: 2.44 (3H, s), 7.60 (1H, s), 7.81 (2H, d, $J=8.6\text{Hz}$), 7.92 (2H, d, $J=8.6\text{Hz}$)

[0353]

Example 2-1

2,2-Dimethylpropionic acid=6-(2,2-dimethylpropionyloxy)-3-isobutyryl-4-(5-methyl-[1,2,4]oxadiazol-3-yl)-2-nitrophenyl ester(compound 2-1)

5 To a mixture of 1-[3,4-dihydroxy-6-(5-methyl-[1,2,4]-oxadiazol-3-yl)-2-nitrophenyl]-2-methylpropane-1-one (compound 1-3) (100mg) and tetrahydrofuran(2mL) were added trimethylacetyl chloride(92 μ L) and triethylamine(100 μ L) under ice bath cooling while stirring. The mixture was stirred for 30
10 minutes, warmed to room temperature, and stirred overnight. The mixture was diluted with ethyl acetate, washed with 1mol/L hydrochloric acid and brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography(eluent: 0%-20%
15 ethyl acetate/hexane, gradient elution) to give the title compound(174mg). The structural formula was illustrated in table 13.

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.20 (6H, d, $J=6.9\text{Hz}$), 1.34 (9H, s), 1.36 (9H, s), 2.65 (3H, s), 2.82 (1H, septet, $J=6.9\text{Hz}$), 8.04 (1H, s)

20 [0354]

Example 3-1

Methyl 4-ethoxycarbonyloxy-3-hydroxy-6-(5-methyl-[1,2,4]-oxadiazol-3-yl)-2-nitrobenzoate(compound 3-1)

 A mixture of methyl 3,4-dihydroxy-6-(5-methyl-[1,2,4]-oxadiazol-3-yl)-2-nitrobenzoate(compound 1-5) (50mg), ethyl
25 chlorocarbonate(0.02mL), potassium carbonate(28mg) and N,N-dimethylformamide(2mL) was stirred at 50°C for 3 hours.

After cooling to room temperature, water and ethyl acetate were added to the mixture. The separated organic layer was washed with water and brine successively, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: 20%-100% ethyl acetate/hexane, gradient elution) to give the title compound (51mg). The structural formula was illustrated in table 13.

¹H-NMR (CDCl₃) δ ppm: 1.42 (3H, t, J=7.2Hz), 2.64 (3H, s), 4.01 (3H, s), 4.38 (2H, q, J=7.2Hz), 8.23 (1H, s), 10.98 (1H, br) [0355]

Example 4-1

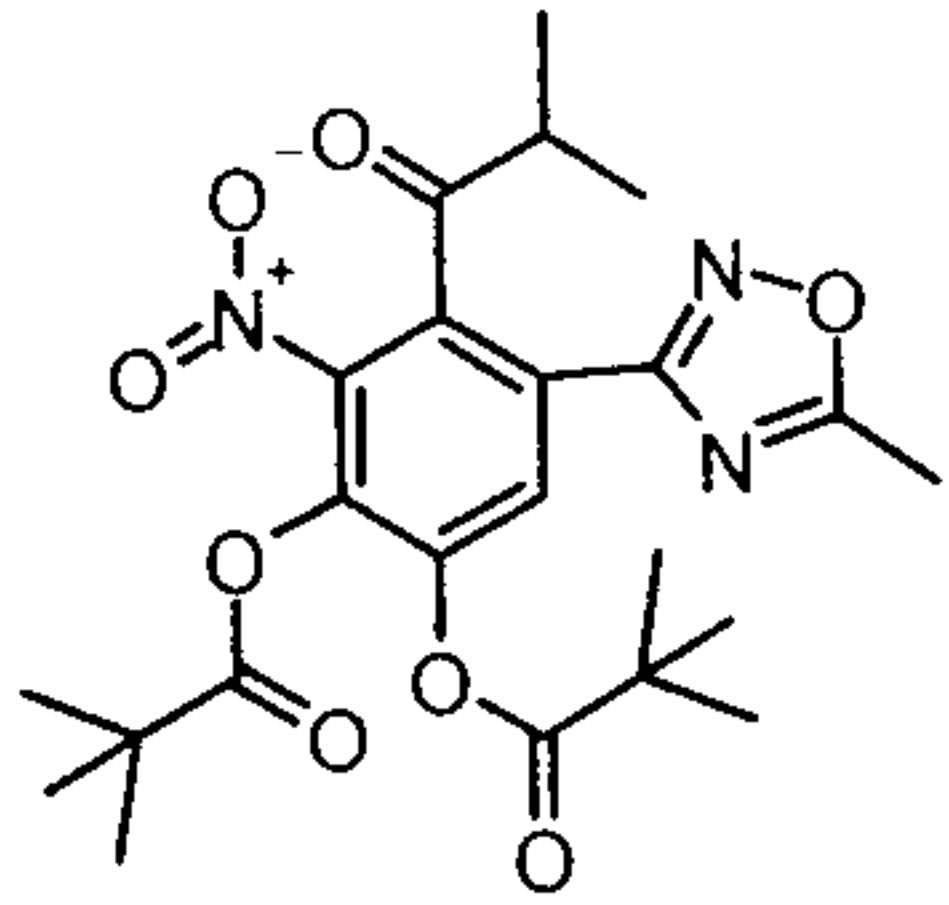
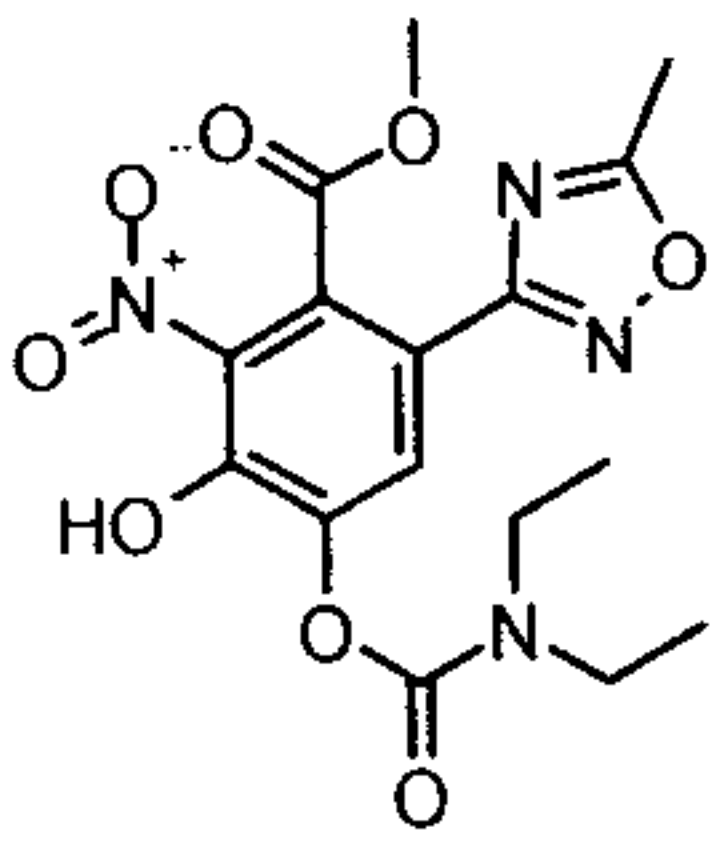
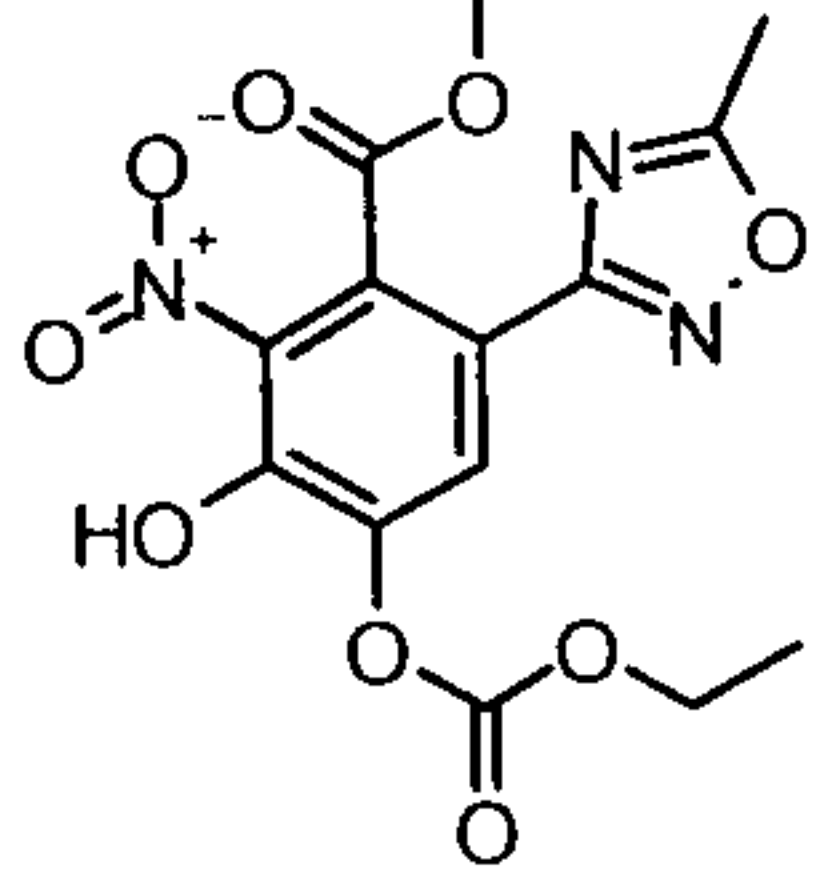
Methyl 4-diethylcarbamoyloxy-3-hydroxy-6-(5-methyl-[1,2,4]-oxadiazol-3-yl)-2-nitrobenzoate (compound 4-1)

A mixture of methyl 3,4-dihydroxy-6-(5-methyl-[1,2,4]-oxadiazol-3-yl)-2-nitrobenzoate (compound 1-5) (50mg), diethylcarbamoyl chloride (0.024mL), 4-dimethylaminopyridine (4mg) and pyridine (2mL) was stirred at room temperature for 3 hours. After addition of ethyl acetate, the mixture was acidified with 2mol/L hydrochloric acid. The separated organic layer was washed with water, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: 20%-100% ethyl acetate/hexane, gradient elution) to give the title compound (31mg). The structural formula was illustrated in table 13.

¹H-NMR (CDCl₃) δ ppm: 1.14-1.27 (6H, m), 2.61-2.67 (3H, m), 3.32-3.46 (4H, m), 3.88-4.02 (3H, m), 8.13-8.19 (1H, m)

[0356]

Table 13

Compound No.	Structure	Compound No.	Structure
2-1		4-1	
3-2			

[0357]

Example 5-1

- 5 [3,4-Dihydroxy-6-(5-methyl-[1,2,4]oxadiazol-3-yl)-2-nitrophenyl]phenylmethanone mono potassium salt (compound 5-1)

To a mixture of [3,4-dihydroxy-6-(5-methyl-[1,2,4]-oxadiazol-3-yl)-2-nitrophenyl]phenylmethanone (compound 1-1) (100mg), water (2.5mL) and tert-butanol (2.5mL) was added a 1mol/L aqueous solution of potassium hydroxide (0.292mL). The mixture was concentrated under reduced pressure to give the title compound (103mg) as an amorphous.

¹H-NMR (DMSO-d₆) δ ppm: 2.38 (3H, s), 6.94 (1H, s), 7.35-7.41 (2H, m), 7.45-7.51 (1H, m), 7.63-7.68 (2H, m)

- 15 [0358]

Compounds 5-2 to 5-6 were prepared in a manner similar to those as described in Example 5-1 using the corresponding 3-nitrobenzene-1,2-diols and sodium hydroxide or potassium hydroxide instead of [3,4-dihydroxy-6-(5-methyl-[1,2,4]-

oxadiazol-3-yl)-2-nitrophenyl]phenylmethanone and potassium hydroxide.

[0359]

Compound 5-2

- 5 [3,4-Dihydroxy-6-(5-methyl-[1,2,4]oxadiazol-3-yl)-2-nitrophenyl]phenylmethanone mono sodium salt

$^1\text{H-NMR}(\text{DMSO-d}_6)\delta$ ppm: 2.38 (3H, s), 6.93 (1H, s), 7.34-7.41 (2H, m), 7.44-7.51 (1H, m), 7.62-7.68 (2H, m)

[0360]

- 10 Compound 5-3

Methyl 3,4-dihydroxy-6-(5-methyl-[1,2,4]oxadiazol-3-yl)-2-nitrobenzoate mono potassium salt

$^1\text{H-NMR}(\text{DMSO-d}_6)\delta$ ppm: 2.56 (3H, s), 3.60 (3H, s), 6.72 (1H, s)

[0361]

- 15 Compound 5-4

Methyl 3,4-dihydroxy-6-(5-methyl-[1,2,4]oxadiazol-3-yl)-2-nitrobenzoate mono sodium salt

$^1\text{H-NMR}(\text{DMSO-d}_6)\delta$ ppm: 2.56 (3H, s), 3.59 (3H, s), 6.68 (1H, s)

[0362]

- 20 Compound 5-5

1-[3,4-Dihydroxy-6-(5-methyl-[1,2,4]oxadiazol-3-yl)-2-nitrophenyl]-2-methylpropan-1-one mono potassium salt

$^1\text{H-NMR}(\text{DMSO-d}_6)\delta$ ppm: 1.04 (6H, d, $J=7.0\text{Hz}$), 2.55 (3H, s), 2.59-2.72 (1H, m), 6.84 (1H, s)

- 25 [0363]

Compound 5-6

1-[3,4-Dihydroxy-6-(5-methyl-[1,2,4]oxadiazol-3-yl)-2-

nitrophenyl]-2-methylpropan-1-one mono sodium salt

$^1\text{H-NMR}$ (DMSO- d_6) δ ppm: 1.03 (6H, d, $J=6.8\text{Hz}$), 2.55 (3H, s),
2.59-2.70 (1H, m), 6.81 (1H, s)

[0364]

5 Test example 1

HUMAN COMT INHIBITORY POTENCY

1) Preparation of recombinant human COMT

(1) Preparation of recombinant human catechol-O-methyl transferase

10 According to the DNA sequence of NCBI (National Center for Biotechnology Information) accession number (BC011935), two oligonucleotide primers were designed to amplify the target DNA sequence coding full-length human catechol-O-methyl transferase (hereinafter referred to as "COMT") as shown in
15 Sequence ID No.1. Sequences of the 5'-primer and the 3'-primer were indicated in Sequence ID No.3 and 4, respectively. For ease in insertion of corresponding PCR product into the desired vector, these primers includes restriction enzyme sites of BamH I and EcoR I on the 5'-side and the 3'-side, respectively.

20 Each of the 5'-primer indicated in Sequence ID No.3 and the 3'-primer indicated in Sequence ID NO.4 was diluted with TE buffer to prepare 15 pmol/ μL solutions. A mixture for PCR reaction was prepared with H_2O (for PCR, 34.8 μL), 25 mmol/L MgSO_4 (2.0 μL), 2 mmol/L dNTPs (5.0 μL) and 10-fold concentrated
25 buffer for KOD plus DNA Polymerase (5.0 μL , TOYOBO). After the addition of each primer pairs (1 μL , 15 pmol) following human liver cDNA (5.0 μL , Clontech), 1.0 μL KOD plus (TOYOBO) was added

to the above reaction mixture. Thereafter, PCR reaction was executed as referred to hereinafter; after the procedure at 94 °C for 2 minutes, PCR reactions were carried out for 40 cycles, each consisting of 94 °C for 15 seconds, 59 °C for 30 seconds, and 68 °C for 1 minutes and then terminated at 68 °C for 5 minutes and at 4 °C for 10 minutes.

PCR product was purified using a QIAquick PCR Purification Kit (QIAGEN) and the desired DNA insert was eluted using EB buffer (30 µL) included in the corresponding kit.

10 [0365]

(2) Double digestion of recombinant human COMT DNA insert and pGEX-2T vector

The obtained recombinant human COMT DNA insert (1.5 µg) was mixed with 10-fold concentrated EcoR I buffer (3.0 µL, New England Biolab), H₂O (11.1 µL), BamH I (1.5 µL, 15 U, 10 U/µL) and EcoR I (1.0 µL, 15 U, 10 U/µL) and then incubated at 37 °C for 1.5 hours. Thereafter 10-fold concentrated loading buffer was added to the mixture. Following the purification on an electrophoresis, a piece of the gel region including objective digested fragment was removed and purified with a MinElute Gel Extraction Kit (QIAGEN). Double digestion and purification of pGEX-2T vector DNA (1.5 µg, Amersham) was also performed in a similar way as described above.

[0366]

25 (3) Ligation and E. coli JM109 transformation

Double-digested DNA of pGEX-2T vector (2.0 µL, 50 ng) and insert DNA (1.24 µL, 33.4 ng) were added to 2-fold concentrated

ligation buffer (3.24 μ L, Promega) and mixed. The mixture was incubated at 25 °C for 1 hour following the addition of T4 ligase (1.0 μ L, 3 U/ μ L, Promega). This solution of ligase-treated mixture (5 μ L) was transferred to E. coli JM109 (100 μ L) thawed at 0 °C, and was gently mixed and incubated at 0 °C for 30 minutes. The mixture was heat-shocked at 42 °C for 40 seconds, without excessive shaking, followed by cooling at 0 °C for 10 minutes. After heat shock step, SOC medium (450 μ L) was added and the mixture was shaken at 37 °C for 1 hour. Each aliquot (50 μ L and 200 μ L) of the mixture was subsequently seeded onto LB plates (a diameter of 9 cm, ampicillin 100 μ g/mL) and statically cultured at 37 °C for 16 hours. As a result, colonies were observed on the plates.

[0367]

(4) Colony selection of JM109 transformed with GST-fusion recombinant human COMT plasmid

Some colonies were selected from above-mentioned statically cultured plates and each colony was inoculated into 2 mL of LB-ampicillin (100 μ g/mL) liquid medium using sterile picks. After the shaking culture at 37 °C for 16 hours, aliquots (200 μ L) of each culture were removed into 1.5 mL microtubes and plasmids were extracted by a phenol extraction. The obtained plasmids were resolubilized in TE buffer and separated by electrophoresis. Primary positive colonies were identified according to the electrophoretic mobilities of their extracted plasmids similar to that of pGEX-2T vector without insert DNA and reconfirmed by double digestion using restriction enzymes

as follows.

DNA solutions (7 μ L) prepared from primary positive colonies indicated above were mixed with 10-fold concentrated EcoR I buffer (0.9 μ L, New England Biolab), then BamH I (0.5 μ L, 10 U/ μ L) and EcoR I (0.5 μ L, 15 U/ μ L) were added to the mixture. The solution was analyzed by electrophoresis after warming (37 °C, 1 hour). Secondary positive colonies were identified as those with a band of about 670bp.

[0368]

10 (5) Extraction and purification of GST-fusion recombinant human COMT plasmid from E. coli JM109

An aliquot (100 μ L) from the culture of E. coli JM109 transformed with GST-fusion recombinant human COMT plasmid, which determined as a secondary positive colony at (4), was stored as a glycerol stock, whereas the rest was centrifuged at 12,000 rpm for 10 minutes to obtain E.coli pellet. Plasmid DNA was purified from the E.coli pellet by QIAGEN Plasmid mini kit (QIAGEN) and its concentration was determined by OD 260 nm (247 ng/ μ L). DNA sequence analysis according to a conventional method confirmed that the DNA sequence indicated in Sequence ID No. 2 was properly inserted at the desired site.

[0369]

(6) Transformation of competent E. Coli BL21 (DE3) CODON PLUS RP by GST-fusion recombinant human COMT plasmid DNA

25 For transformation and plate culture in the same fashion as (3), 1 μ L of purified GST-fusion recombinant human COMT plasmid DNA (1 ng/ μ L) with valid sequence indicated in (5) was added

to 50 μ L of cell suspension of competent E. Coli BL21 (DE3) CODON PLUS RP thawed at 0 °C.

[0370]

(7) Expression of GST-fusion recombinant human COMT

5 A colony was picked up from the plate with transformed E. Coli BL21 (DE3) CODON PLUS RP and cultured with shaking at 37 °C for 15 hours in 5 mL of LB-ampicillin (100 μ g/mL) liquid medium. An aliquot of culture medium (50 μ L) was stored at -80 °C as a glycerol stock. A piece of the glycerol stock was used to
10 inoculate into 150 mL of LB-ampicillin (100 μ g/mL) medium and cultured with shaking at 37 °C for 16 hours. The culture was diluted into 7 culture flasks with LB-ampicillin (100 μ g/mL) medium (500 mL each), and then each culture was grown at 20°C for 4.5 hours with shaking to a cell density of OD 600 nm = 0.44,
15 at which point 50 μ L of isopropyl- β -D-thiogalactopyranoside (1 mol/L) was added to each culture. After that, each culture was incubated under the same conditions for an additional 18 hours. E.coli pellet was harvested by centrifugation for 20 minutes at 9,000 rpm, divided into four equal portions (4 g) and stored
20 at -80°C until use.

[0371]

(8) Thrombin processing of GST-fusion recombinant human COMT

 E.coli pellet obtained in (7) was suspended in BugBuster Reagent (Novagen, 40 mL) containing Bensonase (Novagen, 30 μ L)
25 and rLysozyme (Novagen, 1 μ L) and the E. coli was treated with a gentle rotation at room temperature for 15 minutes. The obtained cell lysate was separated by centrifugation at 12,000 rpm for

20 minutes at 4 °C and the supernatant was recovered. This supernatant was incubated at 4 °C for 1 hour on a rotating platform with a 20 mL of a 50% slurry of Glutathione Sepharose 4B (resin-bed volume of 10 mL), which was previously equilibrated with D-PBS (Dulbecco's phosphate-buffered saline). The resultant resin was separated on a filter from the filtrate and washed five times with 30 mL of D-PBS, followed by three additional washing steps with 30 mL of thrombin processing buffer (150 mmol/L NaCl, 50 mmol/L Tris-HCl pH8.0, 10% glycerol, 2.5 mmol/L CaCl₂, and 0.5% n-octyl- β -D-glucopyranoside). After the last wash, the resin was again suspended with thrombin processing buffer at a final volume of 30 mL. Thirty units of thrombin protease (Amersham Biosciences) was added to the resin suspension, and thrombin processing was allowed to proceed with a gentle rotation for 15 hours at 4 °C. The resin suspension was filtrated and recombinant human COMT solution obtained as a filtrate was stored at -80°C until assayed.

[0372]

2) Measurement of human COMT inhibitory potency

Measurement of human COMT inhibitory potency was performed according to the method of G. Zürcher et al (J. Neurochem., 1982, vol.38, p.191 - 195) with a minor modification. Aliquot (0.25 μ L) of recombinant human COMT prepared in 1) (approximately 1 mg/mL) was preincubated with a test compound for 5 minutes at 37°C in the reaction mixture, composed of 40 μ L potassium phosphate buffer (500 mmol/L, pH7.6), 10 μ L magnesium chloride (100 mmol/L), 10 μ L dithiothreitol (62.5 mmol/L) and 0.5 μ L

adenosine deaminase (2550 units/mL). Control samples were prepared in the same way, but the test compounds were replaced with an equal volume (5 μ L) of dimethyl sulfoxide. After the addition of 20 μ L [^{3} H]-S-adenosyl-L-methionine (12.5 mmol/L, 1.2 Ci/mol; Amersham Biosciences), the reaction was started by the addition of 25 μ L catechol substrate (7 mmol/L). The reaction mixture, final volume 0.25 mL, was incubated at 37°C for 30 minutes. The reaction was then stopped by the addition of 0.25 mL of ice-cold 1 mol/L hydrochloric acid containing 0.1 g/L guaiacol. After the addition of 2.5 mL scintillator OPTI-FLUOR (registered mark) 0 (Packard), and following 1-minute vigorous shaking, the radioactivity present in the organic phase was then directly counted in a liquid scintillation counter (Packard; TRICARB 1900CA). Blanks were incubated without catechol substrate (substrate was added after the termination of reaction). The IC₅₀ value indicates the molar concentration required to inhibit 50% of the enzyme activity. As comparative examples, tolcapone, entacapone and 5-(3-methyl-[1,2,4]oxadiazol-5-yl)-3-nitro-benzene-1,2-diol (comparative example 1), which is described in example 75 of the patent literature 1, were assayed in the similar fashion. These results were shown in Table 14.

[0373]

Table 14

Compound No.	IC ₅₀ (nmol/L)	Compound No.	IC ₅₀ (nmol/L)
1-1	9.4	1-37	4.7
1-3	8.1	1-40	8.8
1-5	9.3	1-41	4.7
1-9	7.7	Tolcapone	9.0
1-20	8.7	Entacapone	11.1
1-22	8.3	Comparative example 1	13.2
1-24	7.6		

[0374]

Test example 2

Rat hepatocyte toxicities

5 After rat cryopreserved hepatocytes 3×10^6 cells/vial, stored at -150°C , was warmed at 37°C , and the hepatocytes were added into a thawing medium with glucose (10 mL) and agitated. The suspension was centrifuged at 1000 rpm for 1 minute. After the supernatant was removed, the cell pellet was suspended in

10 Williams E medium (15 mL). A solution of drug in dimethyl sulfoxide was prepared at 45, 15, 4.5, 1.5, 0.45 mmol/L, then each of the drug solutions and dimethyl sulfoxide as a control was dispensed by 2.0 μL to a test tube. The above cell suspension (300 μL) was dispensed into the tube and re-suspended. Every

15 100 μL of each suspension was dispensed to a 96 well-plate, and the plate was incubated for 4 hours at 37°C in CO_2 incubators.

According to Cell viability assay provided from Promega Corporation, ATP activity was measured. The EC50 value indicates the concentration that shows 50 % of the number of viable cells of control. These results were shown in Table 15.

5 [0375]

Table 15

Compound No.	EC ₅₀ (μmol/L)	Compound No.	EC ₅₀ (μmol/L)
1-1	683	1-22	523
1-2	645	1-24	>1000
1-3	698	Tolcapone	34.3
1-5	>1000	Entacapone	111
1-9	>1000	Comparative example 1	172

[0376]

These results suggest that the compounds of the present invention exhibited extremely minor hepatocyte toxicities as compared with tolcapone, entacapone and comparative example 1.

[0377]

Test example 3

EVALUATION of PLASMA L-DOPA CONCENTRATION

15 (1) Compound administration and plasma sampling

6-week-old male Sprague-Dawley rats weighing 170 g to 190 g (Charles River Laboratories Japan Inc.) were fasted overnight. A suspension of test compounds (0.6 mg/mL) and a mixed suspension of L-dopa (1 mg/mL) and carbidopa (6 mg/mL) were prepared with agate mortar using 0.5% methylcellulose solution as a medium.

The mixed suspension of L-dopa (5 mg/kg) and carbidopa (30 mg/kg) was orally administered either 4 or 6 hours after the oral administration of test compounds (3 mg/kg). Blood samples were obtained at 2 hours after the oral administration of mixed
5 suspension of L-dopa and carbidopa and transferred to tubes containing sodium heparin, ethylene glycol tetraacetic acid and reduced glutathione on ice. Plasma sample for the determination of L-dopa concentration was obtained by centrifugation.

[0378]

10 (2) Measurement of L-dopa concentration

To 0.05 mL of the plasma obtained in (1) described above, was added 0.01 mL of 100 µg/mL aqueous solution of metformin hydrochloride as an internal standard material according to a conventional method and then deproteinization was performed by
15 adding 0.05 mL of 250 mmol/L ethylenediamine-tetraacetic acid disodium salt in 0.5 mol/L perchloric acid solution. After centrifugation, 0.002 mL of its supernatant was injected into LC-MS/MS. Plasma concentration of L-dopa was measured by LC-MS/MS under the condition mentioned below. L-dopa concentration was
20 shown in Table 16 as a percentage of the L-dopa concentration of control group without any test compound administration.

LC

Instrument: Agilent1100

25 Column: Capcellpak C18 MGIII 5 µm 4.6x50 mm

Mobile phase: 0.5% aqueous solution of heptafluorobutyric acid /acetonitrile

Column temperature: 40°C

Flow rate: 0.5 mL/minute

MS/MS

Instrument: API-4000

5 Ionization method: ESI (Turbo Ion Spray)

[0379]

Table 16

Compound No.	Plasma L-dopa (%)	
	4hour	6hour
1-1	182.9±5.0	189.2±32.8
Comparative example 1	143.3±13.3	106.9±18.2

[0380]

The results clearly show that the increase in plasma L-dopa
10 concentration was more sustained when the compound of the present
invention was co-administrated with L-dopa and carbidopa as
compared to that when the comparative example 1 was
co-administrated with L-dopa and carbidopa.

[0381]

15 Test example 4

THE POTENTIATION ON THE EFFECACY of L-DOPA IN UNILATERAL
6-HYDROXYDOPAMINE-LESIONED HEMI-PARKINSONIAN RATS

(1) Drugs

The following compounds were used:

20 6-hydroxydopamine hydrochloride (6-OHDA, Sigma); desipramine
hydrochloride (desipramine, Sigma); L-ascorbic acid (Sigma);
sodium pentobarbital (Nembutal inj., Dainippon Sumitomo Pharma

Co., Ltd); apomorphine hydrochloride hemihydrate (apomorphine, Sigma); 3, 4-dihydroxyphenylalanine (L-dopa, Sigma); carbidopa monohydrate (carbidopa, Kemprotec Ltd.); 0.5% methylcellulose (Wako Pure Chemicals).

5 6-OHDA was dissolved at 2 mg/ml in a saline solution containing 0.2% L-ascorbic acid. Desipramine was dissolved at 10 mg/mL in distilled water in a hot-water bath. Apomorphine was dissolved at 0.1 mg/mL in a saline solution. L-dopa/carbidopa was suspended in a 0.5% methylcellulose solution. Test compounds
10 were dissolved in a solution containing 0.5% dimethylsulfoxide, 20% polyethylene glycol and 79.5% of a 0.1 mol/L aqueous solution of arginine.

[0382]

(2) Preparation of 6-OHDA-lesioned model

15 Preparation of 6-OHDA-lesioned model was performed according to the method of nonpatent literature 6 with a minor modification. Male Sprague-Dawley rats (6-weeks-old, Charles River Laboratories Japan Inc.) were anaesthetized with intraperitoneal sodium pentobarbital (45 mg/kg) administration
20 and placed in a stereotaxic frame (Narishige, Tokyo, Japan). In order to prevent 6-OHDA-induced damage of noradrenergic neurons, intraperitoneal desipramine injection (25 mg/kg) was given 30 minutes before the 6-OHDA injection. After the bregma identification via a middle calvarial incision, the skull was
25 drilled using a dental drill at the site of 6-OHDA injection. The lesion was made by injecting 6-OHDA (8 µg in 4 µL at a speed of 1 µL/minute) unilaterally into the left medial forebrain

bundle (the lesion coordinates; A/P -2.5 mm, L/M -1.8 mm, and V/D -8.0 mm, from the bregma point and surface of the skull) by using a injection cannula (30 gauge needle) connected to a microsyringe (Hamilton). The cannula was carefully removed from the animal after keeping placed on the lesion site for 5 minutes. The skull was filled its hole with dental cement, disinfected, and the scalp incision was surgically sutured. Animals recovered from anesthesia were housed as usual until the day of the experiment.

10 [0383]

(3) Evaluation of turning behavior

Three weeks after the lesion, rats were tested on the basis of their contralateral rotation (single rotation was defined as a 360° turn) in response to 0.1 mg/kg apomorphine given subcutaneously. For behavioral observation, rats were placed in plastic cylinders of radius 20 cm and turning behavior was videotaped and quantified by rat-rotation auto counting system R-RACS (Kissei Wellcom Co., Ltd.). Animals that turned over 100 rotation counts during 1 hour were accepted for further experiments. On the experimental day, animals were fasted for 10 hours from 9am, and all test compounds were orally given at doses of 10 mg/kg with concomitant oral administration of 5 mg/kg L-dopa and 30 mg/kg carbidopa. The drug potency was measured as the number of contralateral turning, and duration of the response was defined as a time period until the animal exhibited less than 10 rotation counts per 10 minutes for more than 60 minutes period. Total counts and the duration of the response

were listed in Table 17. Similarly, the result of the control group that was treated only with L-dopa and carbidopa was shown in the same table.

[0384]

5 Table 17

Compound No.	Duration (minutes)	Total counts
Control	133.8	611.9
1-1	293.8	2060.8
1-2	312.5	2103.0
1-5	321.3	2051.9
1-14	275.0	1678.4

[0385]

From these results, as compared with control animals which were treated only with L-dopa/carbidopa, remarkable potentiation of drug effects were observed in animals administered with compounds of the present invention in combination with L-dopa/carbidopa.

Industrial Applicability

[0386]

Compounds of the present invention exhibit potent COMT inhibitory activities, and are accordingly useful for treating or preventing Parkinson's disease, depression or hypertension. Especially, compounds of the present invention are useful for treating or preventing Parkinson's disease since use of compounds of the present invention in combination with L-dopa increases

the bioavailability of L-dopa remarkably.

Sequence Listing Free Text

[SEQ ID No.1]

Sequence ID No.1 indicates the sequence of recombinant
5 human catechol-O-methyl transferase.

[SEQ ID No.2]

Sequence ID No.2 indicates the DNA sequence, which was
intended to express the recombinant human catechol-O-methyl
transferase shown in sequence ID No. 1, amplified by using primer
10 pair shown in sequence ID No.3 and 4.

[SEQ ID No.3]

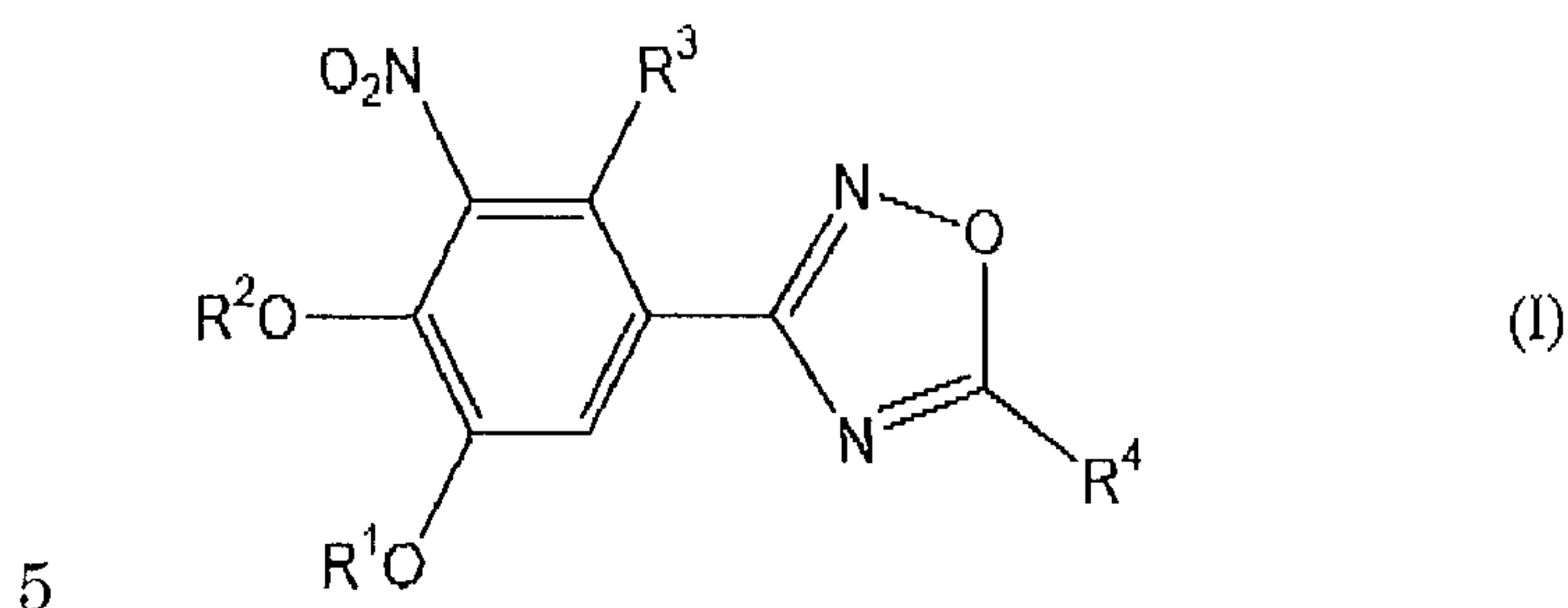
Sequence ID No.3 indicates the sequence of 5'-primer
employed to amplify the DNA sequence shown in sequence ID No.
2.

15 [SEQ ID No.4]

SEQ ID No.4 indicates the sequence of 3'-primer employed
to amplify the DNA sequence shown in sequence ID No.2.

CLAIMS

1. A compound represented by general formula (I):



or a pharmaceutically acceptable salt thereof,
wherein

10 R^1 and R^2 are each independently a hydrogen atom, a $(C_{1-6}$ alkyl)-CO- group, a $(C_{1-6}$ alkoxy)-C(O)- group, an aralkylcarbonyl group or -C(O)NR¹¹R¹², or R^1 and R^2 are joined together to form -C(O)- or a C_{1-6} alkylene group;

R^3 is:

- a) a halo C_{1-6} alkyl group,
- 15 b) a $(C_{1-6}$ alkyl)-CO- group,
- c) a (halo- C_{1-6} alkyl)-C(O)- group,
- d) a cycloalkylcarbonyl group,
- e) an arylcarbonyl group, wherein the ring of the arylcarbonyl group is unsubstituted or substituted with 1 to
- 20 5 substituents, said substituent is independently a halogen atom, a C_{1-6} alkyl group, a halo- C_{1-6} alkyl group, a C_{1-6} alkoxy group, a cycloalkyl C_{1-6} alkoxy group, a hydroxy group, a $(C_{1-6}$ alkoxy)-C(O)- group, -C(O)NR¹¹R¹² or a cyano group,
- 25 f) a heteroarylcarbonyl group, wherein the ring of the heteroarylcarbonyl group is unsubstituted or substituted with 1 to 3 substituents, said substituent is independently

a halogen atom, a C₁₋₆ alkyl group, a halo-C₁₋₆ alkyl group or a C₁₋₆ alkoxy group,

- g) an aralkylcarbonyl group, wherein the ring of the aralkylcarbonyl group is unsubstituted or substituted with 1 to 5 substituents, said substituent is independently a halogen atom, a C₁₋₆ alkyl group, a halo-C₁₋₆ alkyl group or a C₁₋₆ alkoxy group,
- h) an (aryloxy-C₁₋₆ alkyl)-C(O)-group, wherein the ring of the (aryloxy-C₁₋₆ alkyl)-C(O)-group is unsubstituted or substituted with 1 to 5 substituents, said substituent is independently a halogen atom, a C₁₋₆ alkyl group, a halo-C₁₋₆ alkyl group or a C₁₋₆ alkoxy group,
- i) a (C₁₋₆ alkoxy)-C(O)- group,
- j) a cycloalkyloxycarbonyl group,
- k) a (C₁₋₆ alkoxy-C₁₋₆ alkoxy)-C(O)- group,
- l) a carboxy group,
- m) a cyano group,
- n) -C(O)NR¹¹R¹²,
- o) -C(O)C(O)NR¹¹R¹²,
- p) a C₁₋₆ alkylsulfonyl group,
- q) -SO₂NR¹¹R¹² or
- r) a heteroaryl group, wherein the ring of the heteroaryl group is unsubstituted or substituted with 1 to 3 substituents, said substituent is independently a halogen atom, a C₁₋₆ alkyl group, a halo-C₁₋₆ alkyl group or a C₁₋₆ alkoxy group;

R⁴ is:

- a) a C₁₋₆ alkyl group,
- b) a halo-C₁₋₆ alkyl group,
- c) a cycloalkyl group,
- d) a heterocycloalkyl group,
- e) a C₁₋₆ alkoxy- C₁₋₆ alkyl group,

- f) an aryloxy-C₁₋₆ alkyl group,
- g) a (C₁₋₆ alkoxy)-C(O)- C₁₋₆ alkyl group or
- h) a hydroxy C₁₋₆ alkyl group; and

R¹¹ and R¹² are each independently a hydrogen atom, a C₁₋₆ alkyl group, a cycloalkyl group, a bridged cyclic hydrocarbon group, a phenyl group or an aralkyl group, or R¹¹ and R¹², together with the nitrogen atom to which they are bonded, form a cyclic amino group.

2. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein

R¹ and R² are each independently a hydrogen atom, a (C₁₋₆ alkyl)-CO- group, a (C₁₋₆ alkoxy)-C(O)- group or -C(O)NR¹¹R¹², or R¹ and R² are joined together to form -C(O)-;

R³ is:

- a) a halo C₁₋₆ alkyl group,
- b) a (C₁₋₆ alkyl)-CO- group,
- c) a (halo-C₁₋₆ alkyl)-C(O)- group,
- d) a cycloalkylcarbonyl group,
- e) an arylcarbonyl group, wherein the ring of the arylcarbonyl group is unsubstituted or substituted with 1 to 5 substituents, said substituent is independently a halogen atom, a C₁₋₆ alkyl group, a halo-C₁₋₆ alkyl group or a C₁₋₆ alkoxy group,
- f) a heteroarylcarbonyl group, wherein the ring of the heteroarylcarbonyl group is unsubstituted or substituted with 1 to 3 substituents, said substituent is independently a halogen atom, a C₁₋₆ alkyl group, a halo-C₁₋₆ alkyl group or a C₁₋₆ alkoxy group,
- g) an aralkylcarbonyl group, wherein the ring of the aralkylcarbonyl group is unsubstituted or substituted with 1 to 5 substituents, said substituent is independently a

- halogen atom, a C₁₋₆ alkyl group, a halo-C₁₋₆ alkyl group or a C₁₋₆ alkoxy group,
- h) an (aryloxy-C₁₋₆ alkyl)-C(O)-group, wherein the ring of the (aryloxy-C₁₋₆ alkyl)-C(O)-group is unsubstituted or
- 5 substituted with 1 to 5 substituents, said substituent is independently a halogen atom, a C₁₋₆ alkyl group, a halo-C₁₋₆ alkyl group or a C₁₋₆ alkoxy group,
- i) a (C₁₋₆ alkoxy)-C(O)- group,
- j) a cycloalkyloxycarbonyl group,
- 10 k) a (C₁₋₆ alkoxy-C₁₋₆ alkoxy)-C(O)- group,
- l) a carboxy group,
- m) a cyano group,
- n) -C(O)NR¹¹R¹²,
- o) -C(O)C(O)NR¹¹R¹²,
- 15 p) a C₁₋₆ alkylsulfonyl group,
- q) -SO₂NR¹¹R¹² or
- r) a heteroaryl group, wherein the ring of the heteroaryl group is unsubstituted or substituted with 1 to 3 substituents, said substituent is independently a halogen
- 20 atom, a C₁₋₆ alkyl group, a halo-C₁₋₆ alkyl group or a C₁₋₆ alkoxy group;
- R⁴ is:
- a) a C₁₋₆ alkyl group,
- b) a halo-C₁₋₆ alkyl group,
- 25 c) a cycloalkyl group,
- d) a heterocycloalkyl group,
- e) a C₁₋₆ alkoxy- C₁₋₆ alkyl group,
- f) an aryloxy-C₁₋₆ alkyl group or
- g) a (C₁₋₆ alkoxy)-C(O)- C₁₋₆ alkyl group; and
- 30 R¹¹ and R¹² are each independently a hydrogen atom, a C₁₋₆ alkyl group, a cycloalkyl group, a bridged cyclic hydrocarbon group, a phenyl group or an aralkyl group, or R¹¹

and R¹², together with the nitrogen atom to which they are bonded, form a cyclic amino group.

3. The compound according to claim 2, or a
5 pharmaceutically acceptable salt thereof, wherein R¹ and R² are a hydrogen atom.

4. The compound according to claim 3, or a
pharmaceutically acceptable salt thereof, wherein R³ is:

- 10 a) a (C₁₋₆ alkyl)-CO- group,
b) a (halo-C₁₋₆ alkyl)-C(O)- group,
c) a cycloalkylcarbonyl group,
d) an arylcarbonyl group, wherein the ring of the
15 arylcarbonyl group is unsubstituted or substituted with 1 to
5 substituents, said substituent is independently a halogen
atom, a C₁₋₆ alkyl group, a halo-C₁₋₆ alkyl group or a C₁₋₆
alkoxy group,
e) a heteroarylcarbonyl group, wherein the ring of the
heteroarylcarbonyl group is unsubstituted or substituted
20 with 1 to 3 substituents, said substituent is independently
a halogen atom, a C₁₋₆ alkyl group, a halo-C₁₋₆ alkyl group or
a C₁₋₆ alkoxy group,
f) an aralkylcarbonyl group, wherein the ring of the
aralkylcarbonyl group is unsubstituted or substituted with 1
25 to 5 substituents, said substituent is independently a
halogen atom, a C₁₋₆ alkyl group, a halo-C₁₋₆ alkyl group or a
C₁₋₆ alkoxy group,
g) an (aryloxy-C₁₋₆ alkyl)-C(O)- group, wherein the ring of
the (aryloxy-C₁₋₆ alkyl)-C(O)- group is unsubstituted or
30 substituted with 1 to 5 substituents, said substituent is
independently a halogen atom, a C₁₋₆ alkyl group, a halo-C₁₋₆
alkyl group or a C₁₋₆ alkoxy group,

- h) a (C₁₋₆ alkoxy)-C(O)- group,
- i) a cycloalkyloxycarbonyl group,
- j) a (C₁₋₆ alkoxy-C₁₋₆ alkoxy)-C(O)- group,
- k) -C(O)C(O) NR¹¹R¹² or

5 l) a heteroaryl group, wherein the ring of the heteroaryl group is unsubstituted or substituted with 1 to 3 substituents, said substituent is independently a halogen atom, a C₁₋₆ alkyl group, a halo-C₁₋₆ alkyl group or a C₁₋₆ alkoxy group.

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5. The compound according to claim 4, or a pharmaceutically acceptable salt thereof, wherein R⁴ is:

- a) a C₁₋₆ alkyl group,
- b) a cycloalkyl group,
- 15 c) a C₁₋₆ alkoxy- C₁₋₆ alkyl group or
- d) a (C₁₋₆ alkoxy)-C(O)- C₁₋₆ alkyl group.

6. The compound according to claim 5, or a pharmaceutically acceptable salt thereof, wherein R³ is:

- 20 a) a (C₁₋₆ alkyl)-C(O)- group,
- b) a cycloalkylcarbonyl group,
- c) an arylcarbonyl group, wherein the ring of the arylcarbonyl group is unsubstituted or substituted with 1 to 5 substituents, said substituent is independently a halogen
- 25 atom, a C₁₋₆ alkyl group, a halo-C₁₋₆ alkyl group or a C₁₋₆ alkoxy group,
- d) a (C₁₋₆ alkoxy)-C(O)- group,
- e) a cycloalkyloxycarbonyl group,
- f) a (C₁₋₆ alkoxy-C₁₋₆ alkoxy)-C(O)- group or
- 30 g) -C(O)C(O) NR¹¹R¹².

7. The compound according to claim 5, or a pharmaceutically acceptable salt thereof, wherein R^3 is:

a) a (C_{1-6} alkyl)-CO- group,

b) a cycloalkylcarbonyl group,

5 c) an arylcarbonyl group, wherein the ring of the arylcarbonyl group is unsubstituted or substituted with 1 to 5 substituents, said substituent is independently a halogen atom, a C_{1-6} alkyl group, a halo- C_{1-6} alkyl group or a C_{1-6} alkoxy group,

10 d) a (C_{1-6} alkoxy)-C(O)- group or

e) -C(O)C(O) NR¹¹R¹².

8. A compound, or a pharmaceutically acceptable salt thereof, said compound is:

15 [3,4-dihydroxy-6-(5-methyl-[1,2,4]oxadiazol-3-yl)-2-nitrophenyl]phenylmethanone;

1-[3,4-dihydroxy-6-(5-methyl-[1,2,4]oxadiazol-3-yl)-2-nitrophenyl]ethanone;

20 methyl 3,4-dihydroxy-6-(5-methyl-[1,2,4]oxadiazol-3-yl)-2-nitrobenzoate;

N-cyclohexyl-2-[3,4-dihydroxy-6-(5-methyl-[1,2,4]oxadiazol-3-yl)-2-nitrophenyl]-2-oxoacetamide;

25 N-cyclohexyl-2-[3,4-dihydroxy-6-(5-methyl-[1,2,4]oxadiazol-3-yl)-2-nitrophenyl]-N-methyl-2-oxoacetamide;

1-{6-[5-(2-ethoxyethyl)-[1,2,4]oxadiazol-3-yl]-3,4-dihydroxy-2-nitrophenyl}ethanone; or

cyclohexyl-[3,4-dihydroxy-6-(5-methyl-[1,2,4]oxadiazol-3-yl)-2-nitrophenyl]methanone.

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9. A pharmaceutical composition which comprises, as the active ingredient, a compound according to any one of

claims 1 to 8 or a pharmaceutically acceptable salt thereof;
and at least one pharmaceutically acceptable excipient,
carrier or diluent.

- 5 10. A pharmaceutical combination comprising a compound as
defined in any one of claims 1 to 8 or a pharmaceutically
acceptable salt thereof and at least one L-dopa or an
aromatic L-amino acid decarboxylase inhibitor.

