



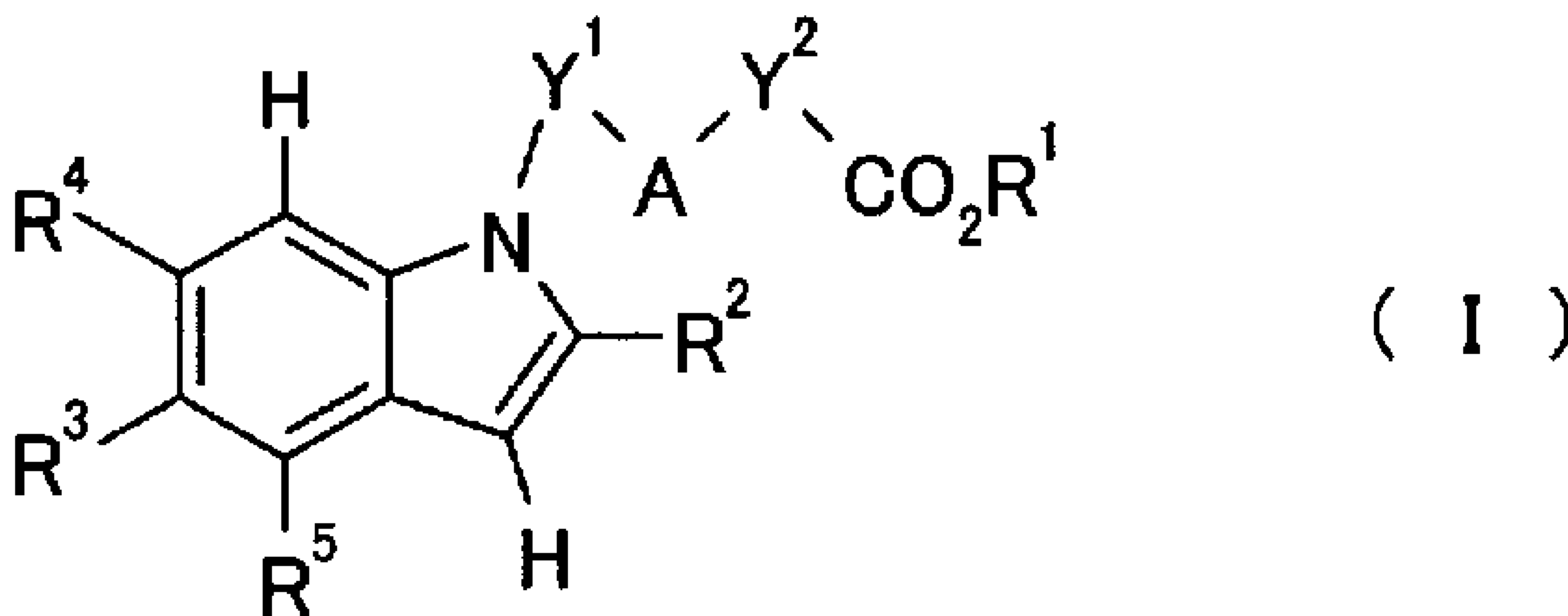
(86) Date de dépôt PCT/PCT Filing Date: 2010/07/26
(87) Date publication PCT/PCT Publication Date: 2011/02/03
(85) Entrée phase nationale/National Entry: 2012/01/20
(86) N° demande PCT/PCT Application No.: JP 2010/062533
(87) N° publication PCT/PCT Publication No.: 2011/013624
(30) Priorités/Priorities: 2009/07/27 (JP2009-173862);
2009/11/04 (JP2009-252862)

(51) Cl.Int./Int.Cl. *C07D 209/08* (2006.01),
A61K 31/404 (2006.01), *A61K 31/422* (2006.01),
A61K 31/427 (2006.01), *A61K 31/4439* (2006.01),
A61P 13/02 (2006.01), *A61P 43/00* (2006.01),
C07D 401/06 (2006.01), *C07D 401/14* (2006.01),
C07D 405/04 (2006.01), *C07D 405/06* (2006.01),
C07D 405/14 (2006.01), *C07D 409/04* (2006.01),
C07D 409/06 (2006.01), *C07D 409/14* (2006.01),
C07D 413/14 (2006.01), *C07D 417/06* (2006.01),
C07D 417/14 (2006.01)

(71) Demandeur/Applicant:
KISSEI PHARMACEUTICAL CO., LTD., JP

(72) Inventeurs/Inventors:

(54) Titre : DERIVE D'INDOLE ET SES SELS PHARMACOLOGIQUEMENT ACCEPTABLES
(54) Title: INDOLE DERIVATIVE OR PHARMACEUTICALLY ACCEPTABLE SALT THEREOF



(57) **Abrégé/Abstract:**

Disclosed is a compound of formula (I), which has EP₁ receptor antagonist activity, or a pharmacologically acceptable salt thereof. (In formula (I), A represents a benzene ring or the like; Y¹ represents a C₁₋₆ alkylene group; Y² represents a single bond or the like; R¹ represents a hydrogen atom, a C₁₋₆ alkyl group or the like; R² represents an optionally substituted phenyl group, an optionally substituted five-membered aromatic heterocyclic group, an optionally substituted six-membered aromatic heterocyclic group or the like; R³ represents a halogen atom, a C₁₋₆ alkoxy group or the like; R⁴ represents a hydrogen atom or the like; and R⁵ represents a hydrogen atom or the like.) The compound of formula (I) is able to be used as an agent for treatment or prevention of LUTS, in particular symptoms of OABS.

(72) **Inventeurs(suite)/Inventors(continued):** TATANI, KAZUYA, JP; KAWAMURA, NAOHIRO, JP; KONDO, TATSUHIRO, JP; KONDO, ATSUSHI, JP

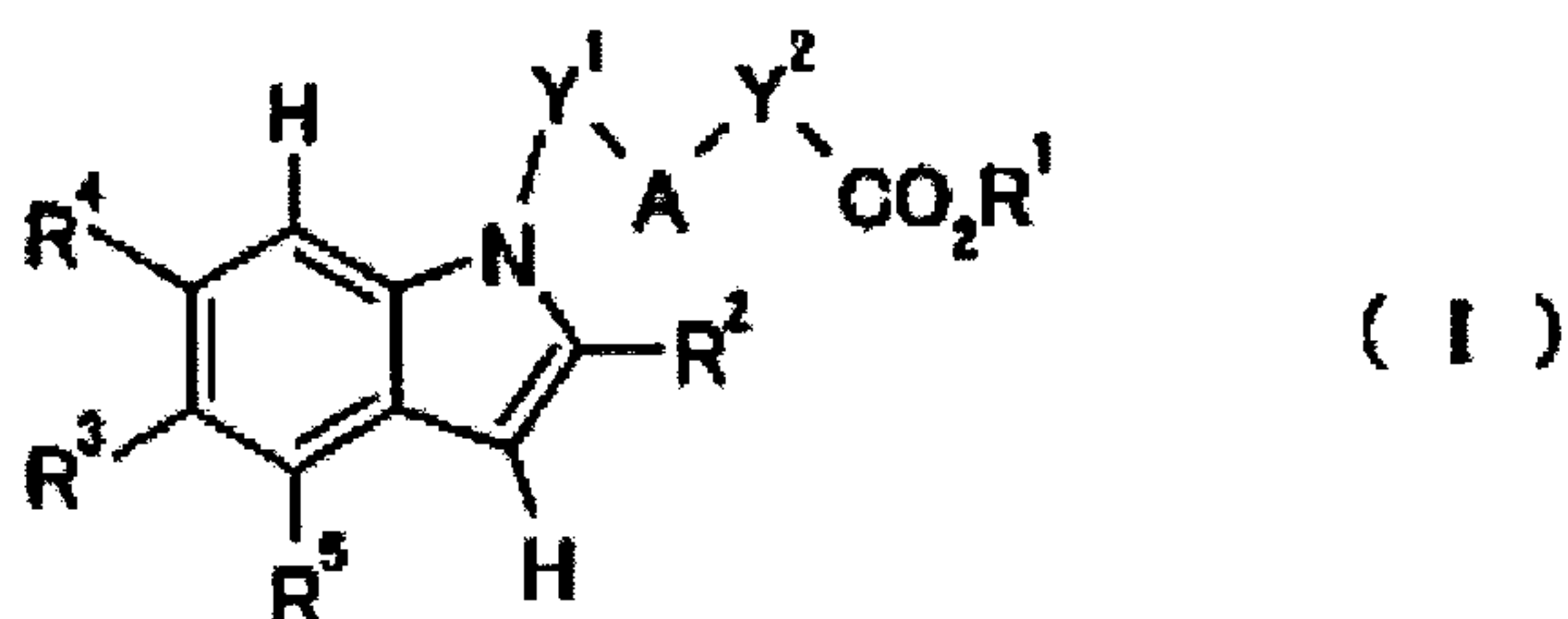
(74) **Agent:** KIRBY EADES GALE BAKER

Abstract

A compound (I) of the present invention, which has an EP₁ receptor antagonism:

[Chem.]

5



[wherein A represents a benzene ring or the like; Y¹ represents a C₁₋₆ alkylene group; Y² represents a single bond or the like; R¹ represents a hydrogen atom, a C₁₋₆ alkyl group or the like; R² represents a phenyl group which may have a substituent, a 5-membered aromatic heterocyclic ring which may have a substituent, a 6-membered aromatic heterocyclic ring which may have a substituent or the like; R³ represents a halogen atom, a C₁₋₆ alkoxy group or the like; R⁴ represents a hydrogen atom or the like; and R⁵ represents a hydrogen atom or the like] or a pharmaceutically acceptable salt thereof is provided. Furthermore, the compound (I) of the present invention can be used as an agent for treating or preventing LUTS, in particular, various symptoms of OABs.

10

15

20

DESCRIPTION

[Title of the Invention]

INDOLE DERIVATIVE OR PHARMACEUTICALLY ACCEPTABLE SALT THEREOF

5

[Technical Field]

[0001]

The present invention relates to an indole derivative having an EP₁ receptor antagonism, which is useful as a pharmaceutical, or a pharmaceutically acceptable salt thereof, a pharmaceutical composition comprising the same, and a pharmaceutical use thereof.

10

[Background Art]

[0002]

15

With an increasingly aging and stressed society, the number of patients with lower urinary tract dysfunction (LUTD) has increased. LUTD is a generic term for urine collection disorder and dysuria, and the symptoms derived from LUTD are lower urinary tract symptoms (LUTS). One of the LUTS is an overactive bladder syndrome (OABs). OABs may be generally called overactive bladder (OAB) in some cases. In any case, it is a disease defined as “a symptom syndrome which essentially has urinary urgency and which is usually accompanied by urinary frequency and nocturia. Urge urinary incontinence is not necessary”. The symptoms associated with OABs interfere with general life such as work, daily life, mental activity, and the like, and thus lower the quality of life (QOL). Currently, a first choice drug as an agent for treating OABs is an anticholinergic agent. However, it is necessary for the anticholinergic agent to be used also in due consideration of an anti-muscarinic effect such as thirst and residual urine, and thus, is not always effective for all patients (see, for example, Non-patent literature 1). Under these circumstances, there is a demand for development of a therapeutic agent which has a different mechanism from that of the anticholinergic agent (see, for example, Non-patent literature 1).

20

25

30

[0003]

Recently, in LUTS, particularly in OABs, the role of urothelium has attracted attention. For LUTS, it has become clear that various chemical mediators are released in the urothelial cells, which cause a micturition reflex through the receptors of bladder

sensory nerve terminals. Among them, one of the chemical mediators, prostaglandin E₂ (PGE₂), binds with a prostaglandin E receptor 1 (EP₁ receptor) in the afferent nerves (especially C fibers) in the urothelium to increase the micturition reflex. In addition, PGE₂ binds with the EP₁ receptors present in the bladder smooth muscle to contract the bladder. In fact, it has been reported that the EP₁ receptor antagonists inhibit both of the increase in the micturition reflex and the increase in the afferent nerve activities by PGE₂ (see, for example, Non-patent literature 2 and Non-patent literature 3). From these, it is suggested that PGE₂ is involved in contraction of the bladder smooth muscle and increase in the bladder sensory nerves through the EP₁ receptors. Furthermore, it is reported that EP₁ receptor antagonists do not increase the amount of the residual urine, but increase the bladder capacity (see, for example, Non-patent literature 4).

[0004]

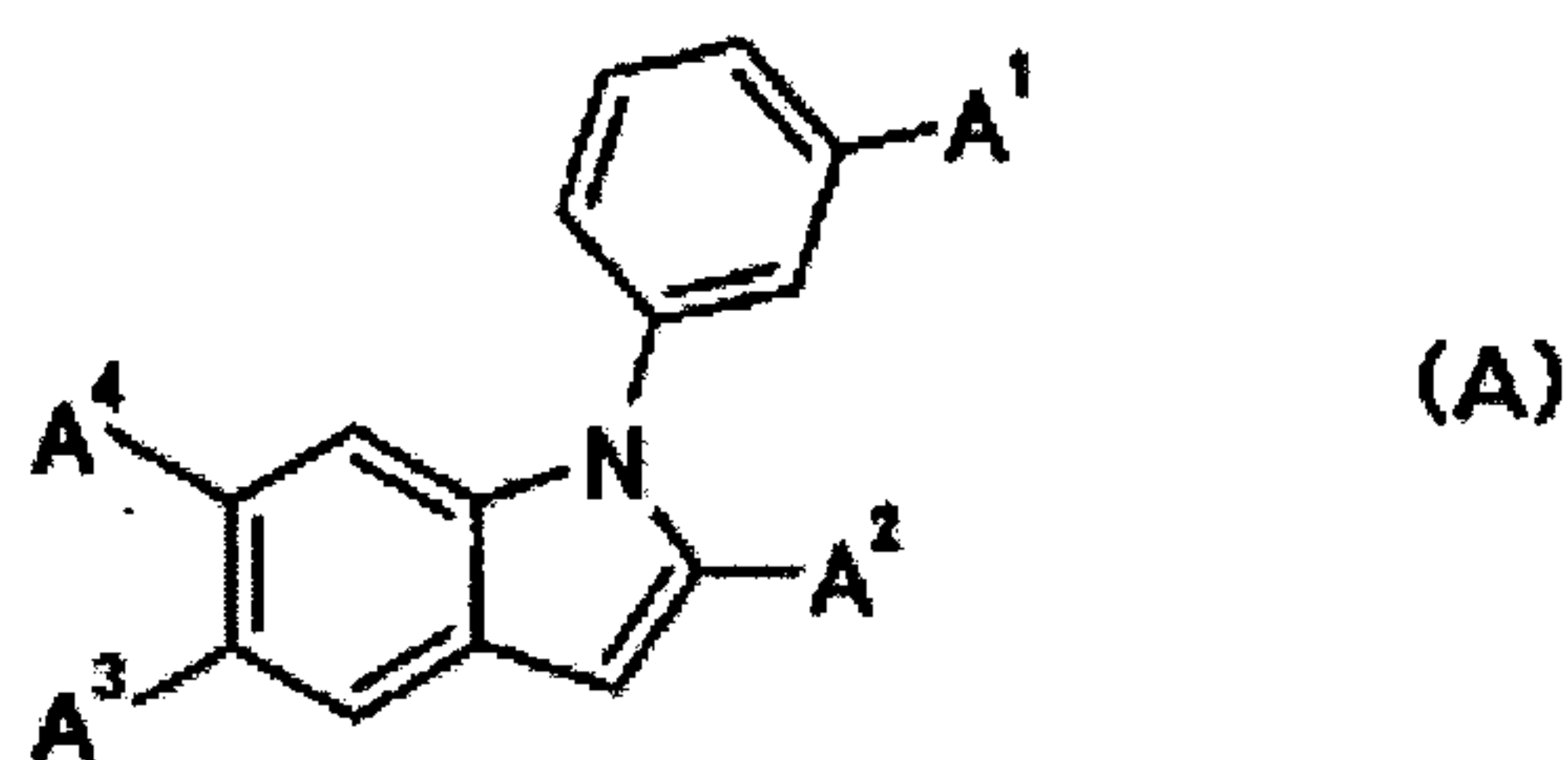
There exist four subtypes, EP₂, EP₃, and EP₄ as well as EP₁, of the PGE₂ receptor. The EP₁ receptor exists in the lungs as well as the bladder and the urothelium, the skeletal muscle, the renal collecting duct, and the like (see, for example, Non-patent literature 2). Therefore, it is expected that by changing the selectivity of the subtypes of the PGE₂ receptor, the target organs of the drugs, or the target tissues, a therapeutic agent for desired diseases can be developed.

[0005]

A compound represented by the general formula (A) is disclosed as a therapeutic drug for Alzheimer's disease (see, for example, Patent literature 1).

[0006]

[Chem. 1]



[0007]

[wherein A¹ represents -L-CO₂H or the like, A² represents a phenyl group which may have substituents, A³ and A⁴ independently represent a hydrogen atom, a halogen atom, an alkyl group, an alkoxy group, a haloalkyl group or a haloalkoxy group or the like, L represents -(CH₂)_n-(CH₂)_n- or -(CH₂)_nO(CH₂)_n- or the like, each n independently represents integer selected from 0 to 8].

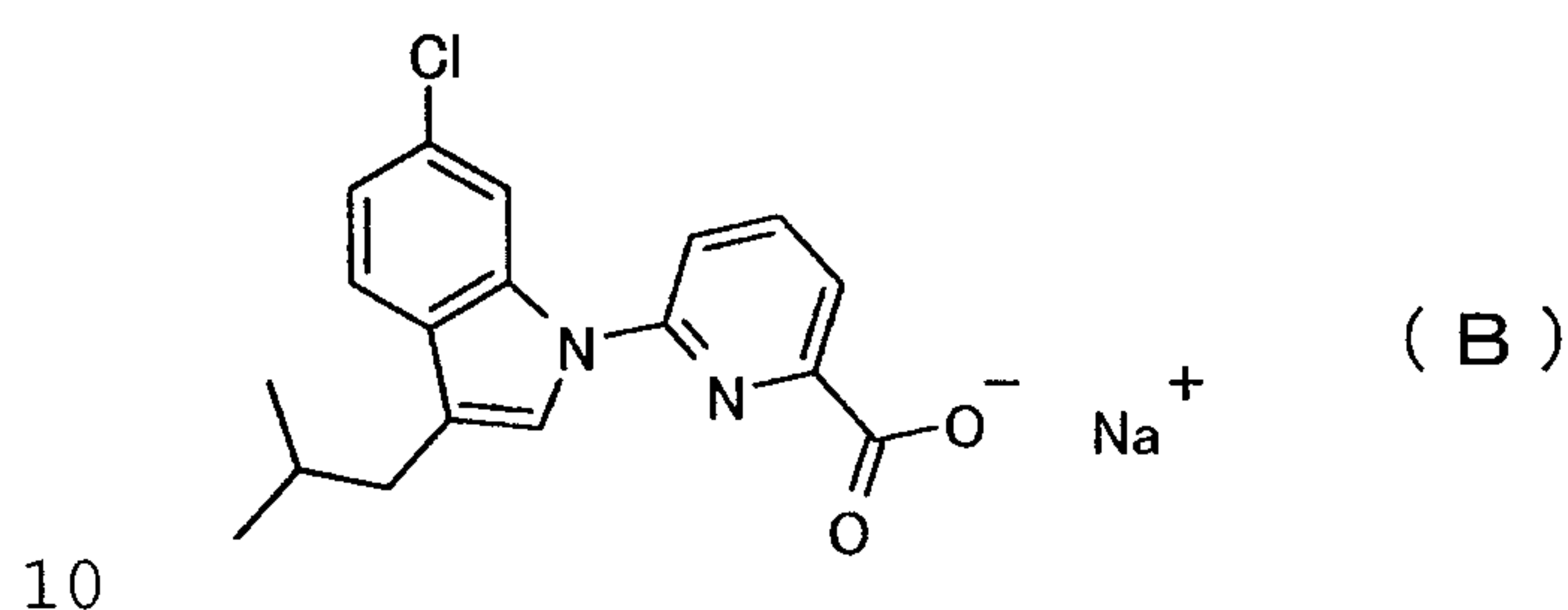
However, there is no suggestion or disclosure that these compounds have an EP₁ receptor antagonism.

[0008]

As an indole derivative having an EP₁ receptor antagonism, a compound
 5 represented by the chemical structural formula (B) (sodium 6-(6-chloro-3-isobutylindol-1-yl)pyridine-2-carboxylate) and a analog thereof are disclosed (see, for example, Non-patent literature 5).

[0009]

[Chem. 2]



However, these compounds differ from the compounds of the present invention in the chemical structural formula in terms of the position, the type, or the like of a substituent.

15

[Citation List]

[Patent Literature]

[0010]

Patent literature 1: International publication WO2006/041874

20

[Non-Patent Literature]

[0011]

Non-patent literature 1: Narihito Seki, "Folia Pharmacologia Japonica", 2007, Vol. 129, p. 368-373

25

Non-patent literature 2: Xiaojun Wang, et al., "Biomedical Research", 2008, Vol. 29, p. 105-111

Non-patent literature 3: Masahito Kawatani, "PAIN RESEARCH", 2004, Vol. 19, p. 185-190

Non-patent literature 4: Masanobu Maegawa, "The Journal of The Japan Neurogenic Bladder Society", 2008, Vol. 19, p. 169

Non-patent literature 5: Adrian Hall, et al., "Bioorganic & Medicinal Chemistry Letters", 2008, p. 2684-2690

[Summary of the Invention]

5 [Objects to Be Solved by the Invention]

[0012]

The present invention is to provide a compound having an EP₁ receptor antagonism or a pharmaceutically acceptable salt thereof, a pharmaceutical composition comprising the same, and a pharmaceutical use thereof.

10

[Means for Solving the Objects]

[0013]

The present inventors have conducted extensive studies on a compound having an EP₁ receptor antagonism, and as a result, they have found that the compounds (I) of the present invention or a pharmaceutically acceptable salt thereof exhibit a potent EP₁ receptor antagonism, thereby completing the present invention.

15

[0014]

That is, the means for solving the above-described objects are presented below.

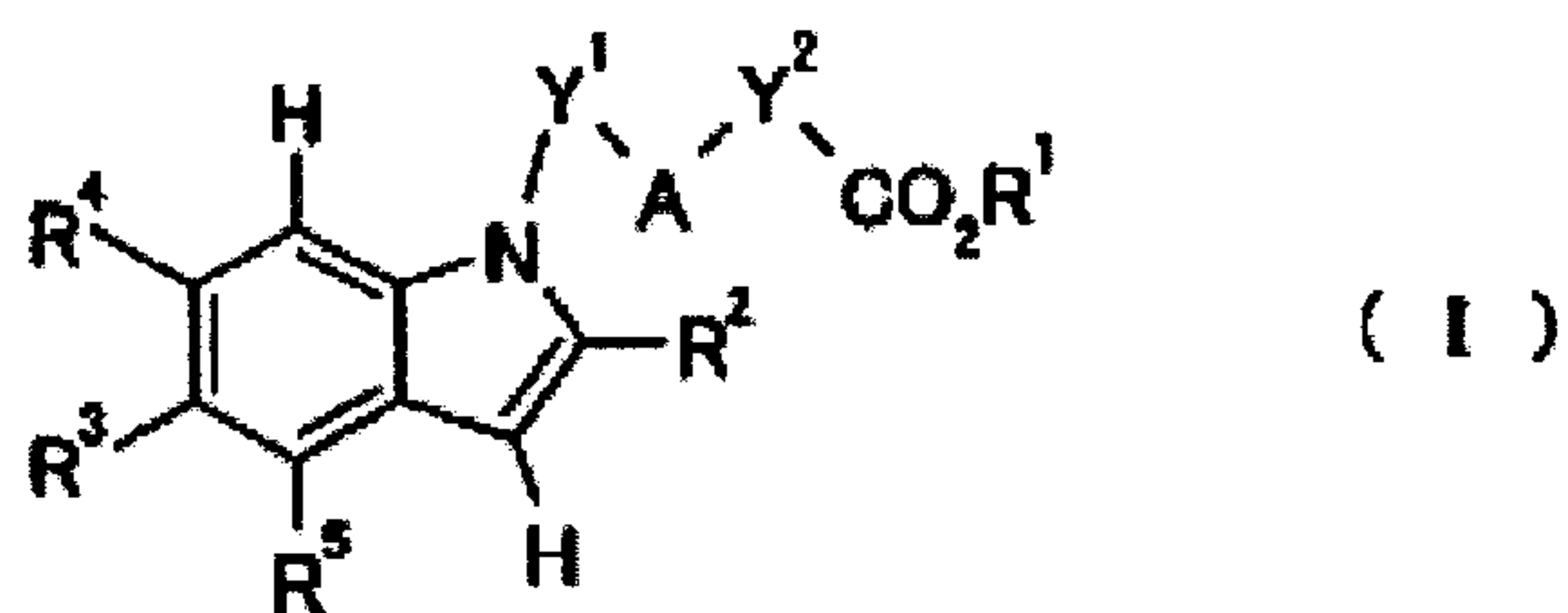
[0015]

20

[1] A compound represented by the general formula (I) or a pharmaceutically acceptable salt thereof:

[0016]

[Chem. 3]



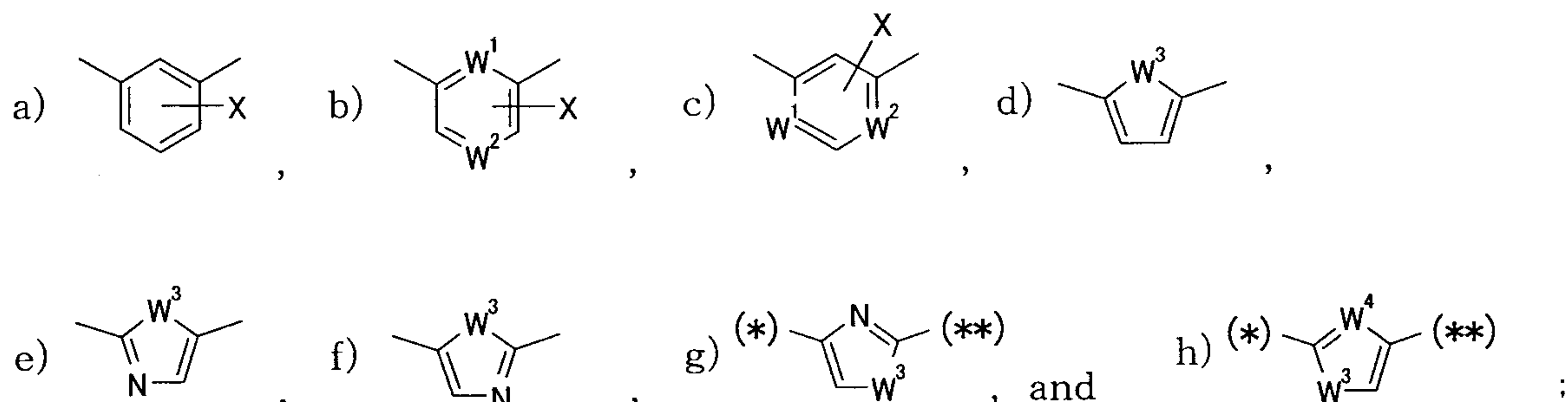
25

[wherein

A represents a group selected from the group consisting of the following a) to h):

[0017]

[Chem. 4]



one of W^1 and W^2 represents a nitrogen atom and the other represents =CH- or a nitrogen atom;

W^3 represents an oxygen atom or a sulfur atom;

5 W^4 represents =CH- or a nitrogen atom;

X represents a hydrogen atom or a halogen atom;

Y^1 represents a C_{1-6} alkylene group;

Y^2 represents a single bond or an oxy- C_{1-6} alkylene group;

R^1 represents a hydrogen atom, a C_{1-6} alkyl group, or a C_{7-10} aralkyl group;

10 R^2 represents a group selected from the group consisting of the following i) to n):

i) a branched C_{3-6} alkyl group,

j) a halo- C_{1-6} alkyl group,

k) a C_{3-6} cycloalkyl group,

l) a phenyl group, in which the ring is unsubstituted or substituted with 1 to 5

15 groups independently selected from the group consisting of: a halogen atom, a C_{1-6} alkyl group, a halo- C_{1-6} alkyl group, a hydroxy- C_{1-6} alkyl group, a C_{1-6} alkoxy group and a cyano group,

m) a 6-membered aromatic heterocyclic group, in which the ring is unsubstituted or substituted with 1 to 4 groups independently selected from the group consisting of: a

20 halogen atom, a C_{1-6} alkyl group, a halo- C_{1-6} alkyl group, a hydroxy- C_{1-6} alkyl group, a C_{1-6} alkoxy group and a cyano group, and

n) a 5-membered aromatic heterocyclic group, in which the ring is unsubstituted or substituted with 1 to 3 groups independently selected from the group consisting of: a

25 C_{1-6} alkoxy group and a cyano group;

R^3 represents a halogen atom, a C_{1-6} alkyl group, a halo- C_{1-6} alkyl group, a hydroxy- C_{1-6} alkyl group, a C_{1-6} alkoxy group, a halo- C_{1-6} alkoxy group, a C_{1-6} alkylsulfanyl group, a C_{3-6} cycloalkyl group, a cyano group, an amino group, or a nitro group;

R^4 represents a hydrogen atom, a halogen atom, a C_{1-6} alkyl group, or a C_{1-6} alkoxy group; and

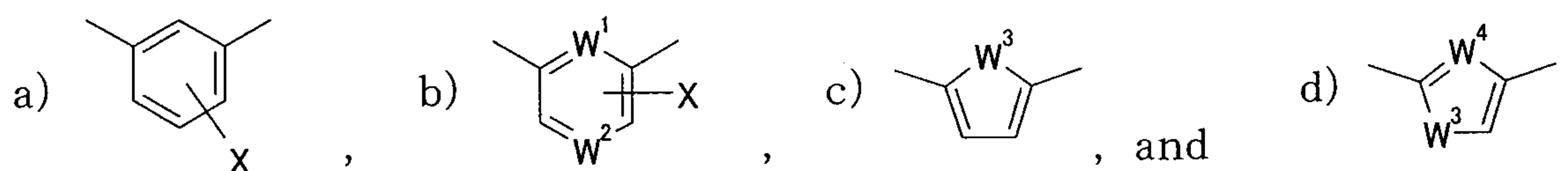
R^5 represents a hydrogen atom, a halogen atom, a C_{1-6} alkyl group, or a C_{1-6} alkoxy group;

5 with the proviso that the bonds with (*) represent binding to Y^1 , and the bonds with (**) represent binding to Y^2 .].

[0018]

[2] The compound or a pharmaceutically acceptable salt thereof as set forth in (1), wherein A is a group selected from the group consisting of the following a) to d):

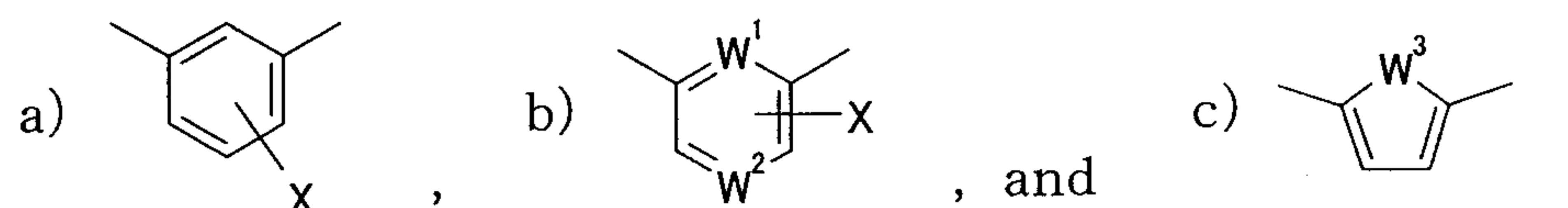
10 [Chem. 5]



[0019]- [0020]

[3] The compound or a pharmaceutically acceptable salt thereof as set forth in (2), wherein A is a group selected from the group consisting of a) to c) below:

15 [Chem. 6]



[4] The compound or a pharmaceutically acceptable salt thereof as set forth in (3), wherein R^2 is a group selected from the group consisting of the following a) to d):

- 20 a) a branched C_{3-6} alkyl group,
b) a C_{3-6} cycloalkyl group,
c) a phenyl group, and
d) a 5-membered aromatic heterocyclic group or a 6-membered aromatic heterocyclic group;

R^4 is a hydrogen atom or a halogen atom; and

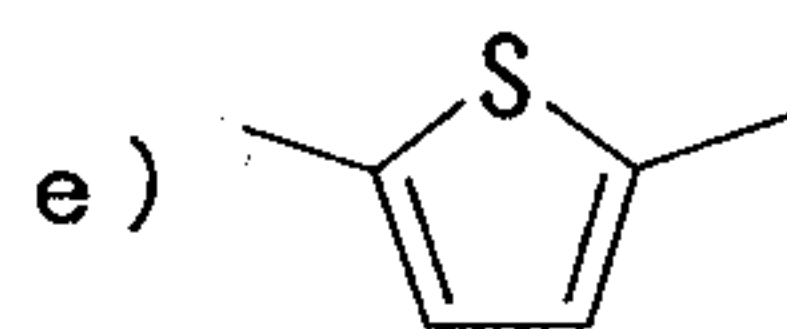
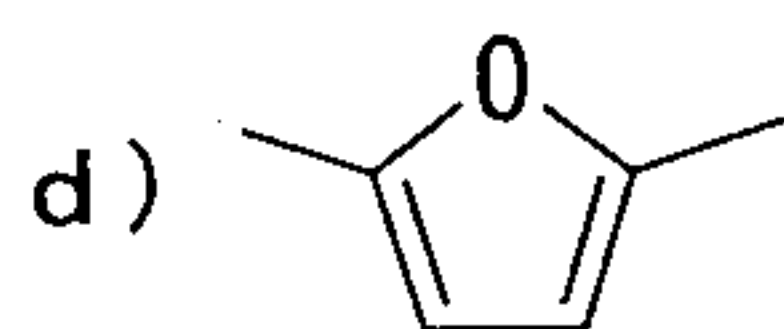
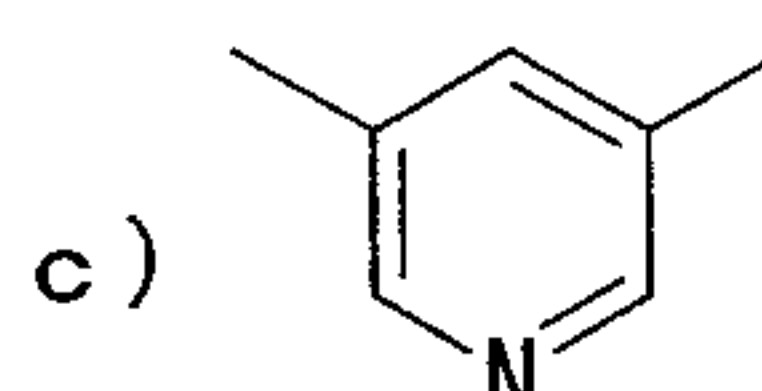
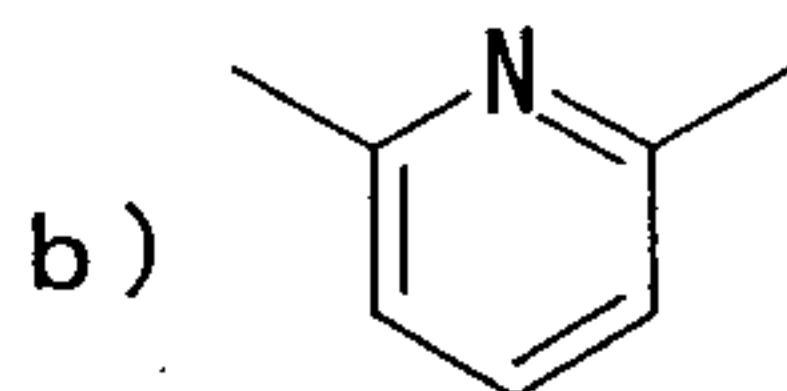
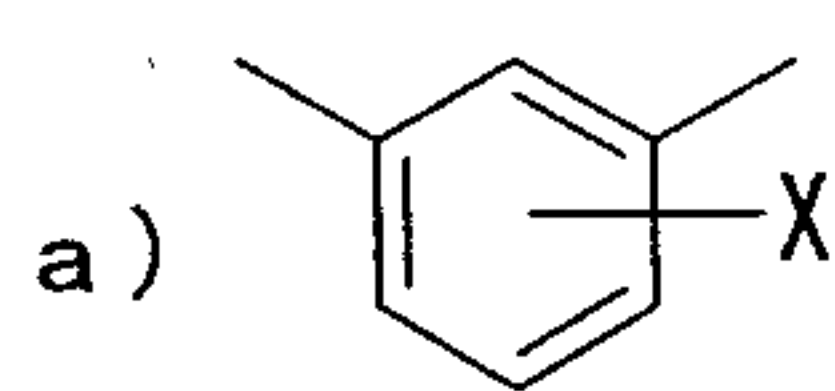
25 R^5 is a hydrogen atom.

[5] The compound or a pharmaceutically acceptable salt thereof as set forth in (4), wherein R^1 is a hydrogen atom.

[0021]-[0022]

30 [6] The compound or a pharmaceutically acceptable salt thereof as set forth in (5), wherein A is a group selected from the group consisting of a) to e) below:

[Chem. 7]



, and

Y^1 is a methylene group and Y^2 is a single bond.

[7] The compound or a pharmaceutically acceptable salt thereof as set forth in (6),
 5 wherein R^3 is a C_{1-6} alkoxy group.

[8] The compound or a pharmaceutically acceptable salt thereof as set forth in (7),
 wherein R^3 is a methoxy group.

[9] The compound or a pharmaceutically acceptable salt thereof as set forth in (6),
 wherein R^3 is a halogen atom.

10 [10] The compound or pharmaceutically acceptable salt thereof as set forth in (9),
 wherein R^3 is a fluorine atom.

[11] The compound or pharmaceutically acceptable salt thereof as set forth in (6),
 wherein R^3 is a C_{1-6} alkyl group.

15 [12] The compound or pharmaceutically acceptable salt thereof as set forth in (11),
 wherein R^3 is a methyl group.

[13] The compound or pharmaceutically acceptable salt thereof as set forth in (6),
 wherein R^2 is an isopropyl group, an isobutyl group, a *sec*-butyl group or a 1-ethylpropyl
 group.

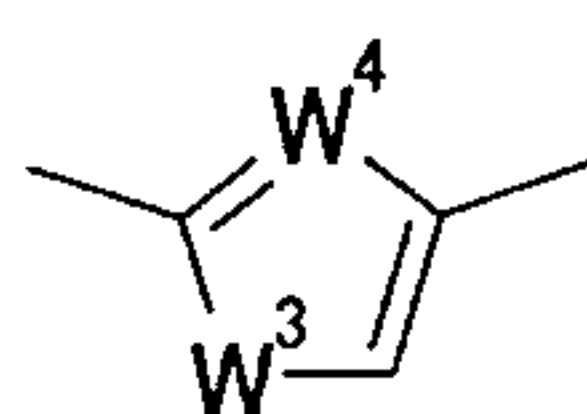
20 [14] The compound or pharmaceutically acceptable salt thereof as set forth in (6),
 wherein R^2 is a phenyl group or a 5-membered aromatic heterocyclic group.

[15] The compound or pharmaceutically acceptable salt thereof as set forth in (14),
 wherein R^2 is a phenyl group, a 3-thienyl group or a 3-furyl group.

[0023]-[0024]

25 [16] The compound or a pharmaceutically acceptable salt thereof as set forth in (2),
 wherein A is a group represented by the following formula:

[Chem. 8]

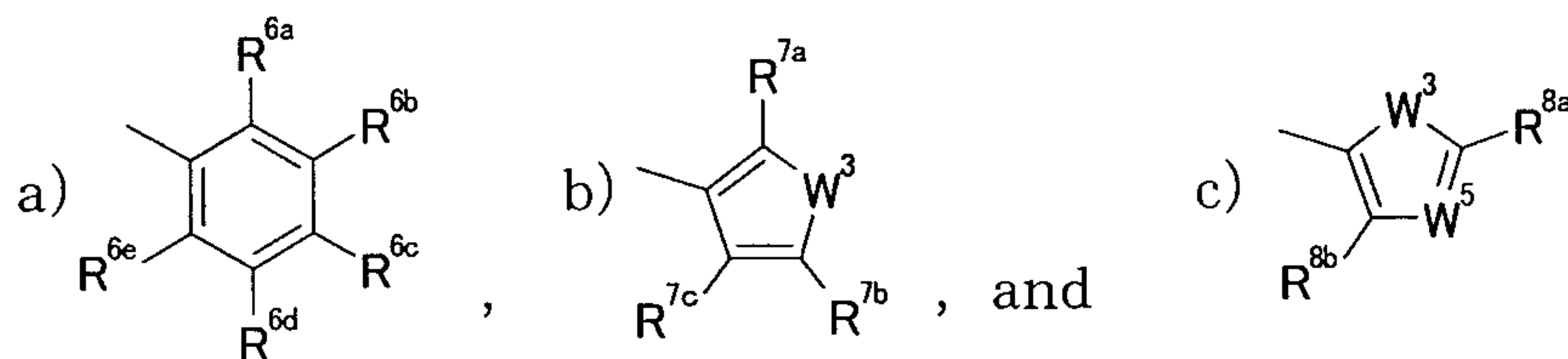


[17] The compound or a pharmaceutically acceptable salt thereof as set forth in (16),
 wherein R^1 is a hydrogen atom.

[0025]-[0026]

[18] The compound or a pharmaceutically acceptable salt thereof as set forth in (3), wherein R^2 is a group selected from the group consisting of the following a) to c):

[Chem. 9]



W^5 is a nitrogen atom or $-CR^{8c}=$;

R^{6a} , R^{6b} , R^{6c} , R^{6d} and R^{6e} are each independently a group selected from a hydrogen atom, a halogen atom, a C_{1-6} alkyl group, a halo- C_{1-6} alkyl group, a hydroxy- C_{1-6} alkyl group, a C_{1-6} alkoxy group, or a cyano group, with the proviso that all of R^{6a} , R^{6b} , R^{6c} , R^{6d} and R^{6e} are not simultaneously a hydrogen atom;

R^{7a} , R^{7b} and R^{7c} are each independently a hydrogen atom, a halogen atom, a C_{1-6} alkyl group, a halo- C_{1-6} alkyl group, a hydroxy- C_{1-6} alkyl group, a C_{1-6} alkoxy group or a cyano group, with the proviso that all of R^{7a} , R^{7b} and R^{7c} are not simultaneously a hydrogen atom; and

R^{8a} , R^{8b} and R^{8c} are each independently a hydrogen atom, a halogen atom, a C_{1-6} alkyl group, a halo- C_{1-6} alkyl group, a hydroxy- C_{1-6} alkyl group, a C_{1-6} alkoxy group or a cyano group, with the proviso that all of R^{8a} , R^{8b} and R^{8c} are not simultaneously a hydrogen atom.

[0027]

[19] The compound or a pharmaceutically acceptable salt thereof as set forth in (18), wherein R^1 is a hydrogen atom.

[20] A pharmaceutical composition comprising the compound or a pharmaceutically acceptable salt thereof as set forth in any one of (1) to (19) as an active ingredient.

[21] An EP_1 receptor antagonist comprising the compound or a pharmaceutically acceptable salt thereof as set forth in any one of (1) to (19) as an active ingredient.

[22] An agent for treating or preventing lower urinary tract symptoms, comprising the compound or a pharmaceutically acceptable salt thereof as set forth in any one of (1) to (19) as an active ingredient.

[23] A method for preventing or treating lower urinary tract symptoms, comprising administering an effective amount of the compound as set forth in any one of (1) to (19) or a pharmaceutically acceptable salt thereof.

[24] A use of the compound as set forth in any one of (1) to (19) or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for preventing or treating lower urinary tract symptoms.

5 [Effects of the Invention]

[0028]

The compound (I) of the present invention or a pharmaceutically acceptable salt thereof exhibits a potent EP₁ receptor antagonism, for example, in a test for confirmation of an EP₁ receptor antagonism. Therefore, the compound (I) of the present invention or a
10 pharmaceutically acceptable salt thereof is useful as an agent for treating or preventing lower urinary tract symptoms (LUTS), in particular, overactive bladder syndrome (OABs) or the like, based on its EP₁ receptor antagonism.

[Embodiments for carrying out the Invention]

15 [0029]

The terms in the specification are defined.

[0030]

The “halogen atom” means a fluorine atom, a chlorine atom, a bromine atom, or an iodine atom. In X, a fluorine atom or a chlorine atom is preferable. In R³, a fluorine
20 atom or a chlorine atom is preferable, and a fluorine atom is more preferable.

[0031]

The “C₁₋₆ alkyl group” means an alkyl group having 1 to 6 carbon atoms, which may be branched. Examples thereof include a methyl group, an ethyl group, a propyl group, an isopropyl group, an *n*-butyl group, an isobutyl group, a *sec*-butyl group, a *tert*-
25 butyl group, an *n*-pentyl group, an isopentyl group, a neopentyl group, a *tert*-pentyl group, a 1-methylbutyl group, a 2-methylbutyl group, a 1,2-dimethylpropyl group, an *n*-hexyl group, an isohexyl group and the like. In R³, a methyl group or an ethyl group is preferable, and a methyl group is more preferable.

[0032]

30 The “branched C₃₋₆ alkyl group” means a branched alkyl group having 3 to 6 carbon atoms. Examples thereof include an isopropyl group, an isobutyl group, a *sec*-butyl group, a *tert*-butyl group, an isopentyl group, a neopentyl group, a *tert*-pentyl group, a 1-methylbutyl group, a 2-methylbutyl group, a 1,2-dimethylpropyl group, a 1-ethylpropyl group, an isohexyl group, and the like. It is preferably an isopropyl group, an isobutyl

group, a *sec*-butyl group or a 1-ethylpropyl group. It is more preferably an isopropyl group, a *sec*-butyl group, or a 1-ethylpropyl group. It is further preferably a *sec*-butyl group.

[0033]

5 The “C₁₋₆ alkoxy group” means an alkoxy group having 1 to 6 carbon atoms, which may be branched. Examples thereof include a methoxy group, an ethoxy group, a propoxy group, an isopropoxy group, a butoxy group, an isobutoxy group, a *sec*-butoxy group, a *tert*-butoxy group, a pentyloxy group, a hexyloxy group and the like. In R³, a methoxy group or an ethoxy group is preferable, and a methoxy group is more preferable.

10 [0034]

The “halo-C₁₋₆ alkyl group” means a C₁₋₆ alkyl group substituted with the same or different 1 to 5 or 6 halogen atoms. Examples thereof include a monofluoromethyl group, a difluoromethyl group, a trifluoromethyl group, a 2-chloroethyl group, a 2-fluoroethyl group, a 2,2-difluoroethyl group, a 1,1-difluoroethyl group, a 1,2-difluoroethyl group, a 15 2,2,2-trifluoroethyl group, a 2,2,2,5,5-pentafluoroethyl group, a 2,2,2-trichloroethyl group, a 3-fluoropropyl group, a 2-fluoropropyl group, a 1-fluoropropyl group, a 3,3-difluoropropyl group, a 2,2-difluoropropyl group, a 1,1-difluoropropyl group, a 1-fluorobutyl group, a 1-fluoropentyl group, a 1-fluorohexyl group, a 2,2,2-trifluoro-1-trifluoromethyl-1-ethyl group and the like. It is preferably a monofluoromethyl group, a 20 trifluoromethyl group or a 2-fluoroethyl group.

[0035]

The “halo-C₁₋₆ alkoxy group” means a C₁₋₆ alkoxy group substituted with the same or different 1 to 5 halogen atoms. Examples thereof include a monofluoromethoxy group, a difluoromethoxy group, a trifluoromethoxy group, a 2-chloroethoxy group, a 2- 25 fluoroethoxy group, a 2,2-difluoroethoxy group, a 1,1-difluoroethoxy group, a 1,2-difluoroethoxy group, a 2,2,2-trifluoroethoxy group, a 2,2,2,5,5-pentafluoroethoxy group, a 2,2,2-trichloroethoxy group, a 3-fluoropropoxy group, a 2-fluoropropoxy group, a 1-fluoropropoxy group, a 3,3-difluoropropoxy group, a 2,2-difluoropropoxy group, a 1,1-difluoropropoxy group, a 4-fluorobutoxy group, a 5-fluoropentyloxy group, a 6- 30 fluorohexyloxy group and the like. It is preferably a monofluoromethoxy group, a difluoromethoxy group or a trifluoromethoxy group.

[0036]

The “hydroxy-C₁₋₆ alkyl group” means a C₁₋₆ alkyl group substituted with a hydroxy group. Examples thereof include a hydroxymethyl group, a 1-hydroxyethyl

group, a 1-hydroxy-1,1-dimethylmethyl group, a 2-hydroxyethyl group, a 2-hydroxy-2-methylpropyl group, a 3-hydroxypropyl group and the like.

[0036]

The “C₁₋₆ alkylsulfanyl” means a group represented by (C₁₋₆ alkyl)-S-. Examples thereof include a methylsulfanyl group, an ethylsulfanyl group, a propylsulfanyl group, a butylsulfanyl group, a pentylsulfanyl group, a hexylsulfanyl group and the like.

[0038]

The “C₃₋₆ cycloalkyl group” means a monocyclic saturated alicyclic hydrocarbon group having 3 to 6 carbon atoms. Examples thereof include a cyclopropyl group, a cyclobutyl group, a cyclopentyl group, a cyclohexyl group and the like. In R², it is preferably a cyclopropyl group or a cyclopentyl group. It is more preferably a cyclopropyl group.

[0039]

The “C₇₋₁₀ aralkyl group” means an alkyl group having 1 to 4 carbon atoms, which is substituted with an aryl group. Examples thereof include a benzyl group, a phenethyl group, a 1-phenylethyl group, a 3-phenylpropyl group, a 4-phenylbutyl group and the like.

[0040]

The “5- or 6-membered aromatic heterocyclic group” means a 5- or 6-membered ring group containing 1 to 4 heteroatoms selected from an oxygen atom, a nitrogen atom, and a sulfur atom in the ring. Examples thereof include a pyridyl group, a pyrimidinyl group, a pyrazinyl group, a pyridazinyl group, a furyl group, a pyrrolyl group, a thienyl group, an imidazolyl group, a pyrazolyl group, a 1,2,4-triazolyl group, an isothiazolyl group, an isoxazolyl group, an oxazolyl group, a thiazolyl group, a 1,3,4-oxadiazolyl group, a 1,2,4-oxadiazolyl group and the like. It is preferably a 5-membered aromatic heterocyclic group, and more preferably a 2-furyl group, a 3-furyl group, a 2-thienyl group or a 3-thienyl group. It is further preferably a 3-furyl group or a 3-thienyl group.

[0041]

The “5-membered aromatic heterocyclic group” means a 5-membered ring group containing 1 to 4 hetero atoms selected from an oxygen atom, a nitrogen atom, and a sulfur atom in the ring. Examples thereof include a furyl group, pyrrolyl group, a thienyl group, an imidazolyl group, a pyrazolyl group, a 1,2,4-triazolyl group, an isothiazolyl group, an isoxazolyl group, an oxazolyl group, a thiazolyl group, a 1,3,4-oxadiazolyl group, a 1,2,4-oxadiazolyl group and the like. It is preferably a 2-furyl group, a 3-furyl group, a 2-

thienyl group or a 3-thienyl group. It is more preferably a 3-furyl group or a 3-thienyl group.

[0042]

The “6-membered aromatic heterocyclic group” means a 6-membered ring group containing 1 to 4 nitrogen atoms in the ring. Examples thereof include a pyridyl group, a pyrimidinyl group, a pyrazinyl group, a pyridazinyl group and the like. It is preferably a pyridyl group, and more preferably a 3-pyridyl group.

[0043]

The “C₁₋₆ alkylene group” means a divalent linear or molecular -chained saturated hydrocarbon chain having 1 to 6 carbon atoms. Examples thereof include -CH₂-, -CH₂CH₂-, -CH(CH₃)-, -(CH₂)₃-, -CH(CH₃)CH₂-, -CH₂CH(CH₃)-, -CH(CH₂CH₃)-, -C(CH₃)₂-, -(CH₂)₄-, -CH(CH₃)-(CH₂)₂-, -(CH₂)₂-CH(CH₃)-, -CH(CH₂CH₃)-CH₂-, -C(CH₃)₂CH₂-, -CH₂-C(CH₃)₂-, -CH(CH₃)-CH(CH₃)-, -(CH₂)₅-, -CH(CH₃)-(CH₂)₃-, -C(CH₃)₂CH₂CH₂-, -(CH₂)₆-, -C(CH₃)₂(CH₂)₃- and the like.

[0044]

The “C₁₋₅ alkylene group” means a divalent linear or molecular-chained saturated hydrocarbon chain having 1 to 5 carbon atoms. Examples thereof include -CH₂-, -(CH₂)₂-, -CH(CH₃)-, -(CH₂)₃-, -CH₂-CH(CH₃)-, -C(CH₃)₂-, -(CH₂)₄-, -(CH₂)₅- and the like.

[0045]

The “oxy-C₁₋₆ alkylene group” means -O-CH₂-, -O-(CH₂)₂-, -CH₂-O-CH₂-, -(CH₂)₂-O-, -O-CH(CH₃)-, -CH(CH₃)-O-, -O-(CH₂)₃-, -(CH₂)₃-O-, -O-CH(CH₃)-CH₂-, -CH(CH₃)-CH₂-O-, -O-C(CH₃)₂-, -C(CH₃)₂-O-, -O-(CH₂)₄-, -O-(CH₂)₅- or -O-(CH₂)₆-. It is preferably -O-CH₂-, -CH₂-O-, -O-(CH₂)₂-, -O-CH(CH₃)-, -O-CH(CH₃)-CH₂- or -O-C(CH₃)₂-. It is more preferably -O-CH₂-, -O-CH(CH₃)- or -O-C(CH₃)₂-.

[0046]

Hereinafter, the present invention is described in more detail.

[0047]

In the case that one or more asymmetric carbon atoms exist in the compound (I) of the present invention, the present invention includes each of compounds in which the respective asymmetric carbon atoms are in an R configuration or S configuration, and compounds having any combination of the configurations. Also, the racemic compound, the racemic mixture, the singular enantiomer, and the diastereomer mixture are encompassed within the scope of the present invention. In the case that geometrical

isomerism exists in the compound (I) of the present invention, the present invention includes any of the geometrical isomers.

[0048]

The compound (I) of the present invention can be converted to a pharmaceutically acceptable salt thereof according to a usual method, as necessary. Such a salt may be presented as an acid addition salt or a salt with a base.

[0049]

Examples of the acid addition salt include acid addition salts with mineral acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and acid addition salts with organic acids such as formic acid, acetic acid, trifluoroacetic acid, methanesulfonic acid, benzene sulfonic acid, *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.

[0050]

Examples of the salt with a base include salts with inorganic bases, such as a sodium salt, a potassium salt, a calcium salt, a magnesium salt and the like, and salts with organic bases or the like such as piperidine, morpholine, pyrrolidine, arginine, lysine and the like.

[0051]

In addition, the compound (I) of the present invention or a pharmaceutically acceptable salt thereof also encompasses hydrates, and solvates with pharmaceutically acceptable solvents such as ethanol and the like.

[0052]

The “EP₁ receptor antagonism” as mentioned in the present invention means an action of inhibiting the binding of a prostaglandin E₂ (PGE₂) to a prostaglandin E receptor 1 (EP₁ receptor).

The EP₁ receptor antagonism reduces the influx amount of calcium into cells and thus decreased or suppressed the intracellular calcium concentration. As the result, the EP₁ receptor antagonism exhibits an action of relaxation of smooth muscles, inhibition of sensory nerve stimulation or the like. Particularly, the EP₁ receptor antagonist acts on the bladder, the urothelium or the like, whereby it is useful as an agent for treating or preventing LUTS, in particular, the symptoms of OABs or the like.

Furthermore, the EP₁ receptor antagonism can be evaluated based on the efficacy of inhibiting the influx amount of calcium into cells by stimulus of a PGE₂ to EP₁ receptor. This efficacy can be evaluated by an in vitro test or in vivo test in accordance with “Pharmacological Test Examples” described in JP2008-214224A.

5 [0053]

Examples of the preferable substituents for the compound (I) of the present invention or a pharmaceutically acceptable salt thereof are as follows.

(I-1) A is preferably a benzene ring, a pyridine ring, a furan ring or a thiazole ring, and more preferably a benzene ring or a pyridine ring.

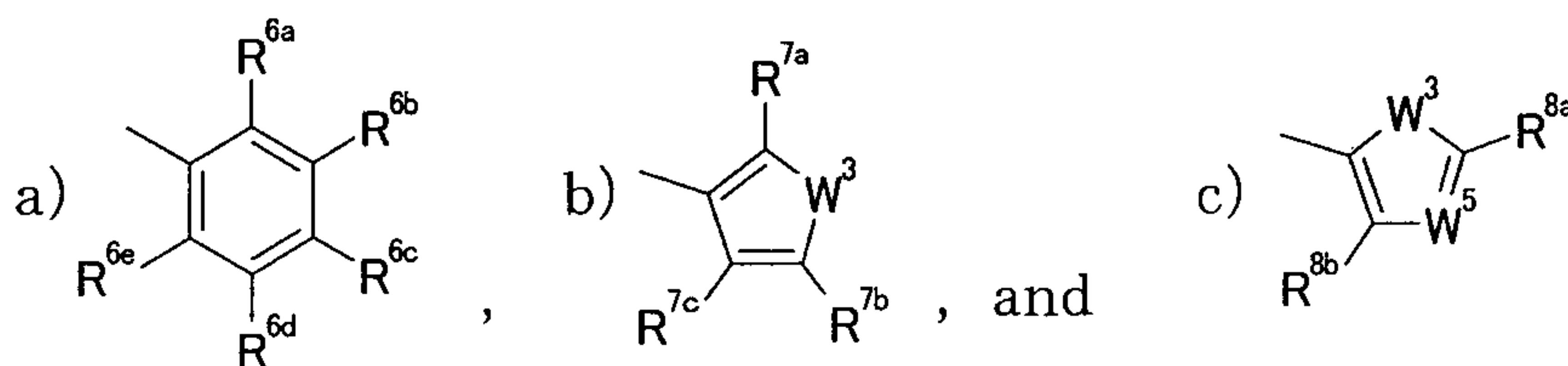
10 (I-2) Y¹ is preferably a methylene group, -CH(CH₃)-, or -C(CH₃)₂-, and more preferably a methylene group.

(I-3) Y² is preferably a single bond or -OCH₂-, and more preferably a single bond.

(I-4) R¹ is preferably a hydrogen atom or a C₁₋₆ alkyl group, and more preferably a hydrogen atom.

15 (I-5) R² is preferably an isopropyl group, an isobutyl group, a *sec*-butyl group, a 1-ethylpropyl group, a phenyl group, a 5-membered aromatic heterocyclic group, a 6-membered aromatic heterocyclic group, a phenyl group, in which the ring is substituted with 1 to 3 groups independently selected from the group consisting of: a halogen atom, a C₁₋₆ alkyl group, a halo-C₁₋₆ alkyl group, a hydroxy-C₁₋₆ alkyl group, a C₁₋₆ alkoxy group
20 and a cyano group, a 6-membered aromatic heterocyclic group, in which the ring is substituted with 1 to 2 groups independently selected from the group consisting of: a halogen atom, a C₁₋₆ alkyl group, a halo-C₁₋₆ alkyl group, a hydroxy-C₁₋₆ alkyl group, a C₁₋₆ alkoxy group and a cyano group, or a 5-membered aromatic heterocyclic group, in which the ring is substituted with 1 to 2 groups independently selected from the group consisting
25 of: a halogen atom, a C₁₋₆ alkyl group, a halo-C₁₋₆ alkyl group, a hydroxy-C₁₋₆ alkyl group, a C₁₋₆ alkoxy group and a cyano group. It is more preferably an isopropyl group, a *sec*-butyl group, a phenyl group, a 3-furyl group, a 3-thienyl group, or a group selected from the group consisting of the following a) to d):

[Chem. 10]



(wherein

R^{6a} , R^{6b} , R^{6c} , R^{6d} , and R^{6e} are each a group selected from the group consisting of the following e) to g):

e) one group of R^{6a} , R^{6b} , R^{6c} , R^{6d} , and R^{6e} is a halogen atom, a C_{1-6} alkyl group, a halo- C_{1-6} alkyl group, a hydroxy- C_{1-6} alkyl group, a C_{1-6} alkoxy group or a cyano group, and the other four groups are hydrogen atoms,

f) two groups of R^{6a} , R^{6b} , R^{6c} , R^{6d} , and R^{6e} are each independently a halogen atom, a C_{1-6} alkyl group, a halo- C_{1-6} alkyl group, a hydroxy- C_{1-6} alkyl group, a C_{1-6} alkoxy group or a cyano group, and the other three groups are hydrogen atoms, and

g) three groups of R^{6a} , R^{6b} , R^{6c} , R^{6d} , and R^{6e} are each independently a halogen atom, a C_{1-6} alkyl group, a halo- C_{1-6} alkyl group, a hydroxy- C_{1-6} alkyl group, a C_{1-6} alkoxy group or a cyano group, and the other two groups are hydrogen atoms;

R^{7a} , R^{7b} , and R^{7c} are each a group selected from the group consisting of h) and i) below:

h) one group of R^{7a} , R^{7b} , and R^{7c} is a halogen atom, a C_{1-6} alkyl group, a halo- C_{1-6} alkyl group, a hydroxy- C_{1-6} alkyl group, a C_{1-6} alkoxy group or a cyano group, and the other two groups are hydrogen atoms, and

i) two groups of R^{7a} , R^{7b} , and R^{7c} are each independently a halogen atom, a C_{1-6} alkyl group, a halo- C_{1-6} alkyl group, a hydroxy- C_{1-6} alkyl group, a C_{1-6} alkoxy group or a cyano group, and the other is a hydrogen atom;

for R^{8a} and R^{8b} , when w^5 is $-CR^{8c}=$, one group of R^{8a} , R^{8b} , and R^{8c} is a halogen atom, a C_{1-6} alkyl group, a halo- C_{1-6} alkyl group, a hydroxy- C_{1-6} alkyl group, a C_{1-6} alkoxy group or a cyano group, the other two groups are hydrogen atoms, and when w^5 is a nitrogen atom, one group of R^{8a} and R^{8b} is a halogen atom, a C_{1-6} alkyl group, a halo- C_{1-6} alkyl group, a hydroxy- C_{1-6} alkyl group, a C_{1-6} alkoxy group or a cyano group, and the other group is a hydrogen atom). It is further preferably a 3-furyl group, a 3-thienyl group or a phenyl group.

(I-6) R^3 is preferably a fluorine atom, a chlorine atom, a methyl group, an ethyl group, a trifluoromethyl group, a methoxy group, an ethoxy group or a difluoromethoxy group, more preferably a fluorine atom, a chlorine atom, a methyl group, a methoxy group, an ethoxy group, or a difluoromethoxy group, further preferably a fluorine atom or a methoxy group, and particularly preferably a methoxy group.

(I-7) R^4 is preferably a hydrogen atom, a fluorine atom or a chlorine atom, and more preferably a hydrogen atom.

[0054]

A preferable embodiment of the compound (I) of the present invention or a pharmaceutically acceptable salt thereof is a compound formed by combinations of preferable substituents described in (I-1) to (I-7).

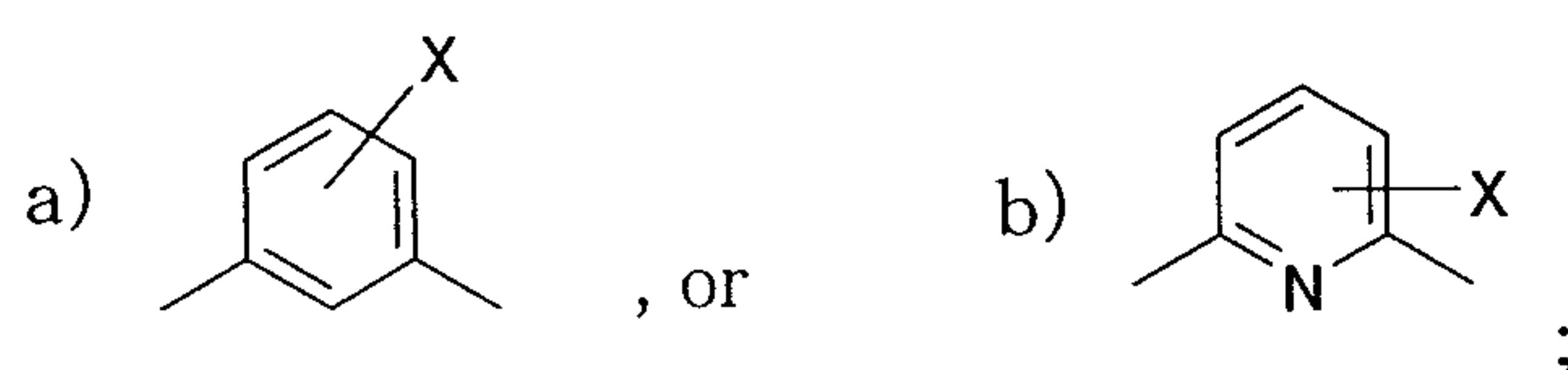
[0055]-[0057]

Embodiment 1

A preferable embodiment of the present invention is as follows:

A is a following:

[Chem. 11]



X is a hydrogen atom, a fluorine atom or a chlorine atom;

Y^1 is a methylene group;

Y^2 is a single bond or $-O-CH_2-$;

R^1 is a hydrogen atom;

R^2 is a phenyl group or a 5-membered aromatic heterocyclic group;

R^3 is a fluorine atom, a methyl group, a methoxy group or an ethoxy group; and

R^4 is a hydrogen atom, a fluorine atom or a chlorine atom.

[0058]

Examples of the concrete compound included in the present embodiment include the following compounds:

3-(5-methoxy-2-phenylindol-1-ylmethyl)benzoic acid (Example 9-1), 3-(5-methyl-2-phenylindol-1-ylmethyl)benzoic acid (Example 9-13), 6-(5-methoxy-2-phenylindol-1-ylmethyl)pyridine-2-carboxylic acid (Example 9-21), 3-(5-methoxy-2-thiophen-3-ylindol-1-ylmethyl)benzoic acid (Example 9-25), 3-(2-furan-3-yl-5-methoxyindol-1-ylmethyl)benzoic acid (Example 9-32), 6-(5-methoxy-2-thiophen-3-ylindol-1-ylmethyl)pyridine-2-carboxylic acid (Example 9-35), 3-(6-fluoro-5-methoxy-2-phenylindol-1-ylmethyl)benzoic acid (Example 9-43), 2-fluoro-3-(5-methoxy-2-phenylindol-1-ylmethyl)benzoic acid (Example 9-44), 6-(6-chloro-5-methoxy-2-phenylindol-1-ylmethyl)pyridine-2-carboxylic acid (Example 25-9), 6-(5-methoxy-6-methyl-2-phenylindol-1-ylmethyl)pyridine-2-carboxylic acid (Example 25-16), 3-[2-(2-fluorophenyl)-5-methoxyindol-1-ylmethyl]benzoic acid (Example 25-17), 3-[2-(3-fluorophenyl)-5-methoxyindol-1-ylmethyl]benzoic acid (Example 25-18), 3-[2-(4-

fluorophenyl)-5-methoxyindol-1-ylmethyl]benzoic acid (Example 25-19), 6-[6-chloro-2-(3-fluorophenyl)-5-methoxyindol-1-ylmethyl]pyridine-2-carboxylic acid (Example 25-23), 6-[6-fluoro-2-(2-fluorophenyl)-5-methoxyindol-1-ylmethyl]pyridine-2-carboxylic acid (Example 25-28), 6-[6-fluoro-2-(3-fluorophenyl)-5-methoxyindol-1-ylmethyl]pyridine-2-carboxylic acid (Example 25-29), 6-[6-fluoro-2-(4-fluorophenyl)-5-methoxyindol-1-ylmethyl]pyridine-2-carboxylic acid (Example 25-31), 6-(6-chloro-5-methoxy-2-thiophen-3-ylindol-1-ylmethyl)pyridine-2-carboxylic acid (Example 25-34), 6-(6-chloro-2-furan-3-yl-5-methoxyindol-1-ylmethyl)pyridine-2-carboxylic acid (Example 25-37), 6-(5-methoxy-6-methyl-2-thiophen-3-ylindol-1-ylmethyl)pyridine-2-carboxylic acid (Example 25-39), 6-[2-(2,5-difluorophenyl)-5-methoxyindol-1-ylmethyl]pyridine-2-carboxylic acid (Example 25-41).

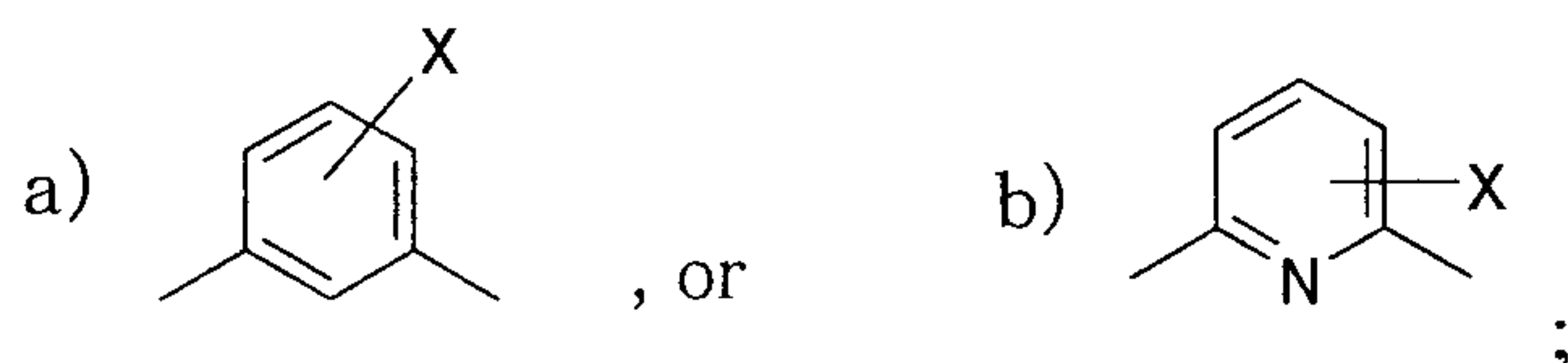
[0059]-[0060]

Embodiment 2

Another preferable embodiment of the present invention is as follows:

A is a following:

[Chem. 12]



X is a hydrogen atom, a fluorine atom or a chlorine atom;

Y^1 is a methylene group;

Y^2 is a single bond or $-O-CH_2-$;

R^1 is a hydrogen atom;

R^2 is an isopropyl group or a *sec*-butyl group;

R^3 is a fluorine atom, a methyl group, a methoxy group or an ethoxy group; and

R^4 is a hydrogen atom, a fluorine atom or a chlorine atom.

[0061]

Examples of the concrete compound included in the present embodiment include the following compounds:

3-(2-isopropyl-5-methoxyindol-1-ylmethyl)benzoic acid (Example 9-15), 6-[6-chloro-5-methoxy-2-(1-methylpropyl)indol-1-ylmethyl]pyridine-2-carboxylic acid (Example 25-44).

[0062]

Embodiment 3

Another preferable embodiment of the present invention is as follows:

 R^1 is a C_{1-6} alkyl group.

5

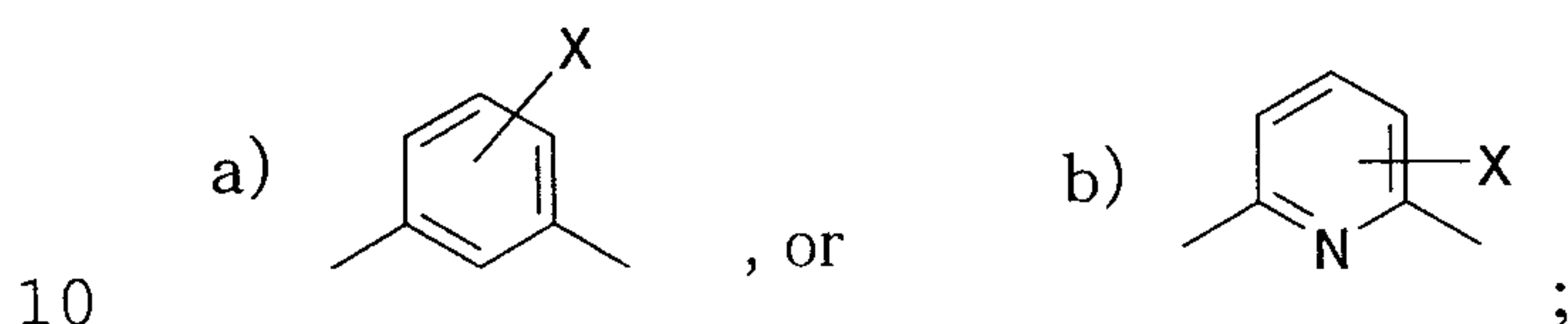
[0063]-[0064]

Embodiment 4

Another preferable embodiment of the present invention is as follows:

A is a following:

[Chem. 13]

 X is a hydrogen atom, a fluorine atom or a chlorine atom; Y^1 is a methylene group; Y^2 is a single bond or $-O-CH_2-$; R^1 is a C_{1-6} alkyl group;

15

 R^2 is an isopropyl group, a *sec*-butyl group, a phenyl group or a 5-membered aromatic heterocyclic group; R^3 is a fluorine atom, a chlorine atom, a methyl group, a methoxy group or an ethoxy group; and R^4 is a hydrogen atom, a fluorine atom or a chlorine atom.

20

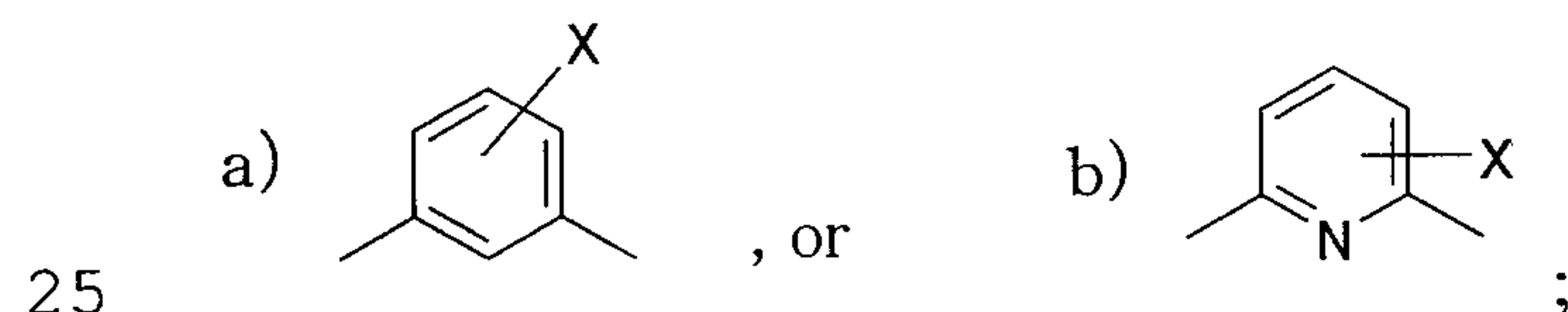
[0065]-[0067]

Embodiment 5

Another preferable embodiment of the present invention is as follows:

A is a following:

[Chem. 14]

 X is a hydrogen atom, a fluorine atom or a chlorine atom; Y^1 is a methylene group; Y^2 is a single bond or $-O-CH_2-$; R^1 is a hydrogen atom;

30

 R^2 is a 6-membered aromatic heterocyclic group;

R^3 is a fluorine atom, a methyl group, a methoxy group or an ethoxy group; and
 R^4 is a hydrogen atom, a fluorine atom or a chlorine atom.

[0068]

Examples of the concrete compound included in the present embodiment include
 5 the following compounds:

3-(5-methoxy-2-pyridin-3-ylindol-1-ylmethyl)benzoic acid (Example 25-13), 6-(6-fluoro-5-methoxy-2-pyridin-3-ylindol-1-ylmethyl)pyridine-2-carboxylic acid (Example 25-33), 6-(6-chloro-5-methoxy-2-pyridin-3-ylindol-1-ylmethyl)pyridine-2-carboxylic acid (Example 25-42).

10 [0069]-[0071]

Embodiment 6

Another preferable embodiment of the present invention is as follows:

A is a following:

[Chem. 15]



15 ;

Y^1 is a methylene group;

Y^2 is a single bond;

R^1 is a hydrogen atom;

R^2 is a phenyl group, which may have a substituent, or a 5-membered aromatic
 20 heterocyclic group, which may have a substituent;

R^3 is a fluorine atom, a methyl group, a methoxy group or an ethoxy group; and

R^4 is a hydrogen atom, a fluorine atom, a chlorine atom or a methyl group.

[0072]

Examples of the concrete compound included in the present embodiment include
 25 the following compounds:

5-[2-(3-fluorophenyl)-5-methoxyindol-1-ylmethyl]furan-2-carboxylic acid (Example 25-11), 5-[6-chloro-5-methoxy-2-phenylindol-1-ylmethyl]furan-2-carboxylic acid (Example 25-26), 5-[5-methoxy-6-methyl-2-phenylindol-1-ylmethyl]furan-2-carboxylic acid (Example 25-36), 5-(6-chloro-2-furan-3-yl-5-methoxyindol-1-ylmethyl)furan-2-carboxylic acid (Example 25-38).
 30

[0073]

Production Process of Compound (I) of the Present Invention

[0074]

The compound (I) of the present invention or a pharmaceutically acceptable salt thereof can be prepared by a method described in the following Schemes 1 to 3, or a similar method thereto, or by a method described in other literature, or a similar method thereto.

[0075]

[A] Synthesis of Compounds (Ia) to (Id)

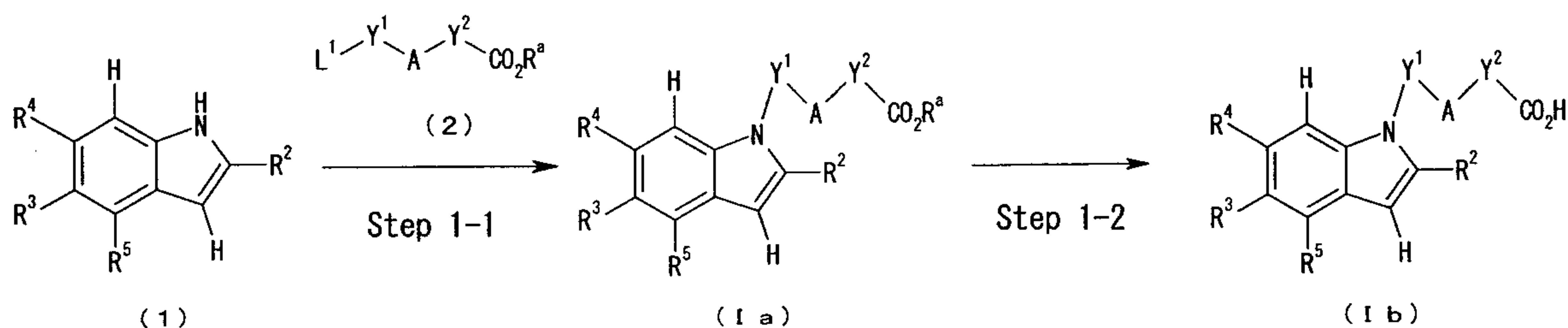
The compound (I) of the present invention can be prepared by the method shown in Schemes 1 or 2 as compounds (Ia) to (Id). Further, when a protecting group is needed, combinations of introduction and cleavage can appropriately be carried out according to a usual method.

[0076]

In the compound (I) of the present invention, the compound (Ia) wherein R^1 is a C_{1-6} alkyl group or a C_{7-10} aralkyl group, and the compound (Ib) wherein R^1 is a hydrogen atom can be prepared by each method shown in Scheme 1 or a similar method thereto, or be prepared according to a method described in other literature or a similar method thereto. Further, when a protective group is needed, combinations of introduction and cleavage can appropriately be carried out according to a usual method.

[0077]

[Chem. 16]
Scheme 1



[0078]

(wherein A, R^2 , R^3 , R^4 , R^5 , Y^1 and Y^2 have the same meanings as defined above; R^a is a C_{1-6} alkyl group or a C_{7-10} aralkyl group; and L^1 represents a chlorine atom, a bromine atom, an iodine atom, a methanesulfonyloxy group or the like).

[0079]

Step 1-1

A compound (Ia) can be prepared by reacting a compound (1) with a compound (2) in a solvent in the presence of a base. As the solvent to be used, *N,N*-dimethylformamide, *N,N*-dimethylacetamide, *N,N*-dimethylimidazolidinone,

tetrahydrofuran, a mixed solvent thereof and the like can be illustrated. As the base to be used, sodium hydride, potassium *tert*-butoxide, lithium bis(trimethylsilyl)amide and the like can be illustrated. The reaction temperature is usually -20°C to a solvent reflux temperature, and the reaction time varies depending on a starting material and a solvent to be used, a reaction temperature or the like, but it is usually 30 minutes to 3 days. Further, the present step can be carried out with addition of sodium iodide, tetra-*n*-butyl ammonium bromide, tetra-*n*-butyl ammonium iodide or the like, if necessary.

Furthermore, the compound (2) used in the present step may be commercially available. Further the compound (2) can be obtained by using the corresponding alcohol as a starting material and converting the hydroxy group into a chlorine atom, a bromine atom, an iodine atom, a methanesulfonyloxy group or the like according to a method described in literature or a similar method thereto.

[0080]

Step 1-2

A compound (Ib) of the present invention can be prepared by treating the compound (Ia) of the present invention according to a conversion method from a ester group to a carboxy group. Such method is well-known to a skilled person in the art, and can be carried out using the method described in "Greene's Protective Groups in Organic Synthesis", edited by Greene & Wuts, fourth edition, Wiley-Interscience, 2006.

[0081]

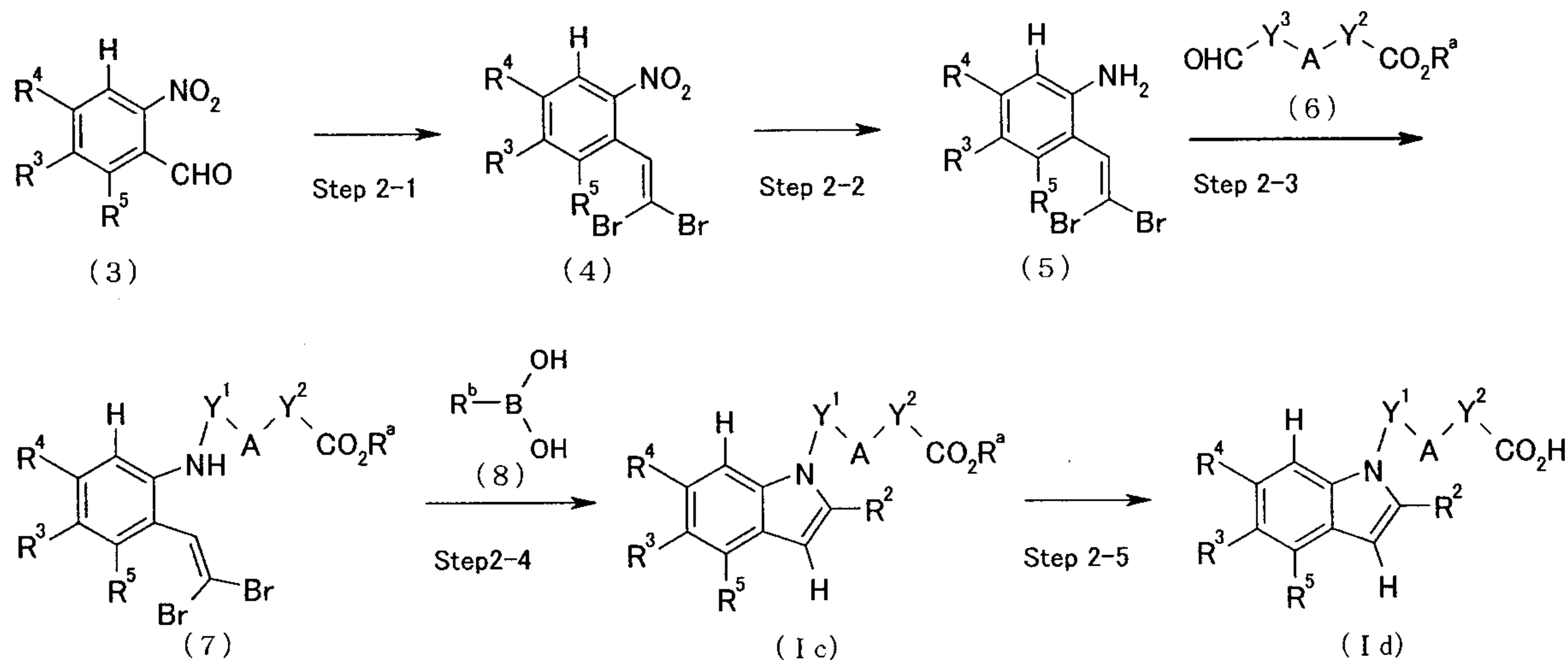
In the compound (I) of the present invention, the compounds (Ic) and (Id), wherein R² is a phenyl group, a 5 or 6-membered aromatic heterocyclic group, a phenyl group, in which the ring is substituted with 1 to 5 groups independently selected from the group consisting of: a halogen atom, a C₁₋₆ alkyl group, a halo-C₁₋₆ alkyl group, a hydroxy-C₁₋₆ alkyl group, a C₁₋₆ alkoxy group and a cyano group, a 6-membered aromatic heterocyclic group, in which the ring is substituted with 1 to 4 groups independently selected from the group consisting of: a halogen atom, a C₁₋₆ alkyl group, a halo-C₁₋₆ alkyl group, a hydroxy-C₁₋₆ alkyl group, a C₁₋₆ alkoxy group and a cyano group, or a 5-membered aromatic heterocyclic group, in which the ring is substituted with 1 to 3 groups independently selected from the group consisting of: a halogen atom, a C₁₋₆ alkyl group, a halo-C₁₋₆ alkyl group, a hydroxy-C₁₋₆ alkyl group, a C₁₋₆ alkoxy group and a cyano group can be prepared by the method shown in Scheme 2 or a similar method thereto, or can be prepared according to a method described in other literature or a similar method thereto. Further,

when a protective group is needed, combinations of introduction and cleavage can appropriately be carried out according to a usual method.

[0082]

[Chem. 17]

Scheme 2



[0083]

(wherein A, R^3 , R^4 , R^5 , R^a , Y^1 and Y^2 have the same meanings as defined above; R^b is a phenyl group, a 5 or 6-membered aromatic heterocyclic group, a phenyl group, in which the ring is substituted with 1 to 5 groups independently selected from the group consisting of: a halogen atom, a C_{1-6} alkyl group, a halo- C_{1-6} alkyl group, a hydroxy- C_{1-6} alkyl group, a C_{1-6} alkoxy group and a cyano group, a 6-membered aromatic heterocyclic group, in which the ring is substituted with 1 to 4 groups independently selected from the group consisting of: a halogen atom, a C_{1-6} alkyl group, a halo- C_{1-6} alkyl group, a hydroxy- C_{1-6} alkyl group, a C_{1-6} alkoxy group and a cyano group, or a 5-membered aromatic heterocyclic group, in which the ring is substituted with 1 to 3 groups independently selected from the group consisting of: a halogen atom, a C_{1-6} alkyl group, a halo- C_{1-6} alkyl group, a hydroxy- C_{1-6} alkyl group, a C_{1-6} alkoxy group and a cyano group; and Y^3 represents a single bond or a C_{1-5} alkylene group).

[0084]

Step 2-1

A compound (4) can be prepared by reacting a compound (3) with carbon tetrabromide and triphenylphosphine in a solvent. As the solvent to be used, dichloromethane, 1,2-dichloroethane, benzene, toluene, tetrahydrofuran, a mixed solvent thereof, and the like can be illustrated. The reaction temperature is usually from -20°C to a solvent reflux temperature, and the reaction time varies depending on a starting material

and a solvent to be used, a reaction temperature or the like, but it is usually 30 minutes to 3 days. Furthermore, the compound (3) used in the present step may be commercially available or can be prepared according to a method described in other literature or a similar method thereto.

5 [0085]

Step 2-2

A compound (5) can be prepared by reducing a nitro group of the compound (4) using a reducing agent. As the reduction method of a nitro group, for example, a method using iron, zinc, tin(II) chloride dihydrate or the like as a reducing agent in a solvent can be
10 illustrated. As the solvent to be used, methanol, ethanol, acetic acid, water, a mixed solvent thereof and the like can be illustrated. The reaction temperature is usually from -20°C to a solvent reflux temperature, and the reaction time varies depending on a starting material and a solvent to be used, a reaction temperature or the like, but it is usually 30 minutes to 3 days.

15 [0086]

Step 2-3

A compound (7) can be prepared by a reductive amination reaction using the compound (5) and the compound (6). As the solvent to be used, tetrahydrofuran, dichloromethane, 1,2-dichloroethane, ethanol, a mixed solvent thereof and the like can be
20 illustrated. As the reducing agent to be used, sodium triacetoxyborohydride, sodium cyanoborohydride and the like can be illustrated. The reaction temperature is usually from -20°C to a solvent reflux temperature, and the reaction time varies depending on a starting material and a solvent to be used, a reaction temperature or the like, but it is usually 30 minutes to 3 days. Furthermore, the compound (6) used in the present step
25 may be commercially available or can be prepared according to a method described in other literature or a similar method thereto.

[0087]

Step 2-4

A compound (Ic) of the present invention can be prepared by reacting the
30 compound (7) with a compound (8) in a solvent in the presence of a palladium catalyst and a base. As the solvent to be used, toluene, tetrahydrofuran, 1,4-dioxane, ethanol, *N,N*-dimethylformamide, water, a mixed solvent thereof and the like can be illustrated. As the palladium catalyst to be used, palladium (II) acetate, bis(triphenylphosphine)palladium (II) dichloride, tetrakis(triphenylphosphine)palladium (0), tris(dibenzylideneacetone)

dipalladium (0) and the like can be illustrated. As the base to be used, potassium phosphate, potassium phosphate monohydrate, potassium carbonate, cesium carbonate, cesium fluoride, sodium carbonate and the like can be illustrated. The reaction temperature is usually from room temperature to a solvent reflux temperature, and the reaction time varies depending on a starting material and a solvent to be used, a reaction temperature or the like, but it is usually 30 minutes to 3 days. Further, the present step may be carried out with addition of a ligand such as 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl, bis(diphenylphosphino)ferrocene or the like, if necessary. Furthermore, the compound (8) used in the present step may be commercially available or can be prepared according to a method described in other literature or a similar method thereto.

[0088]

Step 2-5

The compound (Id) of the present invention can be prepared by treating the compound (Ic) of the present invention according to a method of Step 1-2.

[0089]

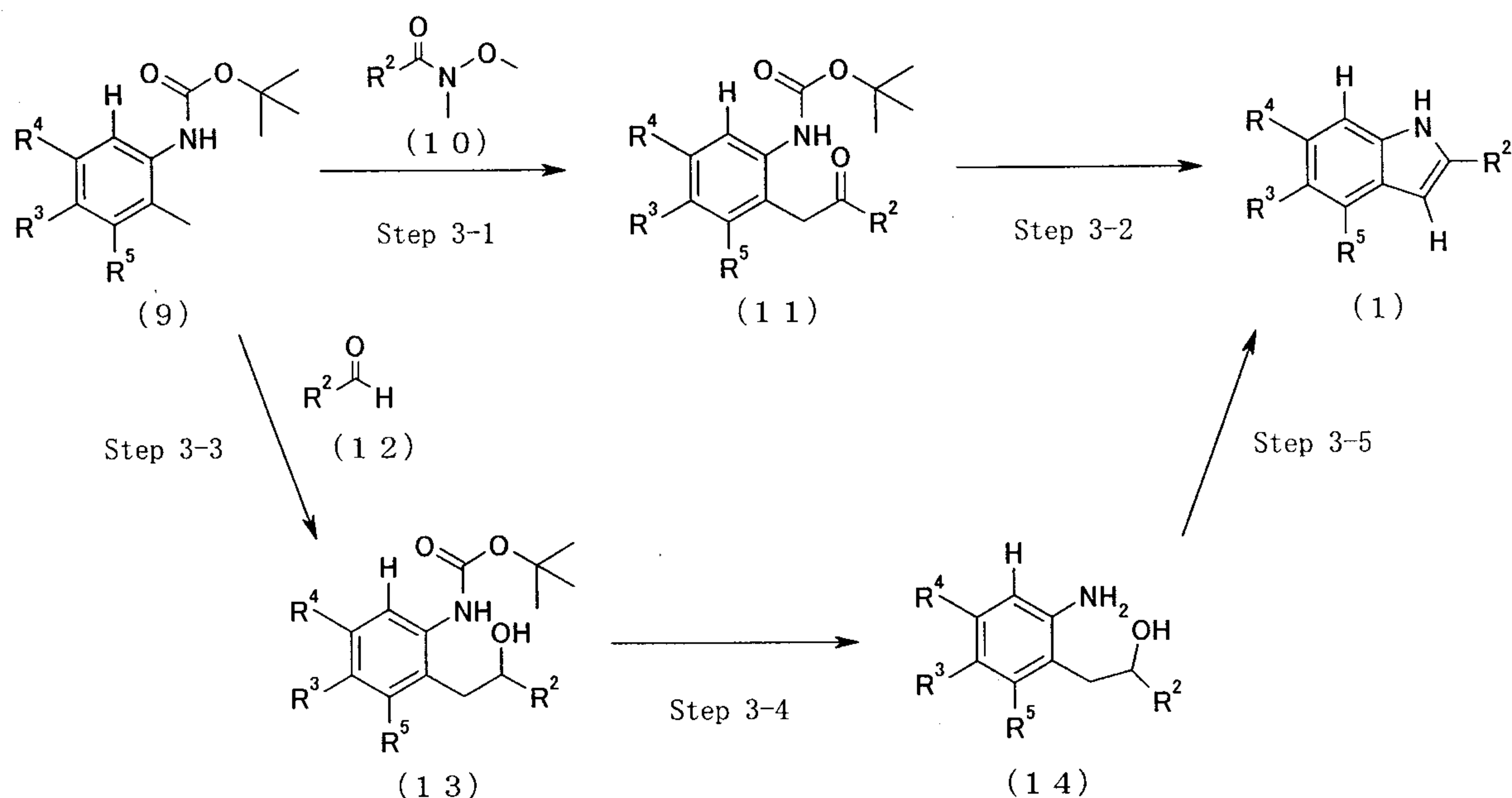
[B] Synthesis of Compound (1)

[0090]

The compound (1) may be commercially available, or can be prepared by a method described in the following Scheme 3 or a similar method thereto, or a method described in other literature or a similar method thereto. Further, when a protective group is needed, combinations of introduction and cleavage can appropriately be carried out according to a usual method.

[0091]

[Chem.18]
Scheme 3



[0092]

(wherein R^2 , R^3 , R^4 and R^5 have the same meanings as defined above)

5 [0093]

Step 3-1

A compound (11) can be prepared by lithiating a compound (9) in a solvent using alkyllithium or the like and then reacting a compound (10) thereto. As the solvent to be used, tetrahydrofuran, diethyl ether, 1,2-dimethoxyethane, 1,4-dioxane, a mixed solvent thereof and the like can be illustrated. As the alkyllithium to be used, *n*-butyllithium, *sec*-butyllithium, *tert*-butyllithium and the like can be illustrated, and *sec*-butyllithium is preferable. The reaction temperature is usually from -78°C to a solvent reflux temperature, and the reaction time varies depending on a starting material and a solvent to be used, a reaction temperature or the like, but it is usually 30 minutes to 1 day.

15 Furthermore, the compounds (9) and (10) used in the present step may be commercially available or can be prepared according to a method described in other literature or a similar method thereto.

[0094]

Step 3-2

20 The compound (1) can be prepared by treating the compound (11) with acid in a solvent. As the solvent to be used, dichloromethane, chloroform, methanol, ethanol, tetrahydrofuran, 1,4-dioxane, a mixed solvent thereof and the like can be illustrated. As the acid to be used, trifluoroacetic acid, methanesulfonic acid, concentrated hydrochloric

acid, concentrated sulfuric acid and the like can be illustrated. The reaction temperature is usually from -78°C to a solvent reflux temperature, and the reaction time varies depending on a starting material and a solvent to be used, a reaction temperature or the like, but it is usually 30 minutes to 3 days.

5 [0095]

Step 3-3

A compound (13) can be prepared by lithiating the compound (9) in a solvent using alkyllithium or the like and then reacting a compound (12) thereto. As the solvent to be used, tetrahydrofuran, diethyl ether, 1,2-dimethoxyethane, 1,4-dioxane, a mixed
10 solvent thereof and the like can be illustrated. As the alkyllithium to be used, *n*-butyllithium, *sec*-butyllithium, *tert*-butyllithium and the like can be illustrated, and *sec*-butyllithium is preferable. The reaction temperature is usually from -78°C to a solvent reflux temperature, and the reaction time varies depending on a starting material and a solvent to be used, a reaction temperature or the like, but it is usually 30 minutes to 1 day.
15 Furthermore, the compound (12) used in the present step may be commercially available or can be prepared according to a method described in other literature or a similar method thereto.

[0096]

Step 3-4

20 A compound (14) can be prepared by treating the compound (13) under acidic condition. This reaction is well-known to a skilled person in the art and can be carried out using the method described in "Greene's Protective Groups in Organic Synthesis" edited by Greene & Wuts, fourth edition, Wiley-Interscience, 2006.

[0097]

25 Step 3-5

The compound (1) can be prepared by oxidizing the compound (14) in a solvent in the presence of a palladium catalyst, a oxidizing agent and a base. As the solvent to be used, *N,N*-dimethylformamide, 1-methyl-2-pyrrolidone, a mixed solvent thereof and the like can be illustrated. As the palladium catalyst to be used, for example,
30 tetrakis(triphenylphosphine)palladium (0) can be illustrated. As the oxidizing agent to be used, for example, mesityl bromide can be illustrated. As the base to be used, potassium carbonate, cesium carbonate, sodium hydride and the like can be illustrated. The reaction temperature is usually from room temperature to a solvent reflux temperature, and the

reaction time varies depending on a starting material and a solvent to be used, a reaction temperature or the like, but it is usually 30 minutes to 3 days.

[0098]

These schemes shown above are exemplification of the method for preparing the compound (I) of the present invention or an intermediate for preparation. These are
5 allowed to be modified to such a scheme that can be readily understood by a person skilled in the art.

[0099]

Also, in the case that there is a need of a protective group according to the kind of
10 the functional group, combinations of introduction and cleavage can be appropriately carried out according to a usual method. The type, introduction, and cleavage of the protective group can be illustrated in reference to the method described in, for example, "Greene's Protective Groups in Organic Synthesis", edited by Theodora W. Greene & Peter G. M. Wuts, fourth edition, Wiley-Interscience, 2006.

15 [0100]

The intermediates used for preparation of the compound (I) of the present invention or a pharmaceutically acceptable salt thereof can be isolated/purified, as necessary, by solvent extraction, crystallization/recrystallization, chromatography, preparative high performance liquid chromatography, or the like, that is an isolation/
20 purification means well-known to a skilled person in the art.

[0101]

Pharmaceutical Composition Comprising Compound (I) of the Present Invention or Pharmaceutically Acceptable Salt thereof

[0102]

25 The pharmaceutical composition comprising the compound (I) of the present invention or a pharmaceutically acceptable salt thereof as an active ingredient is used in various dosage forms according to the usages. Examples of the dosage forms include powders, granules, fine granules, dry syrups, tablets, capsules, injections, liquids, ointments, suppositories, plasters, sublinguals, and the like, which are administered orally
30 or parenterally.

[0103]

These pharmaceutical compositions can be prepared by appropriately mixing or diluting/dissolving with pharmaceutical additives such as an excipient, a disintegrant, a binder, a lubricant, a diluent, a buffering agent, a tonicity agent, a preservative, a wetting

agent, an emulsifier, a dispersant, a stabilizer, a solubilizing aid, and the like by a well-known method according to the dosage forms. In addition, when used in combination with agents other than the EP₁ receptor antagonist, the pharmaceutical compositions can be prepared by formulating the respective active ingredients simultaneously or separately as described above.

[0104]

Pharmaceutical Use of Compound (I) of the Present Invention or Pharmaceutically Acceptable Salt thereof

[0105]

The compound (I) of the present invention or a pharmaceutically acceptable salt thereof exhibits a potent EP₁ receptor antagonism in a test for confirmation of an EP₁ receptor antagonism. Therefore, the compound (I) of the present invention can suppress or decrease the intracellular calcium concentration. Accordingly, a pharmaceutical composition comprising the compound (I) of the present invention or a pharmaceutically acceptable salt thereof as an active ingredient can be used as an agent for treating or preventing diseases or symptoms caused by activation of the EP₁ receptor due to stimulus of a PGE₂.

[0106]

In addition, examples of the diseases with the activation of the EP₁ receptor due to the PGE₂ stimulus include lower urinary tract symptoms (LUTS), inflammatory diseases, pain diseases, osteoporosis, cancer, and the like. The pharmaceutical composition comprising the compound (I) of the present invention or a pharmaceutically acceptable salt thereof as an active ingredient is preferably used as an agent for treating or preventing LUTS, inflammatory diseases, or pain diseases. It is more preferably LUTS.

[0107]

Examples of the disease that causes the lower urinary tract symptoms include overactive bladder (OAB), benign prostatic hyperplasia (BPH), cystitis such as interstitial cystitis and the like, prostatitis, and the like.

[0108]

The "lower urinary tract symptoms" means storage symptoms, voiding symptoms, post micturition symptoms, or the like. The compound (I) of the present invention or a pharmaceutically acceptable salt thereof is preferably used for treatment or prevention of storage symptoms.

[0109]

Examples of the “storage symptoms” include urinary urgency, increased daytime frequency, nocturia, urinary incontinence (stress urinary incontinence, urge urinary incontinence, mixed urinary incontinence, enuresis, nocturnal enuresis, continuous urinary incontinence, and the like), and bladder sensation (increased bladder sensation, reduced bladder sensation, absent bladder sensation, non-specific bladder sensation, and the like). The compound (I) of the present invention or a pharmaceutically acceptable salt thereof is preferably used for treatment or prevention of urinary urgency, increased daytime frequency, nocturia, urge urinary incontinence, mixed urinary incontinence, enuresis, nocturnal enuresis, increased bladder sensation, or non-specific bladder sensation. It is more preferably urinary urgency, increased daytime frequency, nocturia, urge urinary incontinence, or increased bladder sensation. Further, the compound (I) of the present invention or a pharmaceutically acceptable salt thereof is particularly preferably used for treatment or prevention of OABs.

15 [0110]

Combinations or Mixtures of Compound (I) of the Present Invention or Pharmaceutically Acceptable Salt thereof

[0111]

The compound (I) of the present invention or a pharmaceutically acceptable salt thereof can be appropriately used in combination with at least one agent other than the EP₁ receptor antagonist.

[0112]

Examples of the agent that can be used in combination with the compound (I) of the present invention or a pharmaceutically acceptable salt thereof include agents for the treatment of overactive bladder(OAB) , benign prostatic hyperplasia (BPH), cystitis such as interstitial cystitis and the like, prostatitis, and the like, which have different action mechanisms from that of the EP₁ receptor antagonist. Examples of the agent include an anticholinergic agent, an α_1 antagonist, a β agonist, a 5 α -reductase inhibitor, a PDE inhibitor, an acetylcholine esterase inhibitor, an anti-androgen, a progesterone-based hormone, an LH-RH analog, a neurokinin inhibitor, an anti-diuretic, a calcium channel blocker, a direct smooth muscle agonist, a tricyclic antidepressant, a K channel modulator, a sodium channel blocker, an H₁ blocker, a serotonin reuptake inhibitor, a norepinephrine reuptake inhibitor, a dopamine reuptake inhibitor, a GABA agonist, a TRPV1 modulator, an endothelin antagonist, a 5-HT_{1A} antagonist, an α_1 agonist, an opioid agonist, a P₂X

antagonist, a COX inhibitor, a σ agonist, a muscarinic agonist, and the like. It is preferably an anticholinergic agent, an α_1 antagonist, a β agonist, a 5α -reductase inhibitor, a PDE inhibitor, a progesterone-based hormone, an anti-diuretic, a direct smooth muscle agonist, or a tricyclic antidepressant.

5 [0113]

Furthermore, concrete examples of the agent that is used in combination are illustrated as below, but the context of the present invention is not limited thereto. Further, examples of the concrete compound include a free form thereof, and other pharmaceutically acceptable salts.

10 [0114]

Examples of the "anticholinergic agent" include oxybutynin, propiverine, solifenacin, tolterodine, imidafenacin, temiberin, darifenacin, fesoterodine, trospium, propantheline, and the like.

[0115]

15 Examples of the " α_1 antagonist" include urapidil, naphthopidil, tamsulosin, silodosin, prazosin, terazosin, alfuzosin, doxazosin, CR-2991, fiduxosin, and the like.

[0116]

Examples of the " β agonist" include YM-178, KUC-7483, KRP-204, SM-350300, TRK-380, amibegron, clenbuterol, SAR-150640, solabegron, and the like.

20 [0117]

Examples of the " 5α -reductase inhibitor" include dutasteride, TF-505, finasteride, izonsteride, and the like.

[0118]

25 Examples of the "PDE inhibitor" include tadalafil, vardenafil, sildenafil, avanafil, UK-369003, T-0156, AKP-002, etazolate, and the like.

[0119]

Examples of the "acetylcholine esterase inhibitor" include distigmine, donepezil, Z-338, rivastigmine, ganstigmine, BGC-20-1259, galantamine, itopride, NP-61, SPH-1286, tolserine, ZT-1, and the like.

30 [0120]

Examples of the "anti-androgen" include gestonorone, oxendolone, bicalutamide, BMS-641988, CB-03-01, CH-4892789, flutamide, MDV-3100, nilutamide, TAK-700, YM-580, and the like.

[0121]

Examples of the “progesterone-based hormone” include chlormadinone, allylestrenol, and the like.

[0122]

5 Examples of the “LH-RH analog” include AEZS-108, buserelin, deslorelin, goserelin, histrelin, leuprorelin, lutropin, nafarelin, triptorelin, AEZS-019, cetrorelix, degarelix, elagolix, ganirelix, ozarelix, PTD-634, TAK-385, teverelix, TAK-448, TAK-683, and the like.

[0123]

10 Examples of the “neurokinin inhibitor” include KRP-103, aprepitant, AV-608, casopitant, CP-122721, DNK-333, fosaprepitant, LY-686017, netupitant, orvepitant, rolapitant, TA-5538, T-2328, vestipitant, AZD-2624, Z-501, 1144814, MEN-15596, MEN-11420, SAR-102779, SAR-102279, saredutant, SSR-241586, and the like.

[0124]

15 Examples of the “anti-diuretic” include desmopressin, VA-106483, and the like.

[0125]

Examples of the “calcium channel blocker” include amlodipine, cilnidipine, propiverine, temiverine, PD-299685, aranidipine, azelnidipine, barnidipine, benidipine, bevantolol, clevidipine, CYC-381, diltiazem, efonidipine, fasudil, felodipine, gabapentin, gallopamil, isradipine, lacidipine, lercanidipine, lomerizine, manidipine, MEM-1003, nicardipine, nifedipine, nilvadipine, nimodipine, nisoldipine, SB-751689, verapamil, YM-58483, ziconotide, and the like.

[0126]

Examples of the “direct smooth muscle agonist” include flavoxate and the like.

25 [0127]

Examples of the “tricyclic antidepressant” include imipramine, clomipramine, amitriptyline, and the like.

[0128]

30 Examples of the “K channel modulator” include nicorandil, NIP-141, NS-4591, NS-1643, andolrast, diazoxide, ICA-105665, minoxidil, pinacidil, tilisolol, VRX-698, and the like.

[0129]

Examples of the “sodium channel blocker” include bepridil, dronedarone, propafenone, safinamide, SUN-N8075, SMP-986, 1014802, 552-02, A-803467,

brivaracetam, cibenzone, eslicarbazepine, F-15845, flecainide, fosphenytoin, lacosamide, lamotrigine, levobupivacaine, M-58373, mexiletine, moracizine, nerispiridine, NW-3509, oxcarbazepine, pilsicainide, pirmenol, propafenone, NW-1029, ropivacaine, vernakalant, and the like.

5 [0130]

Examples of the "H1 blocker" include acrivastine, alcaftadine, bepotastine, bilastine, cetirizine, desloratadine, ebastine, efletirizine, epinastine, fexofenadine, GSK-835726, levocabastine, levocetirizine, loratadine, mequitazine, mizolastine, NBI-75043, ReN-1869, terfenadine, UCB-35440, vapitazine, YM-344484, diphenhydramine,
10 chlorpheniramine, and the like.

[0131]

Examples of the "serotonin reuptake inhibitor" include UCB-46331, 424887, AD-337, BGC-20-1259, BMS-505130, citalopram, dapoxetine, desvenlafaxine, DOV-102677, DOV-216303, DOV-21947, duloxetine, escitalopram, F-2695, F-98214-TA, fluoxetine,
15 fluvoxamine, IDN-5491, milnacipran, minaprine, NS-2359, NSD-644, paroxetine, PF-184298, SD-726, SEP-225289, SEP-227162, SEP-228425, SEP-228432, sertraline, sibutramine, tesofensine, tramadol, trazodone, UCB-46331, venlafaxine, vilazodone, WAY-426, WF-516, and the like.

[0132]

20 Examples of the "norepinephrine reuptake inhibitor" include AD-337, desvenlafaxine, DOV-102677, DOV-216303, DOV-21947, duloxetine, F-2695, F-98214-TA, milnacipran, NS-2359, NSD-644, PF-184298, SD-726, SEP-225289, SEP-227162, SEP-228425, SEP-228432, sibutramine, tesofensine, tramadol, venlafaxine, bupropion, radafaxine, atomoxetine, DDP-225, LY-2216684, neboglamine, NRI-193, reboxetine,
25 tapentadol, WAY-256805, WAY-260022, and the like.

[0133]

Examples of the "dopamine reuptake inhibitor" include DOV-102677, DOV-216303, DOV-21947, IDN-5491, NS-2359, NSD-644, SEP-225289, SEP-228425, SEP-228432, sibutramine, tesofensine, tramadol, brasofensine, bupropion, NS-27100,
30 radafaxine, safinamide, and the like.

[0134]

Examples of the "GABA agonist" include retigabine, eszopiclone, indiplon, pagoclone, SEP-225441, acamprosate, baclofen, AZD-7325, BL-1020, brotizolam, DP-

VPA, progabide, propofol, topiramate, zopiclone, EVT-201, AZD-3043, ganaxolone, NS-11394, arbaclofen, AZD-3355, GS-39783, ADX-71441, ADX-71943, and the like.

[0135]

Examples of the “TRPV1 modulator” include capsaicin, resiniferatoxin, DE-096,
 5 GRC-6211, AMG-8562, JTS-653, SB-705498, A-425619, A-784168, ABT-102, AMG-628, AZD-1386, JNJ-17203212, NGD-8243, PF-3864086, SAR-115740, SB-782443, and the like.

[0136]

Examples of the “endothelin antagonist” include SB-234551, ACT-064992,
 10 ambrisentan, atrasentan, bosentan, clazosentan, darusentan, fandosentan, S-0139, TA-0201, TBC-3711, zibotentan, BMS-509701, PS-433540, and the like.

[0137]

Examples of the “5-HT_{1A} antagonist” include espidolol, lecozotan, lurasidone, E-2110, REC-0206, SB-649915, WAY-426, WF-516, and the like.

15 [0138]

Examples of the “ α_1 agonist” include CM-2236, armodafinil, midodrine, modafinil, and the like.

[0139]

Examples of the “opioid agonist” include morphine, TRK-130, DPI-125, DPI-
 20 3290, fentanyl, LIF-301, loperamide, loperamide oxide, remifentanyl, tapentadol, WY-16225, oxycodone, PTI-202, PTI-721, ADL-5747, ADL-5859, DPI-221, DPI-353, IPP-102199, SN-11, ADL-10-0101, ADL-10-0116, asimadoline, buprenorphine, CR-665, CR-845, eptazocine, nalbuphine, nalfurafine, pentazocine, XEN-0548, W-212393, ZP-120, nalmefene, and the like.

25 [0140]

Examples of the “P₂X antagonist” include A-740003, AZ-11657312, AZD-9056, GSK-1482160, GSK-31481A, and the like.

[0141]

Examples of the “COX inhibitor” include aceclofenac, ST-679, aspirin, bromfenac,
 30 dexketoprofen, flurbiprofen, FYO-750, ibuprofen, ketoprofen, ketorolac, licofelone, lornoxicam, loxoprofen, LT-NS001, diclofenac, mofezolac, nabumetone, naproxen, oxaprozin, piroxicam, pranoprofen, suprofen, tenoxicam, tiaprofenic acid, tolfenamic acid, zaltoprofen, 644784, ABT-963, ajulemic acid, apricoxib, celecoxib, cimicoxib, etoricoxib,

iguratimod, lumiracoxib, meloxicam, nimesulide, parecoxib, RO-26-2198, valdecoxib, and the like.

[0142]

Examples of the “ σ agonist” include ANAVEX-27-1041, PRS-013, SA-4503,
5 ANAVEX-2-73, siramesine, ANAVEX-7-1037, ANAVEX-1-41, and the like.

[0143]

Examples of the “muscarinic agonist” include AC-260584, cevimeline, MCD-386, NGX-267, NGX-292, sabcomeline, pilocarpine, bethanechol, and the like.

[0144]

10 When the compound (I) of the present invention or a pharmaceutically acceptable salt thereof is used in combination with one or more of the above-described agents, the present invention includes at least one administration method selected from 1) to 5) below:

1) simultaneous administration by a combination preparation,

2) simultaneous administration by the same administration pathway as a separate
15 formulation,

3) simultaneous administration by a different administration pathway as a separate formulation,

4) administration at different times by the same administration pathway as a separate formulation, or

20 5) administration at different times by a different administration pathway as a separate formulation.

Further, in the case of administration at different times as a separate formulation as in 4) or 5), the order of administration of the compound (I) of the present invention and the above-described agents is not particularly limited.

25 [0145]

Furthermore, the compound (I) of the present invention or a pharmaceutically acceptable salt thereof can be used appropriately in combination of one or more of the above-described agents to attain an advantageous effect that is equal to or more than an additive effect in prevention or treatment of the above-described diseases. Alternatively,
30 as compared with a case of being used alone, the amount used can be reduced, the side effects of the agent used together can be reduced, or the side effects of the agent used together can be avoided or mitigated.

[0146]

Usage/Dose of Compound (I) of the Present Invention

[0147]

The pharmaceutical of the present invention can be administered systematically or locally, orally or parenterally (nasal, pulmonary, intravenous, rectal, subcutaneous, intramuscular, transdermal routes, and the like).

5 [0148]

When the pharmaceutical composition of the present invention is used for practical treatments, the dose of the compound (I) of the present invention or a pharmaceutically acceptable salt thereof that is the active ingredient is appropriately determined by taking the patient's age, gender, weight, medical condition, degree of the treatment, and the like
10 into consideration. For example, in case of oral administration, administration can be conducted appropriately at a daily dose in the range from about 0.01 to 1000 mg for an adult (as a body weight of 60 kg), and in case of parenteral administration, administration can be conducted appropriately at a daily dose in the range from about 0.001 to 300 mg for an adult in one portion or in several divided portions. In addition, the dose of the
15 compound (I) of the present invention or a pharmaceutically acceptable salt thereof can be reduced according to the amount of the agent other than an EP₁ receptor antagonist.

[0149]

Hereinbelow, the present invention is illustrated in detail with reference to Examples, Reference Examples, and Test Examples, but the scope of the present invention
20 is not limited thereto.

[Examples]

[0150]

In the symbols used in each of Reference Examples, Examples, and Tables, Ref.
25 No. means Reference Example No., Ex. No. means Example No., Strc means a chemical structural formula, Physical data means physical property values, ¹H-NMR means a proton nuclear magnetic resonance spectrum, CDCl₃ means chloroform-d, and DMSO-d₆ means dimethylsulfoxide-d₆. Further, MS means mass spectroscopy, and ESI means measurement by an electrospray ionization method.

30

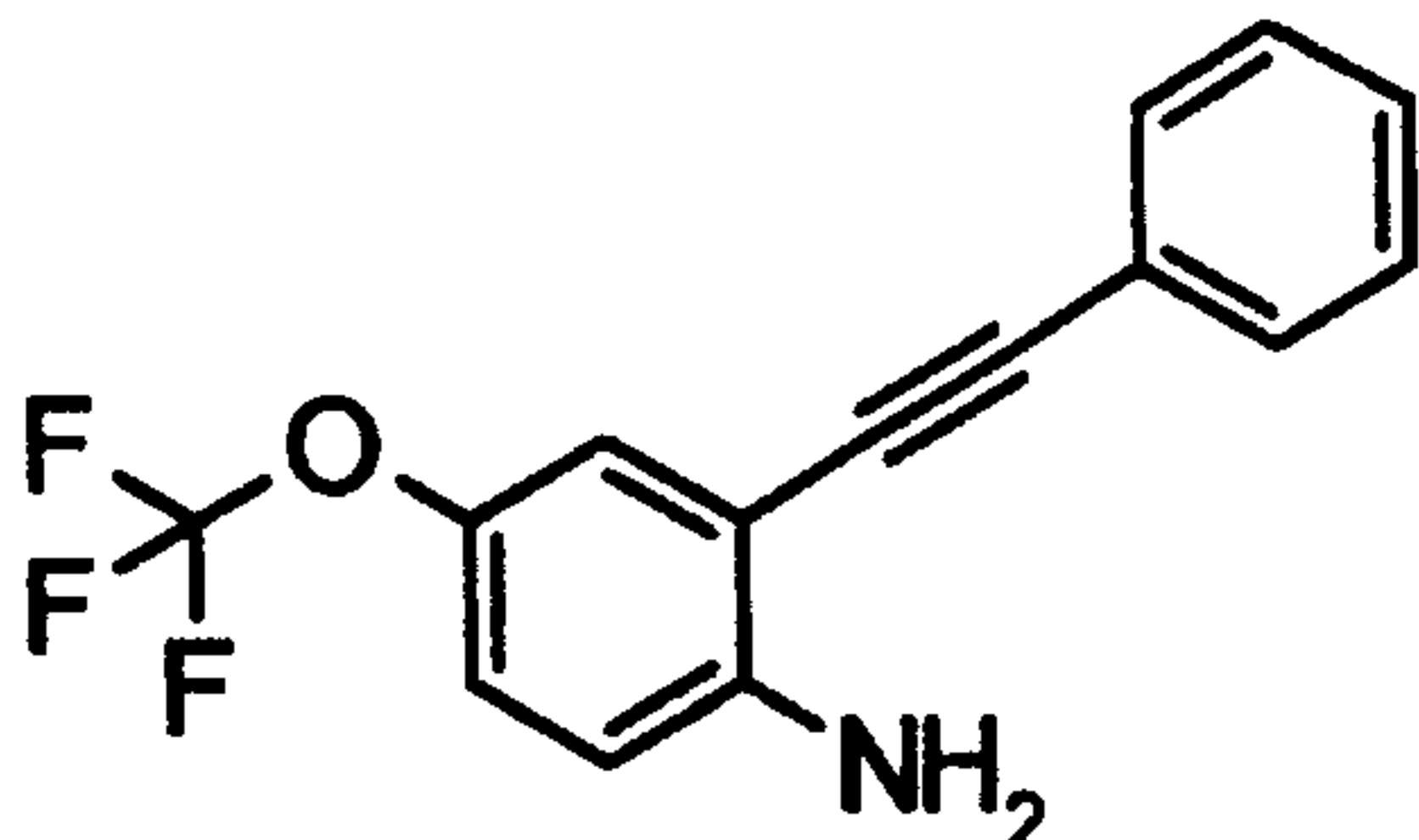
[0151]

Reference Example 1

2-Phenylethynyl-4-trifluoromethoxyaniline

[0152]

[Chem. 19]



[0153]

To a mixture of 2-bromo-4-trifluoromethoxyaniline (0.500g), copper iodide (I)
 5 (18.6mg), bis(triphenylphosphine)palladium (II) dichloride (68.5mg), triethylamine
 (0.817mL) and tetrahydrofuran (7.8mL) was added phenylacetylene (0.279mL) at room
 temperature under stirring, and the mixture was stirred at 80°C for 16 hours. The reaction
 mixture was cooled to room temperature, diluted with diethyl ether (30 mL) and then
 filtered through celite (registered trademark). The filtrate was concentrated under
 10 reduced pressure. The residue was purified by silica gel column chromatography (eluting
 solvent : ethyl acetate-hexane) to obtain the title compound (206mg).

[0154]

¹H-NMR (CDCl₃) δ ppm:

4.32 (2H, br s), 6.70 (1H, d, J=8.8Hz), 6.95-7.10 (1H, m), 7.20-7.30 (1H, m), 7.30-7.45
 15 (3H, m), 7.45-7.60 (2H, m).

[0155]

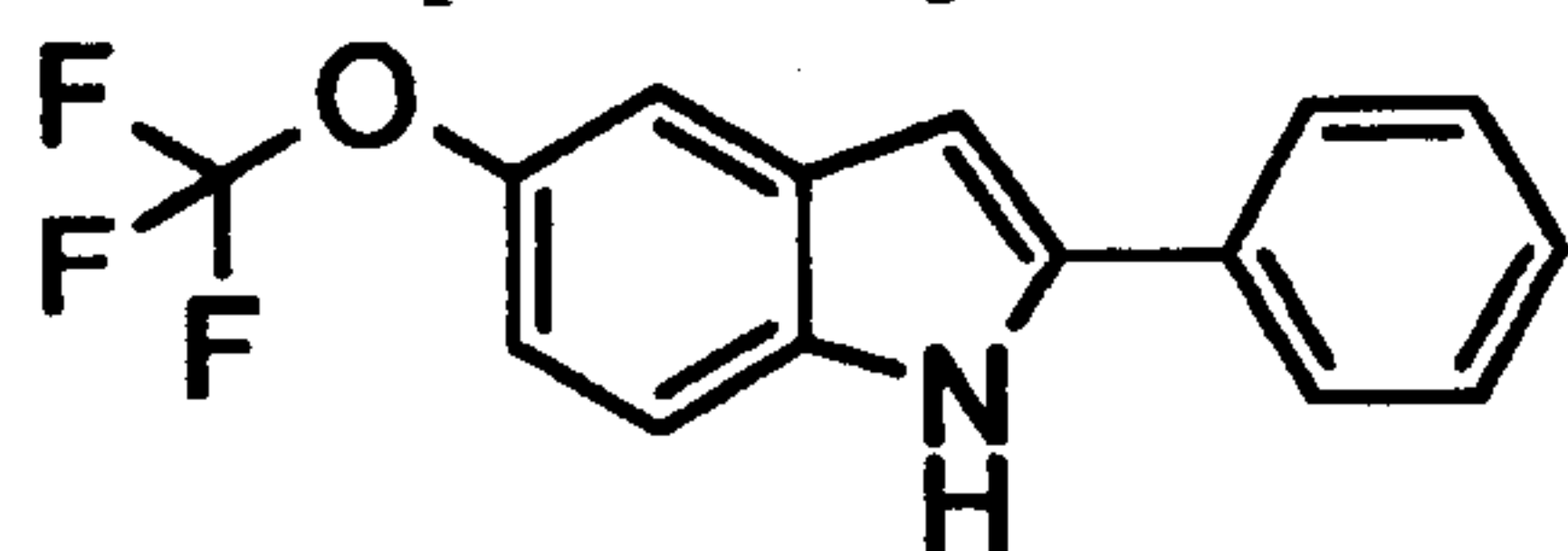
Reference Example 2

2-Phenyl-5-trifluoromethoxyindole

[0156]

20

[Chem. 20]



[0157]

To a solution of potassium *tert*-butoxide (173mg) in 1-methyl-2-pyrrolidone
 (3.7mL) was added dropwise a solution of 2-phenylethynyl-4-trifluoromethoxyaniline
 25 (204mg) in 1-methyl-2-pyrrolidone (3.7mL) at room temperature under stirring, and the
 mixture was stirred for 6 hours. The reaction mixture was diluted with water and
 extracted with ethyl acetate. The organic layer was washed with water, dried over
 anhydrous sodium sulfate and concentrated under reduced pressure. The residue was

purified by silica gel column chromatography (eluting solvent : ethyl acetate-hexane) to obtain the title compound (171mg).

[0158]

¹H-NMR (CDCl₃) δ ppm:

5 6.80-6.90 (1H, m), 7.00-7.15 (1H, m), 7.30-7.55 (5H, m), 7.60-7.75 (2H, m), 8.42 (1H, br s).

[0159]

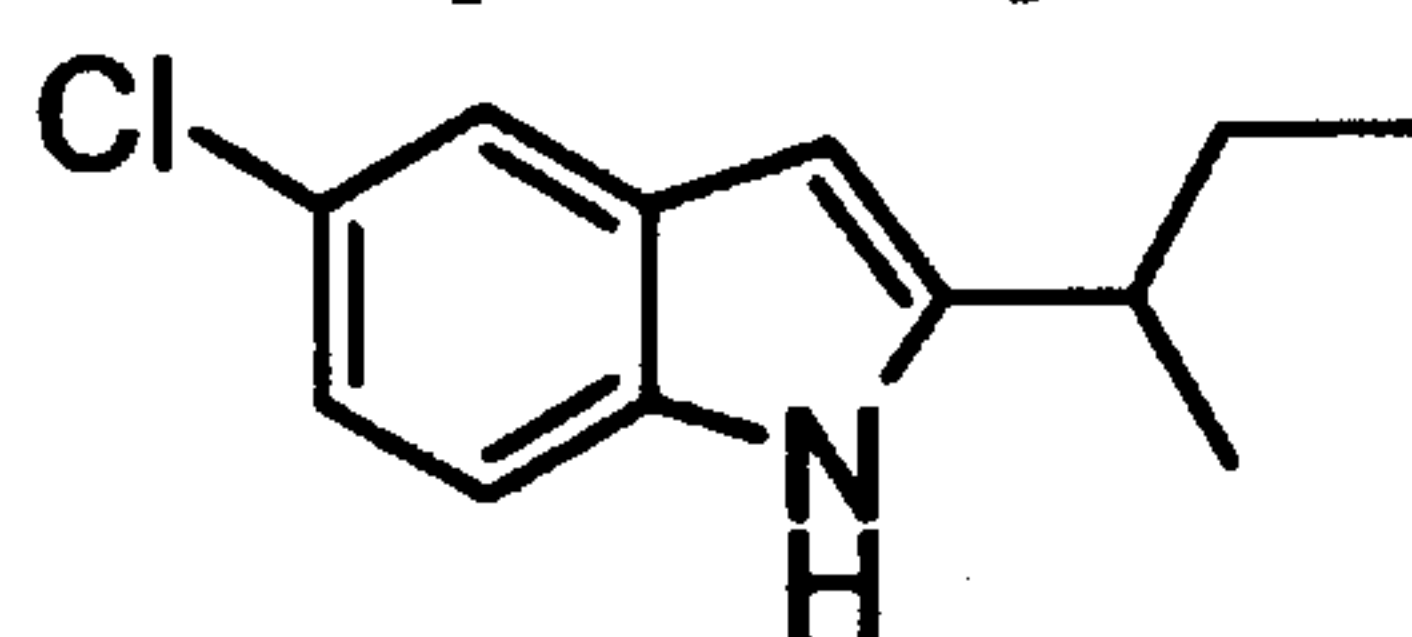
Reference Example 3

5-Chloro-2-(1-methylpropyl)indole

10

[0160]

[Chem. 21]



[0161]

To a solution of *tert*-butyl (4-chloro-2-methylphenyl)carbamate (338mg) in
 15 tetrahydrofuran (6mL) was added dropwise *sec*-butyllithium (1.04mol/L hexane-cyclohexane solution, 2.69mL) at -70°C under an argon atmosphere. The mixture was warmed to -40°C and then stirred for 10 minutes. Then a solution of *N*-methoxy-*N*,2-dimethylbutanamide (203mg) in tetrahydrofuran (0.5mL) was added dropwise, and the mixture was stirred at -40°C for 40 minutes. The mixture was stirred at room temperature
 20 for additional 2 hours. 1mol/L Hydrochloric acid (2.8mL) was added to the reaction mixture under cooling with ice, and this resulting mixture was extracted with diethyl ether. The organic layer was washed with saturated saline, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue (446mg) was dissolved in dichloromethane (4mL). Trifluoroacetic acid (0.8mL) was added and this resulting
 25 mixture was stirred at room temperature for 14 hours. The reaction mixture was diluted with dichloromethane, washed successively with water and a saturated aqueous sodium hydrogen carbonate solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluting solvent : ethyl acetate-hexane) to obtain the title compound (173mg).

30

[0162]

¹H-NMR (CDCl₃) δ ppm:

0.91 (3H, t, J=7.4Hz), 1.33 (3H, d, J=7.0Hz), 1.55-1.80 (2H, m), 2.75-2.90 (1H, m), 6.15-6.25 (1H, m), 7.06 (1H, dd, J=2.0, 8.5Hz), 7.21 (1H, d, J=8.5Hz), 7.45-7.55 (1H, m), 7.90 (1H, br s).

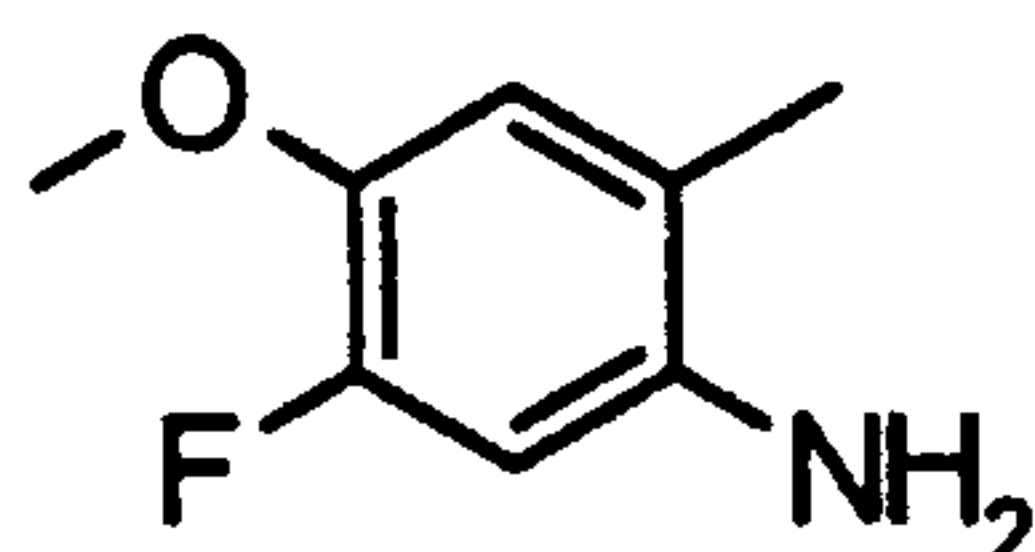
[0163]

5 Reference Example 4

5-Fluoro-4-methoxy-2-methylaniline

[0164]

[Chem. 22]



10 [0165]

To a solution of 2-fluoro-5-methyl-4-nitroanisole (100mg) in tetrahydrofuran-ethanol (1/1, 3mL) was added 10% palladium on carbon powder (56.5wt% aqueous, 30mg) under cooling with ice, and the mixture was stirred at room temperature for 5 hours under a hydrogen atmosphere. The reaction mixture was filtered through celite (registered trademark). The filtrate was concentrated under reduced pressure to obtain the title compound (84.8mg).

[0166]

¹H-NMR (CDCl₃) δ ppm:

2.12 (3H, s), 3.42 (2H, br s), 3.81 (3H, s), 6.46 (1H, d, J=12.5Hz), 6.70 (1H, d, J=9.3Hz).

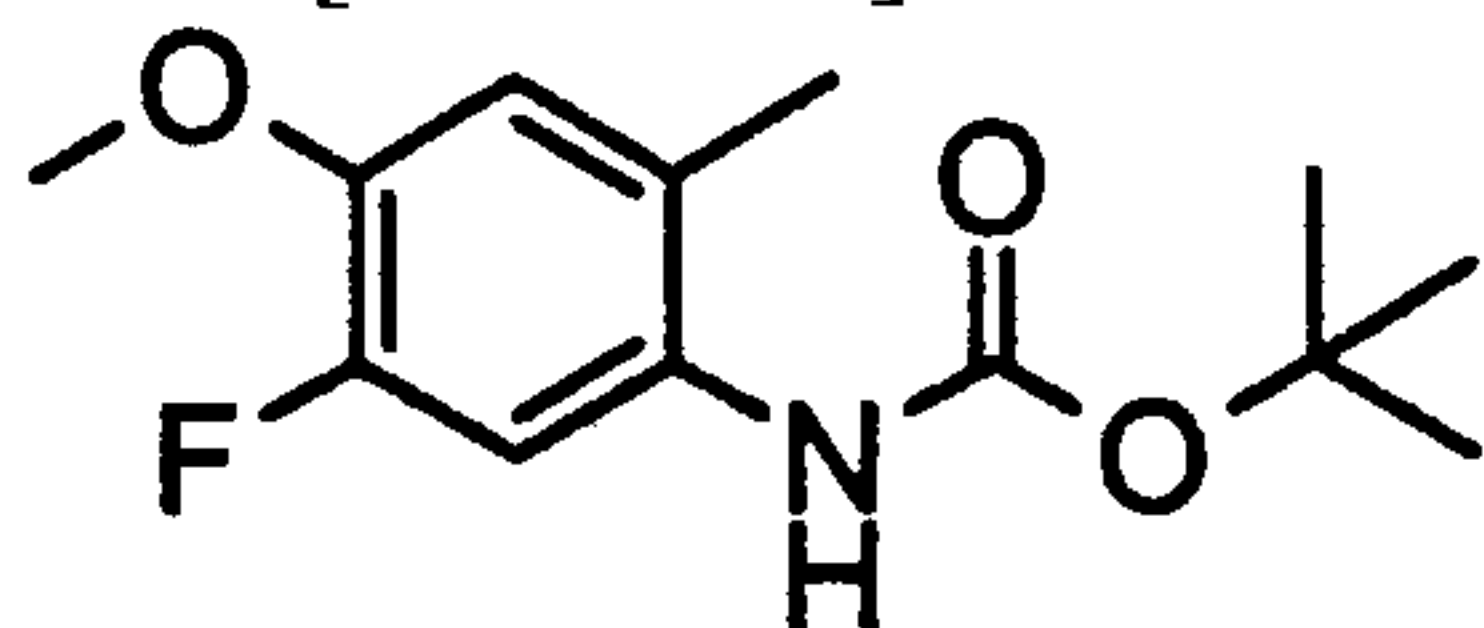
20 [0167]

Reference Example 5

tert-Butyl (5-fluoro-4-methoxy-2-methylphenyl)carbamate

[0168]

[Chem. 23]



25

[0169]

To a solution of 5-fluoro-4-methoxy-2-methylaniline (900mg) in tetrahydrofuran (12mL) was added di-*tert*-butyl dicarbonate (1.27g) at room temperature, and the mixture was stirred overnight at 60°C. The reaction mixture was concentrated under reduced pressure. The residue was purified by aminopropylated silica gel column

30

chromatography (eluting solvent : ethyl acetate-hexane). The fractions of the target were combined and the solvents were evaporated under reduced pressure. Hexane was added to the residue. The precipitate was collected by filtration, washed with hexane and dried under reduced pressure to obtain the title compound (1.24g).

5 [0170]

¹H-NMR (CDCl₃) δ ppm:

1.51 (9H, s), 2.20 (3H, s), 3.85 (3H, s), 6.09 (1H, br s), 6.74 (1H, d, J=9.0Hz), 7.30-7.80 (1H, m).

[0171]

10 Reference Example 6-1

tert-Butyl [4-chloro-2-(4-methyl-2-oxopentyl)phenyl]carbamate

[0172]

To a solution of *tert*-butyl (4-chloro-2-methylphenyl)carbamate (483mg) in tetrahydrofuran (7mL) was added dropwise *sec*-butyllithium (1.04mol/L hexane-cyclohexane solution, 4.3mL) at -40°C under an argon atmosphere, and the mixture was
 15 stirred for 15 minutes. Then a solution of *N*-methoxy-*N*,3-methylbutylamide (319mg) in tetrahydrofuran (1mL) was added dropwise, and the mixture was stirred at -40°C for 15 minutes and at room temperature for 2 hours. Water and 1mol/L hydrochloric acid were added to the reaction mixture and this resulting mixture was extracted with ethyl acetate.
 20 The aqueous layer was extracted once again with ethyl acetate. The combined organic layers were washed with saturated saline, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluting solvent : ethyl acetate-hexane) to obtain the title compound (282mg).

25 In addition, structural formula and spectral data of the title compound were shown in Table 1.

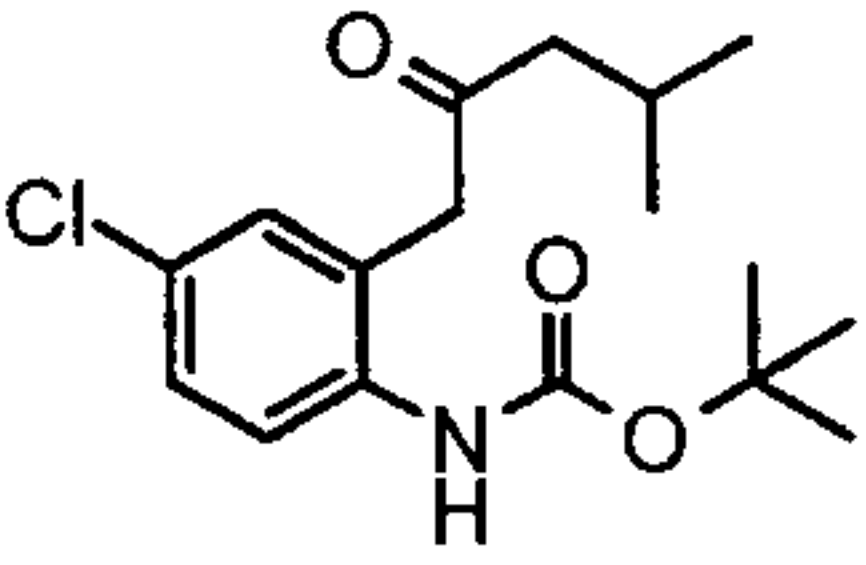
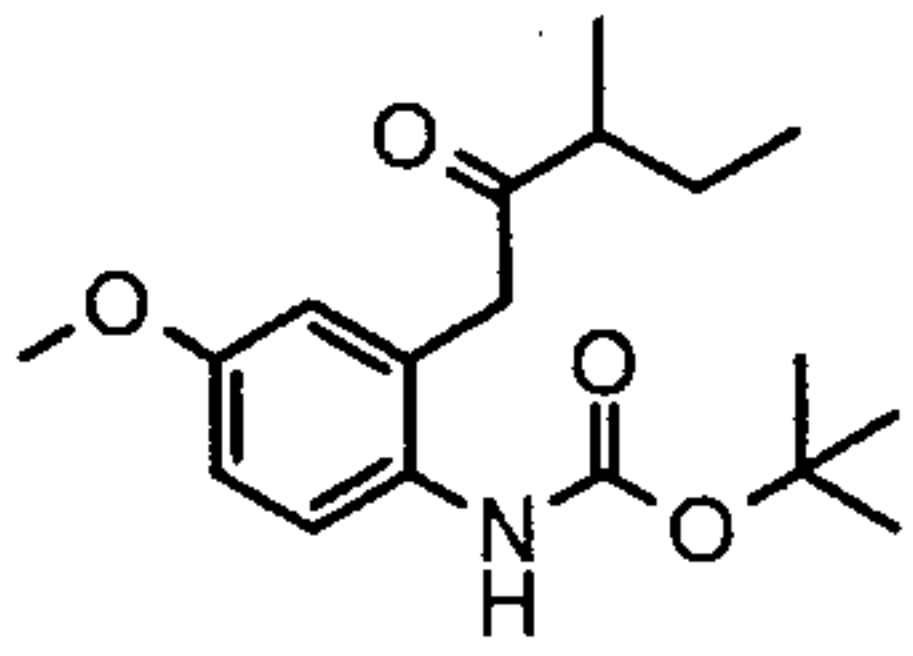
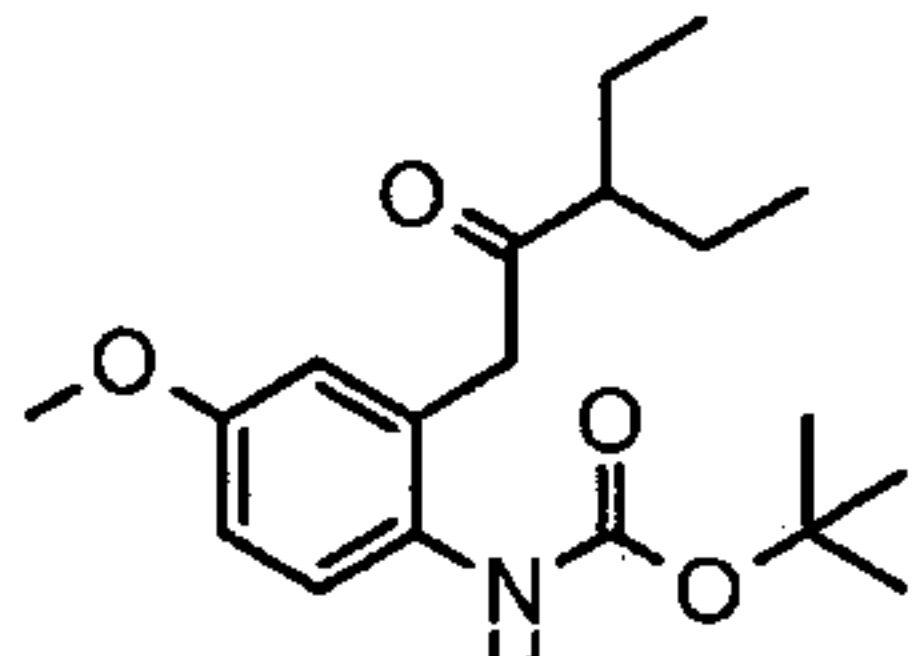
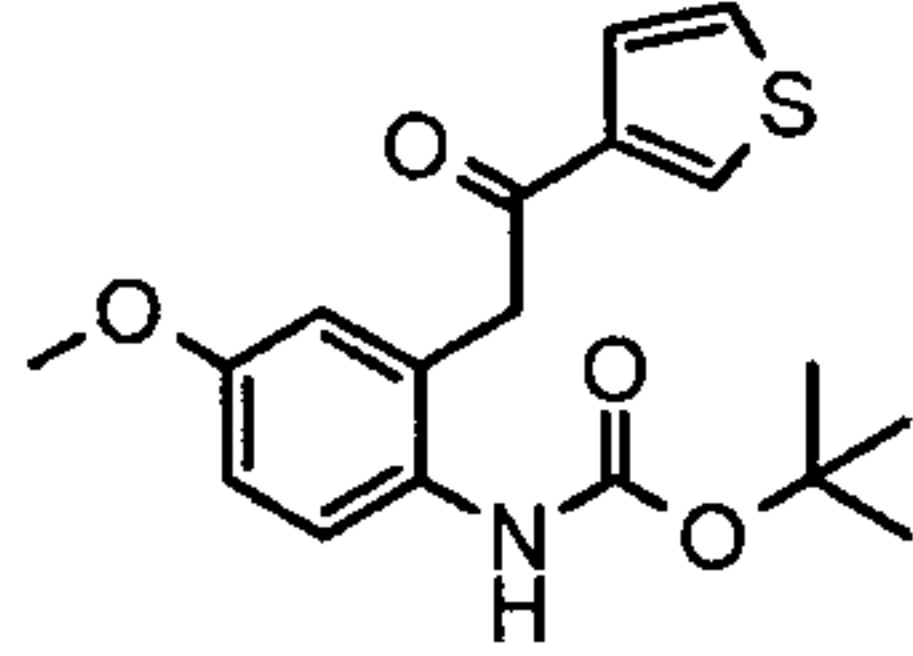
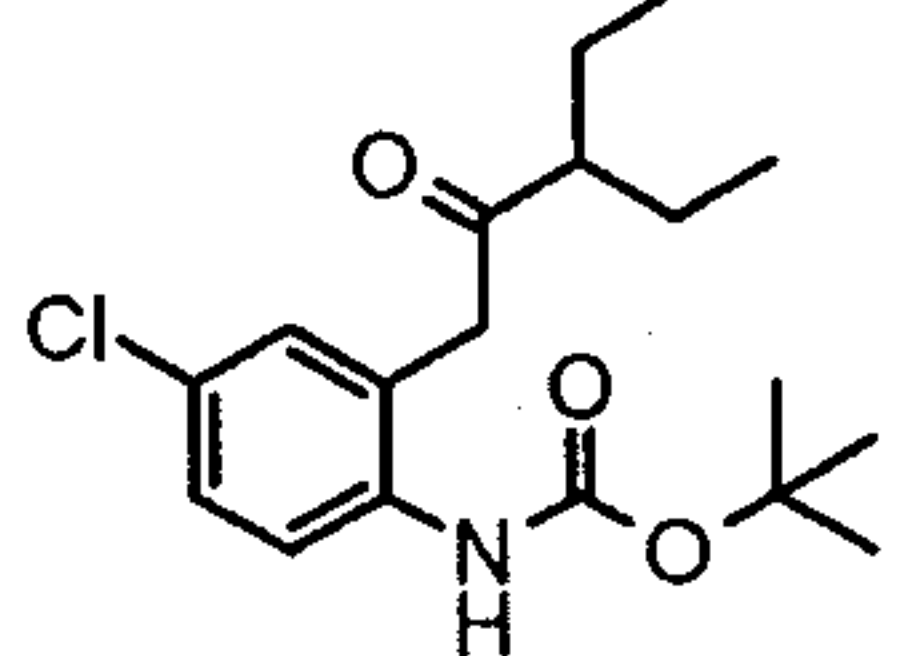
[0173]

Reference Examples 6-2 to 6-8

The compounds shown in Tables 1 to 2 were synthesized in a manner similar to
 30 that of Reference Example 6-1 by using the corresponding starting material and reactants.

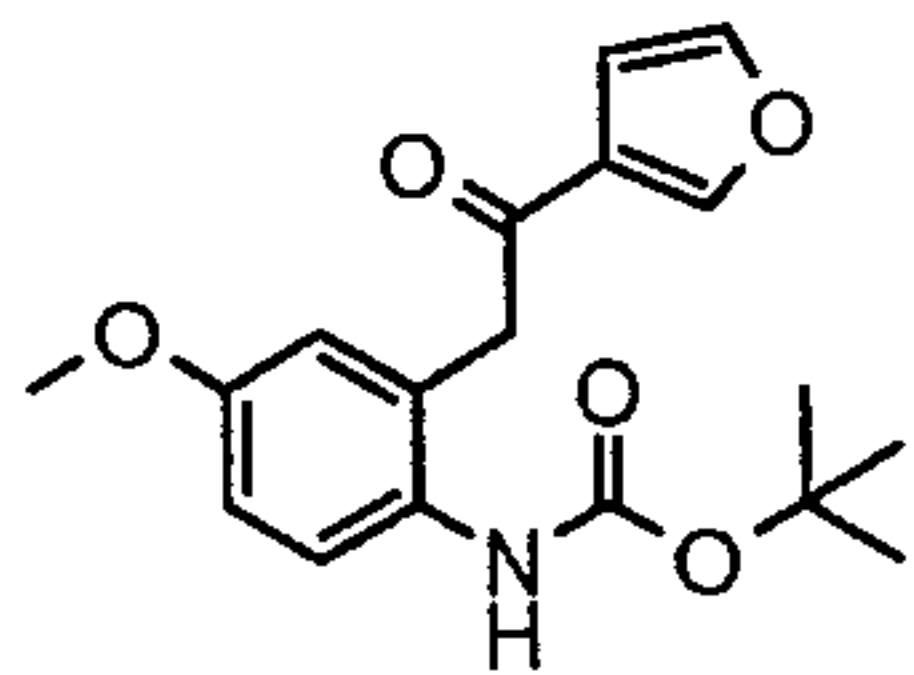
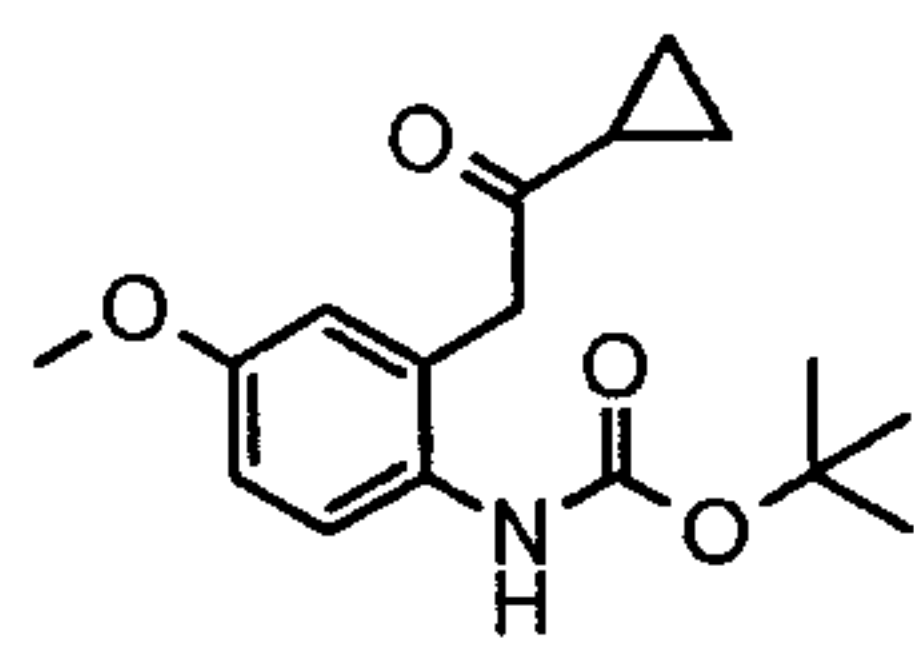
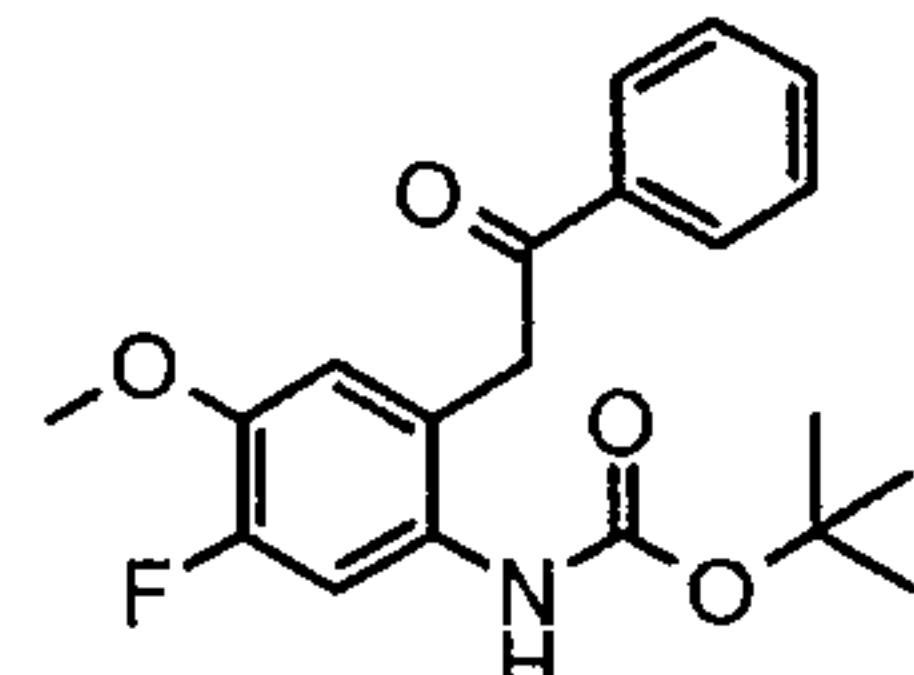
[0174]

[Table 1]

Ref. No.	Strc	Physical data
6-1		¹ H-NMR (CDCl ₃) δ ppm: 0.91 (6H, d, J=6.5Hz), 1.51 (9H, s), 2.05-2.25 (1H, m), 2.45 (2H, d, J=6.8Hz), 3.64 (2H, s), 7.12 (1H, d, J=2.5Hz), 7.23 (1H, dd, J=2.5, 8.8Hz), 7.35-7.90 (2H, m).
6-2		¹ H-NMR (CDCl ₃) δ ppm: 0.86 (3H, t, J=7.5Hz), 1.11 (3H, d, J=6.8Hz), 1.35-1.55 (10H, m), 1.65-1.80 (1H, m), 2.55-2.70 (1H, m), 3.71 (2H, s), 3.77 (3H, s), 6.67 (1H, d, J=3.0Hz), 6.80 (1H, dd, J=3.0, 8.8Hz), 7.11 (1H, br s), 7.40-7.65 (1H, m).
6-3		¹ H-NMR (CDCl ₃) δ ppm: 0.83 (6H, t, J=7.5Hz), 1.40-1.80 (13H, m), 2.45-2.60 (1H, m), 3.70 (2H, s), 3.77 (3H, s), 6.66 (1H, d, J=2.9Hz), 6.81 (1H, dd, J=2.9, 8.8Hz), 7.11 (1H, br s), 7.40-7.65 (1H, m).
6-4		¹ H-NMR (CDCl ₃) δ ppm: 1.49 (9H, s), 3.76 (3H, s), 4.15 (2H, s), 6.74 (1H, d, J=2.9Hz), 6.81 (1H, dd, J=2.9, 8.8Hz), 7.20-7.70 (4H, m), 8.15-8.25 (1H, m).
6-5		¹ H-NMR (CDCl ₃) δ ppm: 0.82 (6H, t, J=7.4Hz), 1.40-1.75 (13H, m), 2.45-2.60 (1H, m), 3.68 (2H, s), 7.10 (1H, d, J=2.5Hz), 7.23 (1H, dd, J=2.5, 8.8Hz), 7.40-7.85 (2H, m).

[0175]

[Table 2]

Ref. No.	Strc	Physical data
6-6		¹ H-NMR (CDCl ₃) δ ppm: 1.50 (9H, s), 3.76 (3H, s), 4.00 (2H, s), 6.71 (1H, d, J=2.8Hz), 6.75-6.85 (2H, m), 7.15-7.70 (3H, m), 8.16 (1H, s).
6-7		¹ H-NMR (CDCl ₃) δ ppm: 0.85-1.00 (2H, m), 1.05-1.15 (2H, m), 1.50 (9H, s), 1.95-2.10 (1H, m), 3.78 (3H, s), 3.80 (2H, s), 6.74 (1H, d, J=2.9Hz), 6.81 (1H, dd, J=2.9, 8.8Hz), 7.00 (1H, br s), 7.40-7.70 (1H, m).
6-8		¹ H-NMR (CDCl ₃) δ ppm: 1.49 (9H, s), 3.83 (3H, s), 4.24 (2H, s), 6.76 (1H, d, J=9.0Hz), 7.40-7.70 (5H, m), 8.00-8.15 (2H, m).

[0176]

Reference Example 7-1

5 5-Chloro-2-isobutylindole

[0177]

To a solution of *tert*-butyl [4-chloro-2-(4-methyl-2-oxopentyl)phenyl]carbamate (280mg) in dichloromethane (4mL) was added trifluoroacetic acid (0.7mL) at room temperature, and the mixture was stirred for 7 hours. The reaction mixture was diluted with ethyl acetate and stopped the reaction by addition of a saturated aqueous sodium hydrogen carbonate solution. The organic layer was washed with saturated saline, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluting solvent : ethyl acetate-hexane) to obtain the title compound (166mg).

15 In addition, structural formula and spectral data of the title compound were shown in Table 3.

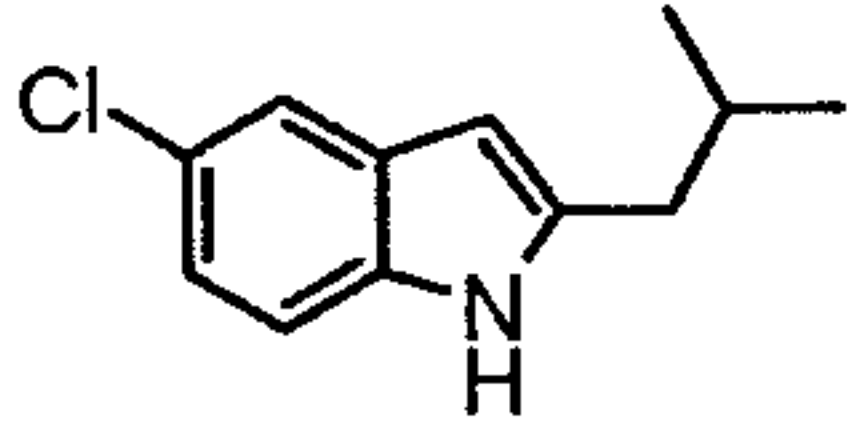
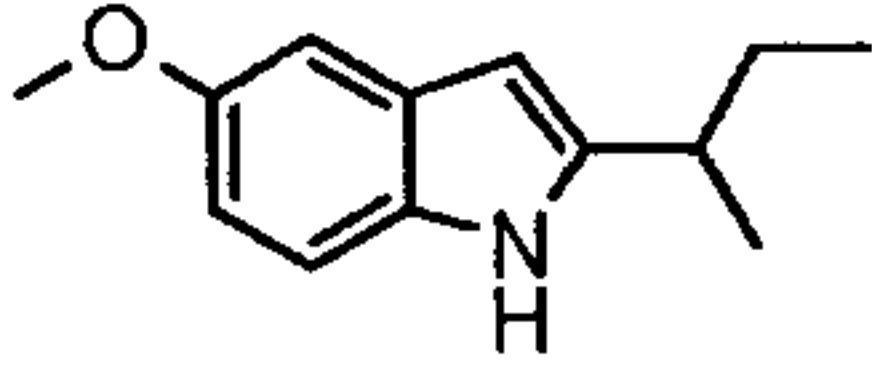
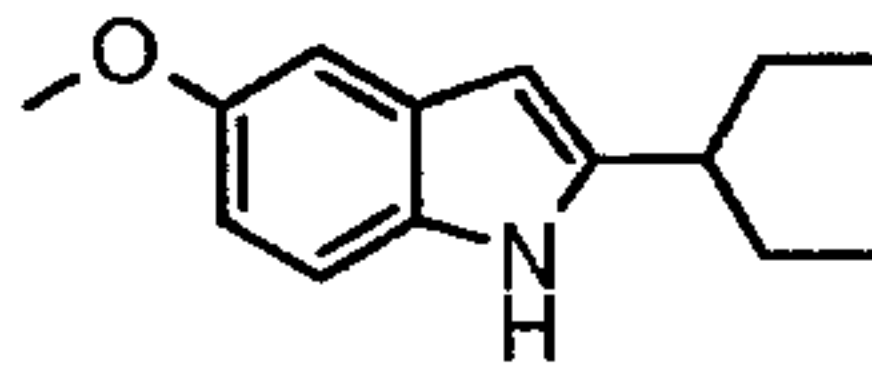
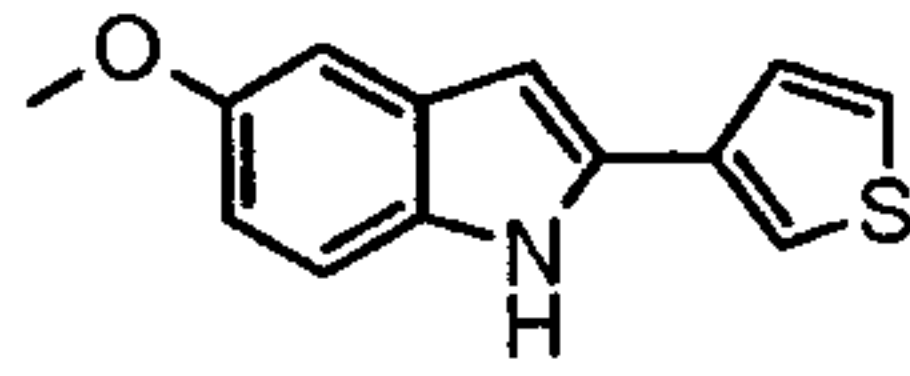
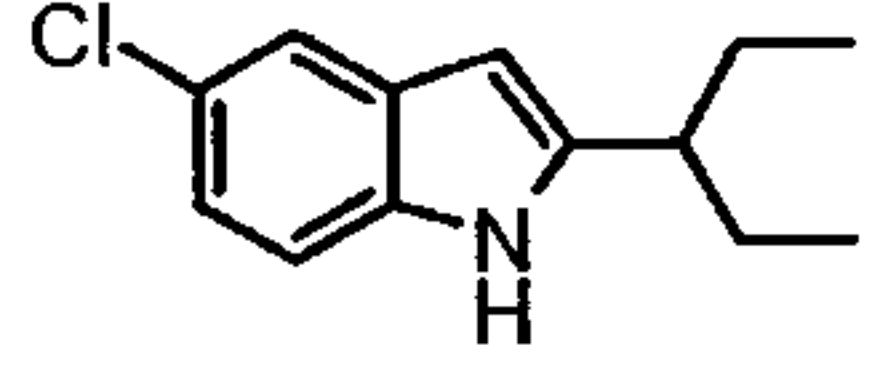
[0178]

Reference Examples 7-2 to 7-8

20 The compounds shown in Tables 3 to 4 were synthesized in a manner similar to that of Reference Example 7-1 by using the corresponding starting material and reactant.

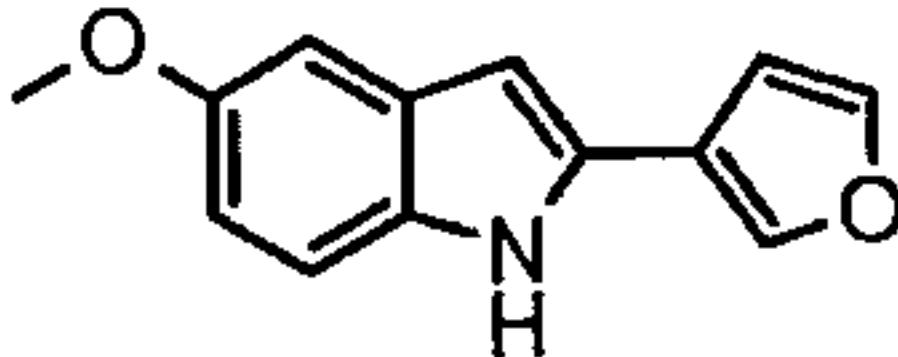
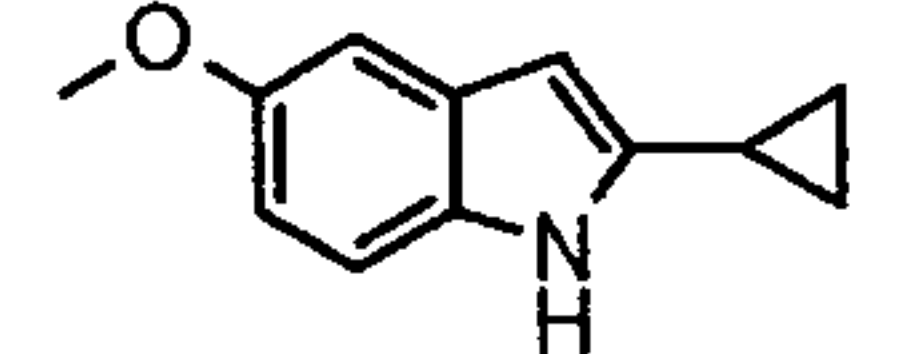
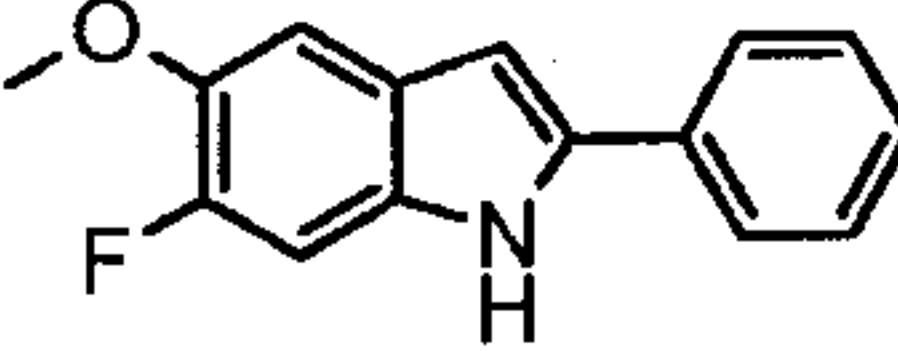
[0179]

[Table 3]

Ref. No.	Struc	Physical data
7-1		¹ H-NMR (CDCl ₃) δ ppm: 0.97 (6H, d, J=6.8Hz), 1.90-2.05 (1H, m), 2.61 (2H, d, J=7.3Hz), 6.15-6.25 (1H, m), 7.06 (1H, dd, J=2.0, 8.5Hz), 7.20 (1H, d, J=8.5Hz), 7.45-7.55 (1H, m), 7.87 (1H, br s).
7-2		¹ H-NMR (CDCl ₃) δ ppm: 0.91 (3H, t, J=7.4Hz), 1.32 (3H, d, J=7.0Hz), 1.55-1.80 (2H, m), 2.75-2.90 (1H, m), 3.84 (3H, s), 6.15-6.20 (1H, m), 6.77 (1H, dd, J=2.4, 8.8Hz), 7.02 (1H, d, J=2.4Hz), 7.19 (1H, d, J=8.8Hz), 7.77 (1H, br s).
7-3		¹ H-NMR (CDCl ₃) δ ppm: 0.86 (6H, t, J=7.4Hz), 1.50-1.85 (4H, m), 2.45-2.65 (1H, m), 3.84 (3H, s), 6.15-6.25 (1H, m), 6.77 (1H, dd, J=2.3, 8.7Hz), 7.02 (1H, d, J=2.3Hz), 7.20 (1H, d, J=8.7Hz), 7.74 (1H, br s).
7-4		¹ H-NMR (CDCl ₃) δ ppm: 3.86 (3H, s), 6.60-6.70 (1H, m), 6.85 (1H, dd, J=2.4, 8.8Hz), 7.07 (1H, d, J=2.4Hz), 7.00-7.10 (1H, m), 7.20-7.35 (1H, m), 7.35-7.45 (3H, m), 8.11 (1H, br s).
7-5		¹ H-NMR (CDCl ₃) δ ppm: 0.86 (6H, t, J=7.4Hz), 1.50-1.85 (4H, m), 2.45-2.65 (1H, m), 6.15-6.25 (1H, m), 7.06 (1H, dd, J=2.0, 8.6Hz), 7.21 (1H, d, J=8.6Hz), 7.49 (1H, d, J=2.0Hz), 7.86 (1H, br s).

[0180]

[Table 4]

Ref. No.	Strc	Physical data
7-6		¹ H-NMR (CDCl ₃) δ ppm: 3.86 (3H, s), 6.50–6.60 (1H, m), 6.65–6.75 (1H, m), 6.83 (1H, dd, J=2.4, 8.7Hz), 7.05 (1H, d, J=2.4Hz), 7.20–7.30 (1H, m), 7.45–7.55 (1H, m), 7.70–7.80 (1H, m), 7.98 (1H, br s).
7-7		¹ H-NMR (CDCl ₃) δ ppm: 0.70–0.80 (2H, m), 0.90–1.00 (2H, m), 1.90–2.00 (1H, m), 3.83 (3H, s), 6.05–6.15 (1H, m), 6.76 (1H, dd, J=2.4, 8.7Hz), 6.98 (1H, d, J=2.4Hz), 7.16 (1H, d, J=8.7Hz), 7.81 (1H, br s).
7-8		¹ H-NMR (CDCl ₃) δ ppm: 3.94 (3H, s), 6.70–6.80 (1H, m), 7.10–7.20 (2H, m), 7.25–7.50 (3H, m), 7.55–7.70 (2H, m), 8.23 (1H, br s).

[0181]

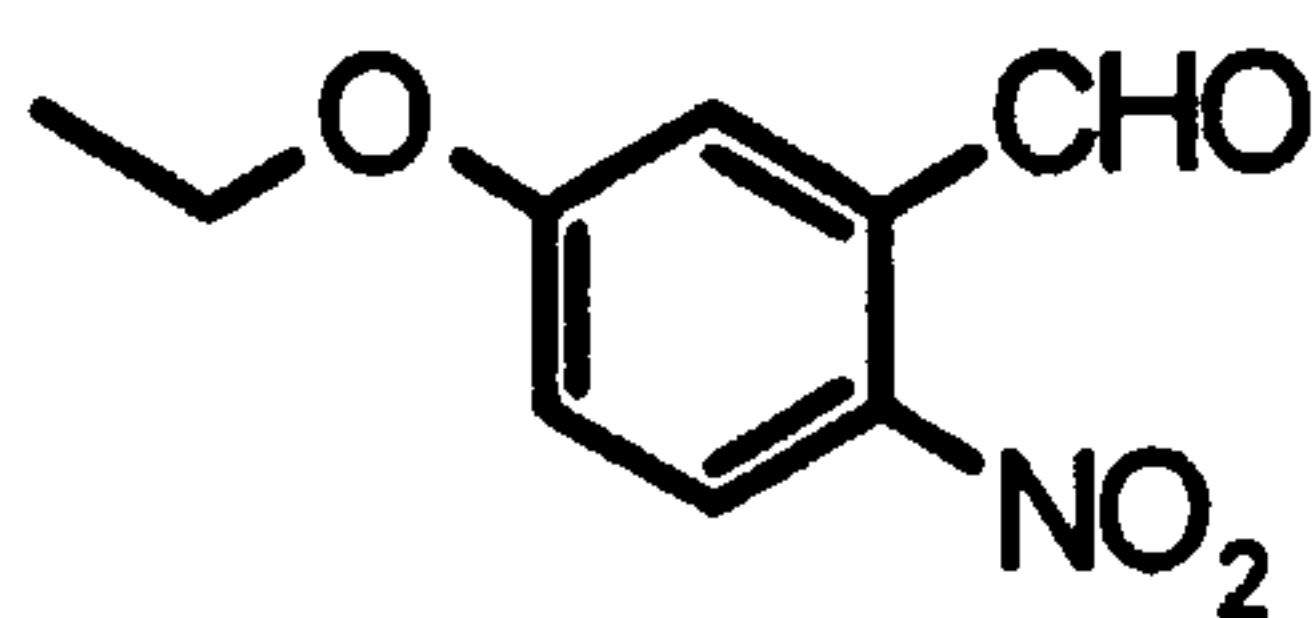
Reference Example 8

5-Ethoxy-2-nitrobenzaldehyde

5

[0182]

[Chem. 24]



[0183]

To a suspension of 5-hydroxy-2-nitrobenzaldehyde (500mg) and cesium carbonate (1.46g) in *N,N*-dimethylformamide (10mL) was added ethyl iodide (0.265mL) at room temperature, and the mixture was stirred for 2 days. Water was added to the reaction mixture and this resulting mixture was extracted with ethyl acetate. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with water and saturated saline, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluting solvent : ethyl acetate-hexane) to obtain the title compound (519mg).

10

15

[0184]

¹H-NMR (CDCl₃) δ ppm:

1.48 (3H, t, J=7.0Hz), 4.18 (2H, q, J=7.0Hz), 7.13 (1H, dd, J=2.9, 9.1Hz), 7.31 (1H, d, J=2.9Hz), 8.16 (1H, d, J=9.1Hz), 10.49 (1H, s).

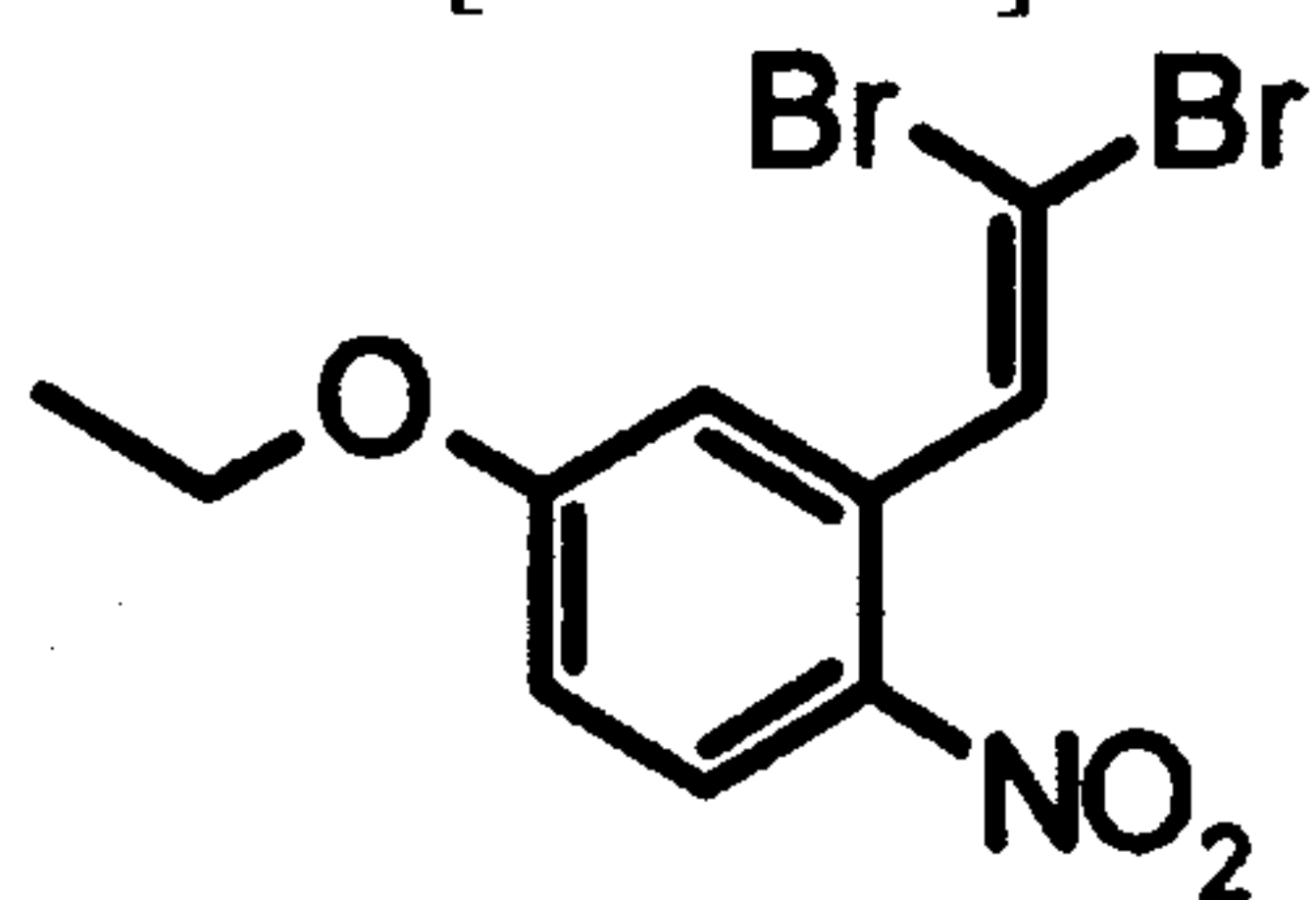
[0185]

5 Reference Example 9

2-(2,2-Dibromovinyl)-4-ethoxynitrobenzene

[0186]

[Chem. 25]



10 [0187]

To a solution of 5-ethoxy-2-nitrobenzaldehyde (519mg) and triphenylphosphine (2.09g) in dichloromethane (13mL) was added a solution of carbon tetrabromide (1.32g) in dichloromethane in three minutes under cooling with ice, and the mixture was stirred overnight at room temperature. Hexane (20 mL) was added to the reaction mixture, and this resulting mixture was stirred for 10 minutes and then filtered through silica gel. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluting solvent : ethyl acetate-hexane) to obtain the title compound (712mg).

[0188]

20 ¹H-NMR (CDCl₃) δ ppm:

1.47 (3H, t, J=6.9Hz), 4.15 (2H, q, J=6.9Hz), 6.90-7.05 (2H, m), 7.80 (1H, s), 8.17 (1H, d, J=9.1Hz).

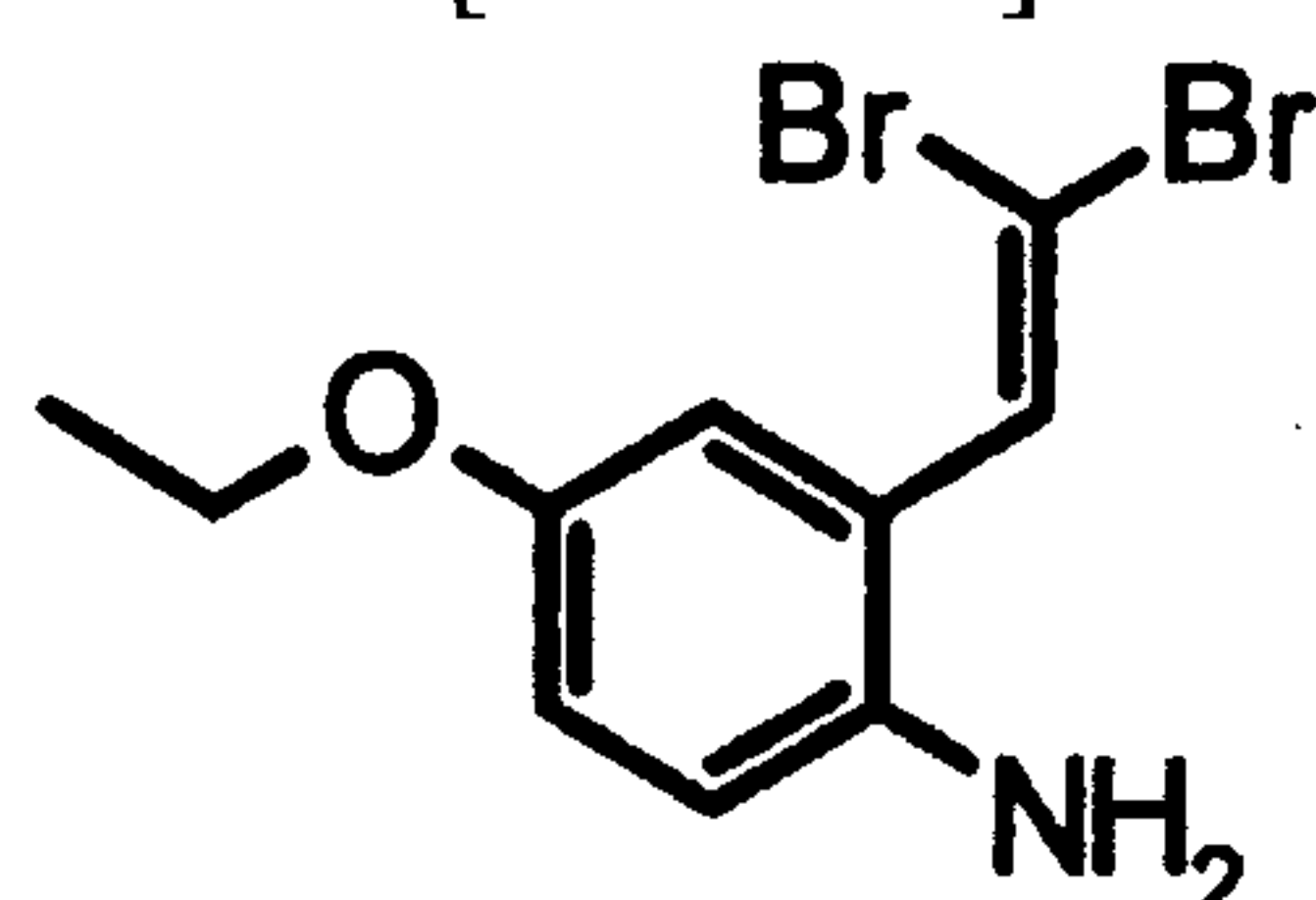
[0189]

Reference Example 10

25 2-(2,2-Dibromovinyl)-4-ethoxyaniline

[0190]

[Chem. 26]



[0191]

To a suspension of 2-(2,2-dibromovinyl)-4-ethoxynitrobenzene (200mg) in methanol (3mL) was added 1% platinum on activated carbon (vanadium doped, 50% hydrous, 27.5mg) at room temperature, and the mixture was stirred for six and a half hours under a hydrogen atmosphere. 1% Platinum on activated carbon (vanadium doped, 50% hydrous, 27.5mg) was added, and the mixture was stirred for additional one hour under a hydrogen atmosphere. The reaction mixture was filtered through celite (registered trademark) and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluting solvent : ethyl acetate-hexane) to obtain the title compound (155mg).

[0192]

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.38 (3H, t, $J=7.0\text{Hz}$), 3.44 (2H, br s), 3.97 (2H, q, $J=7.0\text{Hz}$), 6.55-7.00 (3H, m), 7.34 (1H, s).

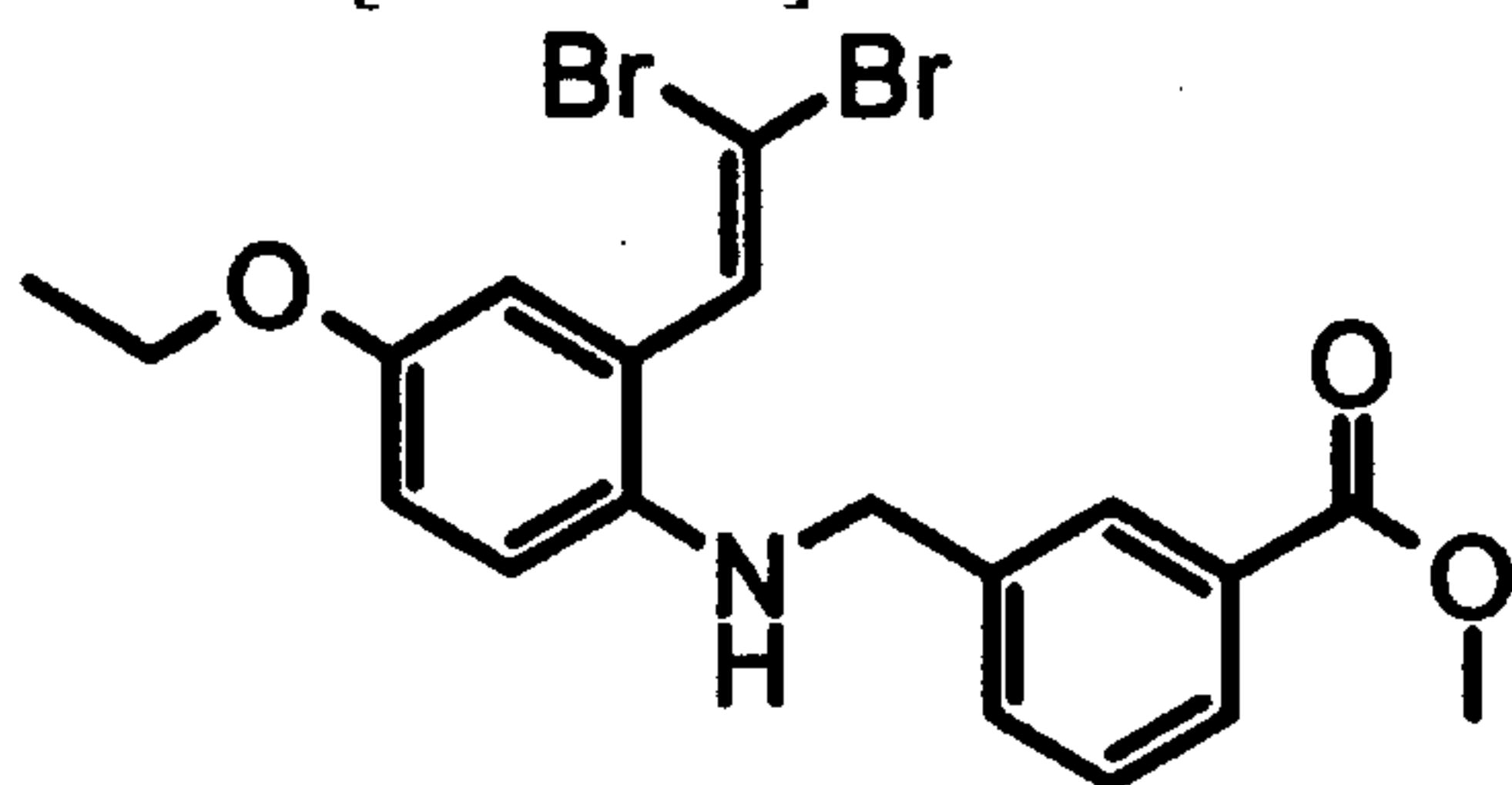
[0193]

Reference Example 11

Methyl 3-{[2-(2,2-dibromovinyl)-4-ethoxyphenylamino]methyl}benzoate

[0194]

[Chem. 27]



[0195]

A suspension of 2-(2,2-dibromovinyl)-4-ethoxyaniline (240mg), methyl 3-(bromomethyl)benzoate (180 mg) and potassium carbonate (124 mg) in *N,N*-dimethylformamide (2mL) was stirred overnight at room temperature. Water was added to the reaction mixture and this resulting mixture was extracted with ethyl acetate. The organic layer was washed with saturated saline, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluting solvent : ethyl acetate-hexane) to obtain the title compound (258mg).

[0196]

¹H-NMR (CDCl₃) δ ppm:

1.37 (3H, t, J=6.9Hz), 3.70-3.85 (1H, m), 3.85-4.05 (5H, m), 4.38 (2H, d, J=5.5Hz), 6.52 (1H, d, J=8.8Hz), 6.70-6.85 (1H, m), 6.90-7.00 (1H, m), 7.34 (1H, s), 7.35-7.50 (1H, m), 7.50-7.65 (1H, m), 7.90-8.15 (2H, m).

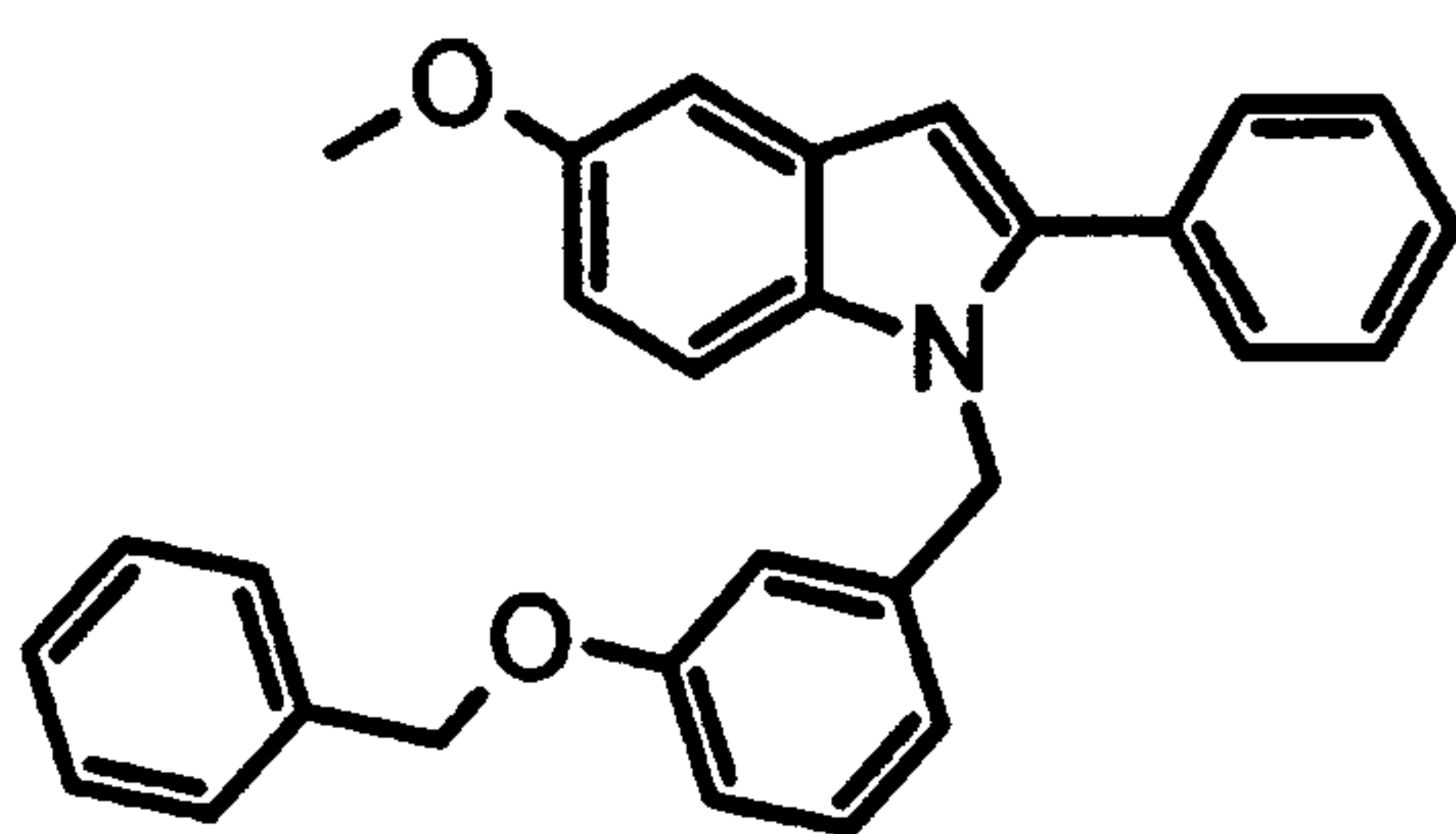
5 [0197]

Reference Example 12

1-(3-Benzyloxybenzyl)-5-methoxy-2-phenylindole

[0198]

[Chem. 28]



10

[0199]

To a solution of 5-methoxy-2-phenylindole (245mg) in *N,N*-dimethylformamide (4.5mL) was added sodium hydride (dispersed in liquid paraffin, minimum 55%, 72 mg) under cooling with ice, and the mixture was stirred at room temperature for 75 minutes.

15 Then a solution of 3-(benzyloxy)benzyl bromide (365mg) in *N,N*-dimethylformamide (1mL) was added dropwise, and the mixture was stirred at 80°C for 15 hours. The reaction mixture was cooled to room temperature. A saturated aqueous ammonium chloride solution-water (2/1) were added and this resulting mixture was extracted with ethyl acetate. The organic layer was washed with saturated saline, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by

20 aminopropylated silica gel column chromatography to obtain the title compound (202mg).

[0200]

¹H-NMR (CDCl₃) δ ppm:

3.87 (3H, s), 4.94 (2H, s), 5.29 (2H, s), 6.55-6.60 (1H, m), 6.60-6.70 (2H, m), 6.75-6.90 (2H, m), 7.06 (1H, d, J=8.8Hz), 7.13 (1H, d, J=2.3Hz), 7.19 (1H, t, J=8.0Hz), 7.25-7.50 (10H, m).

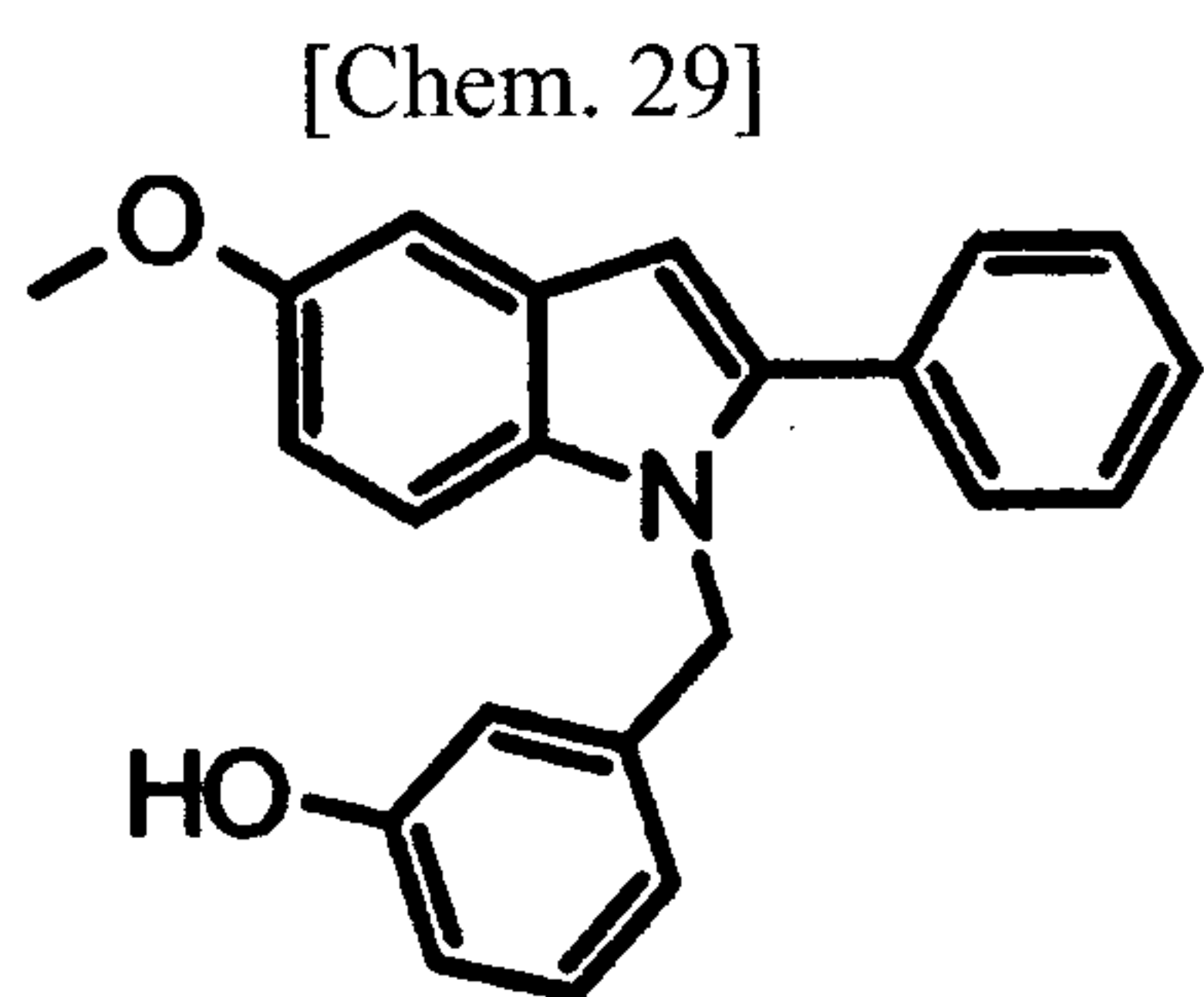
25

[0201]

Reference Example 13

1-(3-Hydroxybenzyl)-5-methoxy-2-phenylindole

30 [0202]



[0203]

1-(3-Benzyloxybenzyl)-5-methoxy-2-phenylindole (200mg) was dissolved in
 5 trifluoroacetic acid-water-dimethyl sulfide (95/5/10, 4.8mL), and the solution was stirred at
 room temperature for 68 hours. The reaction mixture was concentrated under reduced
 pressure. The residue was dissolved in ethyl acetate. The solution was washed
 successively with a saturated aqueous sodium hydrogen carbonate solution and saturated
 saline, dried over anhydrous sodium sulfate and concentrated under reduced pressure.
 10 The residue was purified by silica gel column chromatography (eluting solvent : ethyl
 acetate-hexane) to obtain the title compound (110mg).

[0204]

¹H-NMR (CDCl₃) δ ppm:

3.87 (3H, s), 4.71 (1H, s), 5.28 (2H, s), 6.40-6.50 (1H, m), 6.55-6.60 (1H, m), 6.60-6.75
 15 (2H, m), 6.81 (1H, dd, J=2.5, 8.9Hz), 7.07 (1H, d, J=8.9Hz), 7.10-7.20 (2H, m), 7.30-7.50
 (5H, m).

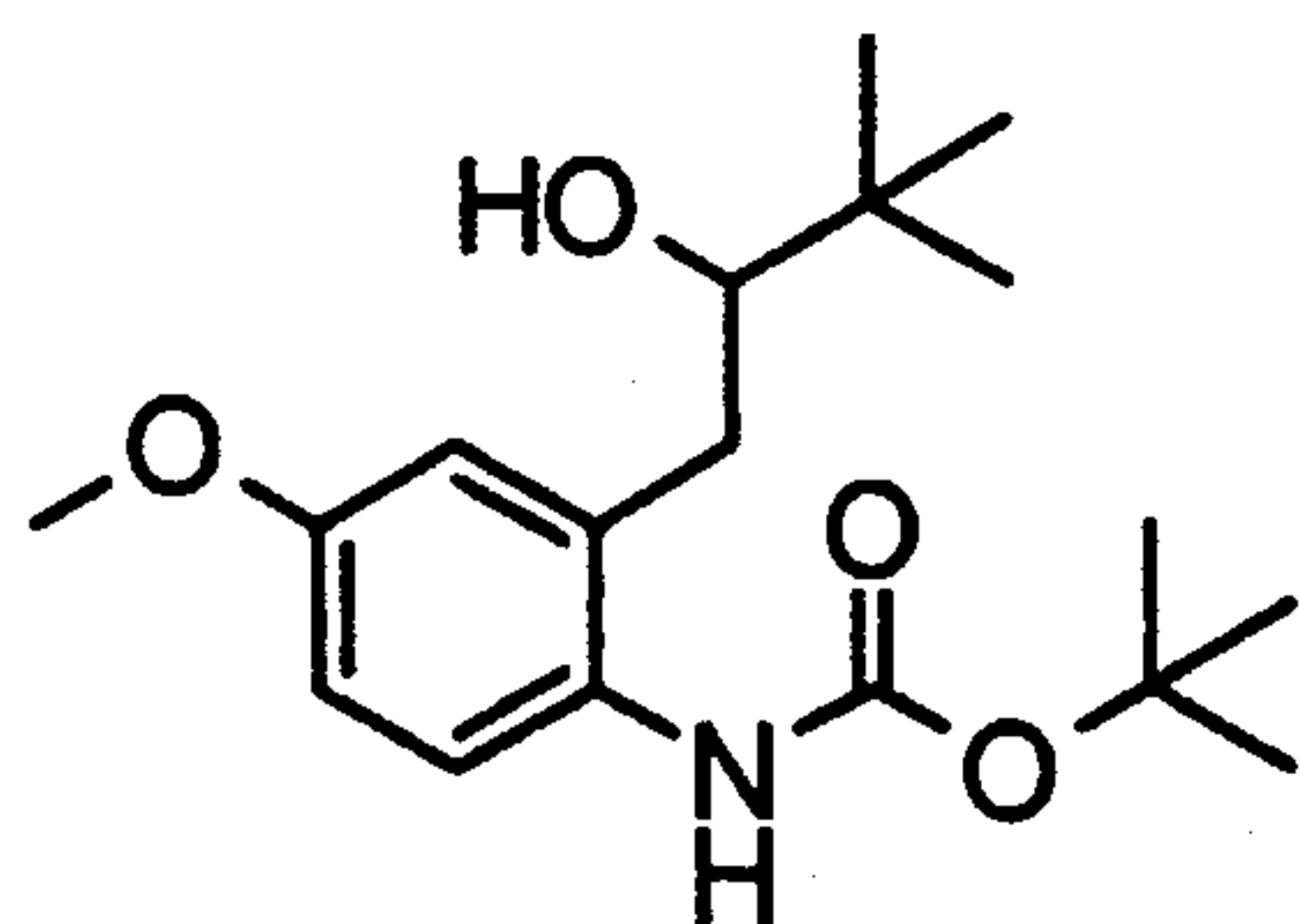
[0205]

Reference Example 14

tert-Butyl [4-methoxy-2-(2-hydroxy-3,3-dimethylbutyl)phenyl]carbamate

[0206]

[Chem. 30]



[0207]

To a solution of *tert*-butyl (4-methoxy-2-methylphenyl)carbamate (475mg) in
 25 tetrahydrofuran (7mL) was added dropwise *sec*-butyllithium (1.04mol/L hexane-
 cyclohexane solution, 4.3mL) at -40°C under an argon atmosphere, and the mixture was

stirred for 15 minutes. Then a solution of trimethylacetaldehyde (0.287mL) in tetrahydrofuran (1mL) was added dropwise, and the mixture was stirred at -40°C for 15 minutes and at room temperature for additional one hour. Water and 1mol/L hydrochloric acid were added to the reaction mixture and this resulting mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated saline, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluting solvent : ethyl acetate-hexane) to obtain the title compound (234mg).

[0208]

10 ¹H-NMR (CDCl₃) δ ppm:

1.00 (9H, s), 1.50 (9H, s), 1.90-2.20 (1H, br), 2.55-2.75 (2H, m), 3.35-3.50 (1H, m), 3.78 (3H, s), 6.65-6.80 (2H, m), 7.20-7.60 (2H, m).

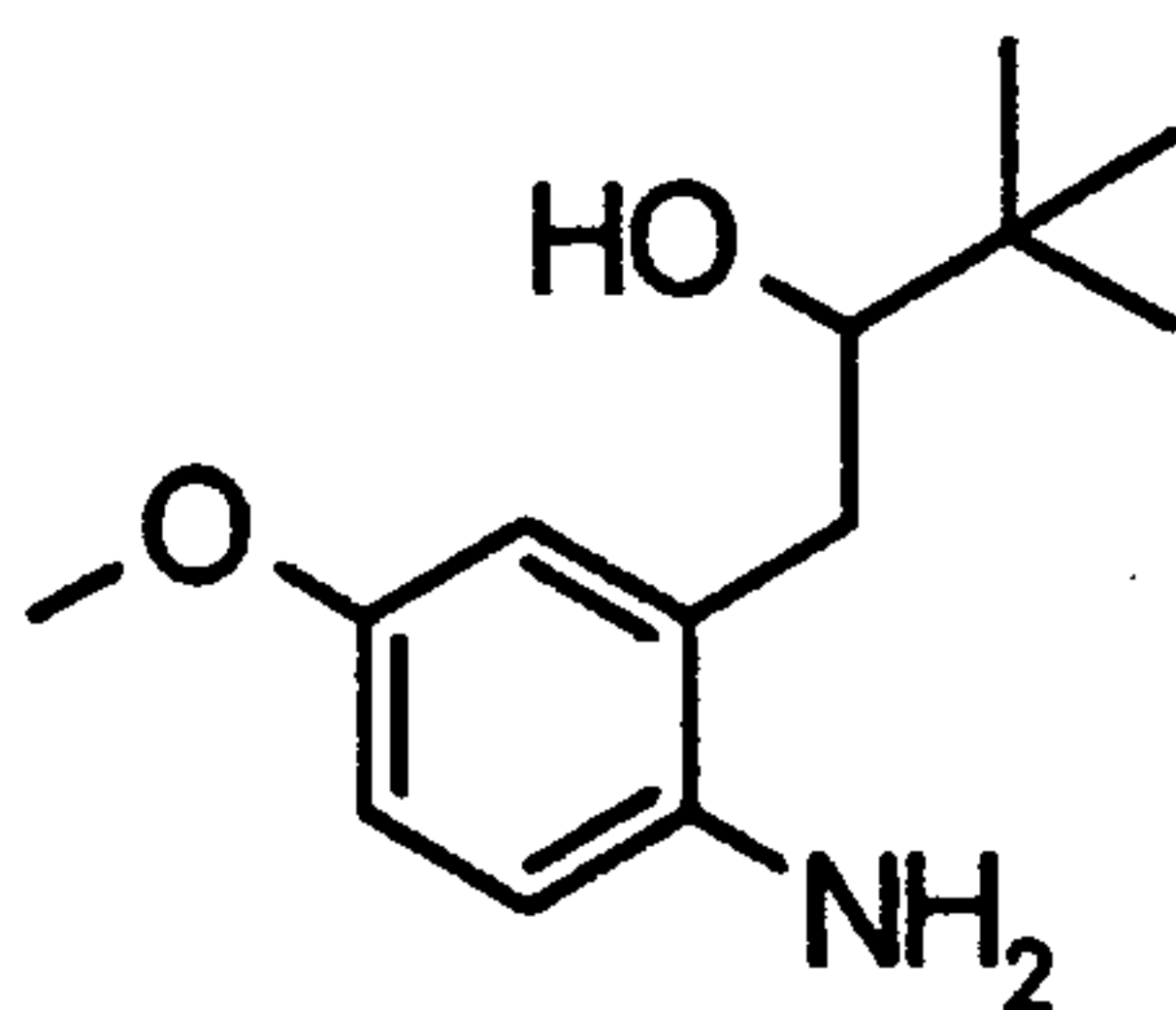
[0209]

Reference Example 15

15 1-(2-Amino-5-methoxyphenyl)-3,3-dimethylbutan-2-ol

[0210]

[Chem. 31]



[0211]

20 To a solution of *tert*-butyl [4-methoxy-2-(2-hydroxy-3,3-dimethylbutyl)phenyl]carbamate (234mg) in dichloromethane (2mL) was added trifluoroacetic acid (1mL) at room temperature, and the mixture was stirred for one hour. The reaction mixture was poured into 5% aqueous sodium hydrogen carbonate solution (40mL) and extracted with ethyl acetate. The organic layer was washed with saturated saline, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to obtain the title compound (157mg).

[0212]

¹H-NMR (CDCl₃) δ ppm:

1.01 (9H, s), 2.40-3.70 (5H, m), 3.75 (3H, s), 6.60-6.70 (3H, m).

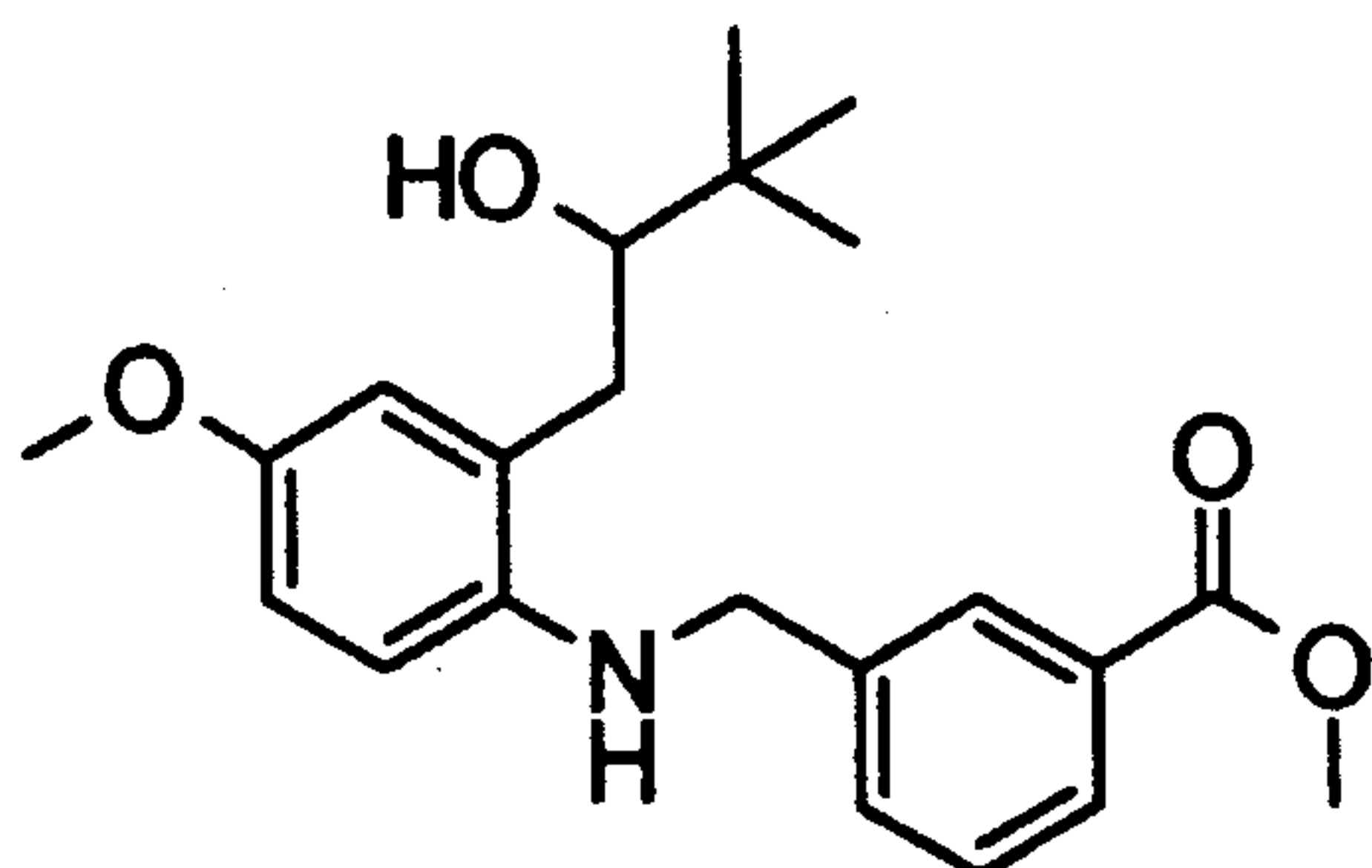
30 [0213]

Reference Example 16

Methyl 3-{[2-(2-hydroxy-3,3-dimethylbutyl)-4-methoxyphenylamino]methyl}benzoate

[0214]

[Chem. 32]



5

[0215]

To a solution of 1-(2-amino-5-methoxyphenyl)-3,3-dimethylbutan-2-ol (155mg) and methyl 3-formylbenzoate (137mg) in acetic acid (2mL) was added sodium triacetoxyborohydride (294mg) at room temperature, and the mixture was stirred for one hour. The reaction mixture was diluted with ethyl acetate and washed with 5% aqueous sodium hydrogen carbonate solution. The organic layer was washed with saturated saline, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluting solvent : ethyl acetate-hexane) to obtain the title compound (205mg).

10

[0216]

¹H-NMR (CDCl₃) δ ppm:

1.00 (9H, s), 2.60-2.75 (2H, m), 3.40-3.55 (1H, m), 3.74 (3H, s), 3.91 (3H, s), 4.25-4.40 (2H, m), 6.56 (1H, d, J=8.5Hz), 6.60-6.75 (2H, m), 7.40 (1H, t, J=7.7Hz), 7.55-7.65 (1H, m), 7.90-8.00 (1H, m), 8.05-8.15 (1H, m).

15

[0217]

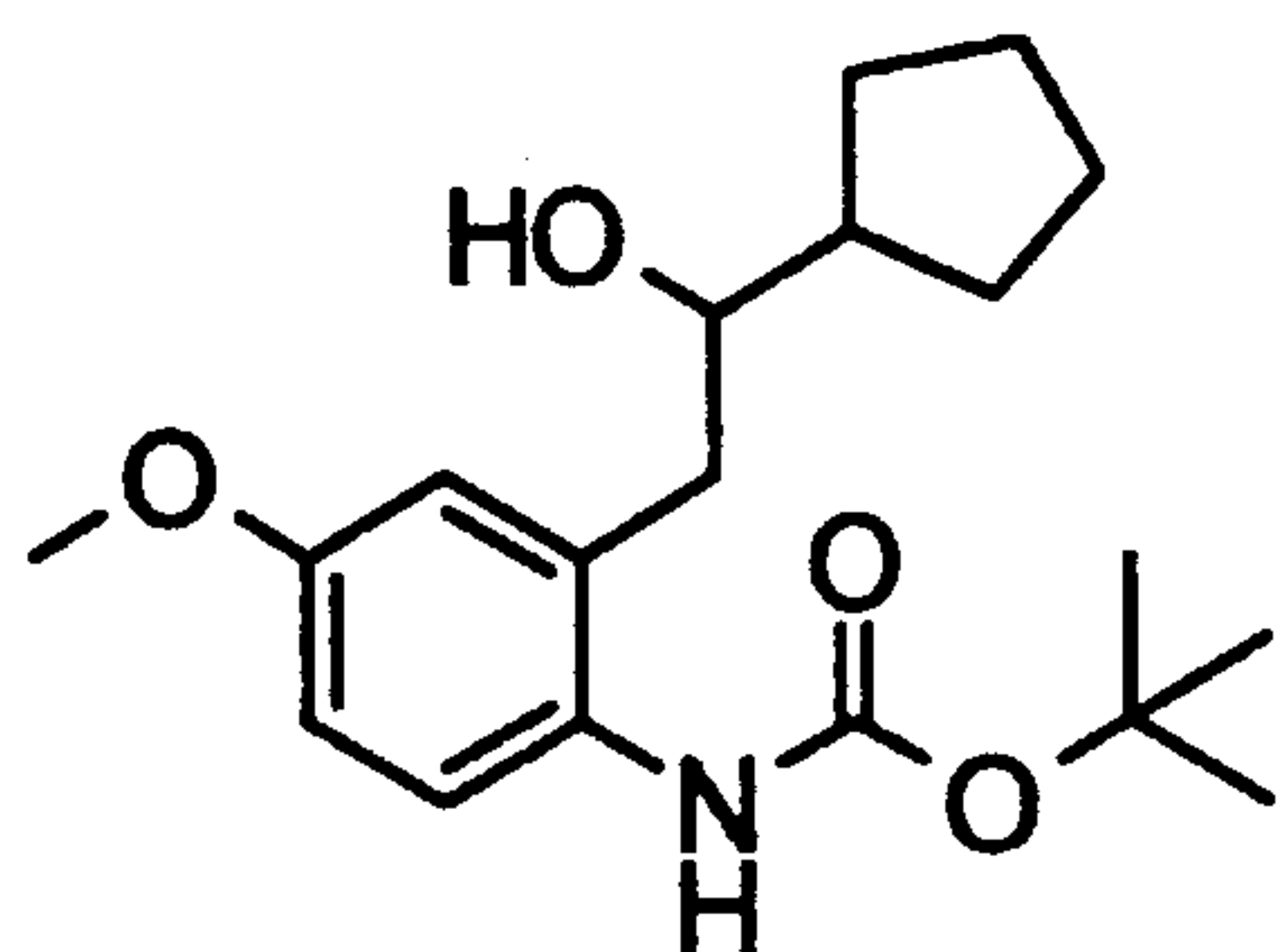
20

Reference Example 17

tert-Butyl [2-(2-cyclopentyl-2-hydroxyethyl)-4-methoxyphenyl]carbamate

[0218]

[Chem. 33]



25

[0219]

To a solution of *tert*-butyl (4-methoxy-2-methylphenyl)carbamate (475mg) in tetrahydrofuran (7mL) was added dropwise *sec*-butyllithium (1.04mol/L hexane-cyclohexane solution, 4.3mL) at -40°C under an argon atmosphere, and the mixture was stirred for 15 minutes. Then a solution of cyclopentanecarboxyaldehyde (0.256mL) in tetrahydrofuran (1mL) was added dropwise, and the mixture was stirred at -40°C for 15 minutes and at room temperature for additional one hour. Water and 1mol/L hydrochloric acid were added to the reaction mixture and this resulting mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated saline, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluting solvent : ethyl acetate-hexane) to obtain the title compound (535mg).

[0220]

¹H-NMR (CDCl₃) δ ppm:

1.20-2.10 (19H, m), 2.70 (1H, dd, J=8.3, 14.0Hz), 2.78 (1H, dd, J=2.9, 14.0Hz), 3.55-3.70 (1H, m), 3.78 (3H, s), 6.69 (1H, d, J=3.0Hz), 6.77 (1H, dd, J=3.0, 8.8Hz), 7.40-7.70 (2H, m).

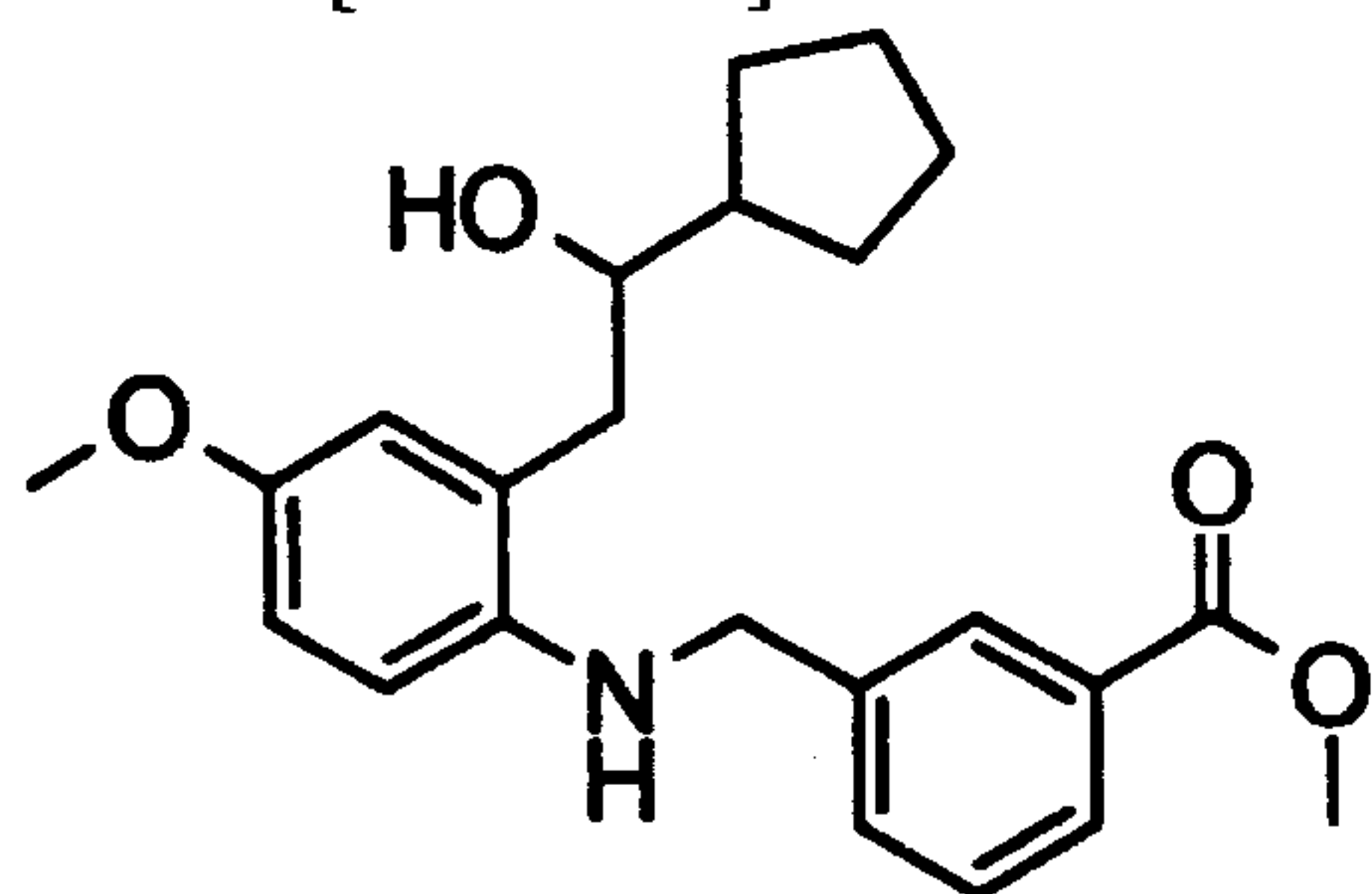
[0221]

Reference Example 18

Methyl 3-{[2-(2-Cyclopentyl-2-hydroxyethyl)-4-methoxyphenylamino]methyl}benzoate

[0222]

[Chem. 34]



[0223]

To a solution of *tert*-butyl [2-(2-cyclopentyl-2-hydroxyethyl)-4-methoxyphenyl]carbamate (530 mg) in dichloromethane (3mL) was added trifluoroacetic acid (1 mL) at room temperature, and the mixture was stirred for one hour. The reaction mixture was poured into 5% aqueous sodium hydrogen carbonate solution (40mL) and extracted with ethyl acetate. The organic layer was washed with saturated saline, dried

over anhydrous magnesium sulfate and concentrated under reduced pressure. To a solution of the residue and methyl 3-formylbenzoate (318mg) in acetic acid (3mL) was added sodium triacetoxyborohydride (684mg) at room temperature, and the mixture was stirred for one hour. The reaction mixture was diluted with ethyl acetate and washed with 5% aqueous sodium hydrogen carbonate solution. The organic layer was washed with saturated saline, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluting solvent : ethyl acetate-hexane) to obtain the title compound (362mg).

[0224]

¹H-NMR (CDCl₃) δ ppm:

1.20-1.70 (6H, m), 1.75-1.90 (2H, m), 1.90-2.10 (1H, m), 2.71 (1H, dd, J=8.3, 14.3Hz), 2.79 (1H, dd, J=3.0, 14.3Hz), 3.60-3.80 (4H, m), 3.91 (3H, s), 4.25-4.40 (2H, m), 6.55 (1H, d, J=8.6Hz), 6.66 (1H, dd, J=2.8, 8.6Hz), 6.70 (1H, d, J=2.8Hz), 7.40 (1H, t, J=7.7Hz), 7.55-7.65 (1H, m), 7.90-8.00 (1H, m), 8.00-8.10 (1H, m).

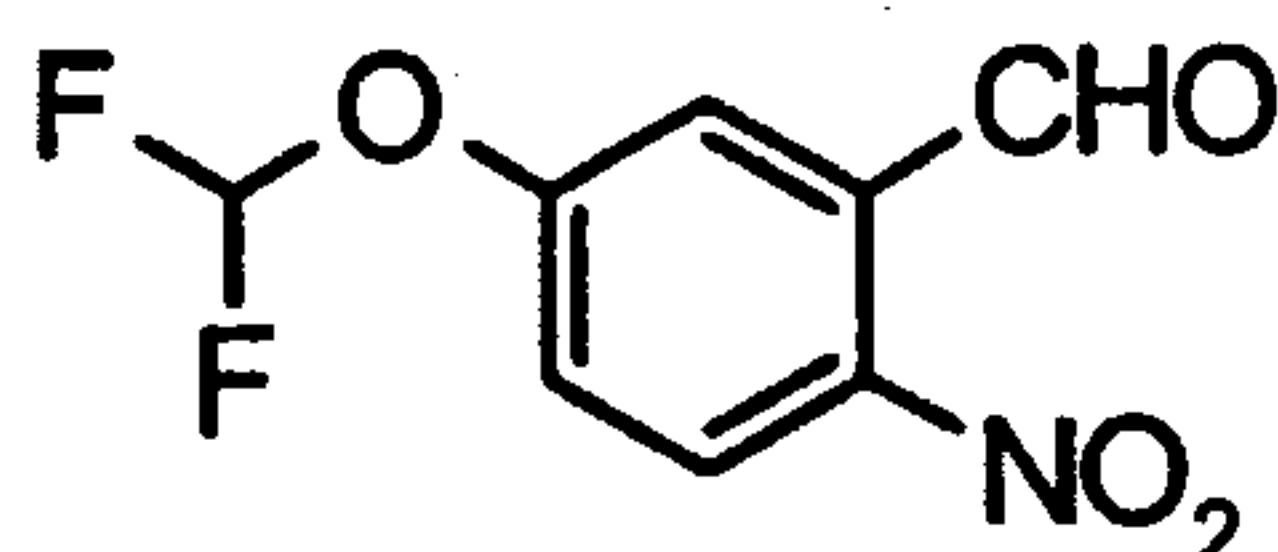
[0225]

Reference Example 19

5-Difluoromethoxy-2-nitrobenzaldehyde

[0226]

[Chem. 35]



[0227]

To a solution of 5-hydroxy-2-nitrobenzaldehyde (500mg) in *N,N*-dimethylformamide (4.3 mL) were added sodium chlorodifluoroacetate (456mg), sodium hydroxide (120mg) and water (0.060mL) at room temperature, and the mixture was stirred at 125°C for one hour. The reaction mixture was cooled to room temperature, diluted with water and then extracted with ethyl acetate. The organic layer was washed successively with water and saturated saline, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluting solvent : ethyl acetate-hexane) to obtain the title compound (240mg).

[0228]

¹H-NMR (CDCl₃) δ ppm:

6.68 (1H, t, J=71.5Hz), 7.46 (1H, dd, J=2.7, 8.9Hz), 7.64 (1H, d, J=2.7Hz), 8.21 (1H, d, J=8.9Hz), 10.46 (1H, s).

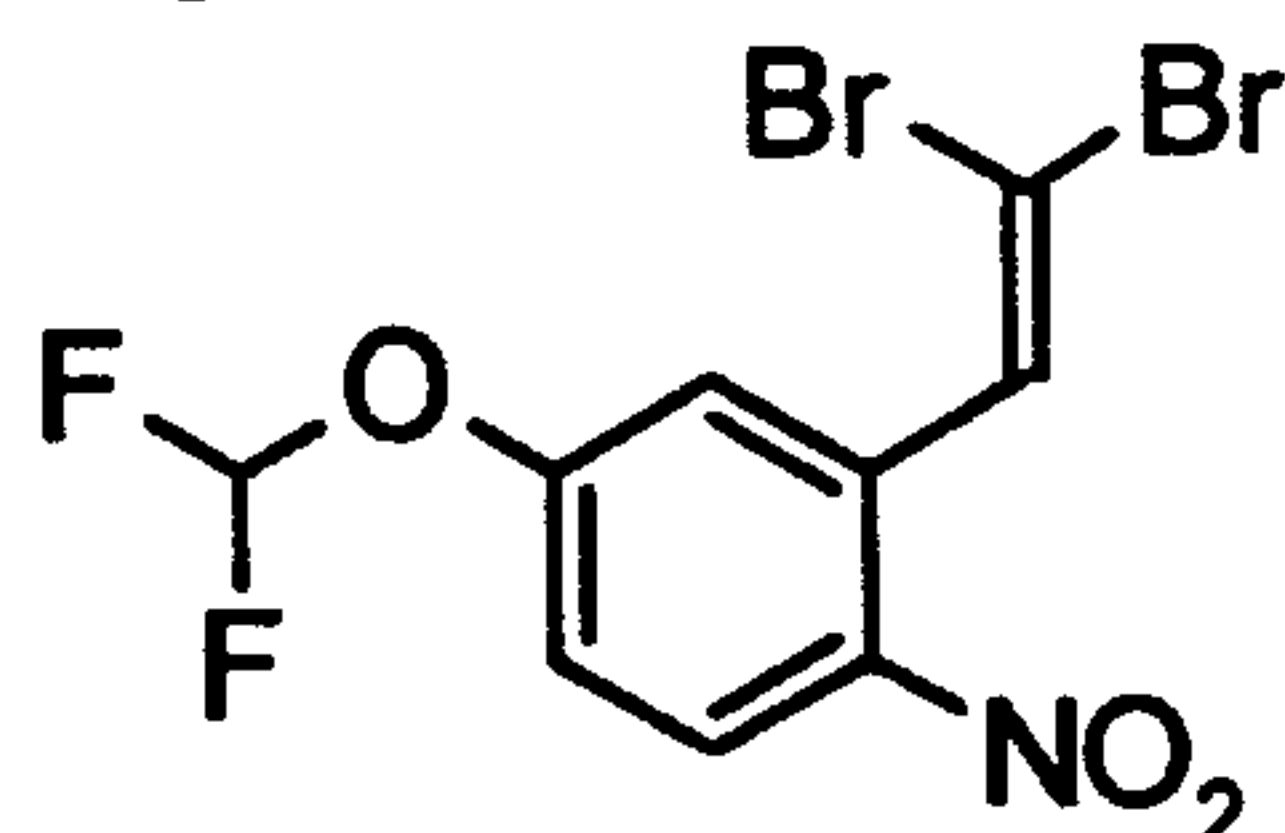
[0229]

Reference Example 20

5 2-(2,2-Dibromovinyl)-4-difluoromethoxynitrobenzene

[0230]

[Chem. 36]



[0231]

10 To a solution of 5-difluoromethoxy-2-nitrobenzaldehyde (238mg) and carbon tetrabromide (545mg) in dichloromethane (5.4mL) was added dropwise a solution of triphenylphosphine (863mg) in dichloromethane (3.6mL) under cooling with ice. The mixture was gradually warmed to room temperature and stirred for 6 hours. The reaction mixture was concentrated under reduced pressure. The residue was suspended in diethyl
15 ether and this resulting mixture was stirred at room temperature for 16 hours. The precipitate was removed by filtration through celite (registered trademark) and washed with diethyl ether. The filtrate was concentrated under reduced pressure to obtain the title compound (536mg).

[0232]

20 ¹H-NMR (CDCl₃) δ ppm:

6.64 (1H, t, J=71.9Hz), 7.20-7.30 (1H, m), 7.30-7.35 (1H, m), 7.77 (1H, s), 8.19 (1H, d, J=9.0Hz).

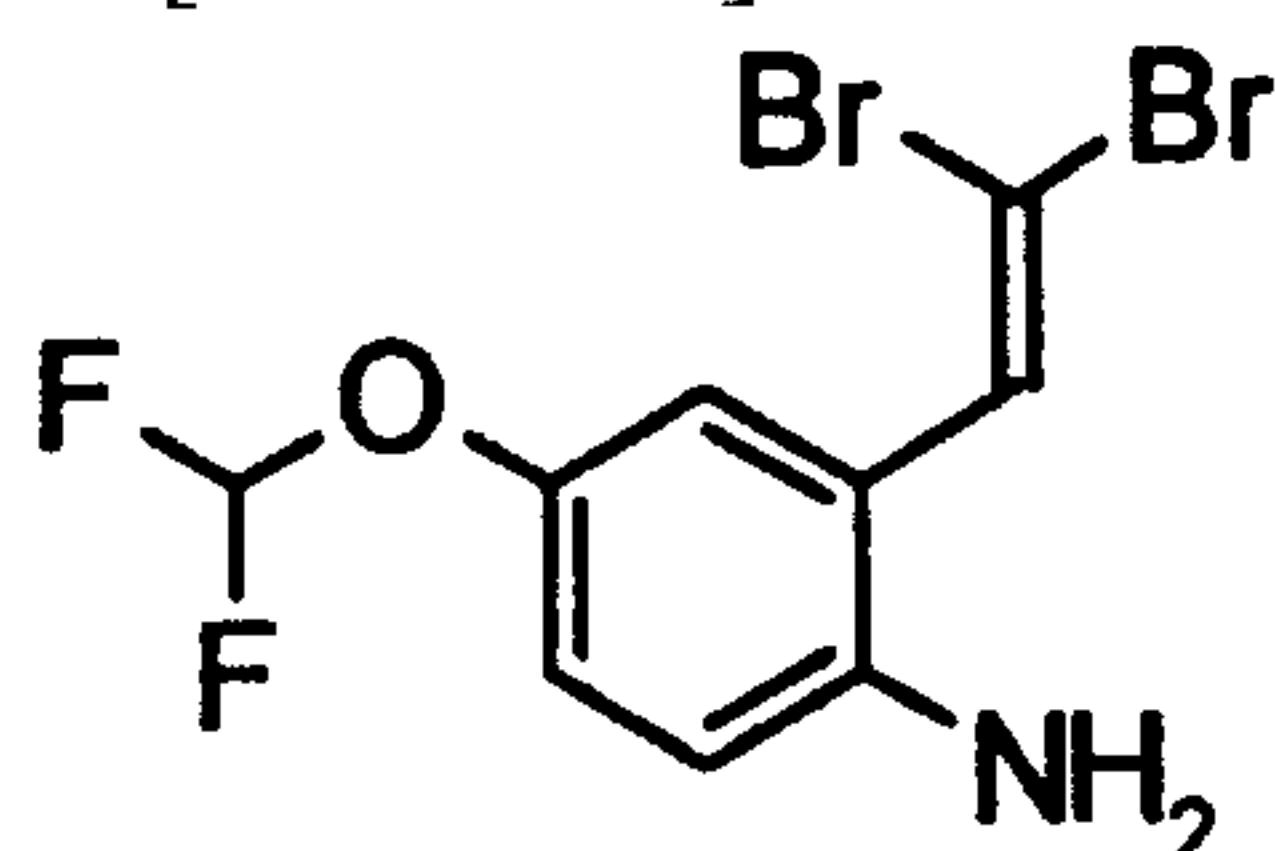
[0233]

Reference Example 21

25 2-(2,2-Dibromovinyl)-4-difluoromethoxyaniline

[0234]

[Chem. 37]



[0235]

To a suspension of 2-(2,2-dibromovinyl)-4-difluoromethoxynitrobenzene (534mg) in ethanol (3.7mL) was added tin (II) chloride dihydrate (742mg) at room temperature, and the mixture was heated under reflux for 3 hours. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. 1mol/L Aqueous sodium hydroxide solution was added to the residue and this resulting mixture was extracted with dichloromethane. The aqueous layer was extracted with dichloromethane. The combined organic layers were washed with saturated saline, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluting solvent : ethyl acetate-hexane) to obtain the title compound (168mg).

[0236]

¹H-NMR (CDCl₃) δ ppm:

3.68 (2H, br s), 6.39 (1H, t, J=74.4Hz), 6.67 (1H, d, J=8.8Hz), 6.96 (1H, dd, J=2.8, 8.8Hz), 7.13 (1H, d, J=2.8Hz), 7.29 (1H, s).

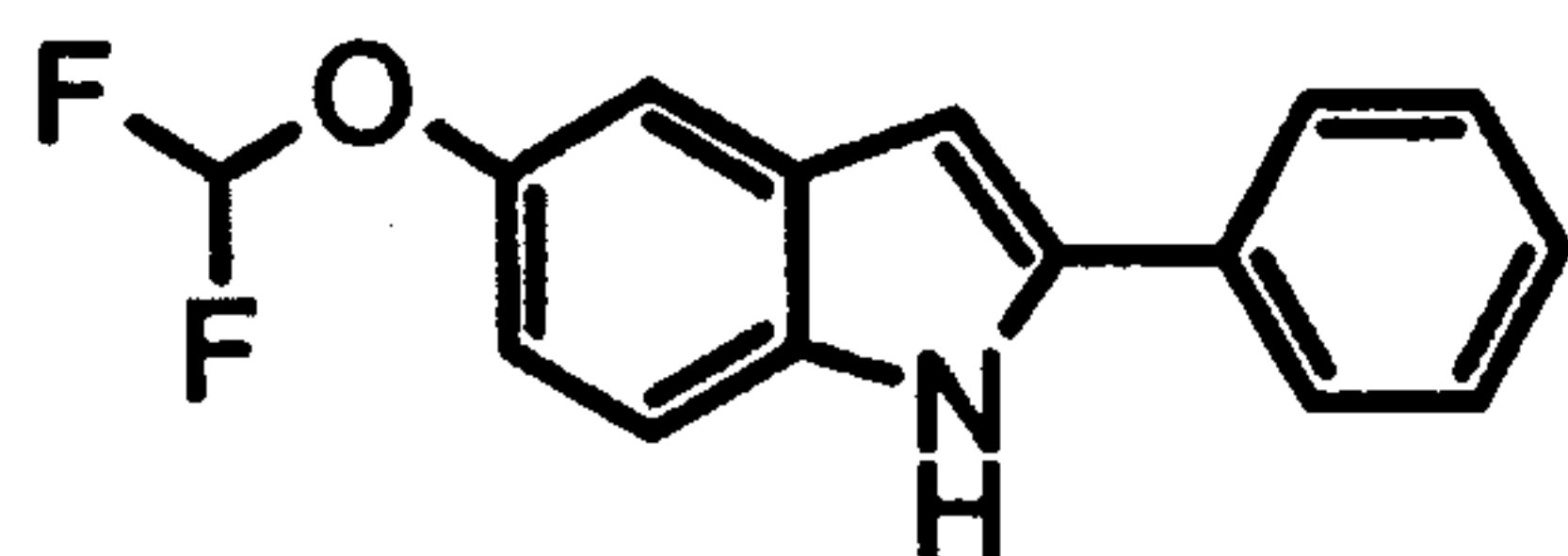
[0237]

Reference Example 22

5-Difluoromethoxy-2-phenylindole

[0238]

[Chem. 38]



[0239]

To a mixture of 2-(2,2-dibromovinyl)-4-difluoromethoxyaniline (166mg), phenylboronic acid (88.5mg) and potassium phosphate monohydrate (557mg) was added a mixture of 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (11.9mg), palladium (II) acetate (3.3mg) and toluene (2.4mL) at room temperature, and the mixture was stirred at 100°C for 3 hours. The reaction mixture was cooled to room temperature, diluted with ethyl acetate and then filtered through celite (registered trademark). The filtrate was washed with saturated saline-water (2/1), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluting solvent : ethyl acetate-hexane) to obtain the title compound (91.2mg).

[0240]

¹H-NMR (CDCl₃) δ ppm:

6.51 (1H, t, J=75.1Hz), 6.75-6.85 (1H, m), 7.00 (1H, dd, J=2.4, 8.7Hz), 7.30-7.40 (3H, m),
7.40-7.50 (2H, m), 7.60-7.70 (2H, m), 8.37 (1H, br s).

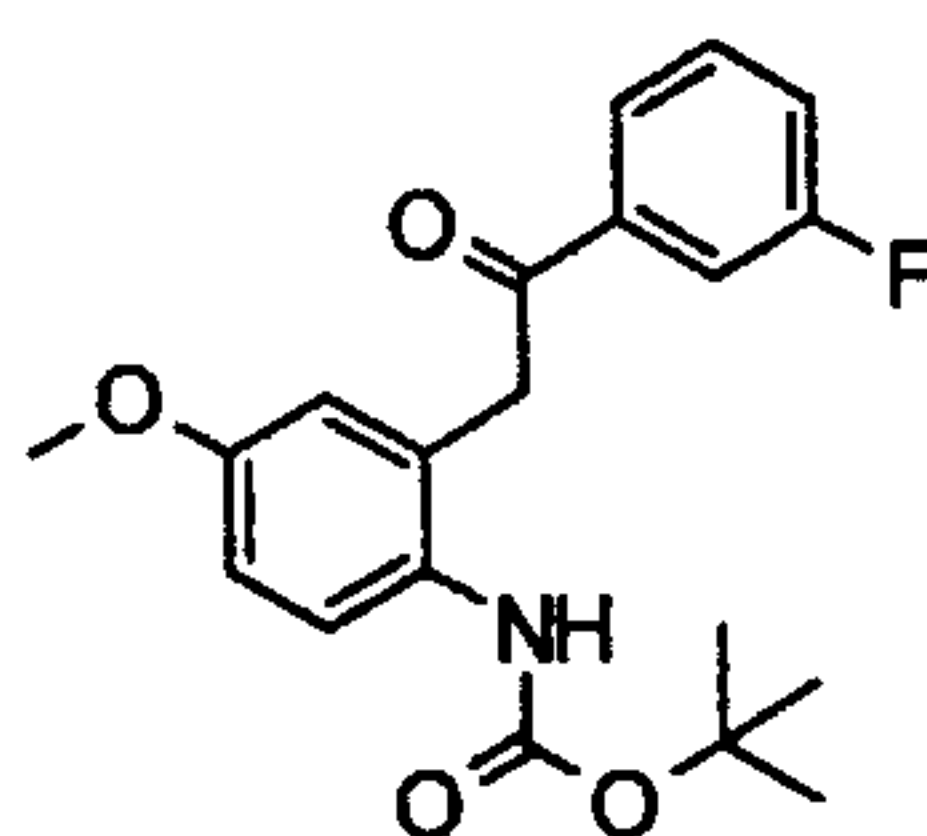
5 [0241]

Reference Example 23

tert-Butyl {2-[2-(3-fluorophenyl)-2-oxoethyl]-4-methoxyphenyl} carbamate

[0242]

[Chem. 39]



10

[0243]

The title compound was synthesized in a manner similar to that of Reference Example 6-1 by using the corresponding starting material and reactants.

[0244]

15 ¹H-NMR (CDCl₃) δ ppm:

1.47 (9H, s), 3.76 (3H, s), 4.24 (2H, s), 6.65-7.15 (3H, m), 7.25-7.40 (1H, m), 7.40-7.60
(2H, m), 7.65-7.80 (1H, m), 7.80-7.90 (1H, m).

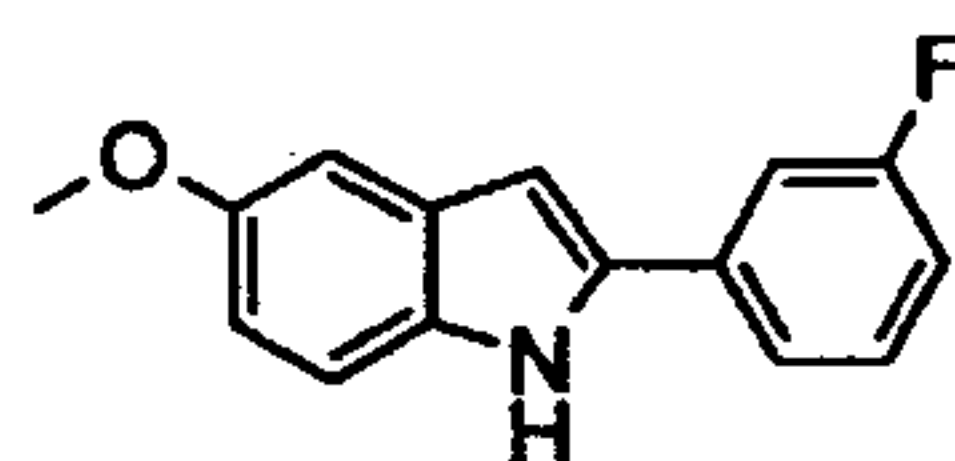
[0245]

Reference Example 24

20 2-(3-Fluorophenyl)-5-methoxyindole

[0246]

[Chem. 40]



[0247]

25 The title compound was synthesized in a manner similar to that of Reference Example 7-1 by using the corresponding starting material.

[0248]

¹H-NMR (CDCl₃) δ ppm:

30 3.87 (3H, s), 6.75-6.80 (1H, m), 6.88 (1H, dd, J=2.4, 8.8Hz), 6.95-7.05 (1H, m),

7.09 (1H, d, J=2.4Hz), 7.25-7.50 (4H, m), 7.90-8.50 (1H, br).

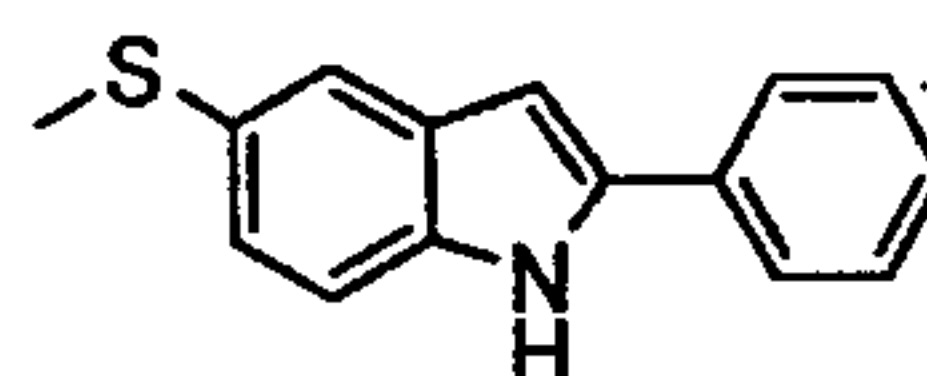
[0249]

Reference Example 25

5-Methylsulfanyl-2-phenylindole

5 [0250]

[Chem. 41]



[0251]

To a solution of 1-benzenesulfonyl-5-methylsulfanyl-2-phenylindole (264mg) in
 10 tetrahydrofuran-methanol (2/1, 6.9mL) was added cesium carbonate (680mg) at room
 temperature, and the mixture was stirred at 50°C for 26 hours. The reaction mixture was
 allowed to cool to ambient temperature and concentrated under reduced pressure. 1mol/L
 Hydrochloric acid was added to the residue and this resulting mixture was extracted with
 ethyl acetate. The organic layer was washed successively with a saturated aqueous
 15 sodium hydrogen carbonate solution and saturated saline, dried over anhydrous sodium
 sulfate and concentrated under reduced pressure. The residue was purified by
 aminopropylated silica gel column chromatography (eluting solvent : ethyl acetate-hexane)
 to obtain the title compound (149mg).

[0252]

20 ¹H-NMR (CDCl₃) δ ppm:

2.53 (3H, s), 6.75-6.80 (1H, m), 7.22 (1H, dd, J=1.9, 8.4Hz), 7.30-7.50 (4H, m), 7.60-7.70
 (3H, m), 8.35 (1H, br s).

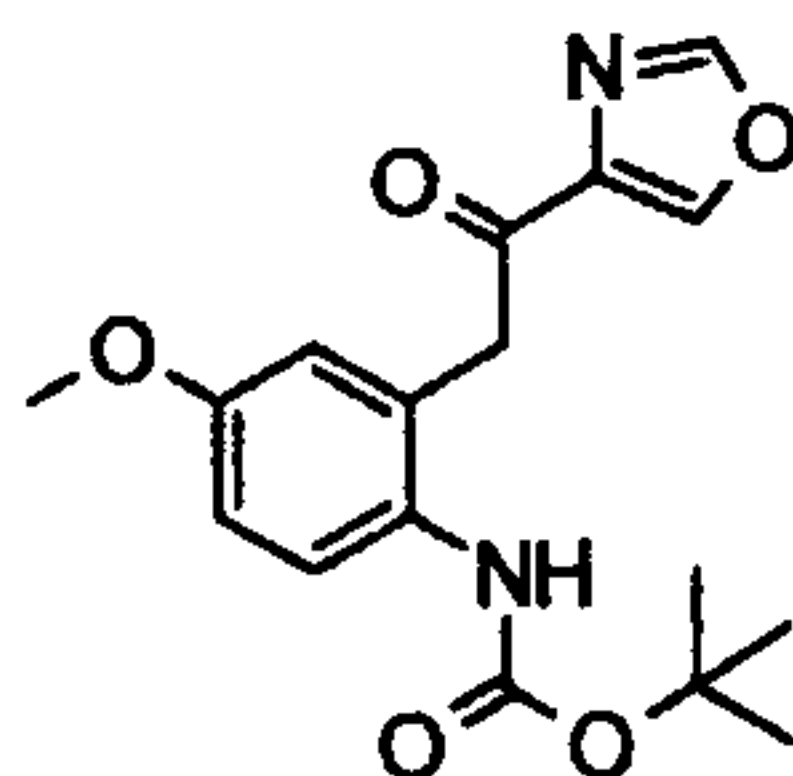
[0253]

Reference Example 26

25 *tert*-Butyl [4-methoxy-2-(2-oxazol-4-yl-2-oxoethyl)phenyl]carbamate

[0254]

[Chem. 42]



[0255]

30 The title compound was synthesized in a manner similar to that of Reference

Example 6-1 by using the corresponding starting material and reactants.

[0256]

¹H-NMR (CDCl₃) δ ppm:

1.52 (9H, s), 3.76 (3H, s), 4.17 (2H, s), 6.75-6.90 (2H, m), 7.35-8.00 (3H, m), 8.28 (1H, d,
5 J=1.0Hz).

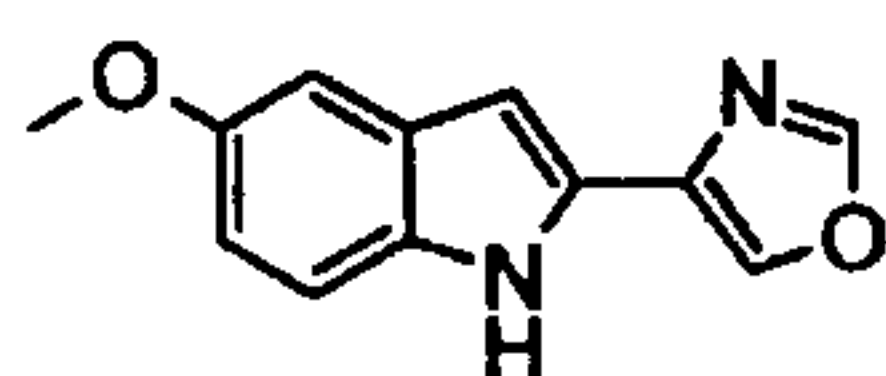
[0257]

Reference Example 27

5-Methoxy-2-oxazol-4-ylindole

[0258]

10 [Chem. 43]



[0259]

The title compound was synthesized in a manner similar to that of Reference Example 7-1 by using the corresponding starting material.

15 [0260]

¹H-NMR (CDCl₃) δ ppm:

3.86 (3H, s), 6.65-6.75 (1H, m), 6.86 (1H, dd, J=2.5, 8.8Hz), 7.06 (1H, d, J=2.5Hz), 7.29
(1H, d, J=8.8Hz), 7.90-8.05 (2H, m), 8.50-9.05 (1H, br).

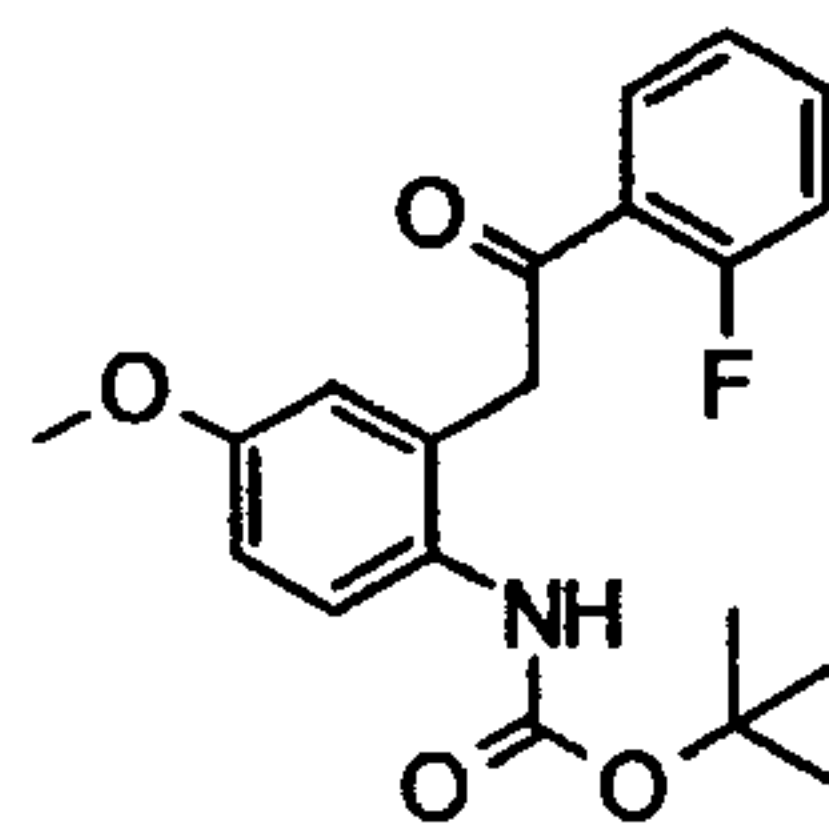
[0261]

20 Reference Example 28

tert-Butyl {2-[2-(2-fluorophenyl)-2-oxoethyl]-4-methoxyphenyl} carbamate

[0262]

[Chem. 44]



25 [0263]

The title compound was synthesized in a manner similar to that of Reference Example 6-1 by using the corresponding starting material and reactants.

[0264]

¹H-NMR (CDCl₃) δ ppm:

30 1.47 (9H, s), 3.76 (3H, s), 4.20-4.35 (2H, m), 6.60-7.10 (3H, m), 7.10-7.30 (2H, m), 7.30-7.70 (2H, m), 7.80-7.90 (1H, m).

[0265]

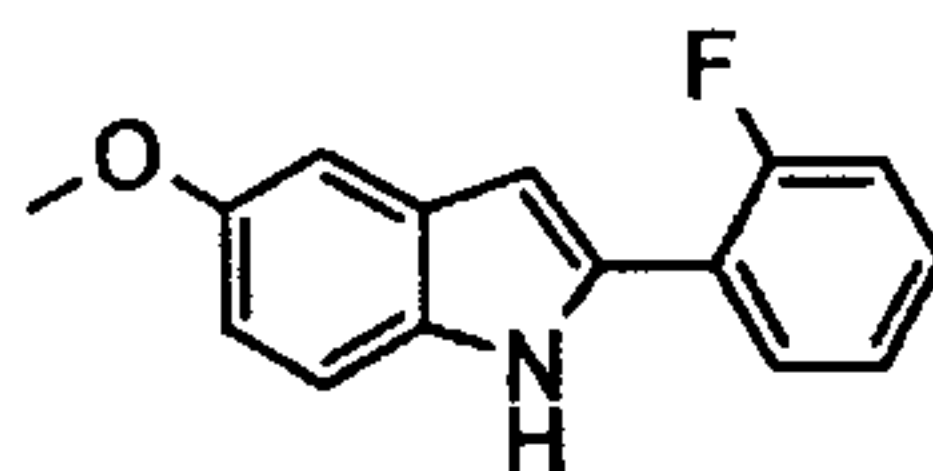
Reference Example 29

2-(2-Fluorophenyl)-5-methoxyindole

[0266]

5

[Chem. 45]



[0267]

The title compound was synthesized in a manner similar to that of Reference Example 7-1 by using the corresponding starting material and reactant.

10

[0268]

¹H-NMR (CDCl₃) δ ppm:

3.87 (3H, s), 6.80-6.95 (2H, m), 7.05-7.35 (5H, m), 7.70-7.85 (1H, m), 8.40-9.15 (1H, br).

[0269]

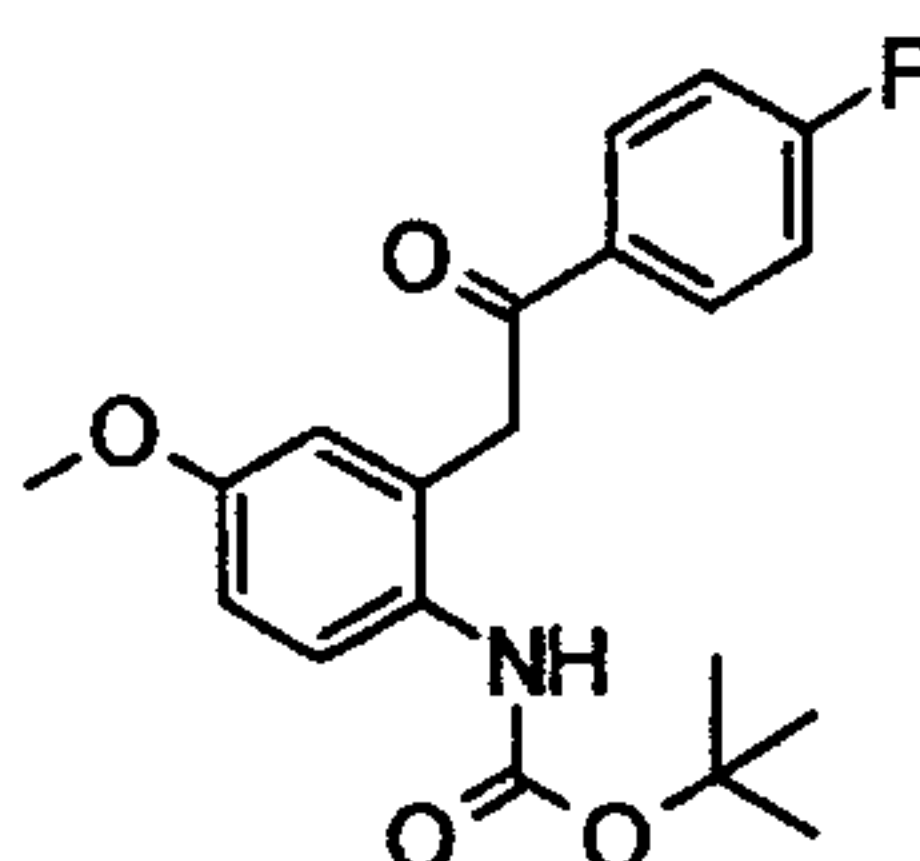
Reference Example 30

15

tert-Butyl {2-[2-(4-fluorophenyl)-2-oxoethyl]-4-methoxyphenyl} carbamate

[0270]

[Chem. 46]



[0271]

20

The title compound was synthesized in a manner similar to that of Reference Example 6-1 by using the corresponding starting material and reactants.

[0272]

¹H-NMR (CDCl₃) δ ppm:

1.48 (9H, s), 3.75 (3H, s), 4.23 (2H, s), 6.70-7.70 (6H, m), 8.00-8.20 (2H, m).

25

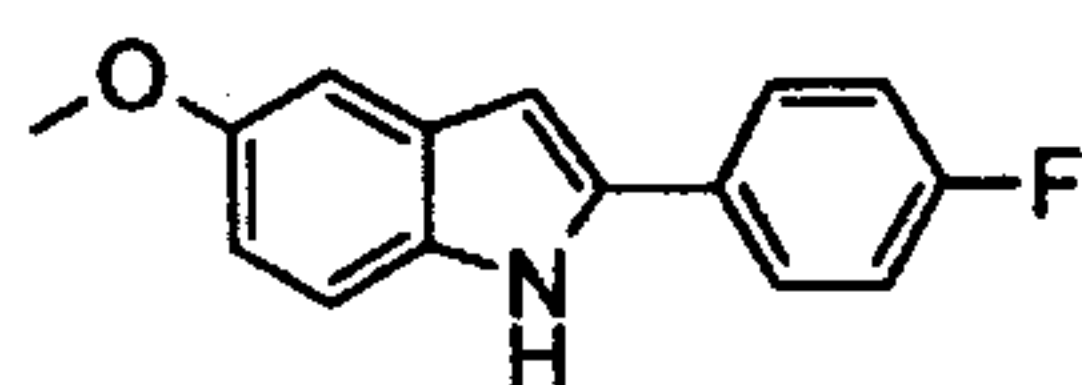
[0273]

Reference Example 31

2-(4-Fluorophenyl)-5-methoxyindole

[0274]

[Chem. 47]



[0275]

The title compound was synthesized in a manner similar to that of Reference Example 7-1 by using the corresponding starting material and reactant.

5 [0276]

¹H-NMR (CDCl₃) δ ppm:

3.86 (3H, s), 6.65-6.75 (1H, m), 6.86 (1H, dd, J=2.5, 8.8Hz), 7.00-7.20 (3H, m), 7.28 (1H, d, J=8.8Hz), 7.55-7.65 (2H, m), 7.90-8.40 (1H, br).

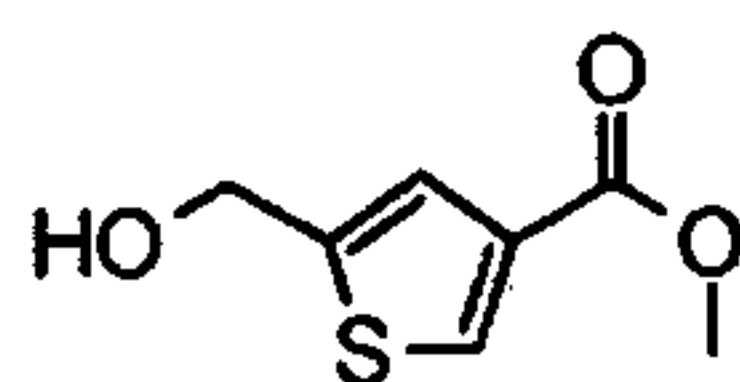
[0277]

10 Reference Example 32

Methyl 5-hydroxymethylthiophene-3-carboxylate

[0278]

[Chem. 48]



15 [0279]

To a solution of methyl 5-formylthiophene-3-carboxylate (500mg) in ethanol (5.9mL) was added sodium borohydride (55.6mg) at room temperature in small portions, and the mixture was stirred for one hour. The reaction mixture was concentrated under reduced pressure. A saturated aqueous sodium hydrogen carbonate solution was added to the residue and this resulting mixture was extracted with ethyl acetate. The aqueous layer was extracted once again with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluting solvent : ethyl acetate-hexane) to obtain the title compound (403mg).

25 [0280]

¹H-NMR (CDCl₃) δ ppm:

1.86 (1H, t, J=6.0Hz), 3.86 (3H, s), 4.75-4.90 (2H, m), 7.35-7.45 (1H, m), 8.04 (1H, d, J=1.3Hz).

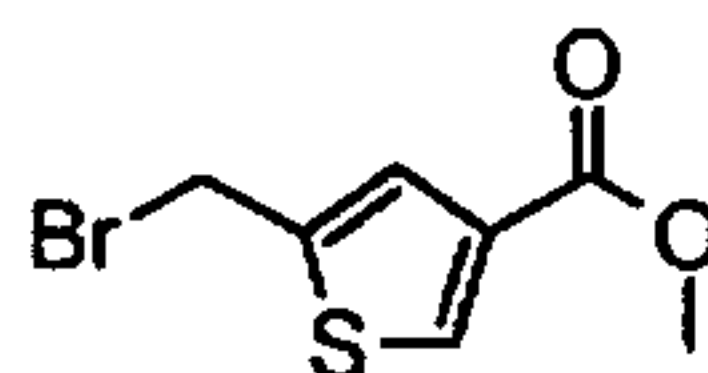
[0281]

30 Reference Example 33

Methyl 5-bromomethylthiophene-3-carboxylate

[0282]

[Chem. 49]



[0283]

To a solution of methyl 5-hydroxymethylthiophene-3-carboxylate (401mg) in ethyl acetate (4.7mL) were added triethylamine (0.390mL) and methanesulfonyl chloride (0.198mL) under cooling with ice. The mixture was stirred under cooling with ice for 40 minutes. The reaction mixture was diluted with ethyl acetate (4.7mL) and filtered through celite (registered trademark). To the filtrate was added lithium bromide monohydrate (733mg) at room temperature, and the mixture was stirred at 50°C for 6 hours. The reaction mixture was allowed to cool to ambient temperature, diluted with water and extracted with ethyl acetate. The organic layer was washed successively with water and saturated saline, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluting solvent : ethyl acetate-hexane) to obtain the title compound (495mg).

15 [0284]

¹H-NMR (CDCl₃) δ ppm:

3.86 (3H, s), 4.68 (2H, s), 7.45-7.55 (1H, m), 8.07 (1H, d, J=1.3Hz).

[0285]

Reference Example 34

20 *tert*-Butyl {2-[2-(3-chlorophenyl)-2-oxoethyl]-4-methoxyphenyl}carbamate

[0286]

The title compound was synthesized in a manner similar to that of Reference Example 6-1 by using the corresponding starting material and reactants.

[0287]

25 ¹H-NMR (CDCl₃) δ ppm:

1.47 (9H, s), 3.76 (3H, s), 4.24 (2H, s), 6.60-7.20 (3H, m), 7.35-7.65 (3H, m), 7.85-8.10 (2H, m).

[0288]

Reference Example 35

30 2-(3-Chlorophenyl)-5-methoxyindole

[0289]

The title compound was synthesized in a manner similar to that of Reference Example 7-1 by using the corresponding starting material and reactant.

[0290]

¹H-NMR (CDCl₃) δ ppm:

3.87 (3H, s), 6.75-6.80 (1H, m), 6.88 (1H, dd, J=2.5, 8.8Hz), 7.05-7.15 (1H, m), 7.20-7.35 (2H, m), 7.36 (1H, t, J=7.8Hz), 7.45-7.55 (1H, m), 7.60-7.65 (1H, m), 8.00-8.40 (1H, br).

[0291]

5 Reference Example 36

N-(2-Bromo-5-chloro-4-methoxyphenyl)-2,2,2-trifluoroacetamide

[0292]

To a solution of 2-bromo-5-chloro-4-methoxyaniline (8.97g) in pyridine (25.3mL) was added dropwise trifluoroacetic anhydride (2.81mL) under cooling with ice. The mixture was stirred at room temperature for 30 hours. Methanol (1.5mL) was added to the reaction mixture and the stirring was continued for additional 40 minutes. The reaction mixture was concentrated under reduced pressure. 1mol/L Hydrochloric acid was added to the residue and this resulting mixture was extracted with ethyl acetate. The organic layer was washed successively with 1mol/L hydrochloric acid, a saturated aqueous sodium hydrogen carbonate solution and saturated saline, dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain the title compound (3.45g).

[0293]

¹H-NMR (DMSO-d₆) δ ppm:

3.92 (3H, s), 7.51 (1H, s), 7.61 (1H, s), 11.21 (1H, s).

20 [0294]

Reference Example 37

6-Chloro-5-methoxy-2-phenylindole

[0295]

To a mixture of *N*-(2-bromo-5-chloro-4-methoxyphenyl)-2,2,2-trifluoroacetamide (512mg), phenylacetylene (0.254mL), copper (I) iodide (17.5mg), triethylamine (549mL) and acetonitrile (12.3mL) was added bis(triphenylphosphine)palladium (II) dichloride (32.5mg). The mixture was stirred at 120°C for 2 hours under irradiation of microwave. The reaction mixture was allowed to cool to ambient temperature. Potassium carbonate (532mg) was added to the reaction mixture. The mixture was stirred at 120°C for additional 2 hours under irradiation of microwave. The reaction mixture was allowed to cool to ambient temperature and filtered through celite (registered trademark). The filtrate was concentrated under reduced pressure and the residue was purified by aminopropylated silica gel column chromatography (eluting solvent : ethyl acetate-hexane) to obtain the title compound (255mg).

[0296]

¹H-NMR (CDCl₃) δ ppm:

3.95 (3H, s), 6.70-6.80 (1H, m), 7.13 (1H, s), 7.30-7.50 (4H, m), 7.60-7.70 (2H, m), 8.00-8.40 (1H, br).

5 [0297]

Reference Example 38

N-(2-Bromo-4-methoxy-5-methylphenyl)-2,2,2-trifluoroacetamide

[0298]

10 The title compound was synthesized in a manner similar to that of Reference Example 36 by using the corresponding starting material.

[0299]

¹H-NMR (DMSO-d₆) δ ppm:

2.11 (3H, s), 3.83 (3H, s), 7.15-7.30 (2H, m), 11.08 (1H, s).

[0300]

15 Reference Example 39

5-Methoxy-6-methyl-2-phenylindole

[0301]

The title compound was synthesized in a manner similar to that of Reference Example 37 by using the corresponding starting material.

20 [0302]

¹H-NMR (CDCl₃) δ ppm:

2.34 (3H, s), 3.88 (3H, s), 6.70-6.80 (1H, m), 7.02 (1H, s), 7.10-7.35 (2H, m), 7.35-7.50 (2H, m), 7.55-7.70 (2H, m), 8.13 (1H, br s).

[0303]

25 Reference Example 40

6-Chloro-2-(2-fluorophenyl)-5-methoxyindole

[0304]

The title compound was synthesized in a manner similar to that of Reference Example 37 by using the corresponding starting material and reactant.

30 [0305]

¹H-NMR (CDCl₃) δ ppm:

3.95 (3H, s), 6.80-6.95 (1H, m), 7.10-7.35 (4H, m), 7.40-7.50 (1H, m), 7.70-7.85 (1H, m), 8.76 (1H, br s).

[0306]

Reference Example 41

6-Chloro-2-(3-fluorophenyl)-5-methoxyindole

[0307]

The title compound was synthesized in a manner similar to that of Reference
5 Example 37 by using the corresponding starting material and reactant.

[0308]

¹H-NMR (CDCl₃) δ ppm:

3.95 (3H, s), 6.70-6.80 (1H, m), 6.95-7.10 (1H, m), 7.12 (1H, s), 7.25-7.50 (4H, m), 8.19
(1H, br s).

10 [0309]

Reference Example 42

6-Chloro-2-(4-fluorophenyl)-5-methoxyindole

[0310]

The title compound was synthesized in a manner similar to that of Reference
15 Example 37 by using the corresponding starting material and reactant.

¹H-NMR (CDCl₃) δ ppm:

3.94 (3H, s), 6.60-6.75 (1H, m), 7.10-7.20 (3H, m), 7.35-7.45 (1H, m), 7.55-7.70 (2H, m),
8.13 (1H, br s).

[0311]

20 Reference Example 43

Methyl 6-(1-bromoethyl)pyridine-2-carboxylate

[0312]

To a solution of methyl 6-ethylpyridine-2-carboxylate (587mg) in carbon
tetrachloride (28.4mL) were added *N*-bromosuccinimide (696mg) and benzoyl peroxide
25 (75%, 11.5mg). The mixture was heated under reflux for 4 hours. The reaction mixture
was allowed to cool to ambient temperature. The insoluble material was removed by
filtration and the filtrate was concentrated under reduced pressure. The residue was
purified by silica gel column chromatography (eluting solvent : ethyl acetate-hexane) to
obtain the title compound (702mg).

30 [0313]

¹H-NMR (CDCl₃) δ ppm:

2.08 (3H, d, J=7.0Hz), 4.01 (3H, s), 5.34 (1H, q, J=7.0Hz), 7.70-7.95 (2H, m), 8.00-8.10
(1H, m).

[0314]

35 Reference Example 44

N-(2-Bromo-5-fluoro-4-methoxyphenyl)-2,2,2-trifluoroacetamide

[0315]

The title compound was synthesized in a manner similar to that of Reference Example 36 by using the corresponding starting material.

5 ¹H-NMR (DMSO-d₆) δ ppm:

3.90 (3H, s), 7.47 (1H, d, J=11.8Hz), 7.54 (1H, d, J=8.8Hz), 11.21 (1H, s).

[0316]

Reference Example 45

6-Fluoro-(2-fluorophenyl)-5-methoxyindole

10 [0317]

The title compound was synthesized in a manner similar to that of Reference Example 37 by using the corresponding starting material and reactant.

[0318]

¹H-NMR (CDCl₃) δ ppm:

15 3.94 (3H, s), 6.80-6.90 (1H, m), 7.05-7.40 (5H, m), 7.65-7.85 (1H, m), 8.55-9.00 (1H, br).

[0319]

Reference Example 46

6-Fluoro-2-(3-fluorophenyl)-5-methoxyindole

[0320]

20 The title compound was synthesized in a manner similar to that of Reference Example 37 by using the corresponding starting material and reactants.

[0321]

¹H-NMR (CDCl₃) δ ppm:

3.94 (3H, s), 6.70-6.80 (1H, m), 6.95-7.10 (1H, m), 7.10-7.20 (2H, m), 7.25-7.45 (3H, m),

25 8.00-8.40 (1H, br).

[0322]

Reference Example 47

6-Fluoro-2-(4-fluorophenyl)-5-methoxyindole

[0323]

30 The title compound was synthesized in a manner similar to that of Reference Example 37 by using the corresponding starting material and reactants.

[0324]

¹H-NMR (CDCl₃) δ ppm:

3.94 (3H, s), 6.60-6.75 (1H, m), 7.05-7.20 (4H, m), 7.50-7.65 (2H, m), 8.00-8.30 (1H, br).

[0325]

Reference Example 48

6-Fluoro-5-methoxy-2-pyridin-3-ylindole

[0326]

5 The title compound was synthesized in a manner similar to that of Reference Example 37 by using the corresponding starting material and reactant.

[0327]

¹H-NMR (CDCl₃) δ ppm:

3.94 (3H, s), 6.75-6.85 (1H, m), 7.10-7.25 (2H, m), 7.30-7.45 (1H, m), 7.85-8.00 (1H, m),
10 8.40-8.75 (2H, m), 8.85-9.00 (1H, m).

[0328]

Reference Example 49

tert-Butyl (5-chloro-4-methoxy-2-methylphenyl)carbamate

[0329]

15 The title compound was synthesized in a manner similar to that of Reference Example 5 by using the corresponding starting material.

¹H-NMR (CDCl₃) δ ppm:

1.51 (9H, s), 2.23 (3H, s), 3.86 (3H, s), 5.65-6.40 (1H, br), 6.72 (1H, s), 7.40-8.10 (1H, br).

[0330]

20 Reference Example 50

tert-Butyl [5-chloro-4-methoxy-2-(2-oxo-2-thiophen-3-ylethyl)phenyl]carbamate

[0331]

The title compound was synthesized in a manner similar to that of Reference Example 6-1 by using the corresponding starting material and reactants.

25 [0332]

¹H-NMR (CDCl₃) δ ppm:

1.49 (9H, s), 3.85 (3H, s), 4.16 (2H, s), 6.73 (1H, s), 6.90-8.00 (4H, m), 8.15-8.30 (1H, m).

[0333]

Reference Example 51

30 6-Fluoro-5-methoxy-2-thiophen-3-ylindole

[0334]

The title compound was synthesized in a manner similar to that of Reference Example 7-1 by using the corresponding starting material and reactant.

[0335]

¹H-NMR (CDCl₃) δ ppm:

3.94 (3H, s), 6.55-6.70 (1H, m), 7.10 (1H, s), 7.35-7.50 (4H, m), 7.90-8.35 (1H, br).

[0336]

Reference Example 52

5 4-Benzyloxy-2-bromo-5-chloroaniline

[0337]

To a suspension of 4-benzyloxy-3-chloroaniline (674mg) and potassium carbonate (1.14g) in dichloromethane (32mL) was added dropwise a solution of bromine (1.25g) in dichloromethane (16mL) at -15°C in one hour, and the mixture was stirred at -15°C for 75
10 minutes. Water was added to the reaction mixture and this resulting mixture was stirred vigorously for additional 10 minutes. The organic layer was separated, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluting solvent : ethyl acetate-hexane) to obtain the title compound (1.13g).

15 [0338]

¹H-NMR (CDCl₃) δ ppm:

3.85 (2H, br s), 5.03 (2H, s), 6.84 (1H, s), 7.07 (1H, s), 7.25-7.55 (5H, m).

[0339]

Reference Example 53

20 *N*-(4-benzyloxy-2-bromo-5-chlorophenyl)-2,2,2-trifluoroacetamide

[0340]

The title compound was synthesized in a manner similar to that of Reference Example 36 by using the corresponding starting material.

[0341]

25 ¹H-NMR (DMSO-d₆) δ ppm:

5.29 (2H, s), 7.30-7.55 (5H, m), 7.55-7.70 (2H, m), 11.22 (1H, s).

[0342]

Reference Example 54

5-Benzyloxy-6-chloro-2-phenylindole

30 [0343]

The title compound was synthesized in a manner similar to that of Reference Example 37 by using the corresponding starting material.

[0344]

¹H-NMR (CDCl₃) δ ppm:

5.19 (2H, s), 6.65-6.80 (1H, m), 7.18 (1H, s), 7.25-7.75 (11H, m), 8.23 (1H, br s).

[0345]

Reference Example 55

Methyl 6-(5-benzyloxy-6-chloro-2-phenylindol-1-ylmethyl)pyridine-2-carboxylate

5 [0346]

To a solution of 5-benzyloxy-6-chloro-2-phenylindole (513mg) in *N,N*-dimethylformamide (7.7mL) was added sodium hydride (in oil, 50 to 72%, 92mg) under cooling with ice under an argon atmosphere, and the mixture was stirred at room temperature for one hour. Then methyl 6-(chloromethyl)pyridine-2-carboxylate (342mg)
10 was added, and the mixture was stirred at 80°C for 18 hours. The reaction mixture was allowed to cool to ambient temperature. A saturated aqueous ammonium chloride solution and water were added to the reaction mixture and this resulting mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated saline, dried over anhydrous sodium sulfate and concentrated under reduced
15 pressure. The residue was purified by silica gel column chromatography (eluting solvent : ethyl acetate-hexane) to obtain the title compound (454mg).

[0347]

¹H-NMR (CDCl₃) δ ppm:

4.03 (3H, s), 5.20 (2H, s), 5.54 (2H, s), 6.55-6.65 (1H, m), 6.65-6.75 (1H, m), 7.15-7.60
20 (12H, m), 7.65-7.75 (1H, m), 7.95-8.10 (1H, m).

[0348]

Reference Example 56

Methyl 6-(6-chloro-5-hydroxy-2-phenylindole-1-ylmethyl)pyridine-2-carboxylate

[0349]

25 A solution of methyl 6-(5-benzyloxy-6-chloro-2-phenylindol-1-ylmethyl)pyridine-2-carboxylate (372mg) in trifluoroacetic acid/water/dimethyl sulfide (95/5/10, 7.7mL) was stirred at room temperature for 80 hours. The reaction mixture was concentrated under reduced pressure. A saturated aqueous sodium hydrogen carbonate solution (20mL) was added to the residue and this resulting mixture was extracted with ethyl acetate. The
30 organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was triturated in dichloromethane/hexane (2/1). The precipitate was collected by filtration, washed with dichloromethane/hexane (2/1), and air-dried to obtain the title compound (213mg).

[0350]

¹H-NMR (CDCl₃) δ ppm:

4.03 (3H, s), 5.33 (1H, s), 5.53 (2H, s), 6.57 (1H, s), 6.69 (1H, d, J=7.8Hz), 7.12 (1H, s), 7.28 (1H, s), 7.30-7.50 (5H, m), 7.65-7.80 (1H, m), 8.01 (1H, d, J=7.5Hz).

[0351]

5 Reference Example 57

tert-Butyl [5-chloro-4-methoxy-2-(2-oxo-2-furan-3-ylethyl)phenyl]carbamate

[0352]

The title compound was synthesized in a manner similar to that of Reference Example 6-1 by using the corresponding starting material and reactants.

10 [0353]

¹H-NMR (CDCl₃) δ ppm:

1.50 (9H, s), 3.85 (3H, s), 4.01 (2H, s), 6.70 (1H, s), 6.75-6.85 (1H, m), 7.00-8.00 (3H, m), 8.15-8.25 (1H, m).

[0354]

15 Reference Example 58

6-Chloro-2-furan-3-yl-5-methoxyindole

[0355]

The title compound was synthesized in a manner similar to that of Reference Example 7-1 by using the corresponding starting material.

20 [0356]

¹H-NMR (CDCl₃) δ ppm:

3.94 (3H, s), 6.45-6.60 (1H, m), 6.60-6.75 (1H, m), 7.09 (1H, s), 7.35-7.40 (1H, m), 7.45-7.55 (1H, m), 7.70-7.80 (1H, m), 7.80-8.20 (1H, br).

[0357]

25 Reference Example 59

tert-Butyl (4-hydroxy-2,5-dimethylphenyl)carbamate

[0358]

A mixture of 4-amino-2,5-dimethylphenol (2.00g), di-*tert*-butyl dicarbonate (3.50g) and tetrahydrofuran (29mL) was heated under reflux overnight. The reaction mixture was allowed to cool to ambient temperature and concentrated under reduced pressure to obtain the title compound (3.80g).

30

[0359]

¹H-NMR (CDCl₃) δ ppm:

1.51 (9H, s), 2.16 (3H, s), 2.18 (3H, s), 4.60-5.00 (1H, br), 5.80-6.25 (1H, br), 6.55 (1H, s), 7.20-7.45 (1H, br).

[0360]

Reference Example 60

5 *tert*-Butyl (4-methoxy-2,5-dimethylphenyl)carbamate

[0361]

To a solution of *tert*-butyl (4-hydroxy-2,5-dimethylphenyl)carbamate (1.25g) and methyl iodide (1.12g) in *N,N*-dimethylformamide (10.5mL) was added potassium carbonate (1.46g), and the mixture was stirred at room temperature for 3 hours. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed successively with water and saturated saline, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluting solvent : ethyl acetate-hexane) to obtain the title compound (1.32g).

15 [0362]

¹H-NMR (CDCl₃) δ ppm:

1.51 (9H, s), 2.17 (3H, s), 2.22 (3H, s), 3.79 (3H, s), 5.75-6.30 (1H, br), 6.62 (1H, s), 7.20-7.55 (1H, br).

[0363]

20 Reference Example 61

tert-Butyl [4-methoxy-5-methyl-2-(2-oxo-2-thiophen-3-ylethyl)phenyl]carbamate

[0364]

The title compound was synthesized in a manner similar to that of Reference Example 6-1 by using the corresponding starting material and reactants.

25 [0365]

¹H-NMR (CDCl₃) δ ppm:

1.49 (9H, s), 2.18 (3H, s), 3.77 (3H, s), 4.15 (2H, s), 6.61 (1H, s), 6.80-7.70 (4H, m), 8.15-8.30 (1H, m).

[0366]

30 Reference Example 62

5-Methoxy-6-methyl-2-thiophen-3-ylindole

[0367]

The title compound was synthesized in a manner similar to that of Reference Example 7-1 by using the corresponding starting material.

[0368]

¹H-NMR (CDCl₃) δ ppm:

2.30-2.40 (3H, m), 3.88 (3H, s), 6.55-6.65 (1H, m), 7.00 (1H, s), 7.13 (1H, s), 7.30-7.45 (3H, m), 8.02 (1H, br s).

5 [0369]

Reference Example 63

tert-Butyl [5-chloro-4-methoxy-2-(2-oxo-2-pyridin-3-ylethyl)phenyl]carbamate

[0370]

The title compound was synthesized in a manner similar to that of Reference
10 Example 6-1 by using the corresponding starting material and reactants.

[0371]

¹H-NMR (CDCl₃) δ ppm:

1.47 (9H, s), 3.85 (3H, s), 4.29 (2H, s), 6.50-7.20 (2H, m), 7.40-7.90 (2H, m), 8.25-8.35 (1H, m), 8.75-8.90 (1H, m), 9.25-9.35 (1H, m).

15 [0372]

Reference Example 64

6-Chloro-5-methoxy-2-pyridin-3-ylindole

[0373]

The title compound was synthesized in a manner similar to that of Reference
20 Example 7-1 by using the corresponding starting material.

[0374]

¹H-NMR (CDCl₃) δ ppm:

3.95 (3H, s), 6.75-6.85 (1H, m), 7.14 (1H, s), 7.38 (1H, dd, J=4.8, 8.0Hz), 7.45 (1H, s), 7.85-8.00 (1H, m), 8.36 (1H, br s), 8.50-8.65 (1H, m), 8.90-9.00 (1H, m).

25 [0375]

Reference Example 65

1-Benzenesulfonyl-5-bromo-2-phenylindole

[0376]

To a suspension of sodium hydride (in oil, minimum 55%, 801mg) in *N,N*-
30 dimethylformamide (30mL) was added dropwise a solution of 5-bromo-2-phenylindole (3.33g) in *N,N*-dimethylformamide (30mL) under cooling with ice and under an argon atmosphere, and the mixture was stirred at room temperature for one hour and a half. Then benzenesulfonyl chloride (1.88mL) was added dropwise and the stirring was continued for additional 17 hours. A saturated aqueous ammonium chloride solution and

water were added to the reaction mixture and this resulting mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated saline, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluting solvent : ethyl acetate-hexane) to obtain the title compound (1.87g).

[0377]

¹H-NMR (CDCl₃) δ ppm:

6.48 (1H, s), 7.15-7.65 (12H, m), 8.19 (1H, d, J=8.8Hz).

[0378]

10 Reference Example 66

1-Benzenesulfonyl-5-formyl-2-phenylindole

[0379]

To a solution of 1-benzenesulfonyl-5-bromo-2-phenylindole (958mg) in tetrahydrofuran (11.6mL) was added dropwise *n*-butyllithium (2.76mol/L hexane solution, 0.84mL) at -78°C under an argon atmosphere, and the mixture was stirred for 30 minutes. Then *N,N*-dimethylformamide (0.535mL) was added dropwise, and the mixture was stirred at -78°C for 30 minutes and at room temperature for 2 hours. A saturated aqueous ammonium chloride solution and water were added to the reaction mixture and this resulting mixture was extracted with ethyl acetate. The organic layer was washed with saturated saline, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluting solvent : ethyl acetate-hexane) to obtain the title compound (225mg).

[0380]

¹H-NMR (CDCl₃) δ ppm:

25 6.60-6.70 (1H, m), 7.20-7.55 (10H, m), 7.91 (1H, dd, J=1.6, 8.7Hz), 7.95-8.05 (1H, m), 8.47 (1H, d, J=8.7Hz), 10.07 (1H, s).

[0381]

Reference Example 67

1-Benzenesulfonyl-5-hydroxymethyl-2-phenylindole

30 [0382]

To a suspension of 1-benzenesulfonyl-5-formyl-2-phenylindole (224mg) in ethanol (2.5mL) was added sodium borohydride (11.7mg), and the mixture was stirred at room temperature for one hour. A saturated aqueous ammonium chloride solution was added to the reaction mixture and the resulting mixture was extracted with ethyl acetate. The

organic layer was washed with saturated saline, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluting solvent : ethyl acetate-hexane) to obtain the title compound (173mg).

5 [0383]

¹H-NMR (CDCl₃) δ ppm:

1.68 (1H, br s), 4.77 (2H, s), 6.50-6.60 (1H, m), 7.20-7.55 (12H, m), 8.29 (1H, d, J=8.5Hz).

[0384]

10 Reference Example 68

1-Benzenesulfonyl-2-phenyl-5-triisopropylsilanyloxymethylindole

[0385]

To a solution of 1-benzenesulfonyl-5-hydroxymethyl-2-phenylindole (171mg) in *N,N*-dimethylformamide (2.4mL) were added imidazole (128mg) and
 15 chlorotriisopropylsilane (0.150mL) under cooling with ice, and the mixture was stirred at room temperature for 20 hours. Water was added to the reaction mixture and this resulting mixture was extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluting solvent : ethyl
 20 acetate-hexane) to obtain the title compound (221mg).

[0386]

¹H-NMR (CDCl₃) δ ppm:

0.95-1.30 (21H, m), 4.90 (2H, s), 6.50-6.60 (1H, m), 7.20-7.55 (12H, m), 8.25 (1H, d, J=8.8Hz).

25 [0387]

Reference Example 69

2-Phenyl-5-triisopropylsilanyloxymethylindole

[0388]

The title compound was synthesized in a manner similar to that of Reference
 30 Example 25 by using the corresponding starting material.

[0389]

¹H-NMR (CDCl₃) δ ppm:

1.00-1.35 (21H, m), 4.93 (2H, s), 6.75-6.85 (1H, m), 7.15-7.25 (1H, m), 7.25-7.40 (2H, m), 7.40-7.50 (2H, m), 7.55-7.75 (3H, m), 8.15-8.45 (1H, br).

[0390]

Reference Example 70

Methyl 6-(2-phenyl-6-triisopropylsilanyloxymethylindol-1-ylmethyl)pyridine-2-carboxylate

5 [0391]

The title compound was synthesized in a manner similar to that of Reference Example 55 by using the corresponding starting material and reactants.

[0392]

¹H-NMR (CDCl₃) δ ppm:

10 1.05-1.25 (21H, m), 4.03 (3H, s), 4.93 (2H, s), 5.60 (2H, s), 6.65-6.75 (2H, m), 7.08 (1H, d, J=8.3Hz), 7.10-7.20 (1H, m), 7.30-7.45 (5H, m), 7.60-7.70 (2H, m), 7.95-8.05 (1H, m).

[0393]

Reference Example 71

tert-Butyl [5-chloro-2-(2-hydroxy-3-methylpentyl)-4-methoxyphenyl]carbamate

15 [0394]

The title compound was synthesized in a manner similar to that of Reference Example 14 by using the corresponding starting material and reactants.

[0395]

¹H-NMR (CDCl₃) δ ppm:

20 0.50-2.30 (19H, m), 2.45-2.95 (2H, m), 3.55-4.05 (4H, m), 6.60-6.80 (1H, m), 7.20-8.00 (2H, m).

[0396]

Reference Example 72

1-(2-Amino-4-chloro-5-methoxyphenyl)-3-methylpentan-2-ol

25 [0397]

The title compound was synthesized in a manner similar to that of Reference Example 15 by using the corresponding starting material.

[0398]

¹H-NMR (CDCl₃) δ ppm:

30 0.75-1.75 (9H, m), 2.45-2.85 (2H, m), 3.30-4.10 (6H, m), 6.60-6.80 (2H, m).

ESI-MS (m/z) : 258, 260 (M+H)⁺

[0399]

Reference Example 73

6-Chloro-5-methoxy-2-(1-methylpropyl)indole

[0400]

A mixture of 1-(2-amino-4-chloro-5-methoxyphenyl)-3-methylpentan-2-ol (602mg), tetrakis(triphenylphosphine)palladium (0) (135mg), potassium carbonate (646mg), 2-bromomesitylene (0.420mL) and *N,N*-dimethylformamide (11.7mL) was stirred at 160°C for one hour under microwave irradiation. The reaction mixture was allowed to cool to ambient temperature. Water was added to the reaction mixture and this resulting mixture was extracted with ethyl acetate. The organic layer was washed with saturated saline, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluting solvent : ethyl acetate-hexane) to obtain the title compound (514mg).

[0401]

¹H-NMR (CDCl₃) δ ppm:

0.91 (3H, t, J=7.4Hz), 1.32 (3H, d, J=6.8Hz), 1.55-1.80 (2H, m), 2.70-2.90 (1H, m), 3.91 (3H, s), 6.10-6.20 (1H, m), 7.05 (1H, s), 7.25-7.35 (1H, m), 7.50-8.00 (1H, br).

[0402]

Reference Example 74

tert-Butyl (4-cyclopropyl-2-methylphenyl)carbamate

[0403]

A mixture of *tert*-butyl (4-iodo-2-methylphenyl)carbamate (1.04g), cyclopropylboronic acid monohydrate (422mg), palladium acetate (35.1mg), tricyclohexylphosphine (87.5mg), tripotassium phosphate monohydrate (2.52g), toluene (8.7mL) and water (0.87mL) was stirred at 100°C for 15 hours. The reaction mixture was allowed to cool to ambient temperature, diluted with ethyl acetate and filtered through celite (registered trademark). The filtrate was washed with water/saturated saline (1/1, 20mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluting solvent : ethyl acetate-hexane) to obtain the title compound (668mg).

[0404]

¹H-NMR (CDCl₃) δ ppm:

0.55-0.70 (2H, m), 0.80-1.00 (2H, m), 1.51 (9H, s), 1.75-1.90 (1H, m), 2.21 (3H, s), 5.85-6.45 (1H, br), 6.75-7.00 (2H, m), 7.45-7.75 (1H, m).

[0405]

Reference Example 75

tert-Butyl [4-cyclopropyl-2-(2-oxo-2-phenylethyl)phenyl]carbamate

[0406]

The title compound was synthesized in a manner similar to that of Reference Example 6-1 by using the corresponding starting material and reactants.

¹H-NMR (CDCl₃) δ ppm:

5 0.55-0.70 (2H, m), 0.80-1.00 (2H, m), 1.49 (9H, s), 1.75-1.90 (1H, m), 4.25 (2H, s), 6.85-7.00 (2H, m), 7.20-7.75 (5H, m), 8.00-8.15 (2H, m).

[0407]

Reference Example 76

5-Cyclopropyl-2-phenylindole

10 [0408]

The title compound was synthesized in a manner similar to that of Reference Example 7-1 by using the corresponding starting material and reactant.

[0409]

¹H-NMR (CDCl₃) δ ppm:

15 0.65-0.75 (2H, m), 0.85-1.00 (2H, m), 1.95-2.10 (1H, m), 6.70-6.80 (1H, m), 6.90-7.00 (1H, m), 7.25-7.50 (5H, m), 7.60-7.70 (2H, m), 8.24 (1H, br s).

[0410]

Example 1-1

Methyl 6-(5-chloro-2-phenylindol-1-ylmethyl)pyridine-2-carboxylate

20 [0411]

To a solution of 5-chloro-2-phenylindole (154mg) in *N,N*-dimethylformamide (1.5mL) was added sodium hydride (dispersed in liquid paraffin, minimum 55%, 31mg) at room temperature, and the mixture was stirred for 15 minutes. Methyl 6-(chloromethyl)pyridine-2-carboxylate (126mg) was added and this resulting mixture was stirred at 50 to 60°C for additional 18 hours. Water, ethyl acetate and a saturated aqueous ammonium chloride solution were added to the reaction mixture. The organic layer was separated. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed successively with water and saturated saline, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by aminopropylated silica gel column chromatography (eluting solvent : ethyl acetate-hexane) to obtain the title compound (112mg).

In addition, structural formula and spectrum data of the title compound are shown in Table 5.

[0412]

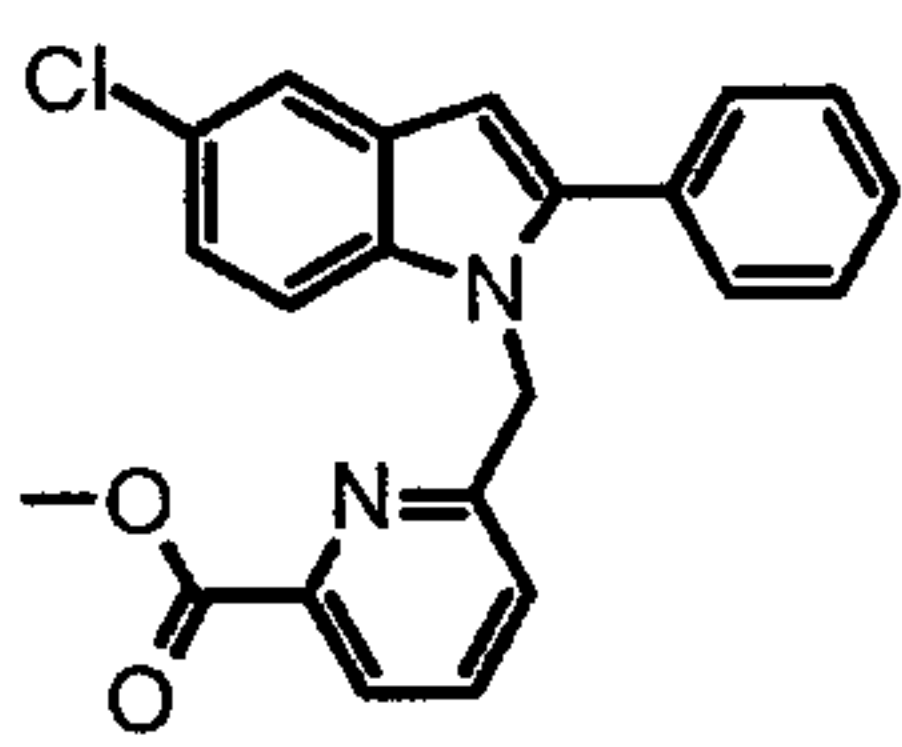
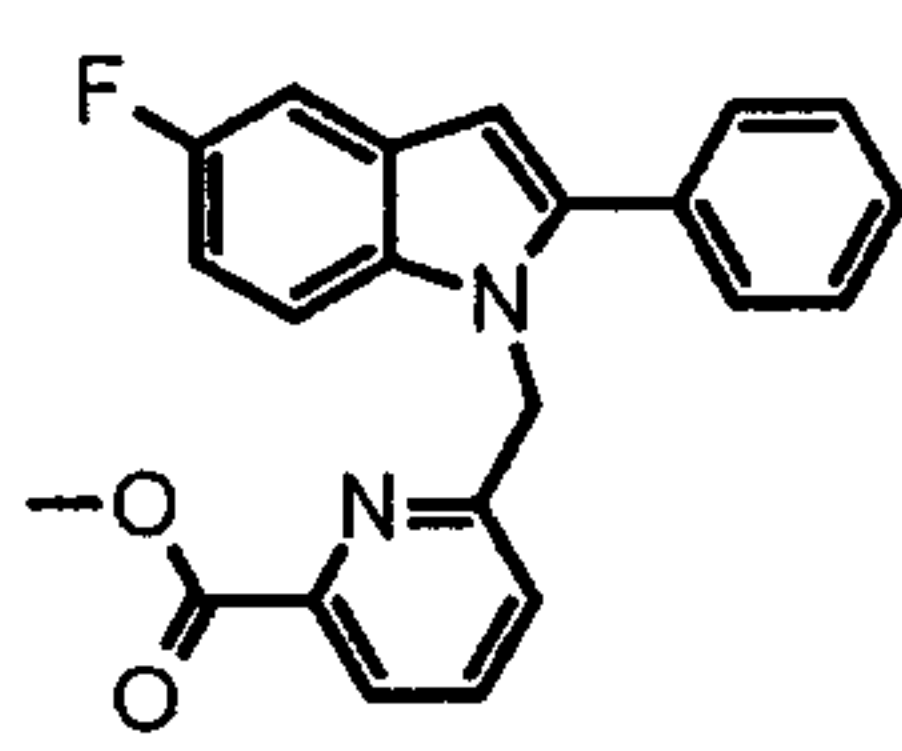
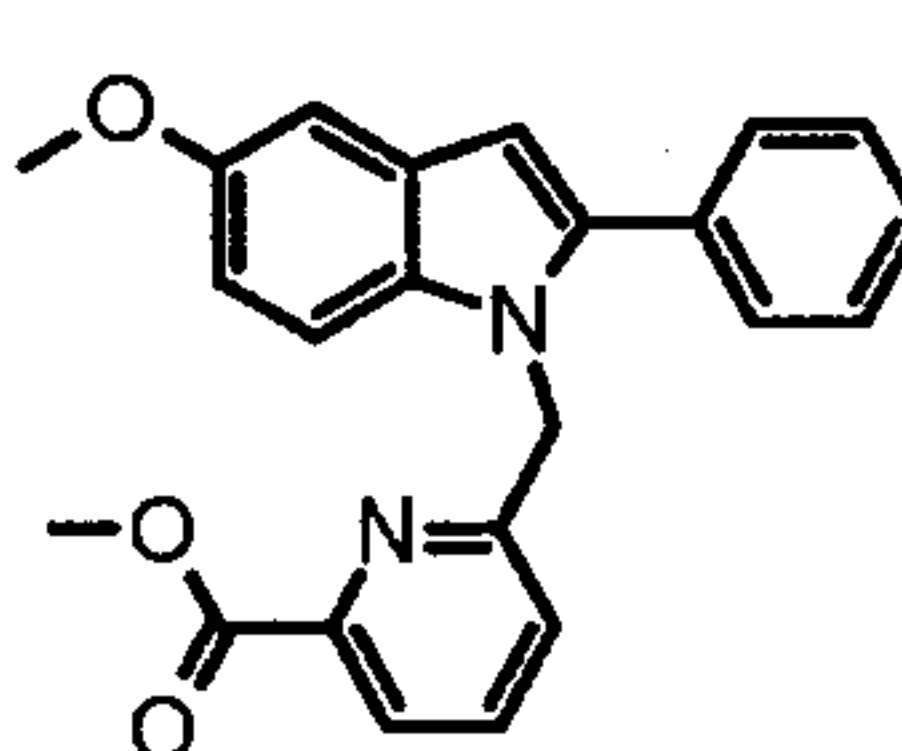
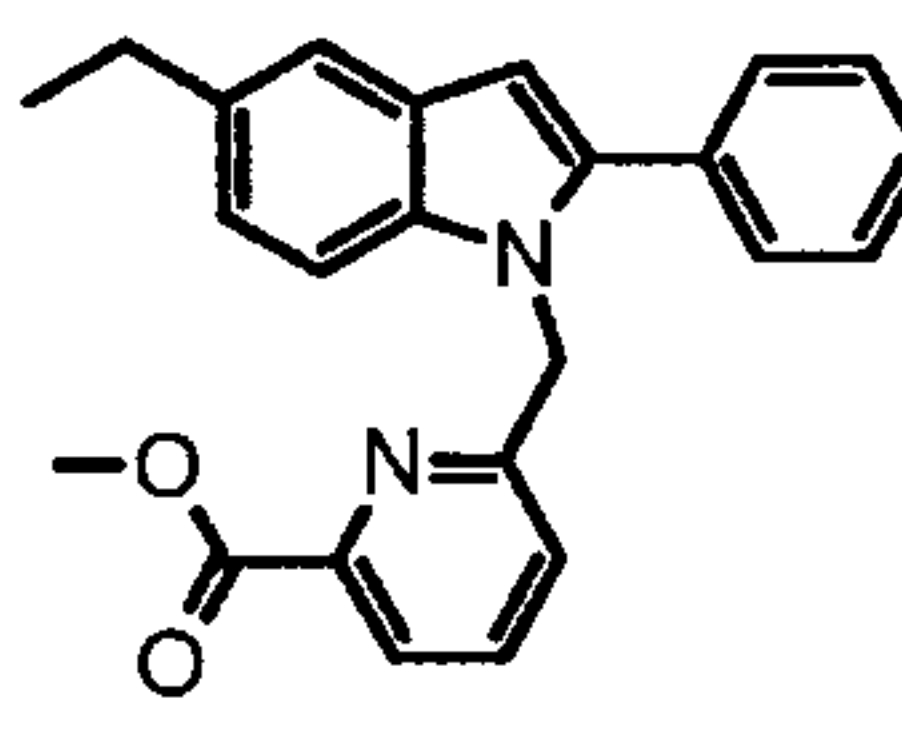
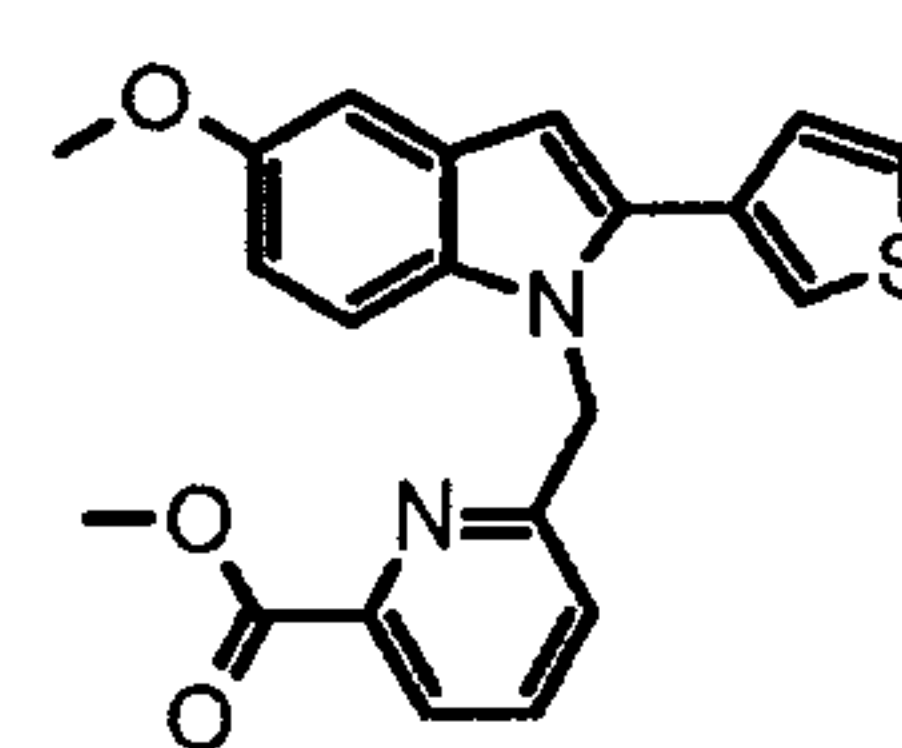
Examples 1-2 to 1-8

The compounds shown in Tables 5 to 6 were synthesized in a manner similar to that of Example 1-1 by using the corresponding starting materials.

[0413]

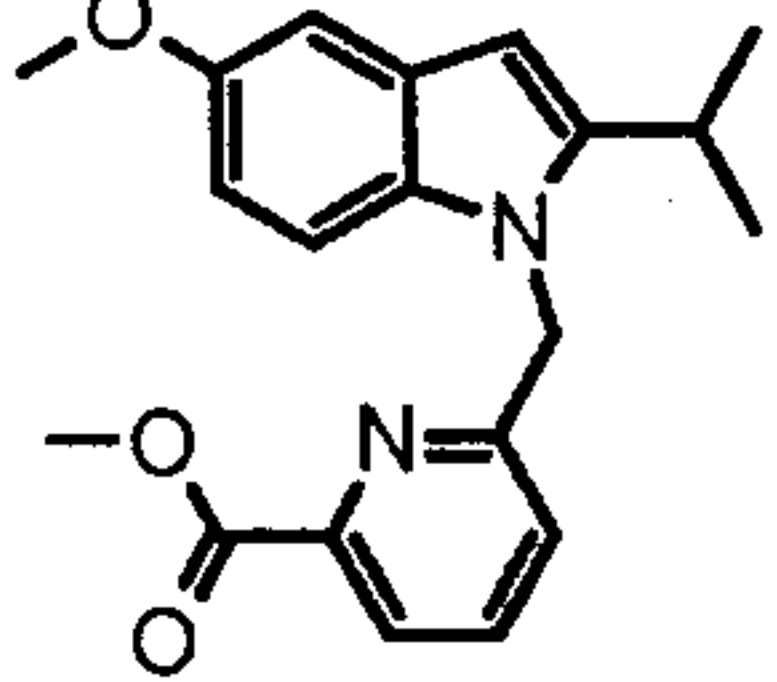
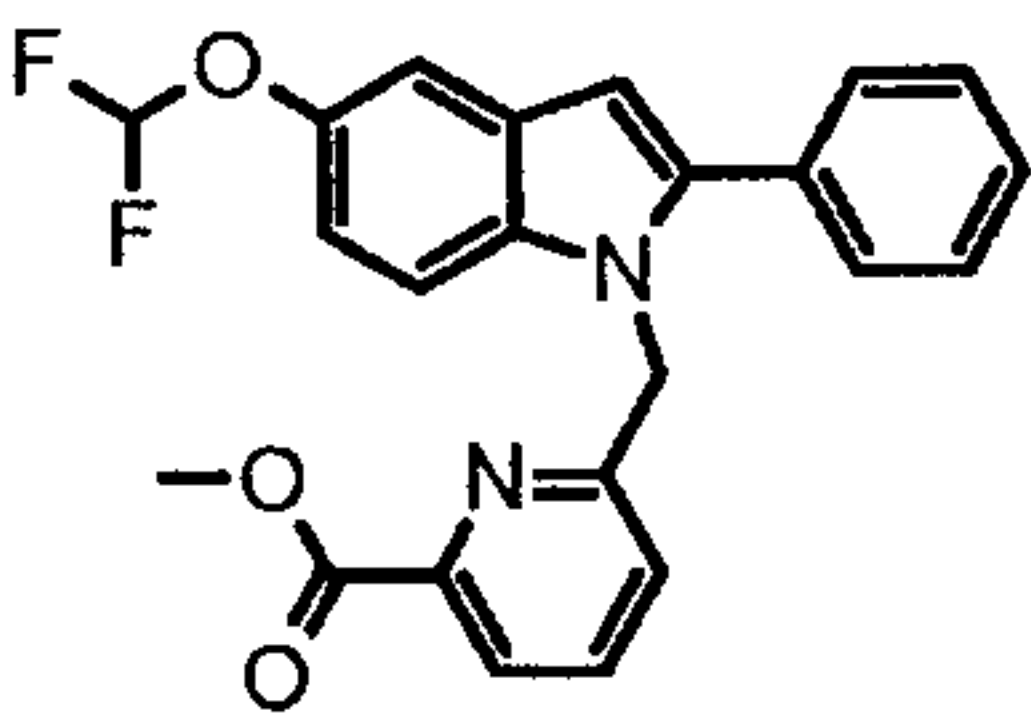
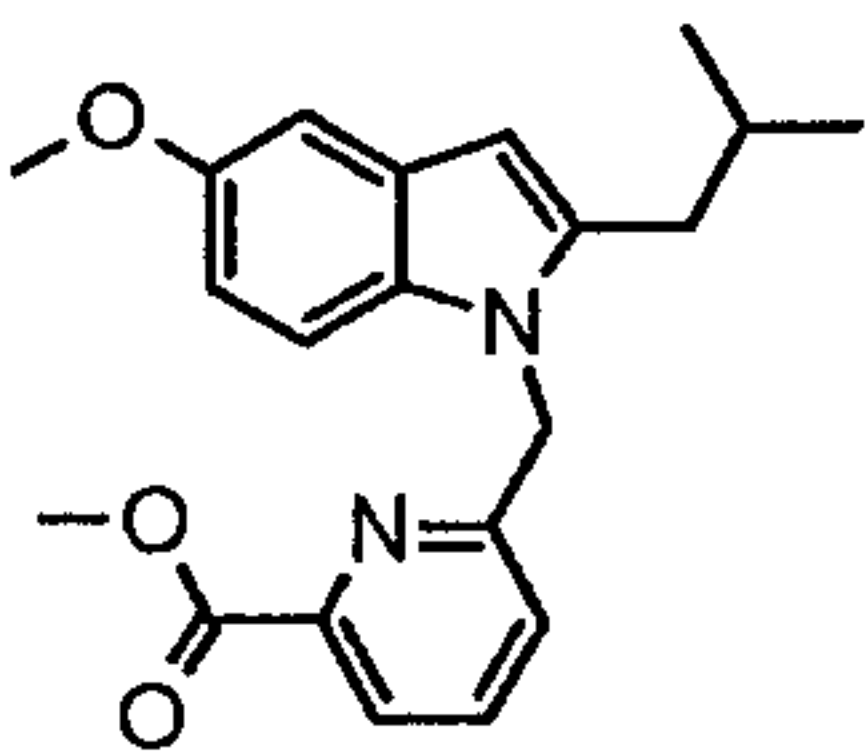
5

[Table 5]

Ex. No.	Strc	Physical data
1-1		¹ H-NMR (CDCl ₃) δ ppm: 4.03 (3H, s), 5.59 (2H, s), 6.60–6.70 (2H, m), 7.00–7.15 (2H, m), 7.35–7.45 (5H, m), 7.60–7.75 (2H, m), 7.95–8.05 (1H, m).
1-2		¹ H-NMR (CDCl ₃) δ ppm: 4.02 (3H, s), 5.59 (2H, s), 6.60–6.75 (2H, m), 6.85–6.95 (1H, m), 7.04 (1H, dd, J=4.3, 8.8Hz), 7.25–7.50 (6H, m), 7.60–7.75 (1H, m), 8.00 (1H, d, J=7.5Hz).
1-3		¹ H-NMR (CDCl ₃) δ ppm: 3.87 (3H, s), 4.02 (3H, s), 5.58 (2H, s), 6.60–6.75 (2H, m), 6.81 (1H, dd, J=2.5, 8.8Hz), 7.02 (1H, d, J=8.8Hz), 7.15 (1H, d, J=2.5Hz), 7.30–7.45 (5H, m), 7.60–7.70 (1H, m), 7.95–8.05 (1H, m).
1-4		¹ H-NMR (CDCl ₃) δ ppm: 1.29 (3H, t, J=7.5Hz), 2.75 (2H, q, J=7.5Hz), 4.03 (3H, s), 5.59 (2H, s), 6.55–6.80 (2H, m), 6.95–7.10 (2H, m), 7.25–7.60 (6H, m), 7.60–7.75 (1H, m), 7.90–8.05 (1H, m).
1-5		¹ H-NMR (CDCl ₃) δ ppm: 3.86 (3H, s), 4.05 (3H, s), 5.63 (2H, s), 6.60–6.70 (1H, m), 6.70–6.80 (1H, m), 6.81 (1H, dd, J=2.5, 8.8Hz), 7.03 (1H, d, J=8.8Hz), 7.13 (1H, d, J=2.5Hz), 7.16 (1H, dd, J=1.3, 5.0Hz), 7.23 (1H, dd, J=1.3, 3.0Hz), 7.36 (1H, dd, J=3.0, 5.0Hz), 7.68 (1H, t, J=7.8Hz), 7.95–8.05 (1H, m).

[0414]

[Table 6]

Ex. No.	Strc	Physical data
1-6		¹ H-NMR (CDCl ₃) δ ppm: 1.27 (6H, d, J=6.8Hz), 2.85-3.00 (1H, m), 3.84 (3H, s), 4.05 (3H, s), 5.55 (2H, s), 6.34 (1H, s), 6.40-6.50 (1H, m), 6.74 (1H, dd, J=2.5, 8.8Hz), 6.98 (1H, d, J=8.8Hz), 7.08 (1H, d, J=2.5Hz), 7.55-7.65 (1H, m), 7.95-8.05 (1H, m).
1-7		¹ H-NMR (CDCl ₃) δ ppm: 4.03 (3H, s), 5.60 (2H, s), 6.30-6.80 (3H, m), 6.95 (1H, dd, J=2.3, 8.8Hz), 7.09 (1H, d, J=8.8Hz), 7.35-7.50 (6H, m), 7.65-7.75 (1H, m), 7.95-8.05 (1H, m).
1-8		¹ H-NMR (CDCl ₃) δ ppm: 0.93 (6H, d, J=6.8Hz), 1.80-1.95 (1H, m), 2.52 (2H, d, J=7.0Hz), 3.84 (3H, s), 4.05 (3H, s), 5.51 (2H, s), 6.31 (1H, s), 6.44 (1H, d, J=7.8Hz), 6.74 (1H, dd, J=2.4, 8.9Hz), 6.99 (1H, d, J=8.9Hz), 7.07 (1H, d, J=2.4Hz), 7.61 (1H, t, J=7.8Hz), 7.99 (1H, d, J=7.8Hz).

[0415]

5 Example 2-1

Ethyl 5-(5-chloro-2-isopropylindol-1-ylmethyl)furan-2-carboxylate

[0416]

To a solution of 5-chloro-2-isopropylindole (136mg) in *N,N*-dimethylformamide (2mL) was added sodium hydride (dispersed in liquid paraffin, minimum 55%, 32mg) under cooling with ice, and the mixture was stirred for 30 minutes. Then ethyl 5-(chloromethyl)furan-2-carboxylate (0.107mL) was added, and the mixture was stirred at 60°C for 20 hours. A saturated aqueous ammonium chloride solution was added to the reaction mixture and this resulting mixture was extracted with ethyl acetate. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with saturated saline, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluting

solvent : ethyl acetate-hexane) to obtain the title compound (133mg).

In addition, structural formula and spectrum data of the title compound are shown in Table 7.

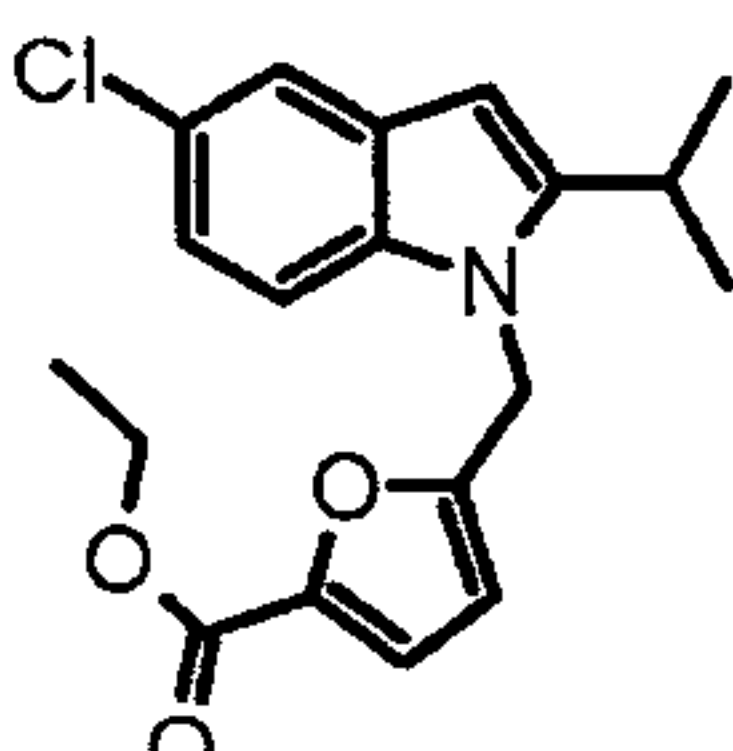
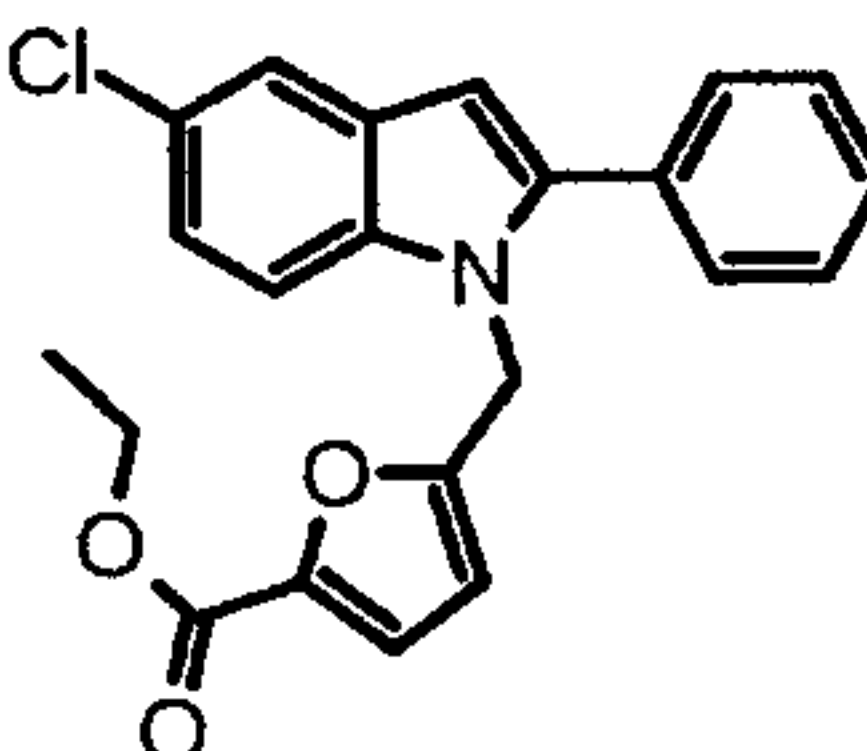
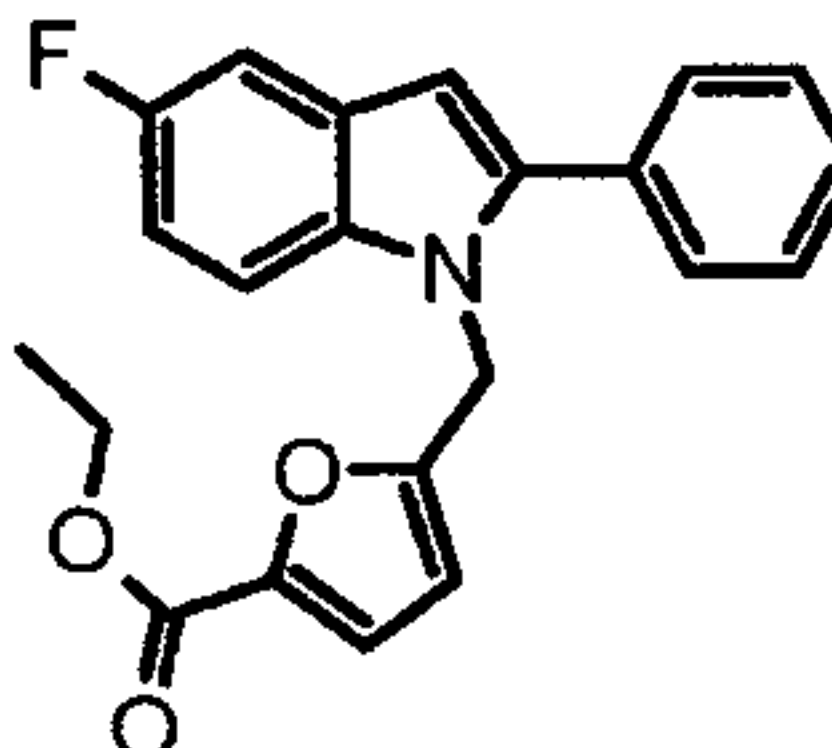
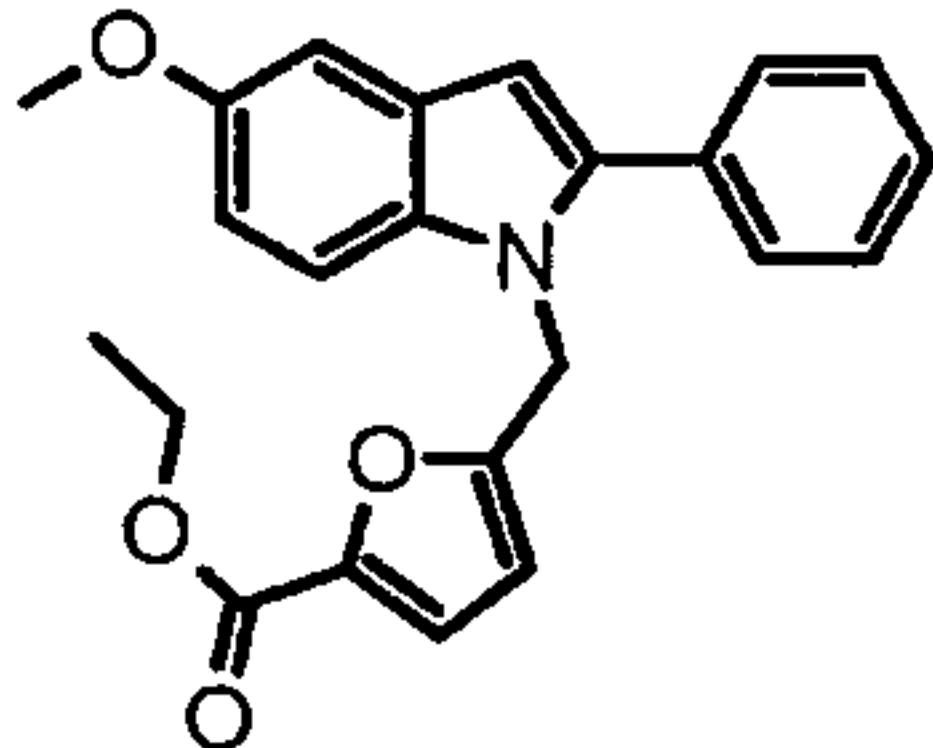
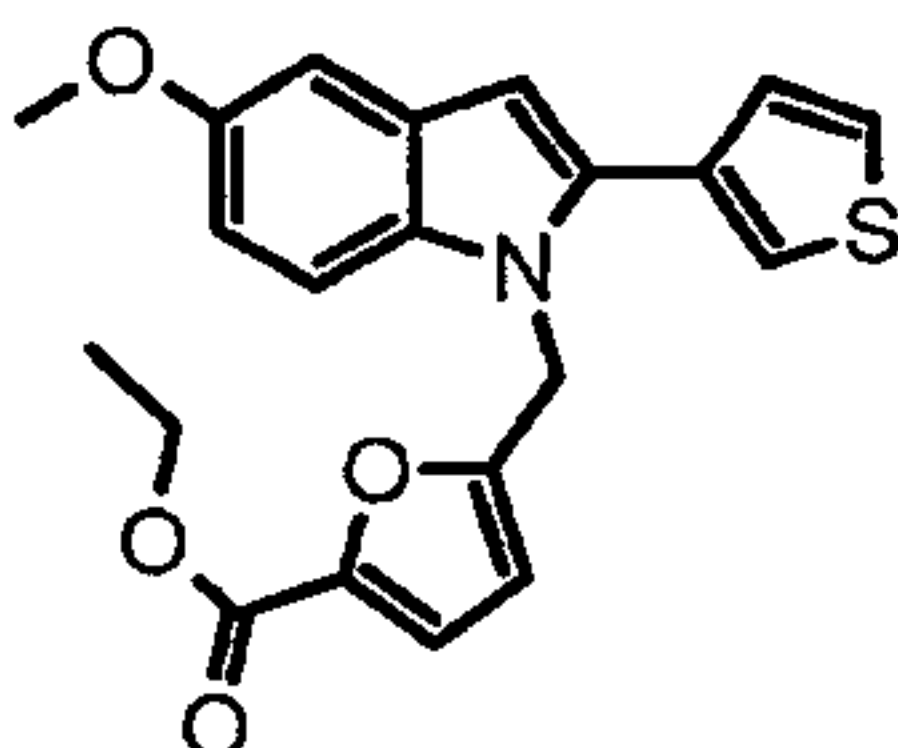
[0417]

5 Examples 2-2 to 2-7

The compounds shown in Tables 7 to 8 were synthesized in a manner similar to that of Example 2-1 by using the corresponding starting materials.

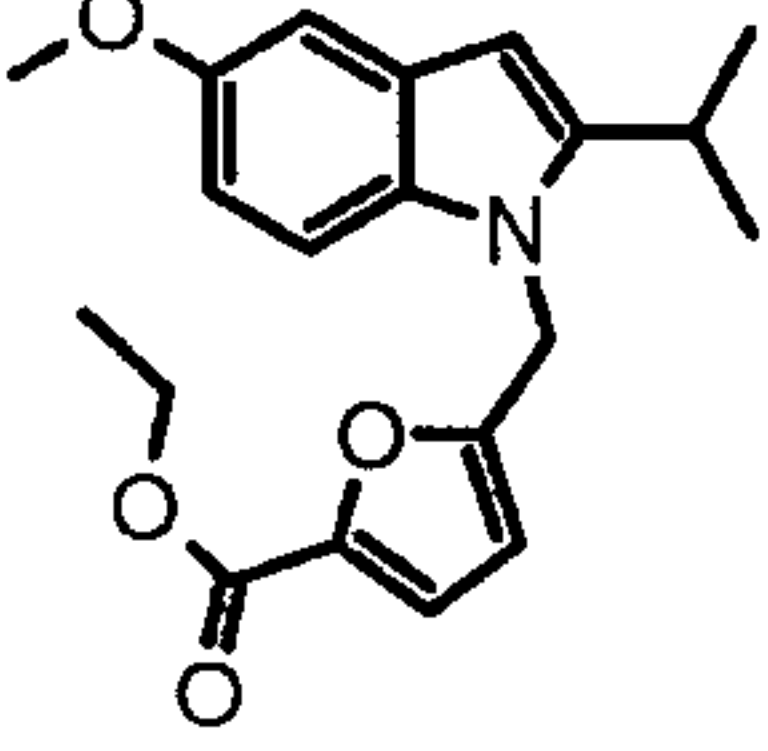
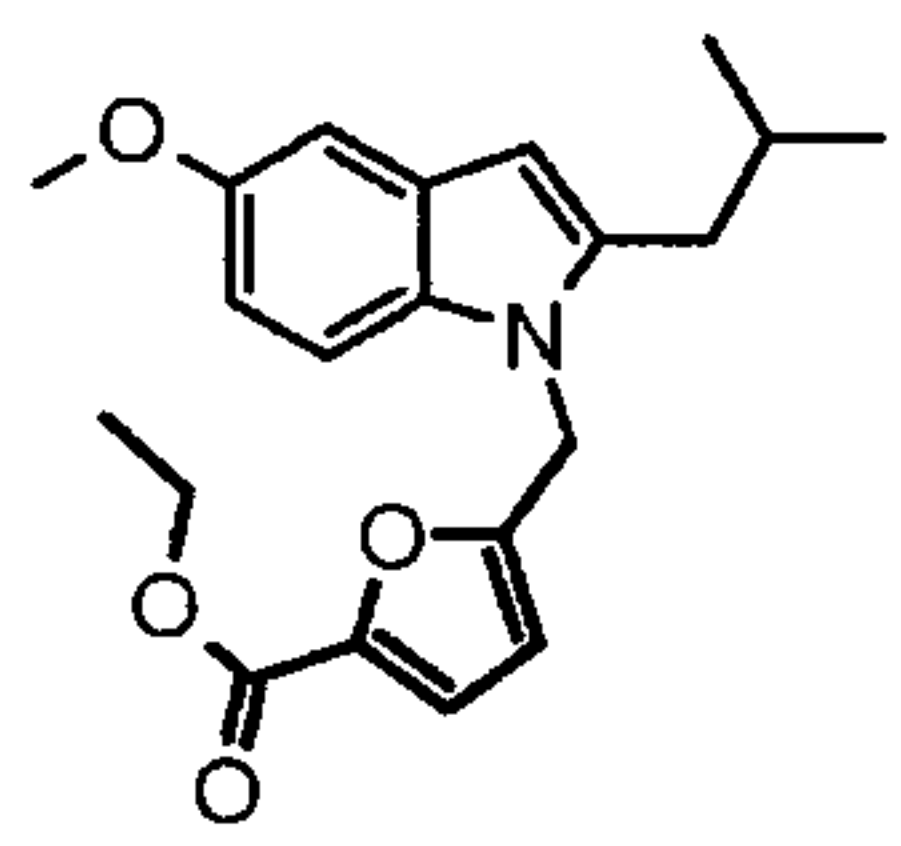
[0418]

[Table 7]

Ex. No.	Strc	Physical data
2-1		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.30–1.40 (9H, m), 2.95–3.15 (1H, m), 4.35 (2H, q, $J=7.0\text{Hz}$), 5.32 (2H, s), 5.80–5.85 (1H, m), 6.29 (1H, s), 6.95–7.15 (3H, m), 7.45–7.55 (1H, m).
2-2		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.37 (3H, t, $J=7.1\text{Hz}$), 4.34 (2H, q, $J=7.1\text{Hz}$), 5.30 (2H, s), 5.97 (1H, d, $J=3.4\text{Hz}$), 6.55 (1H, s), 7.04 (1H, d, $J=3.4\text{Hz}$), 7.16 (1H, dd, $J=2.0, 8.7\text{Hz}$), 7.22 (1H, d, $J=8.7\text{Hz}$), 7.35–7.55 (5H, m), 7.55–7.65 (1H, m).
2-3		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.37 (3H, t, $J=7.1\text{Hz}$), 4.35 (2H, q, $J=7.1\text{Hz}$), 5.30 (2H, s), 5.95–6.05 (1H, m), 6.55–6.60 (1H, m), 6.95 (1H, dt, $J=2.4, 9.0\text{Hz}$), 7.05 (1H, d, $J=3.5\text{Hz}$), 7.22 (1H, dd, $J=4.4, 9.0\text{Hz}$), 7.29 (1H, dd, $J=2.4, 9.4\text{Hz}$), 7.35–7.55 (5H, m).
2-4		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.37 (3H, t, $J=7.2\text{Hz}$), 3.87 (3H, s), 4.35 (2H, q, $J=7.2\text{Hz}$), 5.29 (2H, s), 5.95–6.05 (1H, m), 6.50–6.60 (1H, m), 6.87 (1H, dd, $J=2.4, 9.0\text{Hz}$), 7.05 (1H, d, $J=3.5\text{Hz}$), 7.12 (1H, d, $J=2.4\text{Hz}$), 7.19 (1H, d, $J=9.0\text{Hz}$), 7.35–7.55 (5H, m).
2-5		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.37 (3H, t, $J=7.2\text{Hz}$), 3.86 (3H, s), 4.35 (2H, q, $J=7.2\text{Hz}$), 5.34 (2H, s), 6.00–6.05 (1H, m), 6.55–6.60 (1H, m), 6.86 (1H, dd, $J=2.5, 8.8\text{Hz}$), 7.06 (1H, d, $J=3.3\text{Hz}$), 7.09 (1H, d, $J=2.5\text{Hz}$), 7.18 (1H, d, $J=8.8\text{Hz}$), 7.24 (1H, dd, $J=1.3, 5.0\text{Hz}$), 7.37 (1H, dd, $J=1.3, 2.9\text{Hz}$), 7.41 (1H, dd, $J=2.9, 5.0\text{Hz}$).

[0419]

[Table 8]

Ex. No.	Strc	Physical data
2-6		¹ H-NMR (CDCl ₃) δ ppm: 1.32 (6H, d, J=7.0Hz), 1.36 (3H, t, J=7.1Hz), 2.95-3.10 (1H, m), 3.83 (3H, s), 4.35 (2H, q, J=7.1Hz), 5.30 (2H, s), 5.80-5.90 (1H, m), 6.27 (1H, s), 6.78 (1H, dd, J=2.5, 8.8Hz), 7.00 (1H, d, J=3.3Hz), 7.04 (1H, d, J=2.5Hz), 7.10 (1H, d, J=8.8Hz).
2-7		¹ H-NMR (CDCl ₃) δ ppm: 0.98 (6H, d, J=6.5Hz), 1.37 (3H, t, J=7.1Hz), 1.85-2.05 (1H, m), 2.59 (2H, d, J=7.3Hz), 3.84 (3H, s), 4.35 (2H, q, J=7.1Hz), 5.27 (2H, s), 5.82 (1H, d, J=3.5Hz), 6.24 (1H, s), 6.78 (1H, dd, J=2.3, 9.0Hz), 7.00 (1H, d, J=3.5Hz), 7.03 (1H, d, J=2.3Hz), 7.10 (1H, d, J=9.0Hz).

[0420]

Example 3-1

Methyl 3-(5-methoxy-2-phenylindol-1-ylmethyl)benzoate

5 [0421]

To a solution of 5-methoxy-2-phenylindole (73.0mg) in *N,N*-dimethylformamide (1.6mL) was added sodium hydride (dispersed in liquid paraffin, minimum 55%, 22mg) under cooling with ice, and the mixture was stirred at room temperature for 70 minutes. Then methyl 3-(bromomethyl)benzoate (89.9mg) was added, and the mixture was stirred at 100°C for 6 hours. The reaction mixture was cooled to room temperature. Saturated ammonium chloride-water (2/1) were added and this resulting mixture was extracted with ethyl acetate. The organic layer was washed with saturated saline, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by aminopropylated silica gel column chromatography (eluting solvent : ethyl acetate-hexane) to obtain the title compound (50.6mg).

In addition, structural formula and spectrum data of the title compound are shown in Table 9.

[0422]

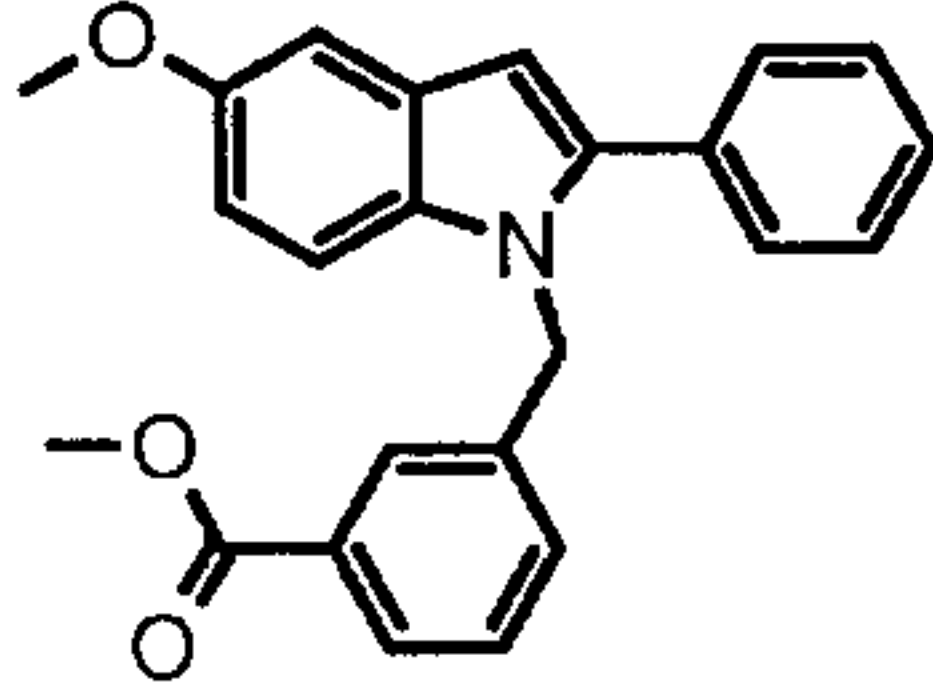
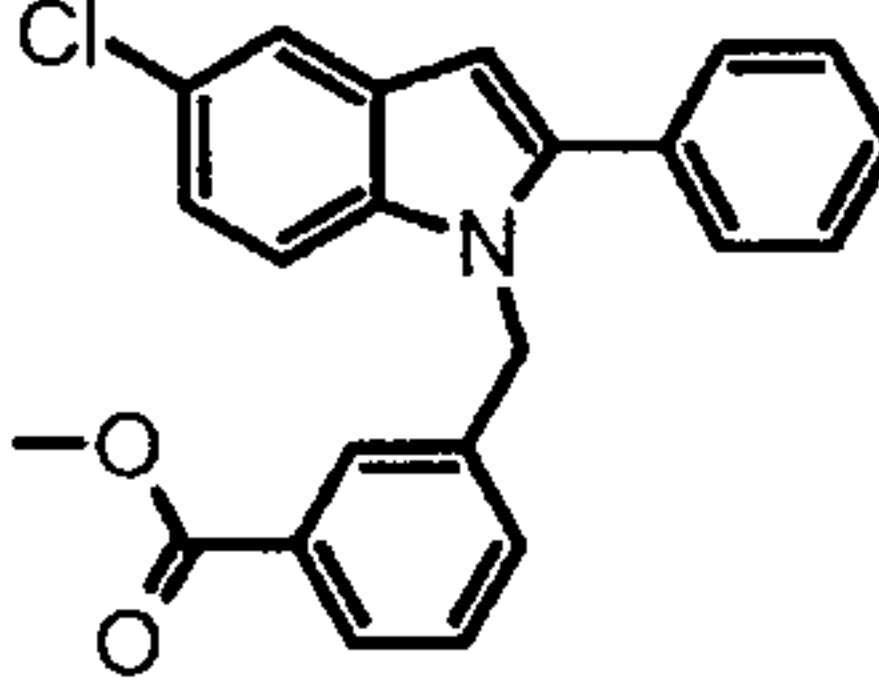
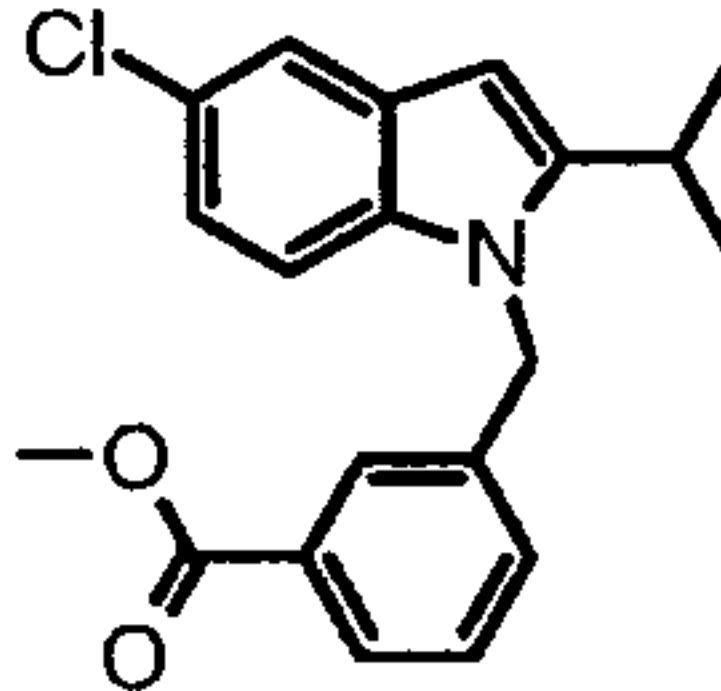
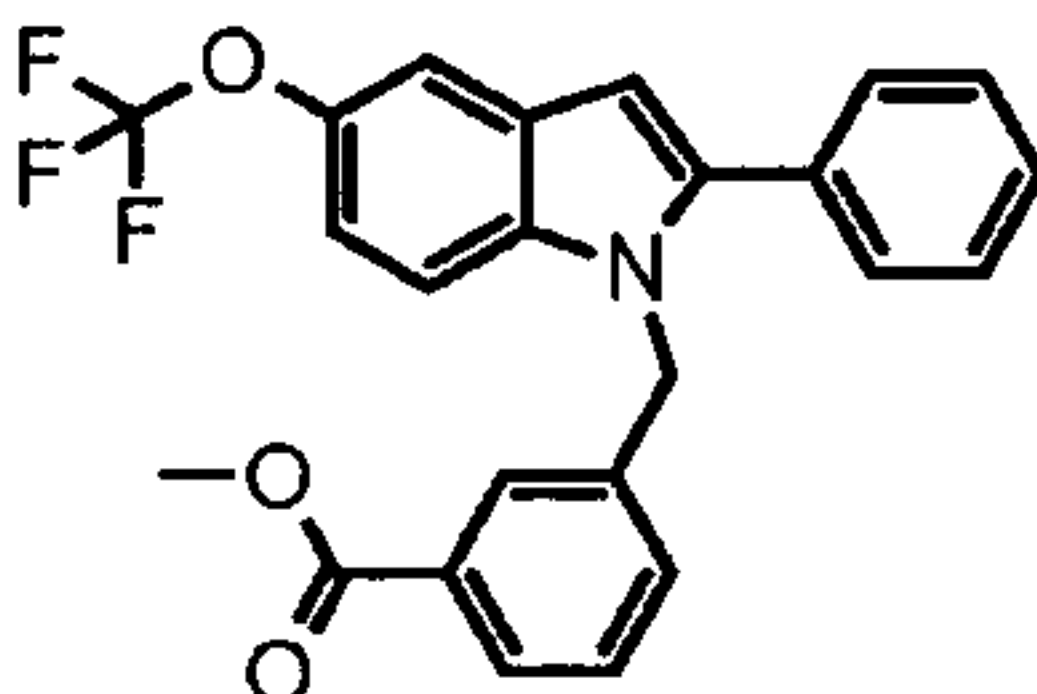
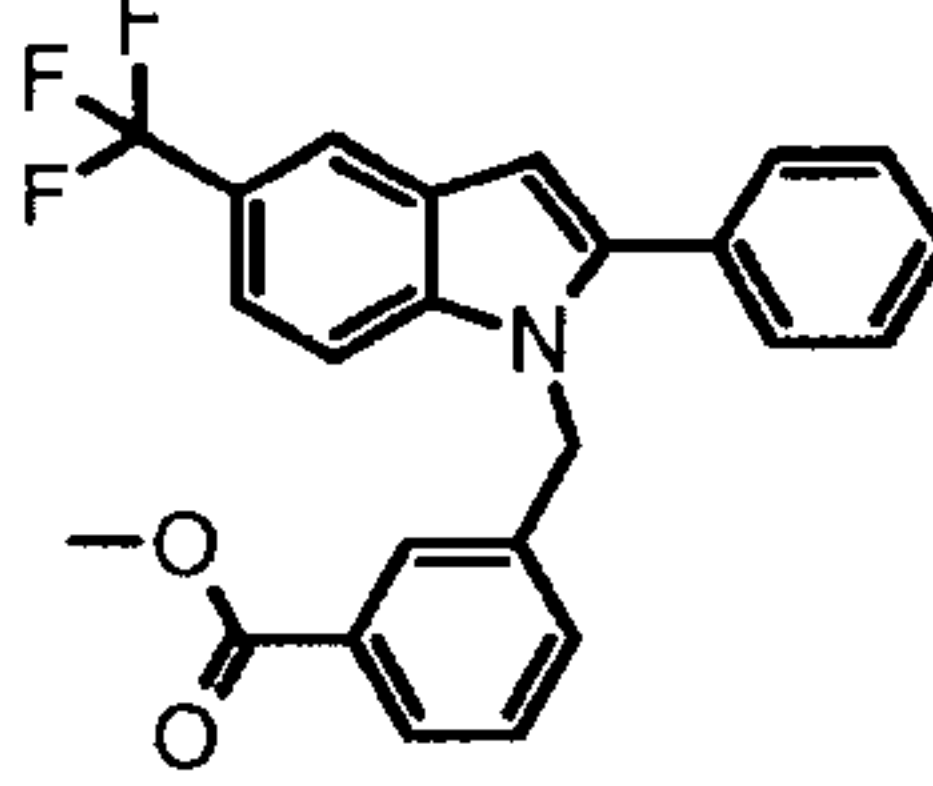
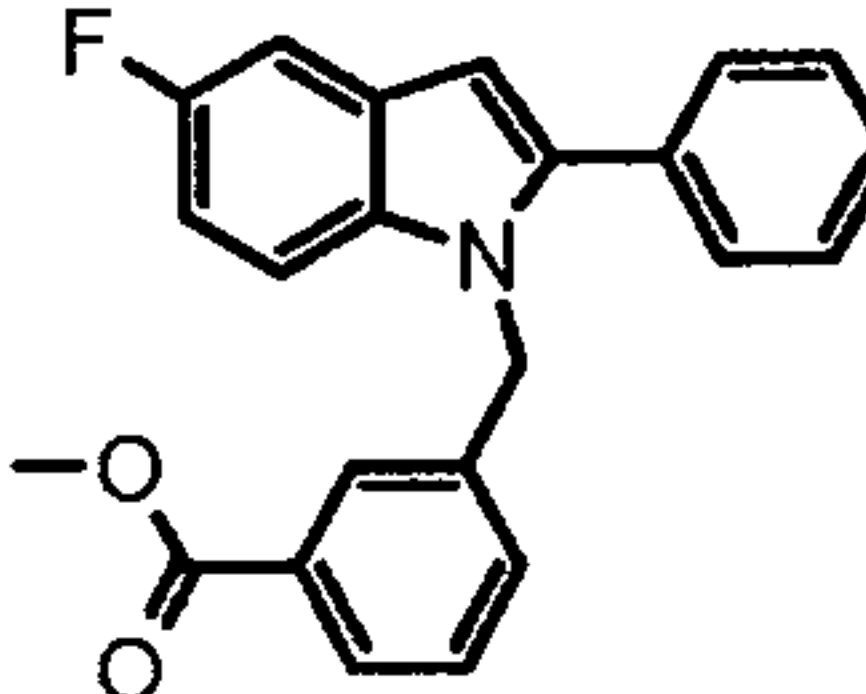
Examples 3-2 to 3-22

The compounds shown in Tables 9 to 12 were synthesized in a manner similar to

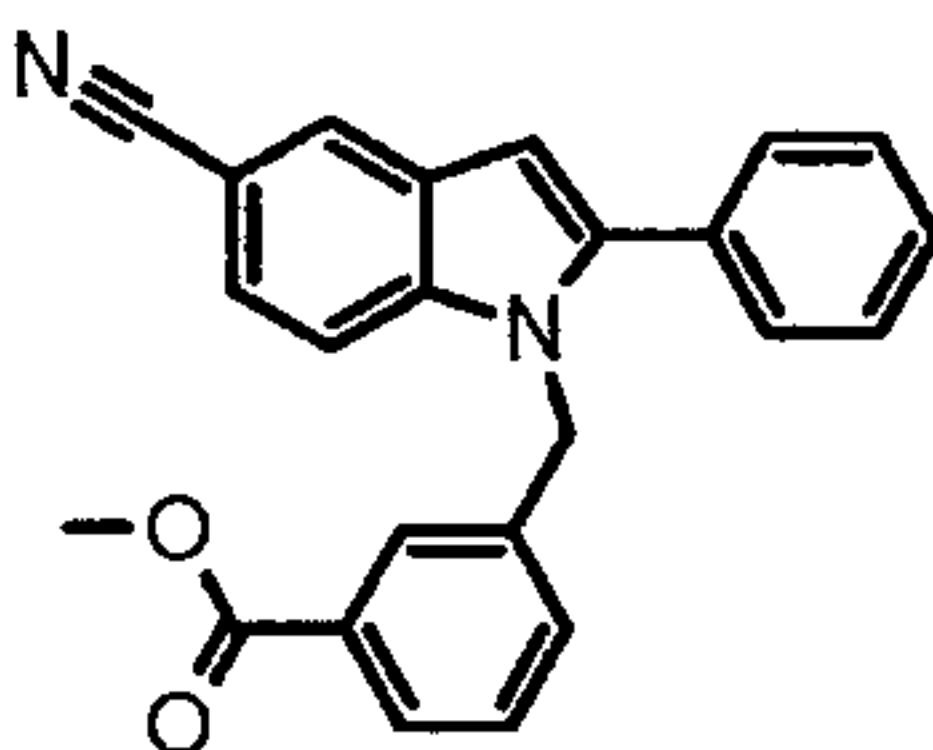
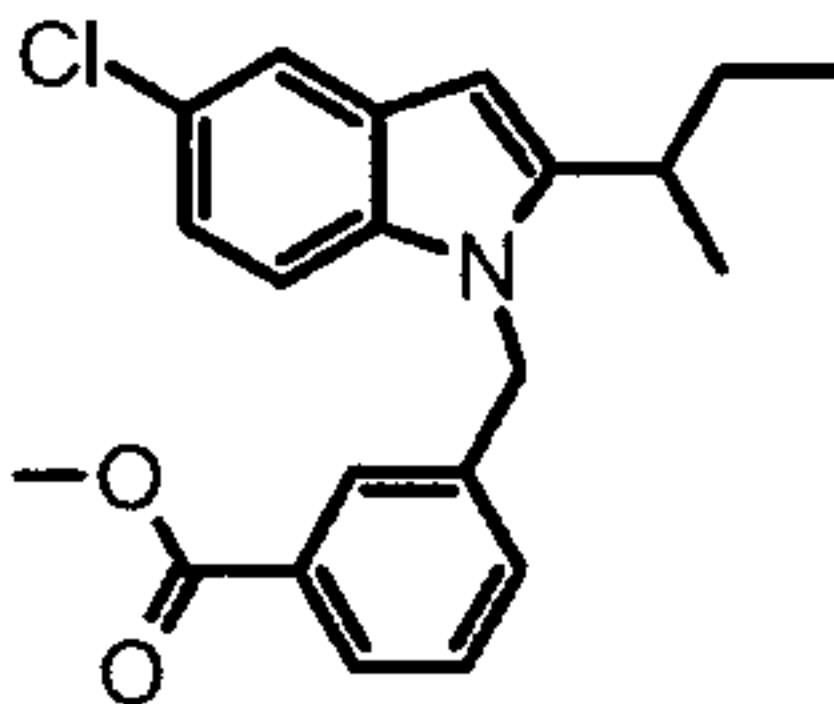
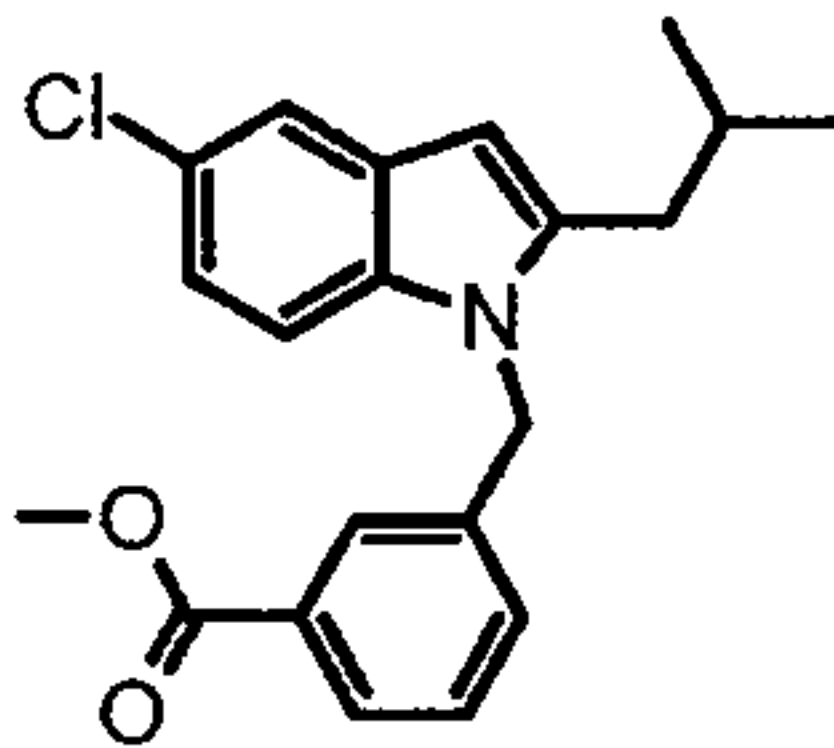
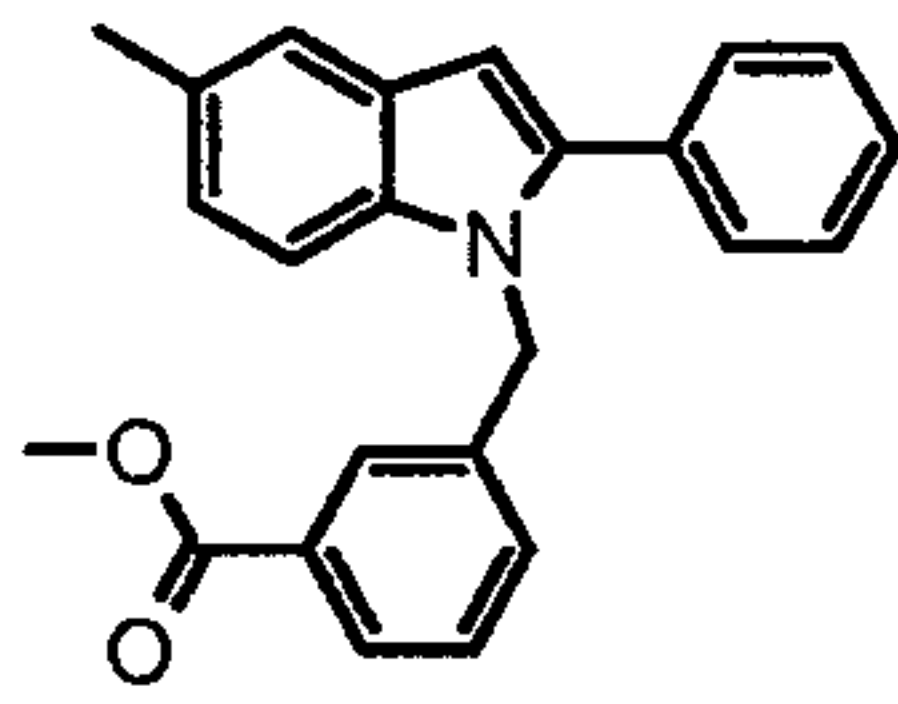
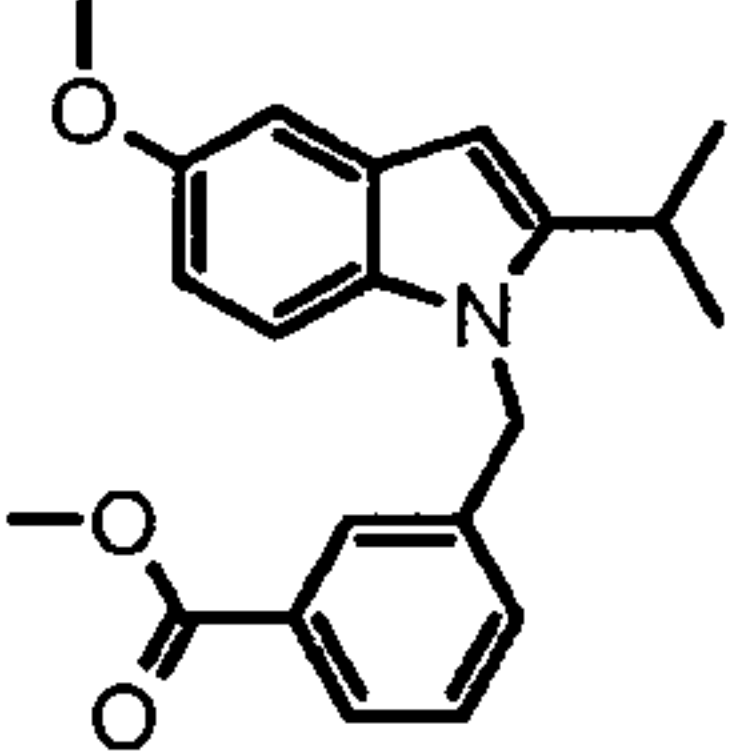
that of Example 3-1 by using the corresponding starting materials.

[0423]

[Table 9]

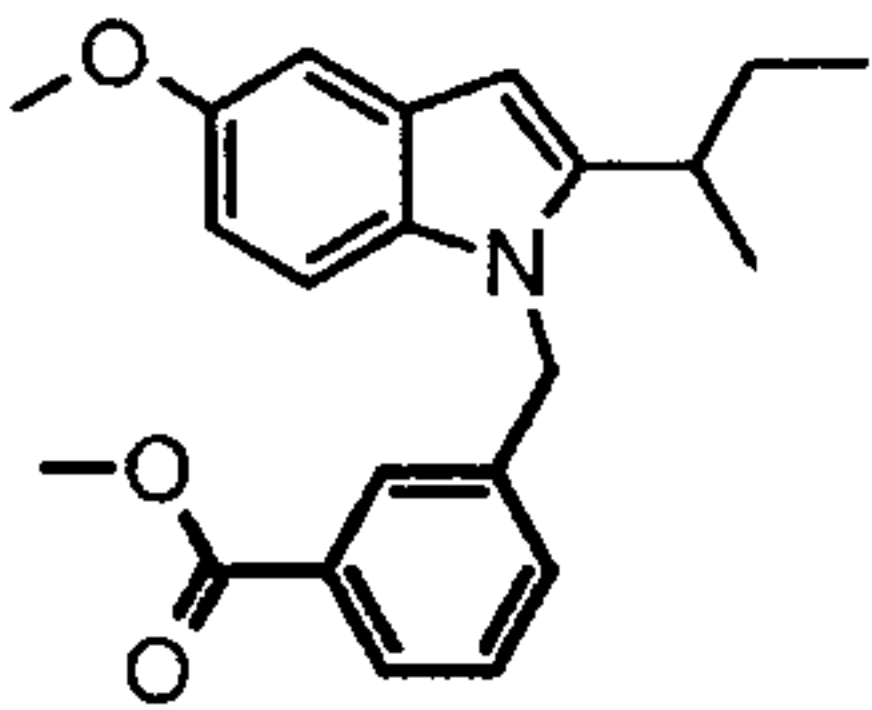
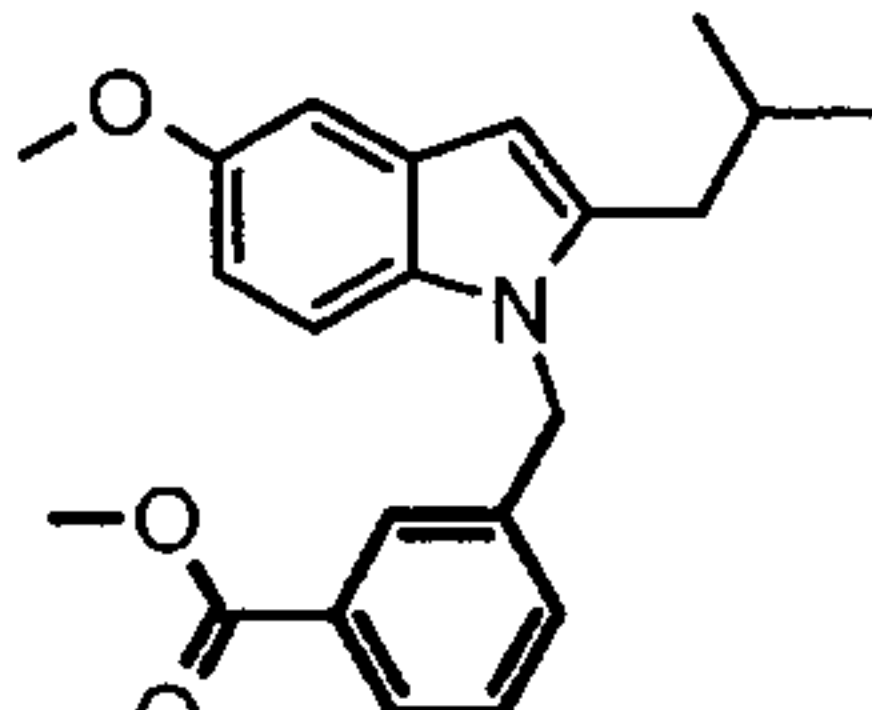
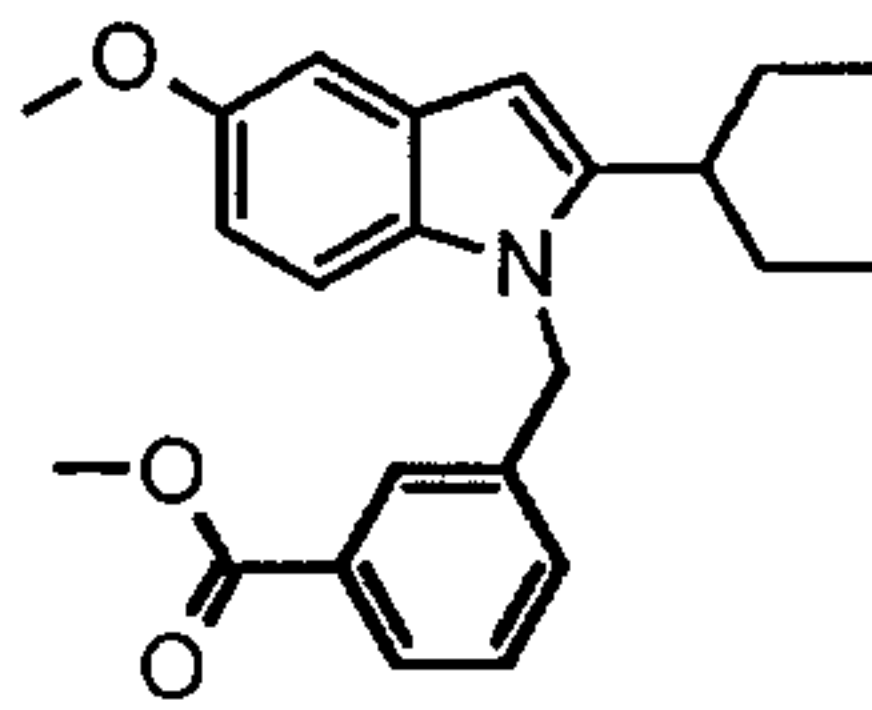
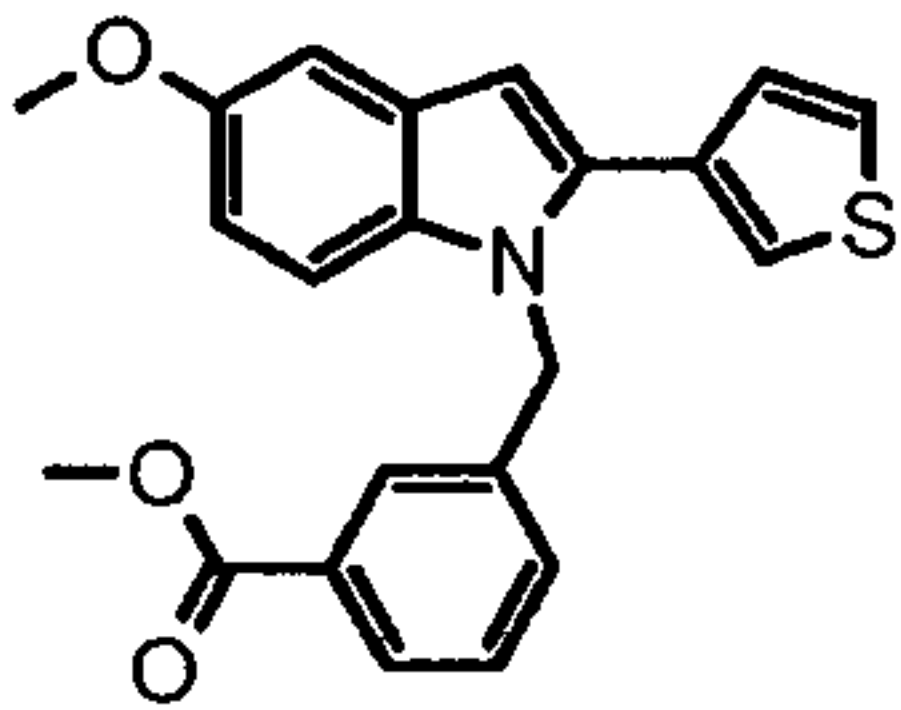
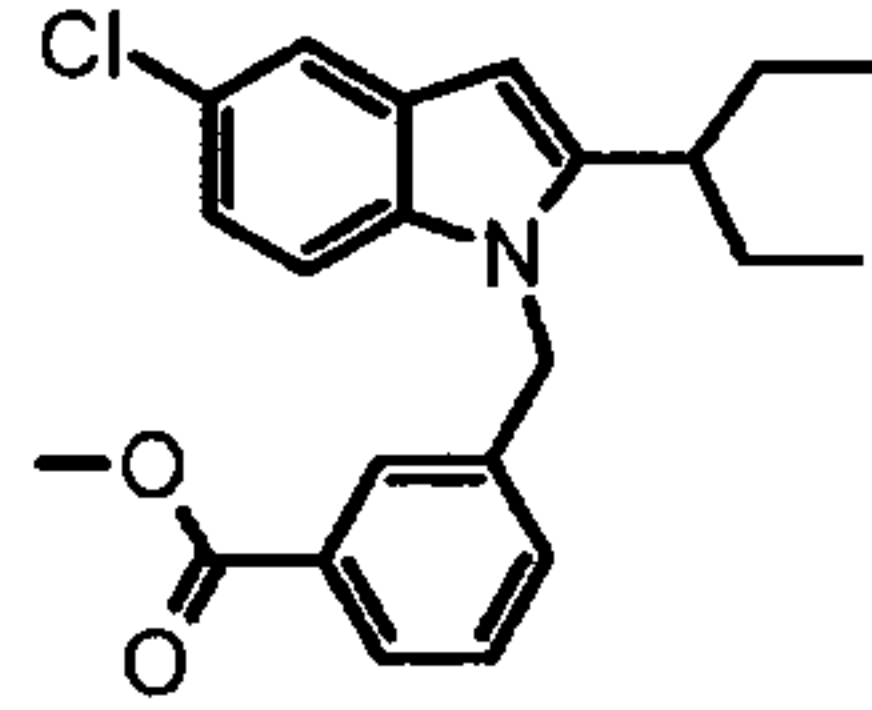
Ex. No.	Strc	Physical data
3-1		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 3.86 (3H, s), 3.89 (3H, s), 5.36 (2H, s), 6.55–6.65 (1H, m), 6.80 (1H, dd, $J=2.5$, 8.8Hz), 7.03 (1H, d, $J=8.8\text{Hz}$), 7.05–7.20 (2H, m), 7.25–7.50 (6H, m), 7.75–7.85 (1H, m), 7.85–7.95 (1H, m).
3-2		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 3.89 (3H, s), 5.38 (2H, s), 6.55–6.65 (1H, m), 7.00–7.15 (3H, m), 7.30–7.45 (6H, m), 7.60–7.65 (1H, m), 7.75–7.80 (1H, m), 7.85–7.95 (1H, m).
3-3		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.29 (6H, d, $J = 7.0\text{Hz}$), 2.85–3.05 (1H, m), 3.90 (3H, s), 5.37 (2H, s), 6.33 (1H, s), 6.80–7.10 (3H, m), 7.25–7.35 (1H, m), 7.50–7.60 (1H, m), 7.75–7.95 (2H, m).
3-4		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 3.89 (3H, s), 5.39 (2H, s), 6.60–6.70 (1H, m), 6.95–7.15 (3H, m), 7.30–7.45 (6H, m), 7.50–7.55 (1H, m), 7.75–7.85 (1H, m), 7.90–8.00 (1H, m).
3-5		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 3.89 (3H, s), 5.43 (2H, s), 6.74 (1H, s), 7.05–7.15 (1H, m), 7.22 (1H, d, $J=8.8\text{Hz}$), 7.30–7.50 (7H, m), 7.75–7.85 (1H, m), 7.90–8.00 (2H, m).
3-6		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 3.89 (3H, s), 5.38 (2H, s), 6.62 (1H, s), 6.89 (1H, dt, $J=2.5$, 9.0Hz), 7.00–7.15 (2H, m), 7.25–7.50 (7H, m), 7.75–7.85 (1H, m), 7.85–7.95 (1H, m).

[Table 10]

Ex. No.	Strc	Physical data
3-7		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 3.89 (3H, s), 5.42 (2H, s), 6.70–6.75 (1H, m), 7.00–7.10 (1H, m), 7.20 (1H, d, $J=8.5\text{Hz}$), 7.30–7.50 (7H, m), 7.70–7.80 (1H, m), 7.90–8.05 (2H, m).
3-8		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 0.86 (3H, t, $J=7.4\text{Hz}$), 1.25 (3H, d, $J=7.0\text{Hz}$), 1.45–1.80 (2H, m), 2.65–2.80 (1H, m), 3.89 (3H, s), 5.36 (2H, s), 6.30 (1H, s), 6.85–7.10 (3H, m), 7.20–7.35 (1H, m), 7.50–7.60 (1H, m), 7.75–7.95 (2H, m).
3-9		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 0.95 (6H, d, $J=6.5\text{Hz}$), 1.80–2.00 (1H, m), 2.54 (2H, d, $J=7.3\text{Hz}$), 3.89 (3H, s), 5.32 (2H, s), 6.30 (1H, s), 6.85–7.10 (3H, m), 7.20–7.40 (1H, m), 7.45–7.60 (1H, m), 7.75–7.85 (1H, m), 7.85–8.00 (1H, m).
3-10		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 2.45 (3H, s), 3.88 (3H, s), 5.37 (2H, s), 6.55–6.60 (1H, m), 6.90–7.15 (3H, m), 7.25–7.50 (7H, m), 7.80–7.95 (2H, m).
3-11		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.28 (6H, d, $J=6.8\text{Hz}$), 2.85–3.05 (1H, m), 3.83 (3H, s), 3.90 (3H, s), 5.35 (2H, s), 6.25–6.35 (1H, m), 6.73 (1H, dd, $J=2.3, 8.9\text{Hz}$), 6.85–6.95 (1H, m), 6.99 (1H, d, $J=8.9\text{Hz}$), 7.07 (1H, d, $J=2.3\text{Hz}$), 7.20–7.35 (1H, m), 7.80–7.95 (2H, m).

[0425]

[Table 11]

Ex. No.	Strc	Physical data
3-12		¹ H-NMR (CDCl ₃) δ ppm: 0.86 (3H, t, J=7.4Hz), 1.24 (3H, d, J=6.8Hz), 1.45–1.85 (2H, m), 2.65–2.80 (1H, m), 3.84 (3H, s), 3.89 (3H, s), 5.34 (2H, s), 6.29 (1H, s), 6.74 (1H, dd, J=2.5, 8.8Hz), 6.85–7.00 (1H, m), 7.02 (1H, d, J=8.8Hz), 7.07 (1H, d, J=2.5Hz), 7.29 (1H, t, J=7.8Hz), 7.75–7.95 (2H, m).
3-13		¹ H-NMR (CDCl ₃) δ ppm: 0.95 (6H, d, J=6.5Hz), 1.80–2.00 (1H, m), 2.54 (2H, d, J=7.3Hz), 3.84 (3H, s), 3.89 (3H, s), 5.31 (2H, s), 6.28 (1H, s), 6.73 (1H, dd, J=2.5, 8.8Hz), 6.90–7.10 (3H, m), 7.29 (1H, t, J=7.8Hz), 7.80–7.95 (2H, m).
3-14		¹ H-NMR (CDCl ₃) δ ppm: 0.79 (6H, t, J=7.4Hz), 1.55–1.70 (4H, m), 2.50–2.65 (1H, m), 3.85 (3H, s), 3.89 (3H, s), 5.34 (2H, s), 6.27 (1H, s), 6.74 (1H, dd, J=2.5, 8.8Hz), 6.90–7.10 (3H, m), 7.20–7.35 (1H, m), 7.80–7.95 (2H, m).
3-15		¹ H-NMR (CDCl ₃) δ ppm: 3.86 (3H, s), 3.89 (3H, s), 5.42 (2H, s), 6.60–6.65 (1H, m), 6.81 (1H, dd, J=2.5, 9.0Hz), 7.04 (1H, d, J=9.0Hz), 7.05–7.25 (4H, m), 7.30–7.40 (2H, m), 7.80–8.00 (2H, m).
3-16		¹ H-NMR (CDCl ₃) δ ppm: 0.79 (6H, t, J=7.4Hz), 1.55–1.75 (4H, m), 2.50–2.65 (1H, m), 3.89 (3H, s), 5.36 (2H, s), 6.29 (1H, s), 6.90–7.10 (3H, m), 7.30 (1H, t, J=7.7Hz), 7.50–7.60 (1H, m), 7.75–7.85 (1H, m), 7.85–7.95 (1H, m).

[0426]

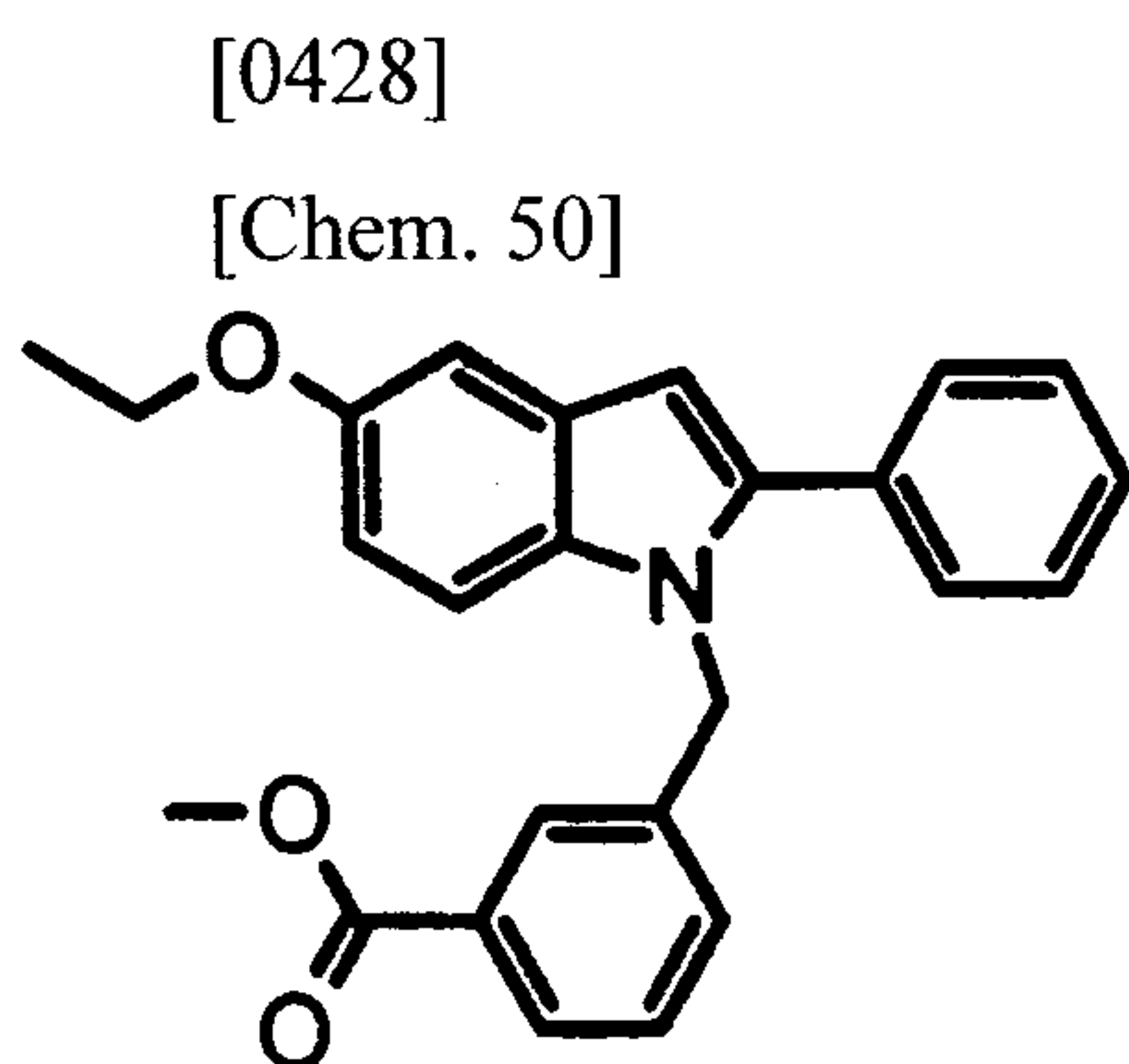
[Table 12]

Ex. No.	Strc	Physical data
3-17		¹ H-NMR (CDCl ₃) δ ppm: 1.29 (3H, t, J=7.6Hz), 2.75 (2H, q, J=7.6Hz), 3.89 (3H, s), 5.37 (2H, s), 6.55–6.65 (1H, m), 6.95–7.20 (3H, m), 7.25–7.55 (7H, m), 7.80–7.95 (2H, m).
3-18		¹ H-NMR (CDCl ₃) δ ppm: 3.86 (3H, s), 3.89 (3H, s), 5.55 (2H, s), 6.35–6.50 (2H, m), 6.78 (1H, s), 6.83 (1H, dd, J=2.5, 8.8Hz), 7.05–7.15 (3H, m), 7.25–7.35 (1H, m), 7.40–7.50 (1H, m), 7.85–7.95 (2H, m).
3-19		¹ H-NMR (CDCl ₃) δ ppm: 3.86 (3H, s), 3.89 (3H, s), 5.42 (2H, s), 6.45–6.55 (1H, m), 6.55–6.65 (1H, m), 6.81 (1H, dd, J=2.4, 8.9Hz), 7.00–7.15 (3H, m), 7.33 (1H, t, J=7.8Hz), 7.40–7.50 (2H, m), 7.80–8.00 (2H, m).
3-20		¹ H-NMR (CDCl ₃) δ ppm: 0.65–0.75 (2H, m), 0.80–0.95 (2H, m), 1.65–1.80 (1H, m), 3.83 (3H, s), 3.90 (3H, s), 5.47 (2H, s), 6.13 (1H, s), 6.75 (1H, dd, J=2.4, 8.9Hz), 6.95–7.10 (3H, m), 7.25–7.35 (1H, m), 7.85–7.95 (2H, m).
3-21		¹ H-NMR (CDCl ₃) δ ppm: 3.89 (3H, s), 3.94 (3H, s), 5.32 (2H, s), 6.57 (1H, s), 6.86 (1H, d, J=11.6Hz), 7.05–7.15 (1H, m), 7.19 (1H, d, J=8.3Hz), 7.30–7.50 (6H, m), 7.75–7.80 (1H, m), 7.85–8.00 (1H, m).
3-22		¹ H-NMR (CDCl ₃) δ ppm: 3.89 (3H, s), 5.38 (2H, s), 6.50 (1H, t, J=74.9Hz), 6.64 (1H, s), 6.95 (1H, dd, J=2.3, 8.8Hz), 7.05–7.15 (2H, m), 7.30–7.50 (7H, m), 7.75–8.00 (2H, m).

[0427]

Example 4

Methyl 3-(5-ethoxy-2-phenylindol-1-ylmethyl)benzoate



5 A suspension of methyl 3-([2-(2, 2-dibromovinyl)-4-ethoxyphenylamino]methyl}benzoate (258mg), phenylboronic acid (134mg), tris(dibenzylideneacetone)dipalladium (0) (25.1mg), tris(2-methylphenyl)phosphine and potassium carbonate (381mg) in toluene (5mL) was stirred at 85°C for 3.5 hours under an argon atmosphere. The reaction mixture was cooled to room temperature, diluted with
10 ethyl acetate and filtered through celite (registered trademark). The filtrate was concentrated under reduced pressure. The residue was purified by aminopropylated silica gel column chromatography (eluting solvent : ethyl acetate-hexane) to obtain the title compound (138mg).

[0430]

15 ¹H-NMR (CDCl₃) δ ppm:
1.44 (3H, t, J=6.9Hz), 3.88 (3H, s), 4.08 (2H, q, J=6.9Hz), 5.36 (2H, s), 6.55-6.60 (1H, m), 6.80 (1H, dd, J=2.5, 8.8Hz), 7.02 (1H, d, J=8.8Hz), 7.05-7.45 (8H, m), 7.75-7.85 (1H, m), 7.85-7.95 (1H, m).

[0431]

20 Example 5-1
Methyl 2-fluoro-5-(5-methoxy-2-phenylindol-1-ylmethyl)benzoate

[0432]

To a solution of 5-methoxy-2-phenylindole (90.9mg) in *N,N*-dimethylformamide (1.8mL) was added sodium hydride (dispersed in liquid paraffin, minimum 55%, 18mg)
25 under cooling with ice and an argon atmosphere, and the mixture was stirred under cooling with ice for 5 minutes and then at room temperature for 15 minutes. Methyl 5-(bromomethyl)-2-fluorobenzoate (101mg) was added at room temperature, and the mixture was stirred at 80°C for 13 hours. The reaction mixture was poured into a saturated aqueous ammonium chloride solution and extracted with ethyl acetate. The organic layer
30 was washed with water and saturated saline, dried over anhydrous sodium sulfate and

concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain the title compound (53.2mg).

In addition, structural formula and spectrum data of the title compound are shown in Table 13.

5 [0433]

Examples 5-2 to 5-6.

The compounds shown in Table 13 were synthesized in a manner similar to that of Example 5-1 by using the corresponding reactants.

[0434]

10 [Table 13]

Ex. No.	Strc	Physical data
5-1		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 3.86 (3H, s), 3.90 (3H, s), 5.31 (2H, s), 6.55–6.60 (1H, m), 6.75–6.90 (1H, m), 6.90–7.45 (9H, m), 7.65–7.70 (1H, m). ESI-MS (m/z): 390 ($\text{M}+\text{H}$) $^+$
5-2		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 3.87 (3H, s), 3.89 (3H, s), 5.34 (2H, s), 6.55–6.65 (1H, m), 6.70–6.90 (2H, m), 7.02 (1H, d, $J=8.8\text{Hz}$), 7.14 (1H, d, $J=2.3\text{Hz}$), 7.30–7.50 (5H, m), 7.50–7.65 (2H, m).
5-3		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 3.87 (3H, s), 3.96 (3H, s), 5.41 (2H, s), 6.60–6.65 (1H, m), 6.65–6.75 (1H, m), 6.82 (1H, dd, $J=2.5, 8.8\text{Hz}$), 6.96 (1H, d, $J=8.8\text{Hz}$), 7.05–7.45 (7H, m), 7.60–7.70 (1H, m).
5-4		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 3.86 (3H, s), 3.89 (3H, s), 5.38 (2H, s), 6.60 (1H, s), 6.83 (1H, dd, $J=2.5, 8.8\text{Hz}$), 7.05 (1H, d, $J=8.8\text{Hz}$), 7.13 (1H, d, $J=2.5\text{Hz}$), 7.30–7.50 (5H, m), 7.80–7.95 (1H, m), 8.30–8.45 (1H, m), 9.00–9.10 (1H, m).
5-5		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.32 (3H, t, $J=7.1\text{Hz}$), 3.87 (3H, s), 4.29 (2H, q, $J=7.1\text{Hz}$), 5.42 (2H, s), 6.50–6.60 (1H, m), 6.65–6.75 (1H, m), 6.86 (1H, dd, $J=2.4,$ 8.9Hz), 7.12 (1H, d, $J=2.4\text{Hz}$), 7.18 (1H, d, $J=8.9\text{Hz}$), 7.35–7.50 (5H, m), 7.58 (1H, d, $J=3.8\text{Hz}$).
5-6		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 3.87 (3H, s), 3.94 (3H, s), 5.41 (2H, s), 6.60 (1H, s), 6.70–6.90 (2H, m), 6.95–7.10 (2H, m), 7.14 (1H, d, $J=2.5\text{Hz}$), 7.30–7.45 (5H, m), 7.75–7.85 (1H, m).

[0435]

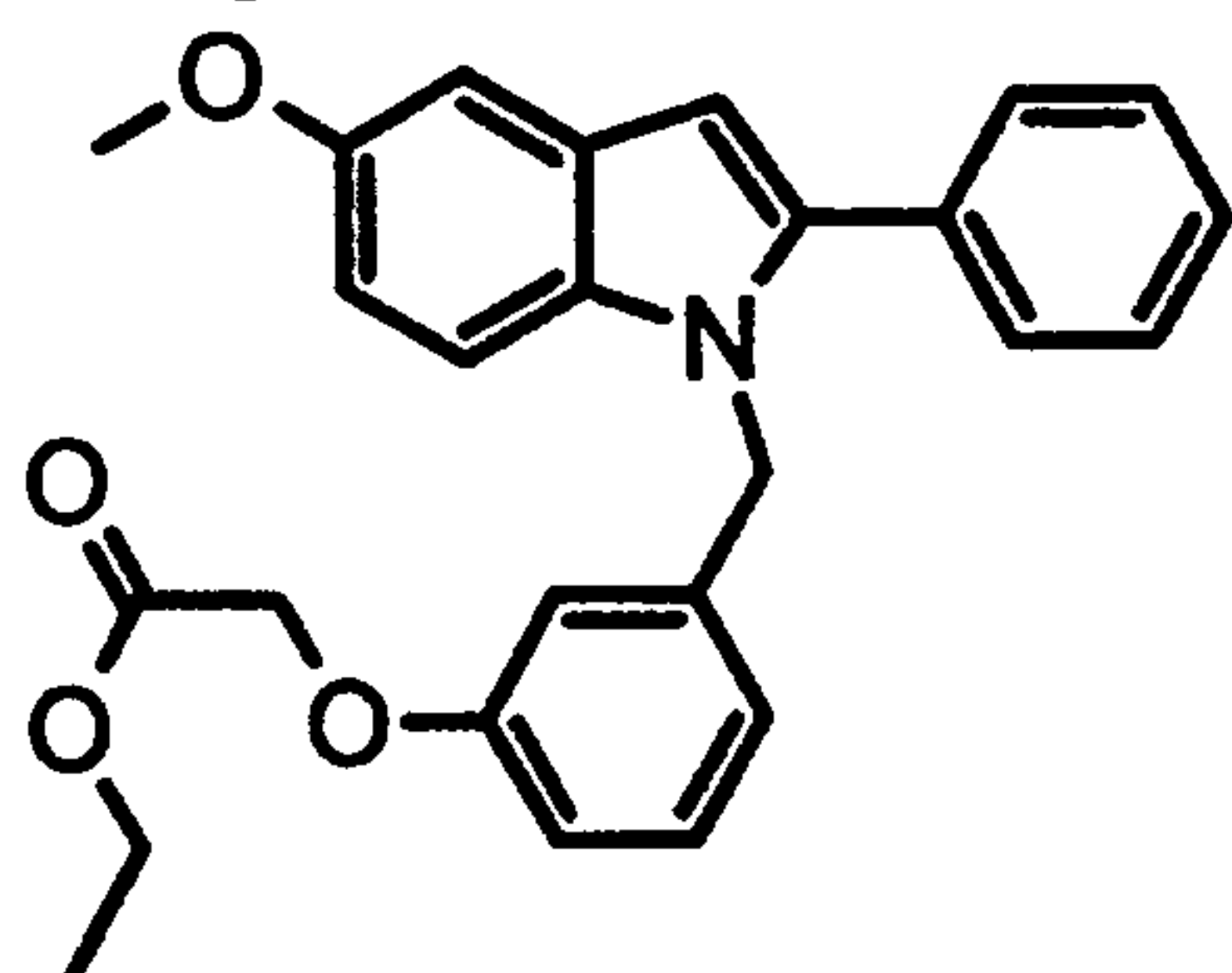
Example 6

Ethyl [3-(5-methoxy-2-phenylindol-1-ylmethyl)phenoxy]acetate

[0436]

5

[Chem. 51]



[0437]

To a solution of 1-(3-hydroxybenzyl)-5-methoxy-2-phenylindole (108mg) in *N,N*-dimethylformamide (1.3mL) was added potassium carbonate (68.2mg) at room temperature. Then ethyl bromoacetate (0.047mL) was added, and the mixture was stirred at room temperature for 3 hours. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with saturated saline, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluting solvent : ethyl acetate-hexane) to obtain the title compound (129mg).

[0438]

¹H-NMR (CDCl₃) δ ppm:

1.25 (3H, t, J=7.2Hz), 3.86 (3H, s), 4.20 (2H, q, J=7.2Hz), 4.51 (2H, s), 5.29 (2H, s), 6.50-6.85 (5H, m), 7.05 (1H, d, J=8.8Hz), 7.12 (1H, d, J=2.3Hz), 7.15-7.25 (1H, m), 7.30-7.50 (5H, m).

[0439]

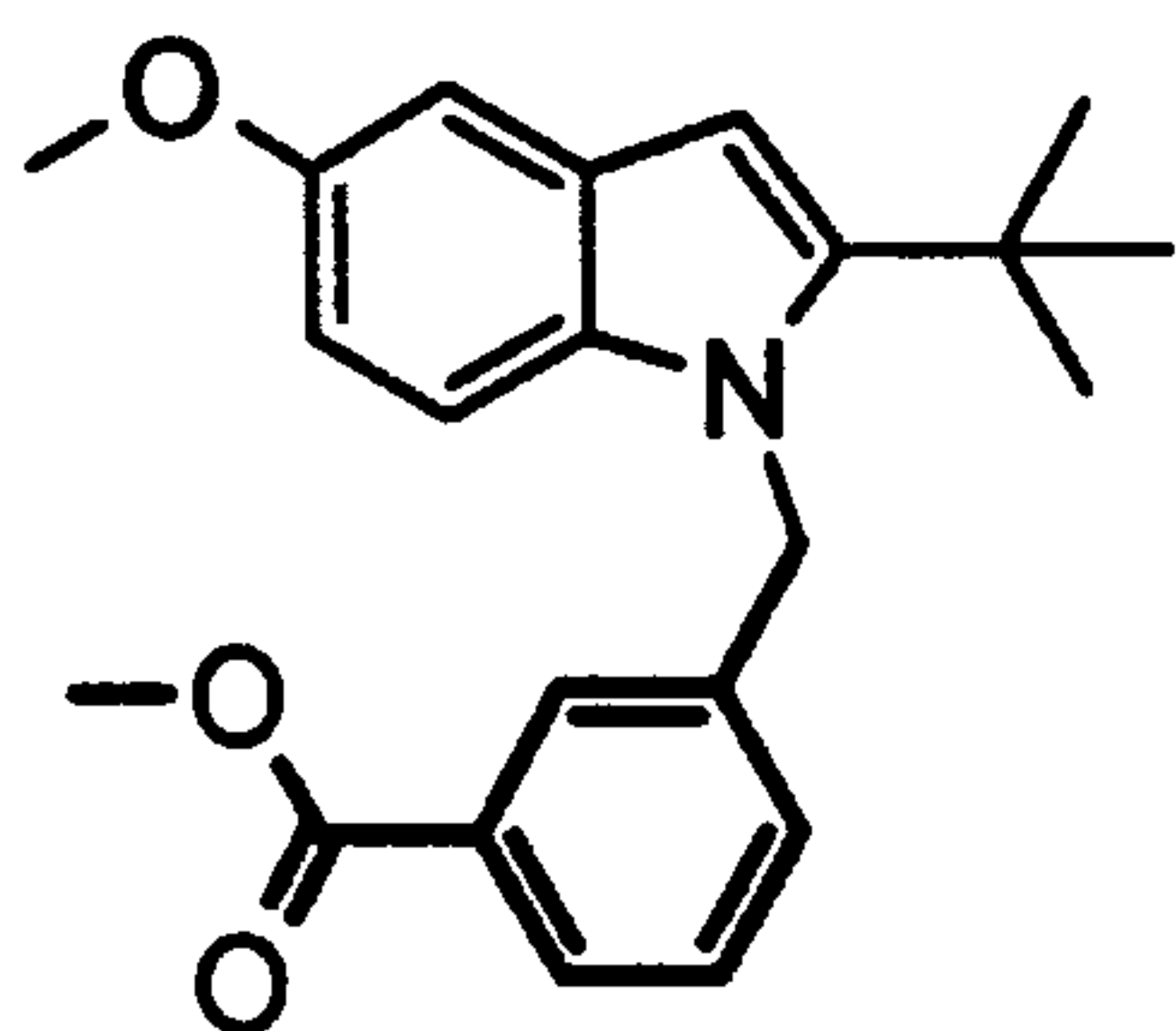
Example 7

Methyl 3-(2-*tert*-butyl-5-methoxyindol-1-ylmethyl)benzoate

[0440]

25

[Chem. 52]



[0441]

To a suspension of methyl 3-{[2-(2-hydroxy-3,3-dimethylbutyl)-4-methoxyphenylamino]methyl}benzoate (200mg), 2-bromomesitylene (0.097mL) and potassium carbonate (148mg) in *N,N*-dimethylformamide (5mL) was added tetrakis(triphenylphosphine)palladium (0) (31.1mg) at room temperature, and this resulting mixture was stirred at 150°C for 2 hours under an argon atmosphere. The reaction mixture was cooled to room temperature, diluted with water and extracted with ethyl acetate. The organic layer was washed with saturated saline, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluting solvent : ethyl acetate-hexane) to obtain the title compound (127mg).

[0442]

¹H-NMR (CDCl₃) δ ppm:

1.40 (9H, s), 3.82 (3H, s), 3.90 (3H, s), 5.59 (2H, s), 6.30-6.40 (1H, m), 6.68 (1H, dd, J=2.4, 8.9Hz), 6.75-6.90 (2H, m), 7.05 (1H, d, J=2.4Hz), 7.20-7.35 (1H, m), 7.75-7.95 (2H, m).

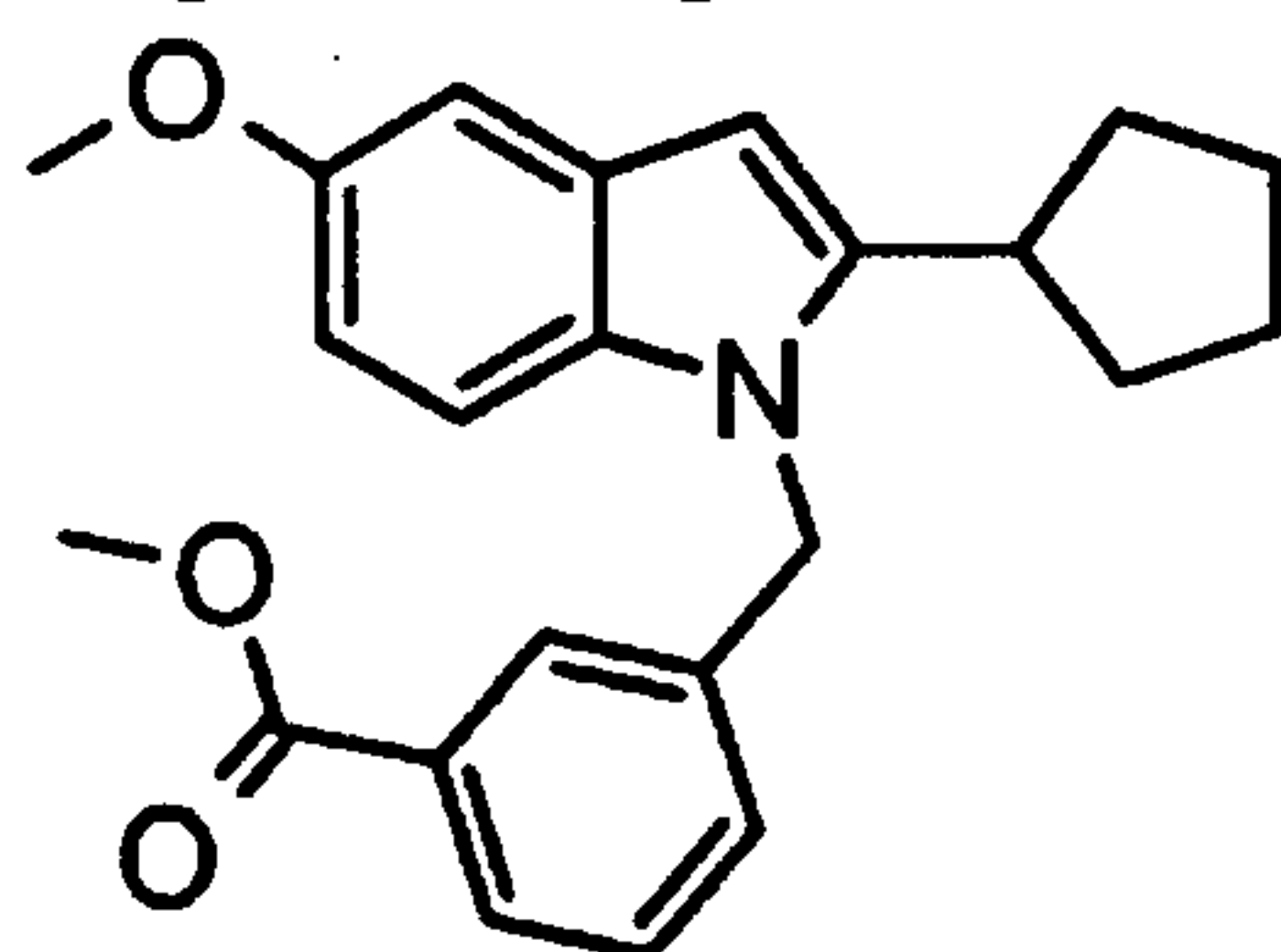
[0443]

Example 8

Methyl 3-(2-cyclopentyl-5-methoxyindol-1-ylmethyl)benzoate

[0444]

[Chem. 53]



[0445]

The title compound was synthesized in a manner similar to that of Example 7 by using the corresponding starting material.

[0446]

¹H-NMR (CDCl₃) δ ppm:

1.55-1.90 (6H, m), 1.90-2.10 (2H, m), 2.95-3.10 (1H, m), 3.83 (3H, s), 3.90 (3H, s), 5.37
 (2H, s), 6.31 (1H, s), 6.72 (1H, dd, J=2.5, 8.8Hz), 6.90-7.10 (3H, m), 7.20-7.35 (1H, m),
 5 7.80-7.95 (2H, m).

[0447]

Example 9-1

3-(5-Methoxy-2-phenylindol-1-ylmethyl)benzoic acid

[0448]

10 To a solution of methyl 3-(5-methoxy-2-phenylindol-1-ylmethyl)benzoate
 (48.6mg) in tetrahydrofuran-methanol (7/3, 1.1mL) was added 2mol/L aqueous sodium
 hydroxide solution (0.196mL) at room temperature, and the mixture was stirred at 60°C for
 2 hours. 1mol/L Hydrochloric acid (10mL) was added to the reaction mixture at room
 temperature and this resulting mixture was extracted with ethyl acetate. The organic layer
 15 was washed successively with water and saturated saline, dried over anhydrous sodium
 sulfate and concentrated under reduced pressure to obtain the title compound (44.7mg).

In addition, structural formula and spectrum data of the title compound are shown
 in Table 14.

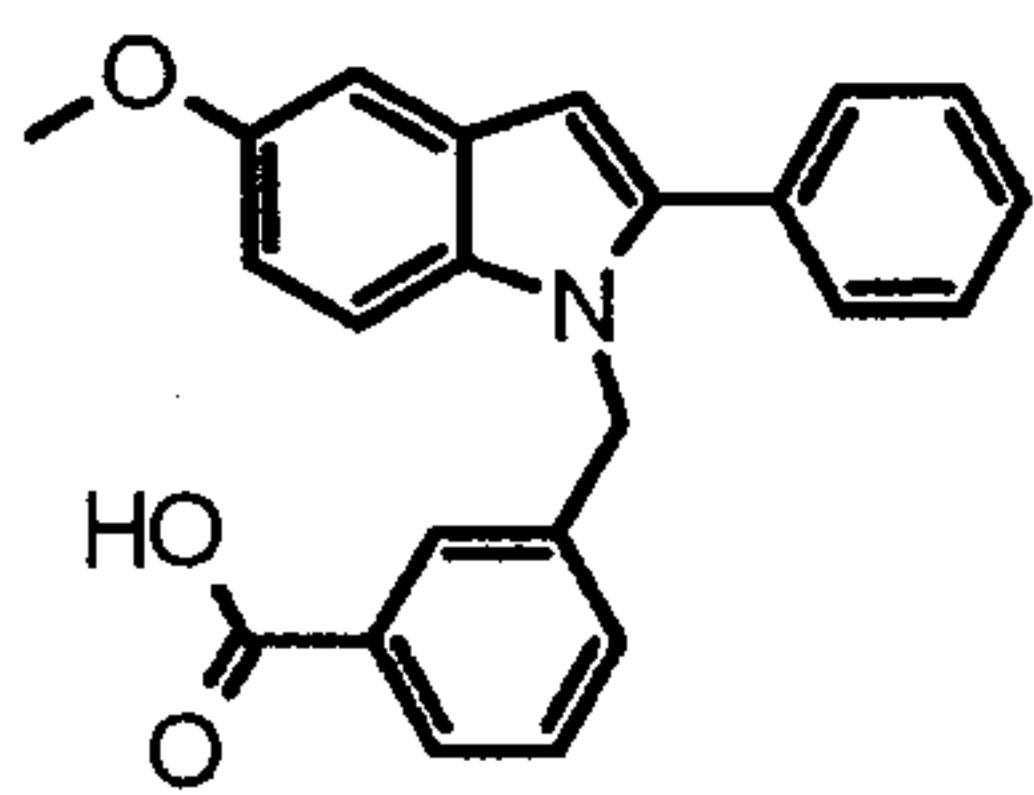
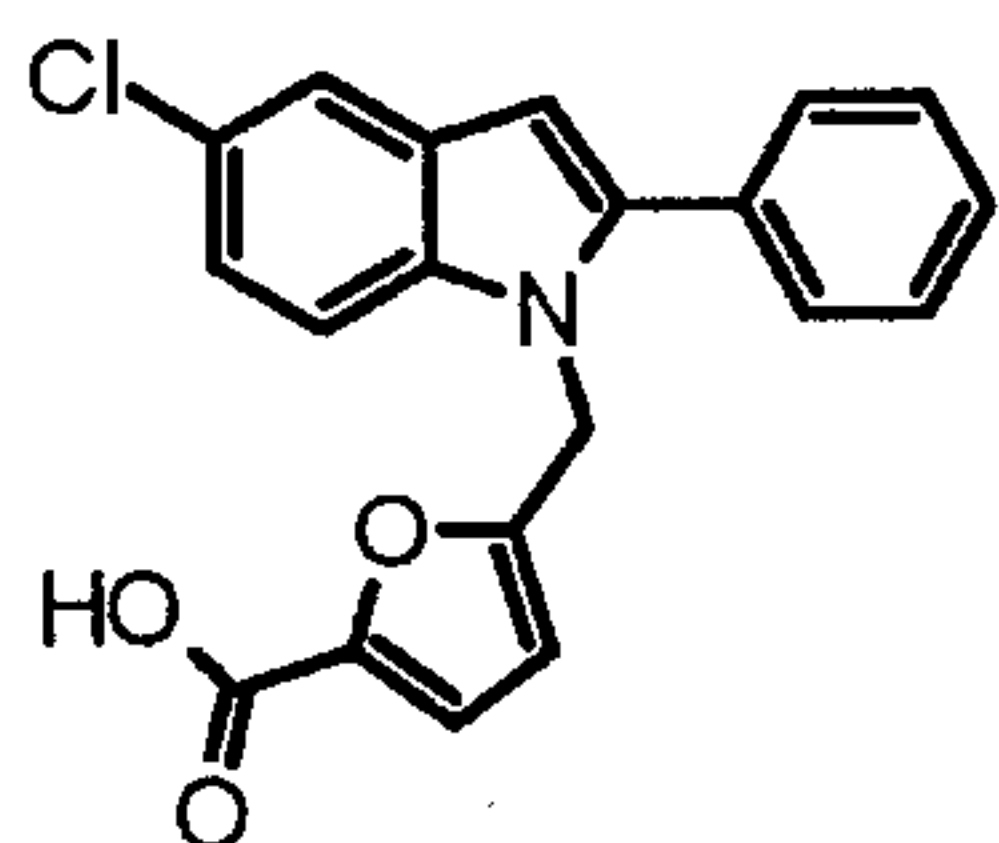
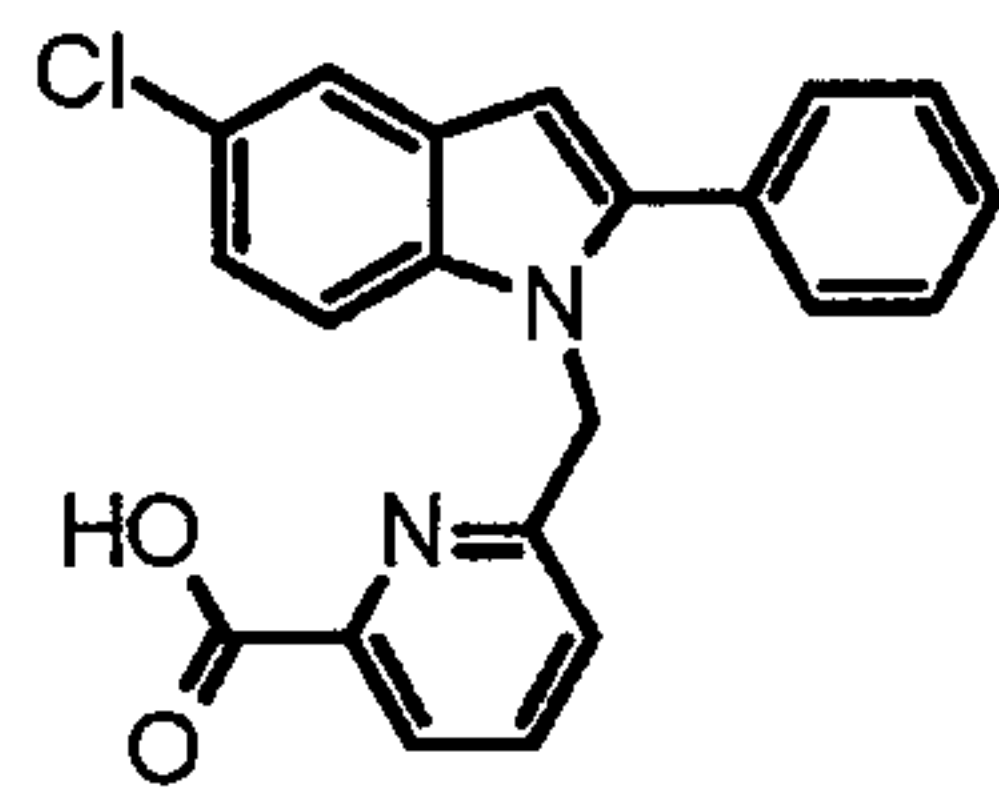
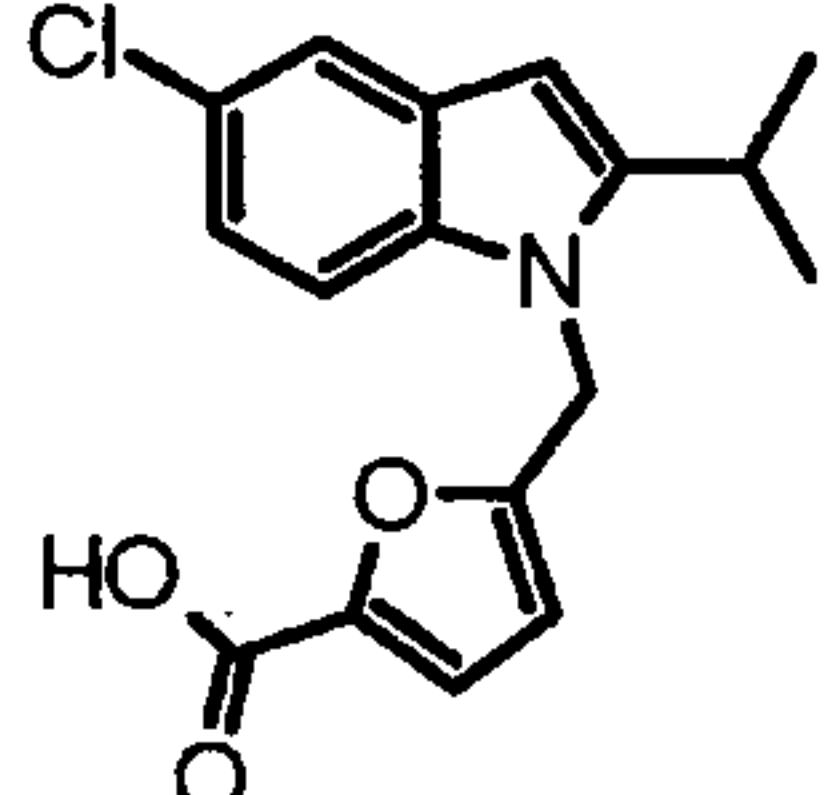
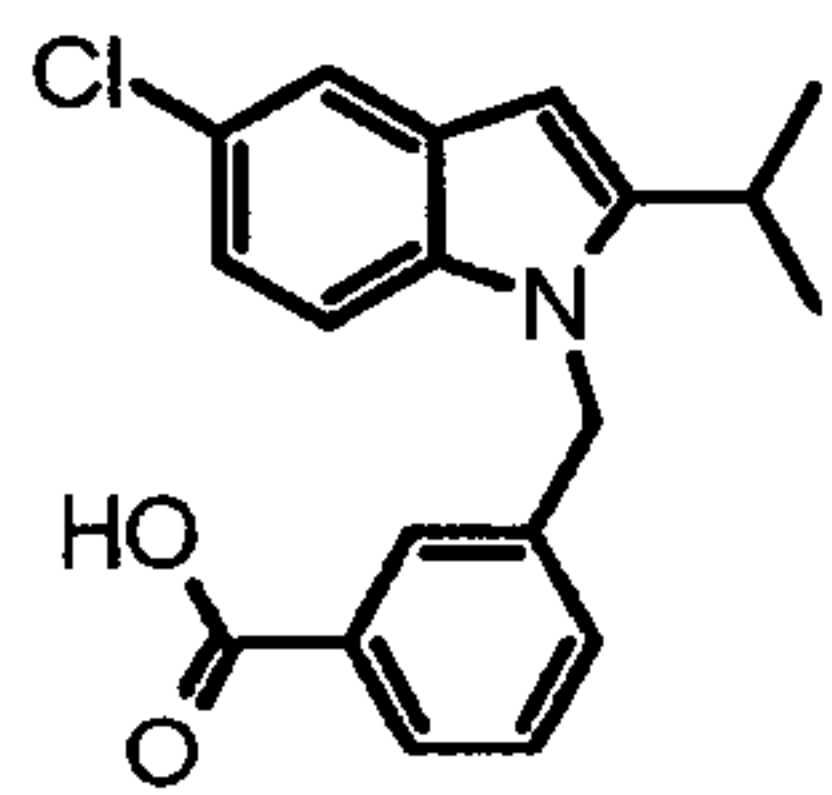
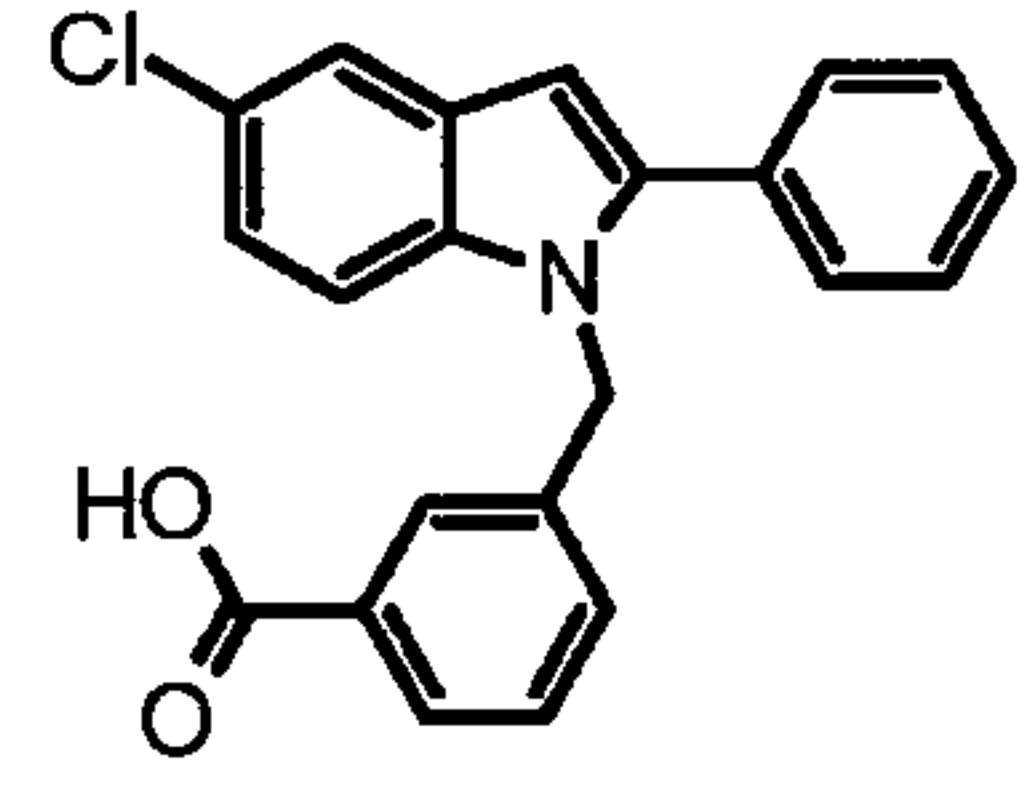
[0449]

20 Examples 9-2 to 9-47

The compounds shown in Tables 14 to 22 were synthesized in a manner similar to
 that of Example 9-1 by using the corresponding starting materials.

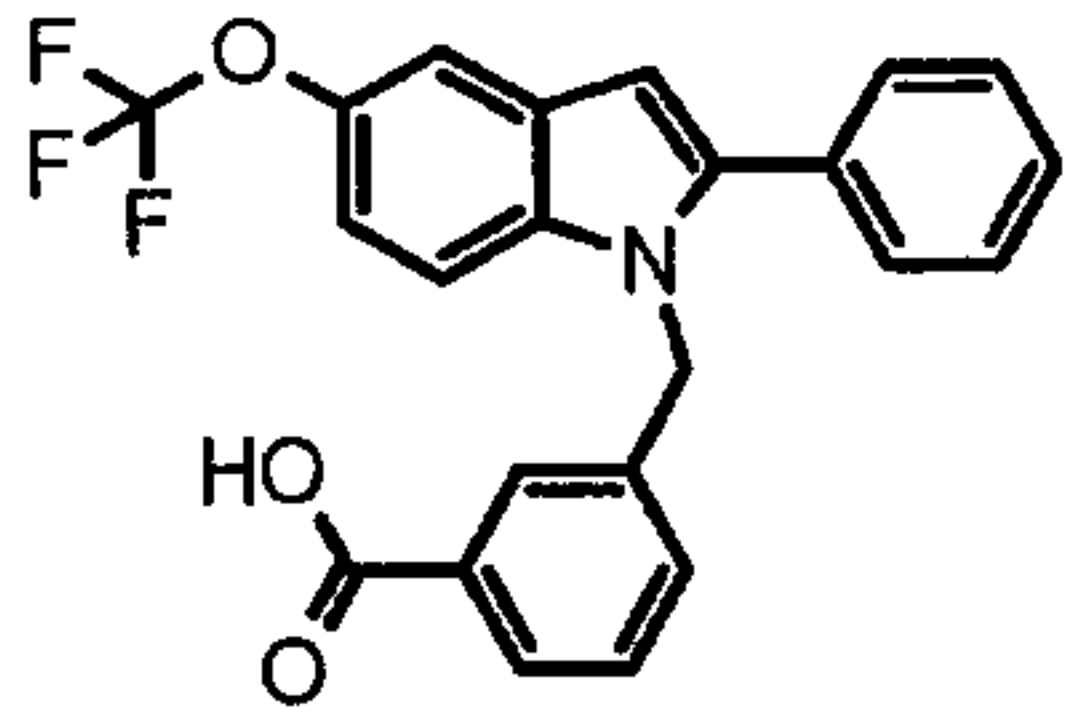
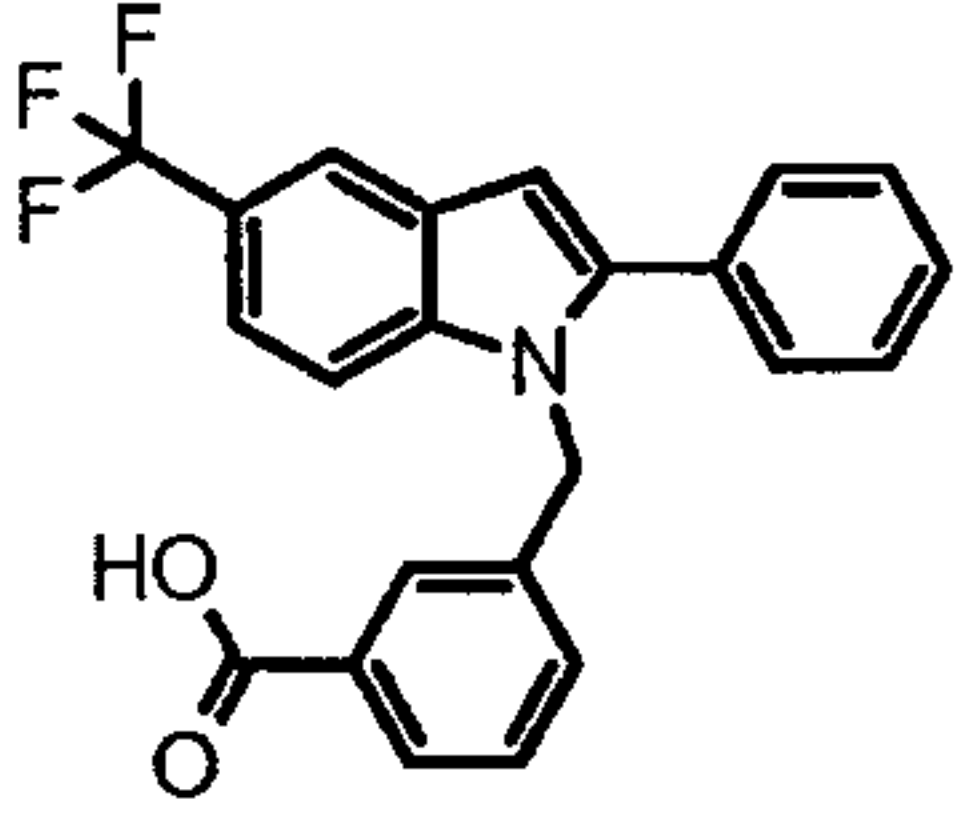
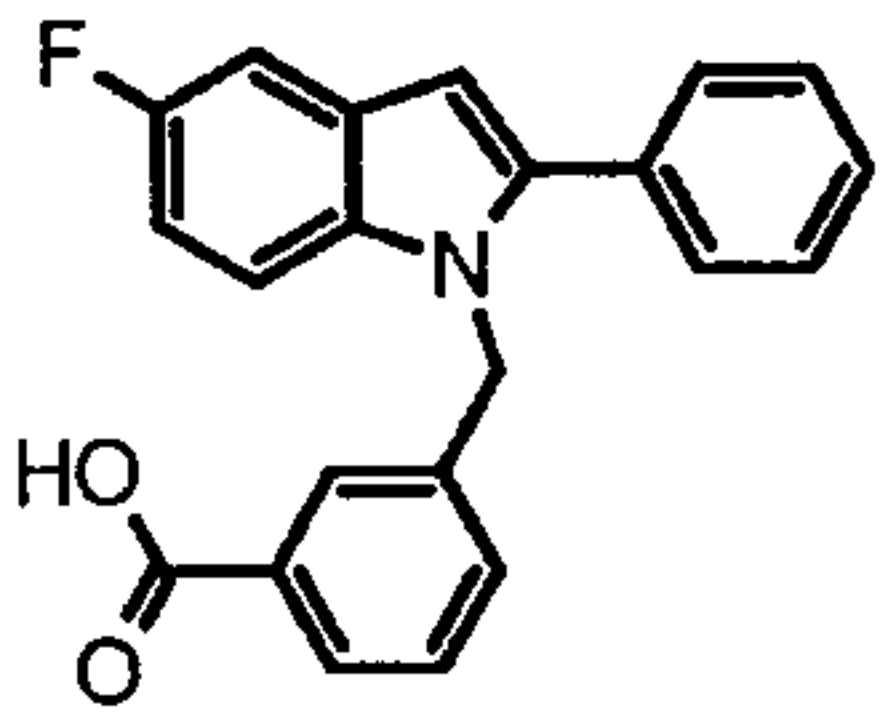
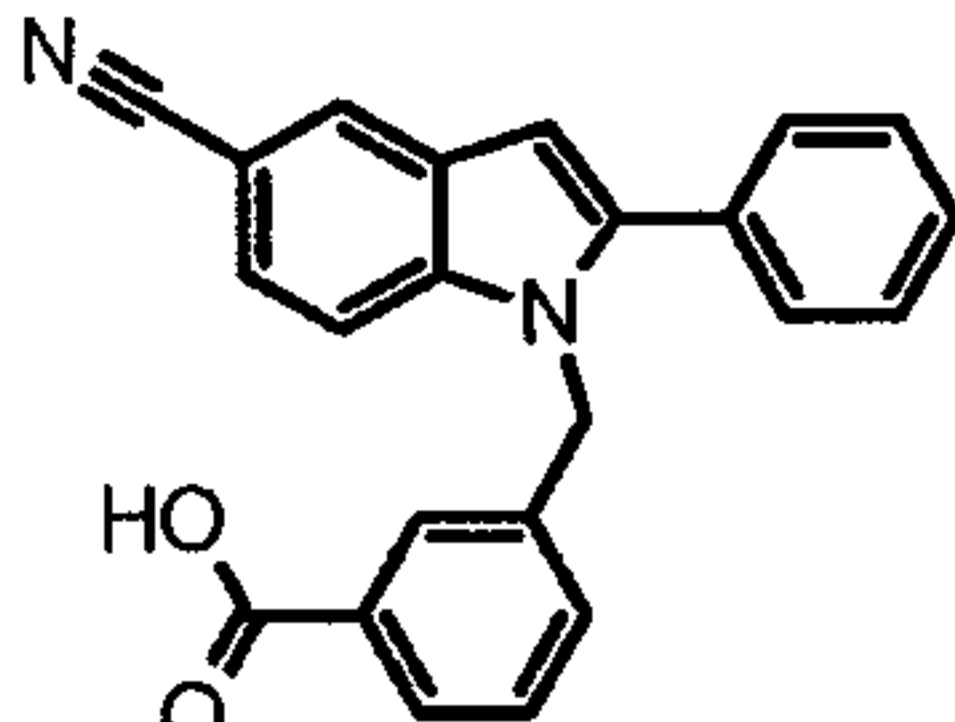
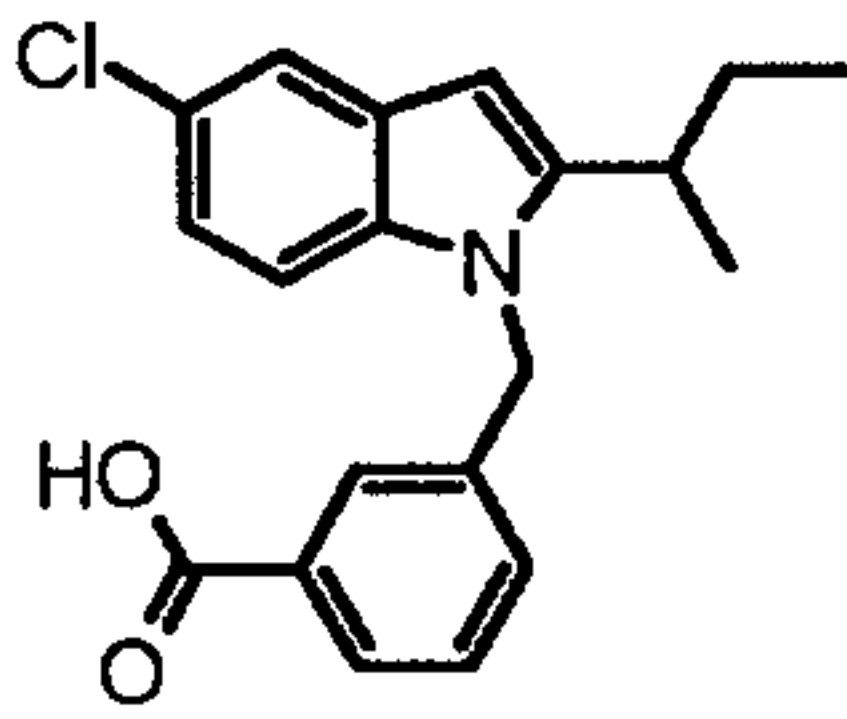
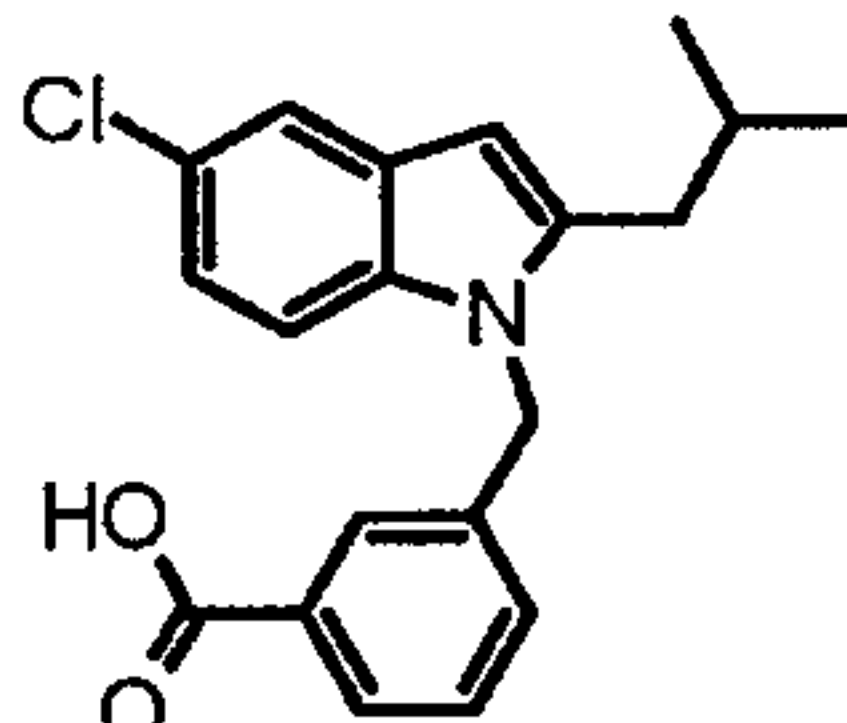
[0450]

[Table 14]

Ex. No.	Strc	Physical data
9-1		$^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 3.77 (3H, s), 5.50 (2H, s), 6.60 (1H, s), 6.76 (1H, dd, $J=2.5, 8.8\text{Hz}$), 7.05–7.15 (2H, m), 7.26 (1H, d, $J=8.8\text{Hz}$), 7.30–7.55 (7H, m), 7.70–7.80 (1H, m), 12.95 (1H, s).
9-2		$^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 5.47 (2H, s), 6.20 (1H, d, $J=3.5\text{Hz}$), 6.62 (1H, s), 7.05 (1H, d, $J=3.5\text{Hz}$), 7.18 (1H, dd, $J=2.1, 8.7\text{Hz}$), 7.40–7.70 (7H, m), 12.60–13.50 (1H, br).
9-3		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 5.52 (2H, s), 6.63 (1H, s), 6.85–7.25 (3H, m), 7.30–7.50 (5H, m), 7.55–7.90 (2H, m), 8.00–8.15 (1H, m).
9-4		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.32 (6H, d, $J=6.8\text{Hz}$), 2.95–3.10 (1H, m), 5.34 (2H, s), 5.80–5.90 (1H, m), 6.30 (1H, s), 7.05–7.20 (3H, m), 7.45–7.55 (1H, m).
9-5		$^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 1.21 (6H, d, $J=6.8\text{Hz}$), 2.95–3.15 (1H, m), 5.55 (2H, s), 6.36 (1H, s), 7.02 (1H, dd, $J=2.0, 8.6\text{Hz}$), 7.10–7.20 (1H, m), 7.34 (1H, d, $J=8.6\text{Hz}$), 7.42 (1H, t, $J=7.7\text{Hz}$), 7.50–7.60 (2H, m), 7.75–7.85 (1H, m), 12.98 (1H, br s).
9-6		$^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 5.55 (2H, s), 6.68 (1H, s), 7.00–7.20 (2H, m), 7.30–7.55 (8H, m), 7.65–7.70 (1H, m), 7.70–7.80 (1H, m), 12.96 (1H, br s).

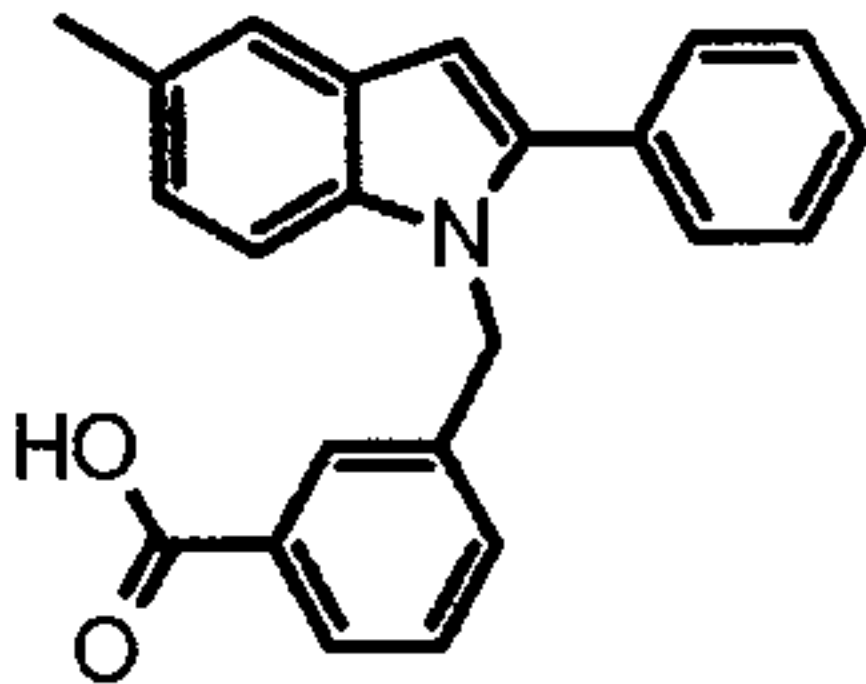
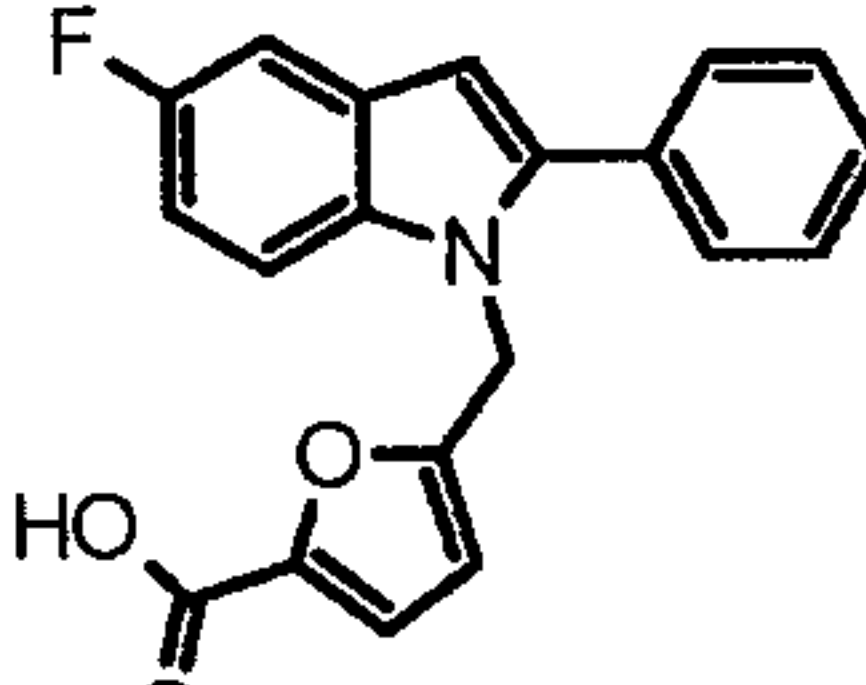
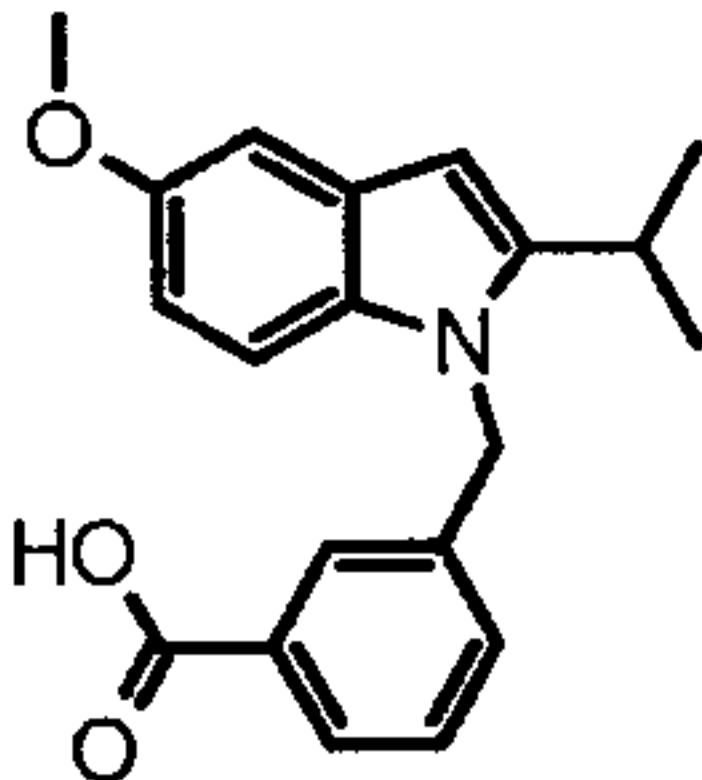
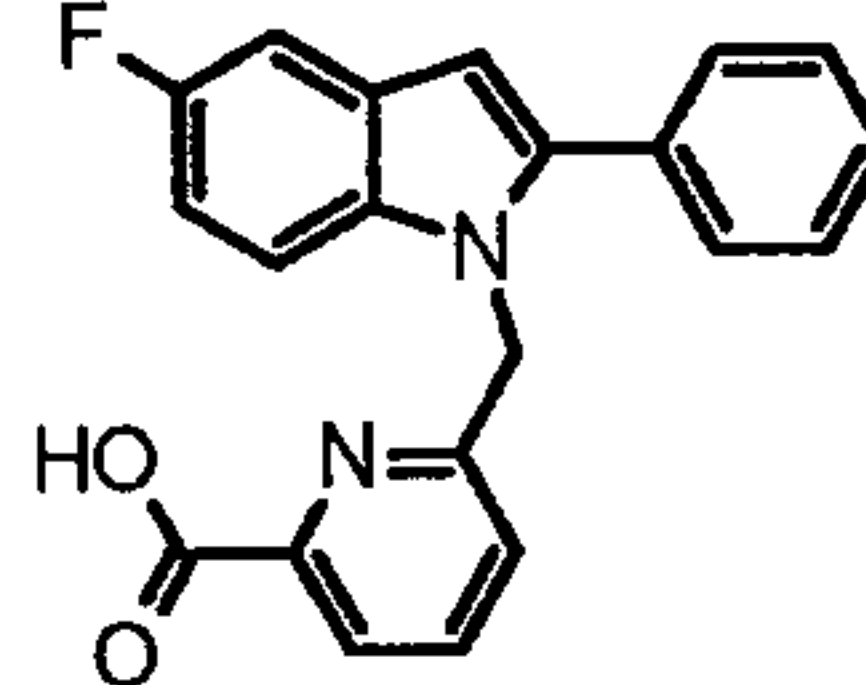
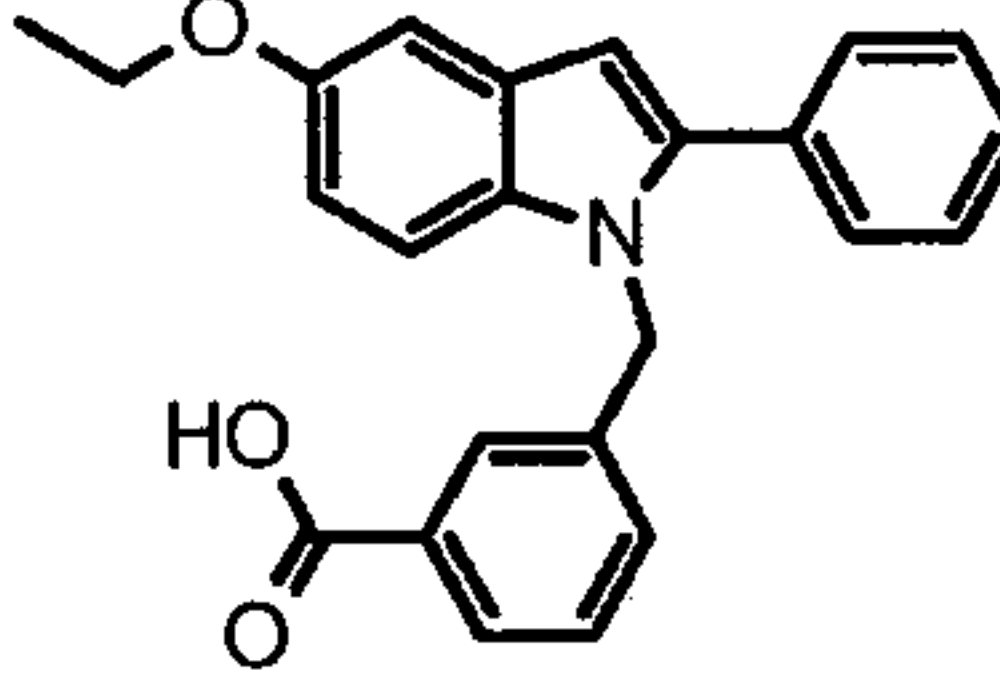
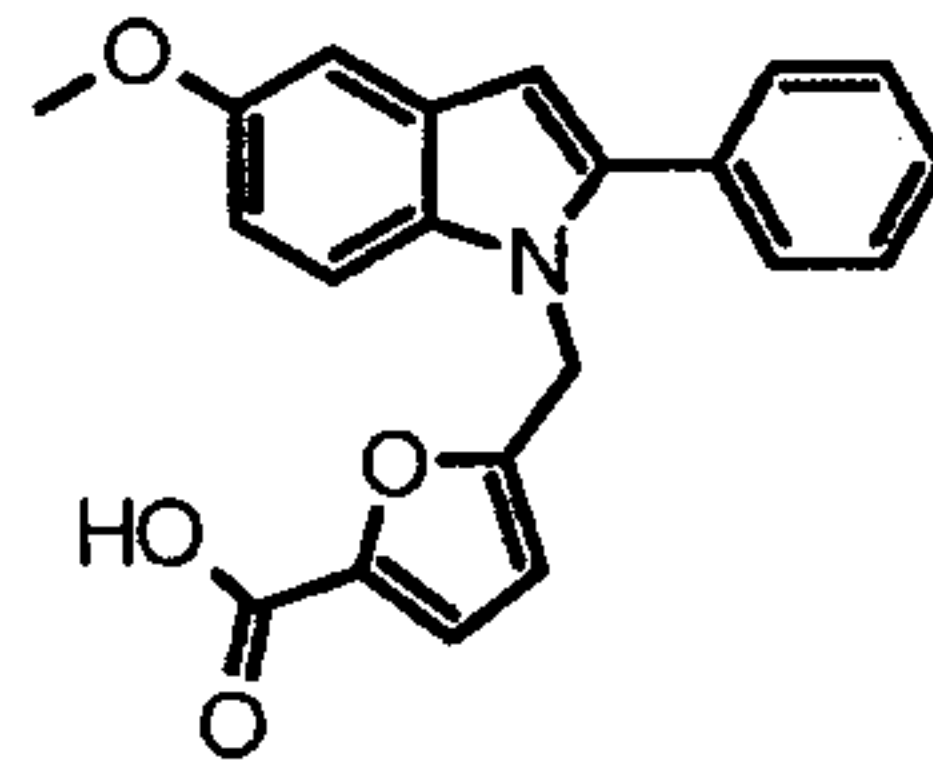
[0451]

[Table 15]

Ex. No.	Strc	Physical data
9-7		$^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 5.57 (2H, s), 6.76 (1H, s), 7.05–7.20 (2H, m), 7.30–7.65 (9H, m), 7.70–7.85 (1H, m), 12.98 (1H, s).
9-8		$^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 5.62 (2H, s), 6.87 (1H, s), 7.05–7.15 (1H, m), 7.37 (1H, t, $J=7.8\text{Hz}$), 7.40–7.55 (7H, m), 7.62 (1H, d, $J=8.8\text{Hz}$), 7.70–7.85 (1H, m), 8.04 (1H, s), 12.98 (1H, br s).
9-9		$^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 5.54 (2H, s), 6.65–6.70 (1H, m), 6.90–7.05 (1H, m), 7.05–7.15 (1H, m), 7.30–7.60 (9H, m), 7.70–7.80 (1H, m), 12.97 (1H, br s).
9-10		$^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 5.62 (2H, s), 6.80–6.90 (1H, m), 7.00–7.15 (1H, m), 7.37 (1H, t, $J=7.8\text{Hz}$), 7.40–7.55 (7H, m), 7.63 (1H, d, $J=8.5\text{Hz}$), 7.70–7.80 (1H, m), 8.15–8.20 (1H, m), 12.98 (1H, br s).
9-11		$^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 0.77 (3H, t, $J=7.3\text{Hz}$), 1.17 (3H, d, $J=6.8\text{Hz}$), 1.40–1.75 (2H, m), 2.75–2.90 (1H, m), 5.54 (2H, s), 6.34 (1H, s), 7.02 (1H, dd, $J=2.0, 8.5\text{Hz}$), 7.10–7.20 (1H, m), 7.30–7.60 (4H, m), 7.75–7.85 (1H, m), 12.97 (1H, br s).
9-12		$^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 0.89 (6H, d, $J=6.5\text{Hz}$), 1.75–1.95 (1H, m), 2.57 (2H, d, $J=7.0\text{Hz}$), 5.51 (2H, s), 6.34 (1H, s), 7.02 (1H, dd, $J=2.0, 8.7\text{Hz}$), 7.10–7.20 (1H, m), 7.30–7.60 (4H, m), 7.75–7.85 (1H, m), 12.98 (1H, br s).

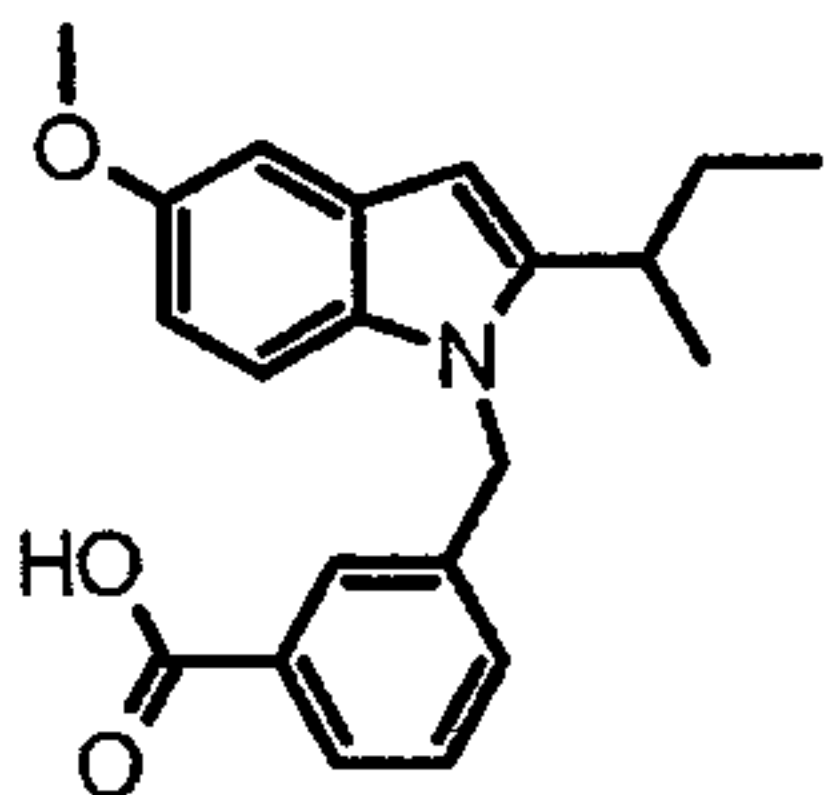
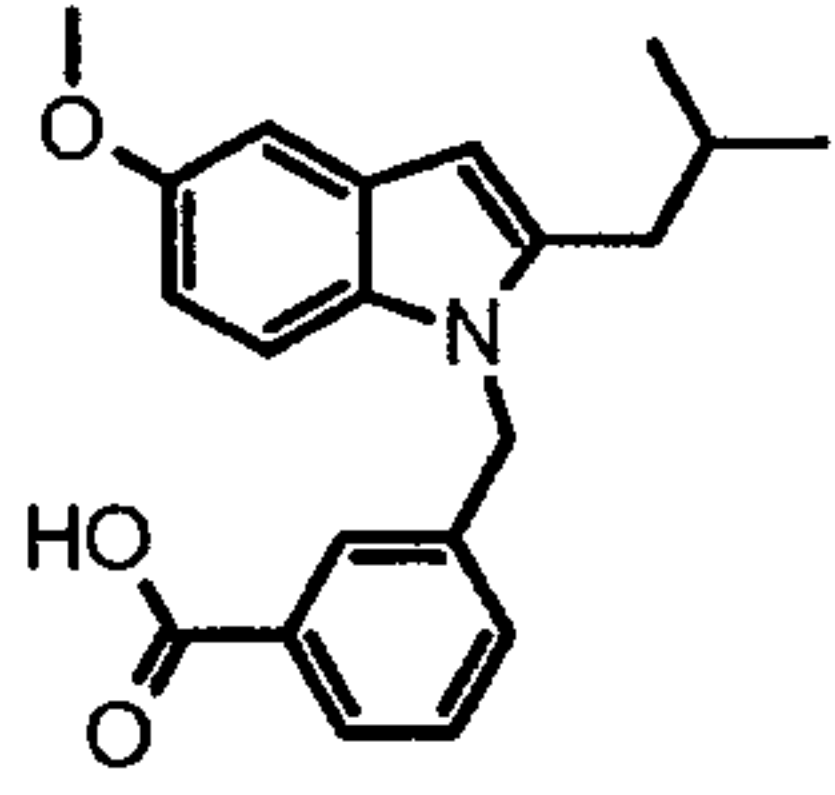
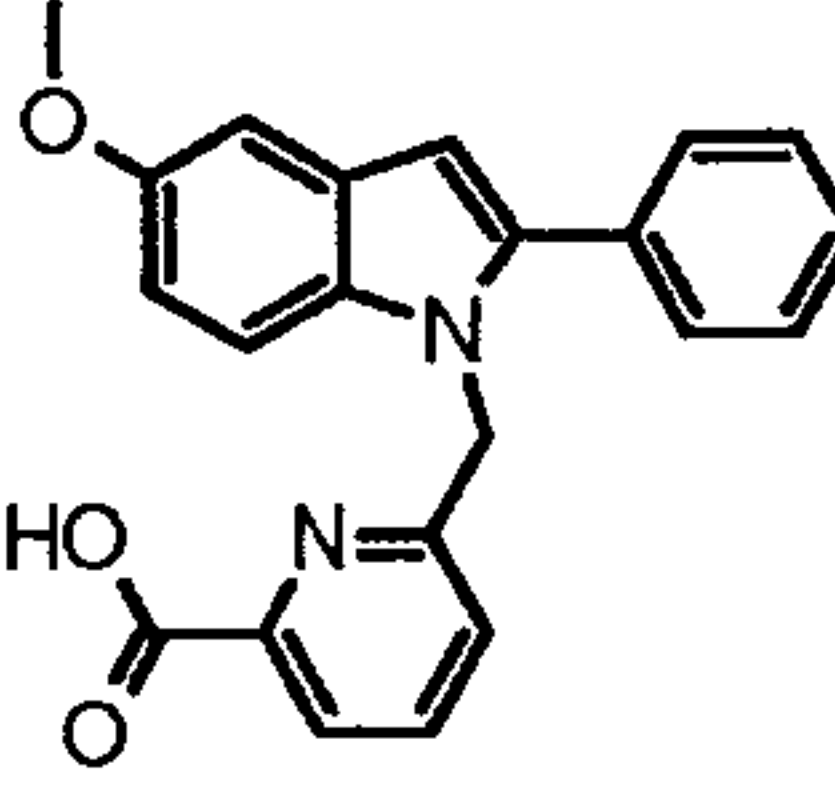
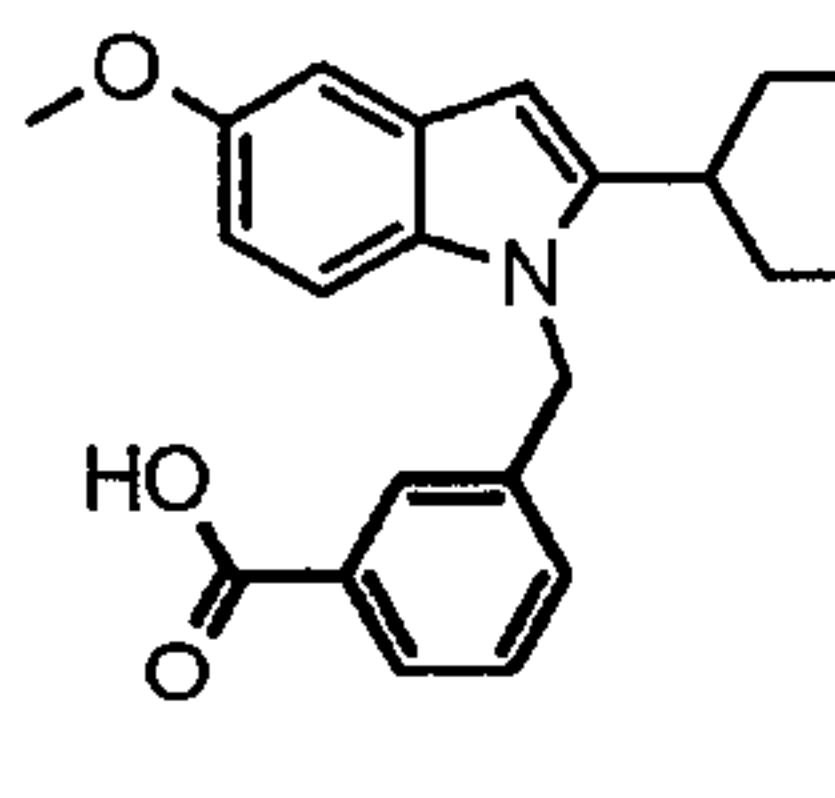
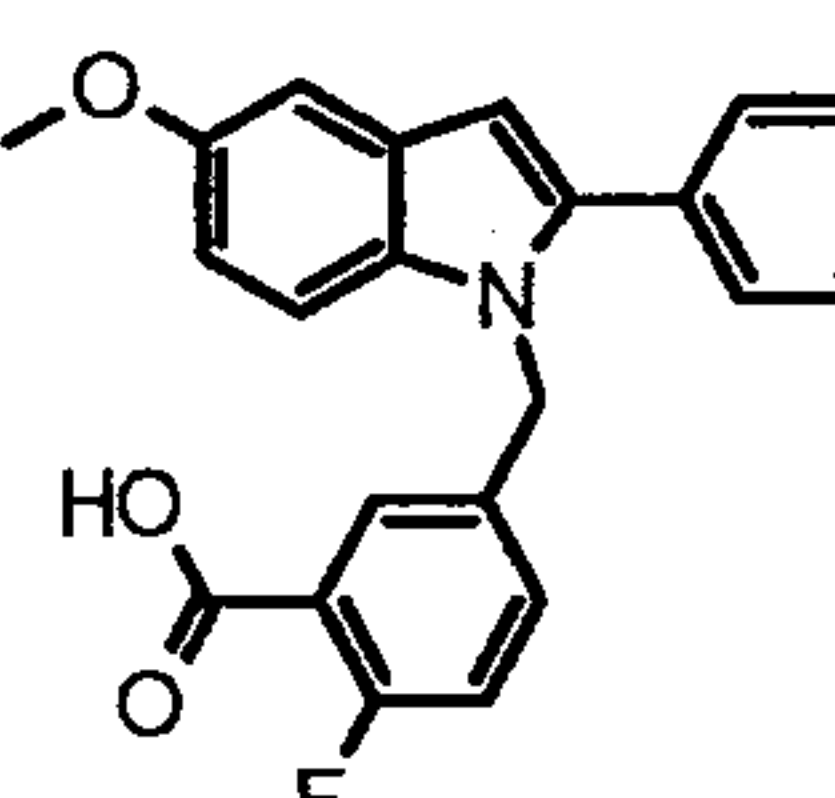
[0452]

[Table 16]

Ex. No.	Strc	Physical data
9-13		$^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 2.38 (3H, s), 5.50 (2H, s), 6.55–6.60 (1H, m), 6.90–7.00 (1H, m), 7.05–7.15 (1H, m), 7.24 (1H, d, $J=8.3\text{Hz}$), 7.30–7.55 (8H, m), 7.70–7.80 (1H, m), 12.91 (1H, br s).
9-14		$^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 5.45 (2H, s), 6.21 (1H, d, $J=3.5\text{Hz}$), 6.62 (1H, s), 6.95–7.10 (2H, m), 7.36 (1H, dd, $J=2.5, 9.8\text{Hz}$), 7.40–7.65 (6H, m), 13.04 (1H, br s).
9-15		$^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 1.20 (6H, d, $J=6.8\text{Hz}$), 2.90–3.10 (1H, m), 3.73 (3H, s), 5.47 (2H, s), 6.26 (1H, s), 6.65 (1H, dd, $J=2.4, 8.8\text{Hz}$), 7.01 (1H, d, $J=2.4\text{Hz}$), 7.10–7.20 (2H, m), 7.40 (1H, t, $J=7.7\text{Hz}$), 7.50–7.60 (1H, m), 7.75–7.85 (1H, m), 12.93 (1H, br s).
9-16		$^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 5.56 (2H, s), 6.69 (1H, s), 6.75–6.85 (1H, m), 6.90–7.05 (1H, m), 7.30–7.65 (7H, m), 7.80–7.95 (2H, m), 12.50–13.80 (1H, br).
9-17		$^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 1.34 (3H, t, $J=7.0\text{Hz}$), 4.02 (2H, q, $J=7.0\text{Hz}$), 5.49 (2H, s), 6.58 (1H, s), 6.75 (1H, dd, $J=2.4, 9.0\text{Hz}$), 7.05–7.15 (2H, m), 7.24 (1H, d, $J=9.0\text{Hz}$), 7.30–7.55 (7H, m), 7.70–7.80 (1H, m), 12.94 (1H, s).
9-18		$^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 3.77 (3H, s), 5.41 (2H, s), 6.18 (1H, d, $J=3.5\text{Hz}$), 6.54 (1H, s), 6.81 (1H, dd, $J=2.5, 9.0\text{Hz}$), 7.07 (1H, d, $J=3.5\text{Hz}$), 7.09 (1H, d, $J=2.5\text{Hz}$), 7.40–7.65 (6H, m), 13.04 (1H, br s).

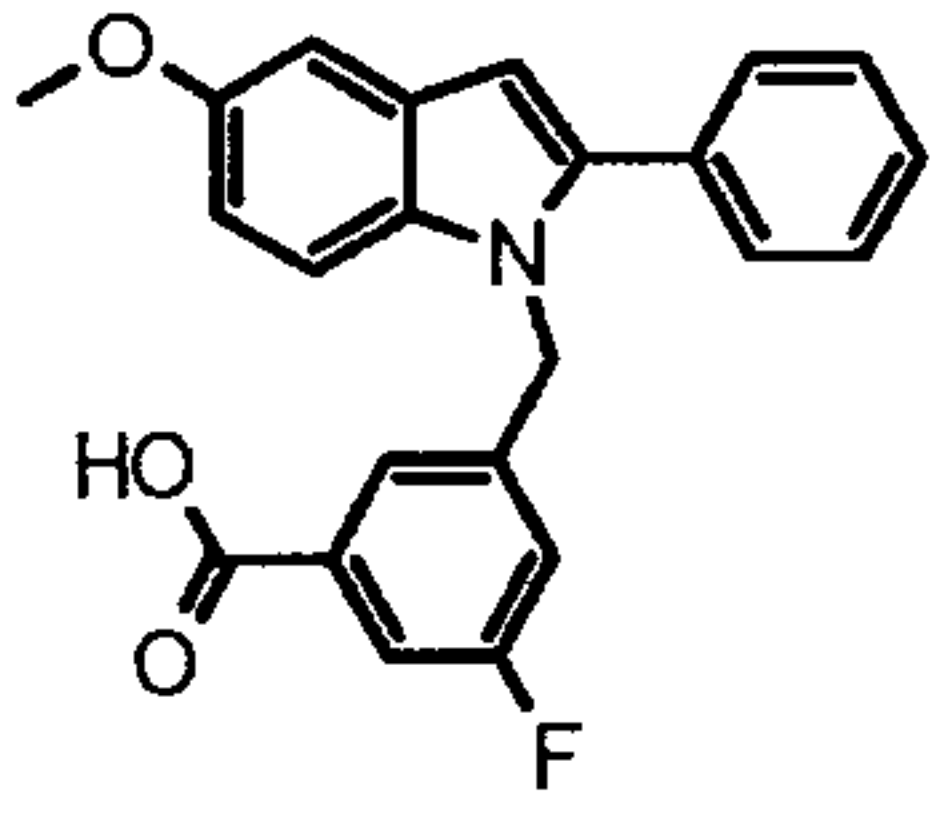
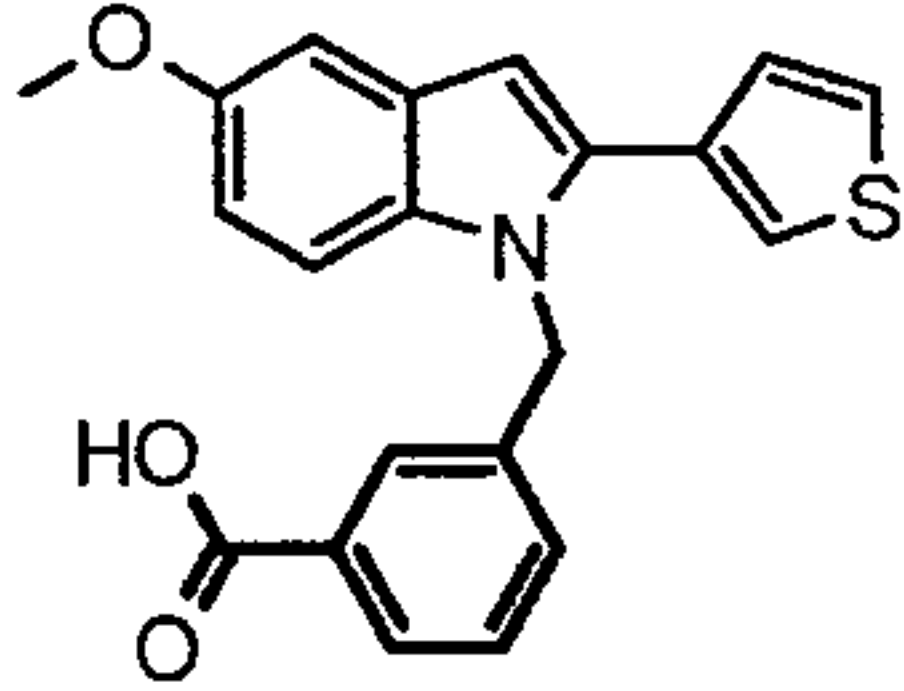
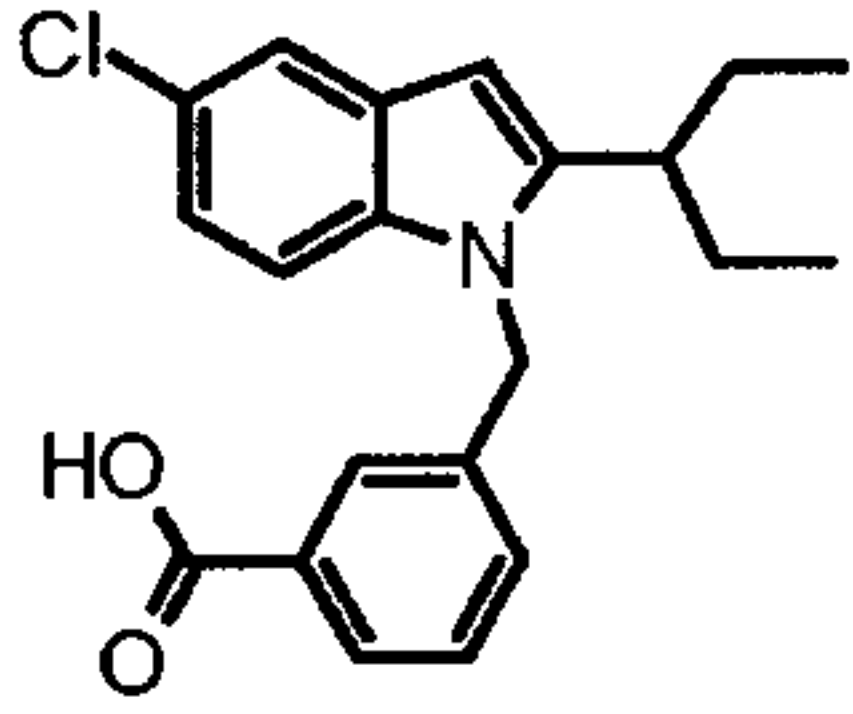
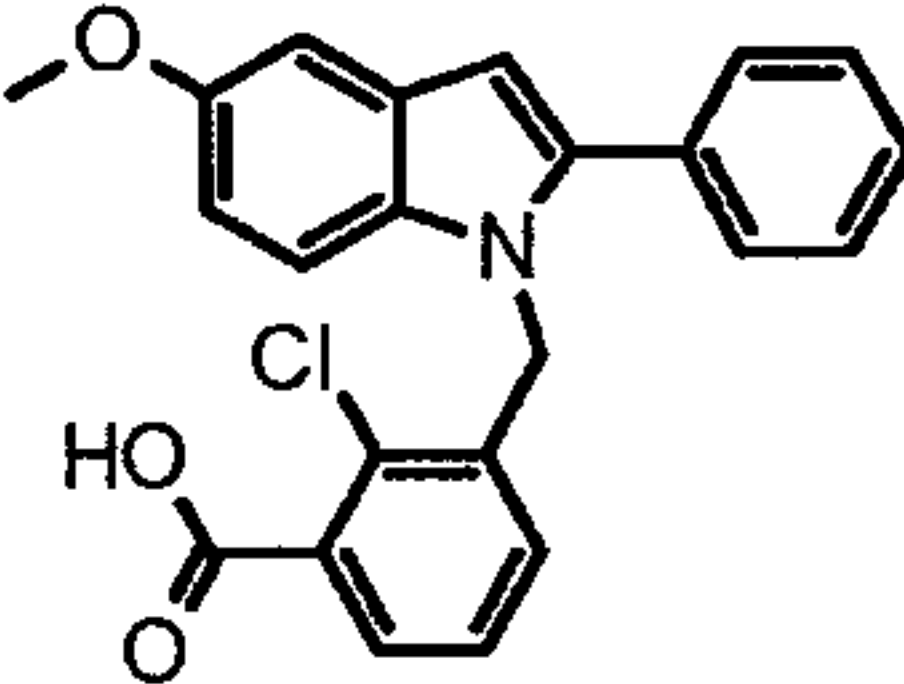
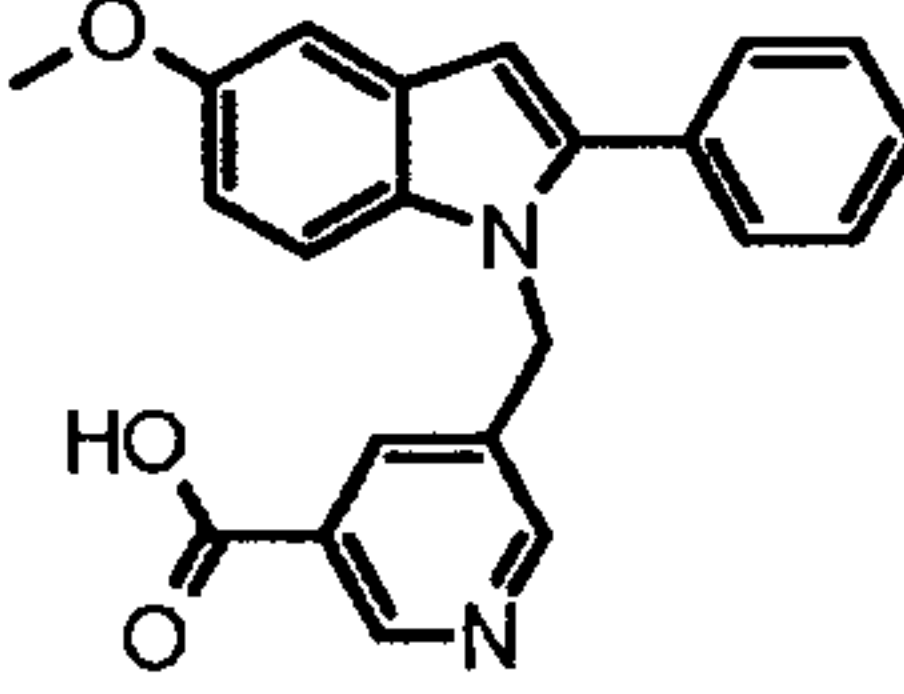
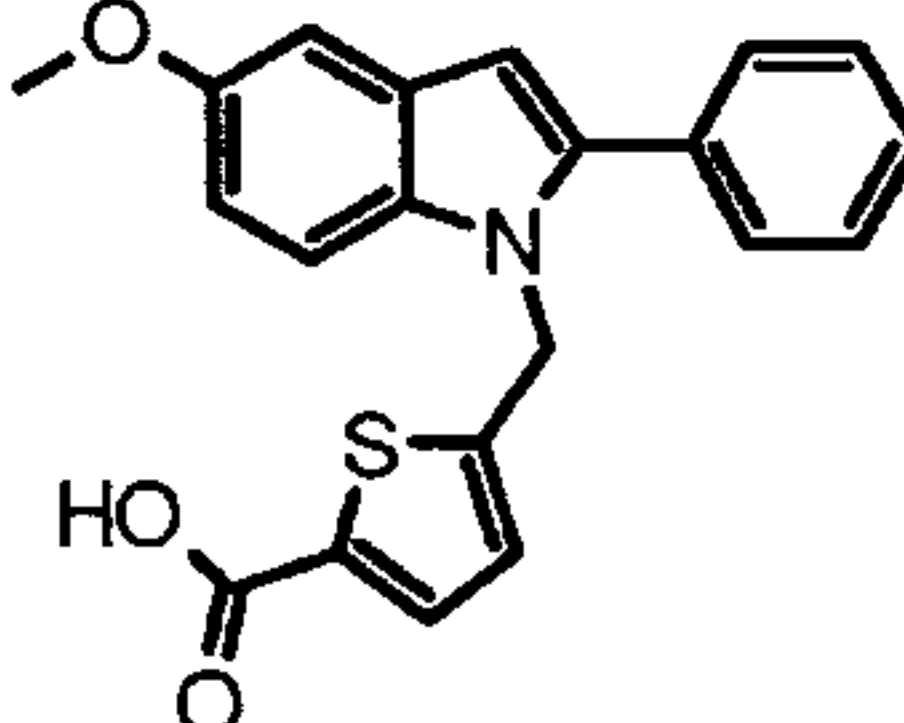
[0453]

[Table 17]

Ex. No.	Strc	Physical data
9-19		$^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ ppm: 0.78 (3H, t, $J=7.3\text{Hz}$), 1.17 (3H, d, $J=6.8\text{Hz}$), 1.40–1.75 (2H, m), 2.70–2.85 (1H, m), 3.74 (3H, s), 5.47 (2H, s), 6.24 (1H, s), 6.65 (1H, dd, $J=2.5, 8.8\text{Hz}$), 7.01 (1H, d, $J=2.5\text{Hz}$), 7.10–7.25 (2H, m), 7.40 (1H, t, $J=7.7\text{Hz}$), 7.50–7.55 (1H, m), 7.75–7.85 (1H, m), 12.97 (1H, br s).
9-20		$^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ ppm: 0.89 (6H, d, $J=6.5\text{Hz}$), 1.70–1.95 (1H, m), 2.54 (2H, d, $J=7.0\text{Hz}$), 3.74 (3H, s), 5.44 (2H, s), 6.24 (1H, s), 6.64 (1H, dd, $J=2.4, 8.9\text{Hz}$), 7.01 (1H, d, $J=2.4\text{Hz}$), 7.10–7.25 (2H, m), 7.41 (1H, t, $J=7.7\text{Hz}$), 7.45–7.55 (1H, m), 7.75–7.85 (1H, m), 12.96 (1H, br s).
9-21		$^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ ppm: 3.77 (3H, s), 5.53 (2H, s), 6.62 (1H, s), 6.65–6.80 (2H, m), 7.13 (1H, d, $J=2.3\text{Hz}$), 7.24 (1H, d, $J=9.0\text{Hz}$), 7.30–7.50 (3H, m), 7.50–7.65 (2H, m), 7.75–7.95 (2H, m), 12.85–13.65 (1H, br).
9-22		$^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ ppm: 0.71 (6H, t, $J=7.4\text{Hz}$), 1.45–1.70 (4H, m), 2.55–2.70 (1H, m), 3.74 (3H, s), 5.47 (2H, s), 6.22 (1H, s), 6.66 (1H, dd, $J=2.3, 8.9\text{Hz}$), 7.01 (1H, d, $J=2.3\text{Hz}$), 7.15–7.30 (2H, m), 7.40 (1H, t, $J=7.7\text{Hz}$), 7.45–7.60 (1H, m), 7.70–7.85 (1H, m), 12.93 (1H, br s).
9-23		$^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ ppm: 3.77 (3H, s), 5.45 (2H, s), 6.59 (1H, s), 6.77 (1H, dd, $J=2.4, 8.9\text{Hz}$), 7.00–7.60 (10H, m), 13.23 (1H, br s).

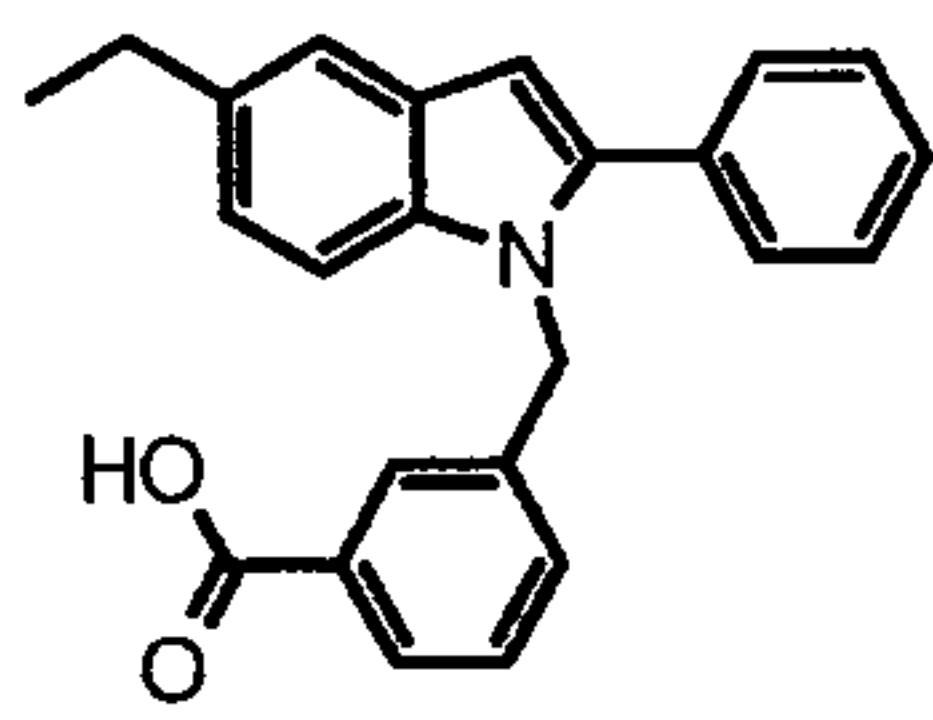
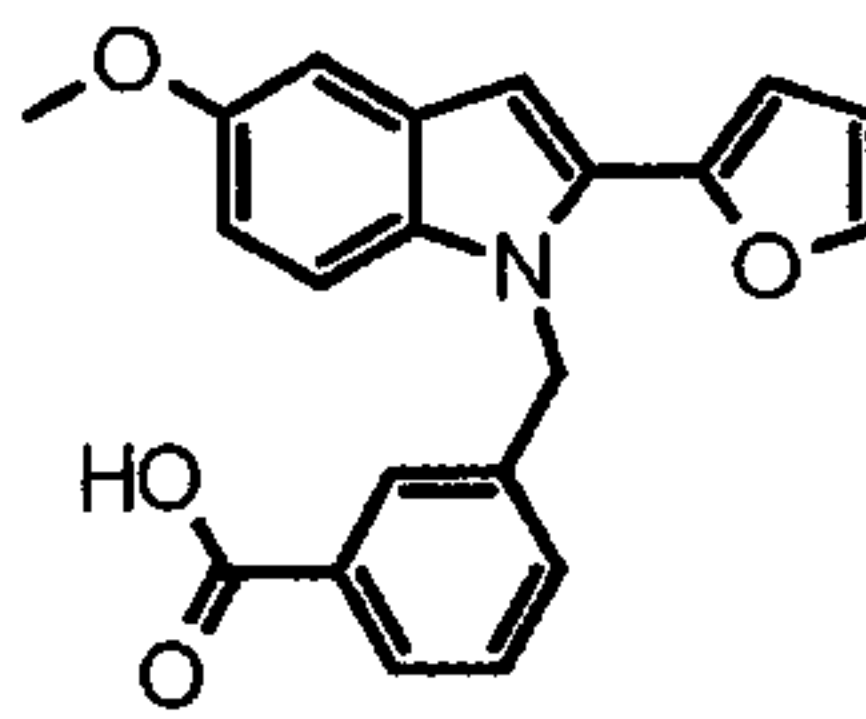
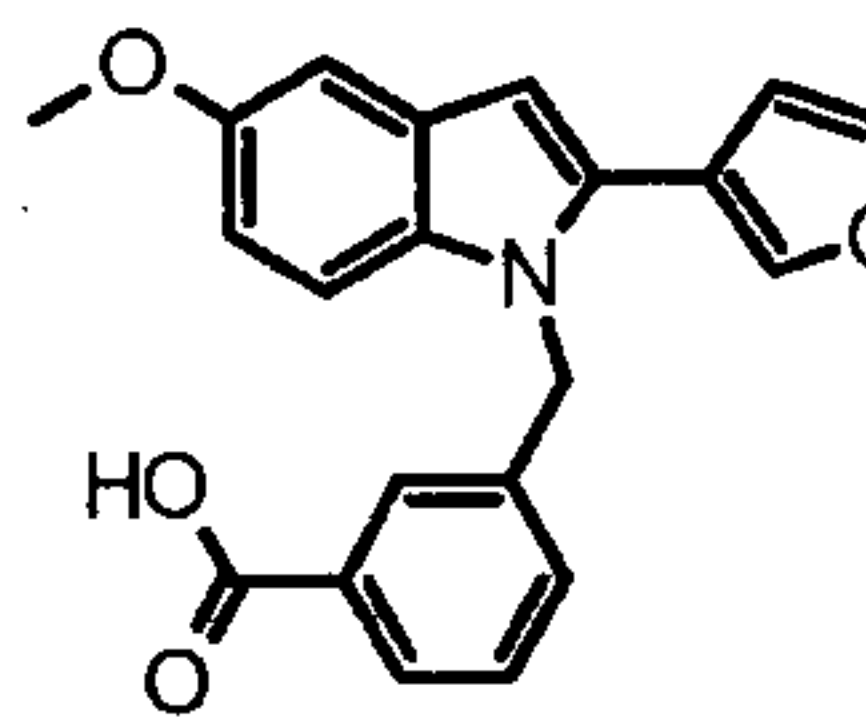
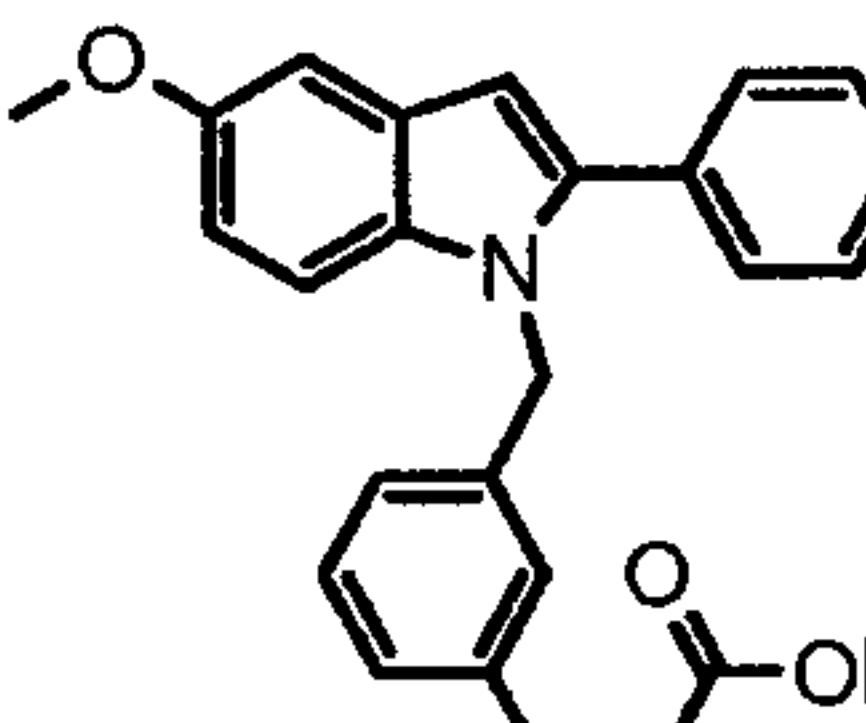
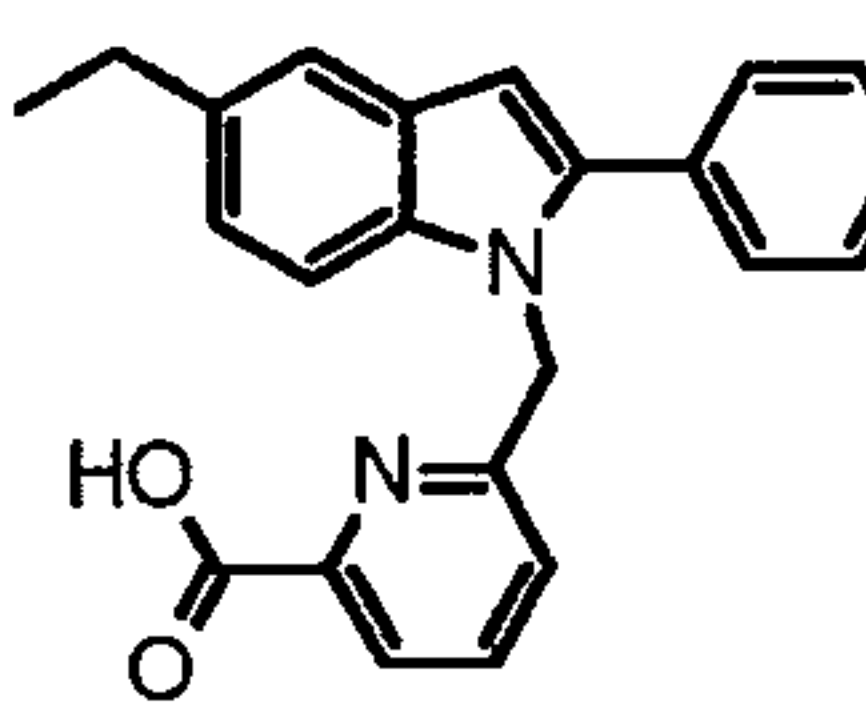
[0454]

[Table 18]

Ex. No.	Strc	Physical data
9-24		$^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 3.77 (3H, s), 5.51 (2H, s), 6.62 (1H, s), 6.78 (1H, dd, $J=2.5, 8.8\text{Hz}$), 6.90–7.00 (1H, m), 7.13 (1H, d, $J=2.5\text{Hz}$), 7.25–7.35 (2H, m), 7.35–7.55 (6H, m), 13.29 (1H, br s).
9-25		$^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 3.76 (3H, s), 5.58 (2H, s), 6.66 (1H, s), 6.75 (1H, dd, $J=2.5, 9.0\text{Hz}$), 7.09 (1H, d, $J=2.5\text{Hz}$), 7.10–7.20 (1H, m), 7.20–7.35 (2H, m), 7.39 (1H, t, $J=7.8\text{Hz}$), 7.50–7.65 (2H, m), 7.66 (1H, dd, $J=3.0, 5.0\text{Hz}$), 7.70–7.80 (1H, m), 12.96 (1H, br s).
9-26		$^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 0.70 (6H, t, $J=7.3\text{Hz}$), 1.45–1.70 (4H, m), 2.60–2.75 (1H, m), 5.54 (2H, s), 6.32 (1H, s), 7.03 (1H, dd, $J=2.1, 8.7\text{Hz}$), 7.15–7.25 (1H, m), 7.35–7.60 (4H, m), 7.75–7.85 (1H, m), 12.95 (1H, br s).
9-27		$^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 3.78 (3H, s), 5.48 (2H, s), 6.25–6.40 (1H, m), 6.60–6.70 (1H, m), 6.77 (1H, dd, $J=2.5, 8.8\text{Hz}$), 7.10–7.30 (3H, m), 7.35–7.50 (5H, m), 7.50–7.60 (1H, m), 13.50 (1H, br s).
9-28		$^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 3.77 (3H, s), 5.57 (2H, s), 6.61 (1H, s), 6.79 (1H, dd, $J=2.4, 8.9\text{Hz}$), 7.12 (1H, d, $J=2.4\text{Hz}$), 7.35–7.55 (6H, m), 7.60–7.70 (1H, m), 8.25–8.35 (1H, m), 8.80–8.90 (1H, m), 13.42 (1H, s).
9-29		$^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 3.77 (3H, s), 5.61 (2H, s), 6.57 (1H, s), 6.75–6.85 (2H, m), 7.10 (1H, d, $J=2.5\text{Hz}$), 7.35–7.60 (7H, m), 12.80–13.20 (1H, br).

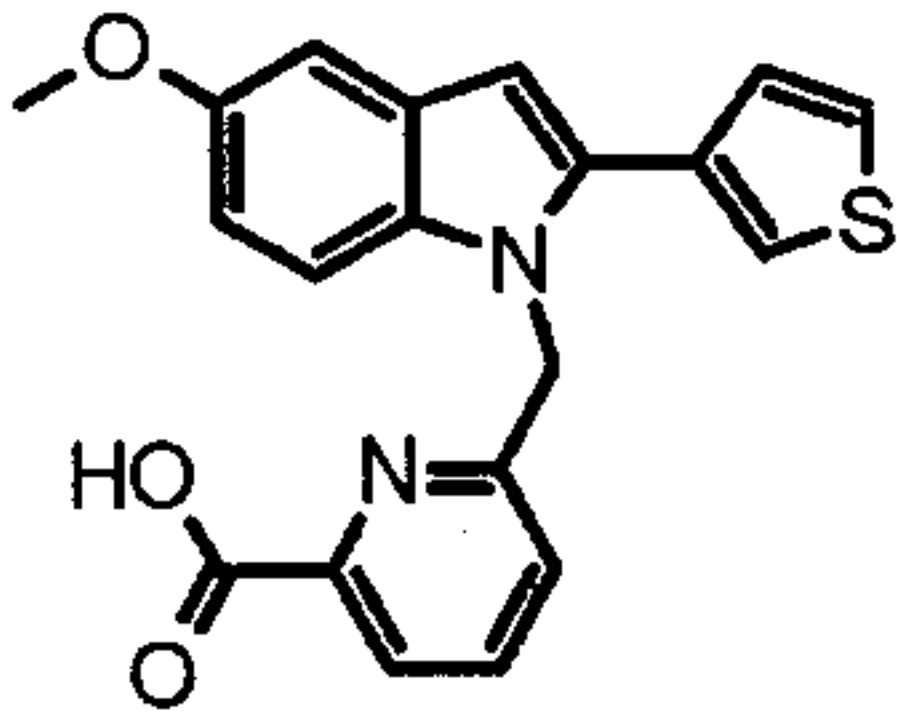
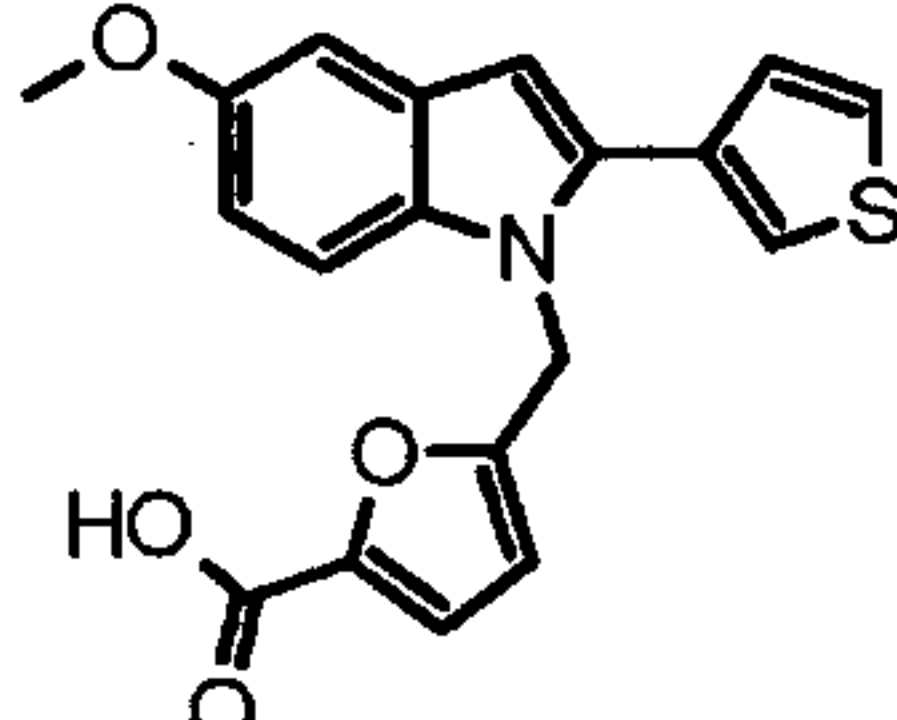
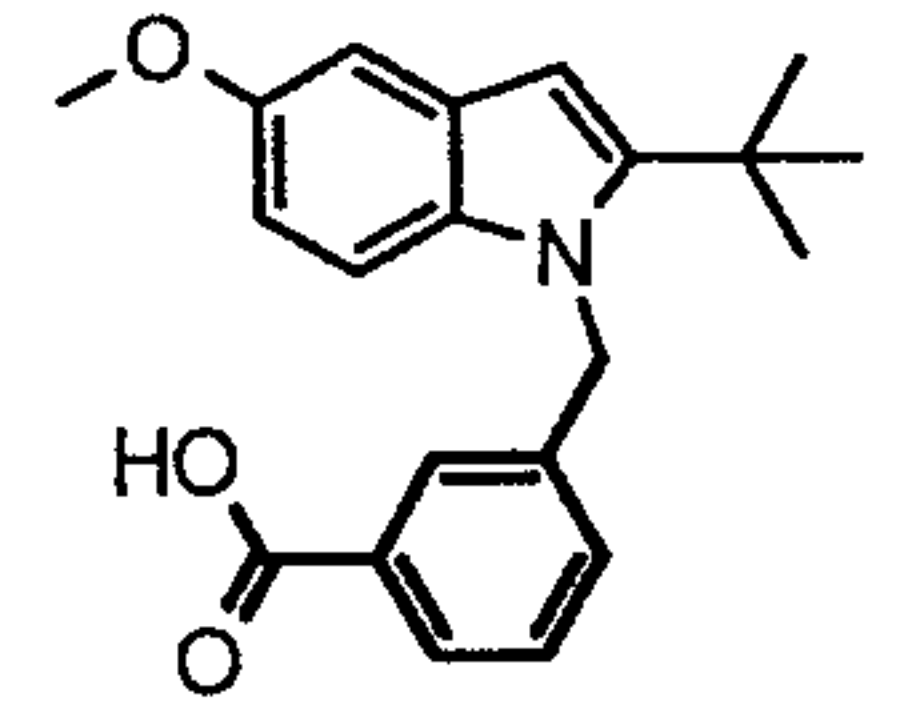
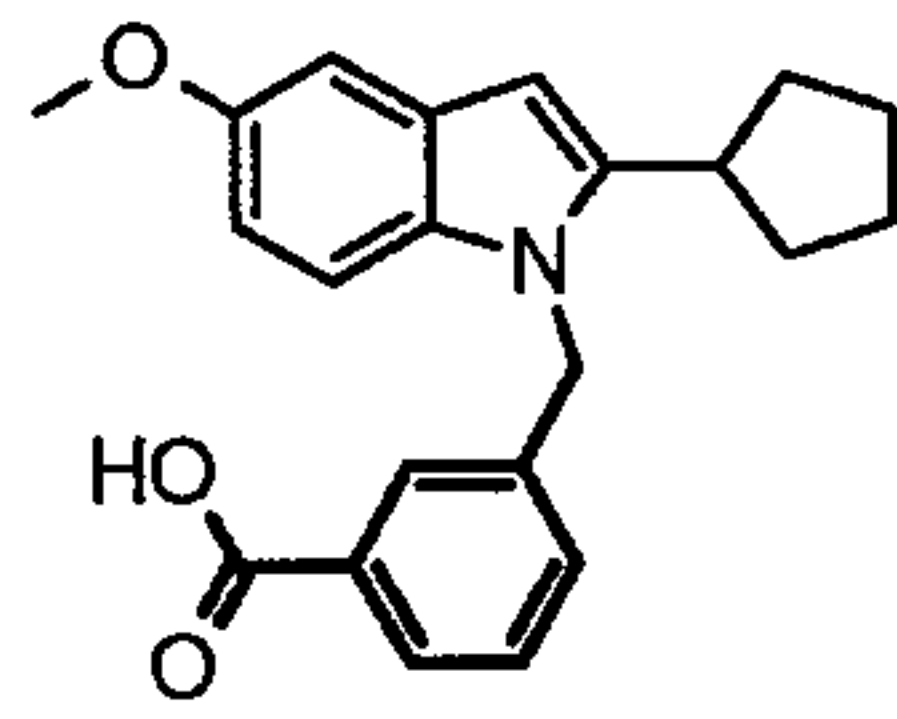
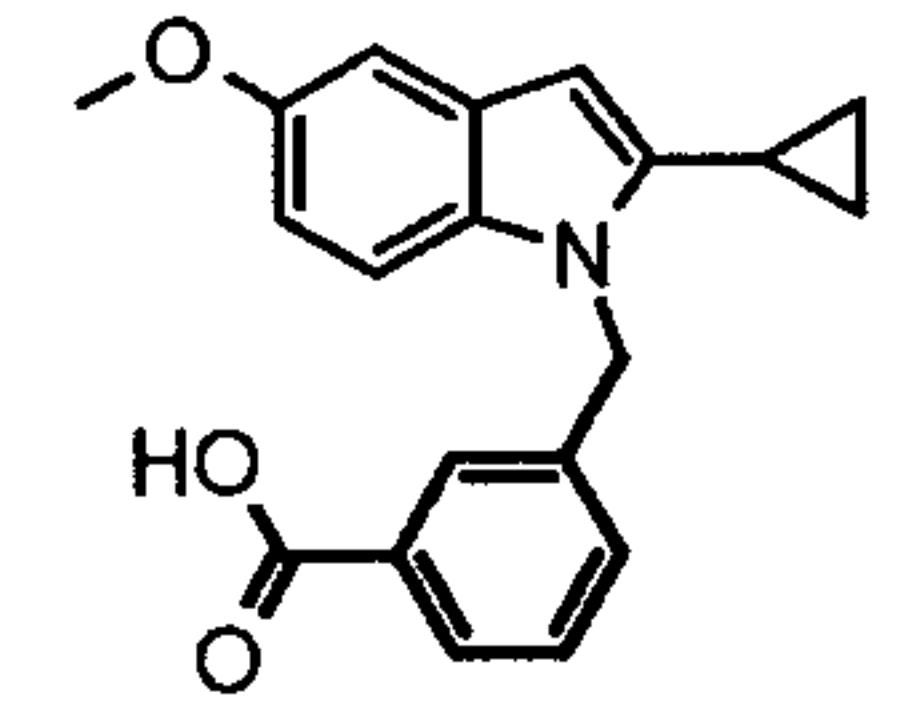
[0455]

[Table 19]

Ex. No.	Strc	Physical data
9-30		¹ H-NMR (DMSO-d ₆) δ ppm: 1.22 (3H, t, J=7.6Hz), 2.67 (2H, q, J=7.6Hz), 5.50 (2H, s), 6.61 (1H, s), 6.95-7.05 (1H, m), 7.05-7.15 (1H, m), 7.26 (1H, d, J=8.3Hz), 7.30-7.55 (8H, m), 7.70-7.80 (1H, m), 12.95 (1H, br s).
9-31		¹ H-NMR (DMSO-d ₆) δ ppm: 3.77 (3H, s), 5.69 (2H, s), 6.55-6.70 (2H, m), 6.75-6.85 (2H, m), 7.11 (1H, d, J=2.5Hz), 7.15-7.25 (1H, m), 7.30-7.50 (2H, m), 7.50-7.60 (1H, m), 7.70-7.85 (2H, m), 12.96 (1H, br s).
9-32		¹ H-NMR (DMSO-d ₆) δ ppm: 3.76 (3H, s), 5.60 (2H, s), 6.67 (1H, s), 6.70-6.85 (2H, m), 7.08 (1H, d, J=2.5Hz), 7.10-7.20 (1H, m), 7.32 (1H, d, J=9.0Hz), 7.39 (1H, t, J=7.7Hz), 7.50-7.55 (1H, m), 7.70-7.80 (2H, m), 7.85-7.95 (1H, m), 12.96 (1H, br s).
9-33		¹ H-NMR (DMSO-d ₆) δ ppm: 3.76 (3H, s), 4.54 (2H, s), 5.39 (2H, s), 6.40-6.55 (2H, m), 6.57 (1H, s), 6.55-6.80 (2H, m), 7.05-7.20 (2H, m), 7.24 (1H, d, J=9.0Hz), 7.35-7.55 (5H, m), 12.99 (1H, br s).
9-34		¹ H-NMR (DMSO-d ₆) δ ppm: 1.22 (3H, t, J=7.6Hz), 2.67 (2H, q, J=7.6Hz), 5.52 (2H, s), 6.55-6.70 (2H, m), 6.90-7.05 (1H, m), 7.21 (1H, d, J=8.3Hz), 7.35-7.50 (4H, m), 7.50-7.60 (2H, m), 7.70-7.90 (2H, m). ESI-MS (m/z) : 355 (M-H) ⁻

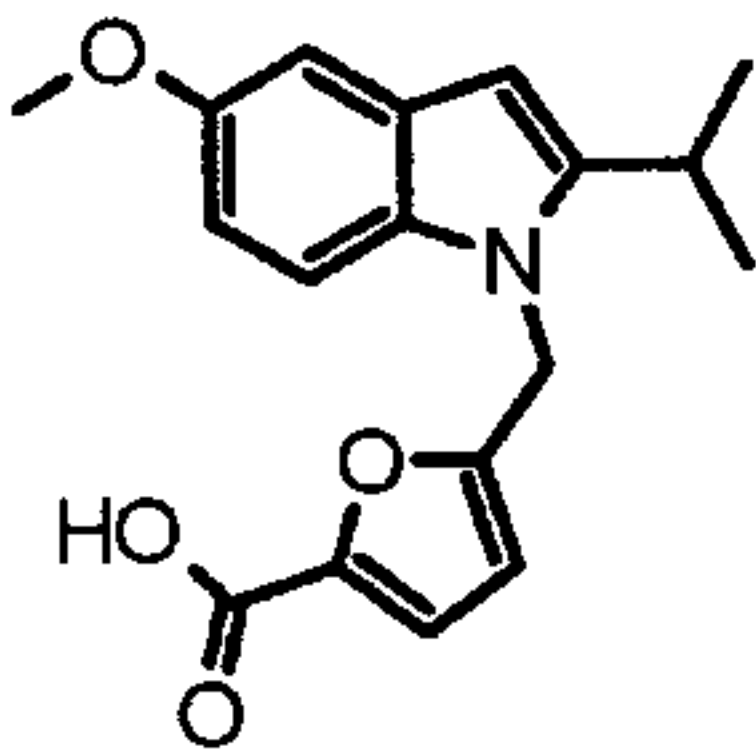
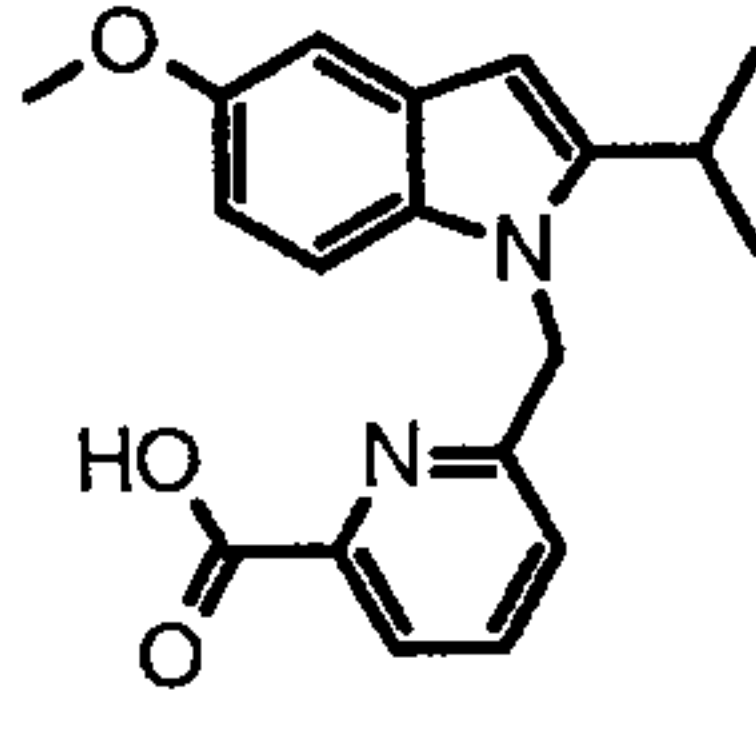
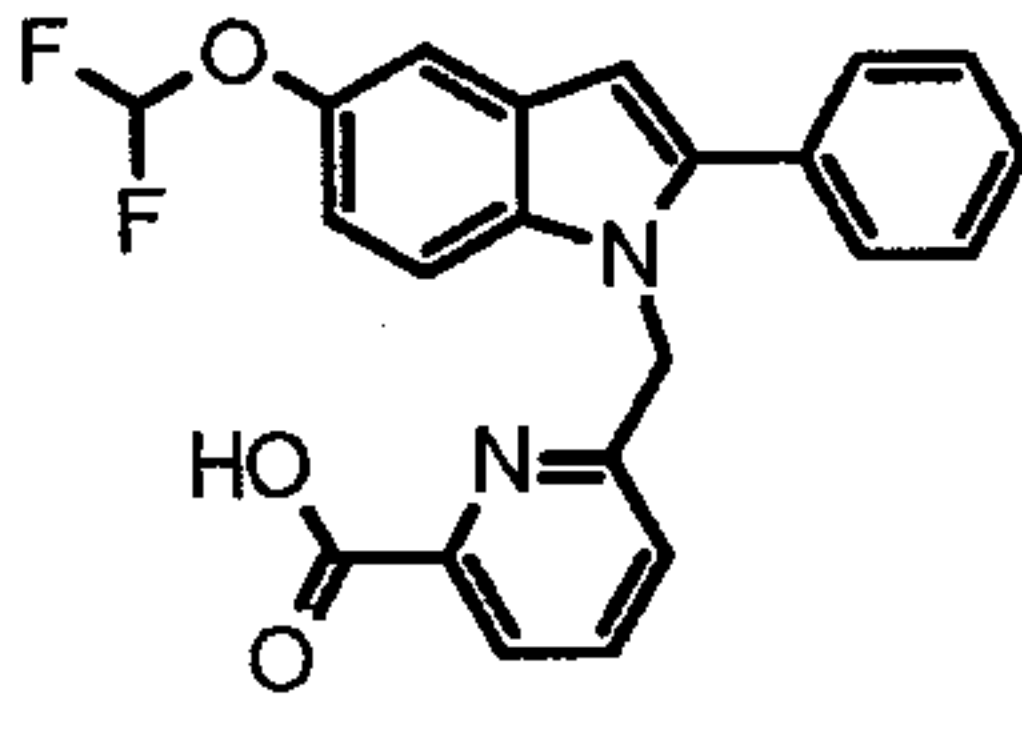
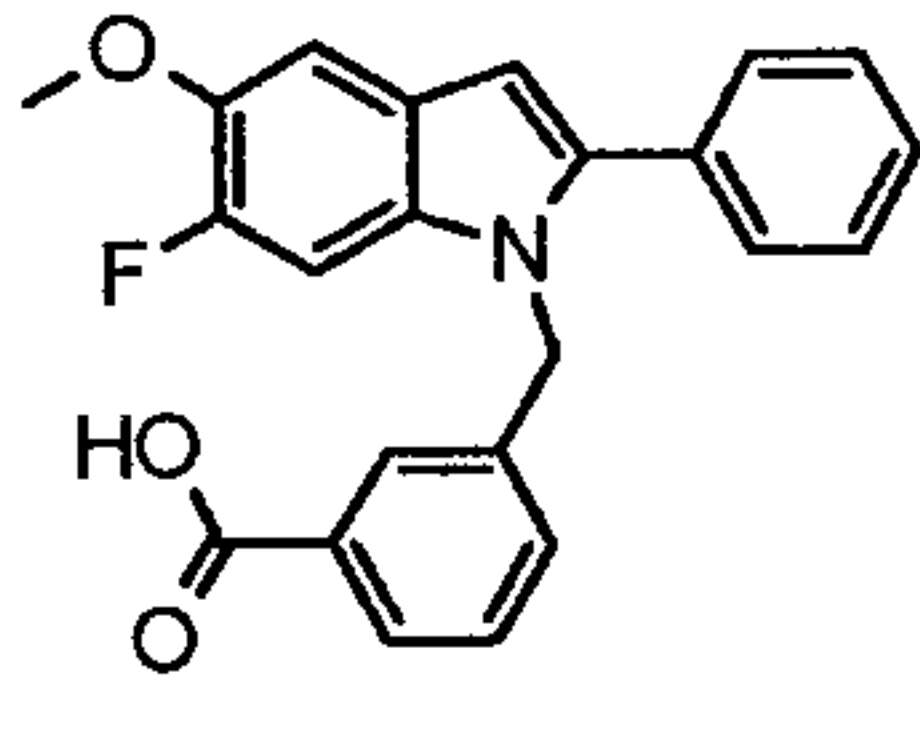
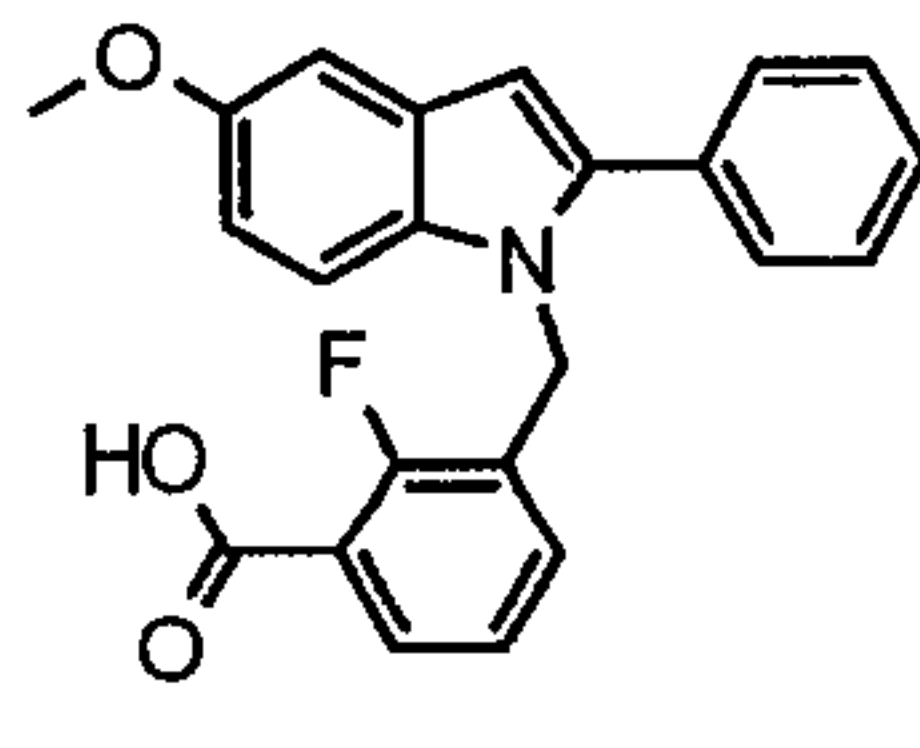
[0456]

[Table 20]

Ex. No.	Strc	Physical data
9-35		¹ H-NMR (DMSO-d ₆) δ ppm: 3.76 (3H, s), 5.59 (2H, s), 6.67 (1H, s), 6.70–6.85 (2H, m), 7.10 (1H, d, J=2.5Hz), 7.28 (1H, d, J=8.8Hz), 7.37 (1H, dd, J=1.3, 5.0Hz), 7.65 (1H, dd, J=2.9, 5.0Hz), 7.77 (1H, dd, J=1.3, 2.9Hz), 7.80–7.95 (2H, m), 13.24 (1H, br s).
9-36		¹ H-NMR (DMSO-d ₆) δ ppm: 3.76 (3H, s), 5.48 (2H, s), 6.25 (1H, d, J=3.3Hz), 6.55–6.60 (1H, m), 6.79 (1H, dd, J=2.5, 8.8Hz), 7.00–7.15 (2H, m), 7.35–7.50 (2H, m), 7.72 (1H, dd, J=2.9, 4.9Hz), 7.76 (1H, dd, J=1.4, 2.9Hz), 13.03 (1H, br s).
9-37		¹ H-NMR (DMSO-d ₆) δ ppm: 1.35 (9H, s), 3.72 (3H, s), 5.68 (2H, s), 6.28 (1H, s), 6.60 (1H, dd, J=2.5, 8.8Hz), 6.92 (1H, d, J=8.8Hz), 6.95–7.05 (2H, m), 7.37 (1H, t, J=7.8Hz), 7.45–7.55 (1H, m), 7.70–7.80 (1H, m), 12.90 (1H, br s).
9-38		¹ H-NMR (DMSO-d ₆) δ ppm: 1.50–1.80 (6H, m), 1.85–2.00 (2H, m), 3.05–3.15 (1H, m), 3.73 (3H, s), 5.48 (2H, s), 6.27 (1H, s), 6.64 (1H, dd, J=2.4, 8.7Hz), 7.00 (1H, d, J=2.4Hz), 7.10–7.20 (2H, m), 7.40 (1H, t, J=7.7Hz), 7.50–7.60 (1H, m), 7.75–7.85 (1H, m), 12.95 (1H, br s).
9-39		¹ H-NMR (DMSO-d ₆) δ ppm: 0.55–0.70 (2H, m), 0.80–0.95 (2H, m), 1.80–1.95 (1H, m), 3.72 (3H, s), 5.56 (2H, s), 6.08 (1H, s), 6.66 (1H, dd, J=2.4, 8.8Hz), 6.96 (1H, d, J=2.4Hz), 7.15–7.30 (2H, m), 7.42 (1H, t, J=7.7Hz), 7.55–7.65 (1H, m), 7.75–7.85 (1H, m), 12.94 (1H, br s).

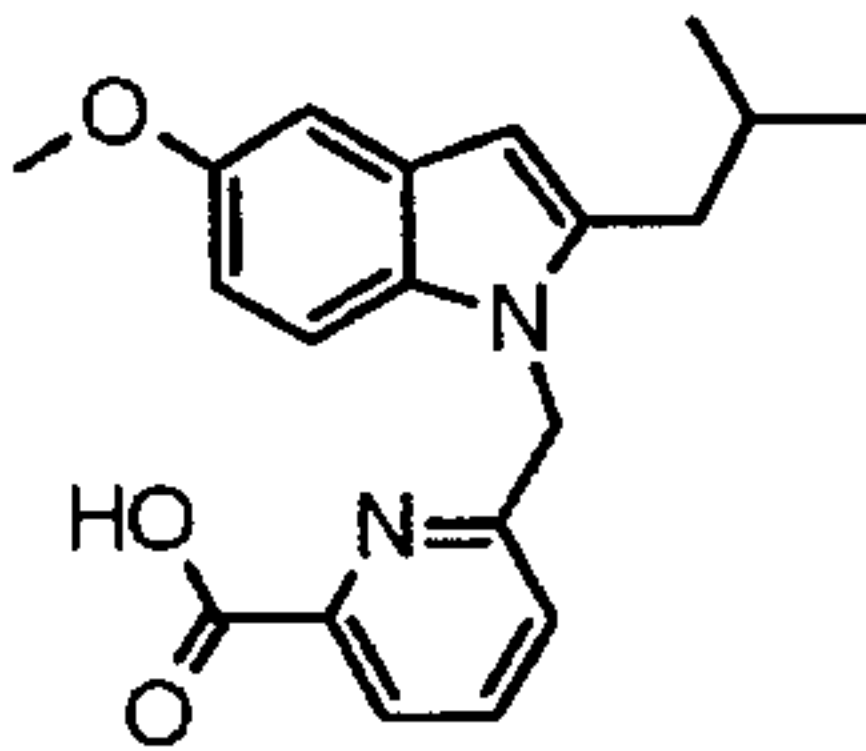
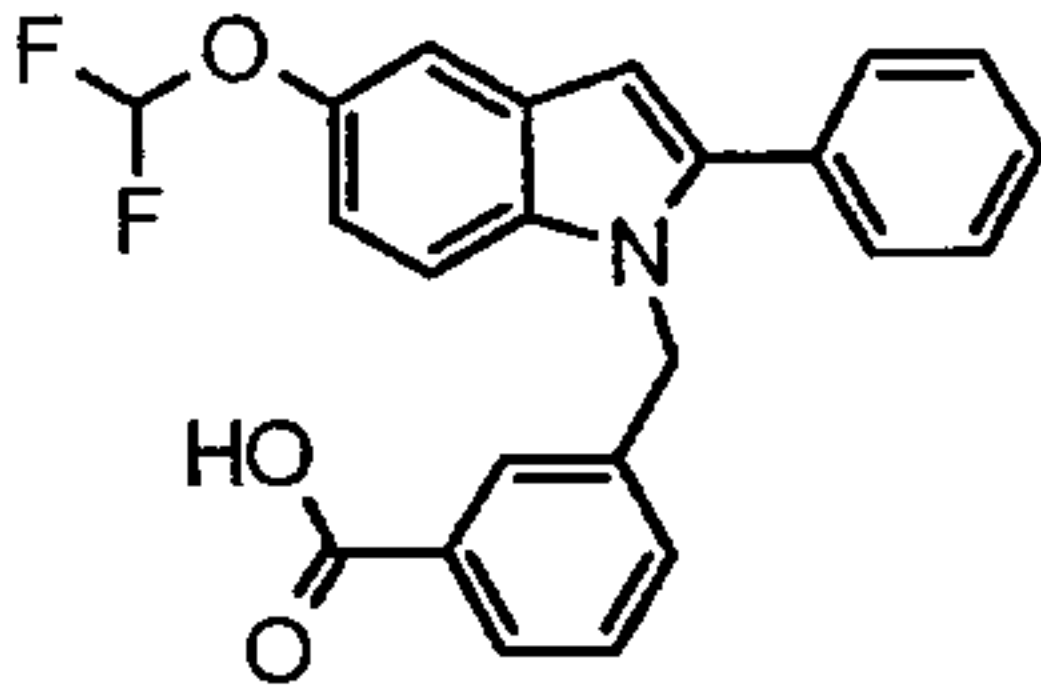
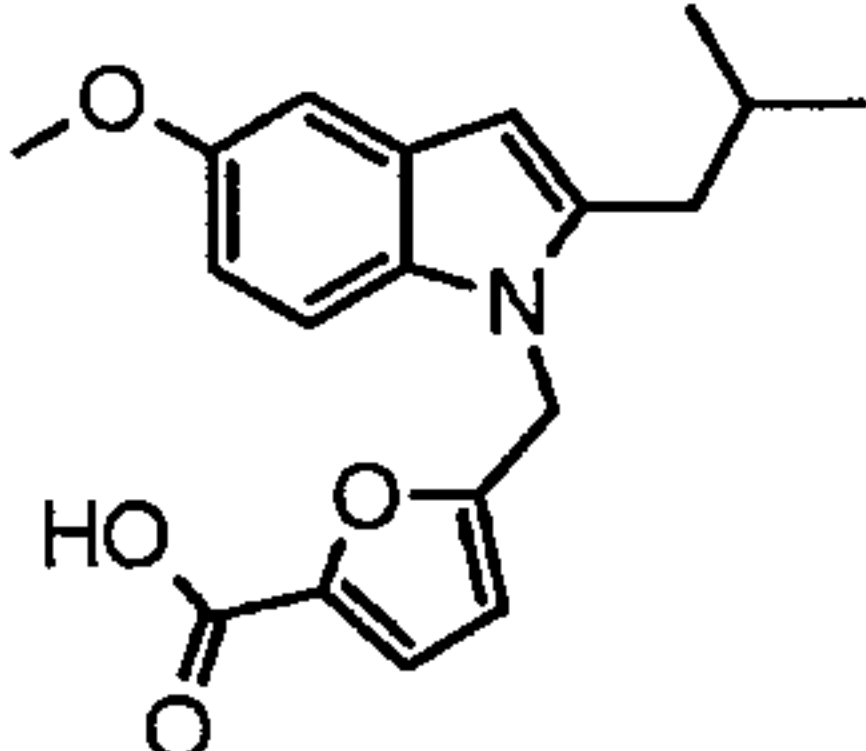
[0457]

[Table 21]

Ex. No.	Strc	Physical data
9-40		$^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 1.27 (6H, d, $J=6.8\text{Hz}$), 3.10–3.30 (1H, m), 3.72 (3H, s), 5.43 (2H, s), 6.20 (1H, s), 6.33 (1H, d, $J=3.4\text{Hz}$), 6.69 (1H, dd, $J=2.4, 8.9\text{Hz}$), 6.97 (1H, d, $J=2.4\text{Hz}$), 7.09 (1H, d, $J=3.4\text{Hz}$), 7.36 (1H, d, $J=8.9\text{Hz}$), 13.00 (1H, br s).
9-41		$^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 1.22 (6H, d, $J=6.8\text{Hz}$), 3.00–3.20 (1H, m), 3.73 (3H, s), 5.52 (2H, s), 6.27 (1H, s), 6.55–6.75 (2H, m), 7.01 (1H, d, $J=2.5\text{Hz}$), 7.20 (1H, d, $J=8.8\text{Hz}$), 7.75–7.95 (2H, m), 13.23 (1H, br s).
9-42		$^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 5.57 (2H, s), 6.72 (1H, s), 6.75–6.85 (1H, m), 6.90–7.35 (2H, m), 7.35–7.55 (5H, m), 7.55–7.65 (2H, m), 7.75–7.95 (2H, m), 12.80–13.65 (1H, br).
9-43		$^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 3.85 (3H, s), 5.49 (2H, s), 6.62 (1H, s), 7.00–7.10 (1H, m), 7.25–7.55 (9H, m), 7.70–7.80 (1H, m), 12.90 (1H, br s).
9-44		$^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 3.77 (3H, s), 5.50 (2H, s), 6.50–6.60 (1H, m), 6.60 (1H, s), 6.78 (1H, dd, $J=2.3,$ 8.9Hz), 7.07 (1H, t, $J=7.8\text{Hz}$), 7.13 (1H, d, $J=2.3\text{Hz}$), 7.30 (1H, d, $J=8.9\text{Hz}$), 7.35–7.50 (5H, m), 7.60–7.75 (1H, m), 13.27 (1H, br s).

[0458]

[Table 22]

Ex. No.	Strc	Physical data
9-45		$^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 0.90 (6H, d, $J=6.5\text{Hz}$), 1.75–1.95 (1H, m), 2.59 (2H, d, $J=7.0\text{Hz}$), 3.74 (3H, s), 5.50 (2H, s), 6.25 (1H, s), 6.55–6.75 (2H, m), 7.02 (1H, d, $J=2.3\text{Hz}$), 7.21 (1H, d, $J=8.8\text{Hz}$), 7.75–7.95 (2H, m), 13.24 (1H, br s).
9-46		$^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 5.55 (2H, s), 6.71 (1H, s), 6.90–7.60 (12H, m), 7.70–7.85 (1H, m), 12.94 (1H, br s).
9-47		$^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 0.95 (6H, d, $J=6.5\text{Hz}$), 1.85–2.05 (1H, m), 2.66 (2H, d, $J=7.3\text{Hz}$), 3.73 (3H, s), 5.40 (2H, s), 6.18 (1H, s), 6.32 (1H, d, $J=3.3\text{Hz}$), 6.69 (1H, dd, $J=2.4, 8.9\text{Hz}$), 6.97 (1H, d, $J=2.4\text{Hz}$), 7.09 (1H, d, $J=3.3\text{Hz}$), 7.36 (1H, d, $J=8.9\text{Hz}$), 13.00 (1H, br s).

[0459]

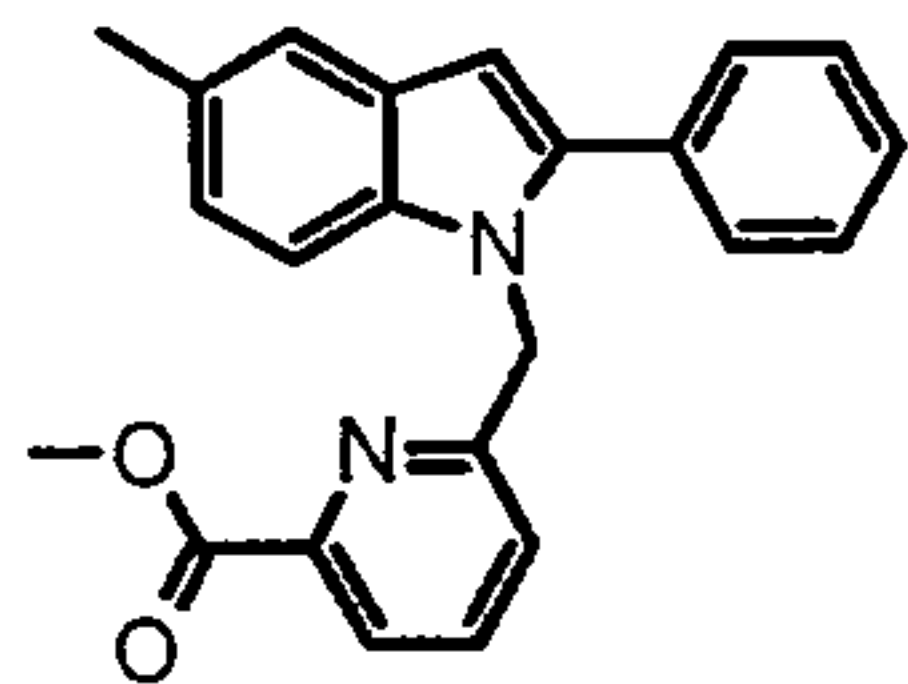
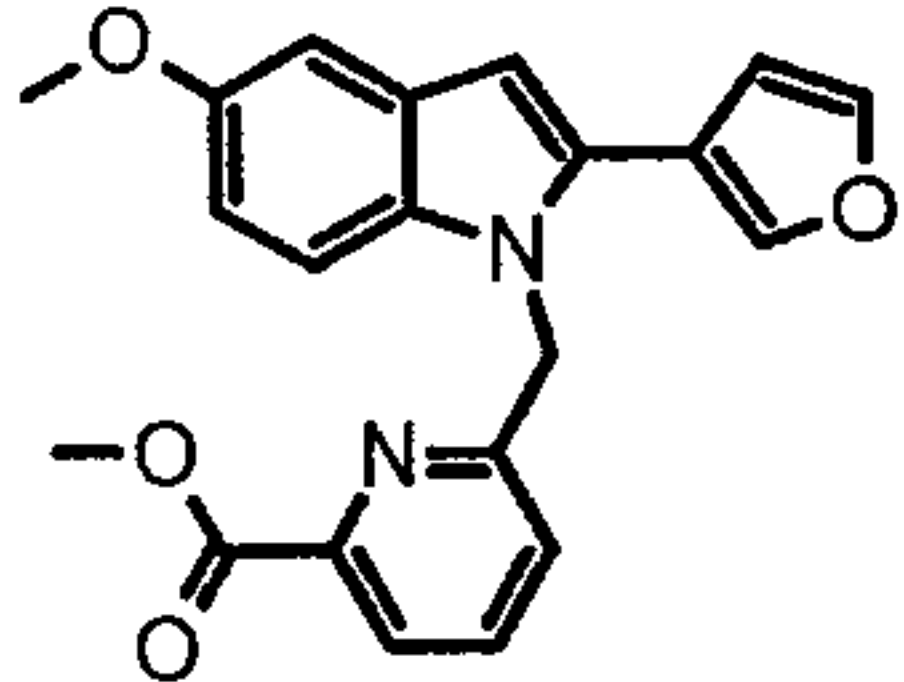
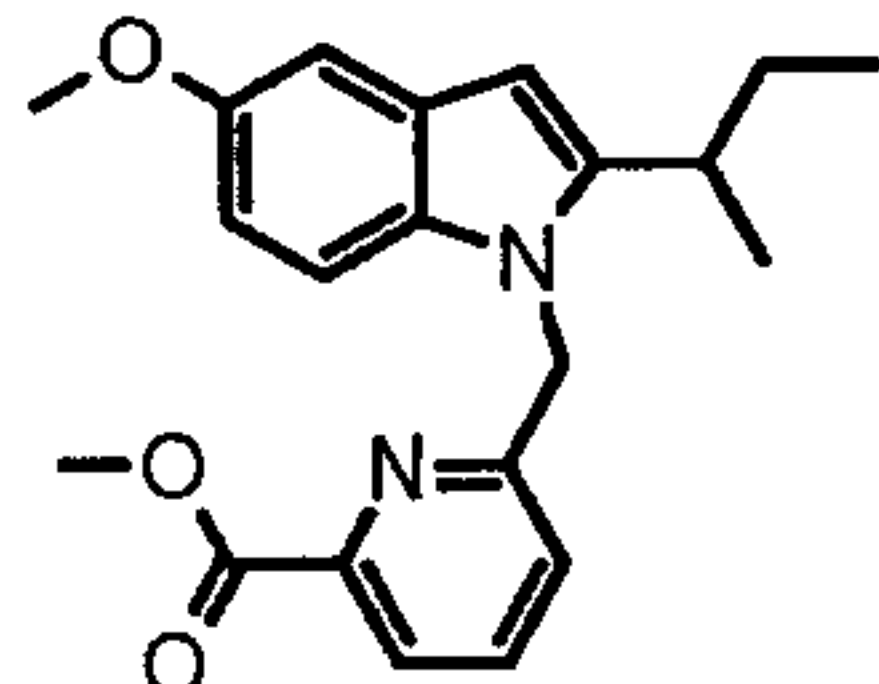
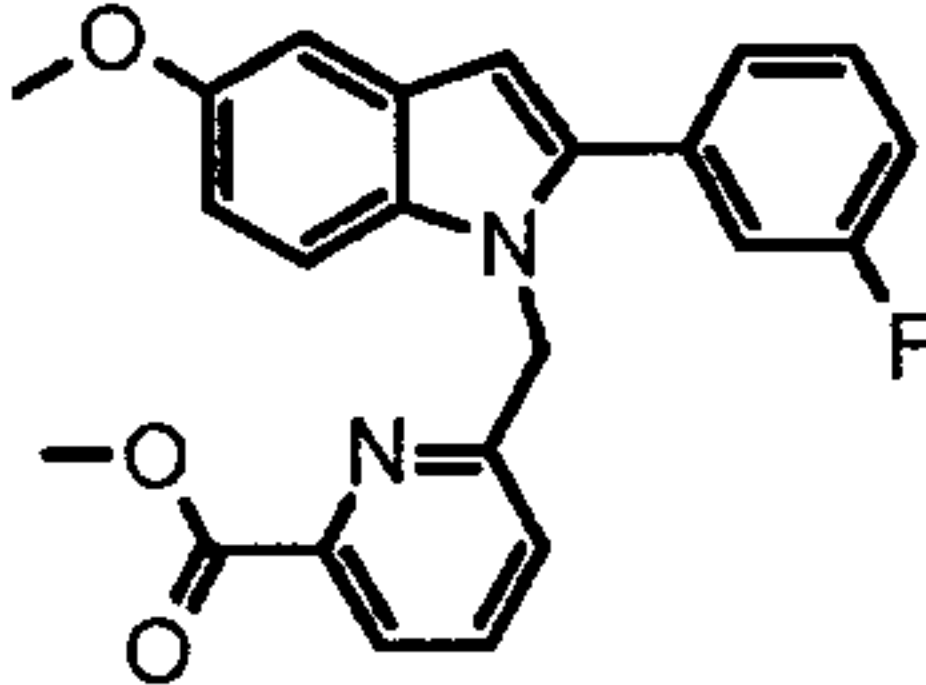
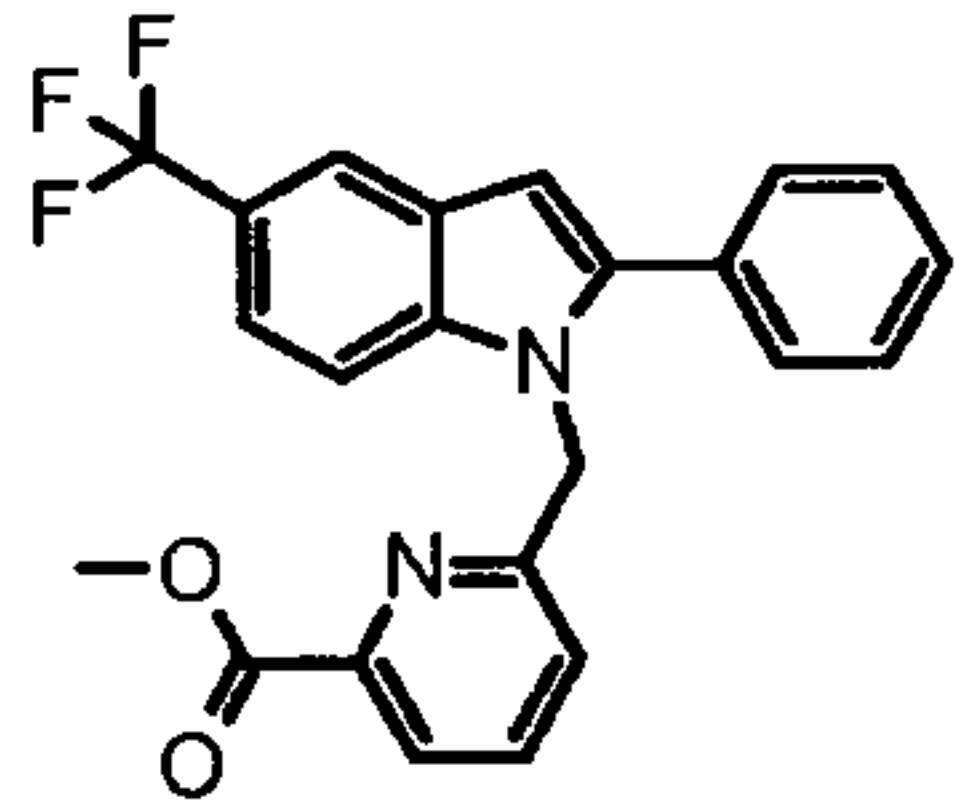
Examples 10-1 to 10-12

[0460]

5 The compounds shown in Tables 23 to 25 were synthesized in a manner similar to that of Example 1-1 by using the corresponding starting materials.

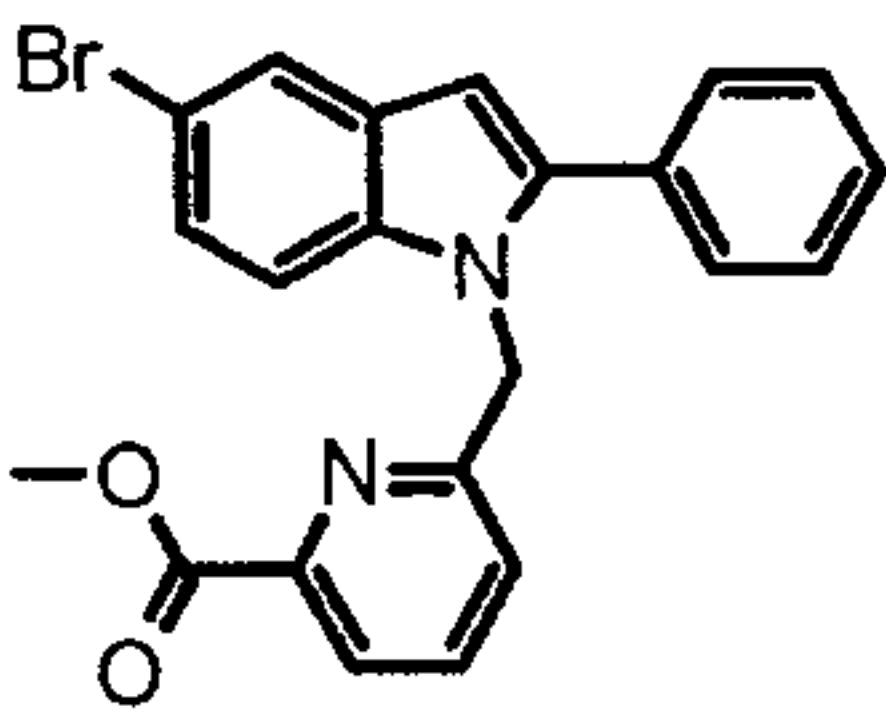
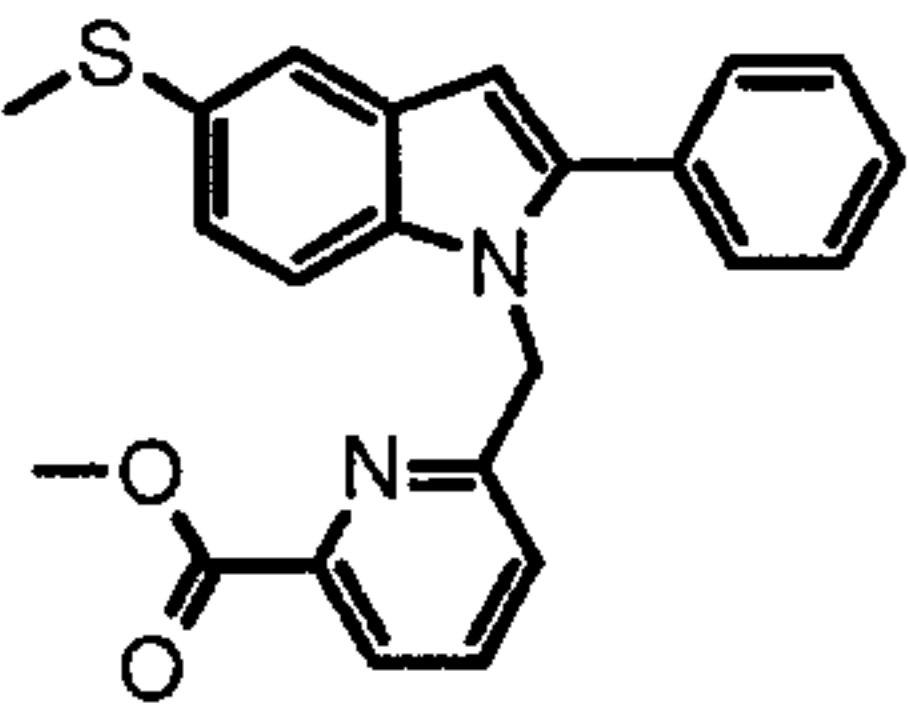
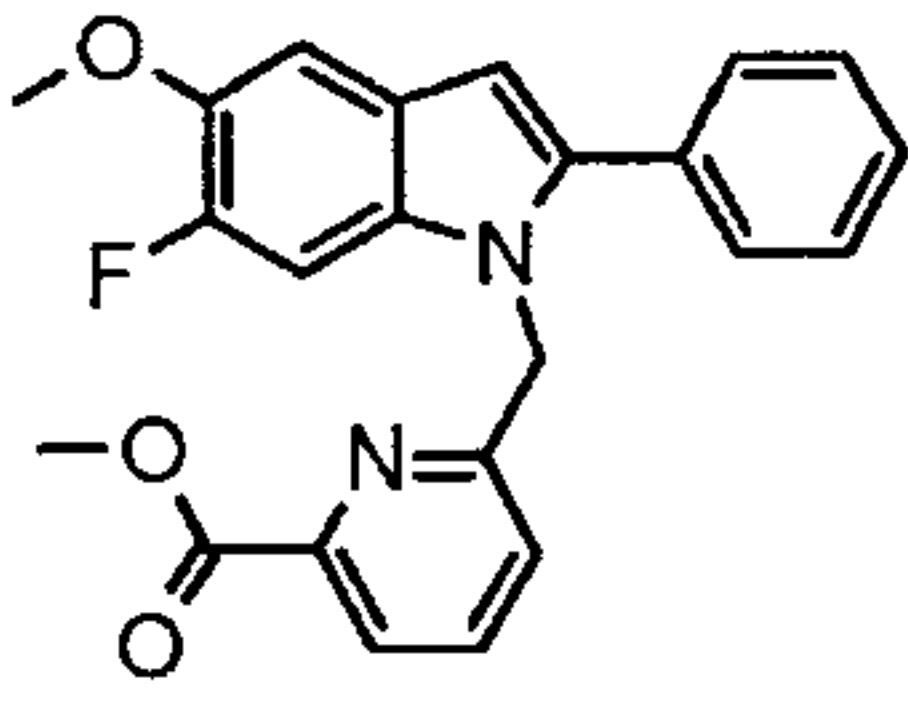
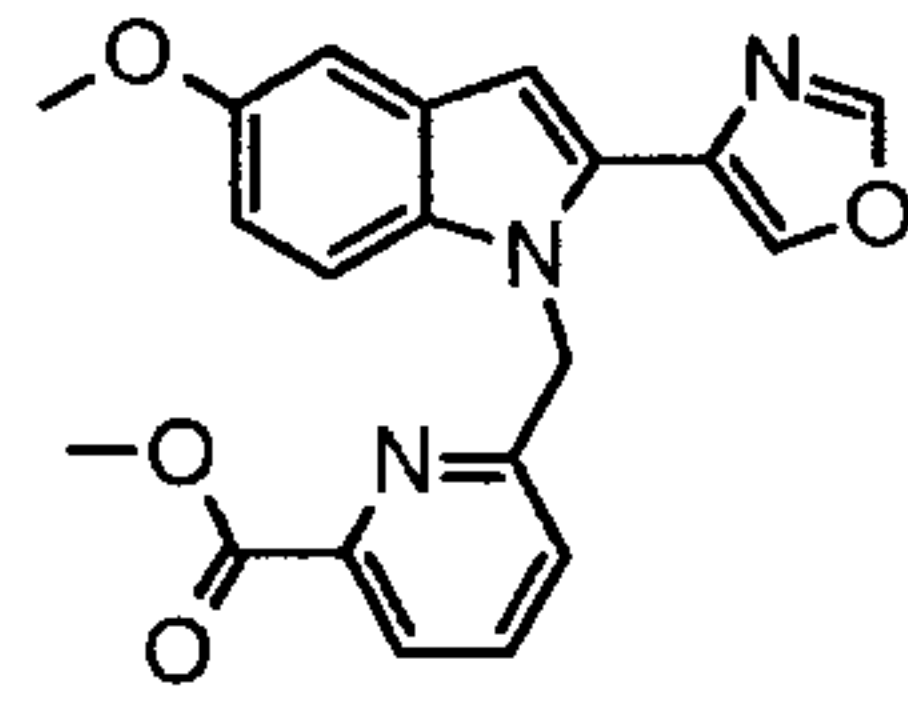
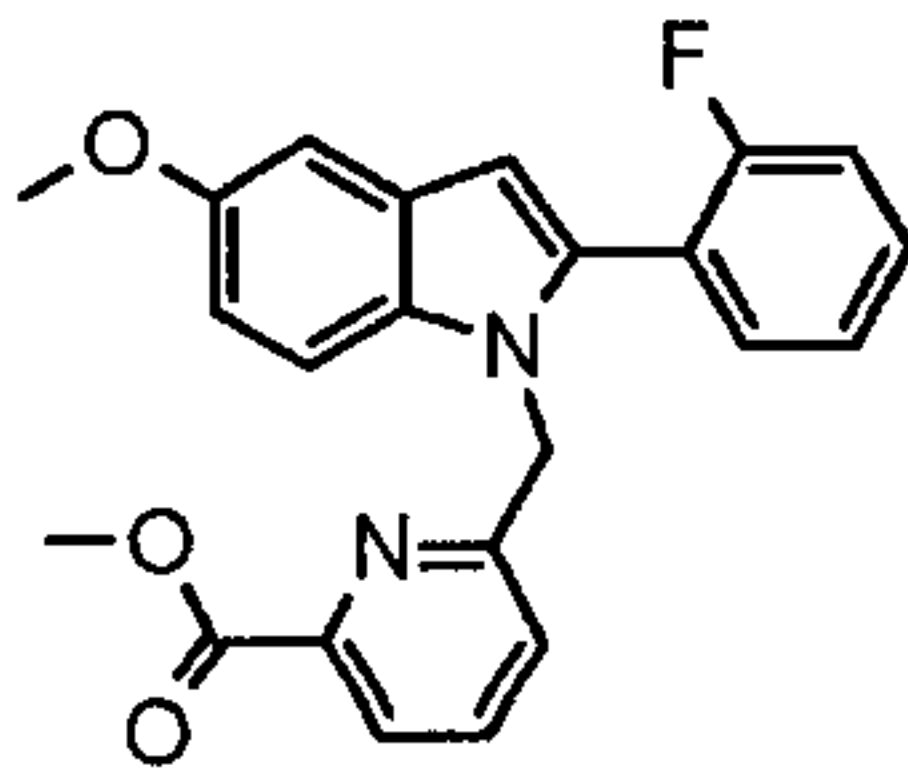
[0461]

[Table 23]

Ex. No.	Strc	Physical data
10-1		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 2.45 (3H, s), 4.02 (3H, s), 5.59 (2H, s), 6.61 (1H, s), 6.70 (1H, d, $J=8.0\text{Hz}$), 6.90–7.10 (2H, m), 7.30–7.55 (6H, m), 7.60–7.70 (1H, m), 7.98 (1H, d, $J=7.5\text{Hz}$).
10-2		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 3.86 (3H, s), 4.05 (3H, s), 5.62 (2H, s), 6.45–6.55 (1H, m), 6.62 (1H, s), 6.65–6.75 (1H, m), 6.82 (1H, dd, $J=2.3$, 8.9Hz), 7.06 (1H, d, $J=8.9\text{Hz}$), 7.12 (1H, d, $J=2.3\text{Hz}$), 7.40–7.55 (2H, m), 7.60–7.70 (1H, m), 7.95–8.05 (1H, m).
10-3		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 0.85 (t, 3H, $J=7.4\text{Hz}$), 1.23 (3H, d, $J=6.8\text{Hz}$), 1.45–1.80 (2H, m), 2.60–2.80 (1H, m), 3.84 (3H, s), 4.05 (3H, s), 5.54 (2H, s), 6.32 (1H, s), 6.40–6.50 (1H, m), 6.75 (1H, dd, $J=2.3$, 8.8Hz), 7.00 (1H, d, $J=8.8\text{Hz}$), 7.08 (1H, d, $J=2.3\text{Hz}$), 7.61 (1H, t, $J=7.8\text{Hz}$), 7.95–8.05 (1H, m).
10-4		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 3.76 (3H, s), 3.86 (3H, s), 5.54 (2H, s), 6.67 (1H, s), 6.77 (1H, dd, $J=2.4$, 8.8Hz), 6.85–6.95 (1H, m), 7.13 (1H, d, $J=2.4\text{Hz}$), 7.15–7.35 (2H, m), 7.35–7.60 (3H, m), 7.80–7.95 (2H, m).
10-5		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 4.03 (3H, s), 5.64 (2H, s), 6.60–6.80 (2H, m), 7.21 (1H, d, $J=8.3\text{Hz}$), 7.30–7.50 (6H, m), 7.69 (1H, t, $J=7.8\text{Hz}$), 7.95–8.05 (2H, m).

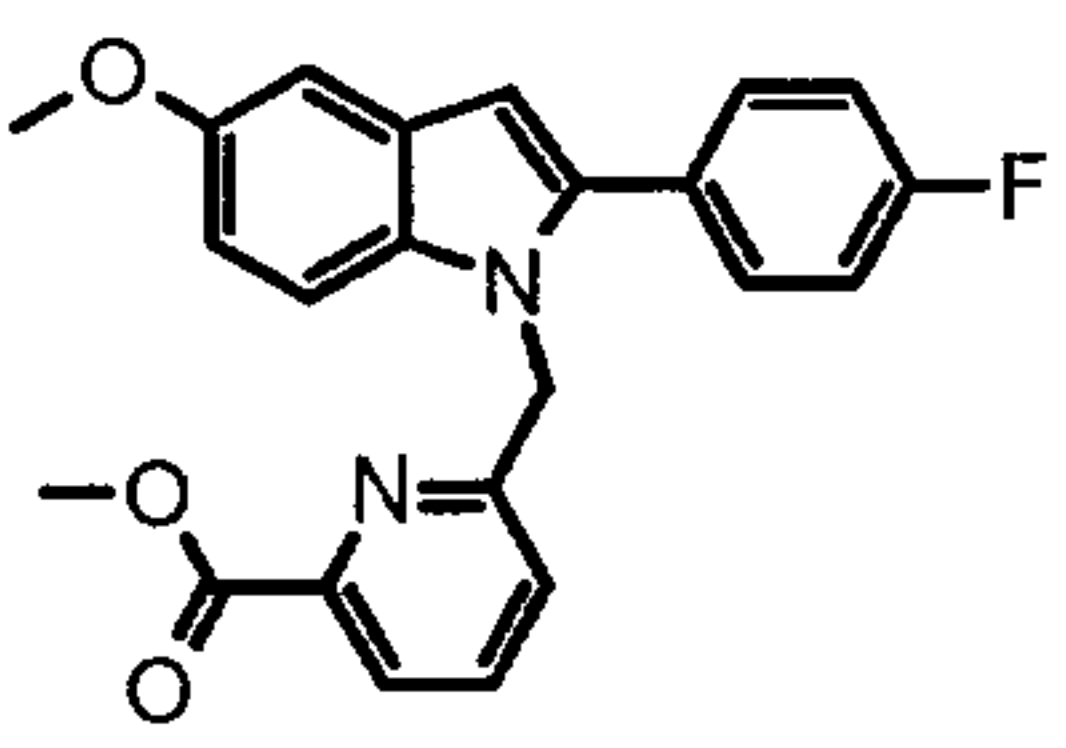
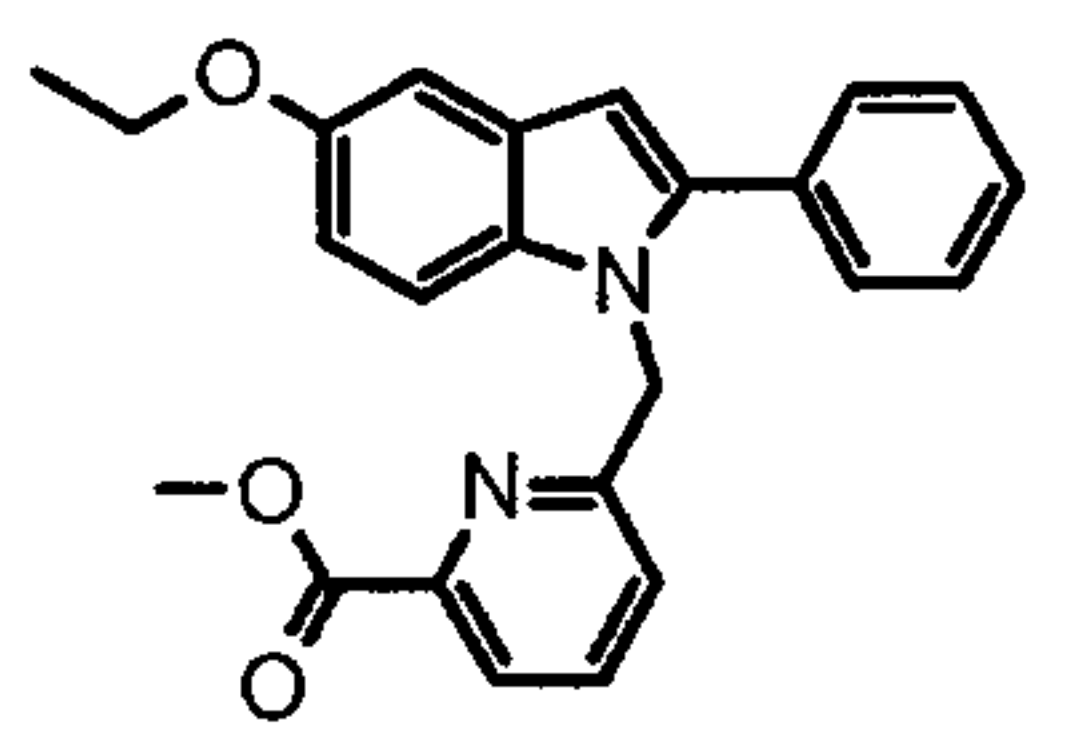
[0462]

[Table 24]

Ex. No.	Strc	Physical data
10-6		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 4.02 (3H, s), 5.59 (2H, s), 6.60–6.70 (2H, m), 7.00 (1H, d, $J=8.7\text{Hz}$), 7.22 (1H, dd, $J=1.8, 8.7\text{Hz}$), 7.30–7.50 (5H, m), 7.60–7.75 (1H, m), 7.81 (1H, d, $J=1.8\text{Hz}$), 7.95–8.05 (1H, m).
10-7		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 2.52 (3H, s), 4.02 (3H, s), 5.59 (2H, s), 6.60–6.75 (2H, m), 7.06 (1H, d, $J=8.5\text{Hz}$), 7.16 (1H, dd, $J=1.8, 8.5\text{Hz}$), 7.30–7.45 (5H, m), 7.60–7.70 (2H, m), 7.95–8.05 (1H, m).
10-8		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 3.94 (3H, s), 4.03 (3H, s), 5.53 (2H, s), 6.55–6.75 (2H, m), 6.80–6.95 (1H, m), 7.20 (1H, d, $J=8.3\text{Hz}$), 7.30–7.45 (5H, m), 7.68 (1H, t, $J=7.8\text{Hz}$), 7.95–8.05 (1H, m).
10-9		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 3.86 (3H, s), 4.05 (3H, s), 5.83 (2H, s), 6.75–6.90 (3H, m), 7.05–7.20 (2H, m), 7.60–7.70 (1H, m), 7.80–7.95 (2H, m), 7.95–8.05 (1H, m).
10-10		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 3.86 (3H, s), 4.01 (3H, s), 5.47 (2H, s), 6.60–6.70 (2H, m), 6.82 (1H, dd, $J=2.4, 8.9\text{Hz}$), 7.01 (1H, d, $J=8.9\text{Hz}$), 7.05–7.20 (3H, m), 7.30–7.45 (2H, m), 7.55–7.70 (1H, m), 7.90–8.00 (1H, m).

[0463]

[Table 25]

Ex. No.	Strc	Physical data
10-11		¹ H-NMR (CDCl ₃) δ ppm: 3.86 (3H, s), 4.03 (3H, s), 5.54 (2H, s), 6.50-6.75 (2H, m), 6.82 (1H, dd, J=2.5, 8.8Hz), 6.95-7.20 (4H, m), 7.30-7.45 (2H, m), 7.60-7.75 (1H, m), 7.90-8.10 (1H, m).
10-12		¹ H-NMR (CDCl ₃) δ ppm: 1.44 (3H, t, J=7.0Hz), 4.02 (3H, s), 4.09 (2H, q, J=7.0Hz), 5.58 (2H, s), 6.55-6.65 (1H, m), 6.65-6.75 (1H, m), 6.80 (1H, dd, J=2.4, 8.9Hz), 7.01 (1H, d, J=8.9Hz), 7.10-7.20 (1H, m), 7.30-7.45 (5H, m), 7.66 (1H, t, J=7.8Hz), 7.95-8.05 (1H, m).

[0464]

Examples 11-1 to 11-7

The compounds shown in Tables 26 to 27 were synthesized in a manner similar to
5 that of Example 2-1 by using the corresponding starting materials.

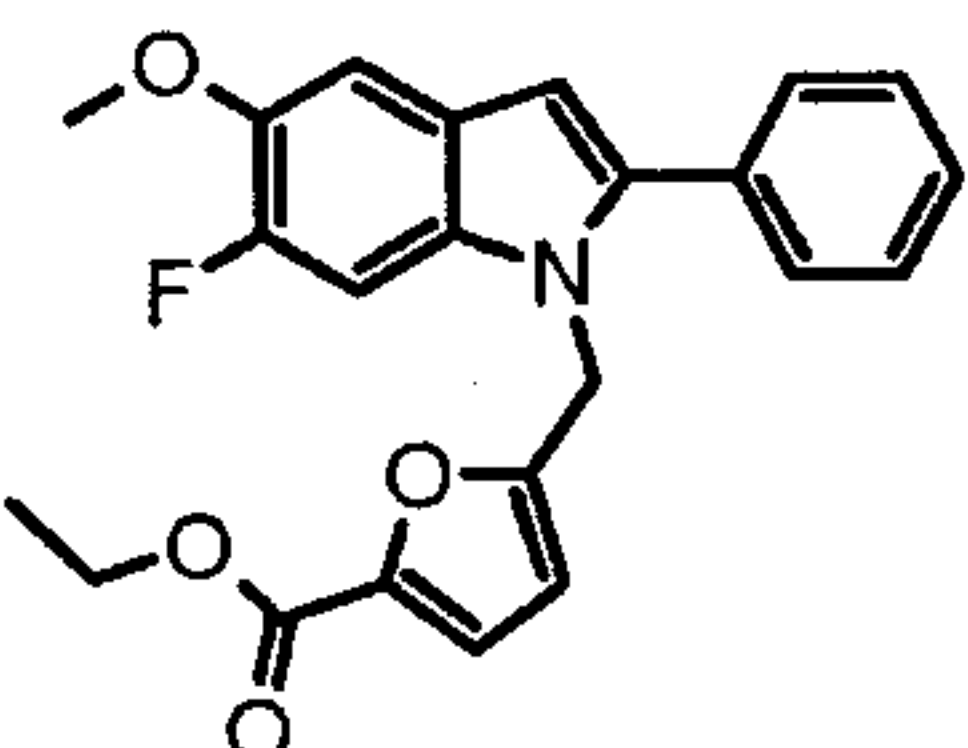
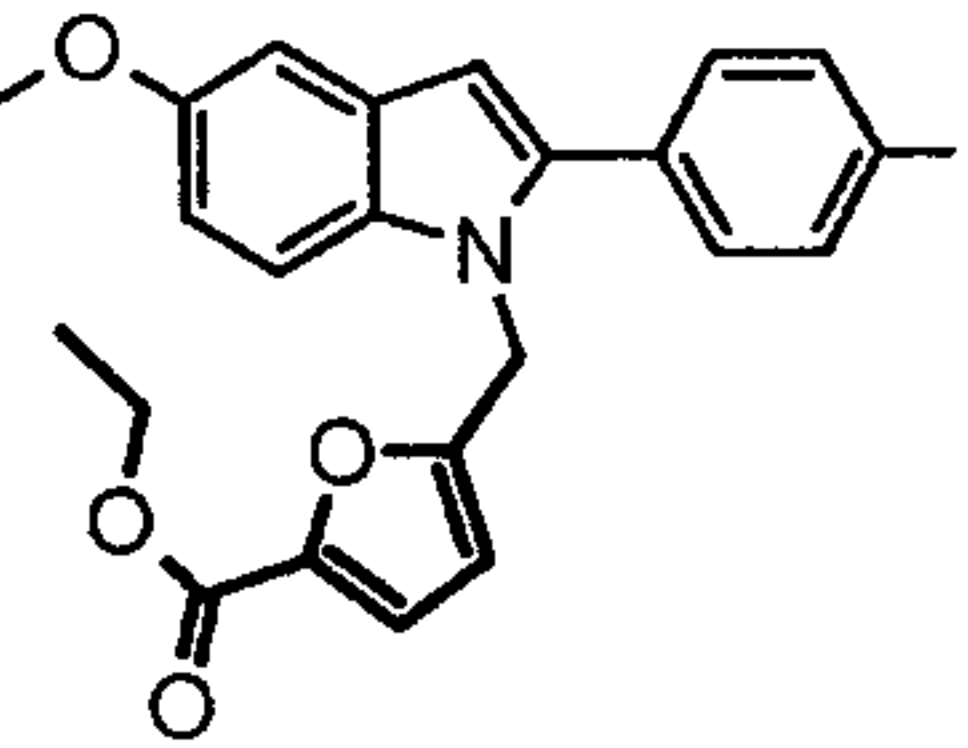
[0465]

[Table 26]

Ex. No.	Strc	Physical data
11-1		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.37 (3H, t, $J=7.1\text{Hz}$), 2.46 (3H, s), 4.34 (2H, q, $J=7.1\text{Hz}$), 5.30 (2H, s), 5.97 (1H, d, $J=3.5\text{Hz}$), 6.54 (1H, s), 7.00–7.10 (2H, m), 7.18 (1H, d, $J=8.3\text{Hz}$), 7.35–7.55 (6H, m).
11-2		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 0.91 (3H, t, $J=7.4\text{Hz}$), 1.28 (3H, d, $J=6.8\text{Hz}$), 1.36 (3H, t, $J=7.1\text{Hz}$), 1.50–1.85 (2H, m), 2.75–2.90 (1H, m), 3.83 (3H, s), 4.35 (2H, q, $J=7.1\text{Hz}$), 5.30 (2H, s), 5.84 (1H, d, $J=3.5\text{Hz}$), 6.25 (1H, s), 6.78 (1H, dd, $J=2.4, 8.8\text{Hz}$), 7.00 (1H, d, $J=3.5\text{Hz}$), 7.04 (1H, d, $J=2.4\text{Hz}$), 7.11 (1H, d, $J=8.8\text{Hz}$).
11-3		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.37 (3H, t, $J=7.1\text{Hz}$), 4.35 (2H, q, $J=7.1\text{Hz}$), 5.35 (2H, s), 5.99 (1H, d, $J=3.5\text{Hz}$), 6.69 (1H, s), 7.05 (1H, d, $J=3.5\text{Hz}$), 7.35–7.55 (7H, m), 7.94 (1H, s).
11-4		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.37 (3H, t, $J=7.1\text{Hz}$), 3.86 (3H, s), 4.36 (2H, q, $J=7.1\text{Hz}$), 5.34 (2H, s), 5.95–6.05 (1H, m), 6.50–6.65 (2H, m), 6.86 (1H, dd, $J=2.5, 8.9\text{Hz}$), 7.05 (1H, d, $J=3.5\text{Hz}$), 7.08 (1H, d, $J=2.5\text{Hz}$), 7.18 (1H, d, $J=8.9\text{Hz}$), 7.45–7.55 (1H, m), 7.55–7.65 (1H, m).
11-5		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.37 (3H, t, $J=7.1\text{Hz}$), 4.34 (2H, q, $J=7.1\text{Hz}$), 5.30 (2H, s), 5.97 (1H, d, $J=3.5\text{Hz}$), 6.50–6.60 (1H, m), 7.04 (1H, d, $J=3.5\text{Hz}$), 7.18 (1H, d, $J=8.7\text{Hz}$), 7.29 (1H, dd, $J=1.9, 8.7\text{Hz}$), 7.35–7.55 (5H, m), 7.75–7.80 (1H, m).

[0466]

[Table 27]

Ex. No.	Strc	Physical data
11-6		¹ H-NMR (CDCl ₃) δ ppm: 1.37 (3H, t, J=7.1Hz), 3.94 (3H, s), 4.35 (2H, q, J=7.1Hz), 5.24 (2H, s), 5.95-6.05 (1H, m), 6.50-6.55 (1H, m), 7.00-7.10 (2H, m), 7.17 (1H, d, J=8.3Hz), 7.35-7.55 (5H, m).
11-7		¹ H-NMR (CDCl ₃) δ ppm: 1.37 (3H, t, J=7.2Hz), 3.86 (3H, s), 4.34 (2H, q, J=7.2Hz), 5.25 (2H, s), 5.95-6.05 (1H, m), 6.45-6.55 (1H, m), 6.87 (1H, dd, J=2.5, 9.0Hz), 7.00-7.25 (5H, m), 7.40-7.50 (2H, m).

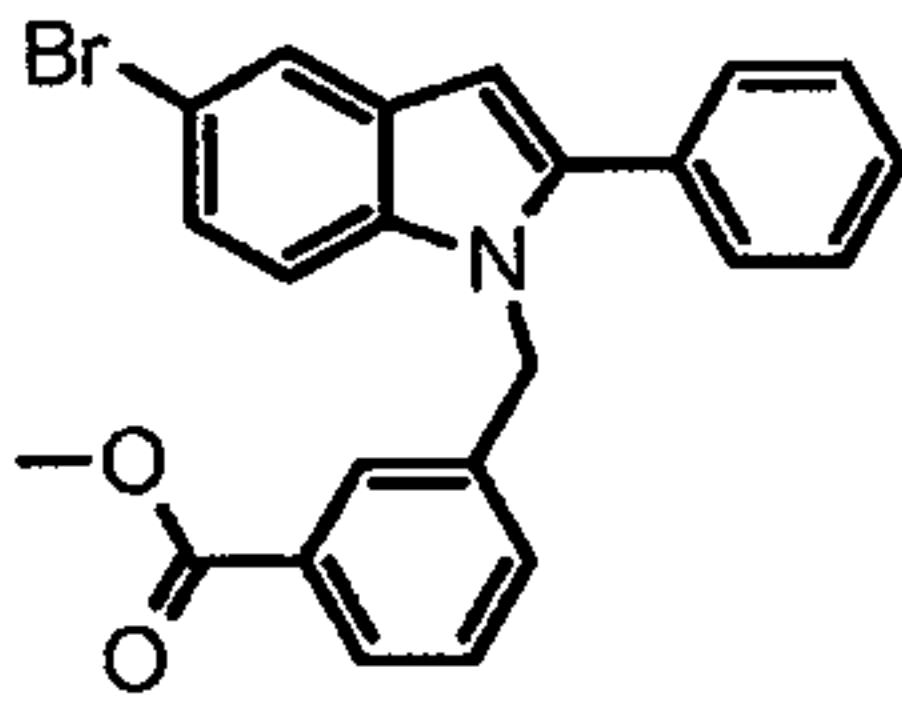
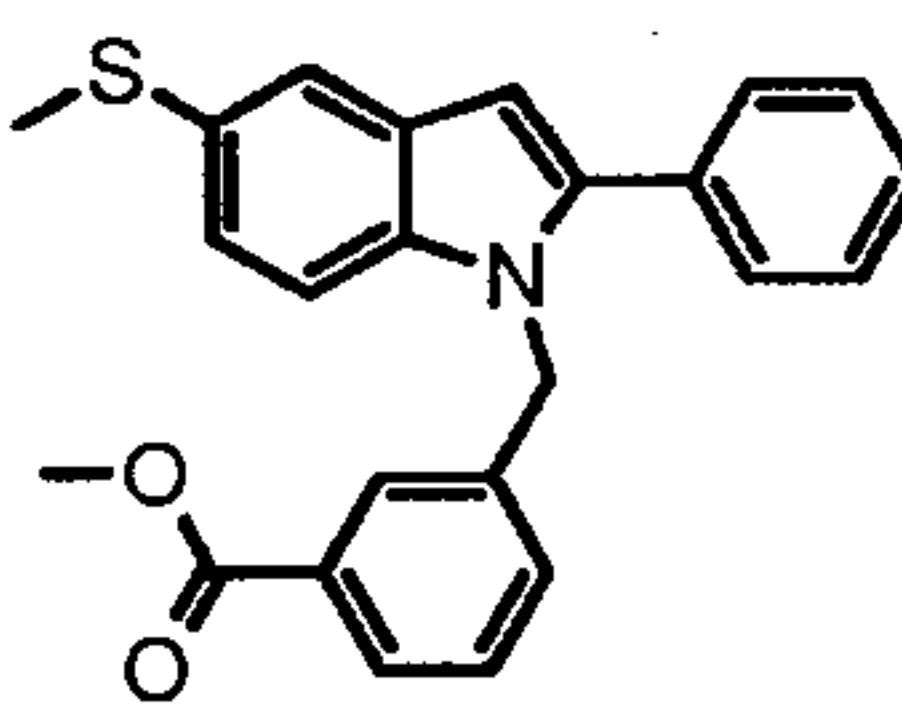
[0467]

Examples 12-1 to 12-2

The compounds shown in Table 28 were synthesized in a manner similar to that of Example 3-1 by using the corresponding starting materials.

[0468]

[Table 28]

Ex. No.	Strc	Physical data
12-1		¹ H-NMR (CDCl ₃) δ ppm: 3.88 (3H, s), 5.37 (2H, s), 6.59 (1H, s), 6.95-7.15 (2H, m), 7.22 (1H, dd, J=1.9, 8.7Hz), 7.25-7.50 (6H, m), 7.70-7.85 (2H, m), 7.85-8.00 (1H, m).
12-2		¹ H-NMR (CDCl ₃) δ ppm: 2.52 (3H, s), 3.89 (3H, s), 5.37 (2H, s), 6.55-6.65 (1H, m), 7.00-7.15 (2H, m), 7.16 (1H, dd, J=1.8, 8.5Hz), 7.25-7.50 (6H, m), 7.60-7.70 (1H, m), 7.75-7.85 (1H, m), 7.85-7.95 (1H, m).

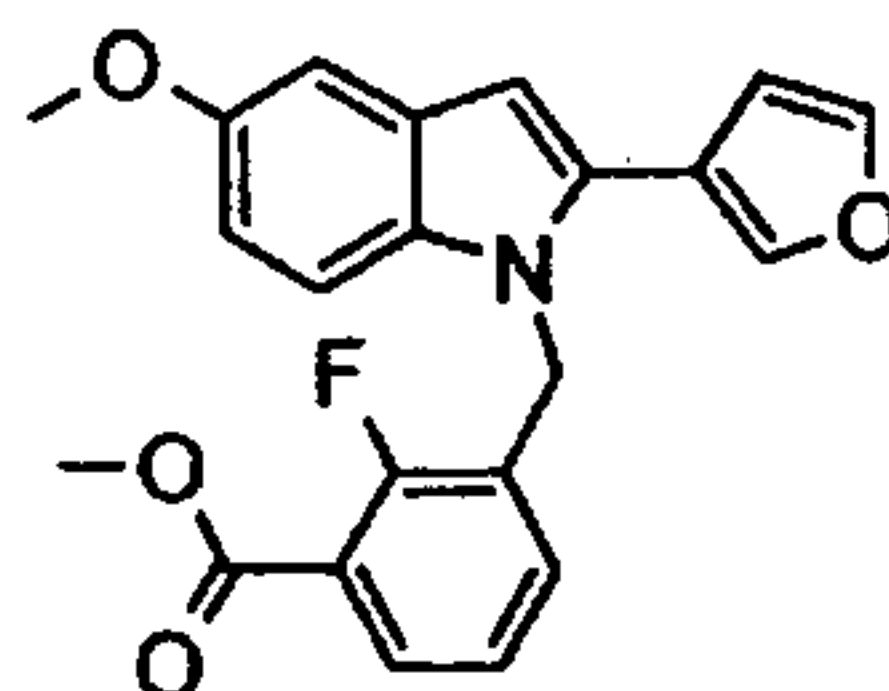
[0469]

10 Example 13

Methyl 2-fluoro-3-(2-furan-3-yl-5-methoxyindol-1-ylmethyl)benzoate

[0470]

[Chem. 54]



[0471]

To a solution of 2-furan-3-yl-5-methoxyindole (200mg) in *N,N*-dimethylformamide (4.7mL) was added sodium hydride (dispersed in liquid paraffin, minimum 55%, 62mg) under cooling with ice, and the mixture was stirred at room temperature for one hour. Then a solution of methyl 3-bromomethyl-2-fluorobenzoate (278mg) in *N,N*-dimethylformamide (0.2mL) was added, and the mixture was stirred at 80°C for 15 hours. The reaction mixture was allowed to cool to ambient temperature. A saturated aqueous ammonium chloride solution-water (2/1) were added to the reaction mixture and this resulting mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated saline, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by aminopropylated silica gel column chromatography (eluting solvent : ethyl acetate-hexane) to obtain the title compound (72mg).

[0472]

¹H-NMR (CDCl₃) δ ppm:

3.86 (3H, s), 3.96 (3H, s), 5.45 (2H, s), 6.40-6.50 (1H, m), 6.55-6.75 (2H, m), 6.83 (1H, dd, J=2.4, 8.9Hz), 6.95-7.15 (3H, m), 7.40-7.50 (2H, m), 7.75-7.85 (1H, m).

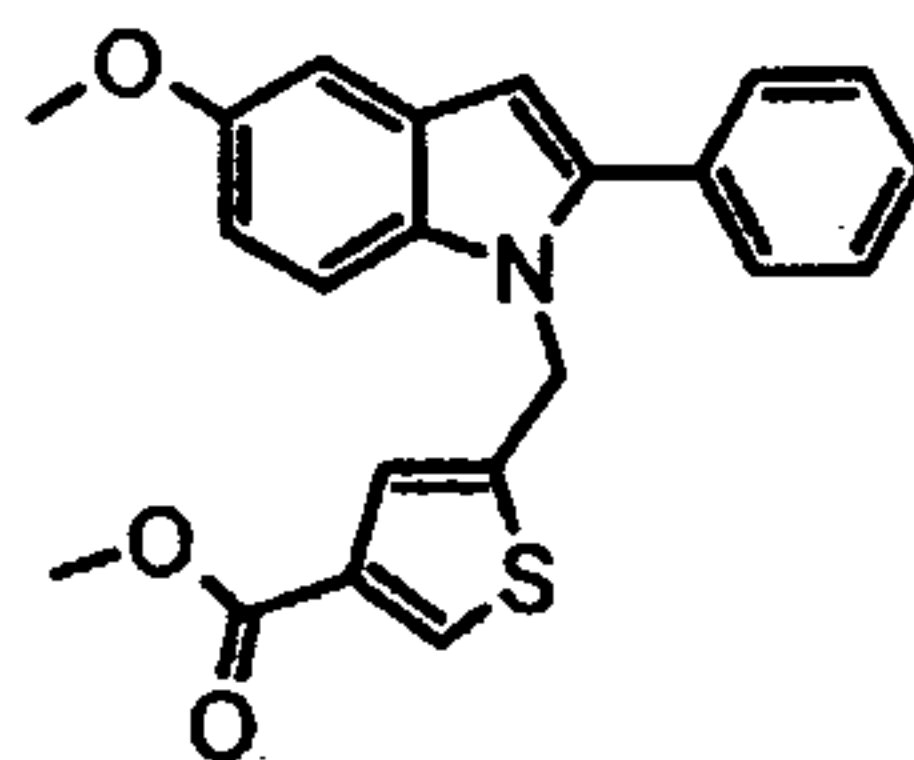
[0473]

Example 14

Methyl 5-(5-methoxy-2-phenylindol-1-ylmethyl)thiophene-3-carboxylate

[0474]

[Chem. 55]



[0475]

The title compound was synthesized in a manner similar to that of Example 5-1 by using the corresponding reactant.

[0476]

¹H-NMR (CDCl₃) δ ppm:

3.81 (3H, s), 3.86 (3H, s), 5.35-5.45 (2H, m), 6.50-6.60 (1H, m), 6.86 (1H, dd, J=2.5, 8.8Hz), 7.05-7.15 (1H, m), 7.15-7.25 (2H, m), 7.35-7.55 (5H, m), 7.91 (1H, d, J=1.5Hz).

[0477]

5 Example 15-1

Ethyl 2-(6-fluoro-5-methoxy-2-phenylindol-1-ylmethyl)thiazole-4-carboxylate

[0478]

To a solution of 6-fluoro-5-methoxy-2-phenylindole (200mg) in *N,N*-dimethylformamide (4.1mL) was added sodium hydride (dispersed in liquid paraffin, 10 minimum 55%, 54mg) under cooling with ice, and the mixture was stirred at room temperature for 70 minutes. Then a solution of ethyl 2-bromomethylthiazole-4-carboxylate (249mg) in *N,N*-dimethylformamide (0.2mL) was added, and the mixture was stirred at 80°C for 25 hours. The reaction mixture was allowed to cool to ambient temperature. A saturated aqueous ammonium chloride solution-water (2/1) were added to 15 the reaction mixture and this resulting mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated saline, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluting solvent : ethyl acetate-hexane) to obtain the title compound (125mg).

20 In addition, structural formula and spectrum data of the title compound are shown in Table 29.

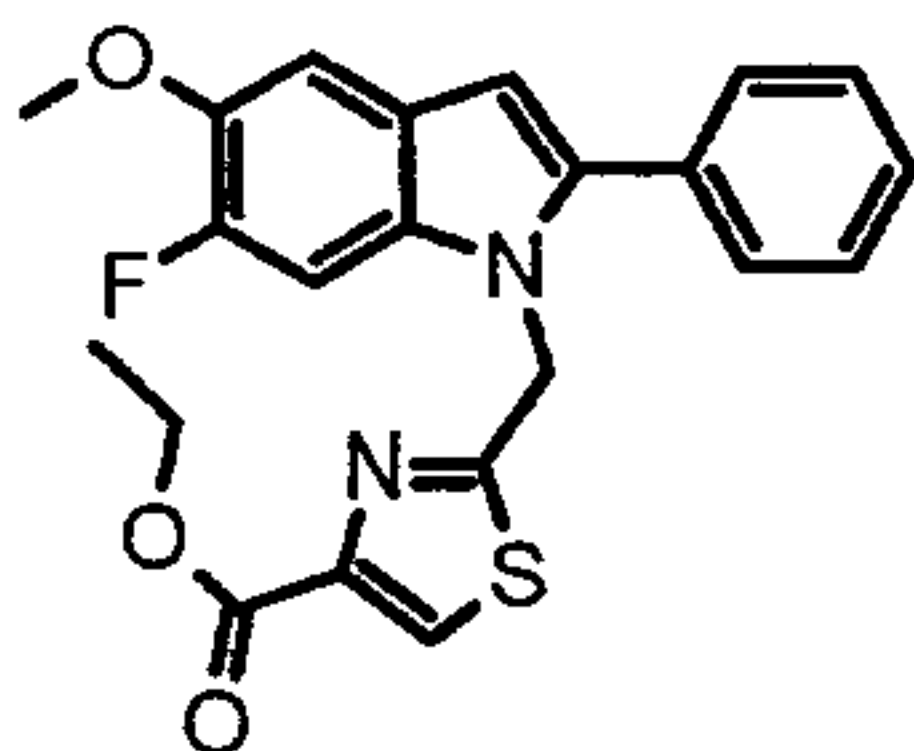
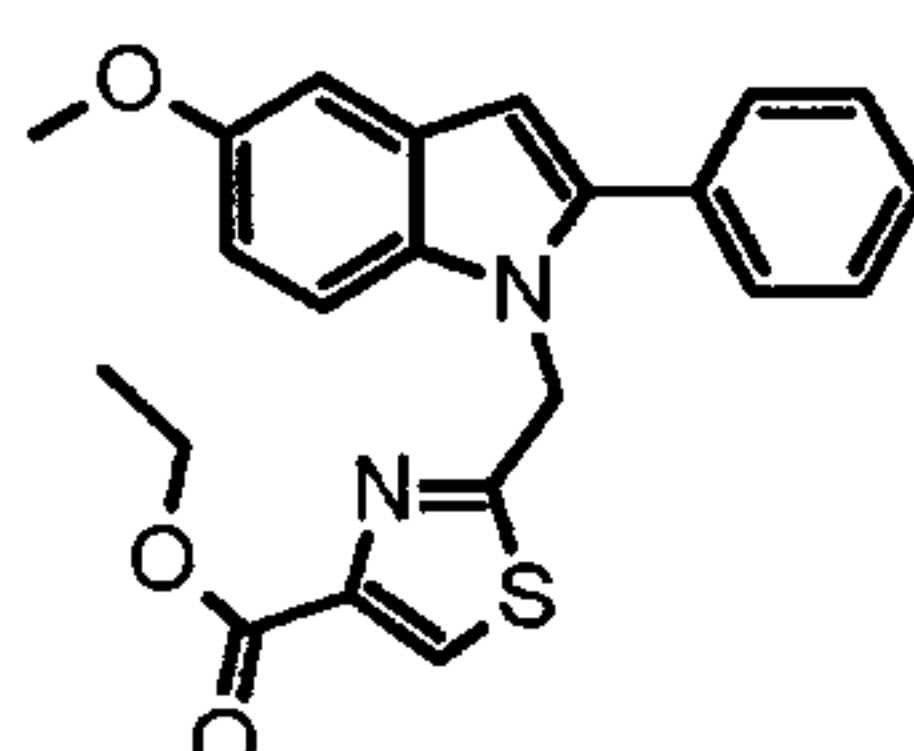
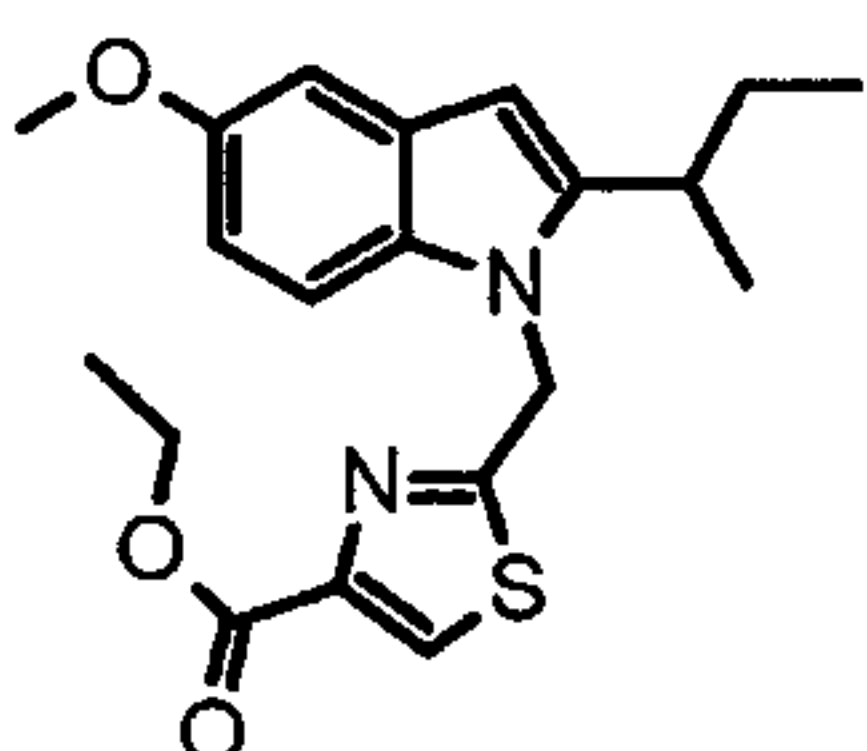
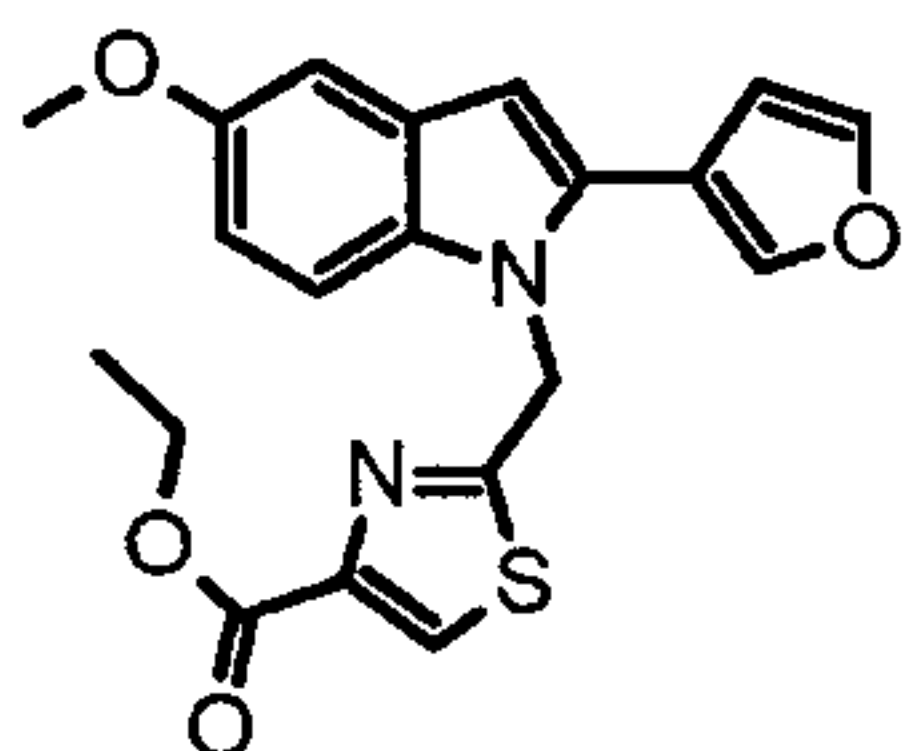
[0479]

Examples 15-2 to 15-4

The compounds shown in Table 29 were synthesized in a manner similar to that of 25 Example 15-1 by using the corresponding starting materials.

[0480]

[Table 29]

Ex. No.	Strc	Physical data
15-1		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.41 (3H, t, $J=7.1\text{Hz}$), 3.94 (3H, s), 4.43 (2H, q, $J=7.1\text{Hz}$), 5.58 (2H, s), 6.60 (1H, s), 7.00 (1H, d, $J=11.3\text{Hz}$), 7.18 (1H, d, $J=8.3\text{Hz}$), 7.35–7.50 (5H, m), 8.03 (1H, s).
15-2		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.40 (3H, t, $J=7.1\text{Hz}$), 3.86 (3H, s), 4.42 (2H, q, $J=7.1\text{Hz}$), 5.62 (2H, s), 6.55–6.65 (1H, m), 6.85 (1H, dd, $J=2.5, 8.8\text{Hz}$), 7.10–7.20 (2H, m), 7.35–7.55 (5H, m), 8.02 (1H, s).
15-3		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 0.89 (3H, t, $J=7.4\text{Hz}$), 1.27 (3H, d, $J=6.8\text{Hz}$), 1.42 (3H, t, $J=7.1\text{Hz}$), 1.50–1.85 (2H, m), 2.70–2.85 (1H, m), 3.84 (3H, s), 4.45 (2H, q, $J=7.1\text{Hz}$), 5.60 (2H, s), 6.31 (1H, s), 6.79 (1H, dd, $J=2.4, 8.8\text{Hz}$), 7.06 (1H, d, $J=2.4\text{Hz}$), 7.10 (1H, d, $J=8.8\text{Hz}$), 8.01 (1H, s).
15-4		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.42 (3H, t, $J=7.1\text{Hz}$), 3.86 (3H, s), 4.45 (2H, q, $J=7.1\text{Hz}$), 5.66 (2H, s), 6.50–6.65 (2H, m), 6.86 (1H, dd, $J=2.4, 9.0\text{Hz}$), 7.05–7.15 (1H, m), 7.16 (1H, d, $J=9.0\text{Hz}$), 7.45–7.60 (2H, m), 8.04 (1H, s).

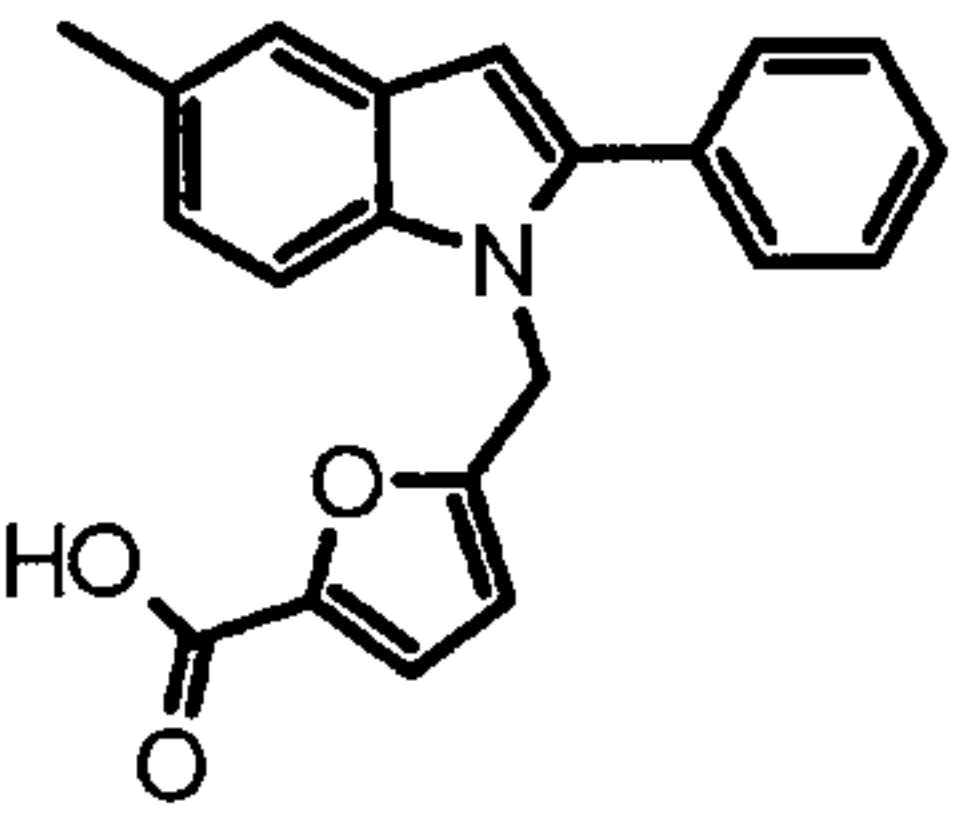
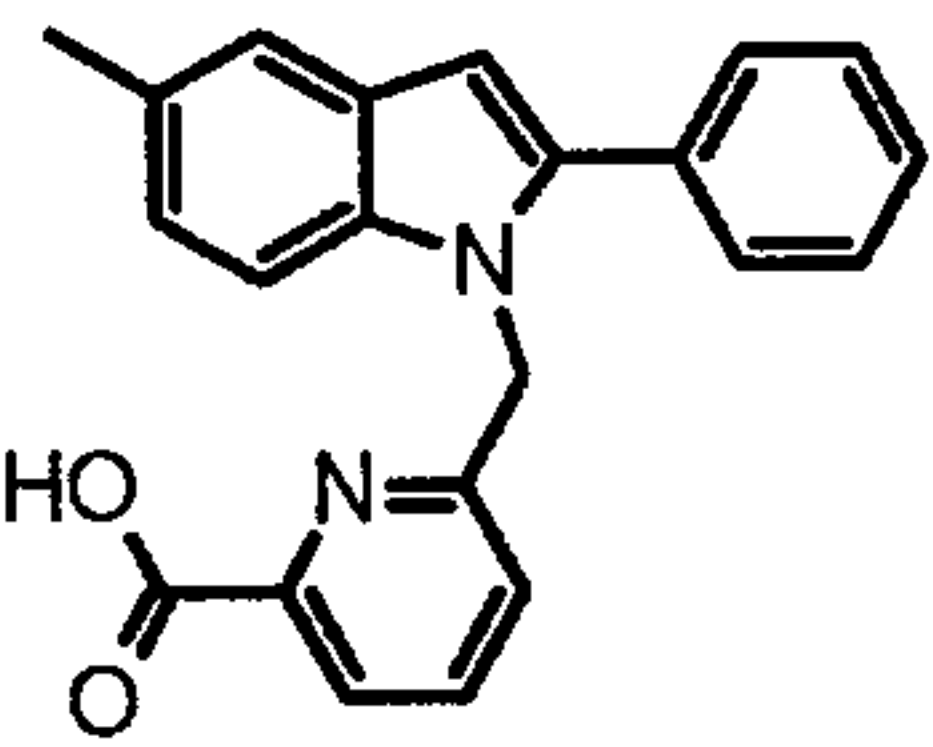
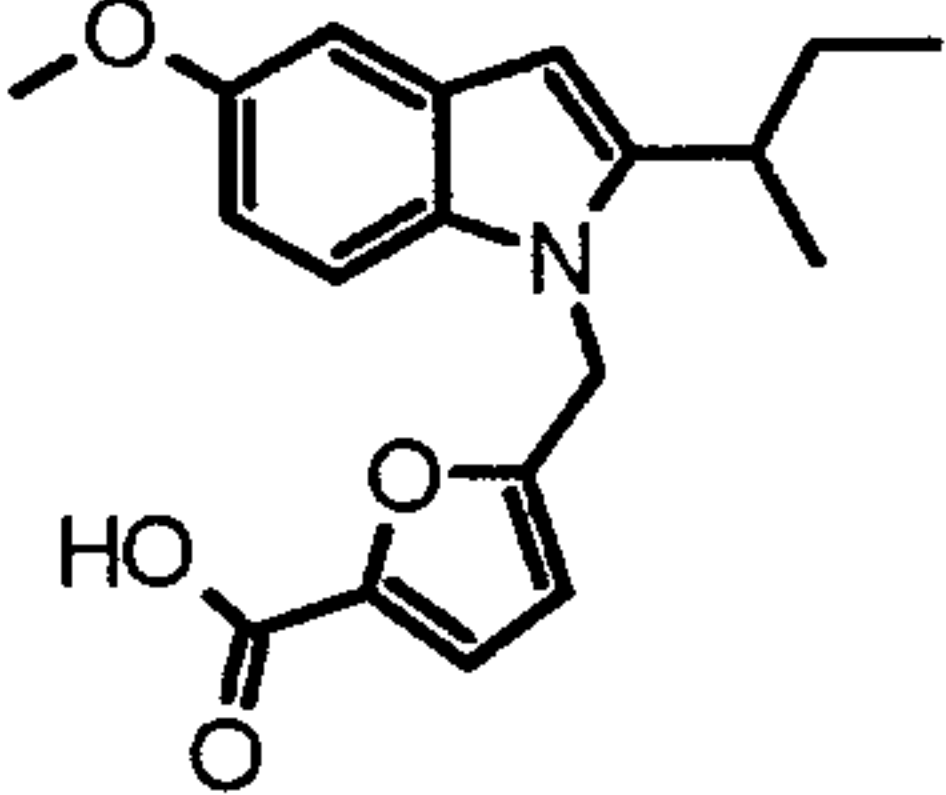
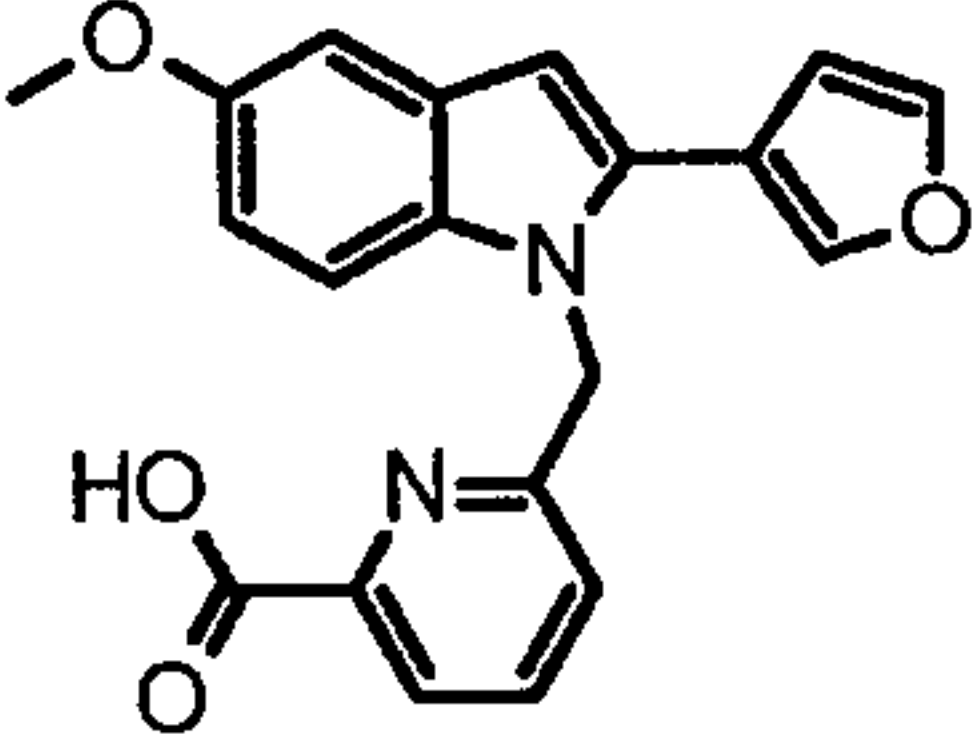
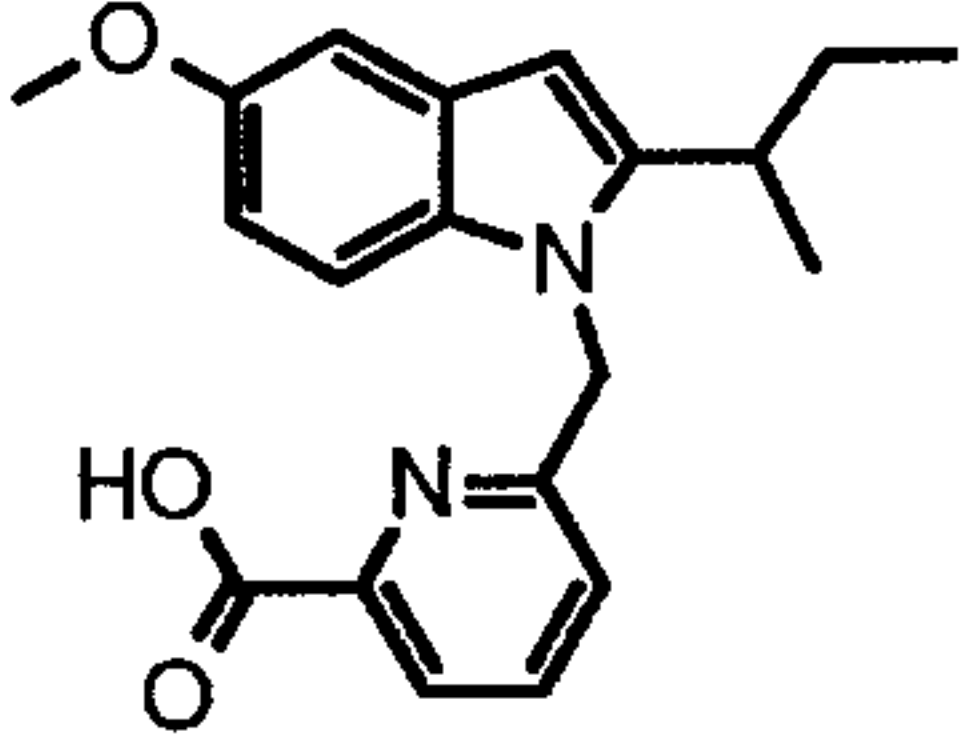
[0481]

Examples 16-1 to 16-27

The compounds shown in Tables 30 to 34 were synthesized in a manner similar to that of Example 9-1 by using the corresponding starting materials.

[0482]

[Table 30]

Ex. No.	Strc	Physical data
16-1		¹ H-NMR (DMSO-d ₆) δ ppm: 2.38 (3H, s), 5.41 (2H, s), 6.16 (1H, d, J=3.5Hz), 6.53 (1H, s), 6.95–7.05 (1H, m), 7.06, (1H, d, J=3.5Hz), 7.30–7.70 (7H, m), 13.01 (1H, br s).
16-2		¹ H-NMR (DMSO-d ₆) δ ppm: 2.38 (3H, s), 5.53 (2H, s), 6.61 (1H, s), 6.65–6.75 (1H, m), 6.90–7.00 (1H, m), 7.21 (1H, d, J=8.5Hz), 7.30–7.65 (6H, m), 7.75–7.95 (2H, m), 12.50–13.90 (1H, br).
16-3		¹ H-NMR (DMSO-d ₆) δ ppm: 0.85 (3H, t, J=7.4Hz), 1.23 (3H, d, J=6.8Hz), 1.45–1.80 (2H, m), 2.95–3.10 (1H, m), 3.73 (3H, s), 5.43 (2H, s), 6.18 (1H, s), 6.34 (1H, d, J=3.5Hz), 6.69 (1H, dd, J=2.3, 8.8Hz), 6.97 (1H, d, J=2.3Hz), 7.09 (1H, d, J=3.5Hz), 7.37 (1H, d, J=8.8Hz), 12.99 (1H, br s).
16-4		¹ H-NMR (DMSO-d ₆) δ ppm: 3.76 (3H, s), 5.60 (2H, s), 6.66 (1H, s), 6.70–6.90 (3H, m), 7.09 (1H, d, J=2.5Hz), 7.35 (1H, d, J=9.0Hz), 7.70–8.10 (4H, m), 12.50–14.00 (1H, br).
16-5		¹ H-NMR (DMSO-d ₆) δ ppm: 0.79 (3H, t, J=7.4Hz), 1.18 (3H, d, J=6.8Hz), 1.40–1.75 (2H, m), 2.80–2.95 (1H, m), 3.73 (3H, s), 5.45–5.60 (2H, m), 6.25 (1H, s), 6.55–6.75 (2H, m), 7.01 (1H, d, J=2.5Hz), 7.23 (1H, d, J=9.0Hz), 7.75–7.95 (2H, m), 12.50–14.00 (1H, br).

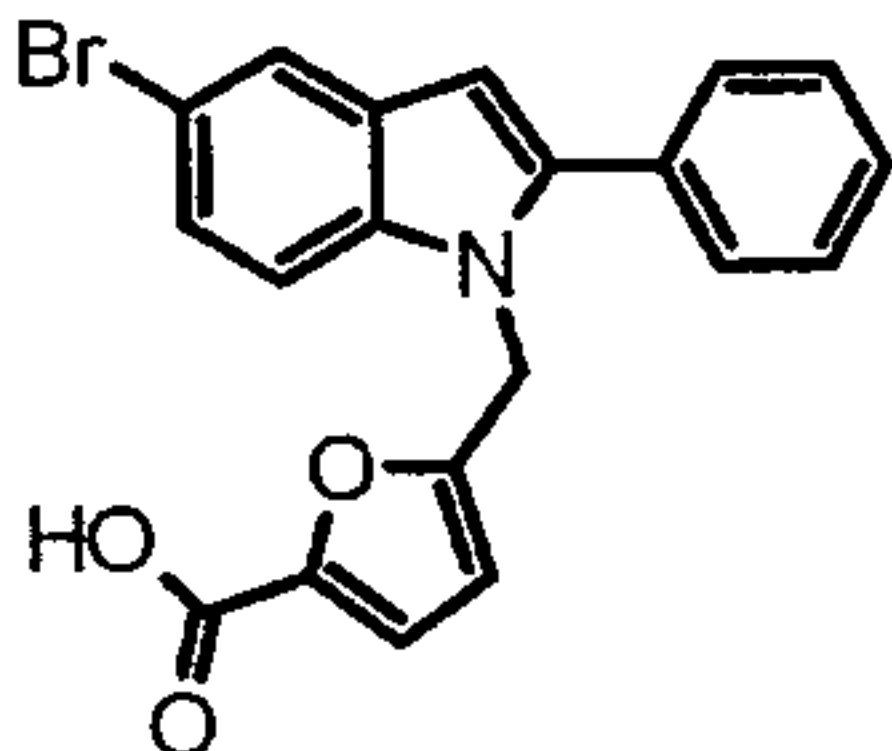
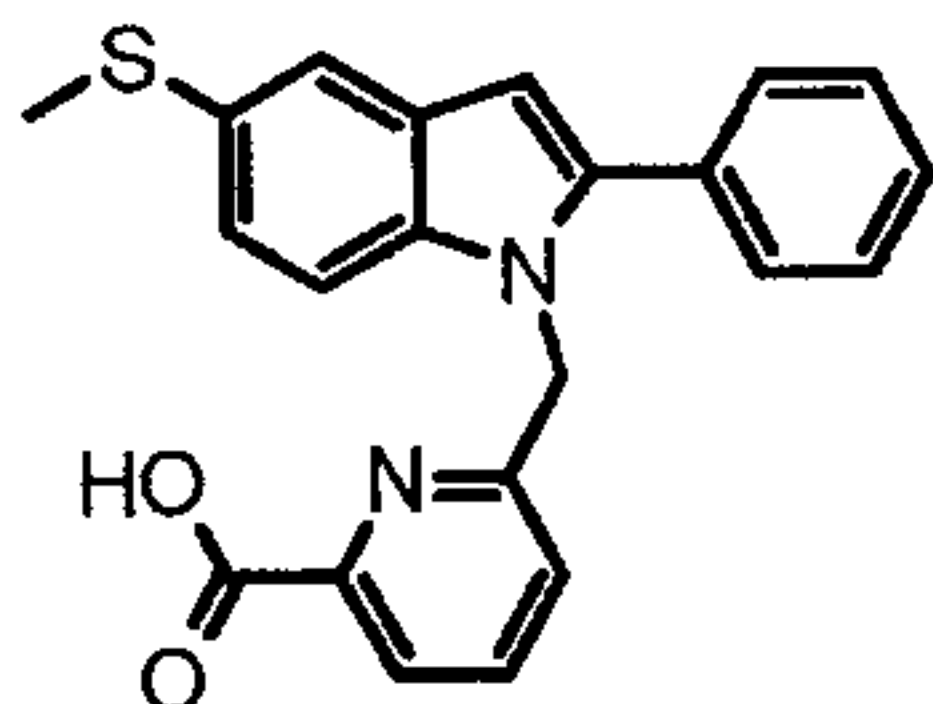
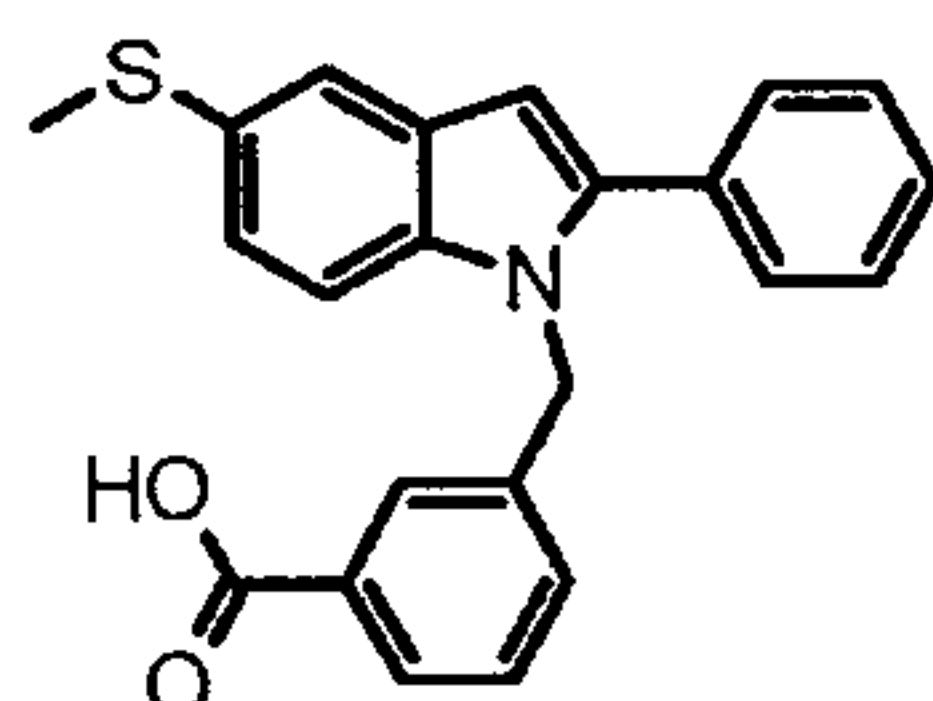
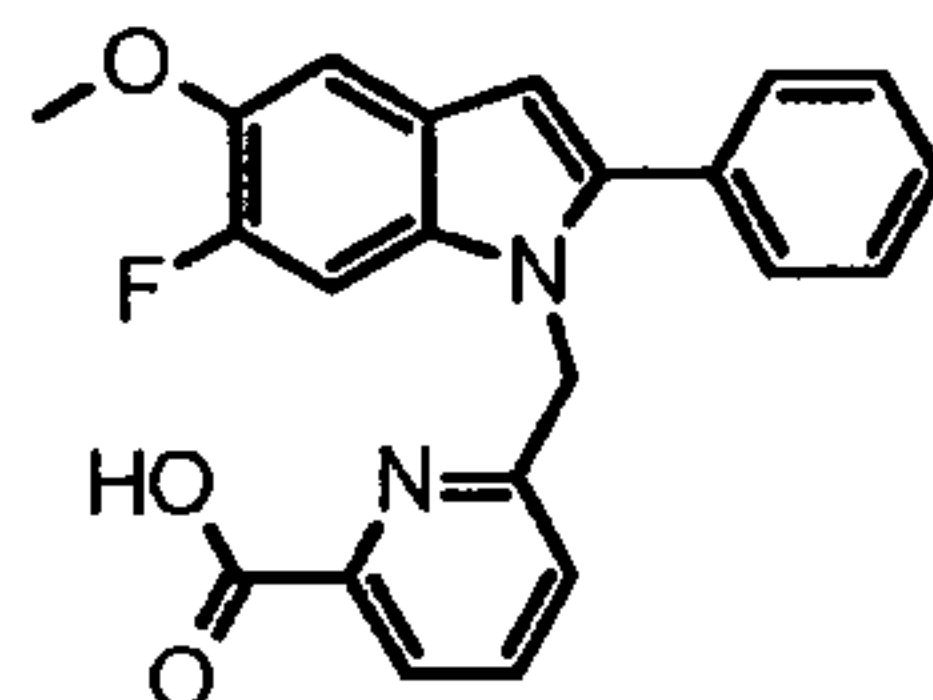
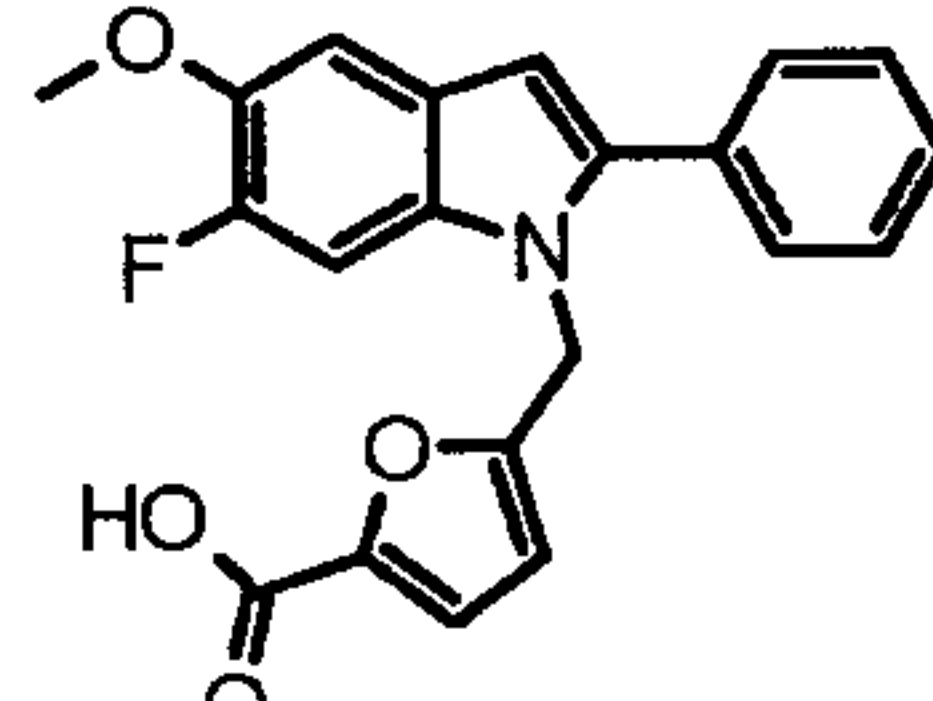
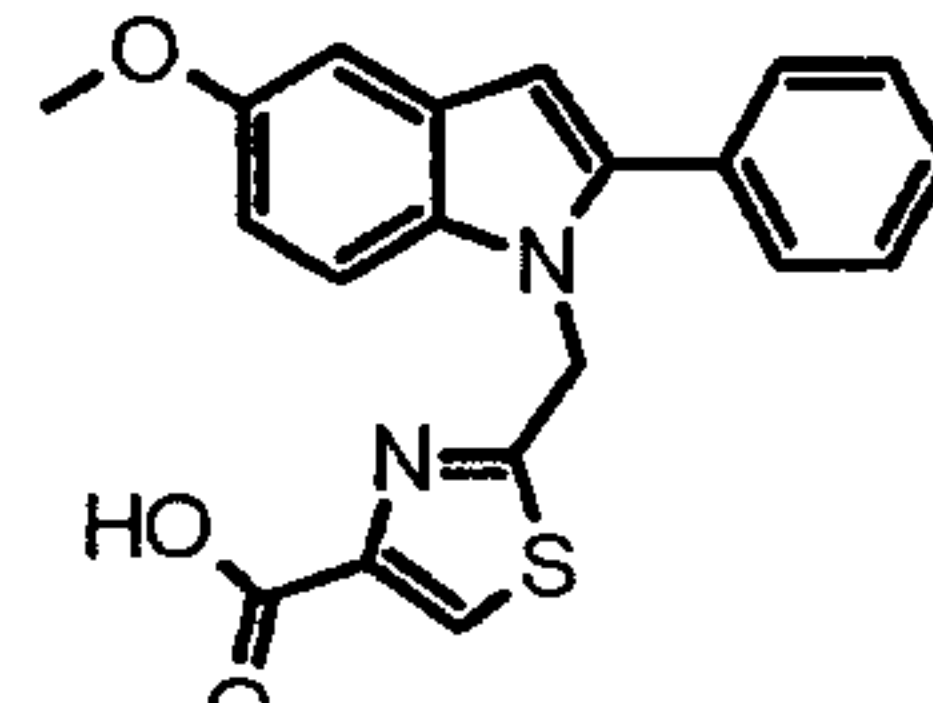
[0483]

[Table 31]

Ex. No.	Strc	Physical data
16-6		¹ H-NMR (DMSO-d ₆) δ ppm: 5.54 (2H, s), 6.22 (1H, d, J=3.5Hz), 6.80 (1H, s), 7.06 (1H, d, J=3.5Hz), 7.40-7.70 (6H, m), 7.79 (1H, d, J=8.5Hz), 8.01 (1H, br s), 13.05 (1H, br s).
16-7		¹ H-NMR (DMSO-d ₆) δ ppm: 5.55 (2H, s), 6.68 (1H, s), 7.00-7.15 (1H, m), 7.24 (1H, dd, J=2.0, 8.8Hz), 7.30-7.60 (8H, m), 7.70-7.90 (2H, m), 12.94 (1H, br s).
16-8		¹ H-NMR (DMSO-d ₆) δ ppm: 3.77 (3H, s), 5.53 (2H, s), 6.65-6.70 (1H, m), 6.77 (1H, dd, J=2.4, 9.0Hz), 6.80-6.90 (1H, m), 7.10-7.15 (1H, m), 7.20-7.30 (2H, m), 7.40-7.55 (3H, m), 7.80-7.90 (2H, m). ESI-MS (m/z) : 377 (M+H) ⁺
16-9		¹ H-NMR (DMSO-d ₆) δ ppm: 5.63 (2H, s), 6.80-6.95 (2H, m), 7.35-7.70 (7H, m), 7.80-7.95 (2H, m), 8.00-8.10 (1H, m), 13.21 (1H, br s).
16-10		¹ H-NMR (DMSO-d ₆) δ ppm: 3.76 (3H, s), 5.49 (2H, s), 6.32 (1H, d, J=3.4Hz), 6.58 (1H, s), 6.79 (1H, dd, J=2.4, 9.0Hz), 6.85-6.95 (1H, m), 7.05 (1H, d, J=2.4Hz), 7.09 (1H, d, J=3.4Hz), 7.47 (1H, d, J=9.0Hz), 7.80-7.90 (1H, m), 8.00-8.10 (1H, m), 13.04 (1H, s).
16-11		¹ H-NMR (DMSO-d ₆) δ ppm: 5.57 (2H, s), 6.69 (1H, s), 6.75-6.85 (1H, m), 7.23 (1H, dd, J=1.9, 8.7Hz), 7.30-7.65 (6H, m), 7.80-7.95 (3H, m), 13.21 (1H, br s).

[0484]

[Table 32]

Ex. No.	Strc	Physical data
16-12		$^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 5.47 (2H, s), 6.20 (1H, d, $J=3.4\text{Hz}$), 6.62 (1H, s), 7.06 (1H, d, $J=3.4\text{Hz}$), 7.30 (1H, dd, $J=1.9, 8.8\text{Hz}$), 7.40–7.70 (6H, m), 7.79 (1H, d, $J=1.9\text{Hz}$), 12.60–13.45 (1H, br).
16-13		$^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 2.48 (3H, s), 5.55 (2H, s), 6.60–6.70 (1H, m), 6.75–6.85 (1H, m), 7.09 (1H, dd, $J=1.8, 8.5\text{Hz}$), 7.31 (1H, d, $J=8.5\text{Hz}$), 7.35–7.65 (6H, m), 7.80–7.95 (2H, m). ESI-MS (m/z) : 375 ($\text{M}+\text{H}$) $^+$
16-14		$^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 2.48 (3H, s), 5.52 (2H, s), 6.60–6.70 (1H, m), 7.05–7.15 (2H, m), 7.25–7.65 (9H, m), 7.70–7.80 (1H, m), 12.93 (1H, br s).
16-15		$^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 3.85 (3H, s), 5.52 (2H, s), 6.60–6.80 (2H, m), 7.25–7.65 (7H, m), 7.75–7.95 (2H, m), 11.90–14.50 (1H, br).
16-16		$^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 3.85 (3H, s), 5.41 (2H, s), 6.18 (1H, d, $J=3.5\text{Hz}$), 6.50–6.60 (1H, m), 7.06 (1H, d, $J=3.5\text{Hz}$), 7.28 (1H, d, $J=8.5\text{Hz}$), 7.40–7.65 (6H, m), 13.02 (1H, br s).
16-17		$^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 3.78 (3H, s), 5.72 (2H, s), 6.60–6.70 (1H, m), 6.82 (1H, dd, $J=2.5, 9.0\text{Hz}$), 7.10–7.20 (1H, m), 7.35–7.65 (6H, m), 8.25 (1H, s), 12.00–14.00 (1H, br).

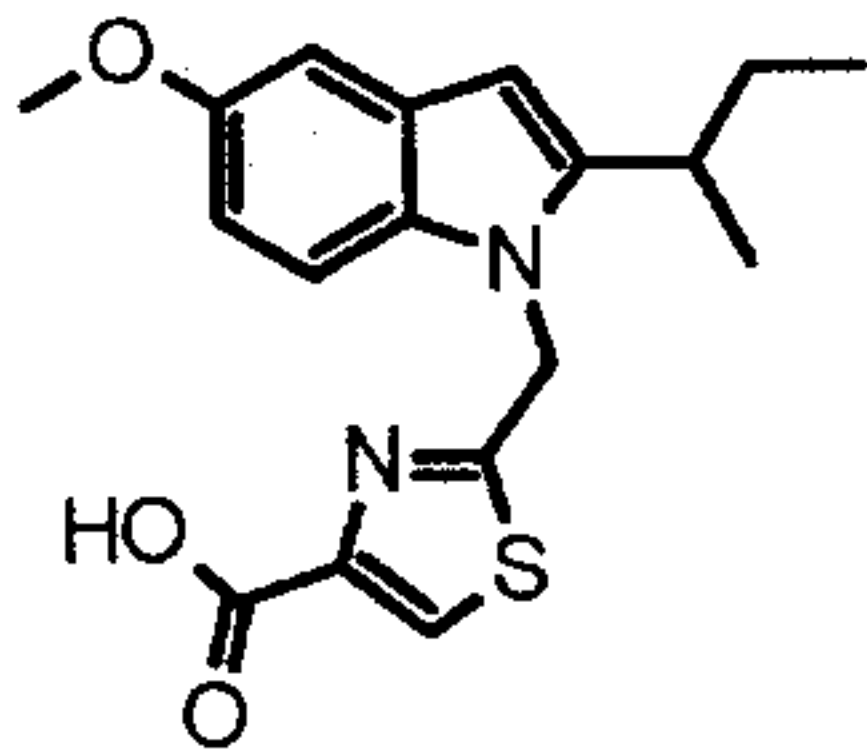
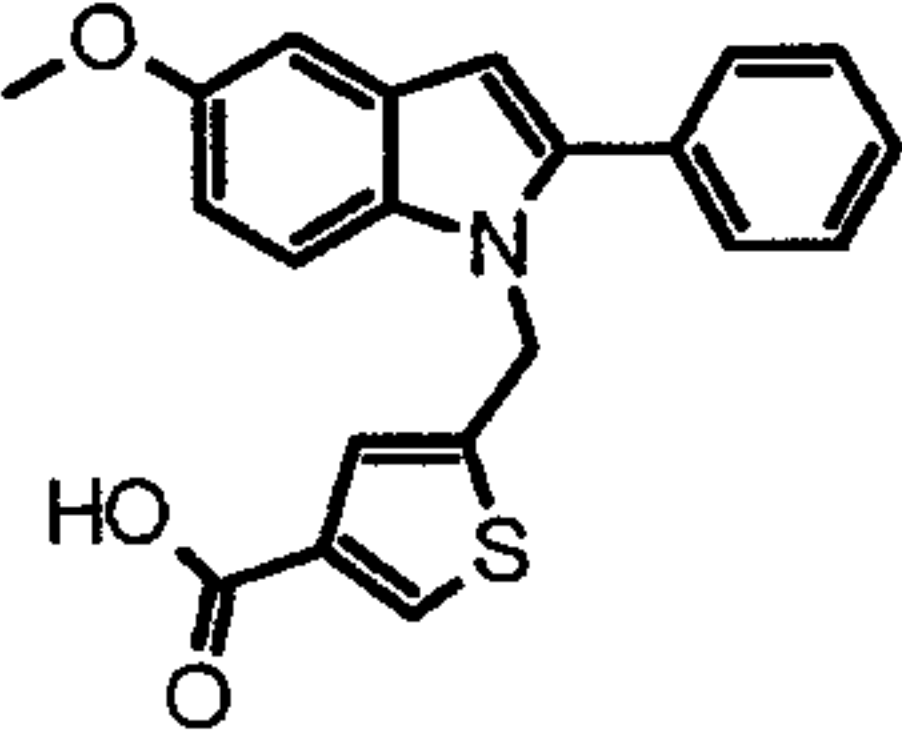
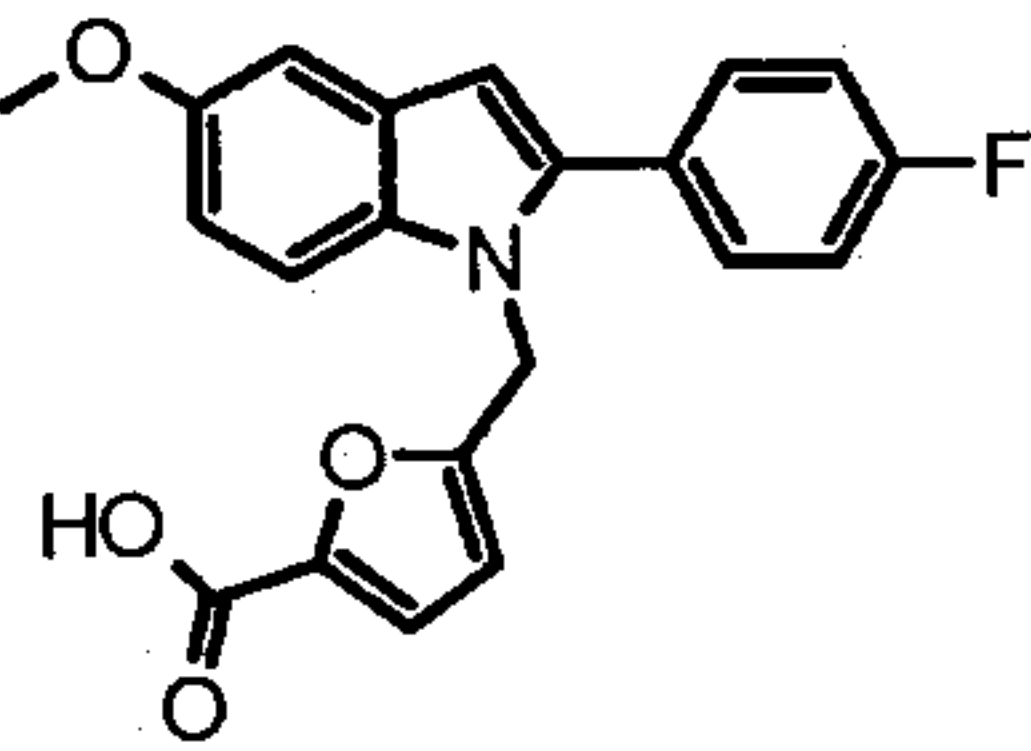
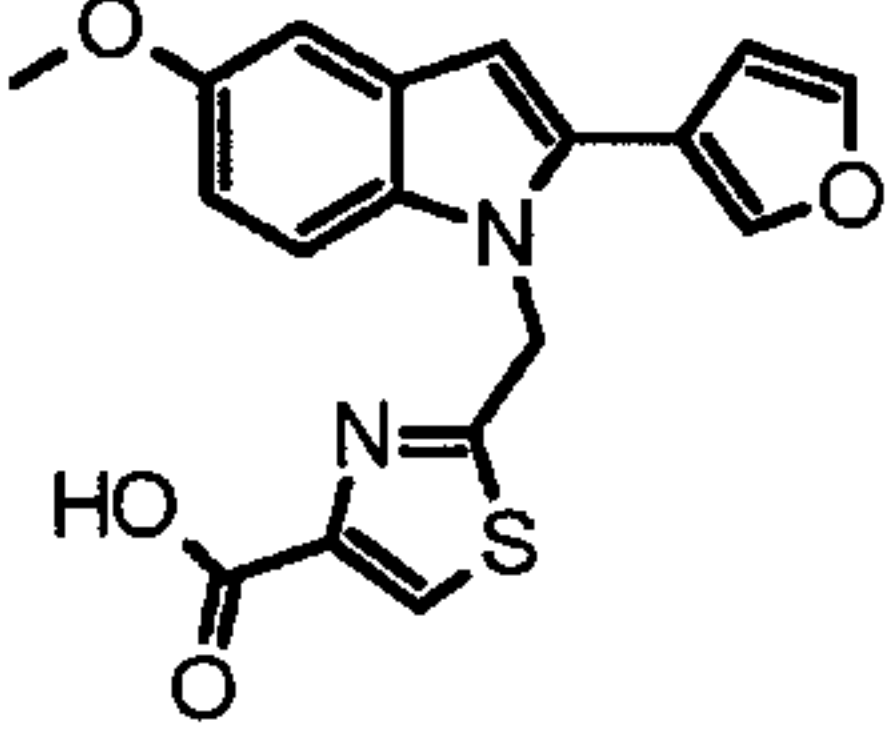
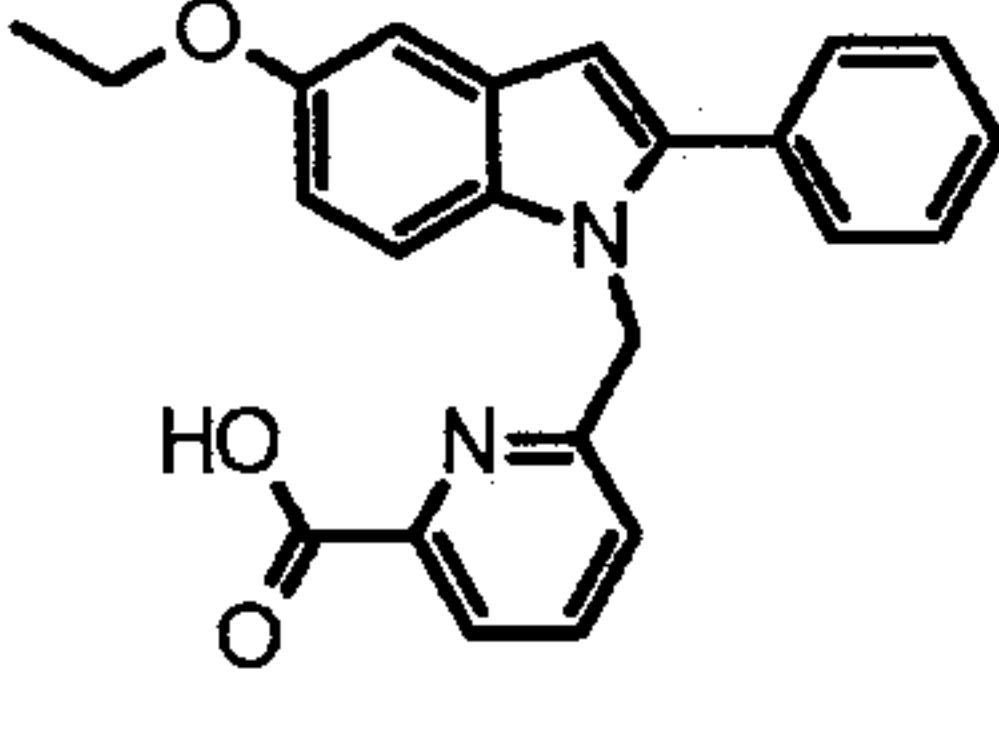
[0485]

[Table 33]

Ex. No.	Strc	Physical data
16-18		¹ H-NMR (DMSO-d ₆) δ ppm: 3.77 (3H, s), 5.82 (2H, s), 6.65-6.75 (1H, m), 6.78 (1H, dd, J=2.5, 8.8Hz), 6.85 (1H, s), 7.13 (1H, d, J=2.5Hz), 7.35 (1H, d, J=8.8Hz), 7.75-7.95 (2H, m), 8.45-8.65 (2H, m), 12.00-14.40 (1H, br).
16-19		¹ H-NMR (DMSO-d ₆) δ ppm: 3.86 (3H, s), 5.73 (2H, s), 6.60-6.70 (1H, m), 7.32 (1H, d, J=8.5Hz), 7.35-7.60 (6H, m), 8.25 (1H, s), 13.01 (1H, br s).
16-20		¹ H-NMR (DMSO-d ₆) δ ppm: 3.77 (3H, s), 5.42 (2H, s), 6.55-6.70 (2H, m), 6.79 (1H, dd, J=2.5, 8.8Hz), 7.15 (1H, d, J=2.5Hz), 7.20-7.40 (3H, m), 7.40-7.60 (2H, m), 7.75-7.90 (2H, m), 12.60-13.80 (1H, br).
16-21		¹ H-NMR (DMSO-d ₆) δ ppm: 3.77 (3H, s), 5.59 (2H, s), 6.40-6.55 (1H, m), 6.60-6.80 (3H, m), 7.00-7.15 (2H, m), 7.32 (1H, d, J=9.0Hz), 7.65-7.80 (2H, m), 7.85-7.95 (1H, m), 13.32 (1H, br s).
16-22		¹ H-NMR (DMSO-d ₆) δ ppm: 3.77 (3H, s), 5.50 (2H, s), 6.60 (1H, s), 6.70-6.85 (2H, m), 7.12 (1H, d, J=2.3Hz), 7.20-7.35 (3H, m), 7.55-7.70 (2H, m), 7.75-7.95 (2H, m), 13.23 (1H, br s).

[0486]

[Table 34]

Ex. No.	Strc	Physical data
16-23		¹ H-NMR (DMSO-d ₆) δ ppm: 0.81 (3H, t, J=7.3Hz), 1.20 (3H, d, J=6.8Hz), 1.45-1.75 (2H, m), 2.85-3.00 (1H, m), 3.74 (3H, s), 5.72 (2H, s), 6.25 (1H, s), 6.71 (1H, dd, J=2.4, 8.9Hz), 7.01 (1H, d, J=2.4Hz), 7.33 (1H, d, J=8.9Hz), 8.28 (1H, s), 13.04 (1H, br s).
16-24		¹ H-NMR (DMSO-d ₆) δ ppm: 3.77 (3H, s), 5.58 (2H, s), 6.56 (1H, s), 6.81 (1H, dd, J=2.4, 8.8Hz), 6.95-7.05 (1H, m), 7.09 (1H, d, J=2.4Hz), 7.40-7.60 (6H, m), 7.98 (1H, d, J=1.5Hz), 12.66 (1H, br s).
16-25		¹ H-NMR (DMSO-d ₆) δ ppm: 3.76 (3H, s), 5.39 (2H, s), 6.20 (1H, d, J=3.4Hz), 6.53 (1H, s), 6.81 (1H, dd, J=2.4, 9.0Hz), 7.06 (1H, d, J=3.4Hz), 7.09 (1H, d, J=2.4Hz), 7.25-7.40 (2H, m), 7.45 (1H, d, J=9.0Hz), 7.55-7.70 (2H, m), 13.03 (1H, br s).
16-26		¹ H-NMR (DMSO-d ₆) δ ppm: 3.77 (3H, s), 5.82 (2H, s), 6.68 (1H, s), 6.75-6.90 (2H, m), 7.08 (1H, d, J=2.3Hz), 7.48 (1H, d, J=8.8Hz), 7.75-7.85 (1H, m), 8.00-8.10 (1H, m), 8.27 (1H, s), 13.07 (1H, br s).
16-27		¹ H-NMR (DMSO-d ₆) δ ppm: 1.34 (3H, t, J=6.9Hz), 4.02 (2H, q, J=6.9Hz), 5.52 (2H, s), 6.60 (1H, s), 6.65-6.80 (2H, m), 7.12 (1H, d, J=2.5Hz), 7.22 (1H, d, J=8.8Hz), 7.35-7.50 (3H, m), 7.50-7.65 (2H, m), 7.75-7.95 (2H, m), 12.00-14.40 (1H, br).

[0487]

Examples 17-1 to 17-23

The compounds shown in Tables 35 to 38 were synthesized in a manner similar to that of Example 1-1 by using the corresponding starting materials.

[0488]

Examples 18-1 to 18-7

5 The compounds shown in Tables 39 to 40 were synthesized in a manner similar to that of Example 2-1 by using the corresponding starting materials.

[0489]

Examples 19-1 to 19-8

10 The compounds shown in Tables 41 to 42 were synthesized in a manner similar to that of Example 3-1 by using the corresponding starting materials.

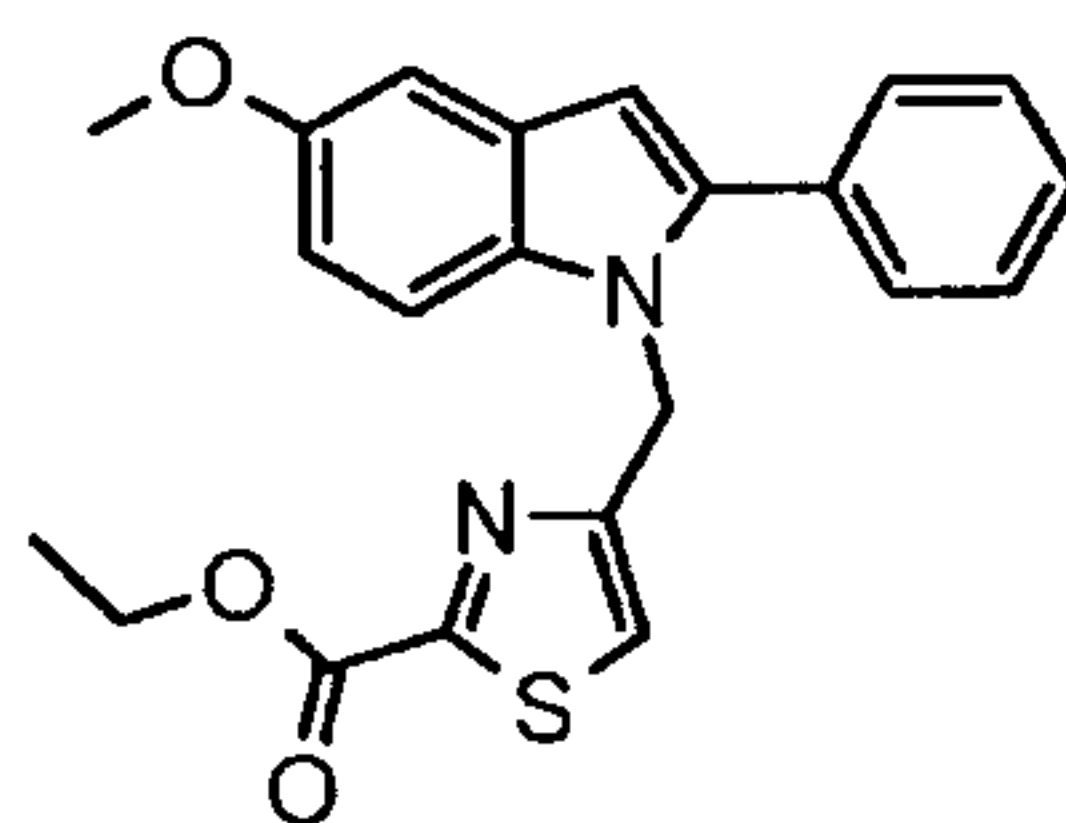
[0490]

Example 20

Ethyl 4-(5-methoxy-2-phenylindol-1-ylmethyl)thiazole-2-carboxylate

[0491]

15 [Chem. 56]



[0492]

The title compound was synthesized in a manner similar to that of Example 5-1 by using the corresponding reactant.

20 [0493]

¹H-NMR (CDCl₃) δ ppm:

1.44 (3H, t, J=7.1Hz), 3.87 (3H, s), 4.49 (2H, q, J=7.1Hz), 5.56 (2H, s), 6.60 (1H, s), 6.78 (1H, s), 6.84 (1H, d, J=2.4, 8.9Hz), 7.08 (1H, d, J=8.9Hz), 7.14 (1H, d, J=2.4Hz), 7.30-7.50 (5H, m).

25 [0494]

Example 21-1

Methyl 2-(5-methoxy-2-phenylindol-1-ylmethyl)oxazole-4-carboxylate

[0495]

30 To a solution of 5-methoxy-2-phenylindole (205mg) in N,N-dimethylformamide (4.6mL) was added sodium hydride (in oil, 50 to 72%, 55mg) under cooling with ice and an argon atmosphere, and the mixture was stirred at room temperature for 2 hours. Then

methyl 2-(chloromethyl)-1,3-oxazole-4-carboxylate (193mg) was added, and the mixture was stirred at 80°C for 22 hours. The reaction mixture was allowed to cool to ambient temperature. A saturated aqueous ammonium chloride solution and water were added to the reaction mixture and this resulting mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated saline, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluting solvent : ethyl acetate-hexane) to obtain the title compound (229mg).

In addition, structural formula and spectrum data of the title compound are shown in Table 42.

[0496]

¹H-NMR (CDCl₃) δ ppm:

3.85 (3H, s), 3.92 (3H, s), 5.39 (2H, s), 6.55 (1H, s), 6.87 (1H, dd, J=2.5, 8.8Hz), 7.10 (1H, d, J=2.5Hz), 7.30 (1H, d, J=8.8Hz), 7.35-7.65 (5H, m), 8.12 (1H, s).

[0497]

Examples 21-2 to 21-3

The compounds shown in Table 42 were synthesized in a manner similar to that of Example 21-1 by using the corresponding starting materials.

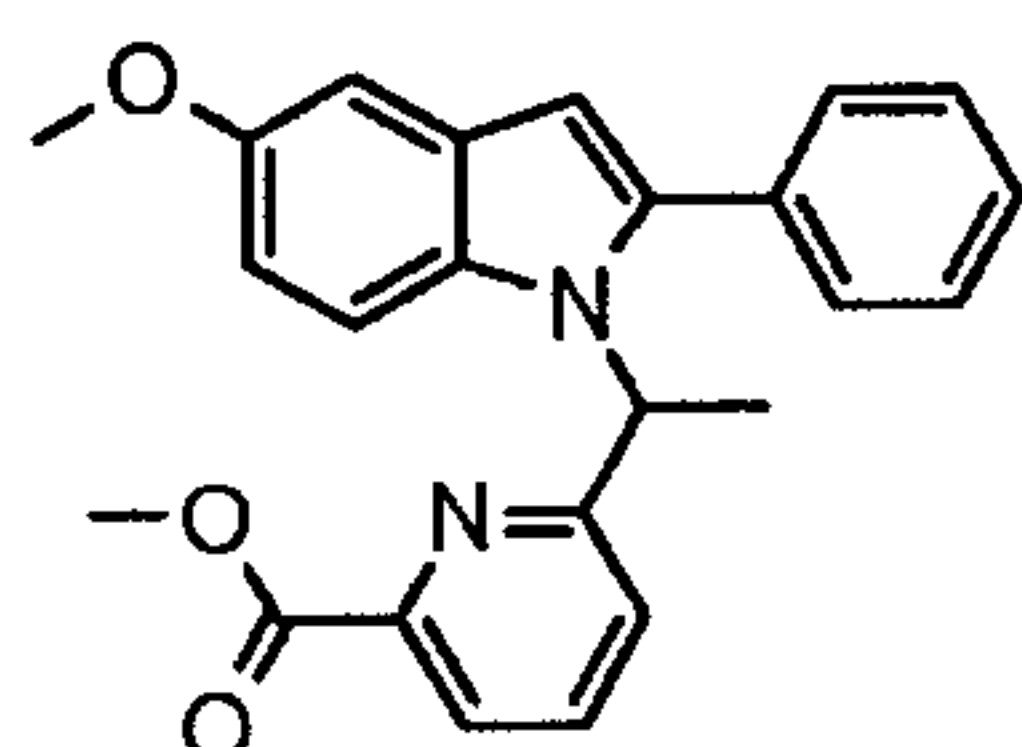
[0498]

Example 22

Methyl 6-[1-(5-methoxy-2-phenylindol-1-yl)ethyl]pyridine-2-carboxylate

[0499]

[Chem. 57]



[0500]

The title compound was synthesized in a manner similar to that of Example 5-1 by using the corresponding reactant.

[0501]

¹H-NMR (CDCl₃) δ ppm:

2.06 (3H, d, J=7.1Hz), 3.84 (3H, s), 4.01 (3H, s), 5.83 (1H, q, J=7.1Hz), 6.54 (1H, s), 6.68 (1H, dd, J=2.5, 8.9Hz), 6.86 (1H, d, J=8.9Hz), 6.95-7.05 (1H, m), 7.05-7.20 (1H, m), 7.30-7.55 (5H, m), 7.65 (1H, t, J=7.8Hz), 7.90-8.05 (1H, m).

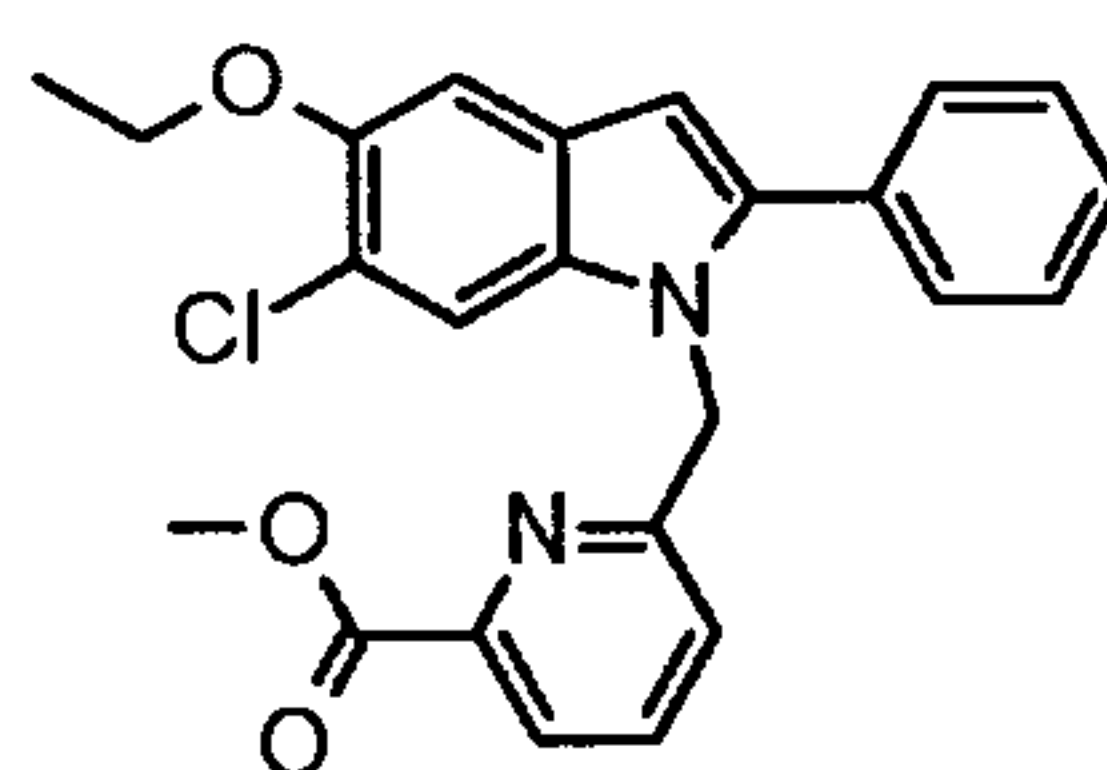
[0502]

5 Example 23

Methyl 6-(6-chloro-5-ethoxy-2-phenylindol-1-ylmethyl)pyridine-2-carboxylate

[0503]

[Chem. 58]



10 [0504]

To a solution of methyl 6-(6-chloro-5-hydroxy-2-phenylindol-1-ylmethyl)pyridine-2-carboxylate (100mg) in *N,N*-dimethylformamide (1 mL) were added, potassium carbonate (70.4mg) and ethyl iodide (0.031mL) and the mixture was stirred at room temperature for 22 hours. The reaction mixture was diluted with water and

15 extracted with ethyl acetate. The organic layer was washed successively with water and saturated saline, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluting solvent : ethyl acetate-hexane) to obtain the title compound (83.9mg).

[0505]

20 ¹H-NMR (CDCl₃) δ ppm:

1.50 (3H, t, J=7.0Hz), 4.03 (3H, s), 4.15 (2H, q, J=7.0Hz), 5.53 (2H, s), 6.55-6.75 (2H, m), 7.15-7.25 (2H, m), 7.30-7.50 (5H, m), 7.65-7.75 (1H, m), 7.95-8.05 (1H, m).

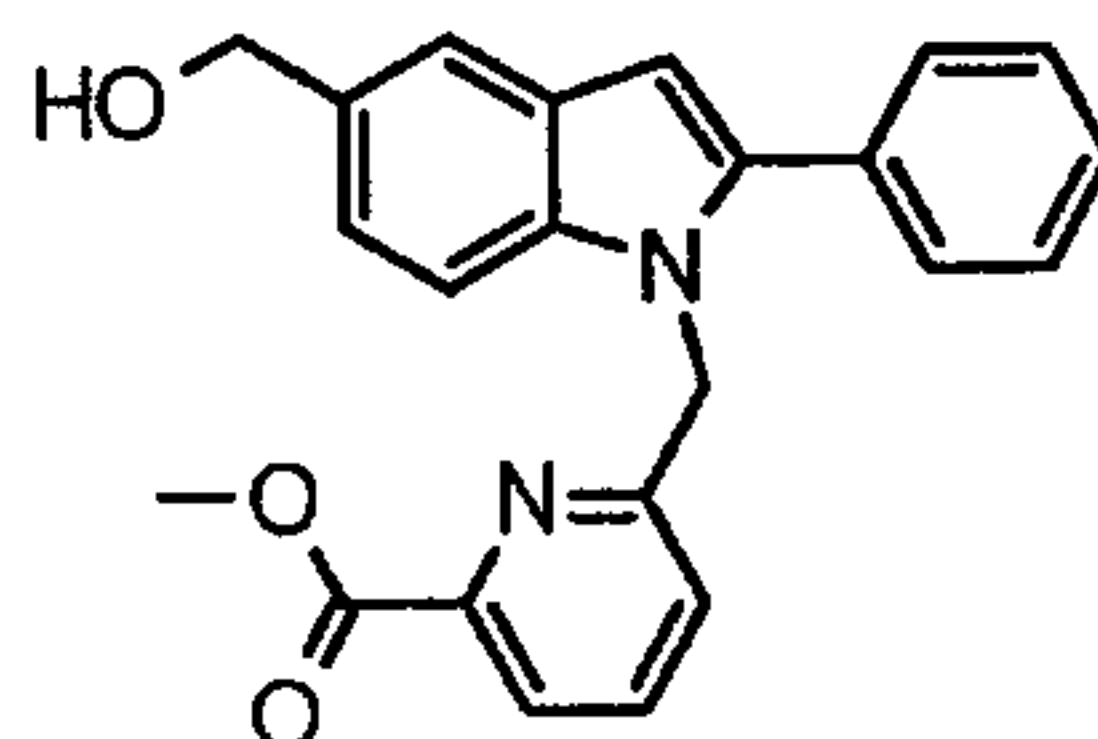
[0506]

Example 24

25 Methyl 6-(5-hydroxymethyl-2-phenylindol-1-ylmethyl)pyridine-2-carboxylate

[0507]

[Chem. 59]



[0508]

To a solution of methyl 6-(2-phenyl-5-triisopropylsilanyloxymethylindol-1-ylmethyl)pyridine-2-carboxylate (77.0mg) in tetrahydrofuran (0.728mL) was added tetrabutylammonium fluoride (1.0mol/L tetrahydrofuran solution, 0.190mL) under cooling with ice. The mixture was stirred under cooling with ice for one hour and then at room temperature for additional 2 hours. A saturated aqueous ammonium chloride solution was added to the reaction mixture and this resulting mixture was extracted with ethyl acetate. The organic layer was washed with saturated saline, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluting solvent : ethyl acetate-hexane) to obtain the title compound (44.4mg).

[0509]

¹H-NMR (CDCl₃) δ ppm:

1.58 (1H, t, J=5.9Hz), 4.03 (3H, s), 4.78 (2H, d, J=5.9Hz), 5.62 (2H, s), 6.65-6.75 (2H, m), 7.12 (1H, d, J=8.4Hz), 7.18 (1H, dd, J=1.6, 8.4Hz), 7.30-7.45 (5H, m), 7.60-7.75 (2H, m), 7.95-8.05 (1H, m).

[0510]

Examples 25-1 to 25-45

[0511]

The compounds shown in Tables 43 to 48 were synthesized in a manner similar to that of Example 9-1 by using the corresponding starting materials.

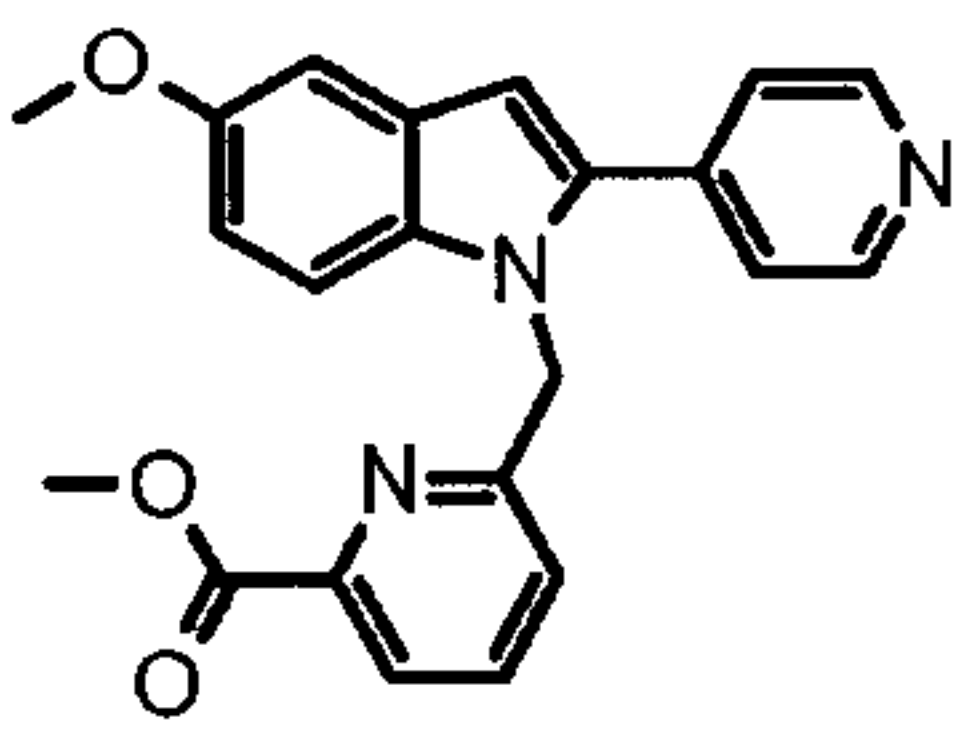
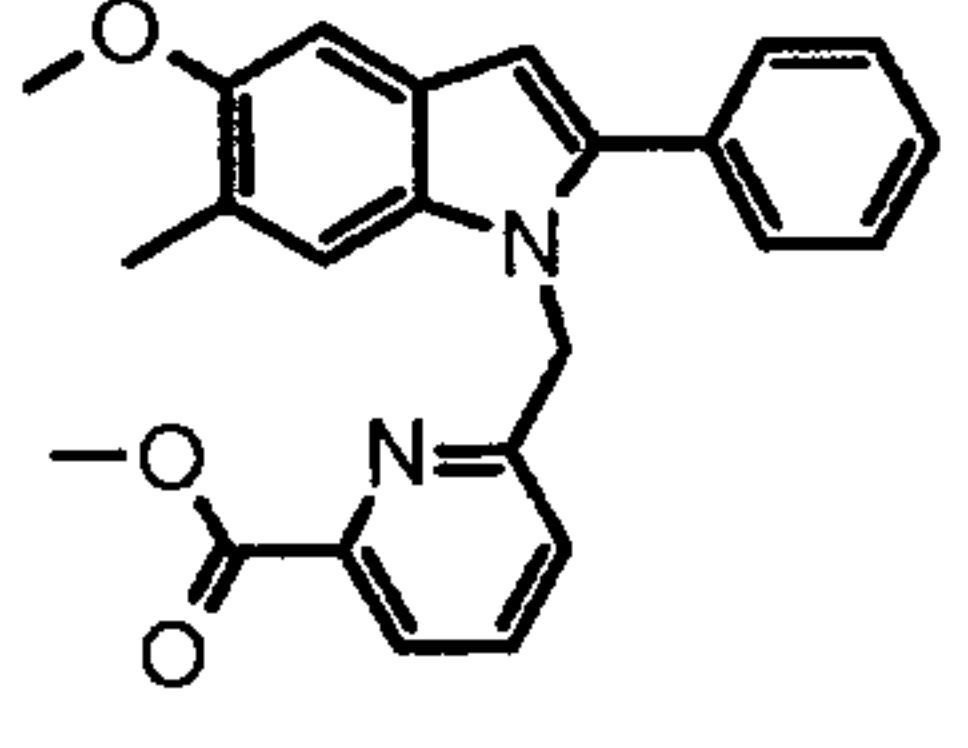
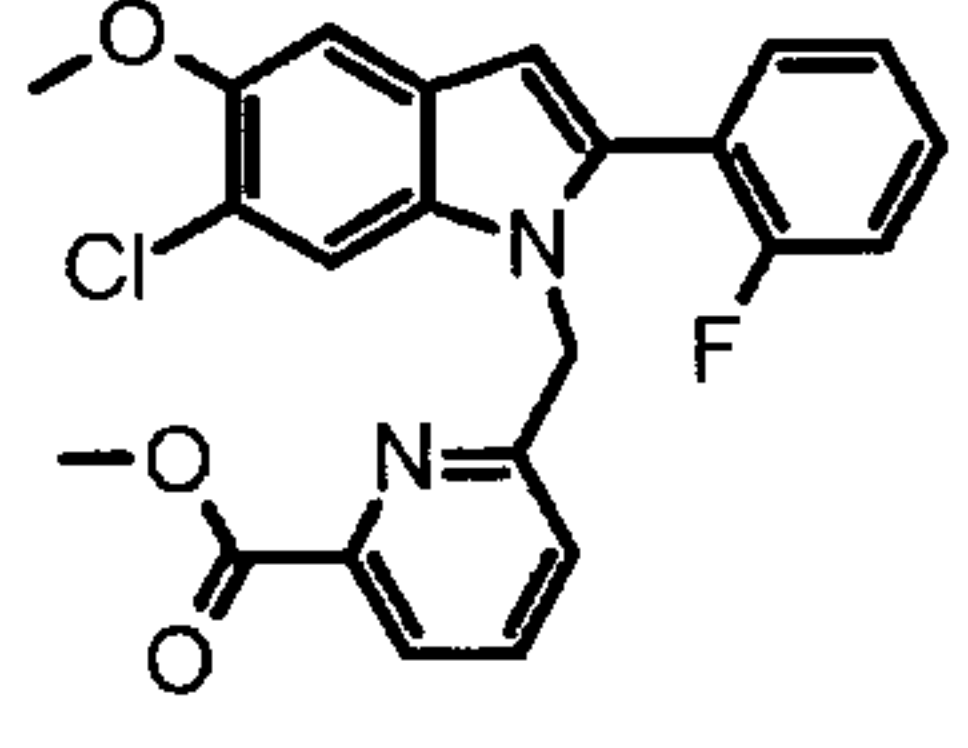
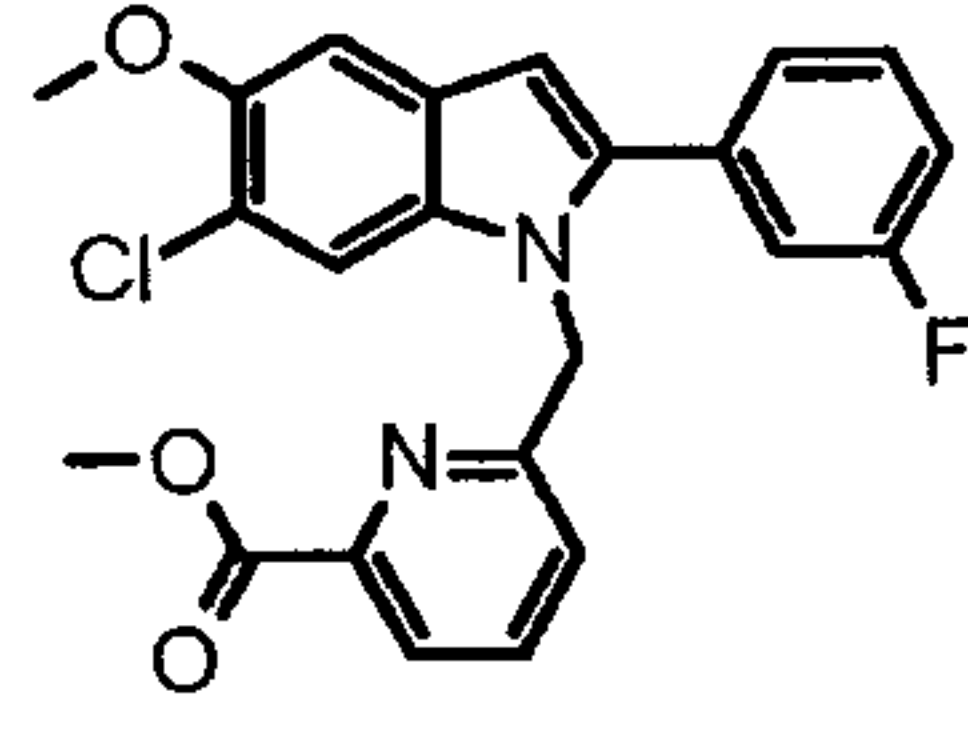
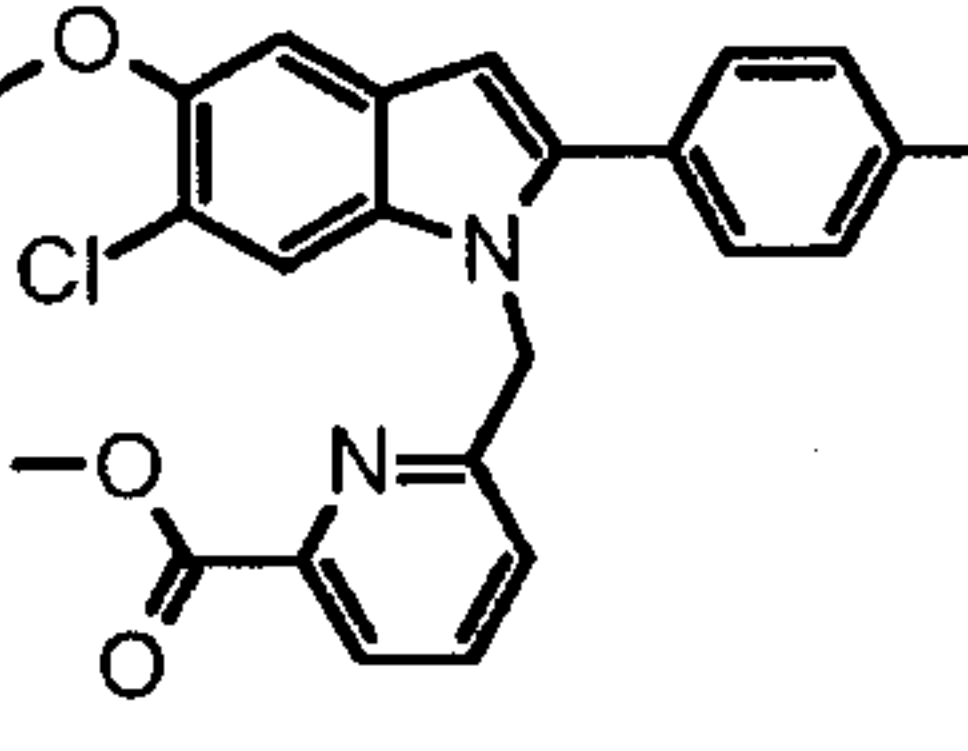
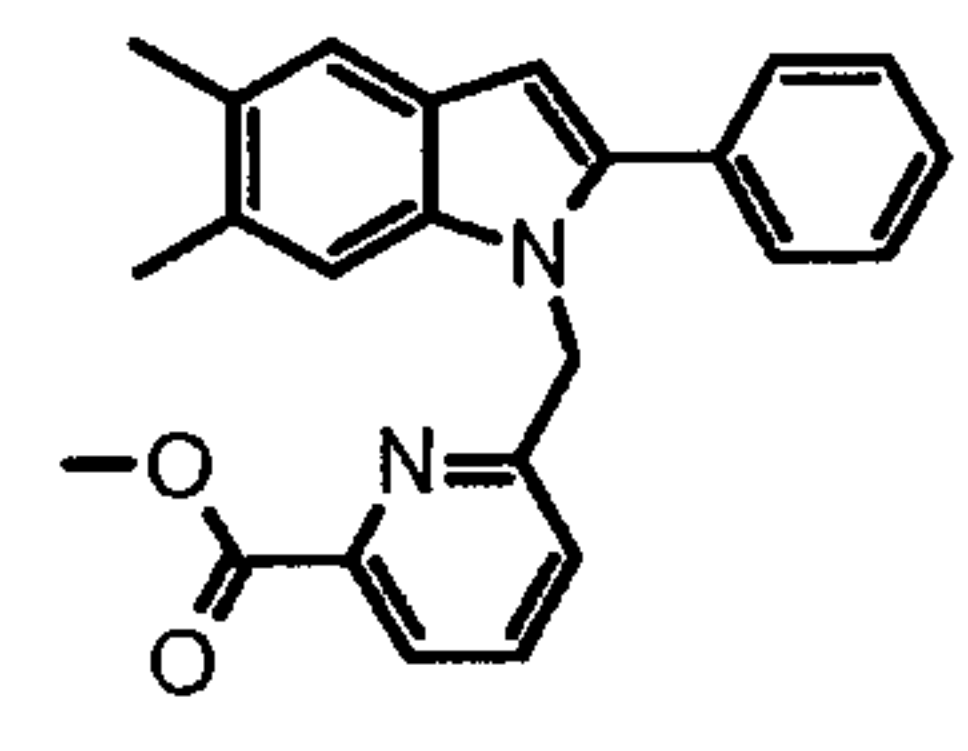
[0512]

[Table 35]

Ex. No.	Strc	Physical Data
17-1		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 3.87 (3H, s), 4.03 (3H, s), 5.57 (2H, s), 6.60–6.70 (2H, m), 6.83 (1H, dd, $J=2.5, 8.9\text{Hz}$), 7.04 (1H, d, $J=8.9\text{Hz}$), 7.10–7.20 (1H, m), 7.20–7.40 (3H, m), 7.40–7.50 (1H, m), 7.67 (1H, t, $J=7.8\text{Hz}$), 7.95–8.05 (1H, m).
17-2		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 2.33 (3H, s), 3.86 (3H, s), 4.02 (3H, s), 5.59 (2H, s), 6.60 (1H, s), 6.66 (1H, d, $J=7.8\text{Hz}$), 6.80 (1H, d, $J=2.5, 8.8\text{Hz}$), 7.01 (1H, d, $J=8.8\text{Hz}$), 7.10–7.30 (5H, m), 7.60–7.70 (1H, m), 7.98 (1H, d, $J=7.5\text{Hz}$).
17-3		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 3.87 (3H, s), 4.00 (3H, s), 5.42 (2H, s), 6.50–6.65 (2H, m), 6.83 (1H, dd, $J=2.5, 9.0\text{Hz}$), 7.05 (1H, d, $J=9.0\text{Hz}$), 7.17 (1H, d, $J=2.5\text{Hz}$), 7.20–7.40 (3H, m), 7.40–7.50 (1H, m), 7.60 (1H, t, $J=7.8\text{Hz}$), 7.85–8.00 (1H, m).
17-4		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 2.21 (3H, s), 3.87 (3H, s), 4.00 (3H, s), 5.35 (2H, s), 6.45–6.60 (2H, m), 6.80 (1H, dd, $J=2.5, 8.8\text{Hz}$), 7.03 (1H, d, $J=8.8\text{Hz}$), 7.10–7.35 (5H, m), 7.61 (1H, t, $J=7.8\text{Hz}$), 7.90–8.00 (1H, m).
17-5		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 3.87 (3H, s), 4.03 (3H, s), 5.55 (2H, s), 6.65–6.75 (2H, m), 6.85 (1H, dd, $J=2.4, 8.9\text{Hz}$), 7.06 (1H, d, $J=8.9\text{Hz}$), 7.10–7.20 (1H, m), 7.25–7.40 (1H, m), 7.60–7.80 (2H, m), 7.95–8.05 (1H, m), 8.59 (1H, dd, $J=1.6, 4.9\text{Hz}$), 8.65–8.75 (1H, m).
17-6		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 3.96 (3H, s), 4.03 (3H, s), 5.54 (2H, s), 6.55–6.75 (2H, m), 7.15–7.25 (2H, m), 7.30–7.45 (5H, m), 7.69 (1H, t, $J=7.8\text{Hz}$), 7.95–8.05 (1H, m).

[0513]

[Table 36]

Ex. No.	Strc	Physical Data
17-7		¹ H-NMR (CDCl ₃) δ ppm: 3.87 (3H, s), 4.04 (3H, s), 5.61 (2H, s), 6.65–6.85 (2H, m), 6.87 (1H, dd, J=2.5, 9.0Hz), 7.06 (1H, d, J=9.0Hz), 7.10–7.20 (1H, m), 7.25–7.40 (2H, m), 7.70 (1H, t, J=7.8Hz), 7.95–8.10 (1H, m), 8.55–8.65 (2H, m).
17-8		¹ H-NMR (CDCl ₃) δ ppm: 2.25 (3H, s), 3.89 (3H, s), 4.03 (3H, s), 5.56 (2H, s), 6.55–6.65 (1H, m), 6.65–6.75 (1H, m), 6.89 (1H, s), 7.08 (1H, s), 7.25–7.45 (5H, m), 7.66 (1H, t, J=7.8Hz), 7.95–8.05 (1H, m).
17-9		¹ H-NMR (CDCl ₃) δ ppm: 3.95 (3H, s), 4.02 (3H, s), 5.43 (2H, s), 6.55–6.70 (2H, m), 7.05–7.25 (4H, m), 7.30–7.45 (2H, m), 7.65 (1H, t, J=7.8Hz), 7.95–8.05 (1H, m).
17-10		¹ H-NMR (CDCl ₃) δ ppm: 3.95 (3H, s), 4.03 (3H, s), 5.53 (2H, s), 6.55–6.75 (2H, m), 7.00–7.25 (5H, m), 7.25–7.45 (1H, m), 7.70 (1H, t, J=7.8Hz), 7.95–8.10 (1H, m).
17-11		¹ H-NMR (CDCl ₃) δ ppm: 3.95 (3H, s), 4.03 (3H, s), 5.49 (2H, s), 6.50–6.75 (2H, m), 7.00–7.15 (2H, m), 7.15–7.25 (2H, m), 7.30–7.45 (2H, m), 7.69 (1H, t, J=7.8Hz), 7.95–8.05 (1H, m).
17-12		¹ H-NMR (CDCl ₃) δ ppm: 2.29 (3H, s), 2.35 (3H, s), 4.03 (3H, s), 5.57 (2H, s), 6.50–6.75 (2H, m), 6.90 (1H, s), 7.25–7.50 (6H, m), 7.65 (1H, t, J=7.8Hz), 7.90–8.05 (1H, m).

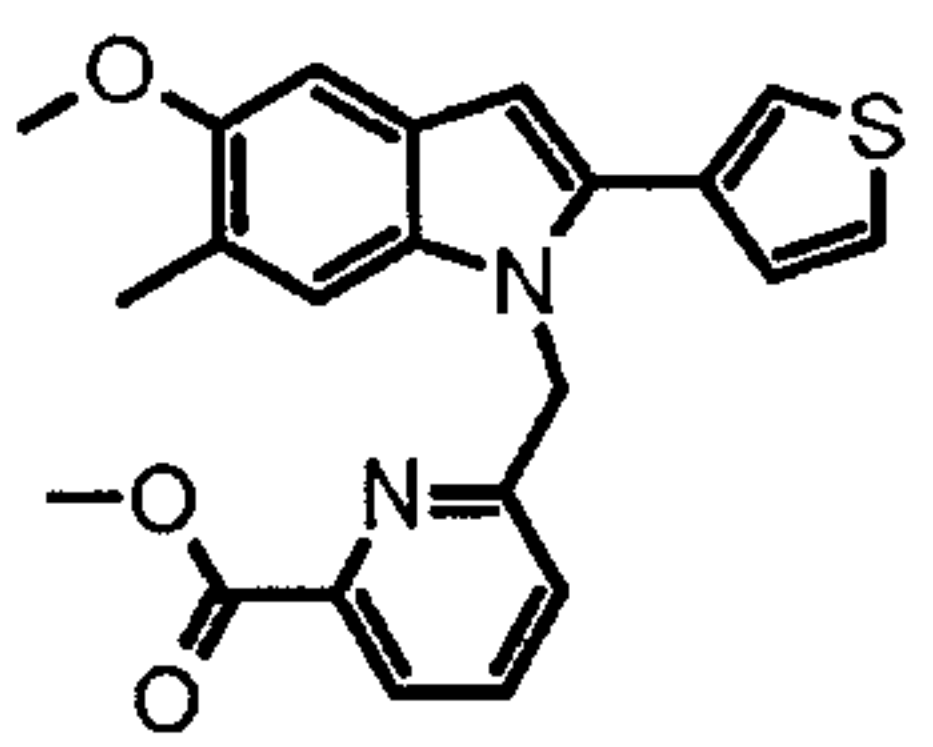
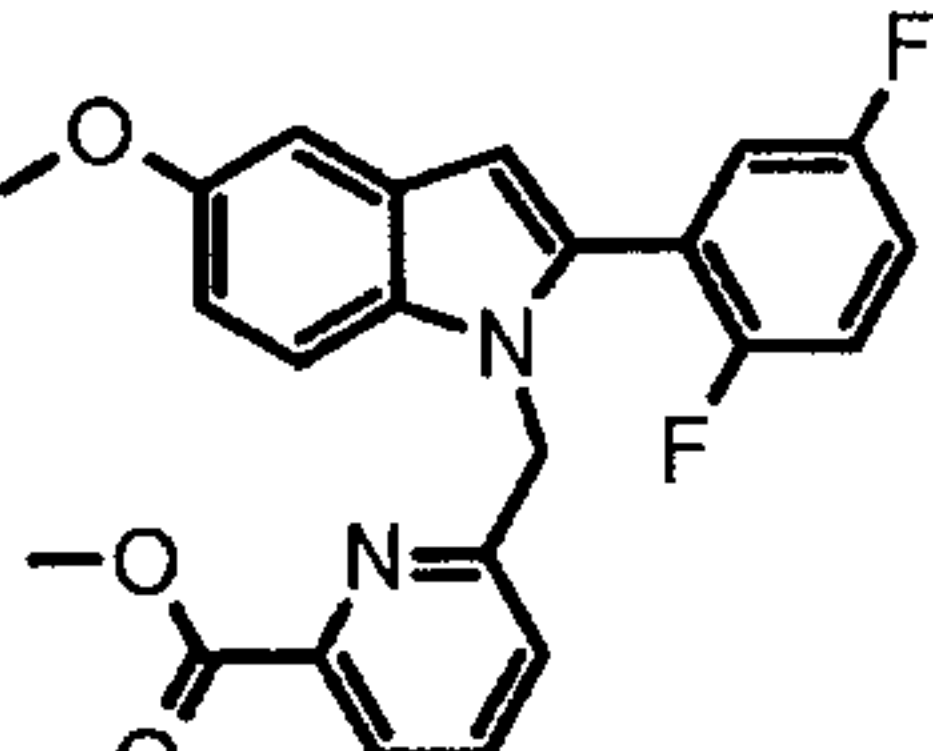
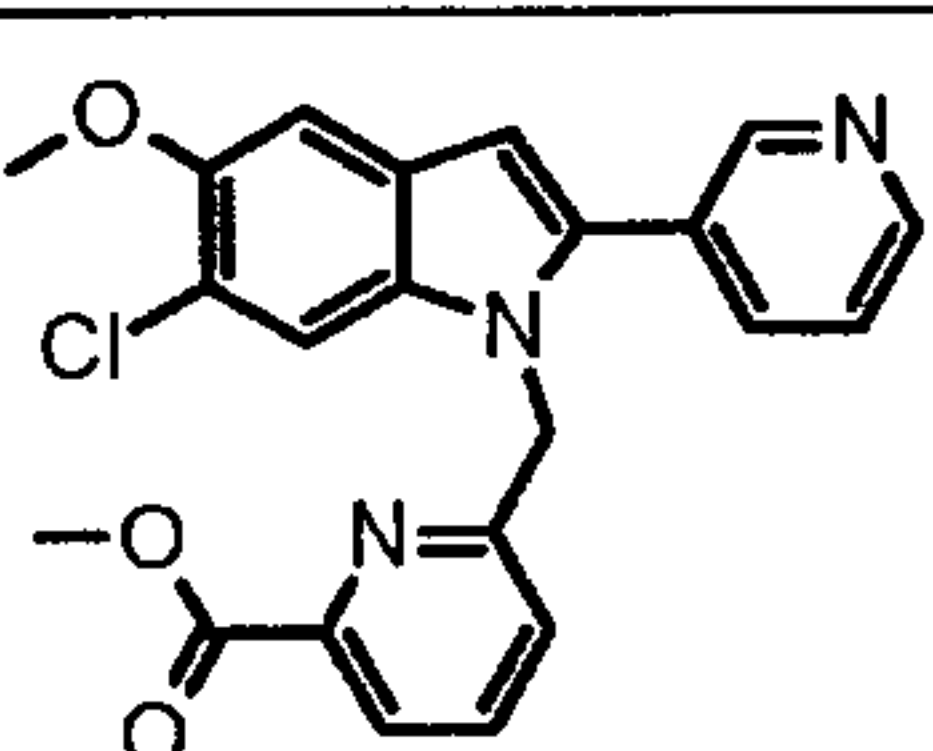
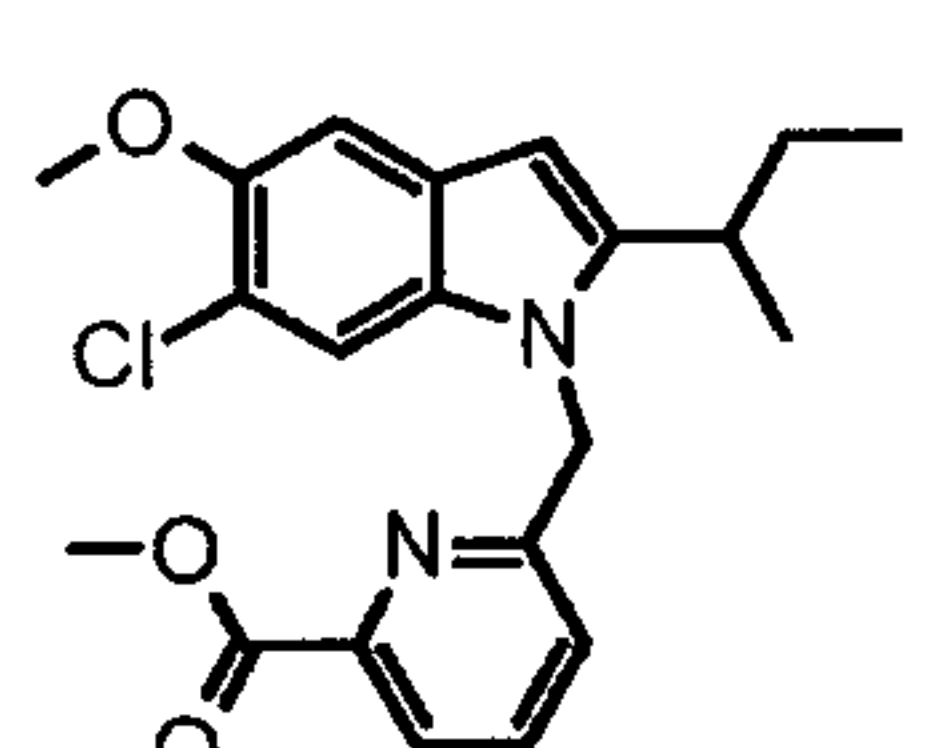
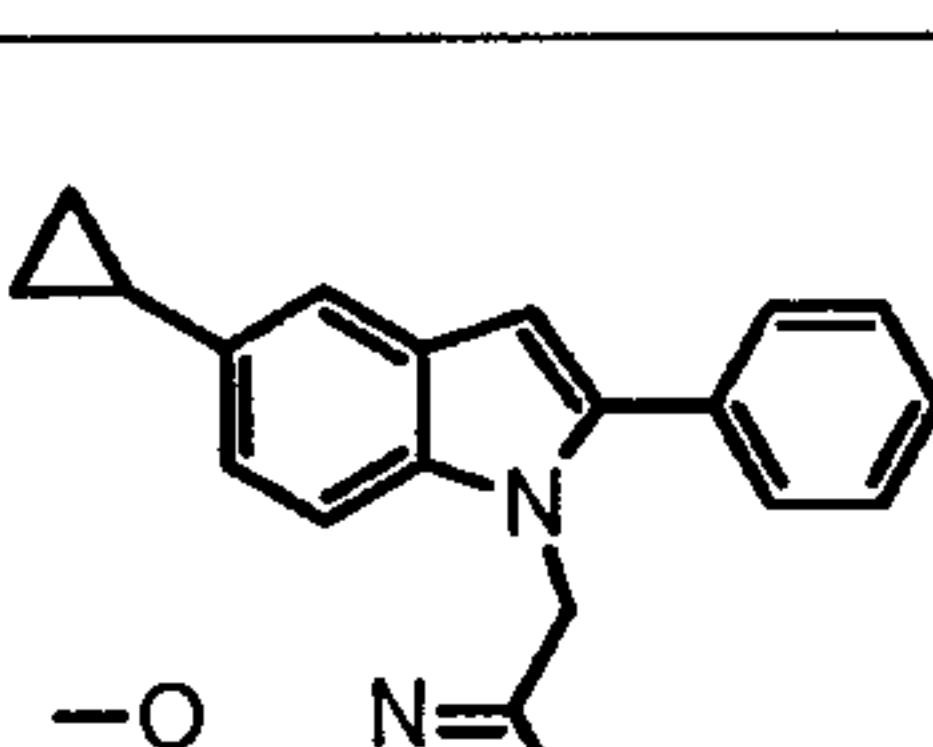
[0514]

[Table 37]

Ex. No.	Strc	Physical Data
17-13		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 3.94 (3H, s), 4.02 (3H, s), 5.42 (2H, s), 6.55–6.70 (2H, m), 6.87 (1H, d, $J=11.3\text{Hz}$), 7.05–7.25 (3H, m), 7.30–7.45 (2H, m), 7.65 (1H, t, $J=7.8\text{Hz}$), 7.90–8.05 (1H, m).
17-14		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 3.94 (3H, s), 4.03 (3H, s), 5.53 (2H, s), 6.55–6.75 (2H, m), 6.89 (1H, d, $J=11.3\text{Hz}$), 7.00–7.25 (4H, m), 7.25–7.45 (1H, m), 7.70 (1H, t, $J=7.8\text{Hz}$), 7.95–8.10 (1H, m).
17-15		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 3.94 (3H, s), 4.03 (3H, s), 5.49 (2H, s), 6.50–6.75 (2H, m), 6.88 (1H, d, $J=11.3\text{Hz}$), 7.00–7.15 (2H, m), 7.19 (1H, d, $J=8.3\text{Hz}$), 7.30–7.45 (2H, m), 7.69 (1H, t, $J=7.8\text{Hz}$), 7.95–8.10 (1H, m).
17-16		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 3.95 (3H, s), 4.03 (3H, s), 5.50 (2H, s), 6.60–6.80 (2H, s), 6.92 (1H, d, $J=11.3\text{Hz}$), 7.22 (1H, d, $J=8.0\text{Hz}$), 7.25–7.40 (1H, m), 7.65–7.80 (2H, m), 7.95–8.10 (1H, m), 8.55–8.65 (1H, m), 8.65–8.75 (1H, m).
17-17		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 3.95 (3H, s), 4.05 (3H, s), 5.59 (2H, s), 6.60–6.80 (2H, m), 7.10–7.35 (4H, m), 7.37 (1H, dd, $J=3.0, 5.0\text{Hz}$), 7.71 (1H, t, $J=7.8\text{Hz}$), 8.00–8.10 (1H, m).
17-18		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 3.95 (3H, s), 4.06 (3H, s), 5.58 (2H, s), 6.45–6.55 (1H, m), 6.55–6.75 (2H, m), 7.16 (1H, s), 7.20–7.25 (1H, m), 7.40–7.55 (2H, m), 7.69 (1H, t, $J=7.8\text{Hz}$), 8.00–8.10 (1H, m).

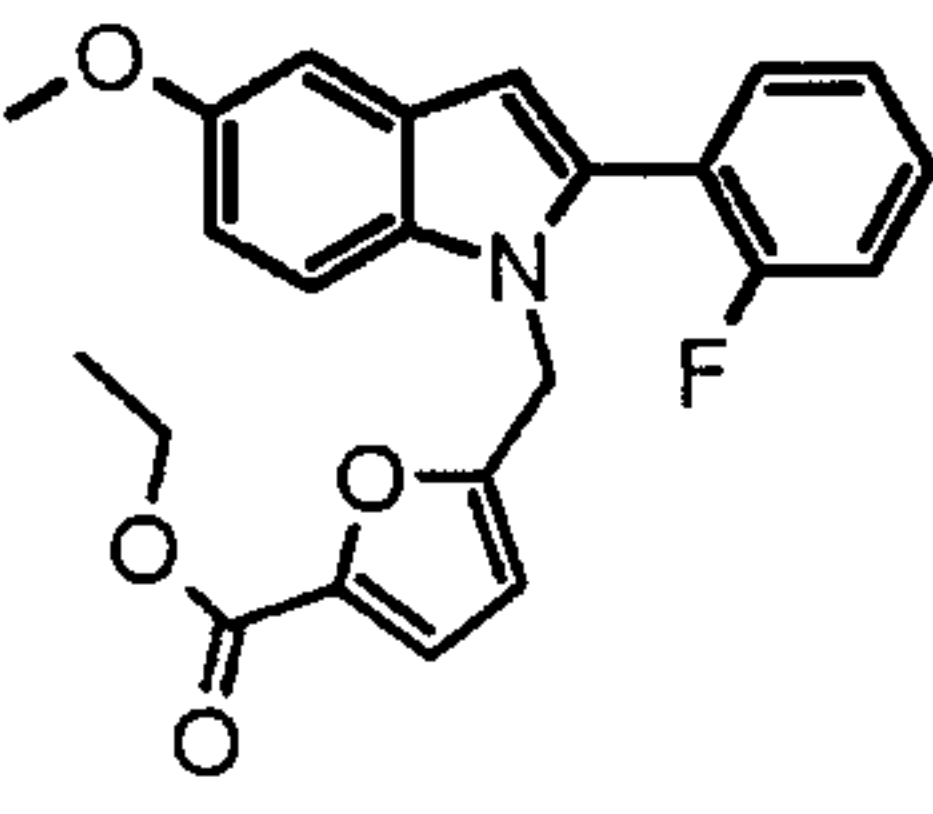
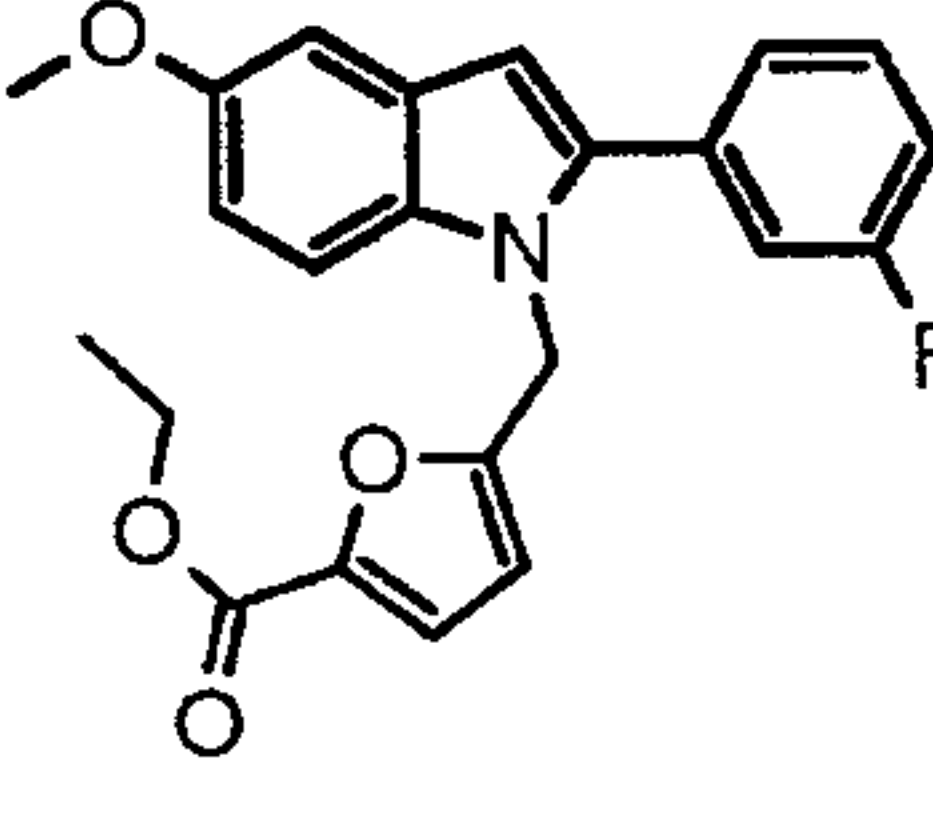
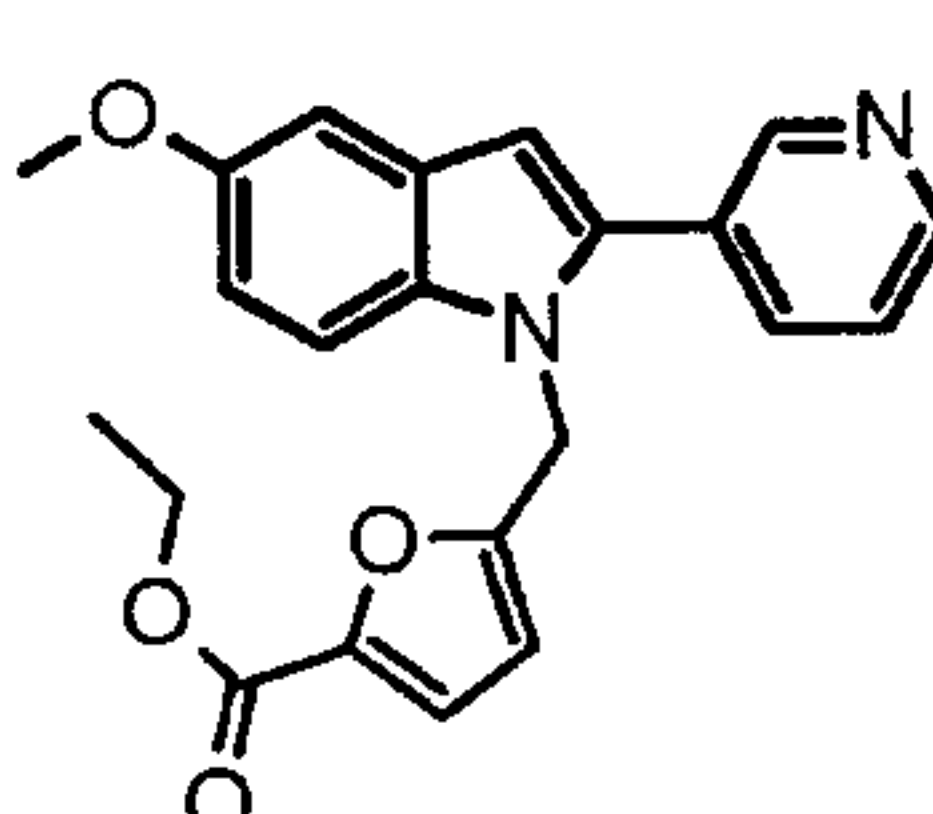
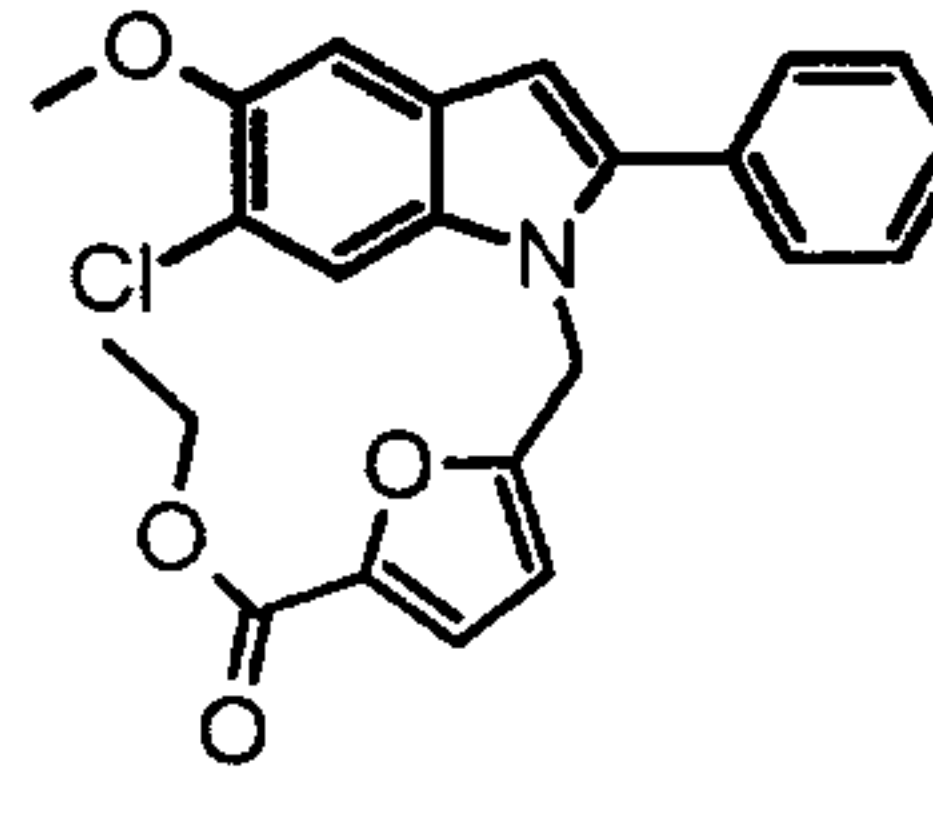
[0515]

[Table 38]

Ex. No.	Strc	Physical Data
17-19		¹ H-NMR (CDCl ₃) δ ppm: 2.25 (3H, s), 3.89 (3H, s), 4.05 (3H, s), 5.61 (2H, s), 6.60–6.80 (2H, m), 6.90 (1H, br s), 7.06 (1H, s), 7.10–7.25 (2H, m), 7.30–7.40 (1H, m), 7.67 (1H, t, J=7.8Hz), 7.95–8.10 (1H, m).
17-20		¹ H-NMR (CDCl ₃) δ ppm: 3.86 (3H, s), 4.02 (3H, s), 5.47 (2H, s), 6.55–6.70 (2H, m), 6.80–6.90 (1H, m), 6.95–7.20 (5H, m), 7.64 (1H, t, J=7.8Hz), 7.97 (1H, d, J=7.8Hz).
17-21		¹ H-NMR (CDCl ₃) δ ppm: 3.96 (3H, s), 4.03 (3H, s), 5.50 (2H, s), 6.60–6.80 (2H, m), 7.20 (1H, s), 7.23 (1H, s), 7.25–7.40 (1H, m), 7.65–7.80 (2H, m), 8.02 (1H, d, J=7.8Hz), 8.55–8.65 (1H, m), 8.65–8.75 (1H, m).
17-22		¹ H-NMR (CDCl ₃) δ ppm: 0.84 (3H, t, J=7.4Hz), 1.23 (3H, d, J=6.9Hz), 1.45–1.80 (2H, m), 2.60–2.75 (1H, m), 3.93 (3H, s), 4.06 (3H, s), 5.50 (2H, s), 6.31 (1H, s), 6.40–6.50 (1H, m), 7.12 (1H, s), 7.15 (1H, s), 7.64 (1H, t, J=7.9Hz), 7.95–8.05 (1H, m).
17-23		¹ H-NMR (CDCl ₃) δ ppm: 0.65–0.75 (2H, m), 0.85–1.00 (2H, m), 1.95–2.10 (1H, m), 4.02 (3H, s), 5.58 (2H, s), 6.55–6.65 (1H, m), 6.65–6.75 (1H, m), 6.91 (1H, dd, J=1.9, 8.5Hz), 7.01 (1H, d, J=8.5Hz), 7.30–7.45 (6H, m), 7.65 (1H, t, J=7.9Hz), 7.90–8.05 (1H, m).

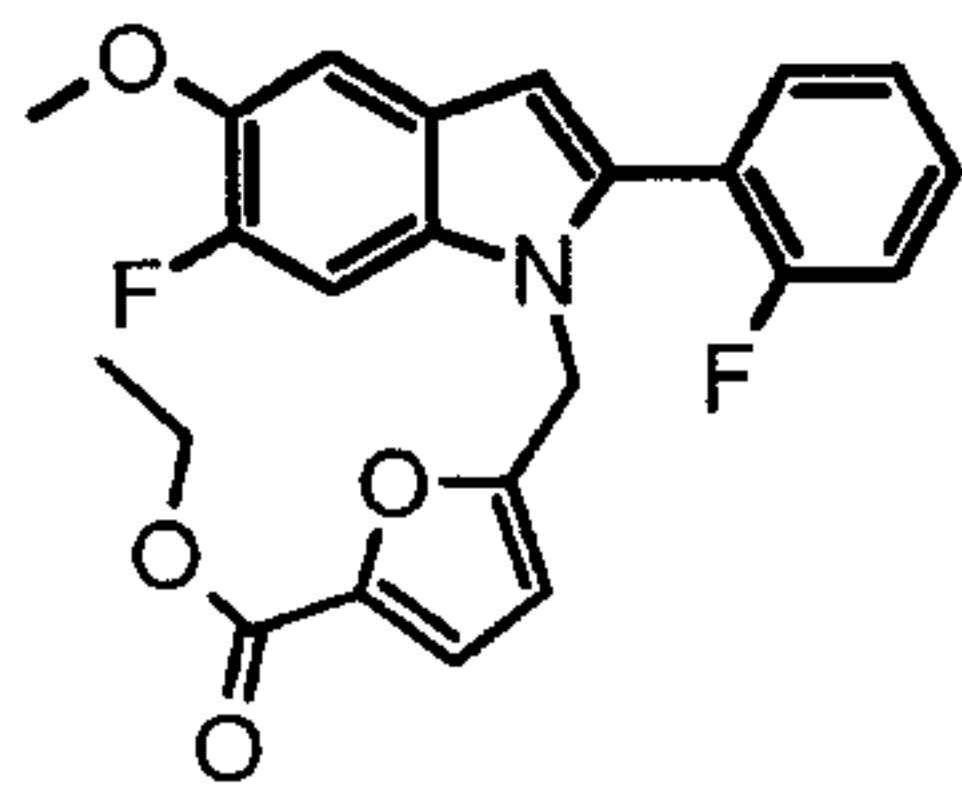
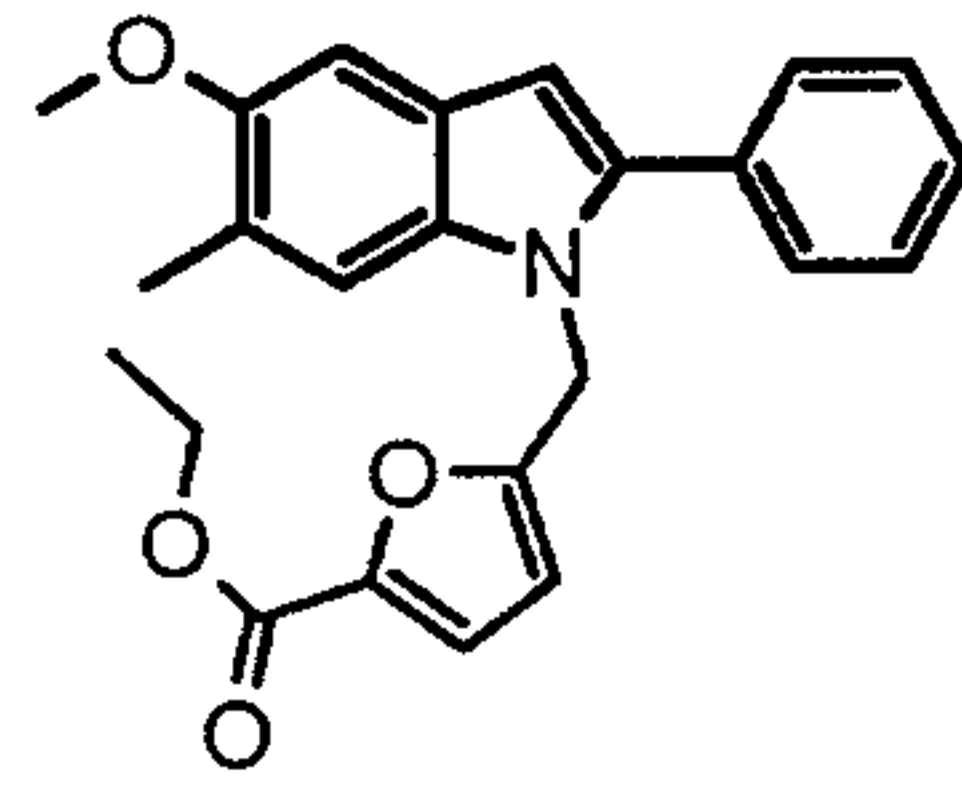
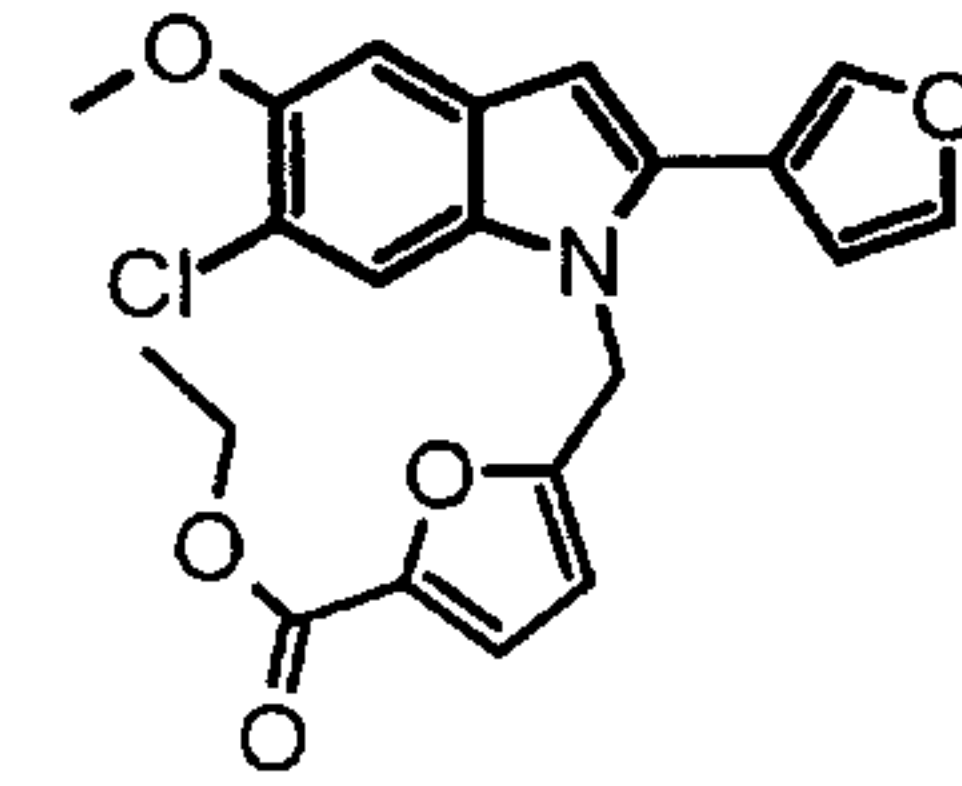
[0516]

[Table 39]

Ex. No.	Strc	Physical Data
18-1		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.35 (3H, t, $J=7.1\text{Hz}$), 3.86 (3H, s), 4.32 (2H, q, $J=7.1\text{Hz}$), 5.23 (2H, s), 5.87 (1H, d, $J=3.5\text{Hz}$), 6.57 (1H, s), 6.88 (1H, dd, $J=2.4, 8.9\text{Hz}$), 6.98 (1H, d, $J=3.5\text{Hz}$), 7.10–7.30 (4H, m), 7.35–7.50 (2H, m).
18-2		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.37 (3H, t, $J=7.1\text{Hz}$), 3.86 (3H, s), 4.35 (2H, q, $J=7.1\text{Hz}$), 5.29 (2H, s), 5.95–6.05 (1H, m), 6.50–6.60 (1H, m), 6.89 (1H, dd, $J=2.5, 8.8\text{Hz}$), 7.00–7.15 (3H, m), 7.15–7.30 (3H, m), 7.35–7.45 (1H, m).
18-3		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.37 (3H, t, $J=7.1\text{Hz}$), 3.87 (3H, s), 4.34 (2H, q, $J=7.1\text{Hz}$), 5.27 (2H, s), 6.00–6.05 (1H, m), 6.55–6.65 (1H, m), 6.91 (1H, dd, $J=2.4, 8.9\text{Hz}$), 7.04 (1H, d, $J=3.5\text{Hz}$), 7.10–7.15 (1H, m), 7.22 (1H, d, $J=8.9\text{Hz}$), 7.35–7.45 (1H, m), 7.75–7.85 (1H, m), 8.60–8.70 (1H, m), 8.70–8.80 (1H, m).
18-4		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.37 (3H, t, $J=7.1\text{Hz}$), 3.95 (3H, s), 4.35 (2H, q, $J=7.1\text{Hz}$), 5.25 (2H, s), 5.95–6.05 (1H, m), 6.50–6.60 (1H, m), 7.06 (1H, d, $J=3.5\text{Hz}$), 7.15 (1H, s), 7.30–7.55 (6H, m).

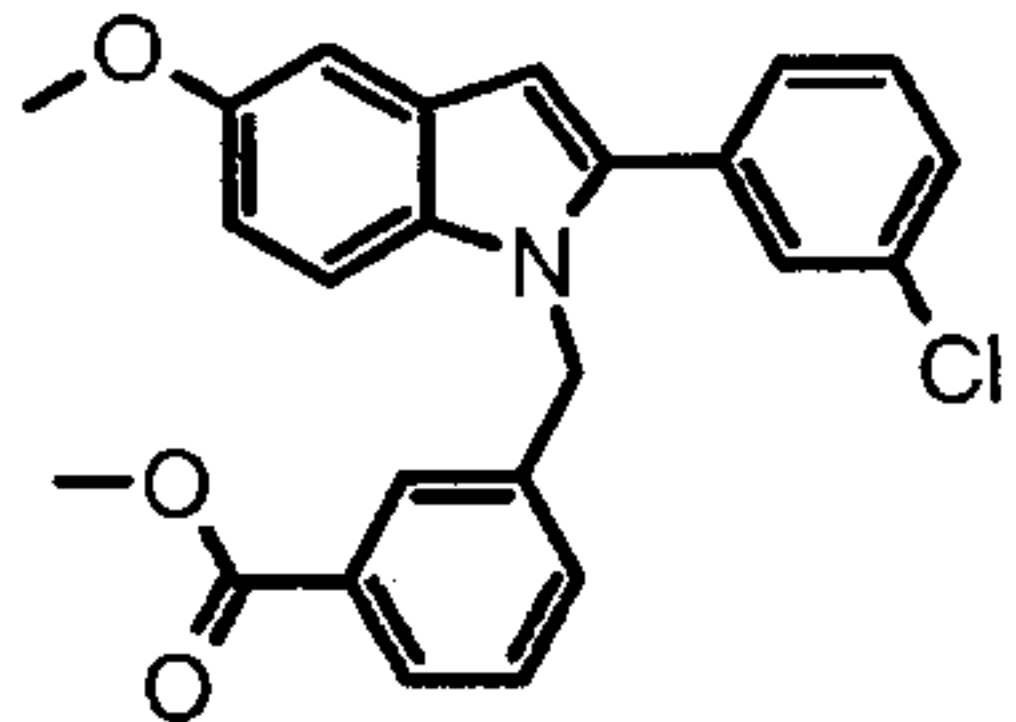
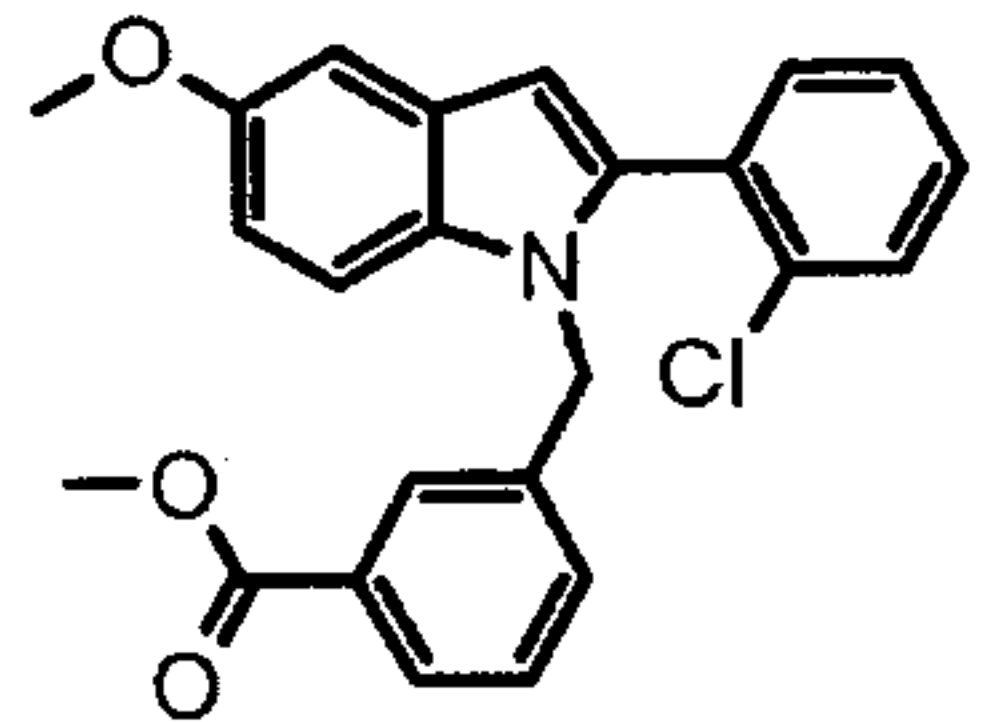
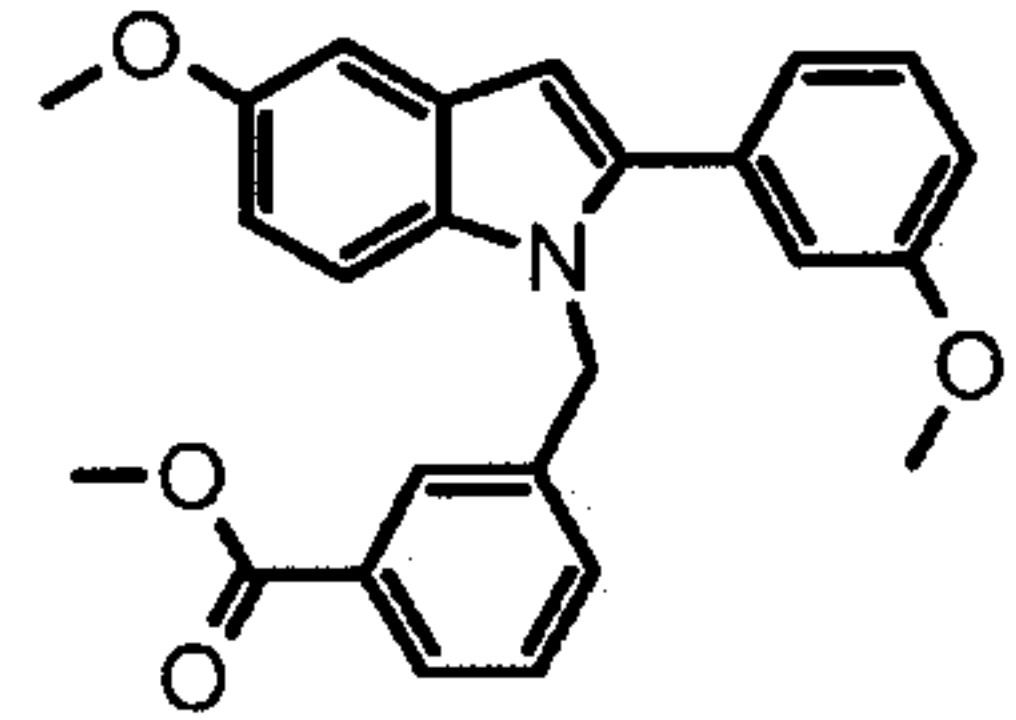
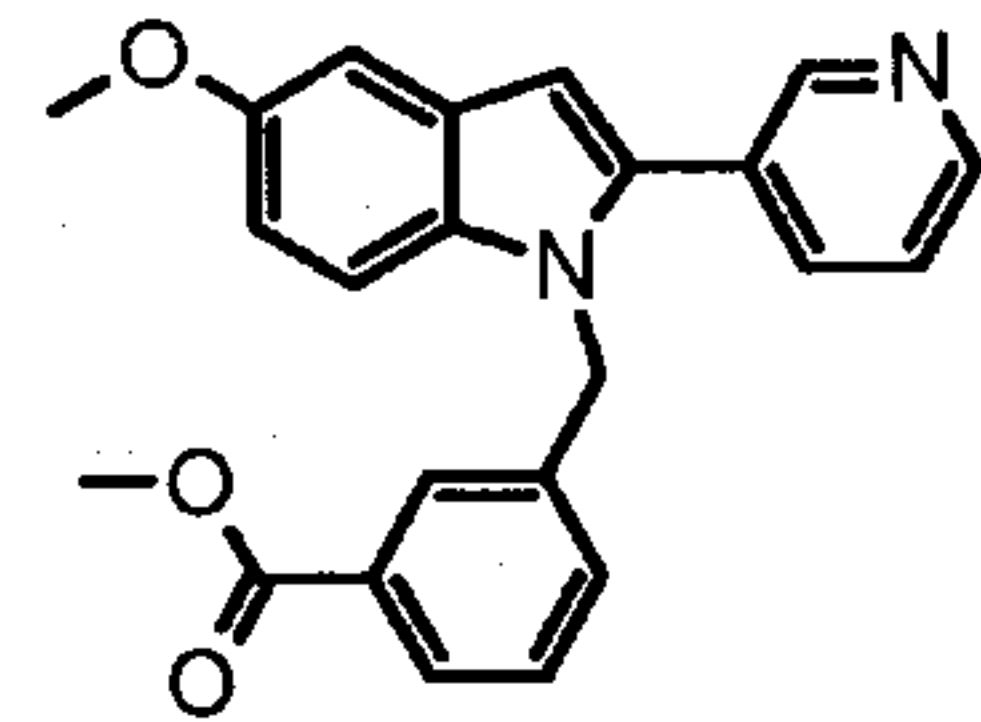
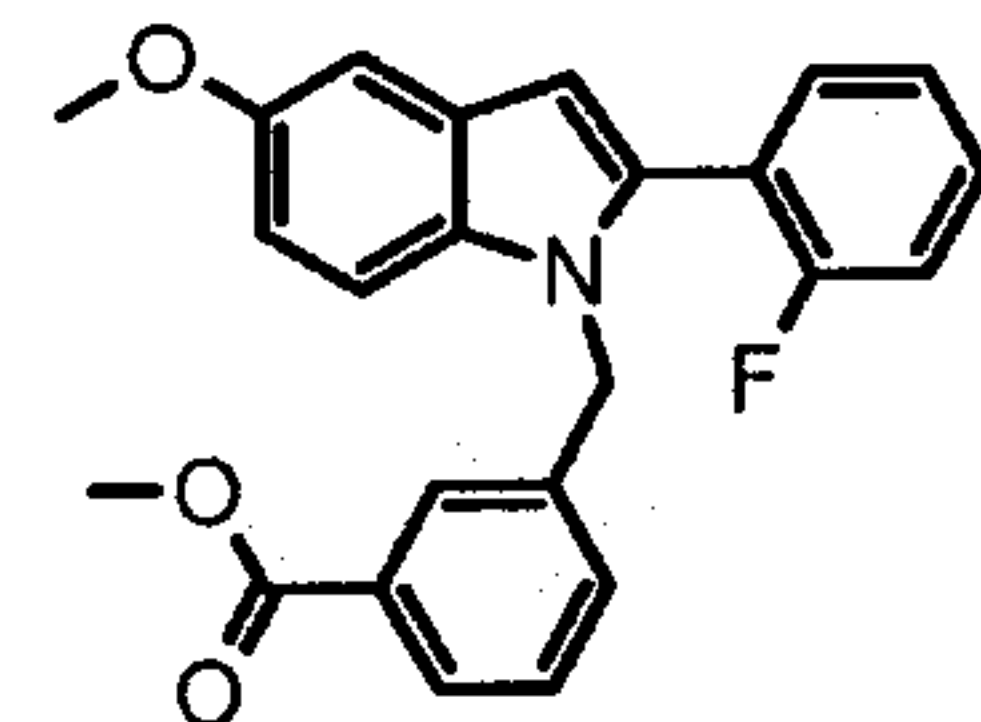
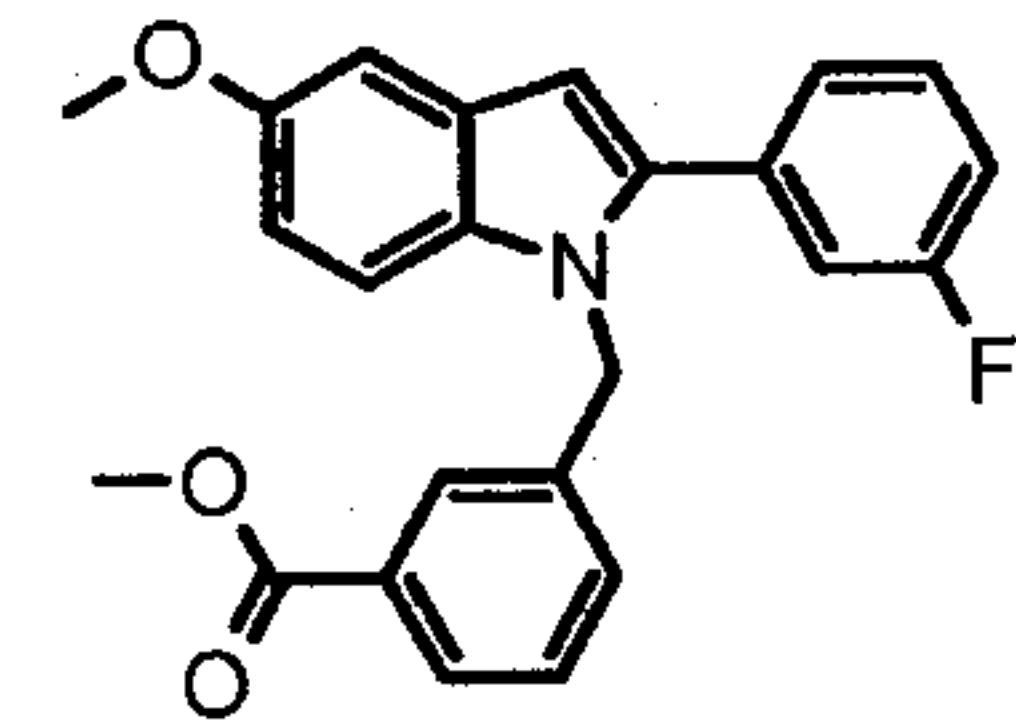
[0517]

[Table 40]

Ex. No.	Strc	Physical Data
18-5		¹ H-NMR (CDCl ₃) δ ppm: 1.36 (3H, t, J=7.2Hz), 3.94 (3H, s), 4.33 (2H, q, J=7.2Hz), 5.17 (2H, s), 5.90 (1H, d, J=3.5Hz), 6.56 (1H, s), 6.95–7.35 (5H, m), 7.35–7.50 (2H, m).
18-6		¹ H-NMR (CDCl ₃) δ ppm: 1.37 (3H, t, J=7.1Hz), 2.32 (3H, s), 3.88 (3H, s), 4.35 (2H, q, J=7.1Hz), 5.27 (2H, s), 5.90–6.05 (1H, m), 6.50–6.55 (1H, m), 7.00–7.10 (3H, m), 7.30–7.55 (5H, m).
18-7		¹ H-NMR (CDCl ₃) δ ppm: 1.38 (3H, t, J=7.2Hz), 3.94 (3H, s), 4.36 (2H, q, J=7.2Hz), 5.30 (2H, s), 6.00–6.10 (1H, m), 6.50–6.65 (2H, m), 7.07 (1H, d, J=3.3Hz), 7.12 (1H, s), 7.30–7.35 (1H, m), 7.45–7.65 (2H, m).

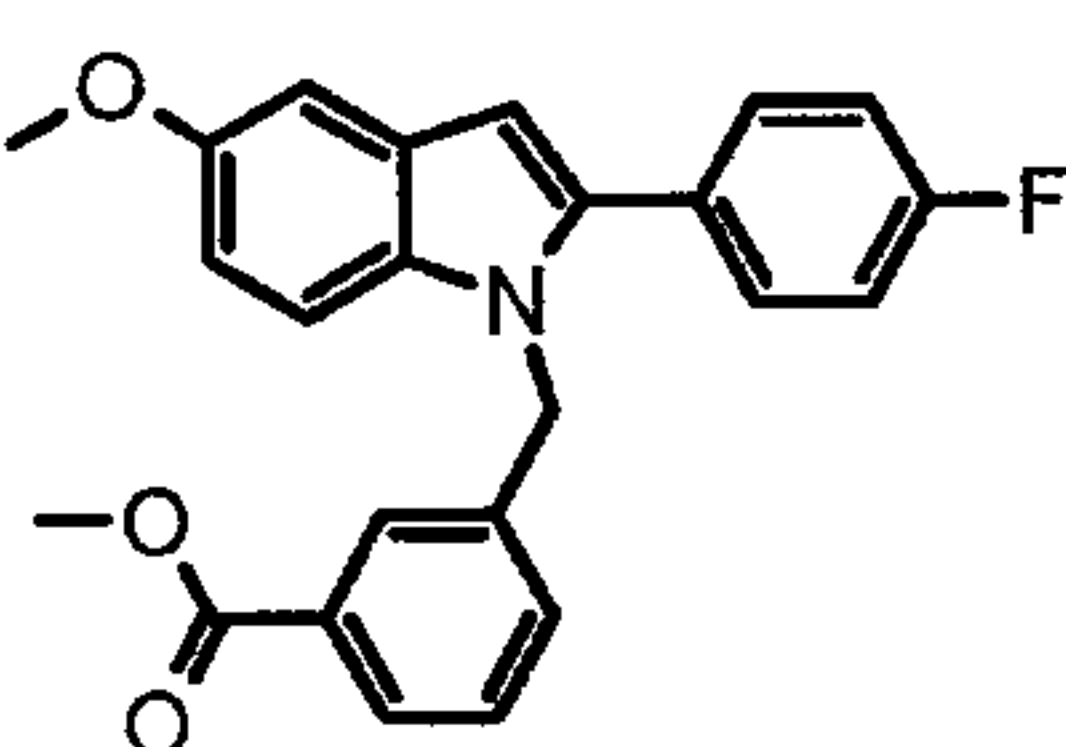
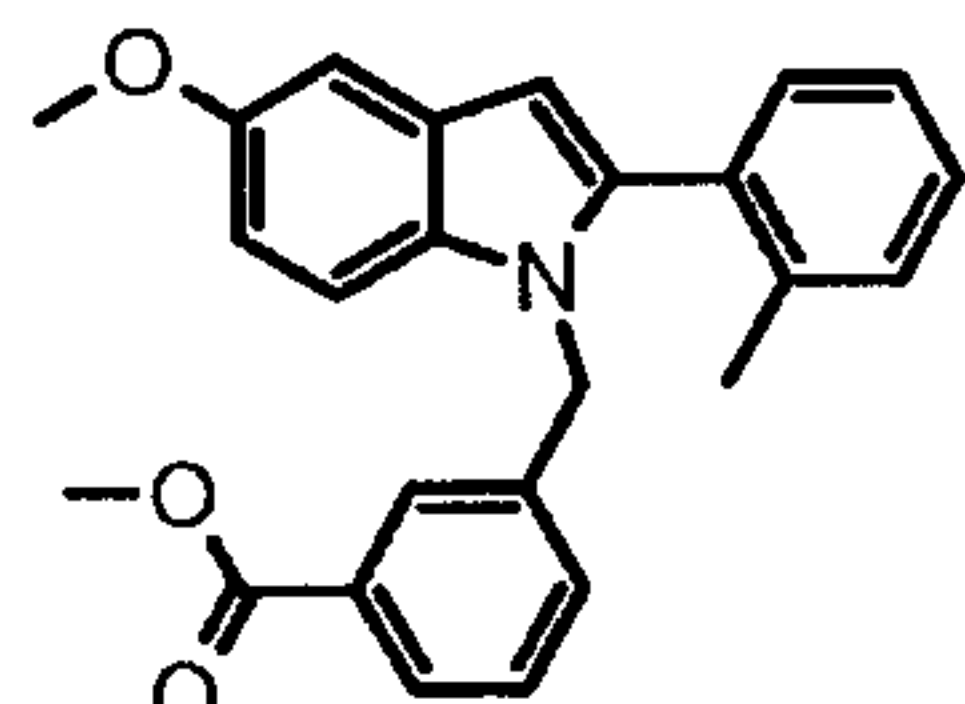
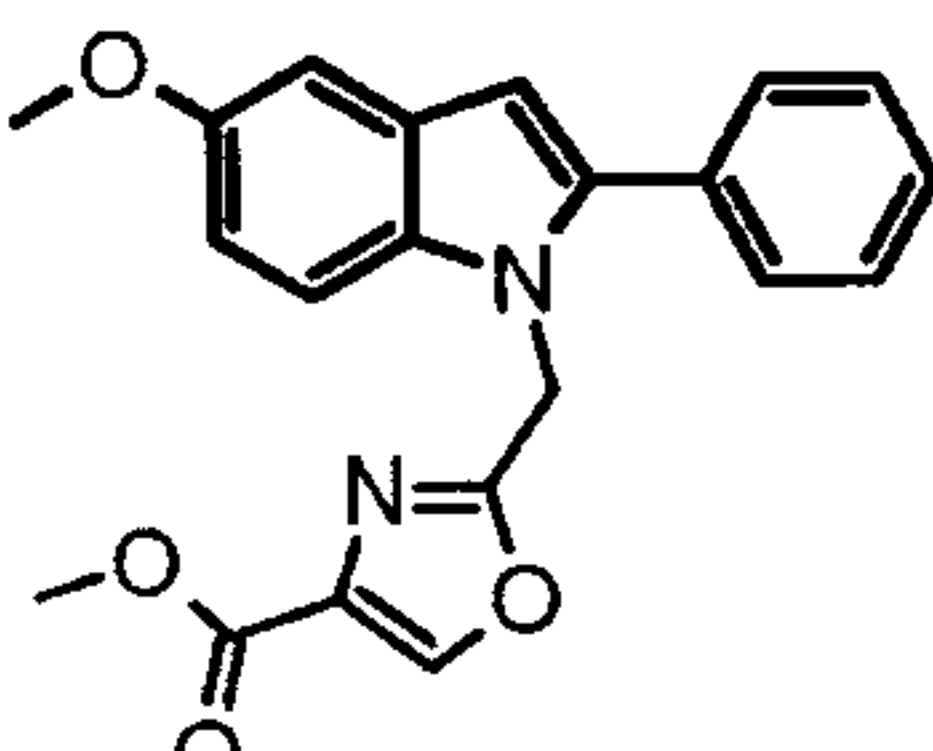
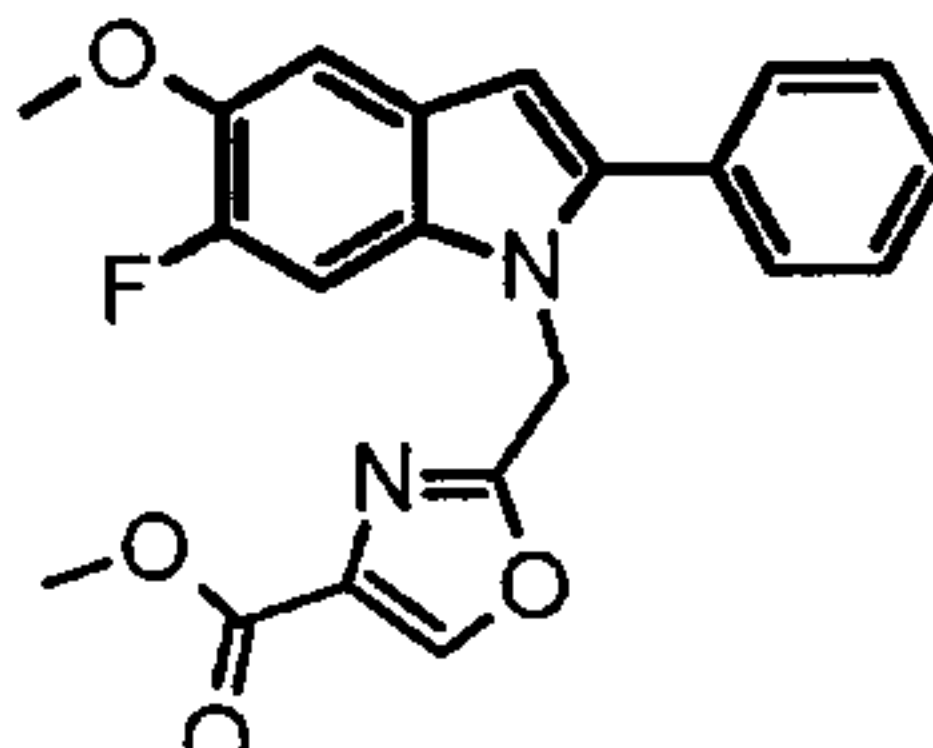
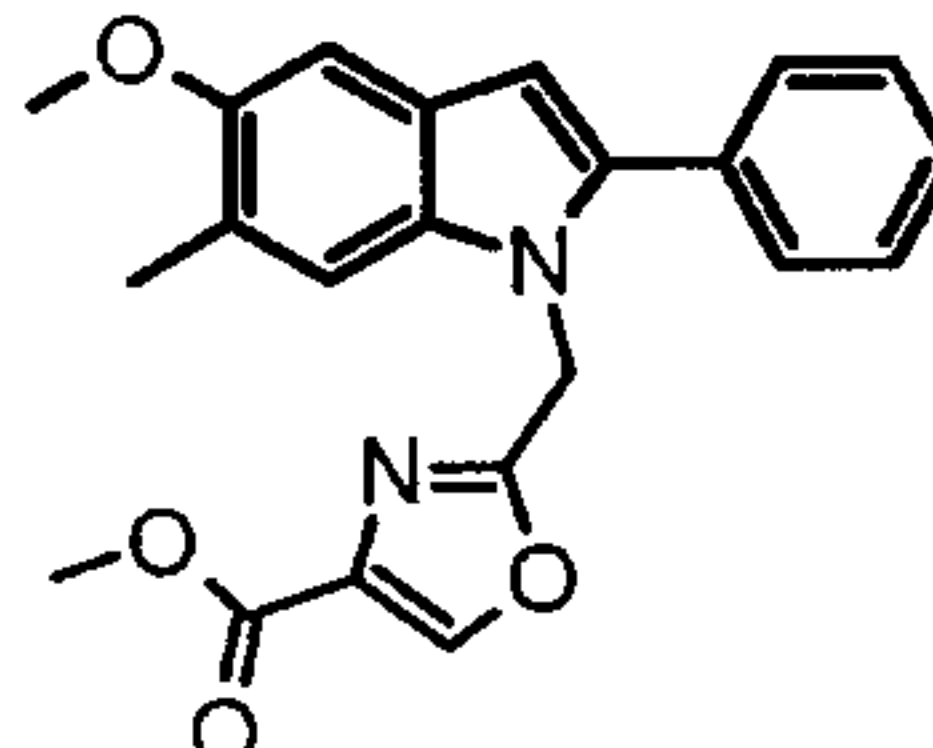
[0518]

[Table 41]

Ex. No.	Strc	Physical Data
19-1		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 3.86 (3H, s), 3.89 (3H, s), 5.35 (2H, s), 6.55–6.65 (1H, m), 6.83 (1H, dd, $J=2.5, 8.8\text{Hz}$), 7.00–7.15 (3H, m), 7.20–7.40 (4H, m), 7.40–7.45 (1H, m), 7.75–7.85 (1H, m), 7.85–7.95 (1H, m).
19-2		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 3.80–3.90 (6H, m), 5.21 (2H, s), 6.50–6.60 (1H, m), 6.83 (1H, dd, $J=2.4, 8.9\text{Hz}$), 6.95–7.05 (1H, m), 7.05–7.40 (6H, m), 7.45–7.55 (1H, m), 7.60–7.70 (1H, m), 7.80–7.90 (1H, m).
19-3		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 3.69 (3H, s), 3.86 (3H, s), 3.89 (3H, s), 5.38 (2H, s), 6.55–6.65 (1H, m), 6.81 (1H, dd, $J=2.4, 8.9\text{Hz}$), 6.85–7.20 (6H, m), 7.20–7.40 (2H, m), 7.75–7.95 (2H, m).
19-4		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 3.80–3.95 (6H, m), 5.36 (2H, s), 6.60–6.70 (1H, m), 6.85 (1H, dd, $J=2.5, 8.8\text{Hz}$), 7.00–7.20 (3H, m), 7.25–7.40 (2H, m), 7.60–7.75 (1H, m), 7.75–7.85 (1H, m), 7.85–7.95 (1H, m), 8.55–8.65 (1H, m), 8.65–8.75 (1H, m).
19-5		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 3.80–3.90 (6H, m), 5.27 (2H, s), 6.60 (1H, s), 6.81 (1H, dd, $J=2.5, 8.8\text{Hz}$), 6.95–7.10 (2H, m), 7.10–7.30 (4H, m), 7.30–7.45 (2H, m), 7.70–7.90 (2H, m).
19-6		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 3.80–3.95 (6H, m), 5.37 (2H, s), 6.55–6.65 (1H, m), 6.82 (1H, dd, $J=2.5, 8.8\text{Hz}$), 7.00–7.25 (6H, m), 7.25–7.40 (2H, m), 7.75–7.95 (2H, m).

[0519]

[Table 42]

Ex. No.	Strc	Physical Data
19-7		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 3.80–3.95 (6H, m), 5.32 (2H, s), 6.55 (1H, s), 6.81 (1H, dd, $J=2.5$, 8.8Hz), 7.00–7.15 (5H, m), 7.25–7.40 (3H, m), 7.75–7.95 (2H, m).
19-8		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 2.16 (3H, s), 3.86 (6H, s), 5.13 (2H, s), 6.40–6.50 (1H, m), 6.81 (1H, dd, $J=2.5$, 8.8Hz), 6.90–7.05 (1H, m), 7.05–7.40 (7H, m), 7.60–7.70 (1H, m), 7.75–7.90 (1H, m).
21-1		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 3.85 (3H, s), 3.92 (3H, s), 5.39 (2H, s), 6.55 (1H, s), 6.87 (1H, dd, $J=2.5$, 8.8Hz), 7.10 (1H, d, $J=2.5\text{Hz}$), 7.30 (1H, d, $J=8.8\text{Hz}$), 7.35–7.65 (5H, m), 8.12 (1H, s).
21-2		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 3.85–4.00 (6H, m), 5.34 (2H, s), 6.50–6.60 (1H, m), 7.10–7.20 (2H, m), 7.35–7.65 (5H, m), 8.14 (1H, s).
21-3		$^1\text{H-NMR}$ (CDCl_3) δ ppm: 2.31 (3H, s), 3.87 (3H, s), 3.92 (3H, s), 5.37 (2H, s), 6.53 (1H, s), 7.03 (1H, s), 7.15 (1H, s), 7.35–7.65 (5H, m), 8.11 (1H, s).

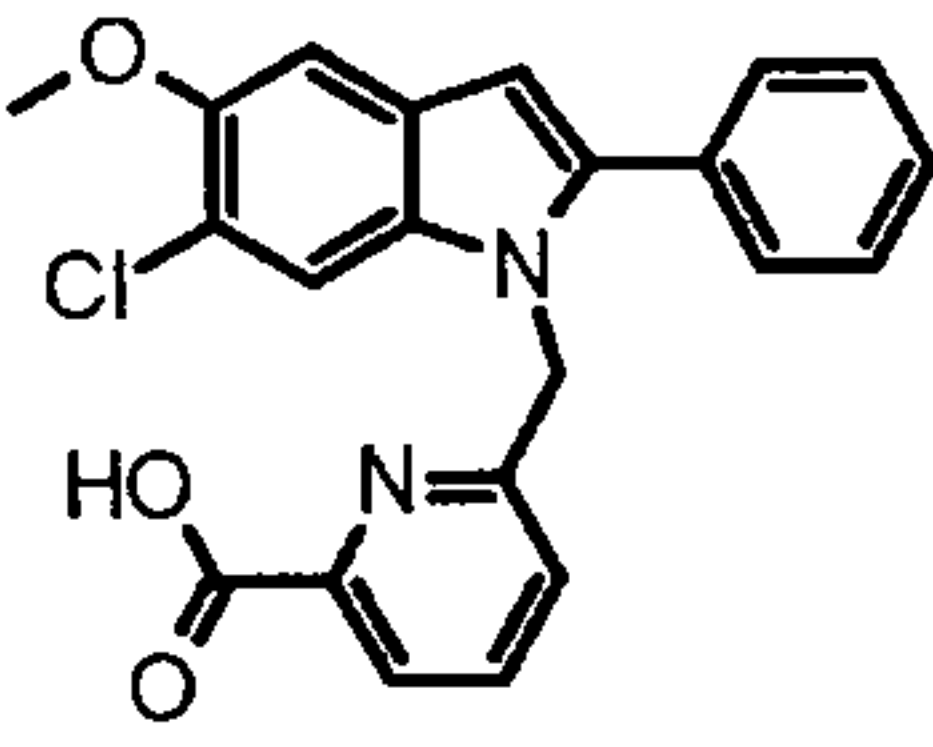
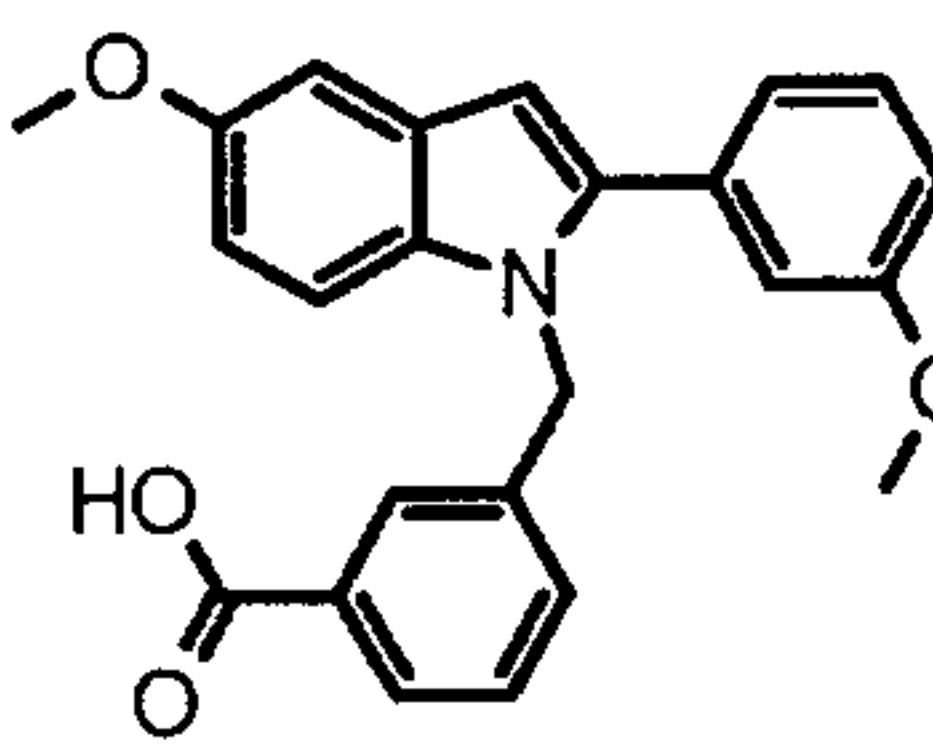
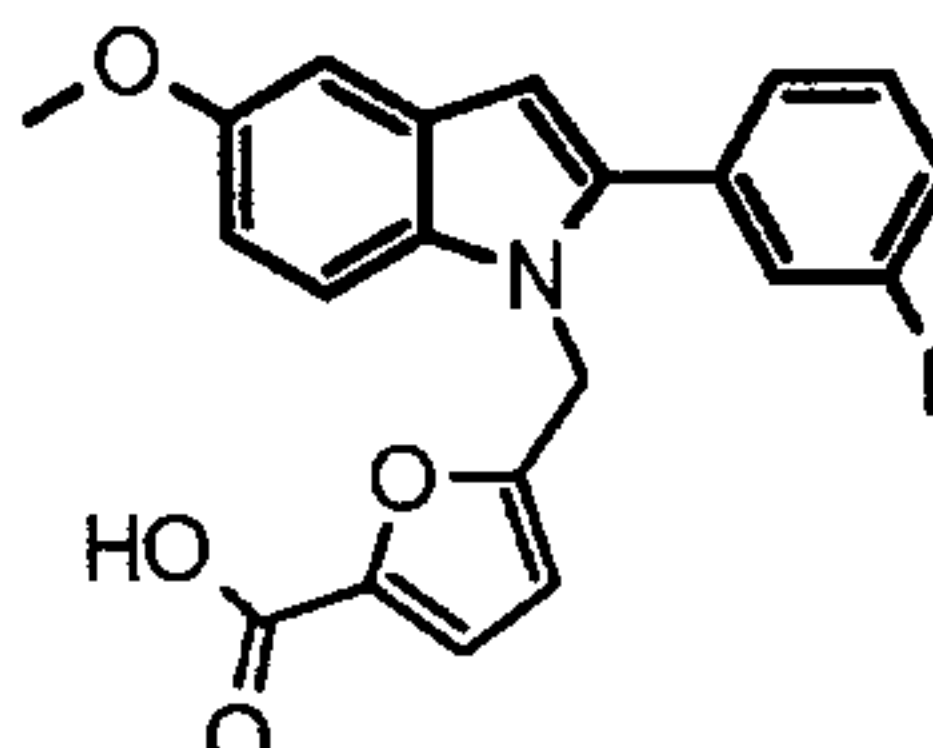
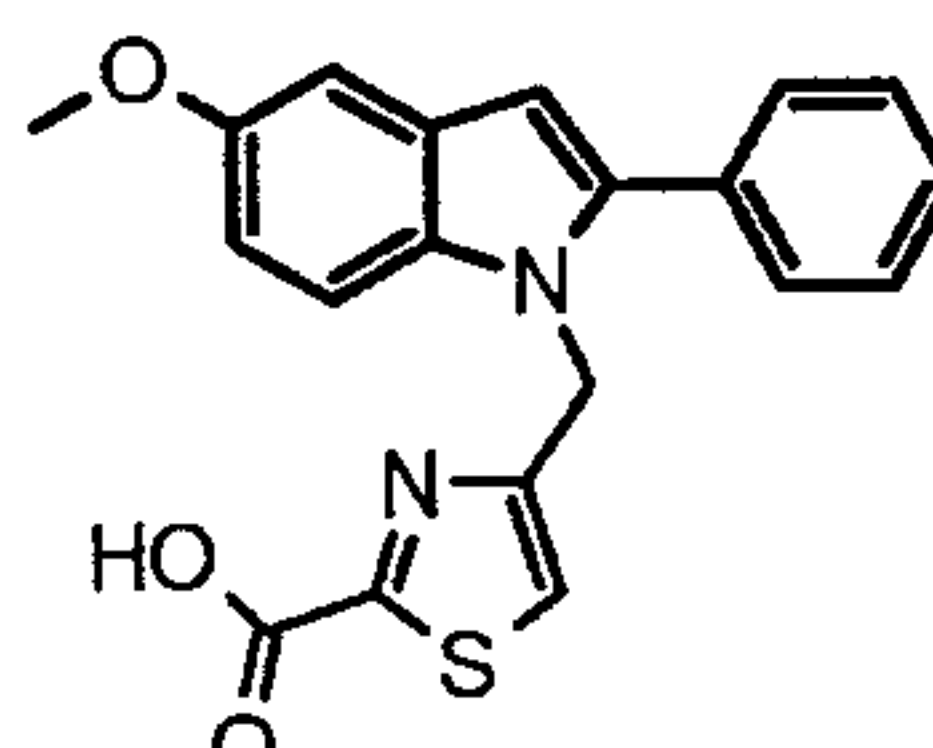
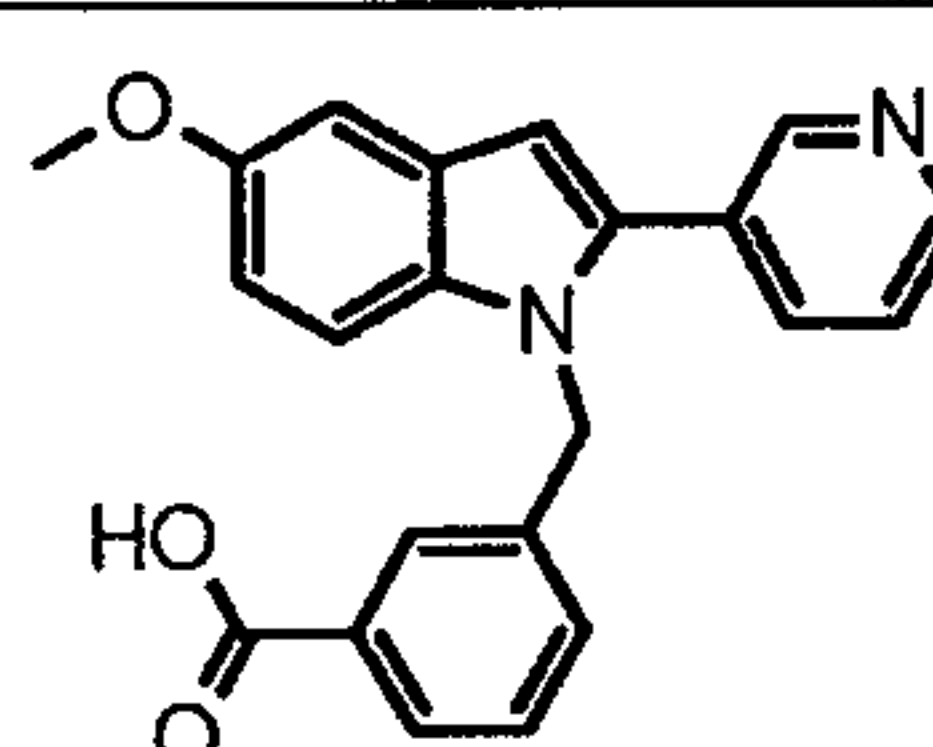
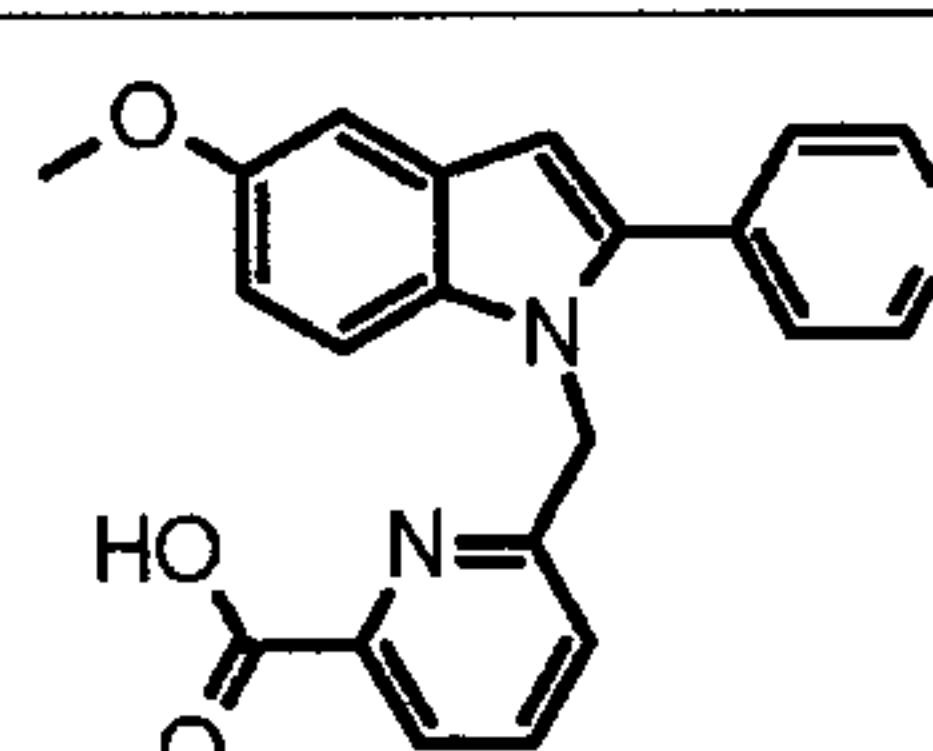
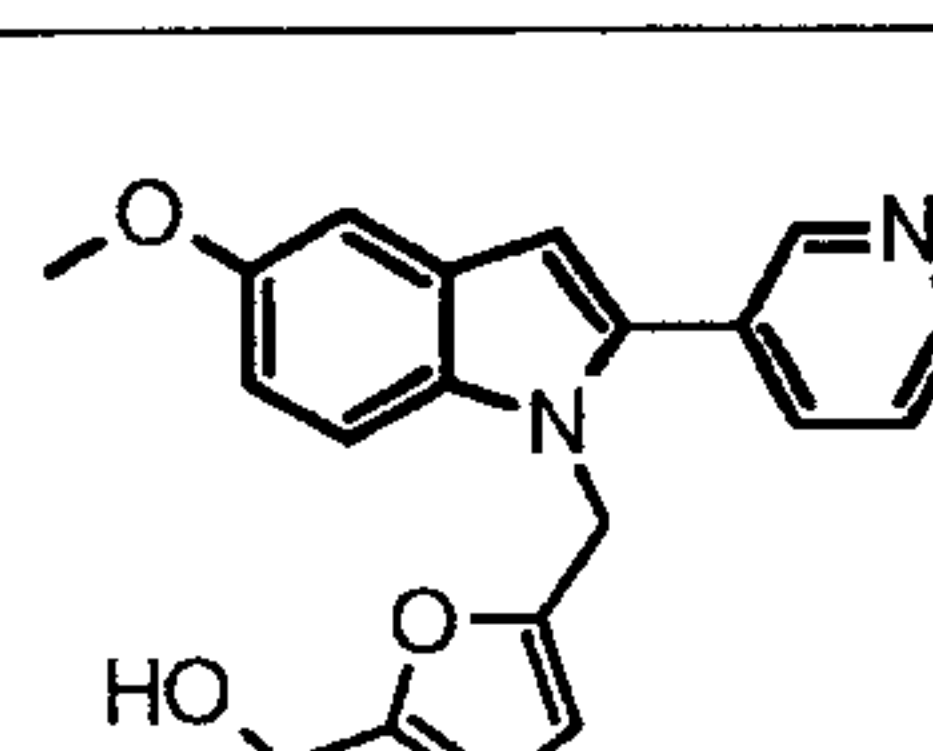
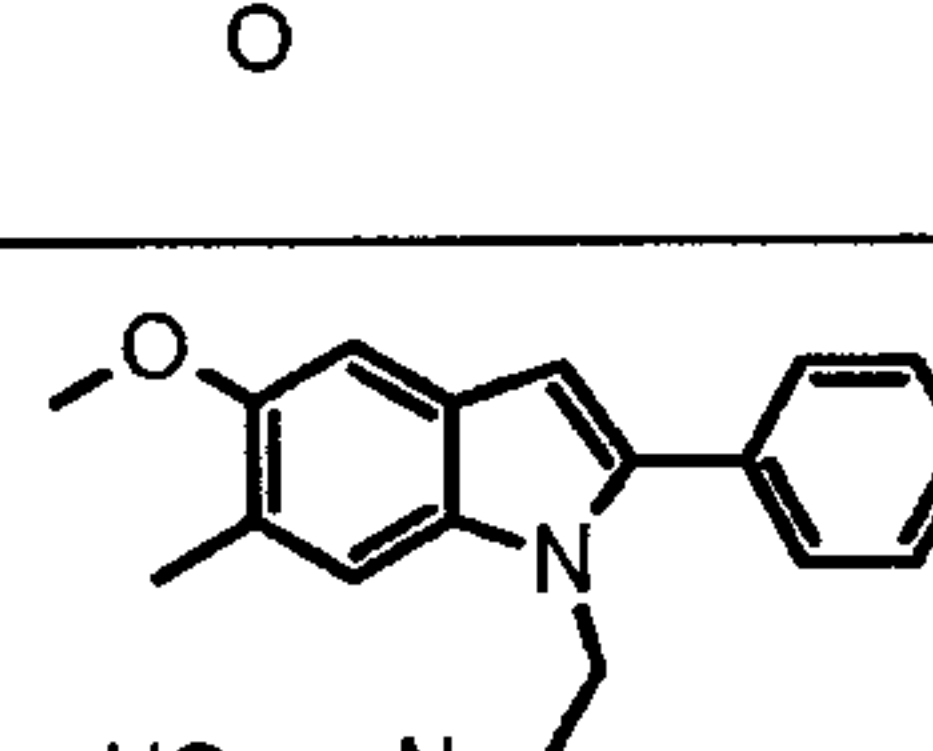
[0520]

[Table 43]

Ex. No.	Strc	Physical Data
25-1		¹ H-NMR (DMSO-d ₆) δ ppm: 3.77 (3H, s), 5.51 (2H, s), 6.67 (1H, s), 6.78 (1H, dd, J=2.5, 8.8Hz), 6.80-6.90 (1H, m), 7.13 (1H, d, J=2.5Hz), 7.28 (1H, d, J=8.8Hz), 7.40-7.60 (3H, m), 7.65-7.75 (1H, m), 7.80-7.95 (2H, m), 13.00-13.50 (1H, br).
25-2		¹ H-NMR (DMSO-d ₆) δ ppm: 3.77 (3H, s), 5.51 (2H, s), 6.68 (1H, s), 6.79 (1H, dd, J=2.4, 8.9Hz), 7.05-7.15 (2H, m), 7.25-7.55 (7H, m), 7.70-7.80 (1H, m), 12.95 (1H, br s).
25-3		¹ H-NMR (DMSO-d ₆) δ ppm: 2.31 (3H, s), 3.77 (3H, s), 5.51 (2H, s), 6.50-6.80 (3H, m), 7.05-7.45 (6H, m), 7.75-7.95 (2H, m), 12.85-13.65 (1H, br).
25-4		¹ H-NMR (DMSO-d ₆) δ ppm: 3.78 (3H, s), 5.34 (2H, s), 6.56 (1H, s), 6.60-6.70 (1H, m), 6.79 (1H, dd, J=2.3, 8.9Hz), 7.15 (1H, d, J=2.3Hz), 7.25-7.65 (5H, m), 7.70-7.90 (2H, m), 12.85-13.50 (1H, br).
25-5		¹ H-NMR (DMSO-d ₆) δ ppm: 3.77 (3H, s), 5.29 (2H, s), 6.50-6.55 (1H, m), 6.79 (1H, dd, J=2.4, 8.9Hz), 6.95-7.05 (1H, m), 7.10-7.15 (1H, m), 7.25-7.55 (6H, m), 7.55-7.65 (1H, m), 7.65-7.75 (1H, m), 12.60-13.20 (1H, br).
25-6		¹ H-NMR (DMSO-d ₆) δ ppm: 3.77 (3H, s), 5.32 (2H, s), 6.06 (1H, d, J=3.5Hz), 6.55 (1H, s), 6.84 (1H, dd, J=2.5, 8.8Hz), 7.01 (1H, d, J=3.5Hz), 7.05-7.15 (1H, m), 7.25-7.60 (5H, m), 12.99 (1H, br s).
25-7		¹ H-NMR (DMSO-d ₆) δ ppm: 2.17 (3H, s), 3.77 (3H, s), 5.28 (2H, s), 6.47 (1H, s), 6.55-6.65 (1H, m), 6.75 (1H, dd, J=2.5, 8.8Hz), 7.13 (1H, d, J=2.5Hz), 7.15-7.40 (5H, m), 7.70-7.90 (2H, m), 13.00-13.35 (1H, br).
25-8		¹ H-NMR (DMSO-d ₆) δ ppm: 3.77 (3H, s), 5.53 (2H, s), 6.72 (1H, s), 6.79 (1H, dd, J=2.5, 8.9Hz), 6.85-6.95 (1H, m), 7.15 (1H, d, J=2.5Hz), 7.32 (1H, d, J=8.9Hz), 7.40-7.50 (1H, m), 7.80-7.95 (2H, m), 8.00-8.15 (1H, m), 8.58 (1H, dd, J=1.5, 4.8Hz), 8.75-8.85 (1H, m), 13.24 (1H, br s).

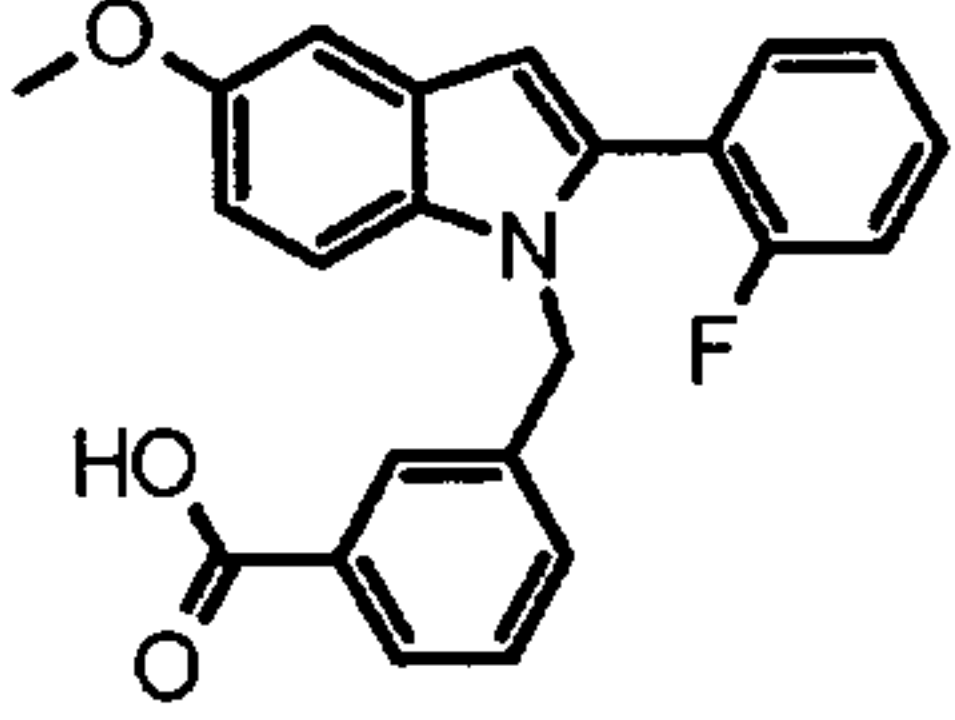
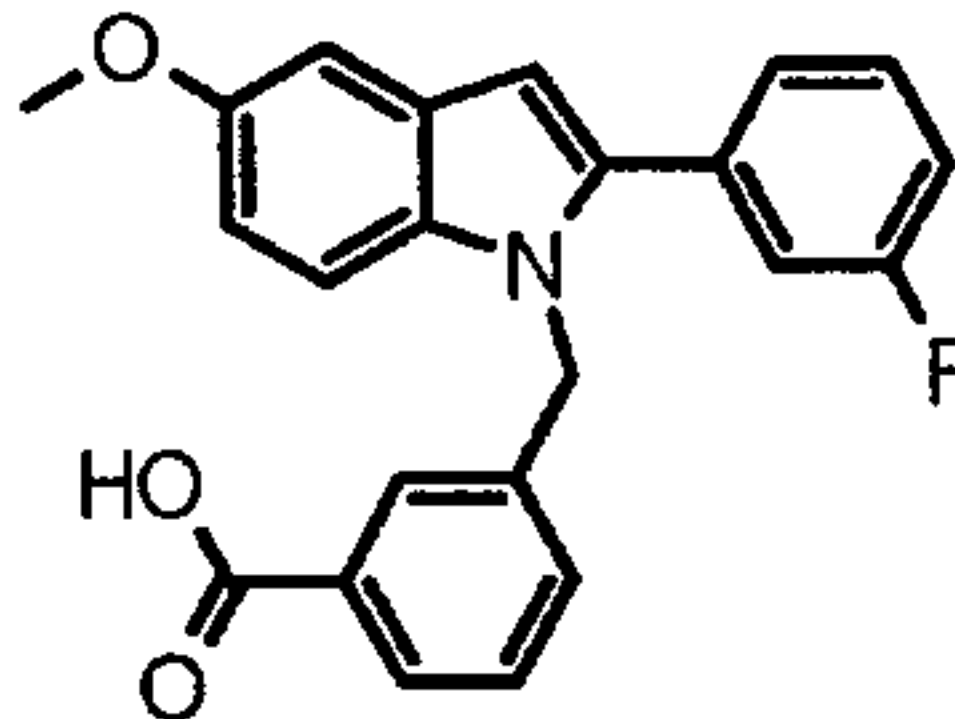
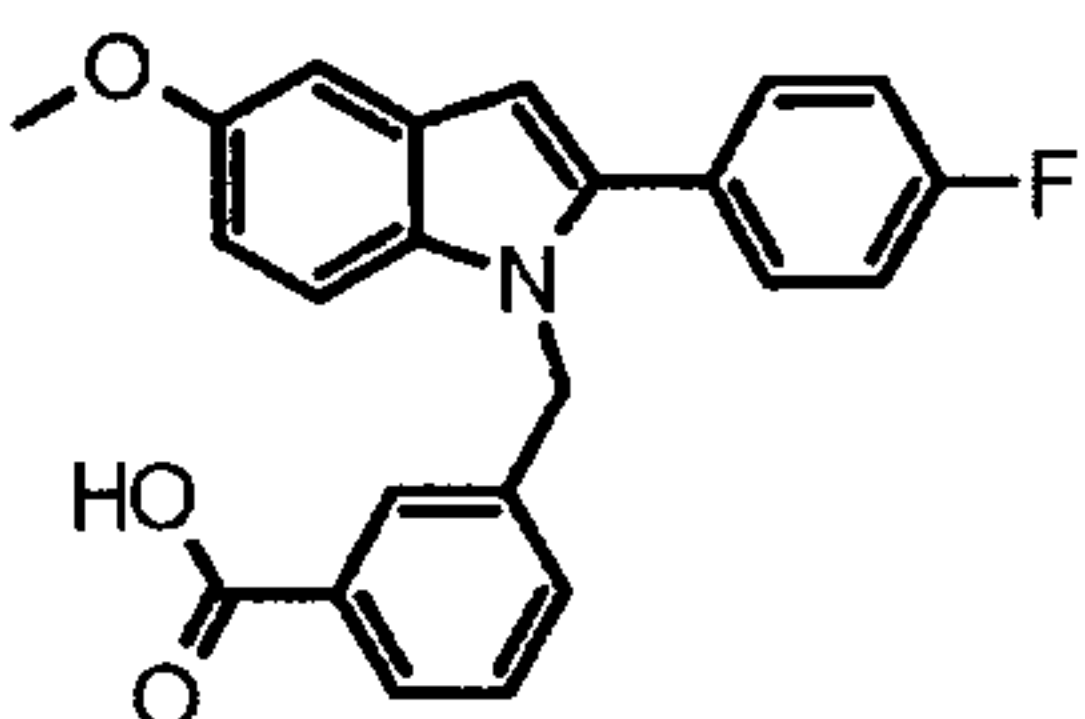
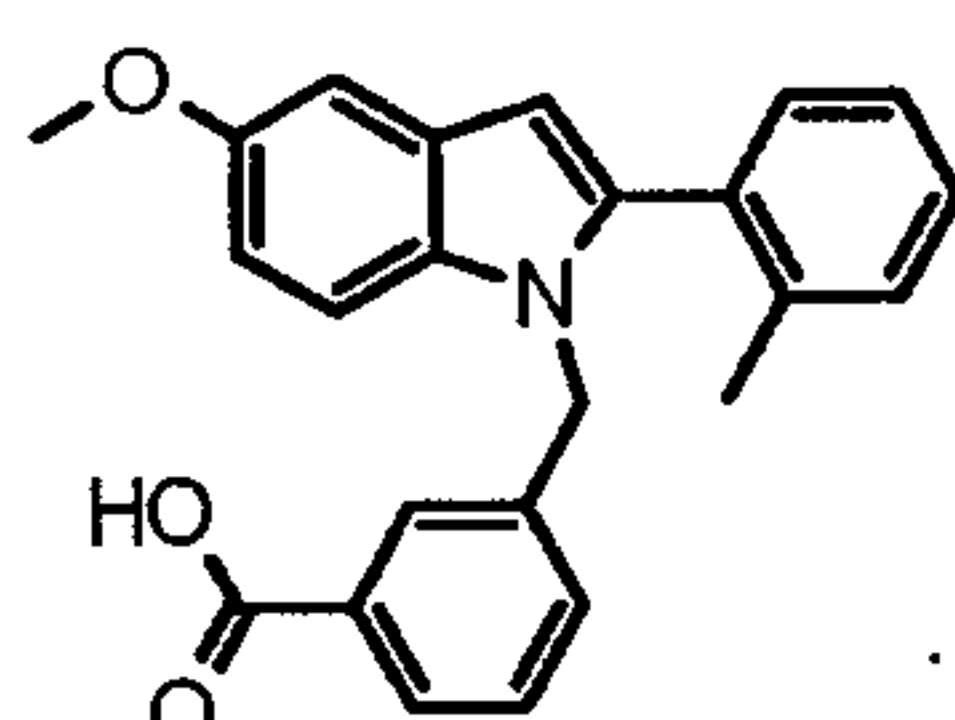
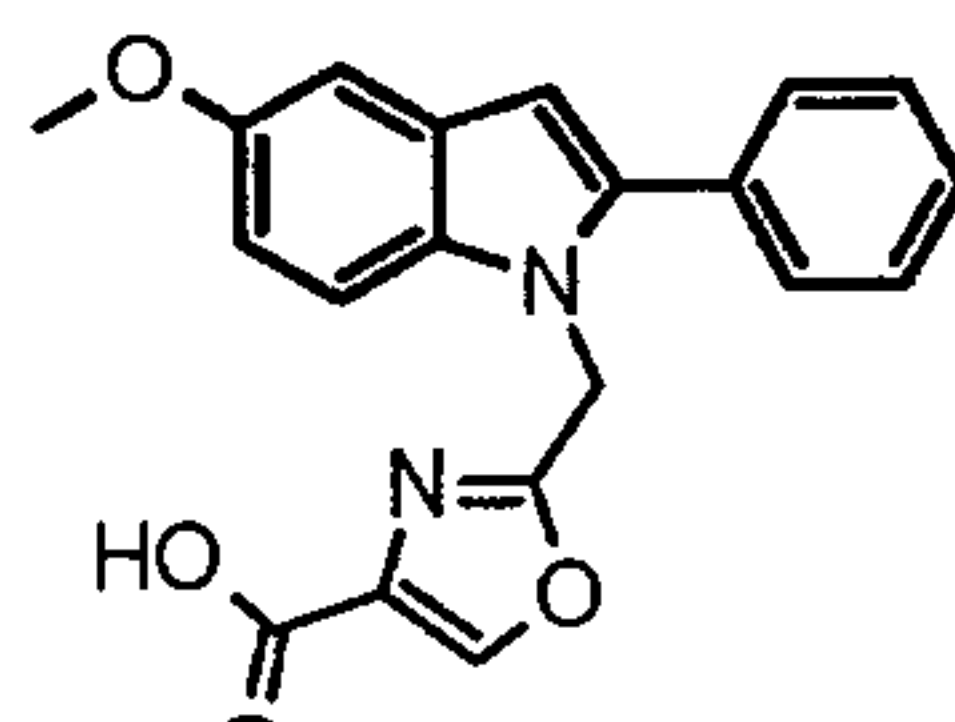
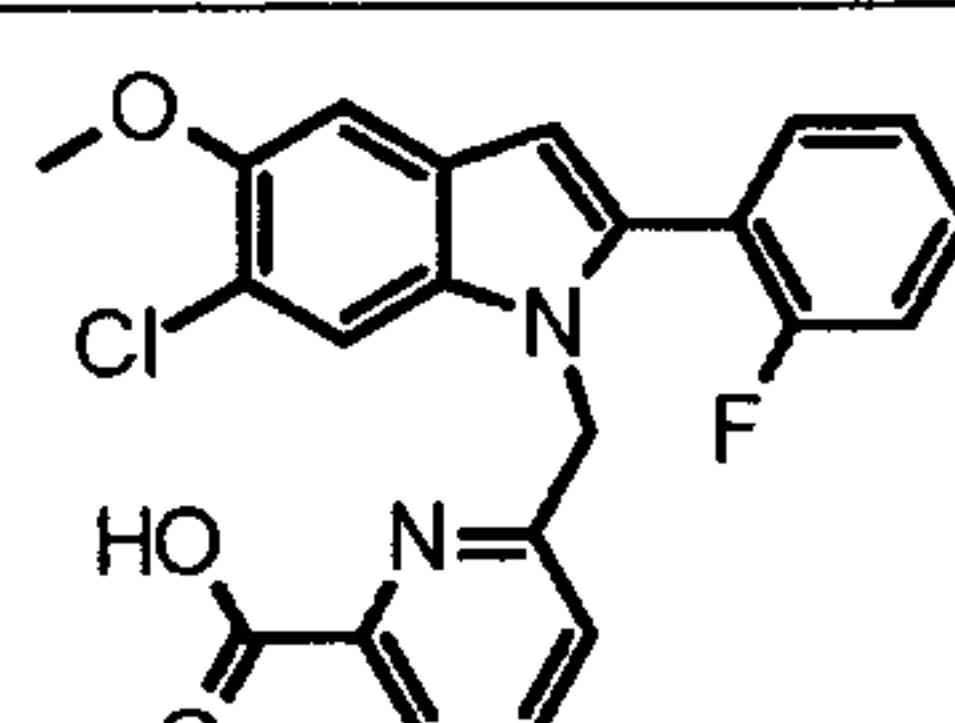
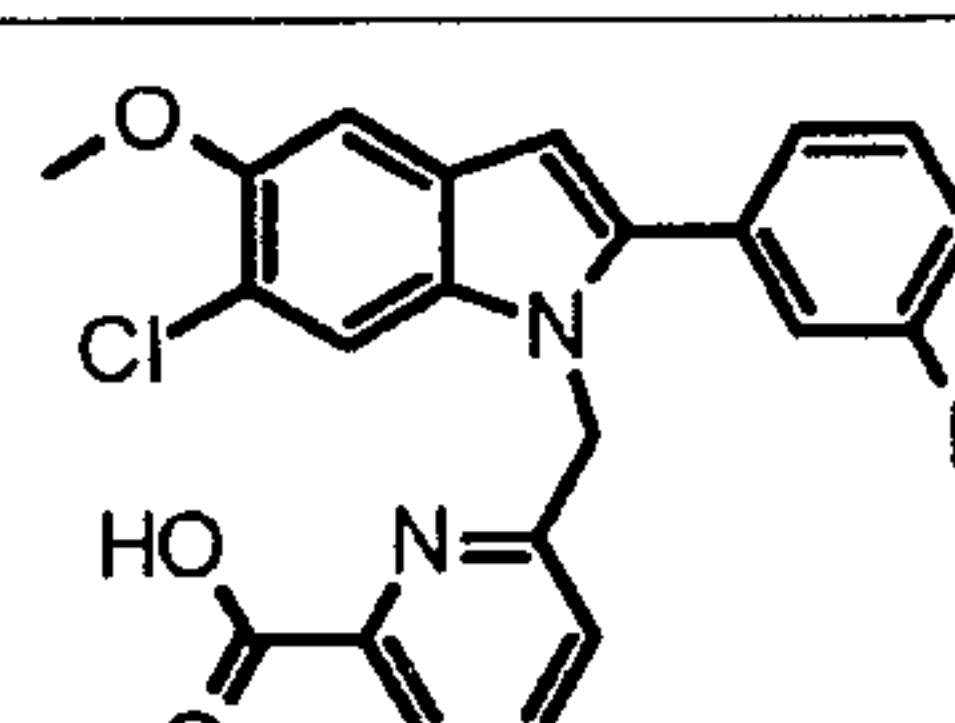
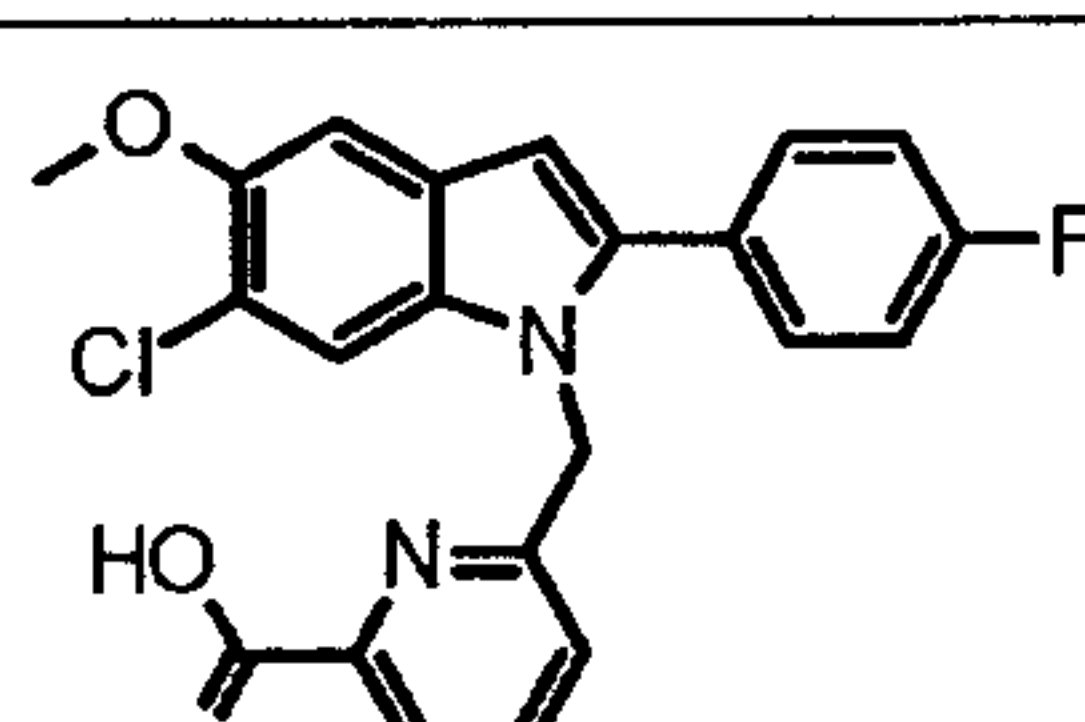
[0521]

[Table 44]

Ex. No.	Strc	Physical Data
25-9		$^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 3.87 (3H, s), 5.55 (2H, s), 6.60–6.80 (2H, m), 7.32 (1H, s), 7.35–7.50 (3H, m), 7.50–7.60 (3H, m), 7.75–7.95 (2H, m), 12.80–13.70 (1H, br).
25-10		$^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 3.69 (3H, s), 3.77 (3H, s), 5.50 (2H, s), 6.55–6.65 (1H, m), 6.76 (1H, dd, $J=2.5, 8.8$), 6.90–7.20 (5H, m), 7.26 (1H, d, $J=8.8\text{Hz}$), 7.30–7.45 (2H, m), 7.45–7.55 (1H, m), 7.70–7.80 (1H, m), 12.96 (1H, br s).
25-11		$^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 3.77 (3H, s), 5.44 (2H, s), 6.23 (1H, d, $J=3.5\text{Hz}$), 6.61 (1H, s), 6.83 (1H, dd, $J=2.5, 8.8\text{Hz}$), 7.00–7.15 (2H, m), 7.20–7.35 (1H, m), 7.35–7.60 (4H, m), 13.04 (1H, br s).
25-12		$^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 3.76 (3H, s), 5.50 (2H, s), 6.57 (1H, s), 6.77 (1H, dd, $J=2.5, 8.8\text{Hz}$), 7.11 (1H, d, $J=2.5\text{Hz}$), 7.33 (1H, d, $J=8.8\text{Hz}$), 7.35–7.55 (4H, m), 7.55–7.70 (2H, m), 13.60–14.50 (1H, br).
25-13		$^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 3.78 (3H, s), 5.57 (2H, s), 6.75–6.90 (2H, m), 7.00–7.20 (2H, m), 7.30–7.50 (3H, m), 7.70–7.85 (2H, m), 8.15–8.30 (1H, m), 8.65–8.90 (2H, m).
25-14		$^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 3.77 (3H, s), 5.61 (2H, s), 6.75–6.90 (3H, m), 7.16 (1H, d, $J=2.5\text{Hz}$), 7.33 (1H, d, $J=9.0\text{Hz}$), 7.60–7.70 (2H, m), 7.80–7.95 (2H, m), 8.55–8.65 (2H, m), 13.25 (1H, br s).
25-15		$^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 3.77 (3H, s), 5.44 (2H, s), 6.24 (1H, d, $J=3.4\text{Hz}$), 6.65 (1H, s), 6.84 (1H, dd, $J=2.3, 8.9\text{Hz}$), 7.06 (1H, d, $J=3.4\text{Hz}$), 7.11 (1H, d, $J=2.3\text{Hz}$), 7.45–7.60 (2H, m), 7.95–8.05 (1H, m), 8.60–8.70 (1H, m), 8.75–8.85 (1H, m), 13.03 (1H, br s).
25-16		$^1\text{H-NMR}$ (DMSO-d_6) δ ppm: 2.18 (3H, s), 3.81 (3H, s), 5.51 (2H, s), 6.55–6.70 (2H, m), 7.10 (1H, s), 7.15 (1H, s), 7.30–7.60 (5H, m), 7.75–7.90 (2H, m), 12.95–13.50 (1H, br).

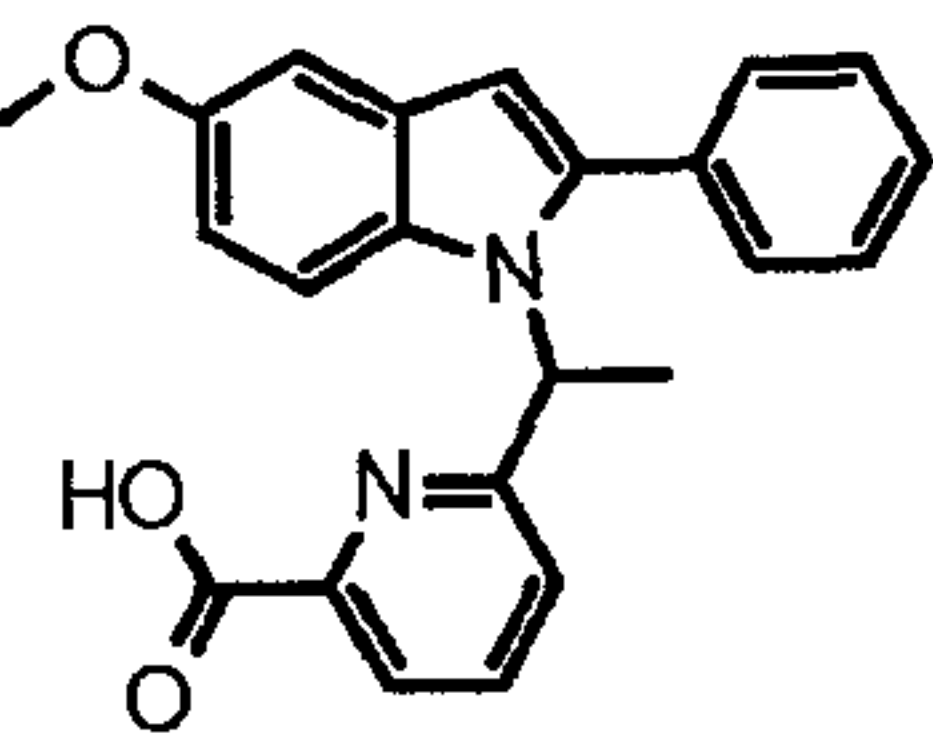
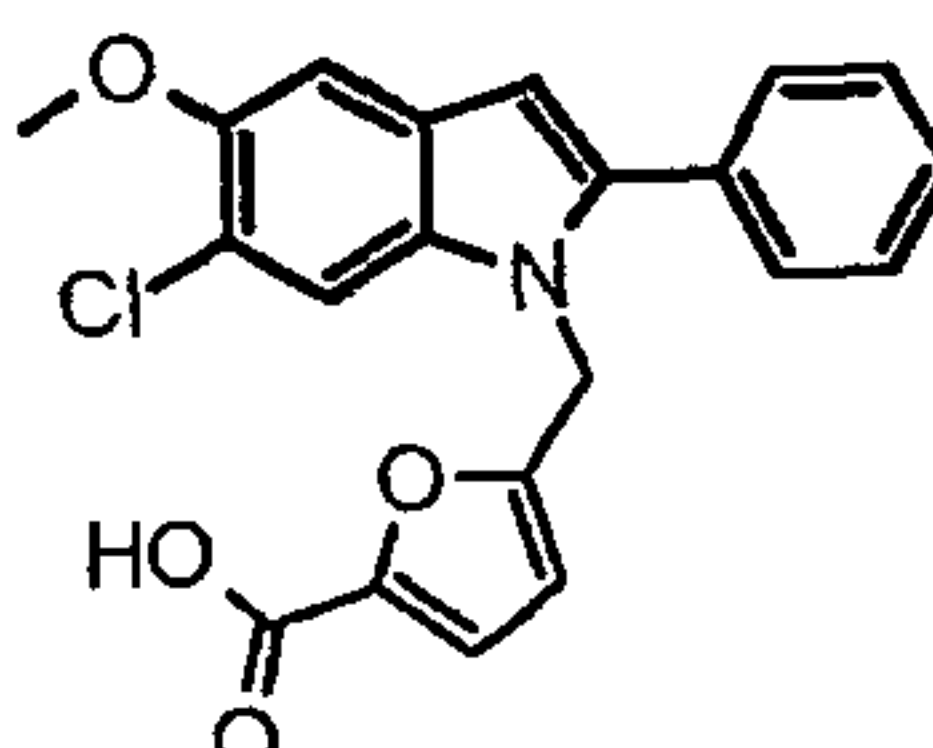
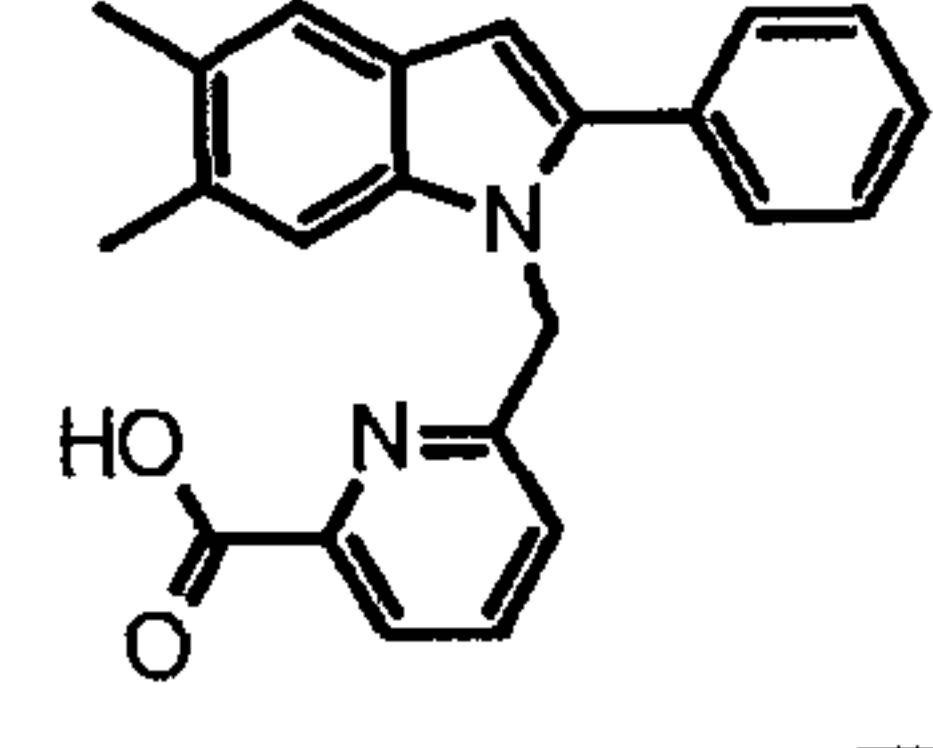
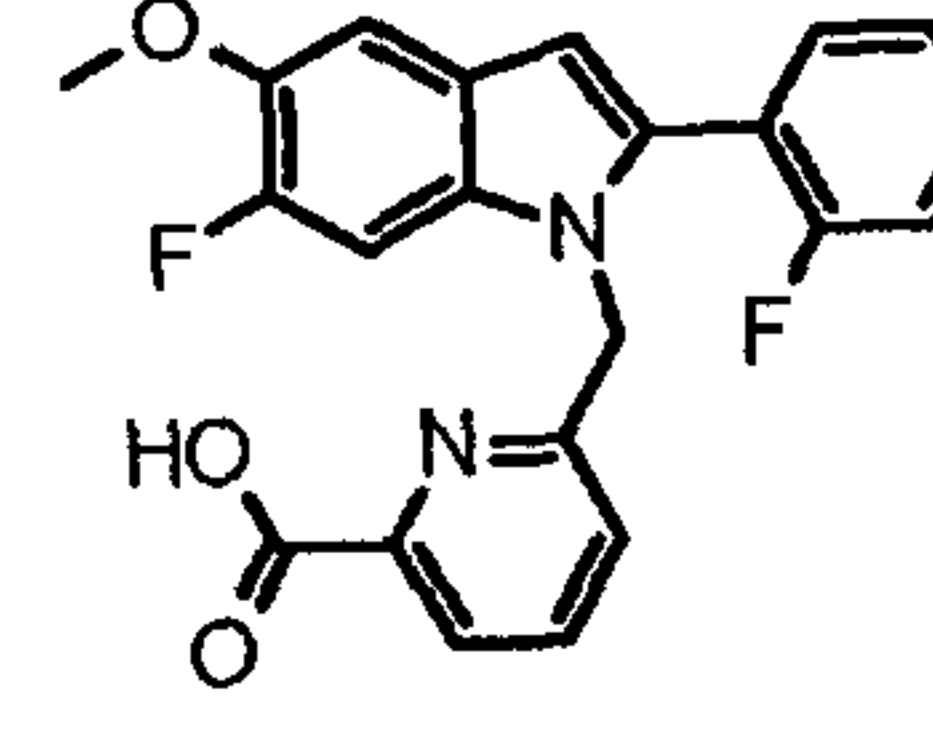
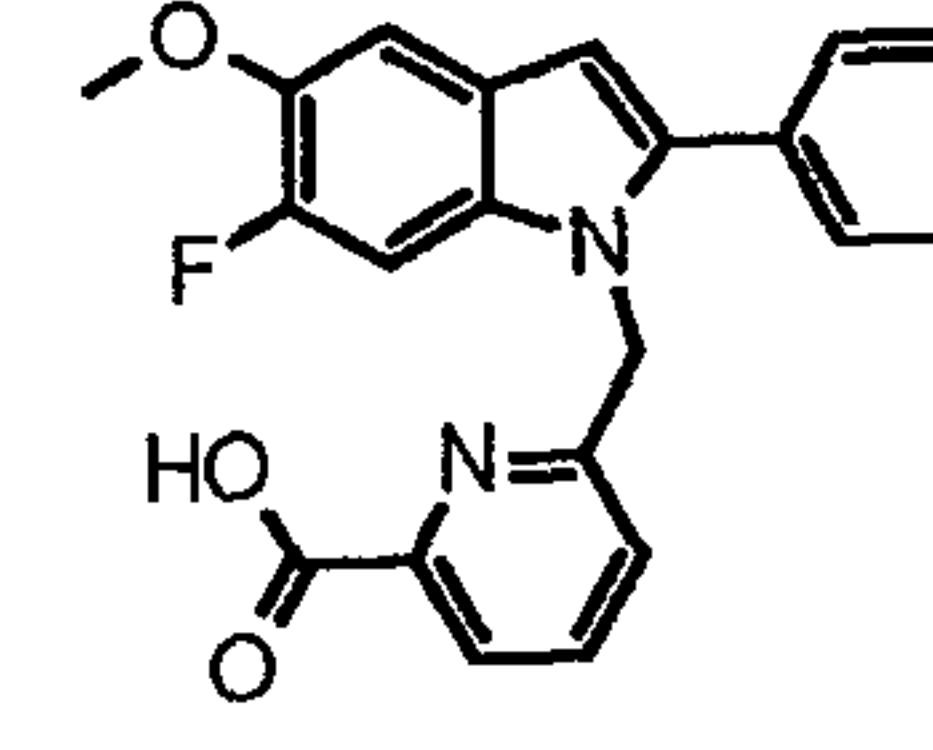
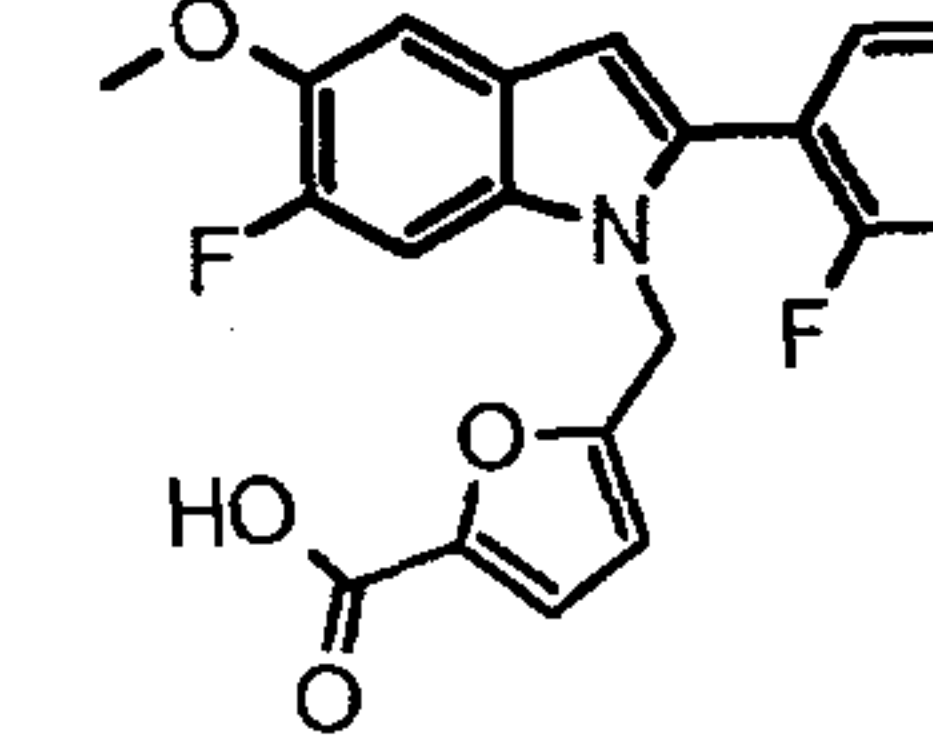
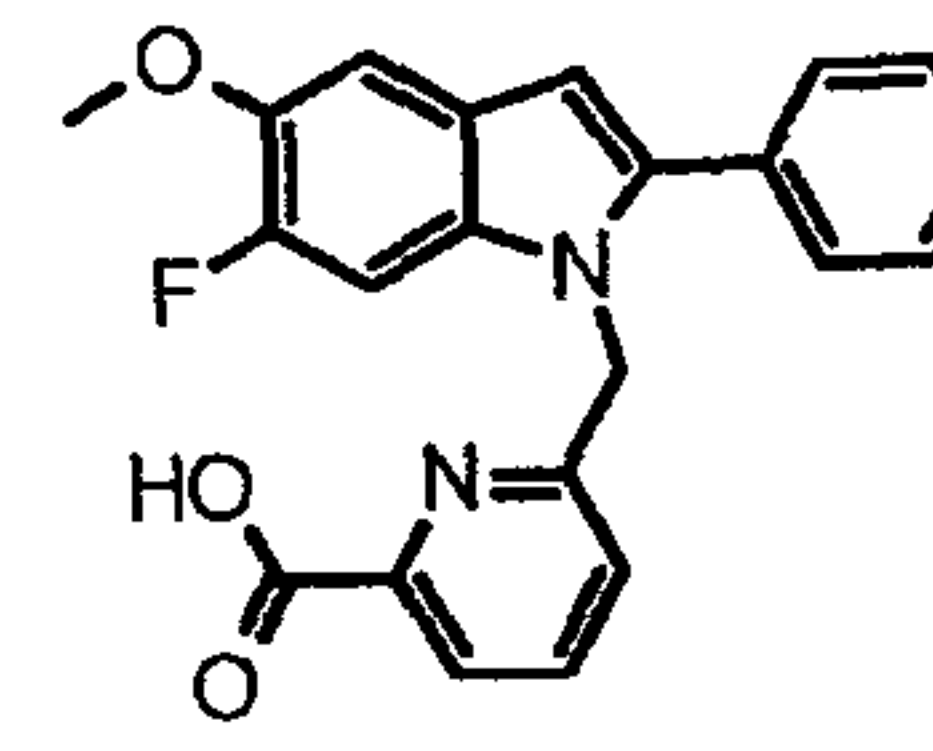
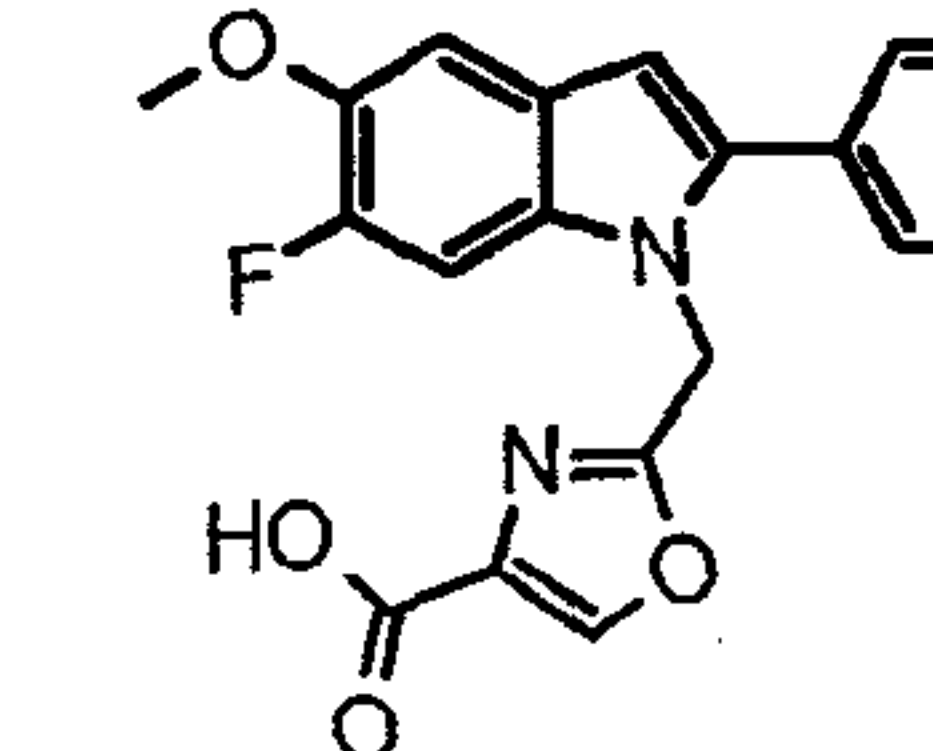
[0522]

[Table 45]

Ex. No.	Strc	Physical Data
25-17		¹ H-NMR (DMSO-d ₆) δ ppm: 3.77 (3H, s), 5.36 (2H, s), 6.59 (1H, s), 6.78 (1H, dd, J=2.3, 8.9Hz), 7.00–7.10 (1H, m), 7.13 (1H, d, J=2.3Hz), 7.20–7.55 (7H, m), 7.65–7.80 (1H, m), 12.91 (1H, br s).
25-18		¹ H-NMR (DMSO-d ₆) δ ppm: 3.77 (3H, s), 5.52 (2H, s), 6.67 (1H, s), 6.79 (1H, dd, J=2.4, 8.9Hz), 7.05–7.15 (2H, m), 7.15–7.55 (7H, m), 7.70–7.80 (1H, m), 12.94 (1H, s).
25-19		¹ H-NMR (DMSO-d ₆) δ ppm: 3.77 (3H, s), 5.48 (2H, s), 6.55–6.65 (1H, m), 6.77 (1H, dd, J=2.5, 8.8Hz), 7.00–7.15 (2H, m), 7.20–7.60 (7H, m), 7.70–7.80 (1H, m), 12.94 (1H, br s).
25-20		¹ H-NMR (DMSO-d ₆) δ ppm: 2.11 (3H, s), 3.77 (3H, s), 5.24 (2H, s), 6.40–6.50 (1H, m), 6.76 (1H, dd, J=2.5, 8.8Hz), 6.95–7.15 (2H, m), 7.20–7.40 (7H, m), 7.65–7.80 (1H, m), 12.90 (1H, s).
25-21		¹ H-NMR (DMSO-d ₆) δ ppm: 3.77 (3H, s), 5.52 (2H, s), 6.50–6.60 (1H, m), 6.83 (1H, dd, J=2.5, 8.8Hz), 7.05–7.15 (1H, m), 7.30–7.65 (6H, m), 8.66 (1H, s), 12.50–13.55 (1H, br).
25-22		¹ H-NMR (DMSO-d ₆) δ ppm: 3.87 (3H, s), 5.44 (2H, s), 6.60–6.75 (2H, m), 7.20–7.70 (6H, m), 7.75–7.90 (2H, m), 12.50–14.00 (1H, br).
25-23		¹ H-NMR (DMSO-d ₆) δ ppm: 3.86 (3H, s), 5.55 (2H, s), 6.65–6.75 (1H, m), 6.80–6.95 (1H, m), 7.15–7.30 (1H, m), 7.32 (1H, s), 7.35–7.65 (4H, m), 7.80–7.95 (2H, m), 12.50–14.00 (1H, br).
25-24		¹ H-NMR (DMSO-d ₆) δ ppm: 3.86 (3H, s), 5.52 (2H, s), 6.60–6.70 (1H, m), 6.75–6.90 (1H, m), 7.20–7.40 (3H, m), 7.50–7.70 (3H, m), 7.80–7.95 (2H, m), 13.20 (1H, br s).

[0523]

[Table 46]

Ex. No.	Strc	Physical Data
25-25		¹ H-NMR (DMSO-d ₆) δ ppm: 1.93 (3H, d, J=7.0Hz), 3.73 (3H, s), 5.72 (1H, q, J=7.0Hz), 6.45-6.70 (2H, m), 6.90 (1H, d, J=9.0Hz), 7.05-7.20 (2H, m), 7.35-7.70 (5H, m), 7.80-8.00 (2H, m). ESI-MS (m/z) : 373 (M+H) ⁺
25-26		¹ H-NMR (DMSO-d ₆) δ ppm: 3.86 (3H, s), 5.44 (2H, s), 6.16 (1H, d, J=3.3Hz), 6.55-6.65 (1H, m), 7.05 (1H, d, J=3.3Hz), 7.28 (1H, s), 7.40-7.65 (5H, m), 7.72 (1H, s), 12.50-13.50 (1H, br).
25-27		¹ H-NMR (DMSO-d ₆) δ ppm: 2.25 (3H, s), 2.28 (3H, s), 5.51 (2H, s), 6.55-6.70 (2H, m), 7.13 (1H, s), 7.30-7.60 (6H, m), 7.75-7.95 (2H, m), 12.50-14.00 (1H, br).
25-28		¹ H-NMR (DMSO-d ₆) δ ppm: 3.86 (3H, s), 5.41 (2H, s), 6.50-6.70 (2H, m), 7.15-7.60 (6H, m), 7.70-7.90 (2H, m). ESI-MS (m/z) : 395 (M+H) ⁺
25-29		¹ H-NMR (DMSO-d ₆) δ ppm: 3.85 (3H, s), 5.53 (2H, s), 6.65-6.75 (1H, m), 6.75-6.90 (1H, m), 7.15-7.60 (6H, m), 7.75-7.95 (2H, m). ESI-MS (m/z) : 395 (M+H) ⁺
25-30		¹ H-NMR (DMSO-d ₆) δ ppm: 3.85 (3H, s), 5.32 (2H, s), 6.07 (1H, d, J=3.5Hz), 6.58 (1H, s), 7.01 (1H, d, J=3.5Hz), 7.25-7.45 (3H, m), 7.45-7.65 (3H, m), 13.02 (1H, br s).
25-31		¹ H-NMR (DMSO-d ₆) δ ppm: 3.85 (3H, s), 5.49 (2H, s), 6.55-6.80 (2H, m), 7.20-7.45 (4H, m), 7.55-7.70 (2H, m), 7.70-7.95 (2H, m). ESI-MS (m/z) : 395 (M+H) ⁺
25-32		¹ H-NMR (DMSO-d ₆) δ ppm: 3.85 (3H, s), 5.52 (2H, s), 6.58 (1H, s), 7.30 (1H, d, J=8.5Hz), 7.35-7.60 (6H, m), 8.62 (1H, s). ESI-MS (m/z) : 367 (M+H) ⁺

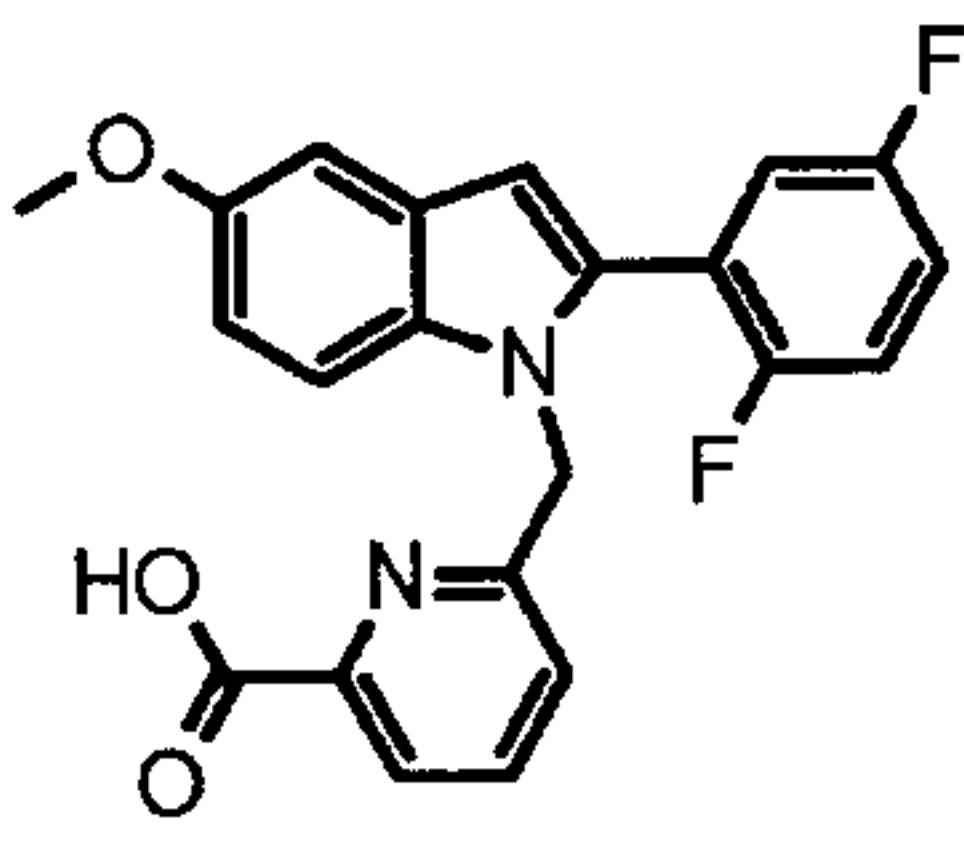
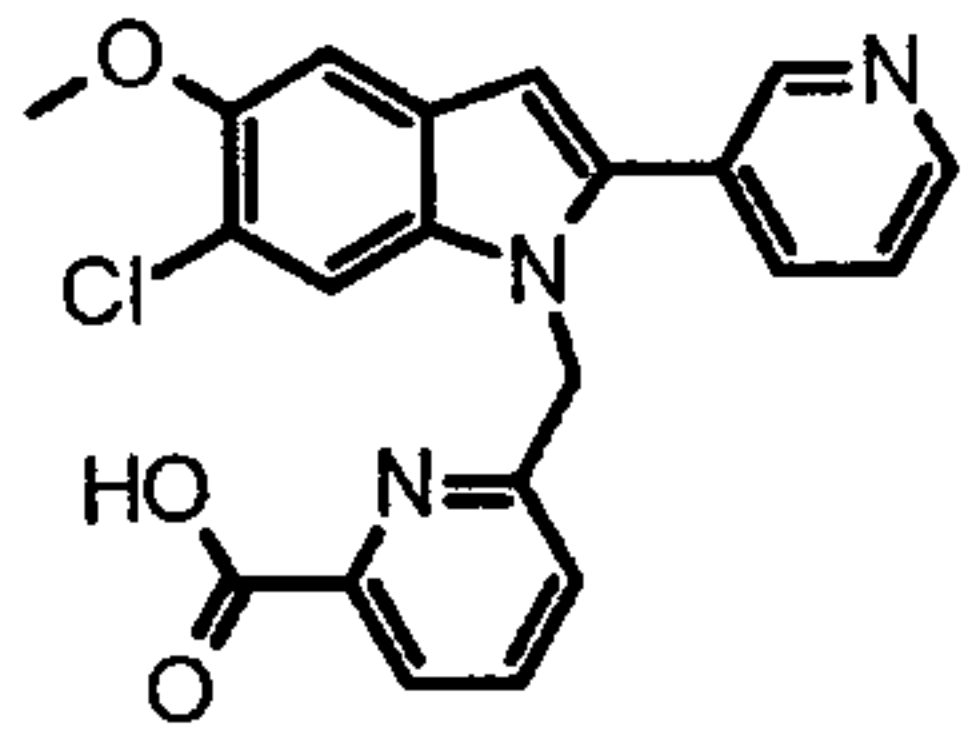
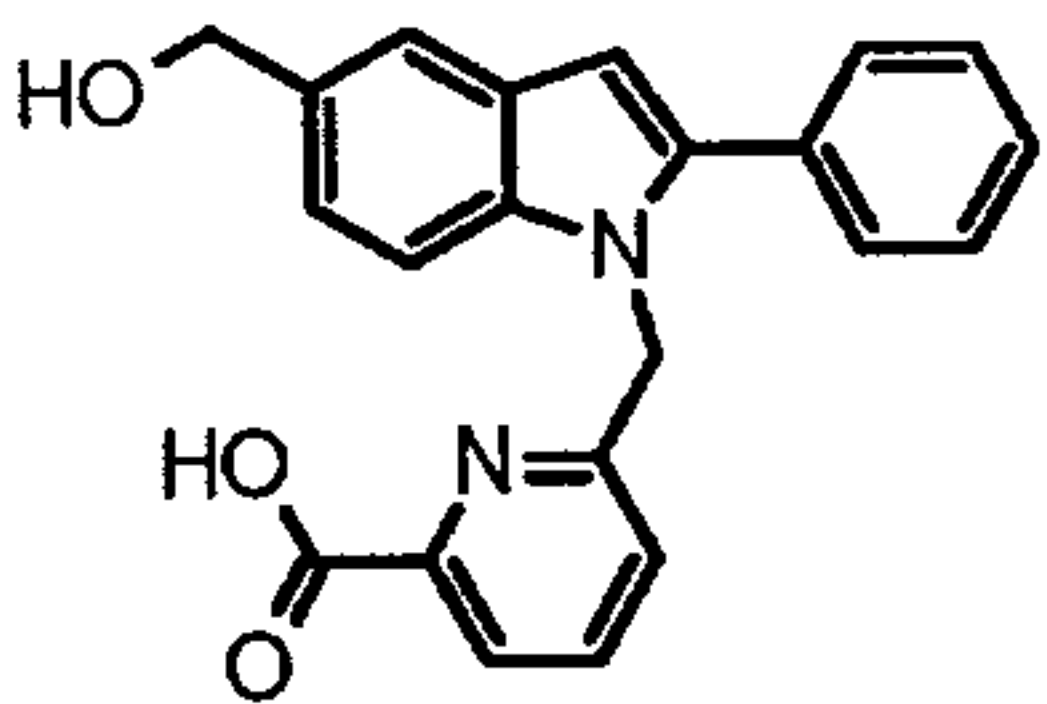
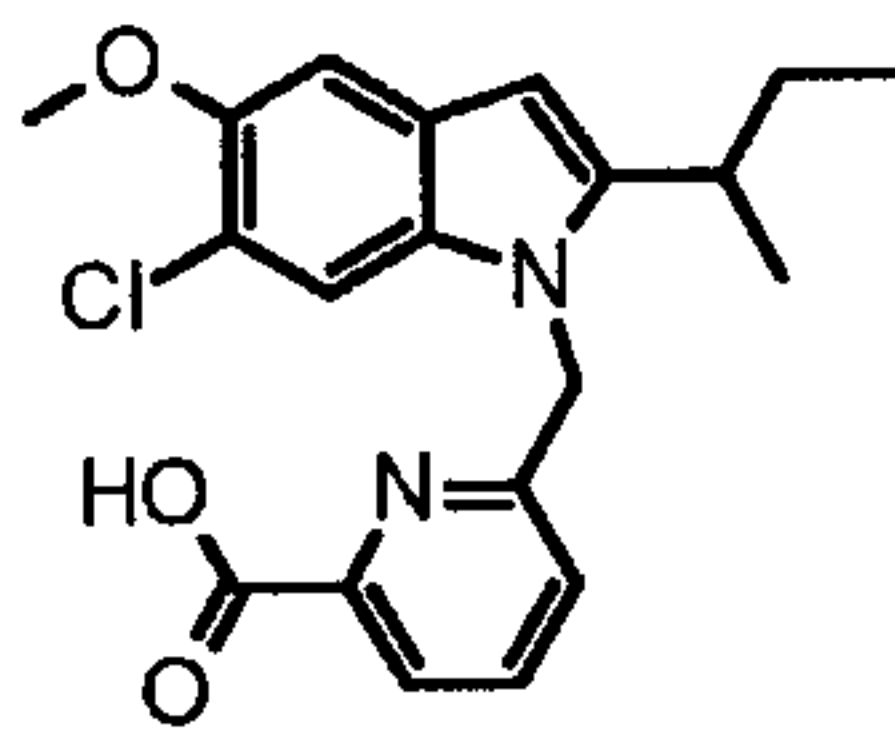
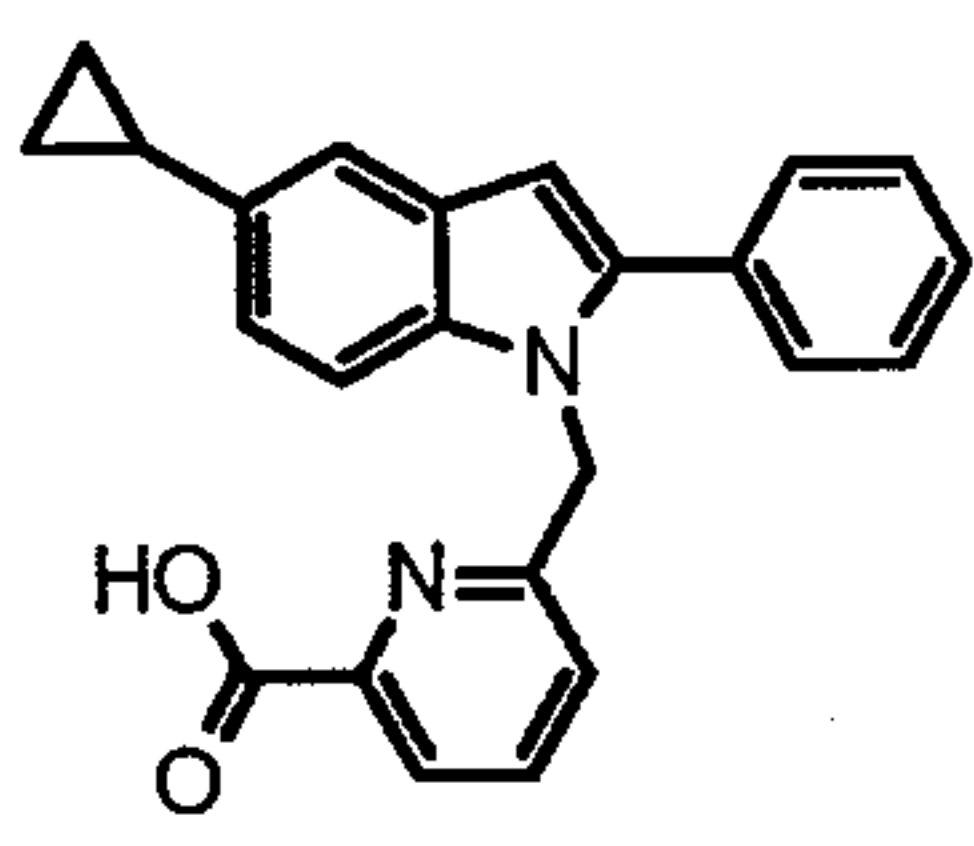
[0524]

[Table 47]

Ex. No.	Strc	Physical Data
25-33		¹ H-NMR (DMSO-d ₆) δ ppm: 3.86 (3H, s), 5.55 (2H, s), 6.82 (1H, s), 7.05–7.20 (1H, m), 7.35 (1H, d, J=8.5Hz), 7.49 (1H, d, J=12.0Hz), 7.65–8.00 (3H, m), 8.40–8.55 (1H, m), 8.65–8.80 (1H, m), 9.00–9.15 (1H, m). ESI-MS (m/z) : 378 (M+H) ⁺
25-34		¹ H-NMR (DMSO-d ₆) δ ppm: 3.86 (3H, s), 5.60 (2H, s), 6.42 (1H, d, J=7.8Hz), 6.70–6.80 (1H, m), 7.25–7.50 (3H, m), 7.60–7.90 (4H, m). ESI-MS (m/z) : 399, 401 (M+H) ⁺
25-35		¹ H-NMR (DMSO-d ₆) δ ppm: 1.38 (3H, t, J=6.9Hz), 4.11 (2H, q, J=6.9Hz), 5.52 (2H, s), 6.45–6.60 (1H, m), 6.60–6.70 (1H, m), 7.32 (1H, s), 7.35–7.60 (6H, m), 7.65–7.85 (2H, m).
25-36		¹ H-NMR (DMSO-d ₆) δ ppm: 2.24 (3H, s), 3.80 (3H, s), 5.38 (2H, s), 6.13 (1H, d, J=3.5Hz), 6.45–6.55 (1H, m), 7.00–7.15 (2H, m), 7.33 (1H, s), 7.35–7.65 (5H, m), 12.50–13.50 (1H, br).
25-37		¹ H-NMR (DMSO-d ₆) δ ppm: 3.86 (3H, s), 5.63 (2H, s), 6.65–6.90 (3H, m), 7.27 (1H, s), 7.60–8.10 (5H, m). ESI-MS (m/z) : 383, 385 (M+H) ⁺
25-38		¹ H-NMR (DMSO-d ₆) δ ppm: 3.84 (3H, s), 5.53 (2H, s), 6.32 (1H, d, J=3.5Hz), 6.60–6.70 (1H, m), 6.85–6.95 (1H, m), 7.09 (1H, d, J=3.5Hz), 7.24 (1H, s), 7.70–7.90 (2H, m), 8.05–8.15 (1H, m), 13.07 (1H, br s).
25-39		¹ H-NMR (DMSO-d ₆) δ ppm: 2.19 (3H, s), 3.81 (3H, s), 5.56 (2H, s), 6.55–6.75 (2H, m), 7.07 (1H, s), 7.15 (1H, s), 7.25–7.40 (1H, m), 7.55–7.90 (4H, m). ESI-MS (m/z) : 379 (M+H) ⁺
25-40		¹ H-NMR (DMSO-d ₆) δ ppm: 2.24 (3H, s), 3.80 (3H, s), 5.45 (2H, s), 6.52 (1H, s), 7.07 (1H, s), 7.25 (1H, s), 7.35–7.70 (5H, m), 8.42 (1H, s). ESI-MS (m/z) : 363 (M+H) ⁺

[0525]

[Table 48]

Ex. No.	Strc	Physical Data
25-41		¹ H-NMR (DMSO-d ₆) δ ppm: 3.77 (3H, s), 5.43 (2H, s), 6.66 (1H, s), 6.75–6.90 (2H, m), 7.14 (1H, d, J=2.5Hz), 7.25–7.70 (4H, m), 7.75–7.95 (2H, m). ESI-MS (m/z) : 395 (M+H) ⁺
25-42		¹ H-NMR (DMSO-d ₆) δ ppm: 3.87 (3H, s), 5.55 (2H, s), 6.75 (1H, s), 6.85–7.00 (1H, m), 7.33 (1H, s), 7.35–7.55 (1H, m), 7.63 (1H, s), 7.80–7.95 (2H, m), 8.00–8.15 (1H, m), 8.50–8.65 (1H, m), 8.70–8.85 (1H, m), 12.80–13.60 (1H, br).
25-43		¹ H-NMR (DMSO-d ₆) δ ppm: 4.55 (2H, d, J=4.7Hz), 4.95–5.15 (1H, m), 5.56 (2H, s), 6.65–6.75 (2H, m), 7.05–7.15 (1H, m), 7.28 (1H, d, J=8.2Hz), 7.35–7.50 (3H, m), 7.50–7.65 (3H, m), 7.75–7.95 (2H, m), 13.23 (1H, br s).
25-44		¹ H-NMR (DMSO-d ₆) δ ppm: 0.77 (3H, t, J=7.4Hz), 1.17 (3H, d, J=6.9Hz), 1.40–1.70 (2H, m), 2.80–2.95 (1H, m), 3.83 (3H, s), 5.45–5.65 (2H, m), 6.30 (1H, s), 6.70 (1H, d, J=7.3Hz), 7.20 (1H, s), 7.55 (1H, s), 7.80–7.95 (2H, m), 13.00–13.50 (1H, br).
25-45		¹ H-NMR (DMSO-d ₆) δ ppm: 0.55–0.70 (2H, m), 0.85–0.95 (2H, m), 1.90–2.05 (1H, m), 5.52 (2H, s), 6.60 (1H, s), 6.72 (1H, d, J=7.6Hz), 6.86 (1H, dd, J=1.6, 8.5Hz), 7.20 (1H, d, J=8.5Hz), 7.25–7.65 (6H, m), 7.75–7.90 (2H, m), 12.00–14.50 (1H, br).

[0526]

Test Example 1

5 Test for Confirmation of EP₁ Receptor Antagonism

[0527]

(1) Preparation of Rat EP₁ Expression Vector

Using Rat Kidney BD Marathon-Ready cDNA (Nippon Becton Dickinson Company, Ltd.) as a template, a forward primer shown in SEQ ID NO. 1, and a reverse primer shown in SEQ ID NO. 2, a first run of PCR was carried out using KOD-Plus-Ver 2.0 (Toyobo Co., Ltd.). Further, using this amplification product as a template, a forward

10

primer shown in SEQ ID NO. 3, and a reverse primer shown in SEQ ID NO. 4, a second run of PCR was carried out in the same manner. The amplification product obtained by the second run of PCR was incorporated into a vector (pcDNA3.1 D/V5-His-TOPO (registered trademark), Invitrogen Japan K. K.). By a conventional method, the vector containing this amplification product was introduced to *E. coli* (One Shot TOP10 Competent Cells, Invitrogen Corporation) to transform. This transformed *E. coli* was cultured in an LB agar medium for one day. After the culture, colonies were selected and cultured in an LB liquid medium containing 50 µg/mL of ampicillin. After the culture, the vector was purified using a QIAprep Spin Miniprep Kit (Qiagen K. K.). The base sequence of the insertion site of this vector (SEQ ID NO. 5) was compared with the rat EP₁ base sequence (Ptger1) registered as an accession number NM_013100 in well-known database (NCBI), and as a result, they all matched except for a single base. Further, the amino acid sequence translated by the base sequence completely matched the amino acid sequence of the rat EP₁ receptor registered as an NCBI accession number NP_037232. Therefore, it was confirmed that the cloned gene sequence was a base sequence of the rat EP₁ receptor and the obtained amino acid sequence was that of the rat EP₁ receptor. The pcDNA3.1 D/V5-His-TOPO (registered trademark) to which the nucleic acid shown in SEQ ID NO. 5 had been inserted was taken as a rat EP₁-expressing vector.

[0528]

20 (2) Preparation of Rat EP₁ Receptor-Expressing Cells

[0529]

(2-1) COS-1 Cell Culture

COS-1 cells (Dainippon Sumitomo Pharma Co., Ltd.) were cultured until it reached confluence in an incubator at 37°C under a 5% CO₂ gas condition, using a D-MEM liquid medium (high glucose and L-glutamine contained, Invitrogen Corporation) to which a penicillin-streptomycin solution (Invitrogen Corporation, final concentration: 100 U/mL as benzylpenicillin; 100 µg/mL as streptomycin) as an antibiotic, MEM nonessential amino acids (Invitrogen Corporation, final Concentration: 0.1 mM), and fetal calf serum (Sanko Junyaku Co., Ltd., final concentration: 10%) were added.

30 [0530]

(2-2) COS-1 Cell Subculture

The cells that had reached confluence were stripped with 0.05% trypsin/0.53 mM EDTA 4Na (Invitrogen Japan K. K.) and resuspended in the liquid medium. The

resuspended cells were diluted and cultured in the liquid medium at a spread ratio from 1:4 to 1:8.

[0531]

(2-3) Preparation of Cells for Introduction of Rat EP₁-Expressing Vector

5 The cells that had reached confluence were stripped with 0.05% trypsin/0.53 mM EDTA-4Na, and resuspended in a D-MEM liquid medium (high glucose and L-glutamine contained, Invitrogen Corporation) to which an MEM nonessential amino acid (final concentration: 0.1 mM) and fetal calf serum (final concentration: 10%) were added. In each well of a Poly D-lysine-coated 96-well microplate (BD BioCoat (registered
10 trademark), Nippon Becton Dickinson Company, Ltd.), this resuspended cell suspension culture was prepared to be 5×10^4 cells/well in 100 μ L of the liquid medium, and seeded thereon. After seeding, the cells were cultured in an incubator at 37°C under a 5% CO₂ gas condition. At a point when the cells for introduction of a rat EP₁-expressing vector were adhered (about 2 hours after seeding), introduction of the rat EP₁-expressing vector
15 was carried out in the following order.

[0532]

(2-4) Introduction of Rat EP₁-Expressing Vector

 For introduction of the rat EP₁-expressing vector, Lipofectamine 2000 (Invitrogen Japan K. K.) was used. The rat EP₁-expressing vector was diluted with OPTI-MEM
20 (registered trademark) I Reduced-Serum Medium (Invitrogen Japan K. K.) to 200 ng/25 μ L/well, and at the same time, Lipofectamine 2000 (Invitrogen Japan K. K.) was also diluted with OPTI-MEM (registered trademark) I Reduced-Serum Medium (Invitrogen Japan K. K.) to 0.5 μ L/25 μ L/well, followed by incubation at room temperature for 5 minutes. After the incubation for 5 minutes, in order to form a complex of the rat EP₁-
25 expressing vector/Lipofectamine 2000, the diluted rat EP₁-expressing vector and the diluted Lipofectamine 2000 were mixed and incubated at room temperature for 30 minutes. After the incubation for 30 minutes, the complex of the rat EP₁-expressing vector/Lipofectamine 2000 was distributed to the cells for introduction of the rat EP₁-
30 expressing vector at 50 μ L/well. The cells to which the complex of the rat EP₁-expressing vector/Lipofectamine 2000 had been distributed were cultured in an incubator at 37°C for 20 hours under a 5% CO₂ gas condition. After the culture for 20 hours, the cells were used for measurement of an intracellular calcium concentration as rat EP₁ receptor-expressing cells.

[0533]

(3) Study on Inhibitory Effect on Increase in Intracellular Calcium Concentration

[0534]

Using the rat EP₁ receptor-expressing cells, the inhibitory effect of each test
5 compound on the increased intracellular calcium concentration induced by prostaglandin
E₂ was studied in Method A or Method B as shown below.

[0535]

Method A:

A 10 mM solution of each test compound in dimethyl sulfoxide was diluted with
10 an assay buffer (20 mM HEPES/Hank's Balanced Salt Solution (HBSS), pH 7.2).

The rat EP₁ receptor-expressing cells were washed with the assay buffer. 100 µL
of a fluorescent calcium indicator (Fluo-4 NW Calcium Assay Kit (Molecular Probes):
prepared by the protocol of the same product, Invitrogen Corporation, 2.5 mM probenecid
contained) was added to each well, followed by incubation in an incubator at 37°C for 60
15 minutes. Then, all the cell supernatants were aspirated and washed with the assay buffer.
After the washing, 100 µL of an assay buffer containing 2.5 mM probenecid was added to
each well, and the intracellular calcium concentration was measured immediately.

The intracellular calcium concentration was measured as a fluorescent signal using
FlexStation (registered trademark) (manufactured by Molecular Devices). 50 µL of each
20 test compound that had been diluted with the assay buffer (final concentrations: 1 nM to 10
µM) was added to each well after 20 seconds from initiating the reading of the fluorescent
signal, and the fluorescence signal was measured for 60 seconds. Then, 50 µL of a
prostaglandin E₂ buffer solution was added to each well (final concentration 10 nM) and
the fluorescence signal was measured for 60 seconds.

25 [0536]

Method B:

A 10 mM solution of each test compound in dimethyl sulfoxide was diluted in an
assay buffer (20 mM HEPES/Hank's Balanced Salt Solution (HBSS), pH 7.2).

The rat EP₁ receptor-expressing cells were washed with the assay buffer. 100 µL
30 of a fluorescent calcium indicator (Calcium kit II, Fluo 4 (Dojindo Laboratories): prepared
by the protocol of the same product, Invitrogen Japan K. K., 2.5 mM probenecid
contained) was added to each well, followed by incubation in an incubator at 37°C for 60
minutes. Then, the intracellular calcium concentration was measured immediately.

The intracellular calcium concentration was measured as a fluorescent signal using FDSS (registered trademark) 7000 (manufactured by Hamamatsu Photonics K. K.). 50 μ L of each test compound (final concentrations: 1 nM to 10 μ M) was added to each well after 20 seconds from initiating the reading of the fluorescent signal, and the fluorescence signal was measured for 60 seconds. Then, 50 μ L of a prostaglandin E₂ buffer solution was added to each well (final concentration 10 nM) and the fluorescence signal was measured for 60 seconds.

[0537]

In Method A or Method B, as a fluorescent signal obtained by the addition of the prostaglandin E₂ with the addition of the assay buffer instead of the test compound was taken as 100% and a signal obtained without the addition of any of the test compound and the prostaglandin E₂ was taken as 0%, the concentration of the test compound showing 50% inhibition from the concentration-response curve was taken as an IC₅₀ value. As the values of the EP₁ receptor antagonism, the obtained IC₅₀ values of each test compound were shown in Table 49 below. As Comparative Example 1, 3-(5-methyl-2-phenylindol-1-yl)carboxylic acid (Compound 27) described in Patent literature 1 was tested in the similar way. Further, as Comparative Example 2, sodium 6-(6-chloro-3-isobutylindol-1-yl)pyridine-2-carboxylate (Compound 12g) described in Non-Patent literature 5 was tested in the similar way. The results of Comparative Example 1 and Comparative Example 2 were shown in Table 49.

[0538]

[Table 49]

Ex. No	IC ₅₀ (nM)	Method	Ex. No	IC ₅₀ (nM)	Method
9-1	21	A	25-23	32	B
9-13	89	A	25-26	17	B
9-15	22	A	25-28	28	B
9-21	13	A	25-29	26	B
9-25	35	A	25-31	33	B
9-32	11	A	25-33	58	B
9-35	23	A	25-34	54	B
9-43	13	A	25-36	35	B
9-44	19	A	25-37	27	B
25-9	67	B	25-38	22	B
25-11	34	B	25-39	37	B
25-12	55	B	25-41	25	B
25-13	38	B	25-42	28	B
25-16	39	B	25-44	51	B
25-17	32	B	Comparative Example 1	>10000	A
25-18	17	B	Comparative Example 2	476	B
25-19	36	B			

[0539]

5 As shown in Table 49, whereas Comparative Example 1 do not exhibit EP₁ receptor antagonism, it is apparent that the compounds of the present invention exhibit potent EP₁ receptor antagonism. Further, it is apparent that the compounds of the present invention exhibit potent EP₁ receptor antagonism, as also compared with Comparative Example 2.

[0540]

Test Example 2

Inhibitory Effect of Compound on Sulprostone-Induced Bladder Contraction

[0541]

Female SD rats were used. Under urethane anesthesia (1.25 g/kg, administered subcutaneously), a tracheal cannula (Size 8, HIBIKI) and a femoral vein cannula for administration (23G needle-equipped PE50) were inserted thereinto. The bladder cannula (PE50) was inserted from the bladder apex. The bladder cannula was connected to a three-way stopcock, and then, one was connected to a pressure transducer and the other was connected to a syringe filled with saline. Saline was injected to the bladder at an injection rate of 3.6 mL/hour and the bladder contraction pressure was recorded at the time of injection with a recorder (RECTI-HORITZ-8K, NEC Corporation). After 10 minutes from stabilization of the bladder contraction pressure during urination, sulprostone was administered subcutaneously (0.3 mg/kg). Then, at the time point when the bladder contraction pressure became constant, a test agent was administered intravenously (1.0 mg/kg). An average bladder contraction pressure during the 10 minutes period before administration of sulprostone was taken as a baseline (0%). Further, an average bladder contraction pressure during the 10 minutes period before administration of the test agent was taken as a maximum bladder contraction pressure (100%). The average bladder contraction pressures were measured during 5 minutes before and after at 15 minutes and 60 minutes from administration of the test agent. The ratio of this measured value to the maximum bladder contraction pressure was calculated by the following equation and taken as an average bladder contraction rate after administration of the test agent: (Average Bladder Contraction Rate after Administration of Test Agent (%)) = (Average Bladder Contraction Pressure after Administration of Test Agent) / (Maximum Bladder Contraction Pressure). In addition, the difference between the maximum bladder contraction rate (100%) and the average bladder contraction rate (%) after administration of the test agent was calculated by the following equation and taken as a bladder contraction inhibition rate of the test agent: (Bladder Contraction Inhibition Rate) = 100% - (Average Bladder Contraction Rate after Administration of Test Agent (%)). The results were shown in Table 50.

[0542]

[Table 50]

Ex No.	Bladder Contraction Inhibition Rate (%)	
	15 Minutes	60 Minutes
9-21	94.5	82.8
16-15	85.0	54.9

[0543]

From the results above, it was found that the compounds of the present invention
5 had potent and sustained inhibition of the bladder contraction even when administered in vivo.

[Sequence List Free Text]

[0544]

<Sequence List 1>

10 SEQ ID NO. 1 is a sequence of a forward primer (5' primer) used for amplification of DNA of SEQ ID NO. 5.

<Sequence List 2>

SEQ ID NO. 2 is a sequence of a reverse primer (3' primer) used for amplification of DNA of SEQ ID NO. 5.

15 <Sequence List 3>

SEQ ID NO. 3 is a sequence of a forward primer (5' primer) used for amplification of DNA of SEQ ID NO. 5.

<SEQ ID NO. 4>

20 SEQ ID NO. 4 is a sequence of a reverse primer (3' primer) used for amplification of DNA of SEQ ID NO. 5.

<SEQ ID NO. 5>

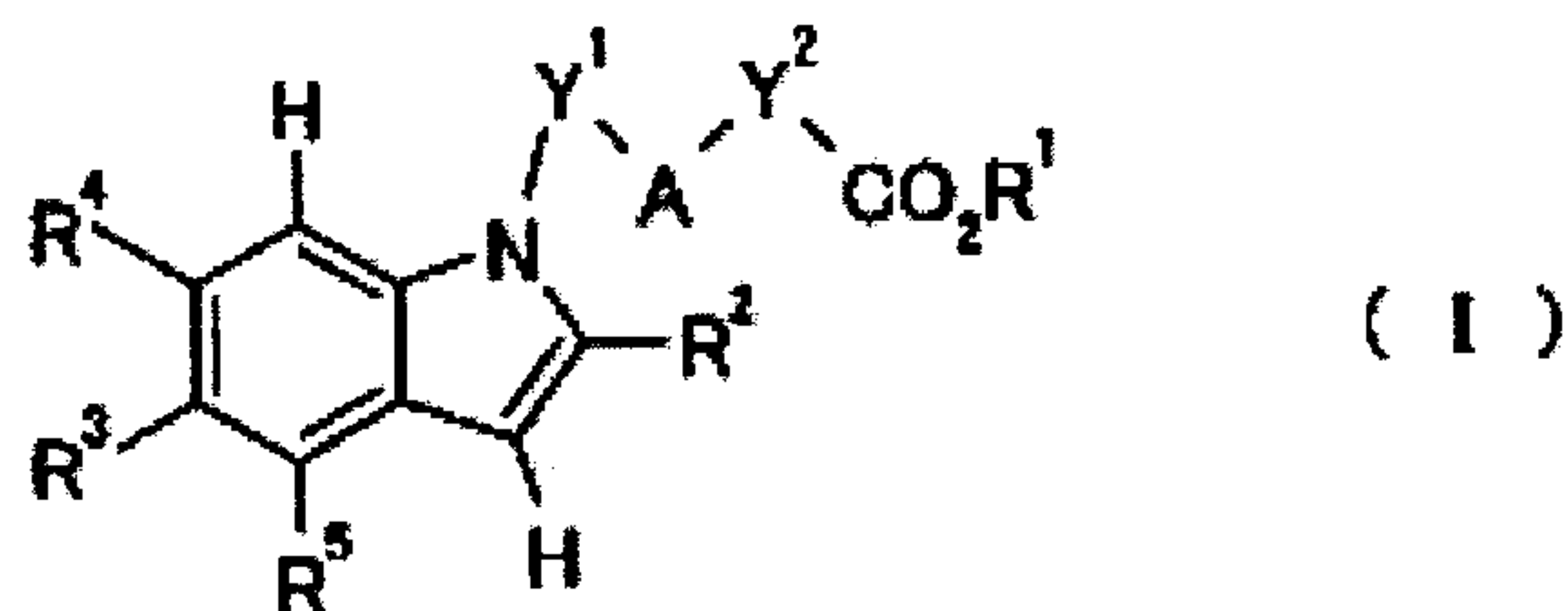
SEQ ID NO. 5 is a DNA sequence for expressing a rat EP1 receptor which is amplified using the primers of SEQ ID NO. 1, SEQ ID NO. 2, SEQ ID NO. 3, and SEQ ID NO. 4.

Claims

[Claim 1]

A compound represented by the general formula (I) or a pharmaceutically acceptable salt thereof:

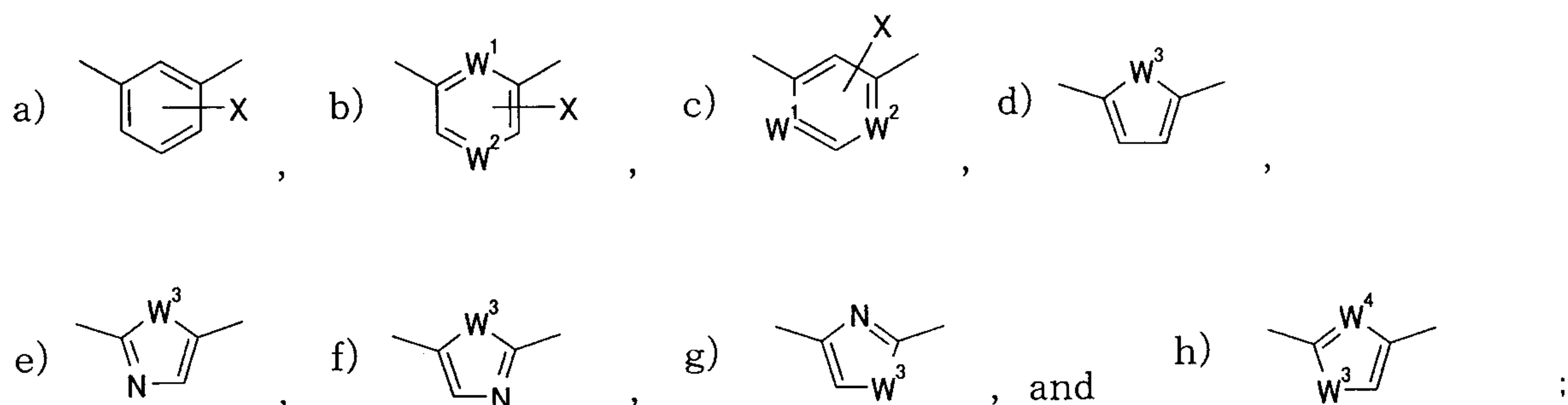
[Chem. 1]



[wherein

A represents a group selected from the group consisting of the following a) to h):

[Chem. 2]



one of W^1 and W^2 represents a nitrogen atom and the other represents =CH- or a nitrogen atom;

15 W^3 represents an oxygen atom or a sulfur atom;

W^4 represents =CH- or a nitrogen atom;

X represents a hydrogen atom or a halogen atom;

Y^1 represents a C_{1-6} alkylene group;

Y^2 represents a single bond or an oxy- C_{1-6} alkylene group;

20 R^1 represents a hydrogen atom, a C_{1-6} alkyl group, or a C_{7-10} aralkyl group;

R^2 represents a group selected from the group consisting of the following i) to n):

i) a branched C_{3-6} alkyl group,

j) a halo- C_{1-6} alkyl group,

k) a C_{3-6} cycloalkyl group,

l) a phenyl group, in which the ring is unsubstituted or substituted with 1 to 5 groups independently selected from the group consisting of: a halogen atom, a C₁₋₆ alkyl group, a halo-C₁₋₆ alkyl group, a hydroxy-C₁₋₆ alkyl group, a C₁₋₆ alkoxy group and a cyano group,

5 m) a 6-membered aromatic heterocyclic group, in which the ring is unsubstituted or substituted with 1 to 4 groups independently selected from the group consisting of: a halogen atom, a C₁₋₆ alkyl group, a halo-C₁₋₆ alkyl group, a hydroxy-C₁₋₆ alkyl group, a C₁₋₆ alkoxy group and a cyano group, and

10 n) a 5-membered aromatic heterocyclic group, in which the ring is unsubstituted or substituted with 1 to 3 groups independently selected from the group consisting of: a halogen atom, a C₁₋₆ alkyl group, a halo-C₁₋₆ alkyl group, a hydroxy-C₁₋₆ alkyl group, a C₁₋₆ alkoxy group and a cyano group;

15 R³ represents a halogen atom, a C₁₋₆ alkyl group, a halo-C₁₋₆ alkyl group, a hydroxy-C₁₋₆ alkyl group, a C₁₋₆ alkoxy group, a halo-C₁₋₆ alkoxy group, a C₁₋₆ alkylsulfanyl group, a C₃₋₆ cycloalkyl group, a cyano group, an amino group, or a nitro group;

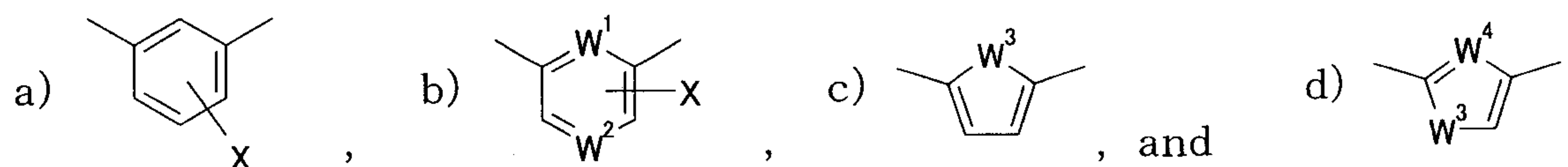
R⁴ represents a hydrogen atom, a halogen atom, a C₁₋₆ alkyl group, or a C₁₋₆ alkoxy group; and

20 R⁵ represents a hydrogen atom, a halogen atom, a C₁₋₆ alkyl group, or a C₁₋₆ alkoxy group;

[Claim 2]

The compound as claimed in claim 1 or a pharmaceutically acceptable salt thereof, wherein A is a group selected from the group consisting of the following a) to d):

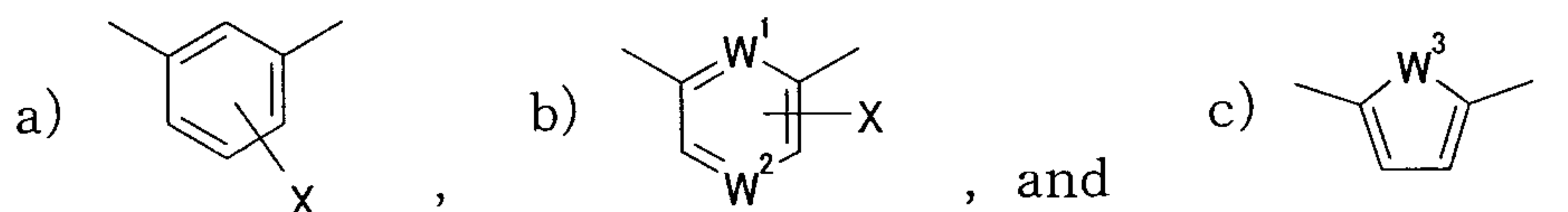
[Chem. 3]



[Claim 3]

The compound as claimed in claim 2 or a pharmaceutically acceptable salt thereof, wherein A is a group selected from the group consisting of a) to c) below:

[Chem. 4]



[Claim 4]

The compound as claimed in claim 3 or a pharmaceutically acceptable salt thereof,
 5 wherein R^2 is a group selected from the group consisting of the following a) to d):

- a) a branched C_{3-6} alkyl group,
- b) a C_{3-6} cycloalkyl group,
- c) a phenyl group, and
- d) a 5-membered aromatic heterocyclic group or a 6-membered aromatic

10 heterocyclic group;

R^4 is a hydrogen atom or a halogen atom;

R^5 is a hydrogen atom.

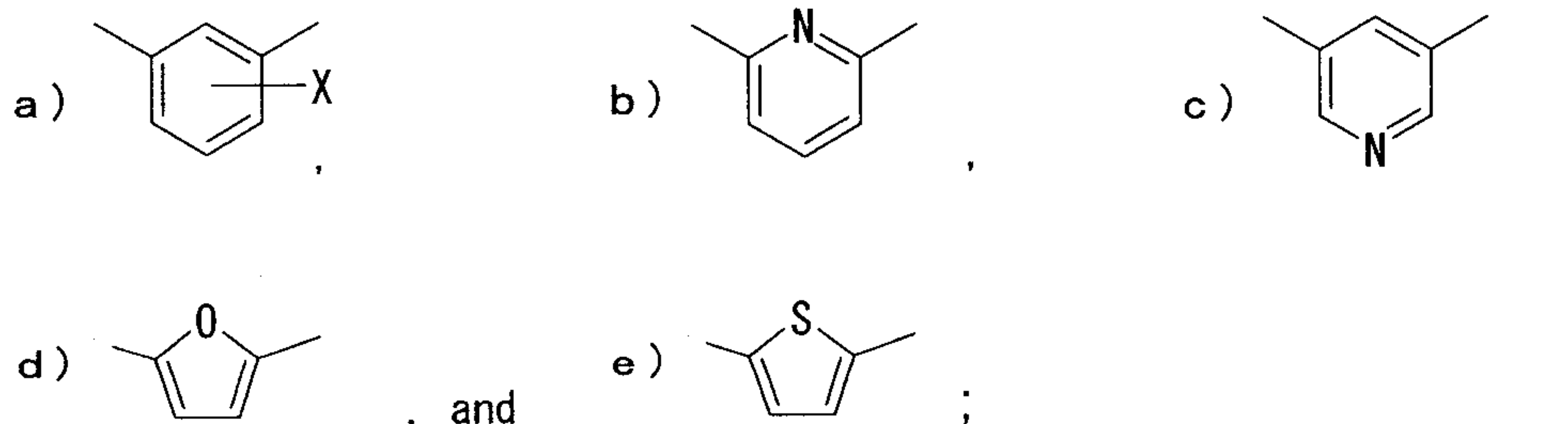
[Claim 5]

The compound as claimed in claim 4 or a pharmaceutically acceptable salt thereof,
 15 wherein R^1 is a hydrogen atom.

[Claim 6]

The compound as claimed in claim 5 or a pharmaceutically acceptable salt thereof,
 wherein A is a group selected from the group consisting of a) to e) below:

[Chem. 5]



20

Y^1 is a methylene group; and Y^2 is a single bond.

[Claim 7]

The compound as claimed in claim 6 or a pharmaceutically acceptable salt thereof,
 wherein R^3 is a C_{1-6} alkoxy group.

25 [Claim 8]

The compound as claimed in claim 7 or a pharmaceutically acceptable salt thereof,
 wherein R^3 is a methoxy group.

[Claim 9]

The compound as claimed in claim 6 or a pharmaceutically acceptable salt thereof, wherein R^3 is a halogen atom.

[Claim 10]

The compound as claimed in claim 9 or a pharmaceutically acceptable salt thereof, wherein R^3 is a fluorine atom.

[Claim 11]

The compound as claimed in claim 6 or a pharmaceutically acceptable salt thereof, wherein R^3 is a C_{1-6} alkyl group.

[Claim 12]

The compound as claimed in claim 11 or a pharmaceutically acceptable salt thereof, wherein R^3 is a methyl group.

[Claim 13]

The compound as claimed in claim 6 or a pharmaceutically acceptable salt thereof, wherein R^2 is an isopropyl group, an isobutyl group, a *sec*-butyl group or a 1-ethylpropyl group.

[Claim 14]

The compound as claimed in claim 6 or a pharmaceutically acceptable salt thereof, wherein R^2 is a phenyl group or a 5-membered aromatic heterocyclic group.

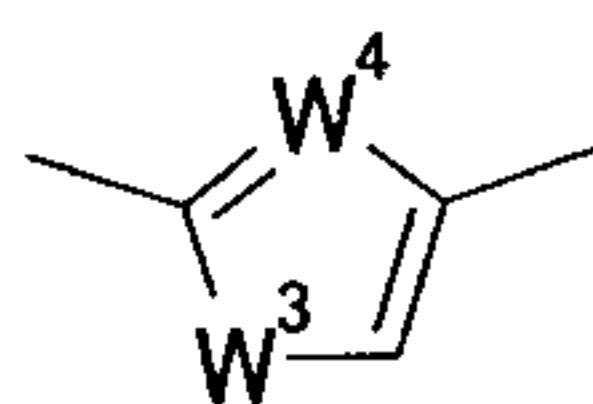
[Claim 15]

The compound as claimed in claim 14 or a pharmaceutically acceptable salt thereof, wherein R^2 is a phenyl group, a 3-thienyl group or a 3-furyl group.

[Claim 16]

The compound as claimed in claim 2 or a pharmaceutically acceptable salt thereof, wherein A is a group represented by the following formula:

[Chem. 6]



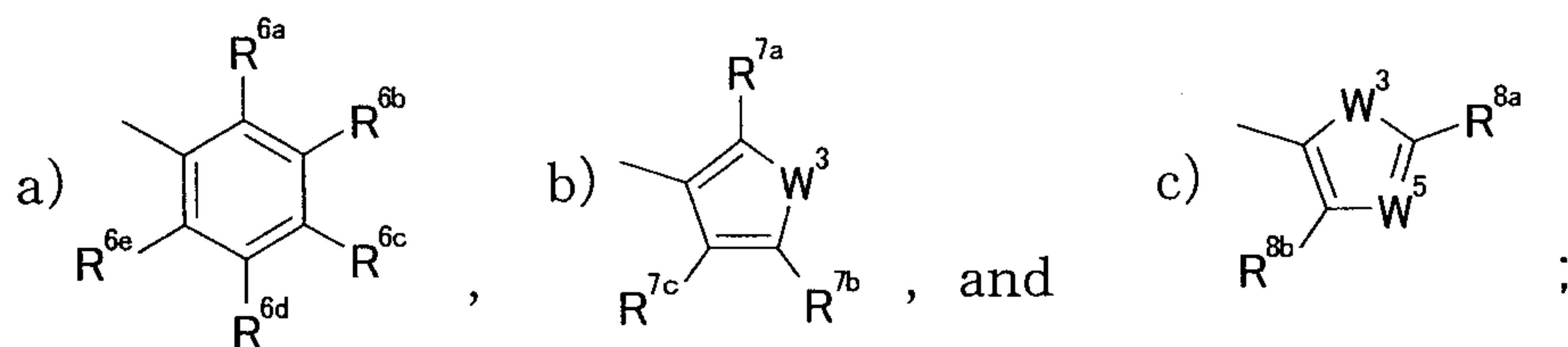
[Claim 17]

The compound as claimed in claim 16 or a pharmaceutically acceptable salt thereof, wherein R^1 is a hydrogen atom.

[Claim 18]

The compound as claimed in claim 3 or a pharmaceutically acceptable salt thereof, wherein R^2 is a group selected from the group consisting of the following a) to c):

[Chem. 7]



W^5 is a nitrogen atom or $-CR^{8c}=$;

R^{6a} , R^{6b} , R^{6c} , R^{6d} and R^{6e} are each independently a group selected from a hydrogen atom, a halogen atom, a C_{1-6} alkyl group, a halo- C_{1-6} alkyl group, a hydroxy- C_{1-6} alkyl group, a C_{1-6} alkoxy group, or a cyano group, with the proviso that all of R^{6a} , R^{6b} , R^{6c} , R^{6d} and R^{6e} are not simultaneously a hydrogen atom;

R^{7a} , R^{7b} and R^{7c} are each independently a hydrogen atom, a halogen atom, a C_{1-6} alkyl group, a halo- C_{1-6} alkyl group, a hydroxy- C_{1-6} alkyl group, a C_{1-6} alkoxy group or a cyano group, with the proviso that all of R^{7a} , R^{7b} , R^{7c} and R^{7d} are not simultaneously a hydrogen atom; and

R^{8a} , R^{8b} and R^{8c} are each independently a hydrogen atom, a halogen atom, a C_{1-6} alkyl group, a halo- C_{1-6} alkyl group, a hydroxy- C_{1-6} alkyl group, a C_{1-6} alkoxy group or a cyano group, with the proviso that all of R^{8a} , R^{8b} and R^{8c} are not simultaneously a hydrogen atom.

[Claim 19]

The compound as claimed in claim 18 or a pharmaceutically acceptable salt thereof, wherein R^1 is a hydrogen atom.

[Claim 20]

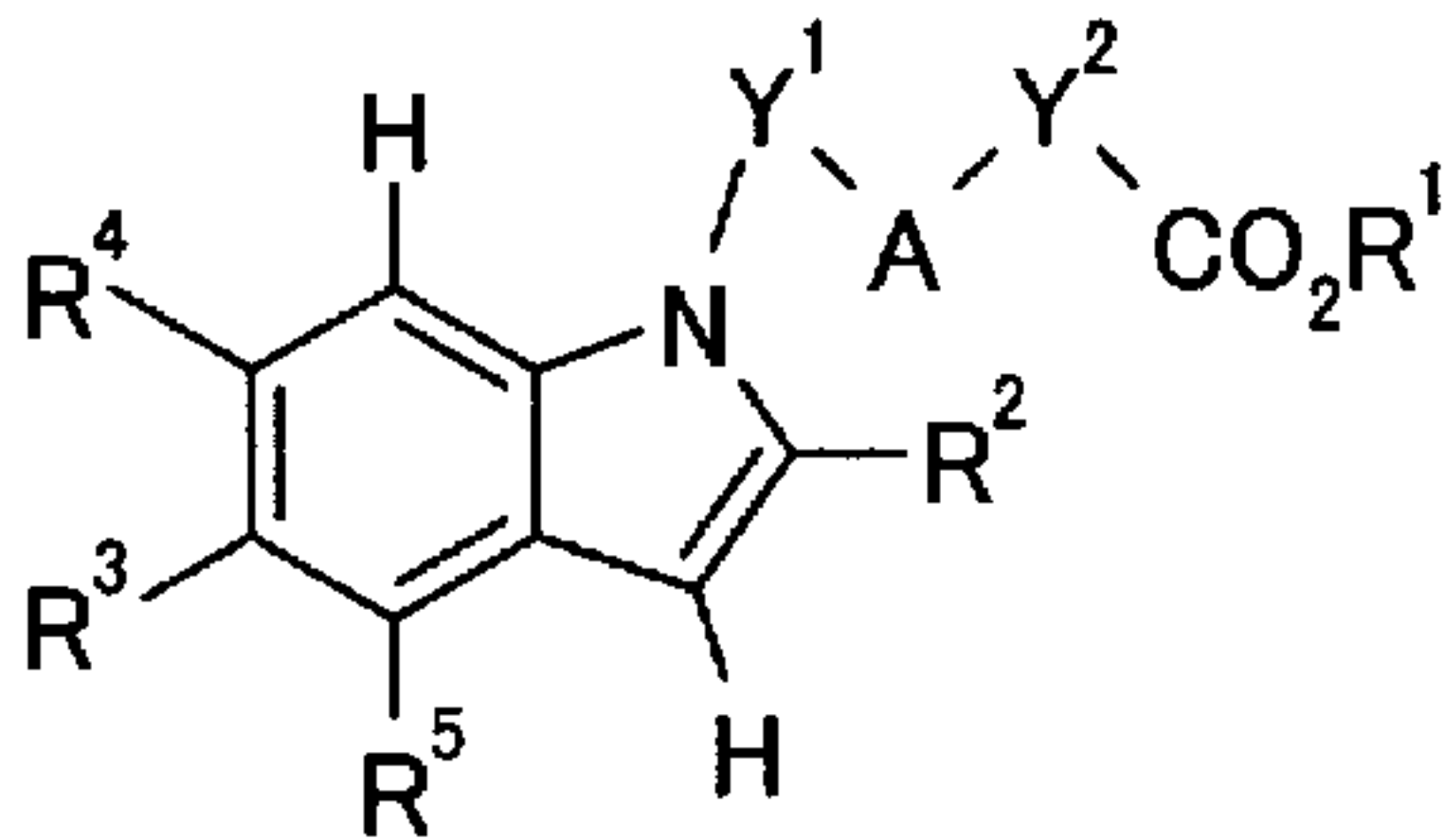
A pharmaceutical composition comprising the compound as claimed in any one of claims 1 to 19 or a pharmaceutically acceptable salt thereof as an active ingredient.

[Claim 21]

An EP_1 receptor antagonist comprising the compound as claimed in any one of claims 1 to 19 or a pharmaceutically acceptable salt thereof as an active ingredient.

[Claim 22]

An agent for treating or preventing lower urinary tract symptoms, comprising the compound as claimed in any one of claims 1 to 19 or a pharmaceutically acceptable salt thereof as an active ingredient.



(I)