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(54) Title: AMINOINDAN DERIVATIVE OR SALT THEREOF

(54) 発明の名称: アミノインダン誘導体又はその塩

(57) Abstract: [PROBLEMS] To provide a compound which can act as an NMDA antagonist having a wide safe range and is useful as a therapeutic agent or a prophylactic agent for Alzheimer's disease, cerebrovascular dementia, Parkinson's disease, ischemic stroke or a pain. [MEANS FOR SOLVING PROBLEMS] A novel compound characterized by having an amino group and a group R¹ [which represents a lower alkyl, a cycloalkyl, a lower alkylene-aryl, an aryl which may have a substituent or the like] on a carbon atom in an indan, cyclopenta[b]thiophene, cyclopenta[b]furan, cyclopenta[b]pyridine or cyclopenta[c]pyridine ring or a 2,3-dihydro-1-benzofuran, 2,3-dihydro-1-benzothiophene or indolin ring or the like and also having groups R² and R³ [which independently represent a lower alkyl or an aryl] on a carbon atom adjacent to the above-mentioned carbon atom, or a salt thereof; and an NMDA antagonist comprising the compound or the salt as an active ingredient.

(57) 要約: 課題 安全域の広いNMDA拮抗薬であり、アルツハイマー病、脳血管性認知症、パーキンソン病、虚血性脳卒中、疼痛の治療剤、又はこれらの予防剤として有用な化合物を提供する。解決手段 インダン、シクロペンタ [b] チオフェン、シクロペンタ [b] フラン、シクロペンタ [b] ピリジン、又はシクロペンタ [c] ピリジン環、或いは、2,3-ジヒドロ-1-ベンゾフラン、2,3-ジヒドロ-1-ベンゾチオフェン、インドリン環等の炭素原子上にアミノ基及びR¹ (低級アルキル、シクロアルキル、-低級アルキレン-アリール、置換基を有しても良いアリール等) を有し、その隣の炭素原子上にR²及びR³ (同一又は異なって、低級アルキル、又はアリール) を有することを特徴とする新規な化合物又はその塩、及びそれらを有効成分とするNMDA拮抗薬。

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Description

AMINOINDANE DERIVATIVE OR SALT THEREOF

TECHNICAL FIELD

5 [0001]

The present invention relates to an aminoindane derivative or a salt thereof which is useful as a medicine, especially as an NMDA receptor antagonist, and to an NMDA receptor antagonist comprising the same as an active
10 ingredient. The aminoindane derivative or a salt thereof and the NMDA receptor antagonist comprising the same as an active ingredient, of the present invention, are useful for treating or preventing Alzheimer's disease, cerebrovascular dementia, Parkinson's disease, ischemic apoplexy, pain, and
15 the like.

BACKGROUND ART

[0002]

Glutamic acid acts as a neurotransmitter in the
20 central nervous system of mammals, and controls the activity of neurocytes or the release of neurotransmitters via a glutamate receptor existing in synapses. At present, a glutamate receptor is classified into an "ionotropic glutamate receptor" and a "metabotropic glutamate receptor"
25 from many pharmacological and biological studies (Hollmann M. and Heinemann S., Annu. Rev. Neurosci., 17 (1994) 31-

108). An NMDA (N-methyl-D-aspartate) receptor is an ion-channel glutamate receptor specifically sensitive to the agonist NMDA (Moriyoshi K. et al., Nature, 354 (1991) 31-37; Meguro H. et al., Nature, 357 (1992) 70-74); and this
5 has high Ca^{2+} permeability (Iino M. et al., J. Physiol., 424 (1990) 151-165). The NMDA receptor is expressed with a specific pattern in a central nervous system (Ozawa S. et al., Prog. Neurobiol., 54 (1998) 581-618).

[0003]

10 From many pharmacological and biological studies, it is believed that an NMDA receptor may participate in high-order neurologic functions such as memory and learning (Morris RG., et al., Nature, 319 (1986) 774-776; Tsien JZ. et al., Cell, 87 (1996) 1327-1338). On the other hand, it
15 is suggested that the acute or chronic NMDA receptor hyperactivity or hypoactivity may participate in various nervous system diseases, for example, ischemic apoplexy, hemorrhagic brain injury, traumatic brain injury, neurodegenerative disorders (e.g., Alzheimer's disease,
20 cerebrovascular dementia, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis), glaucoma, AIDS encephalopathy, dependence, schizophrenia, depression, mania, stress-related diseases, epilepsy, and pain (Beal MF., FASEB J., 6 (1992) 3338-3344; Heresco-Levy U. and
25 Javitt DC., Euro. Neuropsychopharmacol., 8 (1998) 141-152; Hewitt DJ., Clin. J. Pain, 16 (2000) S73-79). Accordingly,

drugs capable of controlling the activity of an NMDA receptor would be extremely useful in clinical application.

[0004]

As drugs capable of controlling the activity of an
5 NMDA receptor, a large number of non-competitive NMDA
receptor antagonists are reported, but many of them have
not been used in clinical application because of their side
effects based on the NMDA receptor-antagonizing effect
thereof, for example, mental aberration such as
10 hallucination or confusion, and giddiness. Some of
already-existing NMDA receptor antagonists, for example,
ketamine and dextromethorphan have been tried against pain
in clinical application (Fisher K. et al., J. Pain Symptom
Manage., 20 (2000) 358-373), but the safety margin in the
15 treatment with them is narrow, and their clinical use is
limitative (Eide PK., et al., Pain, 58 (1994) 347-354).
Memantine is known as a non-competitive NMDA receptor
antagonist that has comparatively few side effects (Parsons
CG., et al., Neuropharmacol., 38 (1999) 735-767); and
20 recently, it has been reported that this may be effective
for Alzheimer's disease (Reisberg B., et al., N. Engl. J.
Med., 348 (2003) 1333-1341). However, the safety margin of
memantine as a medicine is still not satisfactory, and an
NMDA receptor antagonist having a broader safety margin is
25 desired (Ditzler K., Arzneimittelforschung, 41 (1991) 773-
780; Maier C., et al., Pain, 103 (2003) 277-283; Riederer

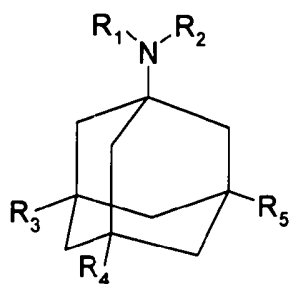
P., et al., Lancet, 338 (1991) 1022-1023). It is expected that creation of such an NMDA receptor antagonist having a broader safety margin may bring about new clinical usefulness of the NMDA receptor antagonist.

5 [0005]

Patent Document 1 describes a pharmaceutical composition for preventing and treating cerebral ischemia, which comprises an adamantane derivative represented by the following general formula or its pharmaceutically

10 acceptable acid-addition salt:

[Chem. 1]



(wherein R₁ and R₂ are the same or different, and each
15 represent hydrogen, a linear or branched alkyl group having
1 to 6 carbon atoms, or the like; R₃ and R₄ are the same or
different, and each represent hydrogen, an alkyl group
having 1 to 6 carbon atoms, or the like; and R₅ represents
hydrogen or a linear or branched alkyl group having 1 to 6
20 carbon atoms. See the official gazette for other symbols
in the formula).

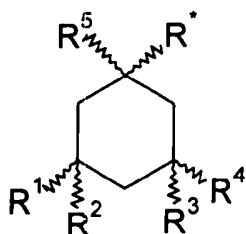
In Patent Document 1, the above-mentioned memantine
is described as Test Compound No. 1 (memantine is a

compound of the formula wherein R_1 , R_2 and R_3 are hydrogen atoms, and R_4 and R_5 are methyl).

[0006]

Furthermore, Patent Document 2 describes 1-amino-
5 alkylcyclohexane represented by the following general
formula as an NMDA receptor antagonist.

[Chem. 2]

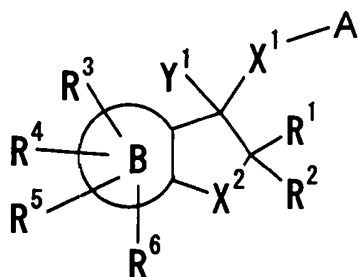


10 (wherein R^* is $-(CH_2)_n-(CR^6R^7)_m-NR^8R^9$; $n + m = 0, 1$ or
2; R^1 to R^9 are each independently selected from a group
consisting of a hydrogen atom and C_{1-6} lower alkyl; and at
least R^1 , R^4 and R^5 are lower alkyl. See the official
gazette for other symbols in the formula).

15 [0007]

Furthermore, the present Applicant reports a cyclic
amine derivative represented by the following general
formula, as an NMDA receptor antagonist in Patent Document
3.

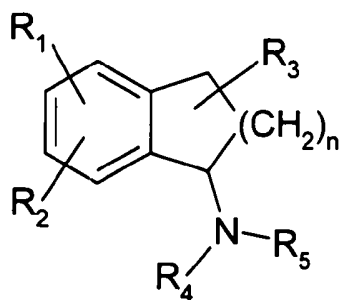
[Chem. 3]



(wherein A represents a 5- to 8-membered cyclic amine optionally having a double bond, optionally having a bridge structure and optionally having substituents of R^7 to R^{11} in the ring, $-NH_2$, $-NH$ (lower alkyl), or $-N$ (lower alkyl) $_2$; ring B represents benzene, thiophene, furan, pyrrole, a 5- to 7-membered cycloalkane, or 5- to 7-membered cycloalkene; X^1 represents a bond, a lower alkylene, or $-L^3-D-L^4-$; and Y^1 represents $-OH$, $-O$ -lower alkyl, $-NH_2$, or $-N_3$. See the official gazette for other symbols in the formula).

In addition, Patent Document 4 describes 1-aminoindane represented by the following general formula as a therapeutic agent for Parkinson's disease, and the like.

[0008]



(wherein R₁ and R₂ independently represent hydrogen, hydroxy, alkyl, alkoxy, or the like; R₃ represents hydrogen, alkyl, hydroxy, alkoxy, and the like, R₄ and R₅ independently represent hydrogen, alkyl, aryl, or the like; and n represents 0, 1, or 2).

[0009]

Patent Document 1: JP-A-2821233

Patent Document 2: Pamphlet of International Patent Publication WO 99/01416

Patent Document 3: Pamphlet of International Patent Publication WO 2006/033318

Patent Document 4: Pamphlet of International Patent Publication WO 95/18617

DISCLOSURE OF THE INVENTION

PROBLEMS TO BE SOLVED BY THE INVENTION

[0010]

With the increase in the aging population, occurrence of Alzheimer's disease, cerebrovascular dementia, ischemic apoplexy and the like increases these days, and thus it is earnestly desired in the medical field to create an NMDA receptor antagonist having a broader safety margin, which is effective for treating or preventing such diseases as well as Parkinson's disease, pain, and the like. It is an object of the present invention to provide a novel aminoindane derivative or a salt thereof having an

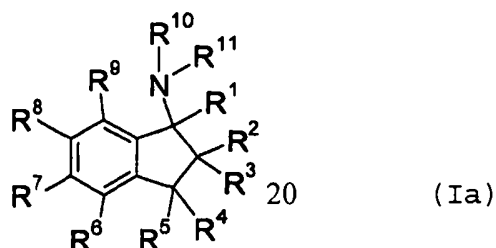
2007274420 10 Nov 2011

excellent NMDA receptor antagonistic activity and having a broader safety margin, and it is another object to provide a medicine comprising the same.

5 MEANS FOR SOLVING THE PROBLEMS

A first aspect of the invention provides a compound represented by the following general formula (Ia) or a salt thereof:

10 [Chem. 9]



(wherein the symbols in the formula (Ia) above have the following meanings, respectively:

25 R^1 : lower alkyl, cycloalkyl, -lower alkylene-aryl, aryl which may be substituted, heteroaryl which may be substituted, or lower alkyl substituted with one or more halogens,

R^2 and R^3 : the same or different, each lower alkyl, or
30 aryl,

R^4 and R^5 : the same or different, each a hydrogen atom, lower alkyl, -O-lower alkyl, -OH, -lower alkylene-OH, or -lower alkylene-O-lower alkyl,

R^6 to R^9 : the same or different, each a hydrogen atom,
35 lower alkyl, -O-lower alkyl, a halogen atom, lower alkyl substituted with one or more halogens, OH, CN, or lower

2007274420 10 Nov 2011

alkenyl,

R¹⁰ and R¹¹: the same or different, each a hydrogen atom, or lower alkyl,

wherein R² and R³ may be taken together with the
5 adjacent carbon atom to form cycloalkyl).

A second aspect of the invention provides a pharmaceutical composition comprising a compound or a salt thereof as defined in the first aspect.

10

A third aspect of the invention provides a use of a compound or a salt thereof as defined in the first aspect for the preparation of an NMDA receptor antagonist or a therapeutic agent for dementia.

15

A fourth aspect of the invention provides a method for treating dementia in a patient, comprising administering a therapeutically effective amount of a compound or a salt thereof as defined in the first aspect to the patient.

20

[0011]

The present inventors have found that a novel aminoindane derivative represented by the following general formula (I) or (Ia), or a salt thereof, which is
25 characterized in that it has an amino group and R¹(lower alkyl, cycloalkyl, -lower alkylene-aryl, aryl which may be substituted, and the like) on carbon atoms of indane, cyclopenta[b]thiophene, cyclopenta[b]furan, cyclopenta[b]pyridine, or cyclopenta[c]pyridine ring, or
30 2,3-dihydro-1-benzofuran, 2,3-dihydro-1-benzothiophene,

2007274420 10 Nov 2011

indoline ring, or the like, and has R² and R³ (the same or different, each lower alkyl or aryl) on carbon atoms beside them has an excellent NMDA receptor antagonistic activity and a broad safety margin, and thus have completed the

5 present invention. Specifically, the present invention relates to an aminoindane derivative represented by the following general formula (I) or (Ia), or a salt thereof (hereinafter this may be referred to as "the compound (I) of the present invention" or "the compound (Ia) of the present

10 invention"). Further, the present invention also relates to an NMDA receptor antagonist, especially a

therapeutic agent or a preventing agent for Alzheimer's disease, cerebrovascular dementia, ischemic apoplexy, pain, etc., that comprises the compound (I) or (Ia), or a salt thereof of the present invention as an active component.

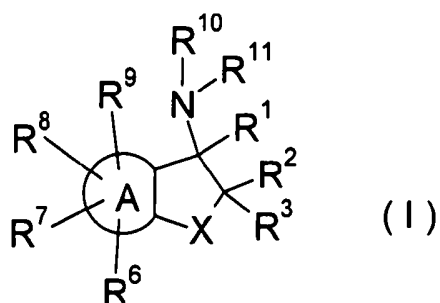
5 Furthermore, the term "aminoindane derivative" as used in the present invention encompasses a wide range of "aminoindane analogs" having rings other than an indane ring, such as cyclopenta[b]thiophene, cyclopenta[b]furan, cyclopenta[b]pyridine, and cyclopenta[c]pyridine rings as
10 described above, and it shall not be limited.

[0012]

The compound (I) or (Ia) of the present invention is distinguished from the compounds as described in Patent Documents 3 and 4 in that it has an amino group, as well as
15 R¹ (lower alkyl, cycloalkyl, -lower alkylene-aryl, aryl which may be substituted, and the like) other than a hydrogen atom on an indane ring, and the like, and has R² and R³ (which may be the same or different, and each represent lower alkyl or aryl) other than hydrogen atoms on
20 α positions thereof.

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

[Chem. 5]



(wherein the symbols in the formula (I) have the
5 following meanings, respectively:

ring A: a 5- or 6-membered hetero ring, or a benzene
ring,

X: C(R⁴)(R⁵), O, S, or N(R¹²),

R¹: lower alkyl, cycloalkyl, -lower alkylene-aryl,
10 aryl which may be substituted, heteroaryl which may be
substituted, or lower alkyl substituted with one or more
halogens,

R² and R³: the same or different, each lower alkyl,
or aryl,

15 R⁴ and R⁵: the same or different, each a hydrogen
atom, lower alkyl, -O-lower alkyl, -OH, -lower alkylene-OH,
or -lower alkylene-O-lower alkyl,

R⁶ to R⁹: the same or different, each a hydrogen
atom, lower alkyl, -O-lower alkyl, a halogen atom, lower
20 alkyl substituted with one or more halogens, OH, CN, lower
alkenyl, or a nitrogen-containing heterocyclic group,

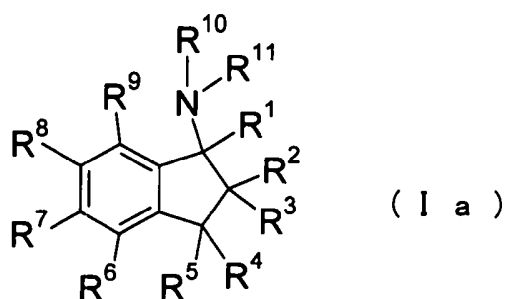
R¹⁰, and R¹¹: the same or different, each a hydrogen
atom, or lower alkyl, and

R¹²: a hydrogen atom or lower alkyl,
provided that R² and R³ may be taken together with
the adjacent carbon atom to form cycloalkyl).

[0013]

5 [2] A compound represented by the following general
formula (Ia) or a salt thereof:

[Chem. 6]



10 (wherein the symbols in the formula (Ia) above have
the following meanings, respectively:

R¹: lower alkyl, cycloalkyl, -lower alkylene-aryl,
aryl which may be substituted, heteroaryl which may be
substituted, or lower alkyl substituted with one or more
15 halogens,

R² and R³: the same or different, each lower alkyl,
or aryl,

R⁴ and R⁵: the same or different, each a hydrogen
atom, lower alkyl, -O-lower alkyl, -OH, -lower alkylene-OH,
20 or -lower alkylene-O-lower alkyl,

R⁶ to R⁹: the same or different, each a hydrogen
atom, lower alkyl, -O-lower alkyl, a halogen atom, lower

alkyl substituted with one or more halogens, OH, CN, lower alkenyl, or a nitrogen-containing heterocyclic group,

R¹⁰ and R¹¹: the same or different, each a hydrogen atom, or lower alkyl,

5 provided that R² and R³ may be taken together with the adjacent carbon atom to form cycloalkyl).

[0014]

[3] A compound or a salt thereof as described in [2], wherein R⁴, R⁵, R¹⁰, and R¹¹ in the formula (Ia) above are
10 each a hydrogen atom.

[4] A compound or a salt thereof as described in [3], wherein R² and R³ in the formula (Ia) above are the same as or different from each other, and each are lower alkyl, or cycloalkyl formed in combination with the adjacent carbon
15 atom.

[5] A compound or a salt thereof as described in [1], which is selected from 2,2-dimethyl-1-phenylindan-1-amine, 1-(4-fluorophenyl)-2,2-dimethylindan-1-amine, 1-(2-methoxyphenyl)-2,2-dimethylindan-1-amine, 1-(3-methoxyphenyl)-2,2-dimethylindan-1-amine, 1,2,2-trimethylindan-1-amine, 1,2,2,5-tetramethylindan-1-amine, 1,2,2,6-tetramethylindan-1-amine, 4-fluoro-1,2,2-trimethylindan-1-amine, 5-fluoro-1,2,2-trimethylindan-1-amine, 7-fluoro-1,2,2-trimethylindan-1-amine, 5-methoxy-
20 1,2,2-trimethylindan-1-amine, 6-methoxy-1,2,2-trimethylindan-1-amine, 6-isopropoxy-1,2,2-trimethylindan-

1-amine, 1-ethyl-2,2-dimethylindan-1-amine, 1-isopropyl-2,2-dimethylindan-1-amine, 1'-methyl-1',3'-dihydrospiro[cyclopropan-1,2'-inden]-1'-amine, 2,4,5,5-tetramethyl-5,5-dihydro-4H-cyclopenta[b]thiophen-4-amine.

5 [0015]

[6] A pharmaceutical composition comprising a compound or a salt thereof as described in [1] or [2].

[7] A pharmaceutical composition as described in [6], which is an NMDA receptor antagonist.

[8] A pharmaceutical composition as described in [6], which is a therapeutic agent for dementia.

[9] A use of a compound or a salt thereof as described in [1] or [2] for preparation of an NMDA receptor antagonist or a therapeutic agent for dementia.

[10] A method for treating dementia, comprising administering a therapeutically effective amount of a compound or a salt thereof as described in [1] or [2] to a patient.

20 EFFECTS OF THE INVENTION

[0016]

The compound of the present invention have an NMDA receptor antagonistic activity, and is thus useful for treating or preventing Alzheimer's disease, cerebrovascular dementia, Parkinson's disease, ischemic apoplexy, pain, and the like.

25

2007274420 30 Mar 2009

BEST MODE FOR CARRYING OUT THE INVENTION

[0017]

Hereinbelow, the present invention is described in detail.

Unless otherwise specifically indicated, the term "lower" as used in the definition of the general formulae in the present specification means a linear or branched carbon chain having 1 to 6 carbon atoms. Accordingly, "lower alkyl" is preferably linear or branched C₁₋₆ alkyl, and examples thereof include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, hexyl, and isohexyl. Among these, preferred are alkyls having 1 to 4 carbon atoms; and particularly preferred are methyl and ethyl.

Examples of the "lower alkylene" include methylene, ethylene, propylene, butylene, and also other branched lower alkylene. Preferred are lower alkylene having 1 to 3 carbon atoms; more preferred are methylene and ethylene; and particularly preferred is methylene.

Examples of the "halogen atom" include a fluorine atom, a chlorine atom, a bromine atom, and an iodine atom. Among these, preferred are a fluorine atom, a chlorine atom, and a bromine atom.

The "lower alkyl substituted with one or more halogens" means any of the hydrogen atoms of the "lower

alkyl" as described above that is substituted with one or more "halogen atoms". Particularly preferred is CF_3 .

The "cycloalkyl" means cycloalkyl having 3 to 8 carbon atoms.

5 The " R^2 and R^3 are taken together with the adjacent carbon atom to form cycloalkyl" specifically means that cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl are formed as such. Preferred is cyclopropyl.

 Examples of the "lower alkenyl" include vinyl, 1- or
10 2-propenyl, isopropenyl, 2-methyl-1-propenyl, 2-methyl-2-propenyl, 1-methyl-1-propenyl, and 1-methyl-2-propenyl. Preferred is vinyl.

 Examples of the "lower alkynyl" preferably include ethynyl, 1-propynyl, 2-propynyl, 1-butyne, 2-butyne, 3-
15 butynyl, and 1-methyl-2-propynyl.

[0018]

 The "aryl" means a mono- to tri-cyclic aromatic hydrocarbon ring group having 6 to 14 carbon atoms. Preferably, examples thereof include phenyl, naphthyl,
20 anthryl, and phenanthryl, and particularly preferred is phenyl.

 The "heteroaryl" means a 5- or 6-membered aromatic hetero ring group having 1 to 4 hetero atoms selected from a nitrogen atom, an oxygen atom, and a sulfur atom.
25 Preferably, examples thereof include thienyl, furyl,

pyrrolyl, thiazolyl, pyridyl, and pyrimidyl, and particularly preferred is thienyl.

As the "-lower alkylene-aryl", particularly preferred are benzyl and phenethyl.

5 Examples of the "substituent" of the "aryl which may be substituted" or the "heteroaryl which may be substituted" include lower alkyl, -O-lower alkyl, a halogen atom, OH, CN, CF₃, -NH₂, -NH(lower alkyl), and -N(lower alkyl)₂, but not limited thereto.

10 The "nitrogen-containing hetero ring group" means a 3 to 7-membered monocyclic nitrogen-containing hetero ring group comprising 1 to 3 nitrogen atoms. Preferred is a 4 to 6-membered monocyclic saturated hetero ring group, and more preferred are azetidyl, pyrrolidyl, and piperidyl.

15 The "5- or 6-membered hetero ring" means thiophene, furan, pyridine rings, and the like. Thus, in the present invention, it is taken together with an adjacent cyclopentane ring to form 5,6-dihydro-5H-cyclopenta[b]thiophene, 5,6-dihydro-5H-cyclopenta[b]furan,
20 6,7-dihydro-5H-cyclopenta[b]pyridine, 6,7-dihydro-5H-cyclopenta[c]pyridine rings, and the like.

Furthermore, "X" means hetero atoms such as O and S, or NR¹², as well as C(R⁴)(R⁵). Here, C(R⁴)(R⁵) means that carbon atoms have substituents of R⁴ and R⁵.

[0019]

Further, the compounds of the present invention include mixtures of various isomers such as tautomers and optical isomers, as well as individual isomers isolated
5 from them.

The compounds of the present invention may form acid-addition salts. Depending on the type of the substituent therein, the compounds may form salts with bases. Specifically, the salts include acid-addition salts with
10 mineral acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, and phosphoric acid; organic acids such as formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid,
15 tartaric acid, citric acid, methanesulfonic acid, and ethanesulfonic acid; or acidic amino acids such as aspartic acid and glutamic acid; as well as salts with an inorganic base such as sodium, potassium, magnesium, calcium, and aluminum; an organic base such as methylamine, ethylamine,
20 and ethanolamine; or a basic amino acid such as lysine, ornithine; and ammonium salts.

Further, the compounds of the present invention include hydrates, pharmaceutically acceptable various solvates, and crystalline polymorphic substances.

25 In addition, naturally, the compounds of the present invention are not limited to those described in the

Examples as described below, and include all the compounds of the above general formula (I) or (Ia), and their pharmaceutically acceptable salts.

[0020]

5 In addition, the compounds of the present invention include prodrugs that are metabolized in living bodies to give the compounds of the above formula (I) or (Ia), or compounds to be converted to their salts. Examples of the groups to form prodrugs of the compounds of the present
10 invention include the groups as described in Prog. Med., 5:2157-2161 (1985), and the groups as described in Pharmaceutical Research, Drug Design, Hirokawa Publishing Company (1990), Vol. 7, Molecular Planning, p. 163-198.

[0021]

15 [Production Processes]

 Taking advantage of the characteristics based on the basic structure or the kind of the substituent therein, the compounds of the present invention may be prepared according to various known production processes. Depending
20 on the kind of the functional group, the functional group in the starting compounds or intermediates may be modified into a suitable protected group, or a group that may be readily converted into a functional group, which may be technically effective in preparing the compounds. After
25 the process, the protective group may be optionally removed, and an intended compound may thus be obtained, if

necessary. Examples of the functional group include a hydroxyl group and a carboxyl group. Examples of their protective groups include the protective groups described in Greene & Wuts' "Protective Groups in Organic Synthesis",
5 2nd Ed. Depending on the reaction condition, these may be used suitably.

Typical production processes for the compounds (I) of the present invention are described below, but it goes without saying that the compounds (Ia) of the present
10 invention can also be prepared by the methods.

[0022]

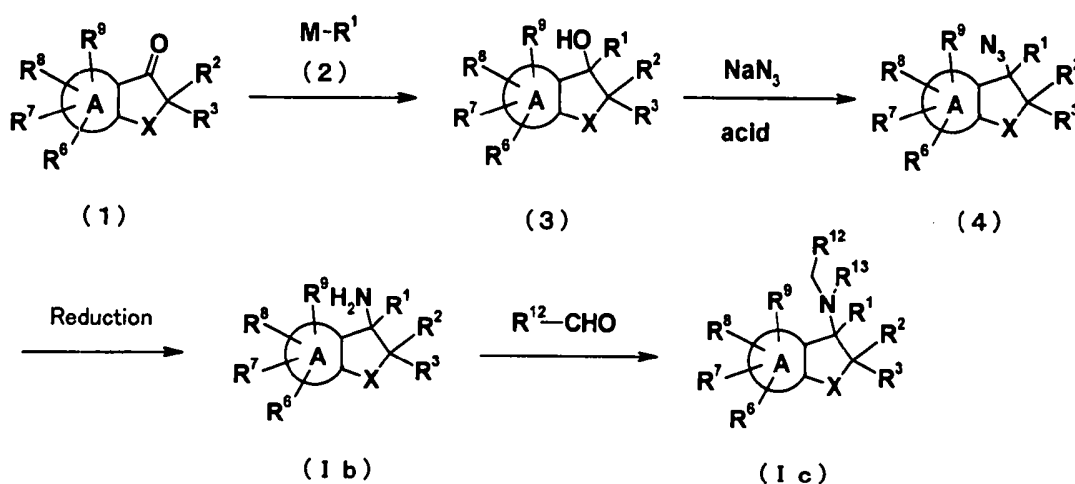
(Production Processes)

The compound (Ib) of the present invention can be prepared by the method represented by the scheme 1. That
15 is, indanone (1), and a Grignard reagent or an organic lithium reagent (2) can be reacted in an inert solvent such as tetrahydrofuran (hereinafter referred to as "THF"), diethyl ether and dichloromethane, from under cooling to at room temperature, and if desired, under heat, to give an
20 alcohol (3). Then, (3) can be further reacted with an azidizing agent such as sodium azide and trimethylsilyl azide, in a solvent such as chloroform, 1,2-dichloroethane, and toluene, in the presence of an acid such as trifluoroacetic acid, sulfuric acid, and methane sulfonic
25 acid, from under cooling to at room temperature, and if desired, under heat, to give an azide (4). Further, (4)

can be subjected to catalytic hydrogen reduction, under a hydrogen atmosphere from at normal pressure to under a pressurized condition, in an inert solvent such as ethanol, ethyl acetate, THF, and acetic acid, using a catalyst such as palladium-carbon, a Raney nickel, and platinum oxide, from at room temperature to under the heating condition, or subjected to hydride reduction in a solvent such as THF and diethyl ether, from under cooling to under heat, using a reducing agent such as lithium aluminum hydride, and (4) can be further reacted with a phosphine reagent such as triphenylphosphine, and tributyl phosphine, in a solvent such as THF, methanol, toluene, water, or a mixed solvent thereof, from at room temperature to under heat, to prepare a compound (Ib) wherein in the compound (I) of the present invention, both of R^{10} and R^{11} are all hydrogen atoms. Furthermore, (Ib) can be reacted with aldehyde in the presence of palladium-carbon, a rhodium carbon catalyst, or the like, in a solvent such as ethanol and THF, under a hydrogen atmosphere, from at room temperature to under heat to prepare a compound (Ic) wherein in the compound (I) of the present invention, at least one of R^{10} and R^{11} is a lower alkyl group. In addition, the compound (I) of the present invention is represented by either the following general formula (Ib) or (Ic).

[0023]

[Chem. 7]



(Scheme 1)

5 (wherein A, X, R^1 to R^3 , and R^6 to R^9 each have the same meanings as described above. Further, R^{12} represents hydrogen or a lower alkyl group, R^{13} represents $-CH_2-R^{12}$ or a hydrogen atom, and M represents alkali metals such as lithium and magnesium halides)

10 [0024]

The compounds (I) of the present invention may be subjected to reaction for group modification known to anyone skilled in the art to give a compound having a desired substituent. Typical reactions for it are
15 described below.

Among the compounds (I) of the present invention, a compound wherein any one of R^6 to R^9 is a cyano group may be prepared by processing the corresponding compound where R^6 to R^9 are bromo groups with $Zn(CN)_2$ in the presence of a

catalyst such as $\text{Pd}(\text{PPh}_3)_4$ in a solvent such as DMF and N-methylpiperidone under heat.

Among the compounds (1) of the present invention, in case where X is $\text{C}(\text{R}^4)(\text{R}^5)$, a compound wherein any one of R^3 to R^6 is an aryl group which may be substituted, lower alkenyl group, or a lower alkynyl group can be prepared by reacting the corresponding compound where any one of R^3 to R^6 is a bromo group or an iodo group, with an arylboronic acid, an alkenylboronic acid, an alkynylboronic acid, or a boronate ester thereof in the presence of a catalyst such as $\text{Pd}(\text{PPh}_3)_4$, $\text{PdCl}_2(\text{dppf})$, or $\text{Pd}_2(\text{dba})_3$ along with a base such as K_2CO_3 , Na_2CO_3 , KOH, CsF, and NaOEt, in a solvent such as DMF, N-methylpiperidone, DME, and toluene, or a mixed solvent thereof with water, under heat (Suzuki reaction).

[0025]

Furthermore, the deprotection may be attained in a suitable solvent in the presence of a suitable base. Specific examples of the base include NaOH, KOH, NaOMe, and NaOEt. Specific examples of the solvent include ethers such as THF, dioxane, and diglyme; alcohols such as MeOH, EtOH, and i-PrOH; MeCN, water; or a mixed solvent. Depending on the type of the reaction substrate and the reaction condition, the solvent may be suitably selected. The reaction temperature may vary depending on the type of the starting compound and the reaction condition, generally

covering from cooling to under reflux, preferably from about 0°C to about 100°C.

In addition, the deprotection may also be attained in the presence of a metal catalyst such as Pd-C, Pd(OH)₂, and
5 PtO₂ in a suitable solvent under a hydrogen atmosphere, but may be attained in the presence of a suitable Lewis acid in a suitable solvent. Examples of the Lewis acid are BCl₃, BBr₃, and AlCl₃, and examples of the solvent are ethers such as THF, dioxane; esters such as ethyl acetate; alcohols
10 such as MeOH, EtOH; MeCN; and a mixture thereof. Depending on the type of the reaction substrate and the reaction condition, the solvent may be suitably selected. The reaction temperature may vary depending on the type of the starting compound and the reaction condition, generally
15 covering from cooling to under reflux, preferably from about -80°C to about 30°C.

Thus prepared, the compounds (I) of the present invention may be isolated as free compounds or as their pharmaceutically acceptable salts. A salt of the compounds
20 (I) of the present invention may be prepared by processing the compounds (I) of the present invention that are in the form of free bases for ordinary reactions for salt formation.

[0026]

25 The compound (I) of the present invention or a pharmaceutically acceptable salt thereof may be isolated

and purified as their hydrates, solvates, or crystalline polymorphic substances. The isolation and purification may be attained through ordinary chemical treatment of extraction, concentration, evaporation, crystallization, 5 filtration, recrystallization, and various types of chromatography.

Various isomers may be isolated by selecting suitable starting compounds, or by separating them based on the difference between the isomers in the physical or chemical 10 properties thereof. For example, optical isomers may be led into stereochemically pure isomers by selecting suitable starting compounds or by racemic resolution of racemic compounds (for example, leading them into diastereomer salts with ordinary optically active acid for 15 optical resolution).

2,2-Dimethyl-1-phenylindan-1-amine, 1-(4-fluorophenyl)-2,2-dimethylindan-1-amine, 1-(2-methoxyphenyl)-2,2-dimethylindan-1-amine, 1-(3-methoxyphenyl)-2,2-dimethylindan-1-amine, 1,2,2-trimethylindan-1-amine, 20 1,2,2,5-tetramethylindan-1-amine, 1,2,2,6-tetramethylindan-1-amine, 4-fluoro-1,2,2-trimethylindan-1-amine, 5-fluoro-1,2,2-trimethylindan-1-amine, 7-fluoro-1,2,2-trimethylindan-1-amine, 5-methoxy-1,2,2-trimethylindan-1-amine, 6-methoxy-1,2,2-trimethylindan-1-amine, 6- 25 isopropoxy-1,2,2-trimethylindan-1-amine, 1-ethyl-2,2-dimethylindan-1-amine, 1-iso propyl-2,2-dimethylindan-1-

amine, 1'-methyl-1',3'-dihydrospiro[cyclopropan-1,2'-inden]-1'-amine, 2,4,5,5-tetramethyl-5,5-dihydro-4H-cyclopenta[b]thiophen-4-amine of the compound of the present invention or a salt thereof can be subjected to optical resolution to its (R)-isomers and (S)-isomers by the above-described method.

[0027]

The NMDA receptor antagonistic activity of the compounds of the present invention was confirmed by the following test methods.

1. MK-801 binding test:

1) Preparation of Specimens of Rat Meninges:

The whole brain was taken out from 30 10-week SD rats (Nippon SLC), and the cerebellum was removed from them. A 0.32 M sucrose solution was added to the part containing the cerebrum, cut in a mixer, and homogenized with a TeflonTM (trademark) homogenizer. This was centrifuged at 2800 rpm and 4°C for 15 minutes, and the resulting supernatant was again centrifuged at 15000 g and 4°C for 20 minutes. The pellets were suspended in 50 mM Tris-HCl (pH 7.5) containing 0.08% Triton X-100, and kept statically on ice for 30 minutes, then centrifuged at 15000 g and 4°C for 20 minutes. The pellets were suspended in 50 mM Tris-HCl (pH 7.5) added thereto, and centrifuged at 15000 g and 4°C for 20 minutes. 50 mM Tris-HCl (pH 7.5) was again added to the pellets, and centrifuged in the same manner as before.

The pellets were suspended in 20 ml of 50 mM Tris-HCl (pH 7.5) added thereto, and homogenized with the TeflonTM (trademark) homogenizer. The membrane specimen was divided into small tubes and stored in a deep freezer (-80°C).

- 5 Before use, this was washed twice with 5 mM Tris-HCl (pH 7.5) of five times that of the membrane specimen. Its concentration was controlled at 1 mg protein/ml with 5 mM Tris-HCl (pH 7.5) added to it, and this was used for assay.

[0028]

- 10 2) [³H] MK-801 binding Assay:

50 µl of the rat membrane specimen (1 mg protein/ ml) was added to a solution of a test compound dissolved in 1 µl of DMSO. Then, 50 µl of a ligand solution (600 nM glutamate, 600 nM glycine, 8 nM [³H] MK-801 (Perkin-Elmer) was added to it and well stirred, and reacted at room temperature for 45 minutes. Using Uni Filter Plate GF/B 96 (Perkin-Elmer) previously coated with 0.2% polyethyleneimine, the membrane specimen was collected, and the filter was well washed with 5 mM Tris-HCl (pH 7.5). 30 µl of Microscinti 20 (Perkin-Elmer) was added to the filter, and the radioactivity trapped by the filter was determined by a microplate scintillation counter (TopCountTM, by Beckman). Based on the MK-801 (final 1 µM) inhibition, 100%, of a control case of DMSO alone, the concentration of the compound for 50% inhibition, IC₅₀ was computed. The [³H]MK-801 binding affinity for the rat

membrane specimen was obtained to be $K_d = 1.6 \text{ nM}$ through
 Scatchard analysis. The K_i value of the compound was
 computed according to the calculation equation: $K_i =$
 $IC_{50}/(1 + \text{radioligand concentration (4 nM) in assay})/K_d$
 5 value (1.6 nM)).

As a result, the compounds of the present invention
 exhibited good NMDA receptor affinity. The K_i values of
 the NMDA receptor affinity of some typical compounds of the
 present invention are shown in Table 1 below.

10

[Table 1]

Compound of the present invention	K_i (μM)	Compound of the present invention	K_i (μM)
Example 2	0.4	Example 38	0.3
Example 10	0.4	Example 41	0.8
Example 17	0.8	Example 42	0.3
Example 18	0.3	Example 43	0.3
Example 21	0.1	Example 44	0.6
Example 23	0.9	Example 48	0.6
Example 36	0.4	Example 59	0.9
Example 37	0.1	Example 61	0.5

[0029]

15 2. Intracellular Calcium Concentration Determination Test
 by FLIPR (Fluorometric Imaging Plate Reader):

1) Preparation of Rat First-Generation Neurocytes:

Anesthetized with ether, Wistar rats (Nippon SLC) of
 pregnancy 19 days were let die from loss of blood by breast
 20 incision. The abdomen was cut open, and the womb was taken

out, and the fetus was taken out of it. The whole brain was taken out, then the hemicerebrum was isolated in Neurobasal medium (Glu, Asp-free) (Gibco), and the meninx was removed. The hemicerebrum was recovered by
5 centrifugation, and suspended in a cell-dispersing solution (0.36 mg/ml papain, 150 U/ml DNase 1, 0.02% L-cysteine monohydrochloride monohydrate, 0.02% bovine serum albumin, 0.5% glucose, Ca^{2+} , Mg^{2+} -free PBS), and processed at 37°C for 15 minutes. This was centrifuged at 400 g for 5
10 minutes, and the supernatant was removed by suction. This was suspended in a neurocyte culture medium (Sumitomo Bakelite), and the cell masses were removed by filtration. The number of the living cells was counted, and 100,000 cells/well were incubated on a 96-well plate (Biocoat
15 PDL96W black/clear, by Nippon Becton Dickinson) (at 37°C in 5% CO_2).

[0030]

2) Intracellular Calcium Concentration Determination by FLIPR (Fluorometric Imaging Plate Reader):

20 The culture of rat first-generation neurocytes (DIV7-9) was removed by suction, and the cells were washed once with a 100 μl assay buffer (Hank's Balanced Salt Solution (Ca^{2+} , Mg^{2+} -free), 20 mM Hepes-NaOH (pH 7.4), 1 mM CaCl_2). 100 μl of the assay buffer containing Fluo3 (Dojin
25 Chemical) was added thereto, and incubated for 1 hour (37°C, 5% CO_2). The cells were washed three times with 100

2007274420 30 Mar 2009

μl of the assay buffer, and then a compound solution dissolved in 1 μl of DMSO, and 100 μl of the assay buffer containing 2.5 μM (final concentration) tetrodotoxin were added to it and incubated for 30 minutes (37°C, 5% CO_2). The fluorescent intensity was measured at intervals of 2 seconds. Ten seconds after the measurement start, 50 μl of a ligand solution (Hank's Balanced Salt Solution (Ca^{2+} , Mg^{2+} -free), 20 mM Hepes-NaOH (pH 7.4), 1 mM CaCl_2 , 9 μM NMDA, 30 μM glycine) containing the test compound solution dissolved in 0.5 μl of DMSO was added to it, and the fluorescent intensity of the system was measured for 120 seconds from the start of the measurement. The data measured for 120 seconds (60 times in total) were averaged. Based on the 10 μM MK-801 inhibition with a control case of DMSO alone of 100%, the concentration of the compound for 50% inhibition, IC_{50} , was computed.

As a result, the compounds of the present invention exhibited a good NMDA receptor antagonizing effect.

[0031]

The pharmaceutical composition that contains, as an active component thereof, one or more of the compounds of the present invention and their pharmaceutically acceptable salts may be formulated, in conjunction with carriers and vehicles for ordinary pharmaceutical application and other additives, as tablets, powders, infinitesimal grains, granules, capsules, pills, liquids, injections,

suppositories, ointments, and fomentations, and is administered orally or parenterally.

The clinical dose to human of the compound of the present invention may be suitably determined, depending on the symptom, the body weight, the age and the sex of a patient to whom the compound is applied. It may be usually from 0.1 to 500 mg/adult/day for oral administration, and from 0.01 to 100 mg/adult/day for non-oral administration, and this may be administered all at once or in several times. The dose may vary under various conditions, and as the case may be, it may be smaller than the above-mentioned dose range.

The solid composition for oral administration of the compound of the present invention may be tablets, powders, granules, or the like. In the solid composition, one or more active substances may be mixed with at least one inert diluent, such as lactose, mannitol, glucose, hydroxypropyl cellulose, microcrystalline cellulose, starch, polyvinylpyrrolidone, and magnesium metasilicate aluminate. According to an ordinary manner, the composition may contain any other additive than such an inert diluent, for example, a lubricant such as magnesium stearate, a disintegrator such as calcium cellulose glycolate, a stabilizer such as lactose, a solubilizer, and a solubilizing adjuvant such as glutamic acid and aspartic

acid. The tablets and pills may be coated with a sugar or with a gastric-coating or enteric-coating film.

[0032]

The liquid composition for oral administration
5 includes pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs, and contains ordinary inert diluents such as purified water and ethyl alcohol. The composition may contain any other additives than such an inert diluent, for example, auxiliary agents such as a
10 solubilizer, a dissolution promoter, a wetting agent, a suspending agent, as well as a sweetener, a flavoring, a fragrance, and a preservative. The injection for non-oral administration includes sterilized aqueous or non-aqueous solutions, suspensions, and emulsions. The diluent for the
15 aqueous solution and suspension include, for example, distilled water for injection and physiological saline. The diluent for the non-aqueous solution and suspension includes, for example, propylene glycol, polyethylene glycol, vegetable oil such as olive oil, alcohols such as
20 ethyl alcohols, Polysorbate 80 (trade name).

The composition may further contain any other additive such as an isotonizer, a preservative, a wetting agent, an emulsifier, a dispersant, a stabilizer, a solubilizer, and a dissolution promoter. These may be
25 sterilized by filtration through a bacteria-trapping filter, or by addition of a germicide, or through

irradiation with light. As the case may be, a germ-free solid composition may be prepared, and it may be dissolved in germ-free water or germ-free solvent for injection to give the intended liquid composition before use.

5

EXAMPLES

[0033]

Hereinbelow, the compounds of the present invention are described with reference to the following Examples.

10 The starting compounds for the compounds of the present invention include novel compounds, and thus their production examples are illustrated as Reference Examples.

Reference Example 1

To a solution of 3-hydroxymethylindan-1-one (1.23 g)
15 and methyl iodide (4.31 g) in THF (20 ml) was added 55% oily sodium hydride (1.33 g) under ice-cooling, followed by stirring at the same temperature for 1 hour. To the reaction liquid was added a saturated aqueous ammonium chloride solution, followed by extraction with ethyl
20 acetate, washed with saturated brine, and then dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent; n-hexane:ethyl acetate=10:1) to obtain a compound of Reference Example 1
25 as an oily substance.

Reference Example 2

To a solution of t-BuOK (3.0 g) in THF (7 ml) was added a solution of methyl 3-oxoindane-1-carboxylate (1.0 g) in THF (2 ml) at -20°C, followed by stirring at the same
5 temperature for 30 minutes. To this was added methyl iodide (4.5 g), followed by stirring for 30 minutes while warming to room temperature. The reaction liquid was ice-cooled, and partitioned between 1 N hydrochloric acid and ethyl acetate. The organic layer was washed with saturated
10 brine, and then dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure to obtain a compound of Reference Example 2 (1.2 g) as an oily substance.

Reference Example 3

15 To a solution of the compound of Reference Example 2 (3.2 g) in DMSO (20 ml) was added LiCl (1.2 g), followed by stirring at 200°C for 2 hours. After cooling the reaction, it was partitioned between 1 N hydrochloric acid and ethyl acetate, and the organic layer was washed with water and
20 saturated brine. It was dried over anhydrous magnesium sulfate, and the solvent was then evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent; n-hexane:ethyl acetate=4:1) to
25 obtain a compound of Reference Example 3 (1.9 g) as an oily substance.

2007274420 30 Mar 2009

[0034]

Reference Example 4

To a solution of the compound of Reference Example 2 (2.6 g) in methanol (30 ml) was added sodium borohydride (2.1 g) under ice-cooling, followed by heating under reflux for 30 minutes. The reaction liquid was cooled, followed by addition of a saturated aqueous ammonium chloride solution and extraction with ethyl acetate. Further, it was washed with a saturated aqueous sodium hydrogen carbonate solution and saturated brine, and then dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure to obtain a compound of Reference Example 4 (2.0 g) as an oily substance.

Reference Example 5

A compound of Reference Example 5 was prepared from the compound of Reference Example 4 in the same manner as in Reference Example 1.

Reference Example 6

To a solution of the compound of Reference Example 5 (0.99 g) in methanol (8 ml) was added a 10 M aqueous sodium hydroxide solution (8 ml), followed by stirring at 60°C for 12 hours. Methanol was evaporated under reduced pressure, and then ice-cooled, followed by addition of concentrated hydrochloric acid for neutralization and further stirring at room temperature for 1 hour. The precipitate was collected by filtration, and dried under reduced pressure to obtain a

compound of Reference Example 6 (0.94 g) as a colorless amorphous substance.

Reference Example 7

To a solution of the compound of Reference Example 6
5 (0.94 g) and ammonium chloride (0.64 g), 1-
hydroxybenzotriazole (0.54 g) in DMF (10 ml) was added N-
[3-(dimethylamino)propyl]-N'-ethylcarbodiimide
hydrochloride (1.2 g), followed by stirring at room
temperature for 3 days. To this was added saturated
10 aqueous ammonia solution, followed by stirring for one more
day, and then the precipitate was collected by filtration,
and dried under reduced pressure to obtain a compound of
Reference Example 7 (0.62 g) as a colorless crystal,
Reference Example 8

15 The present compound was prepared from 4-methylindan-
1-one in the same manner as in Reference Example 2.

Reference Example 9

The present compound was prepared from 4-
trifluoromethylindan-1-one in the same manner as in
20 Reference Example 2.

[0035]

Reference Example 10

The present compound was prepared from 5-
trifluoromethylindan-1-one in the same manner as in
25 Reference Example 2.

Reference Example 11

To 3-(3-trifluoromethylphenyl)propionic acid was added trifluoromethanesulfonic acid at room temperature, followed by stirring at 60°C for 3 hours. The reaction liquid was put into cold water, followed by extraction with a mixed solvent of ethyl acetate and THF. The organic layer was washed with saturated brine, and dried over anhydrous sodium sulfate, and the solvent was then evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent; n-hexane:ethyl acetate=9:1 to 5:1) to obtain 5-trifluoromethylindane (2.2 g) and a compound of Reference Example 11 (0.70 g) as colorless solids, respectively.

Reference Example 12

The present compound was prepared from the compound of Reference Example 11 in the same manner as in Reference Example 2.

Reference Example 13

To a solution of 7-bromo-4-fluoro-2,2-dimethylindan-1-one (3.7 g) in toluene (30 ml) were added tributyl(vinyl)tin (7.0 g), tris(dibenzylideneacetone)dipalladium (0.40 g), and a 0.49 M solution (2.7 ml) of tri(t-butyl)phosphine in n-hexane, at followed by stirring at 70°C for 12 hours. The reaction liquid was cooled, and a saturated aqueous potassium fluoride solution was added thereto, followed by stirring at room temperature for 30 minutes. Then, the

insoluble materials were removed by filtration through Celite. The filtrate was extracted with ethyl acetate, washed with saturated brine, and then dried over anhydrous magnesium sulfate, and the solvent was evaporated under
5 reduced pressure. The residue was purified by silica gel column chromatography (eluent; n-hexane:ethyl acetate=10:1) to obtain a compound of Reference Example 13 (1.7 g) as an oily substance.

Reference Example 14

10 A solution of 2-bromo-5-fluorobenzaldehyde (1.5 g), malonic acid (1.5 g), and piperidine (0.07 ml) in pyridine (10 ml) was heated for 1 day under reflux. The reaction liquid was concentrated under reduced pressure, 1 N hydrochloric acid was then added thereto for
15 neutralization, and crystallized precipitates were collected by filtration. This was dissolved in methanol (10 ml), and a 5% rhodium carbon catalyst (150 mg) was added thereto, followed by stirring at room temperature for 12 hours under a hydrogen atmosphere (1 atm). The
20 insoluble materials was removed by filtration through Celite, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent; chloroform:methanol=10:1) to obtain a compound of Reference Example 14 (0.50 g) as a colorless
25 solid.

[0036]

Reference Example 15

The present compound was prepared from the compound of Reference Example 14 in the same manner as in Reference
5 Example 11.

Reference Example 16

The present compound was prepared from the compound of Reference Example 15 in the same manner as in Reference Example 1.

10 Reference Example 17

The present compound was prepared from 3-(3-bromo-5-methoxy phenyl)propionic acid in the same manner as in Reference Example 11.

Reference Example 18

15 The present compound was prepared from the compound of Reference Example 17 in the same manner as in Reference Example 2.

Reference Examples 19 to 25

The present compound was prepared from each of the
20 corresponding indanone and a Grignard reagent in the same manner as in Reference Example 28.

Reference Example 26

The present compound was prepared from 1-bromo-2-fluorobenzene and the corresponding indanone in the same
25 manner as in Reference Example 29.

Reference Example 27

The present compound was prepared from each of the corresponding indanone and a Grignard reagent in the same manner as in Reference Example 28.

5 Reference Example 28

To a solution of 2,2-dimethylindan-1-one (0.63 g) in THF was added a 1 M solution of (4-fluorophenyl)magnesium bromide in THF (7.8 ml) at room temperature, followed by stirring at the same temperature for 2 hours. To the
10 reaction liquid was added a saturated aqueous ammonium chloride solution, followed by extraction with ethyl acetate, and the organic layer was washed with saturated brine. It was dried over anhydrous magnesium sulfate, the solvent was evaporated under reduced pressure, and the
15 residue was purified by silica gel column chromatography (eluent; n-hexane:ethyl acetate=30:1) to obtain a compound of Reference Example 28 (0.99 g) as an oily substance.

Reference Example 29

To a solution of 2-bromoanisole (1.4 g) in diethyl
20 ether (10 ml) was added a 1.6 M solution (4.6 ml) of n-butyl lithium in n-hexane at -78°C, followed by stirring at the same temperature for 1 hour. To this was added 2,2-dimethylindan-1-one (0.60 g), followed by further stirring at the same temperature for 1 hour. A saturated aqueous
25 ammonium chloride solution was added thereto, followed by extraction with ethyl acetate, and the organic layer was

washed with saturated brine, and dried over anhydrous magnesium sulfate. Then, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent; n-hexane:ethyl acetate=30:1) to obtain a compound of Reference Example 29 (0.62 g) as an oily substance.

[0037]

Reference Example 30

The present compound was prepared from each of the corresponding indanone and a Grignard reagent in the same manner as in Reference Example 28.

Reference Examples 31 and 32

The present compound was prepared from each corresponding indanone in the same manner as in Reference Example 29.

Reference Examples 33 to 41

The present compound was prepared from each corresponding indanone in the same manner as in Reference Example 42.

Reference Example 42

To a solution of 2,2,6-trimethylindan-1-one (1.8 g) in THF (35 ml) was added a 1.4 M solution (15 ml) of methyl magnesium bromide in THF/toluene (25:75), and warmed to room temperature, followed by stirring for 2 hours. After completion of the reaction, a saturated aqueous ammonium chloride solution was added thereto under ice-cooling,

followed by stirring, and extracted with ethyl acetate.

The organic layer was washed with saturated brine, and then dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was

5 purified by silica gel column chromatography (eluent; n-hexane:ethyl acetate=10:1) to obtain a compound of Reference Example 42 (1.9 g) as an oily substance.

Reference Example 43

To a solution of 6-methoxy-2,2-dimethylindan-1-one
10 (2.2 g) in THF (40 ml) was added a 1.4 M solution (17 ml) of methyl magnesium bromide in THF/toluene (25:75) under ice-cooling, and warmed to room temperature, followed by stirring for 2 hours. After completion of the reaction, a saturated aqueous ammonium chloride solution was added
15 thereto under ice-cooling, followed by stirring and extraction with ethyl acetate. The organic layer was washed with saturated brine, and then dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel
20 column chromatography (eluent; n-hexane:ethyl acetate=10:1) to obtain a compound of Reference Example 43 (2.3 g) as an oily substance.

Reference Example 44

To a solution of 6-fluoro-2,2-dimethylindan-1-one
25 (0.47 g) in THF (9 ml) was added a 0.96 M solution (5.5 ml) of methyl magnesium bromide in THF under ice-cooling,

followed by warming to room temperature and stirring for 2 hours. After completion of the reaction, a saturated aqueous ammonium chloride solution was added thereto under ice-cooling, followed by stirring and extraction with ethyl acetate. The organic layer was washed with saturated brine, and then dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent; n-hexane:ethyl acetate=10:1) to obtain a compound of Reference Example 44 (0.45 g) as an oily substance.

[0038]

Reference Example 45

To a solution of 6-bromo-2,2-dimethylindan-1-one (3.8 g) in THF (60 ml) was added a 1.4 M solution (17 ml) of methyl magnesium bromide in THF/toluene (25:75) under ice-cooling, followed by warming to room temperature and stirring for 2 hours. After completion of the reaction, a saturated aqueous ammonium chloride solution was added thereto under ice-cooling, followed by stirring and extraction with ethyl acetate. The organic layer was washed with saturated brine, and then dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent; n-hexane:ethyl acetate=5:1) to obtain a compound of Reference Example 45 (3.8 g) as an oily substance.

Reference Example 46

To a solution of 2,2-dimethyl-6-trifluoromethylindan-1-one (1.7 g) in THF (15 ml) was added a 1.4 M solution (10 ml) of methyl magnesium bromide in THF/toluene (25:75) under ice-cooling, followed by warming to room temperature and stirring for 1 hour. After completion of the reaction, a saturated aqueous ammonium chloride solution was added thereto under ice-cooling, followed by stirring and extraction with ethyl acetate. The organic layer was washed with saturated brine, and then dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent; n-hexane:ethyl acetate=6:1) to obtain a compound of Reference Example 46 (1.7 g) as an oily substance.

Reference Examples 47 to 54

The present compound was prepared from the corresponding indanone in the same manner as in Reference Example 42.

[0039]

Reference Example 55

To a solution of 2,2-dimethylindan-1-one (2.0 g) and trimethyl(trifluoromethyl)silane (2.7 g) in THF (20 ml) was added a 1 M solution (12 ml) of tributyl ammonium fluoride in THF under ice-cooling, followed by slowly warming to room temperature and stirring for 5 hours. 1 N

hydrochloric acid was added thereto, followed by extraction with diethyl ether, washing with a saturated aqueous sodium chloride solution, and then drying over anhydrous magnesium sulfate. The solvent was evaporated under reduced

5 pressure, and the residue was purified by silica gel column chromatography (eluent; n-hexane:ethyl acetate=10:1) to obtain a compound of Reference Example 55 (2.9 g) as an oily substance.

Reference Example 56

10 To a solution of 2,2-dimethylindan-1-one (2.0 g) in THF (20 ml) was added a 0.5 M solution of ethyllithium in benzene/cyclohexane (9:1) (37 ml) at -78°C, followed by stirring at the same temperature for 2 hours. To the reaction liquid was added a saturated aqueous ammonium
15 chloride solution, followed by extraction with ethyl acetate, and drying over anhydrous sodium sulfate, and the solvent was then evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent; n-hexane:ethyl acetate=3:1) to obtain a compound
20 of Reference Example 56 (2.1 g) as an oily substance.

Reference Example 57

The present compound was prepared from the corresponding indanone in the same manner as in Reference Example 56.

Reference Example 58 to 61

The present compound was prepared from the corresponding indanone and Grignard reagent in the same manner as in Reference Example 42.

5 [0040]

Example 1

2,2-Dimethyl-1-phenylindan-1-amine monofumarate

To a solution of 2,2-dimethyl-1-phenylindan-1-ol (736 mg) in chloroform (10 ml) were added sodium azide (412 mg) and trifluoroacetic acid (1.4 ml) under ice-cooling, followed by stirring at the same temperature for 2 hours. It was alkalified by addition of 10% aqueous ammonia, and then extracted with ethyl acetate, and the organic layer was washed with saturated brine. The solvent was evaporated under reduced pressure to obtain an azide (798 mg). Thereafter, this was dissolved in methanol (10 ml), and 10% palladium/carbon (85 mg) was added thereto, followed by stirring at room temperature for 3 days under a hydrogen atmosphere (normal pressure). The reaction mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by basic silica gel column chromatography (eluent; n-hexane:ethyl acetate=30:1 to 5:1) to obtain an amine (437 mg). A portion thereof (119 mg) and fumaric acid (59 mg) were dissolved in methanol, and the solvent was then evaporated under reduced pressure. The residue was

recrystallized from acetone to obtain a compound of Example 1 (168 mg) as a colorless crystal.

Example 2

The present compound was prepared in the same manner
5 as in Example 1.

Example 3

cis-3-(Methoxymethyl)-2,2-dimethyl-1-phenylindan-1-amine hydrochloride

Example 4

10 trans-3-Hydroxy methyl-2,2-dimethyl-1-phenylindan-1-amine hydrochloride

To a solution of the compound of Reference Example 20 (1.8 g) in methylene chloride (30 ml) were added sodium azide (1.3 g) and trifluoroacetic acid (2.5 ml), followed
15 by stirring at the same temperature for 30 minutes. It was alkalified by addition of 10% aqueous ammonia, and extracted with ethyl acetate, and the organic layer was washed with saturated brine. The solvent was evaporated under reduced pressure to obtain an azide. Thereafter,
20 this was dissolved in methanol (30 ml), and 10% palladium/carbon (0.5 g) was added thereto, followed by stirring at room temperature for 4 hours under a hydrogen atmosphere (normal pressure). The reaction mixture was filtered through Celite, and the filtrate was concentrated
25 under reduced pressure. The residue was purified by silica gel column chromatography (eluent;

chloroform:methanol=20:1) to obtain an amine (1.2 g).

Further, a portion thereof (1.1 g) was dissolved in methylene chloride (10 ml), and a 1 M solution (4.5 ml) of boron tribromide in methylene chloride was added thereto

5 under ice-cooling, followed by stirring for 2 hours. To the reaction liquid were added alumina and methanol, followed by stirring at room temperature for 1 hour, and the solvent was then evaporated under reduced pressure.

The residue was purified by silica gel column

10 chromatography (eluent; chloroform:methanol=4:1) to obtain free forms of the compounds of Examples 3 and 4,

respectively. To each of the solutions in ethyl acetate was added a 4 N solutions of HCl in ethyl acetate, and the solvent was then evaporated under reduced pressure. The

15 residue was crystallized from n-hexane to obtain a compound of Example 3 (350 mg), and a compound of Example 4 (97 mg) as colorless crystals, respectively.

[0041]

Example 5

20 trans-2-Methyl-1,2-diphenylindan-1-amine
hydrochloride

Example 6

cis-2-Methyl-1,2-diphenylindan-1-amine hydrochloride

A hydrochloride of a diastereomer mixture obtained in
25 the same manner as in Example 17 from 1,2-diphenylindan-1-ol was recrystallized from ethanol to obtain a compound of

Example 5, and further, the filtrate was concentrated under reduced pressure, and then was purified by alumina/silica gel column chromatography (eluent; chloroform). Thus obtained residue was crystallized from n-hexane to make its hydrochloride by an ordinary method, thereby obtaining a compound of Example 6 as a colorless crystal, respectively.

Examples 7 and 8

The present compounds were prepared in the same manner as in Example 1.

10 Example 9

The present compound was prepared in the same manner as in Example 21.

Example 10

N,2,2-trimethyl-1-phenylindan-1-amine hydrochloride

15 To a solution of a desalted compound of Example 1 (125 mg) in ethanol (5 ml) were added an aqueous 37% formaldehyde solution (0.2 ml) and 10% palladium/carbon, followed by stirring at room temperature for 1 day under a hydrogen atmosphere (normal pressure). The reaction mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure, and then partitioned between a saturated aqueous sodium hydrogen carbonate solution and ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by basic silica gel

column chromatography (eluent; n-hexane:ethyl acetate=20:1 to 5:1). Then, the residue was dissolved in a 4 N solution of HCl in ethyl acetate, and the solvent was evaporated under reduced pressure. The residue was washed with a
5 mixed solvent of diisopropyl ether and 1,4-dioxane to obtain a compound of Example 10 (115 mg) as a colorless crystal.

Example 11

The present compound was prepared by reacting for a
10 longer time in the same manner as in Example 10.

Examples 12 to 16

The present compounds were prepared in the same manner as in Example 17.

[0042]

15 Example 17

1-(4-Fluorophenyl)-2,2-dimethylindan-1-amine
monofumarate

To a solution of the compound of Reference Example 28 (984 mg) in chloroform (12 ml) were added sodium azide (500
20 mg) and trifluoroacetic acid (1.7 ml) under ice-cooling, followed by stirring at room temperature for 3 hours. It was alkalified by addition of 10% aqueous ammonia, and extracted with chloroform, and then the organic layer was washed with saturated brine. It was dried over anhydrous
25 magnesium sulfate, and the solvent was then evaporated under reduced pressure. The residue was purified by silica

gel column chromatography (eluent; n-hexane:ethyl acetate=40:1) to obtain an azide (1.08 g). Thereafter, this was dissolved in methanol (13 ml), and 10% palladium/carbon (102 mg) was added thereto, followed by
5 stirring at room temperature for 3 hours under a hydrogen atmosphere (normal pressure). The reaction mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by basic silica gel column chromatography (eluent; n-hexane:ethyl
10 acetate=30:1 to 5:1) to obtain an amine (562 mg). A portion thereof (100 mg) and fumaric acid (51 mg) were dissolved in methanol, and the solvent was then evaporated under reduced pressure. The residue was washed with a mixed solvent of diisopropyl ether and 1,4-dioxane to
15 obtain a compound of Example 17 (127 mg) as a colorless crystal.

[0043]

Example 18

1-(2-Methoxy phenyl)-2,2-dimethylindan-1-amine
20 hydrochloride

To a solution of the compound of Reference Example 29 (620 mg) in chloroform (9 ml) were added sodium azide (304 mg) and trifluoroacetic acid (1 ml) under ice-cooling, followed by stirring at room temperature for 3 hours. It
25 was alkalified by addition of 10% aqueous ammonia, and then extracted with chloroform, and the organic layer was washed

with saturated brine. It was dried over anhydrous sodium sulfate, and the solvent was then evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent; n-hexane:ethyl acetate=30:1) to
5 obtain an azide (635 mg). Thereafter, this was dissolved in methanol (8 ml), and 10% palladium/carbon (62 mg) was added thereto, followed by stirring at room temperature for 3 hours under a hydrogen atmosphere (normal pressure). The reaction mixture was filtered through Celite, and the
10 filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent; chloroform:methanol=30:1) to obtain an amine (357 mg). Further, this was dissolved in ethyl acetate, a 4 N solution of HCl in ethyl acetate was added thereto, and the
15 solvent was evaporated under reduced pressure. The residue was washed with n-hexane to obtain a compound of Example 18 (231 mg) as a colorless crystal.

Examples 19 and 20

The present compounds were prepared in the same
20 manner as in Example 18.

[0044]

Example 21

1-(3-Hydroxyphenyl)-2,2-dimethylindan-1-amine

To a solution of the compound of Example 19 (150 mg)
25 in methylene chloride (2 ml) was added a 1 M solution of boron tribromide in methylene chloride (0.67 ml) under ice-

cooling, followed by stirring for 2 hours. A saturated aqueous sodium hydrogen carbonate solution was added thereto, followed by extraction with chloroform, and drying over anhydrous magnesium sulfate, and the solvent was then
5 evaporated under reduced pressure. The residue was purified by basic silica gel column chromatography (eluent; n-hexane:ethyl acetate=1:1 to 0:1) to obtain a compound of Example 21 (51 mg) as a colorless amorphous substance.

Example 22

10 The present compound was prepared in the same manner as in Example 18.

Example 23

1,2,2-Trimethylindan-1-amine hydrochloride

To a solution of 1,2,2-trimethylindan-1-ol (406 mg)
15 in chloroform (6 ml) were added sodium azide (300 mg) and trifluoroacetic acid (1 ml) under ice-cooling, followed by stirring at room temperature for 1 hour. It was alkalified by addition of 10% aqueous ammonia, and then extracted with chloroform, and the organic layer was washed with saturated
20 brine. It was dried over anhydrous magnesium sulfate, and the solvent was then evaporated under reduced pressure to obtain an azide. Then, this was dissolved in methanol (6 ml), and 10% palladium-carbon (40 mg) was added thereto, followed by stirring at room temperature for 3 hours under
25 a hydrogen atmosphere (normal pressure). The reaction mixture was filtered through Celite, and the filtrate was

concentrated under reduced pressure. The residue was purified by basic silica gel column chromatography (eluent; n-hexane:ethyl acetate=30:1 to 5:1) to obtain an amine (140 mg) as an oily substance. Further, this was dissolved in ethyl acetate, a 4 N solution of HCl in ethyl acetate was added thereto, and the solvent was evaporated under reduced pressure. The residue was crystallized from diisopropyl ether to obtain a compound of Example 23 (153 mg) as a colorless crystal.

10 Example 24

cis-1,2,2,3-Tetramethylindan-1-amine hydrochloride

Example 25

trans-1,2,2,3-Tetramethylindan-1-amine hydrochloride

The same procedure as in Example 23 using the compound of Reference Example 33 was carried out, and the resulting diastereomer was separated, and purified by silica gel column chromatography (eluent; chloroform:methanol: saturated aqueous ammonia=50:1:0.1 to 20:1:0.1), and each was made into its hydrochloride by an ordinary method, thereby obtaining a compound of Example 24, and a compound of Example 25 as colorless crystals, respectively.

Example 26

The present compound was prepared in the same manner as in Example 23.

[0045]

Example 27

cis-3-Methoxy-1,2,2-trimethylindan-1-amine
hydrochloride

5 To a 3 N aqueous solution (10 ml) of sodium hydroxide
were added bromine (0.18 ml) and the compound of Reference
Example 7 (0.62 g) under ice-cooling, followed by stirring
at room temperature for 3 days. An aqueous Na₂SO₃ solution
was added thereto, followed by stirring, extraction with
10 methylene chloride, and washing with saturated brine. It
was dried over anhydrous magnesium sulfate, and the solvent
was then evaporated under reduced pressure. The residue
was purified by basic silica gel column chromatography
(eluent; n-hexane:ethyl acetate=4:1), and thereafter, by
15 neutral silica gel column chromatography (eluent;
chloroform:methanol:saturated brine=50:1:0.1) to obtain an
amine (179 ml) as an oily substance. This was made into
its hydrochloride, and then crystallized from n-hexane to
obtain a compound of Example 27 (89 mg) as a colorless
20 crystal.

[0046]

Example 28

1,2,2,4-Tetramethylindan-1-amine hydrochloride

Example 29

25 4-Fluoro-1,2,2-trimethylindan-1-amine hydrochloride

Example 30

4-Trifluoromethyl-1,2,2-trimethylindan-1-amine
hydrochloride

Example 31

5 1,2,2,5-Tetramethylindan-1-amine hydrochloride

Example 32

5-Methoxy-1,2,2-trimethylindan-1-amine hydrochloride

Example 33

5-Fluoro-1,2,2-trimethylindan-1-amine·hydrochloride

10 Example 34V

5-Chloro-1,2,2-trimethylindan-1-amine hydrochloride

Example 35

5-Trifluoromethyl-1,2,2-trimethylindan-1-amine
hydrochloride

15 The compounds of Examples 28 to 35 as described above
were prepared from the corresponding alcohols in the same
manner as in Example 23.

Example 36

1,2,2,6-Tetramethylindan-1-amine·hydrochloride

20 To a solution of the compound of Reference Example 42
(1.9 g) in chloroform (38 ml) were added sodium azide (1.3
g) and trifluoroacetic acid (4.6 mg) under ice-cooling,
followed by stirring at the same temperature for 1 hour.
It was alkalified by addition of 10% aqueous ammonia, and
25 then extracted with chloroform, and the organic layer was
washed with saturated brine. It was dried over anhydrous

magnesium sulfate, and the solvent was then evaporated under reduced pressure to obtain an azide. Then, this was dissolved in methanol (38 ml), and 10% palladium-carbon (200 mg) was added thereto, followed by stirring at room
5 temperature for 12 hours under a hydrogen atmosphere (normal pressure). The reaction mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent; chloroform: methanol=10:1)
10 to obtain an amine (720 mg) as an oily substance. Further, this was dissolved in ethyl acetate, a 4 N HCl solution in ethyl acetate was added thereto, and the solvent was evaporated under reduced pressure. The residue was crystallized from n-hexane/diethylether to obtain a
15 compound of Example 36 (227 mg) as a colorless crystal.

[0047]

Example 37

6-Hydroxy-1,2,2-trimethylindan-1-amine hydrochloride

To a solution of a free form (96 mg) of the compound
20 of Example 38 in 1,2-dichloroethane (2 ml) was added a 1 M boron tribromide solution in methylene chloride (0.5 ml) under ice-cooling, followed by stirring at room temperature for 3 hours. To the reaction liquid was slowly added water under ice-cooling and stirred, followed by extraction with
25 ethyl acetate, and then washing with saturated brine. It was dried over anhydrous magnesium sulfate, and the solvent

was then evaporated under reduced pressure. The residue was recrystallized from diisopropyl ether to obtain an amine (48 mg) as a colorless crystal. Further, this was made into its hydrochloride by an ordinary method, and then
5 crystallized from a mixed solvent of diethylether and n-hexane to obtain a compound of Example 37 (47 mg) as a colorless crystal.

Example 38

6-Methoxy-1,2,2-trimethylindan-1-amine hydrochloride

10 To a solution of the compound of Reference Example 43 (2.3 g) in chloroform (40 ml) were added sodium azide (1.4 g) and trifluoroacetic acid (4.8 ml) under ice-cooling, followed by stirring at the same temperature for 1 hour. It was alkalified by addition of 10% aqueous ammonia, and
15 then extracted with chloroform, and the organic layer was washed with saturated brine. It was dried over anhydrous magnesium sulfate, and the solvent was then evaporated under reduced pressure to obtain an azide. Then, this was dissolved in methanol (25 ml), and 10% palladium-carbon
20 (330 mg) was added thereto, followed by stirring at room temperature for 12 hours under a hydrogen atmosphere (normal pressure). The reaction mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel
25 column chromatography (eluent; chloroform: methanol=10:1) to obtain an amine (1.1 g) as an oily substance. Further,

a portion thereof (270 mg) was made into its hydrochloride by an ordinary method, and recrystallized from a mixed solvent of diethylether and ethyl acetate to obtain a compound of Example 38 (107 mg) as a colorless crystal.

5 Example 39

The present compound was prepared in the same manner as in Example 40.

[0048]

Example 40

10 6-Isopropoxy-1,2,2-trimethylindan-1-amine
hydrochloride

To a solution of a free form (179 mg) of the compound of Example 37 in THF (3 ml) were added 2-propanol (5 ml), diethylazodicarboxylate (0.55 ml), and triphenylphosphine
15 (300 mg), followed by stirring at room temperature for 1 day. The reaction liquid was concentrated under reduced pressure, and then partitioned between ethyl acetate and 1 N hydrochloric acid. The aqueous layer was neutralized with a 1 N aqueous sodium hydroxide solution, followed by
20 extraction with ethyl acetate, washed with saturated brine, and then dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by basic silica gel column chromatography (eluent; n-hexane:ethyl acetate=10:1) to obtain an
25 isopropoxy derivative (171 mg) as an oily substance. This was made into its hydrochloride by an ordinary method, and

then crystallized from diethylether to obtain a compound of Example 40 (128 mg) as a colorless crystal.

Example 41

6-Fluoro-1,2,2-trimethylindan-1-amine hydrochloride

5 To a solution of a compound of Reference Example 44 (444 mg) in chloroform (8 ml) were added sodium azide (300 mg) and trifluoroacetic acid (1 ml) under ice-cooling, followed by stirring at room temperature for 1 hour. It was alkalified by addition of 10% aqueous ammonia, and then
10 extracted with chloroform, and the organic layer was washed with saturated brine. It was dried over anhydrous magnesium sulfate, and the solvent was then evaporated under reduced pressure to obtain an azide. Then, this was dissolved in methanol (6 ml), and 10% palladium-carbon (80
15 mg) was added thereto, followed by stirring at room temperature for 3 hours under a hydrogen atmosphere (normal pressure). The reaction mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by basic silica gel
20 column chromatography (eluent; n-hexane:ethyl acetate=1:1) to obtain an amine (327 mg) as an oily substance. Further, this was dissolved in ethyl acetate, a 4 N HCl solution in ethyl acetate was added thereto, and the solvent was evaporated under reduced pressure. The residue was
25 crystallized from diethylether to obtain a compound of Example 41 (310 mg) as a colorless crystal.

Example 42

6-Bromo-1,2,2,-trimethylindan-1-amine hydrochloride

To a solution of a compound of Example 45 (3.8 g) in chloroform (60 ml) were added sodium azide (1.9 g) and
5 trifluoroacetic acid (3.4 ml) under ice-cooling, followed by stirring at the same temperature for 1 hour. It was alkalified by addition of 10% aqueous ammonia, and then extracted with chloroform, and the organic layer was washed with saturated brine. It was dried over anhydrous
10 magnesium sulfate, and the solvent was then evaporated under reduced pressure to obtain an azide. Then, this was dissolved in methanol (50 ml), and triphenylphosphine (7.8 g) was added thereto, followed by heating under reflux for 1 day.
15 Since the reaction was not completed, tributylphosphine (3.0 g) was further added thereto, followed by stirring at room temperature for 3 hours, and then the reaction liquid was concentrated under reduced pressure. The residue was purified by silica gel column
20 chromatography (eluent; chloroform: methanol=10:1) to obtain an amine (1.2 g) as an oily substance. Further, a portion thereof (204 mg) was made into its hydrochloride by an ordinary method, and recrystallized from ethyl acetate to obtain a compound of Example 42 (222 mg) as a colorless
25 crystal.

[0049]

Example 43

6-Trifluoromethyl-1,2,2-trimethylindan-1-amine
hydrochloride

5 To a solution of a compound of Example 46 (1.6 mg) in
methylene chloride (20 ml) were added sodium azide (0.85 g)
and trifluoroacetic acid (2.5 ml) under ice-cooling,
followed by stirring at the same temperature for 1 hour.
It was alkalified by addition of 10% aqueous ammonia, and
10 then extracted with chloroform, and the organic layer was
washed with saturated brine. It was dried over anhydrous
magnesium sulfate, and the solvent was then evaporated
under reduced pressure to obtain an azide. Then, this was
dissolved in methanol (100 ml), and 10% palladium-carbon
15 (0.5 g) was added thereto, followed by stirring at room
temperature for 15 hours under a hydrogen atmosphere
(normal pressure). The reaction mixture was filtered
through Celite, and the filtrate was concentrated under
reduced pressure. The residue was partitioned between 1 N
20 hydrochloric acid and ethyl acetate, and the aqueous layer
was alkalified with sodium hydrogen carbonate, extracted
with ethyl acetate, washed with water and saturated brine,
and then dried over anhydrous magnesium sulfate, and the
solvent was evaporated under reduced pressure to obtain an
25 amine (1.1 g) as an oily substance. Further, this was made
into its hydrochloride by an ordinary method, and then

crystallized from a mixed solvent of n-hexane and diethylether to obtain a compound of Example 43 (1.1 g) as a colorless crystal.

Example 44

5 6-Cyano-1,2,2-trimethylindan-1-amine hydrochloride

To a solution of a free form of the compound of Example 42 (112 mg) in N-methylpyrrolidone were added zinc cyanide (63 mg), calcium hydroxide (40 mg) and tetrakis(triphenylphosphine)palladium (150 mg), followed by
10 stirring under heat at 110°C for 1 day. The reaction liquid was cooled, and then ethyl acetate and water were added thereto, followed by stirring. The insoluble materials were removed by filtration through Celite. The filtrate was separated out, and the organic layer was
15 washed with saturated brine, and dried over anhydrous sodium sulfate, and the solvent was then evaporated under reduced pressure. The residue was purified by silica gel chromatography (eluent; chloroform:methanol=10:1) to obtain a cyano derivative form (78 mg) as an oily substance.
20 Further, this was made into its hydrochloride by an ordinary method, and crystallized from ethyl acetate to obtain a compound of Example 44 (79 mg) as a colorless crystal.

[0050]

25 Example 45

1,2,2-Trimethyl-6-vinylindan-1-amine hydrochloride

To a solution of a free form of the compound of Example 42 (0.67 g) in toluene (7 ml) were added tributyl(vinyl)tin (1.3 g), tris(dibenzylideneacetone)dipalladium (0.15 g) and tri(t-butyl)phosphine (0.32 g), followed by stirring under heat at 70°C for 2 hours. An aqueous potassium fluoride solution was added thereto, followed by stirring for 1 hour, and the insoluble materials were removed by filtration through Celite. The filtrate was extracted with ethyl acetate, washed with saturated brine, and dried over anhydrous sodium sulfate, and the solvent was then evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent; n-hexane:ethyl acetate=8:1) to obtain an amine (349 mg) as an oily substance. Further, a portion thereof (157 mg) was made into its hydrochloride by an ordinary method, and crystallized from n-hexane to obtain a compound of Example 45 (38 mg) as a colorless crystal.

Example 46

20 1,2,2-Trimethyl-6-(piperidin-1-yl)indan-1-amine
hydrochloride

To a solution of a free form of the compound of Example 42 (144 mg) in toluene (3 ml) were added piperidine (0.07 ml), palladium diacetate (7 mg), sodium t-butoxide
25 (81 mg), and tri(2-methylphenyl)phosphine (18 mg), followed by stirring under heat at 80°C for 1 day. The reaction

2007274420 30 Mar 2009

liquid was cooled, and then partitioned between ethyl acetate and water, and the organic layer was washed saturated brine. It was dried over anhydrous sodium sulfate, and the solvent was then evaporated under reduced pressure. The residue was purified by basic silica gel column chromatography (eluent; chloroform:methanol=10:1) to obtain an amine (75 mg) as an oily substance. Further, this was made into its dihydrochloride by an ordinary method, and crystallized from ethyl acetate to obtain a compound of Example 46 (61 mg) as a colorless crystal.

Example 47

The present compound was prepared from compound of Example 47 in the same manner as in Example 41.

Example 48

7-Fluoro-1,2,2-trimethylindan-1-amine hydrochloride

To a solution of the compound of Reference Example 51 (774 mg) in chloroform (15 ml) were added sodium azide (370 mg) and trifluoroacetic acid (1.3 ml) under ice-cooling, followed by stirring at the same temperature for 1 hour. It was alkalified by addition of 10% aqueous ammonia, and then extracted with chloroform, and the organic layer was washed with saturated brine. It was dried over anhydrous magnesium sulfate, and the solvent was then evaporated under reduced pressure to obtain an azide (700 g). Then, a portion thereof (480 mg) was dissolved in methanol (10 ml), and 10% palladium-carbon (50 mg) was added thereto,

followed by stirring at room temperature for 1 day under a hydrogen atmosphere (normal pressure). The reaction mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure to obtain an oily substance. This was made into its hydrochloride by an ordinary method, and crystallized from ethyl acetate to obtain a compound of Example 48 (55 mg) as a colorless crystal.

[0051]

10 Example 49

The present compound was prepared in the same manner as in Example 41.

Example 50

The present compound was prepared in the same manner as in Example 42.

Example 51

7-Ethyl-4-fluoro-1,2,2-trimethylindan-1-amine hydrochloride

To a solution of a free form of the compound of Example 52 (79 mg) in methanol (20 ml) was added 10% palladium-carbon (50 mg), followed by stirring at room temperature for 12 hours under a hydrogen atmosphere (normal pressure). The insoluble materials were removed by filtration through Celite, and the solvent was then evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent;

2007274420 30 Mar 2009

chloroform: methanol=10:1) and then made into its hydrochloride by an ordinary method to obtain a compound of Example 51 (53 mg) as a pale yellow amorphous substance.

Examples 52 and 53

The present compounds were prepared in the same manner as in Example 43.

Example 54

The present compound was prepared in the same manner as in Example 41.

Example 55

The present compound was prepared in the same manner as in Example 42.

Example 56

The present compound was prepared in the same manner as in Example 41.

Example 57

2,2-Dimethyl-1-trifluoromethylindan-1-amine
hydrochloride

To a solution of the compound of Example 55 (2.3 g) in chloroform (30 ml) were added sodium azide (1.3 g) and concentrated sulfuric acid (1.6 ml) under ice-cooling, followed by stirring at room temperature for 2 hours. The reaction solution was further ice-cooled, and 10% aqueous ammonia was added thereto, followed by stirring and extraction with chloroform. The organic layer was washed with saturated brine, and then dried over anhydrous sodium

2007274420 30 Mar 2009

sulfate, and the solvent was evaporated under reduced pressure. The residue was dissolved in methanol (20 ml), and 10% palladium-carbon (200 mg) was added thereto, followed by stirring at room temperature for 12 hours under a hydrogen atmosphere (normal pressure). The insoluble materials were removed by filtration through Celite, and the solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate, followed by extraction with 1 M hydrochloric acid. The aqueous layer was alkalified with 1 M sodium hydroxide, and extracted with ethyl acetate. It was washed with saturated brine, and dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure to obtain an amine (1.17 g). This was made into its hydrochloride by an ordinary method, and then crystallized from a mixed solvent of diethylether and ethyl acetate to obtain a compound of Example 57 (234 mg) as a colorless crystal.

[0052]

Example 58

1-Ethyl-2,2-dimethylindan-1-amine hydrochloride

To a solution of a compound of Reference Example 56 (606 mg) in chloroform (9 ml) were added sodium azide (414 mg) and trifluoroacetic acid (1.4 ml) under ice-cooling, followed by stirring at room temperature for 1 hour. It was alkalified by addition of 10% aqueous ammonia, and then extracted with chloroform, and the organic layer was washed

with saturated brine. It was dried over anhydrous magnesium sulfate, and the solvent was then evaporated under reduced pressure to obtain an azide. Then, this was dissolved in methanol (9 ml), and 10% palladium-carbon (700
5 mg) was added thereto, followed by stirring at room temperature for 3 hours under a hydrogen atmosphere (normal pressure). The reaction mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by basic silica gel
10 column chromatography (eluent; n-hexane:ethyl acetate=5:1) to obtain an amine (339 mg) as an oily substance. Further, this was made into its hydrochloride by an ordinary method, and then crystallized from diisopropyl ether to obtain a compound of Example 58 (190 mg) as a colorless crystal.

15 Example 59

The present compound was prepared in the same manner as in Example 58.

Example 60

1-Isopropyl-2,2-dimethylindan-1-amine hydrochloride

20 To a solution of 1-isopropyl-2,2-dimethylindan-1-ol (175 mg) in chloroform (3 ml) were added sodium azide (114 mg) and trifluoroacetic acid (0.4 ml) under ice-cooling, followed by stirring at room temperature for 3 days. It was alkalified by addition of 10% aqueous ammonia, and then
25 extracted with chloroform, and the organic layer was washed with saturated brine. It was dried over anhydrous

2007274420 30 Mar 2009

magnesium sulfate, and the solvent was then evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent; n-hexane:ethyl acetate=30:1) to obtain an azide (106 mg) as an oily substance. Then, this was dissolved in methanol (3 ml), and 10% palladium-carbon (15 mg) was added thereto, followed by stirring at room temperature for 1 day under a hydrogen atmosphere (normal pressure). The reaction mixture was filtered through Celite, and the solvent was evaporated under reduced pressure to obtain an amine (71 mg) as an oily substance. Further, a portion thereof (20 mg) was made into its hydrochloride by an ordinary method, and crystallized from diisopropyl ether to obtain a compound of Example 60 (16 mg) as a colorless crystal.

Examples 61 to 63

The present compound was prepared in the same manner as in Example 60.

[0053]

Example 64

trans-2-Ethyl-1,2-dimethylindan-1-amine hydrochloride

Example 65

cis-2-Ethyl-1,2-dimethylindan-1-amine hydrochloride

The same procedure as in Example using the compound of Reference Example 60 was carried out, and the resulting diastereomer was separated and resulting diastereomer was separated and purified by basic silica gel column chromatography (eluent; n-hexane:ethyl acetate=20:1

to 10:1), and the resulting amine was made into its hydrochloride by an ordinary method, thereby obtaining a compound of Example 64 and a compound of Example 65, as colorless amorphous substances, respectively.

5 Example 66

1'-Methyl-1',3'-dihydrospiro[cyclopropan-1,2'-inden]-
1'-amine hydrochloride

Example 67

1'-Methyl-1',3'-dihydrospiro[cyclopentan-1,2'-inden]-
1'-amine hydrochloride

The present compound was prepared in the same manner as in Example 58.

Examples 68 and 69

The present compounds were prepared in the same manner as in Example 58.

[0054]

The structural formulae and the physicochemical data of the compounds of the above Reference Examples and the compounds of the above Examples are shown in the following
20 Tables 2 to 14. The compounds shown in Table 15 may be readily produced similarly to the above Examples or Production Processes or according to the modifications apparent to one skilled in the art. The symbols in the Tables have the following meanings.

25 Rf.: Reference Example, Ex.: Example, STRUCTURE: structural formula, DATA: data, SALT: salt, Ph: phenyl, Me:

methyl, Et: ethyl, OMe: methoxy, thienyl: thienyl, iPr:
isopropyl, vinyl: vinyl, 1-Pip: 1-piperidinyl, n-Bu: normal
butyl, c-Hex: cyclohexyl, c-Pr: cyclopropyl, c-Pn:
cyclopentyl, Bn: benzyl, NMR: nuclear magnetic resonance
5 spectrum (TMS internal standard), MS: mass spectrometry,
fumarate: fumaric acid, HCl salt: hydrochloride, 2HCl salt:
2hydrochloride, free base: a free form

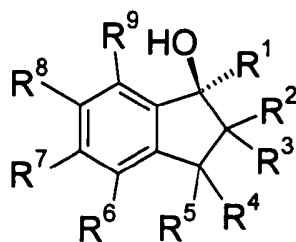
[Table 2]

Rf.	STRUCTURE	DATA	Rf.	STRUCTURE	DATA
1		FAB-MS (m/z); 205 [(M+1) ⁺]	2		EI-MS (m/z); 232 [M ⁺]
3		EI-MS (m/z); 174 [M ⁺]	4		EI-MS (m/z); 234 [M ⁺]
5		EI-MS (m/z); 248 [M ⁺]	6		EI-MS (m/z); 234 [M ⁺]
7		FAB-MS (m/z); 234 [(M+1) ⁺]	8		EI-MS (m/z); 174 [M ⁺]
9		EI-MS (m/z); 228 [M ⁺]	10		EI-MS (m/z); 228 [M ⁺]
11		EI-MS (m/z); 200 [M ⁺]	12		EI-MS (m/z); 228 [M ⁺]

[Table 3]

Rf.	STRUCTURE	DATA	Rf.	STRUCTURE	DATA
13		EI-MS (m/z); 204 [M ⁺]	14		FAB-MS (m/z); 245, 247 [(M-1) ⁺]
15		EI-MS (m/z); 228, 230 [M ⁺]	16		EI-MS (m/z); 256, 258 [M ⁺]
17		EI-MS (m/z); 240, 242 [M ⁺]	18		FAB-MS (m/z); 269, 271 [(M+1) ⁺]

[Table 4]

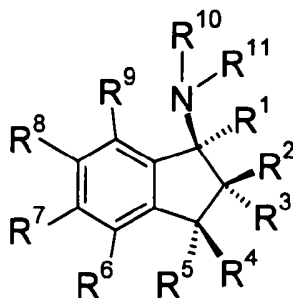


Rf.	R ¹	R ² , R ³	R ⁴ , R ⁵	R ⁶ /R ⁷ /R ⁸ /R ⁹	DATA
19	Ph	Et, Et	H, H	H / H / H / H	EI-MS (m/z); 266 [M ⁺]
20	Ph	Me, Me	CH ₂ OMe, H	H / H / H / H	FAB-MS (m/z); 281 [(M-1) ⁺]
21	Ph	Me, Me	H, H	H / H / Me / H	EI-MS (m/z); 252 [M ⁺]
22	Ph	Me, Me	H, H	H / H / OMe / H	FAB-MS (m/z); 267 [(M-1) ⁺]
23	2-Me-Ph	Me, Me	H, H	H / H / H / H	EI-MS (m/z); 252 [M ⁺]
24	3-Me-Ph	Me, Me	H, H	H / H / H / H	NMR(CDCl ₃): 0.65(3H, s), 1.20(3H, s), 2.35(3H, s) ppm.
25	4-Me-Ph	Me, Me	H, H	H / H / H / H	ESI-MS (m/z); 235 [(M-17) ⁺]
26	2-F-Ph	Me, Me	H, H	H / H / H / H	EI-MS (m/z); 256 [M ⁺]
27	3-F-Ph	Me, Me	H, H	H / H / H / H	FAB-MS (m/z); 239 [(M-17) ⁺]
28	4-F-Ph	Me, Me	H, H	H / H / H / H	EI-MS (m/z); 256 [M ⁺]
29	2-OMe-Ph	Me, Me	H, H	H / H / H / H	EI-MS (m/z); 268 [M ⁺]
30	3-OMe-Ph	Me, Me	H, H	H / H / H / H	NMR(CDCl ₃): 0.67(3H, s), 1.20(3H, s), 3.79(3H, s) ppm.
31	4-OMe-Ph	Me, Me	H, H	H / H / H / H	FAB-MS (m/z); 251 [(M-17) ⁺]
32	2-thienyl	Me, Me	H, H	H / H / H / H	EI-MS (m/z); 227 [(M-17) ⁺]
33	Me	Me, Me	Me, H	H / H / H / H	EI-MS (m/z); 190 [M ⁺]
34	Me	Me, Me	Me, Me	H / H / H / H	EI-MS (m/z); 204 [M ⁺]
35	Me	Me, Me	H, H	Me / H / H / H	EI-MS (m/z); 190 [M ⁺]
36	Me	Me, Me	H, H	F / H / H / H	EI-MS (m/z); 194 [M ⁺]
37	Me	Me, Me	H, H	CF ₃ / H / H / H	EI-MS (m/z); 244 [M ⁺]

[Table 5]

Rf.	R ¹	R ² , R ³	R ⁴ , R ⁵	R ⁶ /R ⁷ /R ⁸ /R ⁹	DATA
38	Me	Me, Me	H, H	H / Me / H / H	EI-MS (m/z); 190 [M ⁺]
39	Me	Me, Me	H, H	H / F / H / H	EI-MS (m/z); 194 [M ⁺]
40	Me	Me, Me	H, H	H / Cl / H / H	ESI-MS (m/z); 193 [M ⁺ -17]
41	Me	Me, Me	H, H	H / CF ₃ / H / H	EI-MS (m/z); 244 [M ⁺]
42	Me	Me, Me	H, H	H / H / Me / H	EI-MS (m/z); 290 [M ⁺]
43	Me	Me, Me	H, H	H / H / OMe / H	EI-MS (m/z); 206 [M ⁺]
44	Me	Me, Me	H, H	H / H / F / H	EI-MS (m/z); 194 [M ⁺]
45	Me	Me, Me	H, H	H / H / Br / H	EI-MS (m/z); 254, 256 [M ⁺]
46	Me	Me, Me	H, H	H / H / CF ₃ / H	EI-MS (m/z); 244 [M ⁺]
47	Me	Me, Me	H, H	H / H / H / Me	EI-MS (m/z); 190 [M ⁺]
48	Me	Me, Me	H, H	H / H / H / CF ₃	EI-MS (m/z); 244 [M ⁺]
49	Me	Me, Me	H, H	F / H / H / Br	NMR(CDCl ₃): 1.18(3H, s), 1.43(3H, s) ppm.
50	Me	Me, Me	H, H	F / H / H / vinyl	EI-MS (m/z); 220 [M ⁺]
51	Me	Me, Me	H, H	Br / H / H / F	EI-MS (m/z); 272, 274 [M ⁺]
52	Me	Me, Me	H, H	H/OMe/OMe/H	ESI-MS (m/z); 259 [M ⁺ +23]
53	Me	Me, Me	H, H	H / OMe / H / Br	EI-MS (m/z); 284, 286 [M ⁺]
54	Me	Me, Me	H, H	H / H / F / OMe	ESI-MS (m/z); 247 [M ⁺ +23]
55	CF ₃	Me, Me	H, H	H / H / H / H	EI-MS (m/z); 230 [M ⁺]
56	Et	Me, Me	H, H	H / H / H / H	EI-MS (m/z); 173 [M ⁺ -17]
57	Et	Me, Me	H, H	Me / H / H / H	NMR(DMSO-d ₆): 0.80(3H, t), 0.87(3H, s), 1.06(3H, s) ppm.
58	c-Hex	Me, Me	H, H	H / H / H / H	FAB-MS (m/z); 245 [M ⁺ +1]
59	Bn	Me, Me	H, H	H / H / H / H	EI-MS (m/z); 235 [M ⁺ -17]
60	Me	Me, Et	H, H	H / H / Me / H	EI-MS (m/z); 204 [M ⁺]
61	Me	c-Pn	H, H	H / H / H / H	EI-MS (m/z); 202 [M ⁺]

[Table 6]



Ex.	R ¹	R ² R ³	R ⁴ R ⁵	R ⁶ /R ⁷ R ⁸ /R ⁹	R ¹⁰ R ¹¹	DATA
1	Ph	Me Me	H H	H / H H / H	H H	[fumarate] FAB-MS(m/z); 238 [(M+1) ⁺] ¹ H NMR(DMSO-d ₆): 0.60(3H, s), 1.10(3H, s), 2.66(1H, d, J=15.7 Hz), 2.81(1H, d, J=15.7 Hz), 6.53(2H, s), 7.12(2H, d, J=7.33 Hz), 7.22-7.35(7H, m).
2	Ph	Et Et	H H	H / H H / H	H H	[fumarate] FAB-MS(m/z); 266 [(M+1) ⁺]
3	Ph	Me Me	CH ₂ OMe H	H / H H / H	H H	[HCl salt] FAB-MS(m/z); 282 [(M+1) ⁺]
4	Ph	Me Me	H CH ₂ OH	H / H H / H	H H	[HCl salt] FAB-MS(m/z); 268 [(M+1) ⁺]
5	Ph	Me Ph	H H	H / H H / H	H H	[HCl salt] FAB-MS(m/z); 300 [(M+1) ⁺]
6	Ph	Ph Me	H H	H / H H / H	H H	[HCl salt] FAB-MS(m/z); 300 [(M+1) ⁺]
7	Ph	Me Me	H H	H / H Me / H	H H	[fumarate] FAB-MS(m/z); 252 [(M+1) ⁺]
8	Ph	Me Me	H H	H / H OMe / H	H H	[free base] FAB-MS(m/z); 251 [(M-16) ⁺]

[Table 7]

Ex.	R ¹	R ² R ³	R ⁴ R ⁵	R ⁶ /R ⁷ R ⁸ /R ⁹	R ¹⁰ R ¹¹	DATA
9	Ph	Me Me	H H	H / H OH / H	H H	[free base] FAB-MS(m/z); 254 [(M+1) ⁺]
10	Ph	Me Me	H H	H / H H / H	Me H	[HCl salt] FAB-MS(m/z); 252 [(M+1) ⁺] ¹ H NMR(DMSO-d ₆): 0.42(3H, s), 1.35(3H, s), 2.28(3H, t, J=5.07 Hz), 2.80(1H, d, J=16.6 Hz), 3.55(1H, d, J=16.6 Hz), 7.35-7.55(9H, m), 9.31-9.61(2H, br).
11	Ph	Me Me	H H	H / H H / H	Me Me	[HCl salt] FAB-MS(m/z); 266 [(M+1) ⁺]
12	2-Me-Ph	Me Me	H H	H / H H / H	H H	[HCl salt] FAB-MS(m/z); 252 [(M+1) ⁺]
13	3-Me-Ph	Me Me	H H	H / H H / H	H H	[fumarate] FAB-MS(m/z); 252 [(M+1) ⁺]
14	4-Me-Ph	Me Me	H H	H / H H / H	H H	[HCl salt] FAB-MS(m/z); 252 [(M+1) ⁺]
15	2-F-Ph	Me Me	H H	H / H H / H	H H	[HCl salt] FAB-MS(m/z); 256 [(M+1) ⁺]
16	3-F-Ph	Me Me	H H	H / H H / H	H H	[fumarate] FAB-MS(m/z); 256 [(M+1) ⁺]
17	4-F-Ph	Me Me	H H	H / H H / H	H H	[fumarate] FAB-MS(m/z); 256 [(M+1) ⁺] ¹ H NMR(CD ₃ OD): 0.76(3H, s), 1.27(3H, s), 2.88(1H, d, J=16.6 Hz), 2.99(1H, d, J=16.6 Hz), 6.68(2H, s), 7.12-7.21(4H, m), 7.30-7.50(4H, m).

[Table 8]

Ex.	R ¹	R ² R ³	R ⁴ R ⁵	R ⁶ /R ⁷ R ⁸ /R ⁹	R ¹⁰ R ¹¹	DATA
18	2-OMe-Ph	Me Me	H H	H / H H / H	H H	[HCl salt] FAB-MS(m/z); 268 [(M+1) ⁺] ¹ H NMR(CD ₃ OD): 0.92(3H, s), 1.34(3H, s), 2.82(1H, d, J=15.9 Hz), 2.87(1H, d, J=15.9 Hz), 4.00(3H, s), 6.34(1H, d, J=8.05 Hz), 6.83(1H, t, J=7.63 Hz), 7.19(1H, d, J=7.93 z), 7.31-7.50(5H, m).
19	3-OMe-Ph	Me Me	H H	H / H H / H	H H	[free base] FAB-MS(m/z); 268 [(M+1) ⁺]
20	4-OMe-Ph	Me Me	H H	H / H H / H	H H	[HCl salt] FAB-MS(m/z); 268 [(M+1) ⁺]
21	3-OH-Ph	Me Me	H H	H / H H / H	H H	[free base] FAB-MS(m/z); 254 [(M+1) ⁺] ¹ H NMR(DMSO-d ₆): 0.58(3H, s), 1.01(3H, s), 2.62(1H, d, J=15.1 Hz), 2.70(1H, d, J=15.1 Hz), 6.49-6.65(3H, m), 7.01(1H, t, J=7.88), 7.15-7.27(4H, m), 9.08(1H, s).
22	2-thienyl	Me Me	H H	H / H H / H	H H	[fumarate] FAB-MS(m/z); 243 [M ⁺]
23	Me	Me Me	H H	H / H H / H	H H	[HCl salt] FAB-MS(m/z); 176 [(M+1) ⁺] ¹ H NMR(DMSO-d ₆): 1.04(3H, s), 1.09(3H, s), 1.45(3H, s), 2.74(1H, d, J=15.9 Hz), 2.97(1H, d, J=15.9 Hz), 7.23-7.35(3H, m), 7.48-7.55(1H, m), 8.27-8.46(3H, br).
24	Me	Me Me	Me H	H / H H / H	H H	[HCl salt] EI-MS(m/z); 189 [M ⁺]
25	Me	Me Me	H Me	H / H H / H	H H	[HCl salt] EI-MS(m/z); 189 [M ⁺]
26	Me	Me Me	Me Me	H / H H / H	H H	[HCl salt] FAB-MS(m/z); 204 [(M+1) ⁺]

[Table 9]

Ex.	R ¹	R ² R ³	R ⁴ R ⁵	R ⁶ /R ⁷ R ⁸ /R ⁹	R ¹⁰ R ¹¹	DATA
27	Me	Me Me	OMe H	H / H H / H	H H	[HCl salt] FAB-MS(m/z); 206 [(M+1) ⁺]
28	Me	Me Me	H H	Me / H H / H	H H	[HCl salt] EI-MS(m/z); 189 [M ⁺]
29	Me	Me Me	H H	F / H H / H	H H	[HCl salt] FAB-MS(m/z); 194 [(M+1) ⁺] ¹ H NMR(DMSO-d ₆): 1.07(3H, s), 1.11(3H, s), 1.46(3H, s), 2.78(1H, d, J=16.0 Hz), 2.99(1H, d, J=16.0 Hz), 7.13-7.19(1H, m), 7.33-7.43(2H, m), 8.56(3H, brs).
30	Me	Me Me	H H	CF ₃ / H H / H	H H	[HCl salt] FAB-MS(m/z); 244 [(M+1) ⁺]
31	Me	Me Me	H H	H / Me H / H	H H	[HCl salt] EI-MS(m/z); 189 [M ⁺] ¹ H NMR(DMSO-d ₆): 1.02(3H, s), 1.09(3H, s), 1.43(3H, s), 2.30(3H, s), 2.67(1H, d, J=15.9 Hz), 2.95(1H, d, J=15.9 Hz), 7.05-7.10(2H, m), 7.40(1H, d, J=7.7 Hz), 8.38(3H, brs).
32	Me	Me Me	H H	H / OMe H / H	H H	[HCl salt] FAB-MS(m/z); 206 [(M+1) ⁺] ¹ H NMR(DMSO-d ₆): 1.00(3H, s), 1.09(3H, s), 1.41(3H, s), 2.66(1H, d, J=15.9 Hz), 2.98(1H, d, J=15.9 Hz), 3.75(3H, s), 6.80-6.86(2H, m), 7.38-7.42(1H, m), 8.20(3H, br).
33	Me	Me Me	H H	H / F H / H	H H	[HCl salt] FAB-MS(m/z); 194 [(M+1) ⁺] ¹ H NMR(DMSO-d ₆): 1.02(3H, s), 1.08(3H, s), 1.43(3H, s), 2.73(1H, d, J=16.2 Hz), 2.99(1H, d, J=16.2 Hz), 7.07-7.15(2H, m), 7.55(1H, dd, J=9.2, 5.4 Hz), 8.33(3H, br).
34	Me	Me Me	H H	H / Cl H / H	H H	[HCl salt] FAB-MS(m/z); 193 [(M-16) ⁺]

[Table 10]

Ex.	R ¹	R ² R ³	R ⁴ R ⁵	R ⁶ /R ⁷ R ⁸ /R ⁹	R ¹⁰ R ¹¹	DATA
35	Me	M e M e	H H	H / CF ₃ H / H	H H	[HCl salt] FAB-MS(m/z); 244 [(M+1) ⁺]
36	Me	M e M e	H H	H / H Me / H	H H	[HCl salt] EI-MS(m/z); 189 [M ⁺] ¹ H NMR(DMSO-d ₆): 1.03(3H, s), 1.08(3H, s), 1.43(3H, s), 2.31(3H, s), 2.67(1H, d, J=15.6 Hz), 2.92(1H, d, J=15.6 Hz), 7.11(1H, brd, J=7.7 Hz), 7.15(1H, d, J=7.7 Hz), 7.34(1H, brs), 8.41(3H, brs).
37	Me	M e M e	H H	H / H OH / H	H H	[HCl salt] EI-MS(m/z); 189 [M ⁺] ¹ H NMR(DMSO-d ₆): 1.02(3H, s), 1.08(3H, s), 1.39(3H, s), 2.60(1H, d, J=15.3 Hz), 2.83(1H, d, J=15.3 Hz), 6.72(1H, dd, J=8.1, 2.1 Hz), 6.87(1H, d, J=2.1 Hz), 7.04(1H, d, J=8.1 Hz), 8.24(3H, brs), 9.47(1H, s).
38	Me	M e M e	H H	H / H OMe / H	H H	[HCl salt] FAB-MS(m/z); 206 [(M+1) ⁺] ¹ H NMR(DMSO-d ₆): 1.04(3H, s), 1.07(3H, s), 1.43(3H, s), 2.66(1H, d, J=15.6 Hz), 2.86(1H, d, J=15.6 Hz), 3.76(3H, s), 6.87(1H, dd, J=2.5, 8.2 Hz), 7.14-7.18(2H, m), 8.37(3H, brs).
39	Me	M e M e	H H	H / H OEt / H	H H	[HCl salt] EI-MS(m/z); 219 [M ⁺]
40	Me	M e M e	H H	H / H OiPr / H	H H	[HCl salt] EI-MS(m/z); 233 [M ⁺] ¹ H NMR(DMSO-d ₆): 1.04(3H, s), 1.07(3H, s), 1.27(3H, d, J=6.0 Hz), 1.28(3H, d, J=6.0 Hz), 1.42(3H, s), 2.65(1H, d, J=15.5 Hz), 2.84(1H, d, J=15.5 Hz), 4.59(1H, m), 6.83(1H, dd, J=8.3, 2.3 Hz), 7.10(1H, d, J=2.3 Hz), 7.14(1H, d, J=8.3 Hz), 8.37(3H, brs).
41	Me	M e M e	H H	H / H F / H	H H	[HCl salt] FAB-MS(m/z); 194 [(M+1) ⁺] ¹ H NMR(DMSO-d ₆): 1.06(3H, s), 1.07(3H, s), 1.45(3H, s), 2.72(1H, d, J=15.6 Hz), 2.97(1H, d, J=15.6 Hz), 7.09-7.16(1H, m), 7.29(1H, dd, J=8.3, 5.2 Hz), 7.44(1H, dd, J=9.2, 2.6 Hz), 8.62(3H, brs).

[Table 11]

Ex.	R ¹	R ² R ³	R ⁴ R ⁵	R ⁶ /R ⁷ R ⁸ /R ⁹	R ¹⁰ R ¹¹	DATA
42	Me	Me Me	H H	H / H Br / H	H H	[HCl salt] EI-MS(m/z); 253, 255 [M ⁺] ¹ H NMR(DMSO-d ₆): 1.05(3H, s), 1.06(3H, s), 1.44(3H, s), 2.72(1H, d, J=16.1 Hz), 2.91(1H, d, J=16.1 Hz), 7.25(1H, d, J=8.1 Hz), 7.50(1H, dd, J=8.1, 1.8 Hz), 7.74(1H, d, J=1.8 Hz), 8.53(3H, brs).
43	Me	Me Me	H H	H / H CF ₃ / H	H H	[HCl salt] FAB-MS(m/z); 244 [(M+1) ⁺] ¹ H NMR(DMSO-d ₆): 1.06(3H, s), 1.08(3H, s), 1.46(3H, s), 2.84(1H, d, J=16.3 Hz), 3.02(1H, d, J=16.3 Hz), 3.19- 3.50(1H, br), 7.50(1H, d, J=7.8 Hz), 7.66(1H, brd, J=7.8 Hz), 7.94(1H, brs), 8.20-8.56(2H, br).
44	Me	Me Me	H H	H / H CN / H	H H	[HCl salt] EI-MS(m/z); 200 [M ⁺] ¹ H NMR(DMSO-d ₆): 1.04(3H, s), 1.08(3H, s), 1.49(3H, s), 2.85(1H, d, J=16.7 Hz), 3.07(1H, d, J=16.7 Hz), 7.51(1H, d, J=7.9 Hz), 7.80(1H, dd, J=7.9, 1.5 Hz), 8.00(1H, brs), 8.62(3H, br).
45	Me	Me Me	H H	H / H vinyl / H	H H	[HCl salt] EI-MS(m/z); 201 [M ⁺]
46	Me	Me Me	H H	H / H 1-Pip / H	H H	[2HCl salt] FAB-MS(m/z); 259 [(M+1) ⁺]
47	Me	Me Me	H H	H / H H / Me	H H	[HCl salt] EI-MS(m/z); 189 [M ⁺]
48	Me	Me Me	H H	H / H H / F	H H	[HCl salt] EI-MS(m/z); 193 [M ⁺] ¹ H NMR(DMSO-d ₆): 1.06(3H, s), 1.10(3H, s), 1.51(3H, s), 2.79(1H, d, J=16.2 Hz), 3.03(1H, d, J=16.2 Hz), 7.05-7.15(2H, m), 7.38(1H, dt, J=5.1, 7.8 Hz), 8.42(3H, br).
49	Me	Me Me	H H	H / H H / CF ₃	H H	[HCl salt] FAB-MS(m/z); 244 [(M+1) ⁺]

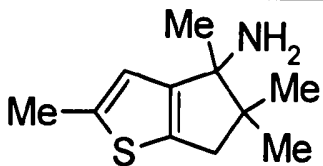
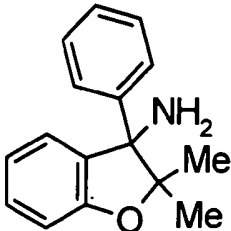
[Table 12]

Ex.	R ¹	R ² R ³	R ⁴ R ⁵	R ⁶ /R ⁷ R ⁸ /R ⁹	R ¹⁰ R ¹¹	DATA
50	Me	Me Me	H H	F / H H / Br	H H	[HCl salt] ESI-MS(m/z); 273 [(M+1) ⁺]
51	Me	Me Me	H H	F / H H / Et	H H	[HCl salt] EI-MS(m/z); 221 [M ⁺]
52	Me	Me Me	H H	F / H H / vinyl	H H	[HCl salt] EI-MS(m/z); 219 [M ⁺]
53	Me	Me Me	H H	Br / H H / F	H H	[HCl salt] EI-MS(m/z); 271, 273 [M ⁺]
54	Me	Me Me	H H	H / OMe OMe / H	H H	[HCl salt] FAB-MS(m/z); 219 [(M-16) ⁺]
55	Me	Me Me	H H	H / OMe H / Br	H H	[HCl salt] FAB-MS(m/z); 267, 269 [(M-16) ⁺]
56	Me	Me Me	H H	H / H F / OMe	H H	[HCl salt] FAB-MS(m/z); 224 [(M+1) ⁺]
57	CF ₃	Me Me	H H	H / H H / H	H H	[HCl salt] FAB-MS(m/z); 230 [(M+1) ⁺]
58	Et	Me Me	H H	H / H H / H	H H	[HCl salt] FAB-MS(m/z); 173 [(M-16) ⁺] ¹ H NMR(CD ₃ OD): 1.02(3H, t, J=7.5 Hz), 1.16(3H, s), 1.23(3H, s), 1.84-1.97(1H, m), 1.99-2.10(1H, m), 2.89(2H, t, 16.7 Hz), 7.25-7.41(4H, m).
59	Et	Me Me	H H	Me / H H / H	H H	[HCl salt] EI-MS(m/z); 203 [M ⁺]

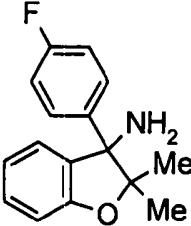
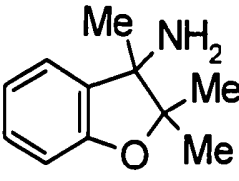
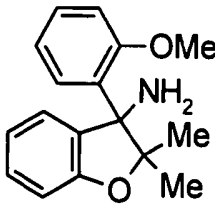
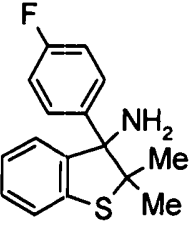
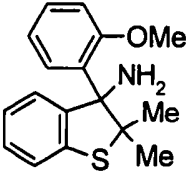
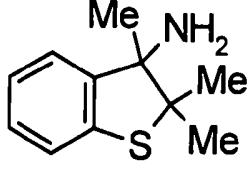
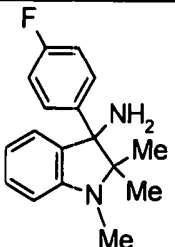
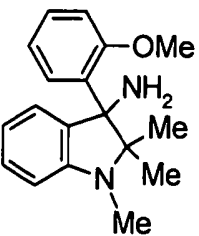
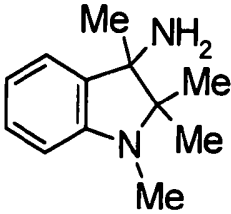
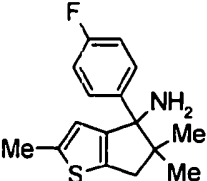
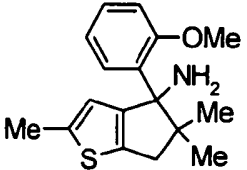
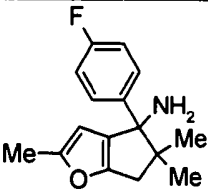
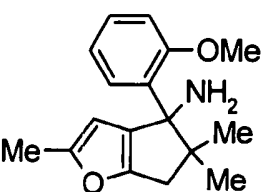
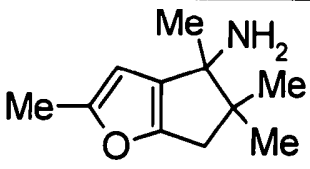
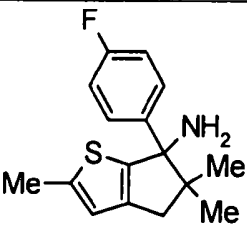
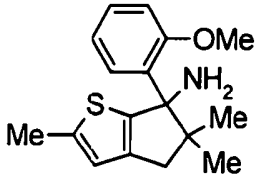
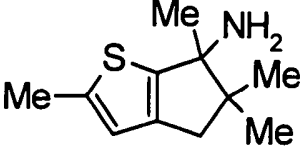
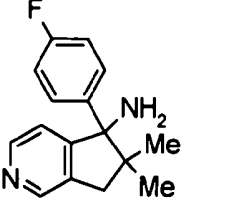
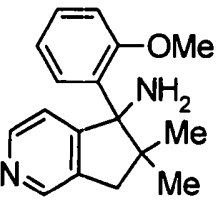
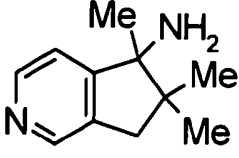
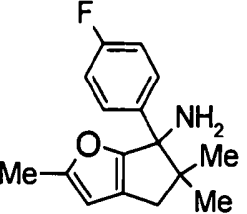
[Table 13]

Ex.	R ¹	R ² R ³	R ⁴ R ⁵	R ⁶ /R ⁷ R ⁸ /R ⁹	R ¹⁰ R ¹¹	DATA
60	i-Pr	Me Me	H H	H / H H / H	H H	[HCl salt] FAB-MS(m/z); 204 [(M+1) ⁺] ¹ H NMR(CD ₃ OD): 0.90(3H, d, J=6.8 Hz), 1.10(3H, d, J=6.8 Hz), 1.10(3H, s), 1.39(1H, s), 2.29-2.40(1H, m), 2.71(1H, d, J=16.1 Hz), 3.05(1H, d, J=16.1 Hz), 7.23-7.40(4H, m).
61	n-Bu	Me Me	H H	H / H H / H	H H	[HCl salt] FAB-MS(m/z); 218 [(M+1) ⁺]
62	c-Hex	Me Me	H H	H / H H / H	H H	[fumarate] FAB-MS(m/z); 244 [(M+1) ⁺]
63	Bn	Me Me	H H	H / H H / H	H H	[fumarate] FAB-MS(m/z); 252 [(M+1) ⁺]
64	Me	Me Et	H H	H / H Me / H	H H	[HCl salt] EI-MS(m/z); 203 [M ⁺]
65	Me	Et Me	H H	H / H Me / H	H H	[HCl salt] EI-MS(m/z); 203 [M ⁺]
66	Me	c-Pr	H H	H / H H / H	H H	[HCl salt] FAB-MS(m/z); 157 [(M-16) ⁺] ¹ H NMR(DMSO-d ₆): 0.56-0.63(1H, m), 0.69-0.76(1H, m), 0.87-0.95(1H, m), 1.09-1.16(1H, m), 1.39(3H, s), 2.77(1H, d, J=16.5 Hz), 3.31(1H, d, J=16.5 Hz), 7.25-7.40(3H, m), 7.56-7.61(1H, m), 8.37(3H, brs).
67	Me	c-Pn	H H	H / H H / H	H H	[HCl salt] EI-MS(m/z); 201 [M ⁺]

[Table 14]

Ex.	STRUCTURE	DATA
68		[HCl salt] FAB-MS(m/z); 179 [(M-15)⁺] ¹H NMR(DMSO-d₆): 1.07(3H, s), 1.18(3H, s), 1.40(3H, s), 2.42(3H, s), 2.64(1H, d, J=15Hz), 2.96(1H, d, J=15 Hz), 6.76(1H, s), 8.35(3H, br).
69		[HCl salt] FAB-MS(m/z); 239 [M⁺] ¹H NMR(DMSO-d₆): 0.85(3H, s), 1.66(3H, s), 6.95-7.13(2H, m), 7.33-7.54(7H, m), 9.37(3H, br).

[Table 15]

2007274420 10 Nov 2011

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" or "comprising", will be understood to imply the inclusion of a
5 stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

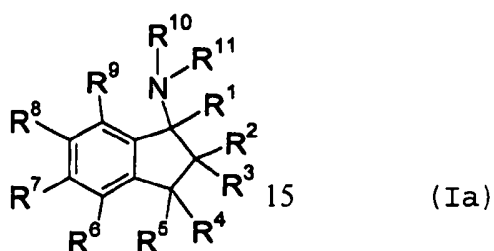
The reference in this specification to any prior
10 publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that the prior publication (or information derived from it) or known matter forms part of the common general knowledge in
15 the field of endeavour to which this specification relates.

2007274420 10 Nov 2011

The claims defining the invention are as follows:

1. A compound represented by the following general formula (Ia) or a salt thereof:

5 [Chem. 9]



(wherein the symbols in the formula (Ia) above have the following meanings, respectively:

20 R^1 : lower alkyl, cycloalkyl, -lower alkylene-aryl, aryl which may be substituted, heteroaryl which may be substituted, or lower alkyl substituted with one or more halogens,

R^2 and R^3 : the same or different, each lower alkyl, or
25 aryl,

R^4 and R^5 : the same or different, each a hydrogen atom, lower alkyl, -O-lower alkyl, -OH, -lower alkylene-OH, or -lower alkylene-O-lower alkyl,

R^6 to R^9 : the same or different, each a hydrogen atom,
30 lower alkyl, -O-lower alkyl, a halogen atom, lower alkyl substituted with one or more halogens, OH, CN, or lower alkenyl,

R^{10} and R^{11} : the same or different, each a hydrogen atom, or lower alkyl,

35 wherein R^2 and R^3 may be taken together with the adjacent carbon atom to form cycloalkyl).

2007274420 10 Nov 2011

2. A compound or a salt thereof according to Claim 1, wherein R^4 , R^5 , R^{10} , and R^{11} are each a hydrogen atom.

3. A compound or a salt thereof according to Claim 2, wherein R^2 and R^3 are the same as or different from each other, and each are lower alkyl, or together form cycloalkyl in combination with the adjacent carbon atom.

4. A compound or a salt thereof according to Claim 1, selected from the group consisting of 2,2-dimethyl-1-phenylindan-1-amine, 1-(4-fluorophenyl)-2,2-dimethylindan-1-amine, 1-(2-methoxyphenyl)-2,2-dimethylindan-1-amine, 1-(3-methoxyphenyl)-2,2-dimethylindan-1-amine, 1,2,2-trimethylindan-1-amine, 1,2,2,5-tetramethylindan-1-amine, 1,2,2,6-tetramethylindan-1-amine, 4-fluoro-1,2,2-trimethylindan-1-amine, 5-fluoro-1,2,2-trimethylindan-1-amine, 7-fluoro-1,2,2-trimethylindan-1-amine, 5-methoxy-1,2,2-trimethylindan-1-amine, 6-methoxy-1,2,2-trimethylindan-1-amine, 6-isopropoxy-1,2,2-trimethylindan-1-amine, 1-ethyl-2,2-dimethylindan-1-amine, 1-isopropyl-2,2-dimethylindan-1-amine, and 1'-methyl-1',3'-dihydrospiro[cyclopropan-1,2'-inden]-1'-amine.

5. A compound according to claim 1, wherein the compound is 1,2,2,6-tetramethylindan-1-amine.

6. A compound according to claim 1, wherein the compound is 1,2,2-trimethylindan-1-amine.

2007274420 10 Nov 2011

7. A compound according to claim 1, wherein the compound is 6-methoxy-1,2,2-trimethylindan-1-amine.

8. A pharmaceutical composition comprising a compound
5 or a salt thereof according to any one of Claims 1 to 7.

9. A pharmaceutical composition according to Claim 8, which is an NMDA receptor antagonist.

10 10. A pharmaceutical composition according to Claim 8, which is a therapeutic agent for dementia.

11. A use of a compound or a salt thereof according to any one of Claims 1 to 7 for the preparation of an NMDA
15 receptor antagonist or a therapeutic agent for dementia.

12. A method for treating dementia in a patient, comprising administering a therapeutically effective amount of a compound or a salt thereof according to any one of
20 Claims 1 to 7 to the patient.

13. A compound as defined in Claim 1, substantially as hereinbefore described with reference to the Examples.