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(54) Title: A CYCLOALKANE DERIVATIVE

(57) Abstract: The present invention relates to a novel cycloalkane derivative which exhibits an excellent psychotropic action and has less side effect.



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DESCRIPTION

A CYCLOALKANE DERIVATIVE

5 TECHNICAL FIELD

[0001] The present invention relates to a novel cycloalkane derivative and an acid addition salt thereof which are useful as a psychotropic compound. In more detail, the compound of the present invention is useful as
10 a medicament for treating, for example, schizophrenia, senile insanity, bipolar disorder, depression, neurosis, senile dementia and associated symptoms thereof.

BACKGROUND ART

15 [0002] Patent References 1 - 3 disclose some cycloalkane derivatives which have psychotropic action.

The compounds disclosed in Patent References 1 and 2 are different from the derivatives of the present invention on the structures of group D and aromatic heterocyclyl group Ar attached to the piperazine ring in the general
20 formula [1] of the present invention.

In addition, the compounds disclosed in Patent Reference 3, which have a cyclic amide structure in the side chain, are different from the derivatives of the
25 present invention.

Furthermore, psychotropic drugs which have been currently used can be accompanied with some disorders such as side effects in CNS, extrapyramidal disorder (e.g. catalepsy), oversedation, as well as cognitive decline.

5 Consequently, the disorders of such drugs have been a serious problem in clinical field (Non-patent Reference 1).

[Prior Art]

[Patent Reference]

[0003]

10 [Patent Reference 1] JP-5(1993)-17440 A

[Patent Reference 2] JP-8(1996)-333368 A

[Patent Reference 3] WO 96/14297

[Non-patent Reference]

[0004]

15 [Non-patent Reference 1] The Pharmacological basis of therapeutics, A. Goodman Gilman, L. S. Goodman et al, New York (1985) P 387, GENDAI IRYO, 22, P22, (1990)

DISCLOSURE OF INVENTION

20 (Problem to Be Solved by the Invention)

[0005] The purpose of the present invention is to provide a good psychotropic drug which has less side effect.

Especially, the purpose is to provide a psychotropic drug which exhibits an excellent effect for improving a broad

25 spectrum of schizophrenia such as positive symptom,

negative symptom, and cognitive dysfunction, while never almost causing abnormal electrocardiogram, weight gain, increased blood glucose, etc., i.e. the desired drug is very safe and could be administered for a long term.

5

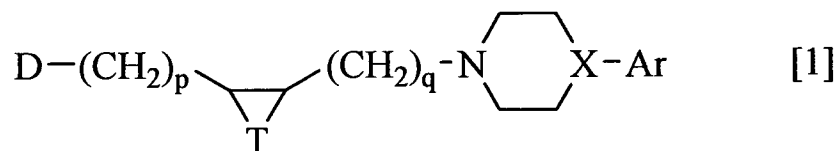
(Means to Solve the Problem)

[0006] The present inventor has extensively studied to reach the above object and then has found that the novel cycloalkane derivatives of the present invention exhibit the desired pharmacological actions and further reduce the side effects. Based upon the new findings, the present invention has been completed.

[0007] The present invention relates to the following inventions.

15 Term 1

A cycloalkane derivative of formula [1]:

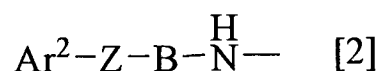


wherein

p and q are independently 1 or 2;

20 T is $-(CH_2)_n-$ wherein n is 1 to 4, or $-C(=CH_2)-$;

D is the group of formula [2]:

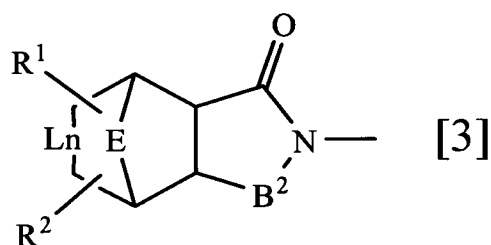


wherein Ar^2 is an aromatic heterocyclyl group or an aromatic carbocyclyl group wherein the aromatic heterocyclyl group and the aromatic carbocyclyl group may be substituted with 1 or 2 substituents selected independently from the group consisting of nitro group, cyano group, halogen atom, lower alkyl group, lower alkoxy group, trifluoromethyl group, trifluoromethoxy group and phenoxy group, and further the lower alkyl group, the alkoxy group and the phenoxy group may be substituted with one or more halogen atoms which are the same or different;

B is carbonyl group or sulfonyl group,

Z is single bond, lower alkylene, lower alkenylene, or ethynylene,

the group of formula [3]:



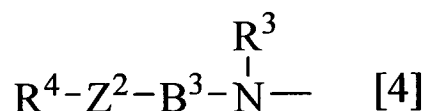
wherein B^2 is carbonyl group or sulfonyl group;

Ln is single or double bond;

E is lower alkylene which may be optionally substituted with one or two lower alkyl groups which are the same or different, oxygen atom, or two hydrogen atoms which are attached at the both ends (i.e., E is not a bridge);

R^1 and R^2 are independently hydrogen atom, hydroxy, lower alkyl group, or lower cycloalkyl group, which may be independently connected to any one of the carbon atoms which compose the ring of formula [3], or R^1 and R^2 may be
 5 connected to the same carbon atom if possible, wherein the lower alkyl group and the lower cycloalkyl group may be substituted with one or more substituents selected independently from the group consisting of hydroxy group and fluorine atom, or

10 the group of formula [4]:



wherein B^3 is carbonyl group or sulfonyl group;

Z^2 is single bond, oxygen atom, or $-NR^5-$;

R^3 , R^4 and R^5 are independently hydrogen atom or lower
 15 alkyl, or R^3 and R^4 , or R^4 and R^5 may be connected together directly or via lower alkylene to form a ring;

X is N, CH or C(OH); and

Ar is aromatic heterocyclyl group, aromatic hydrocarbon group, benzoyl, or phenoxy, wherein the
 20 aromatic heterocyclyl group, the aromatic hydrocarbon group, the benzoyl, and the phenoxy may be substituted with one or more substituents selected independently from the group consisting of lower alkyl, lower alkoxy and halogen atom;

provided that Ar is not benzisothiazolyl group when D is the substituent of formula [3],
or an acid additive salt thereof.

[0008]

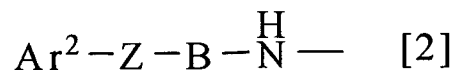
5 Term 2

The cycloalkane derivative of Term 1
wherein

p and q are 1,

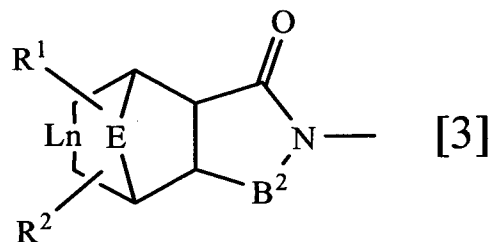
T is $-(CH_2)_n-$ wherein n is 1 to 4,

10 D is the group of formula [2]:



wherein Ar^2 and B are defined as Term 1, and Z is single bond, methylene, vinylene or ethynylene, or

the group of formula [3]:



15

wherein B^2 , E, R^1 , R^2 and Ln are defined as Term 1, and

X is N or CH,

or an acid additive salt thereof.

[0009]

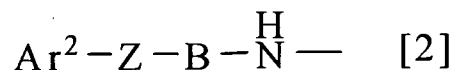
20 Term 3

The cycloalkane derivative of Term 2

wherein

T is $-(\text{CH}_2)_n-$ wherein n is 3 or 4,

D is the group of formula [2]:



5 wherein Ar^2 and B are defined as Term 2, and Z is single bond, methylene or vinylene, or an acid additive salt thereof.

[0010]

Term 4

10 The cycloalkane derivative of Term 2 or 3 wherein Z is single bond or vinylene, or an acid additive salt thereof.

[0011]

Term 5

15 An antipsychotic agent comprising the cycloalkane derivative of any one of Terms 1-4 or an acid addition salt thereof.

[0012]

Term 6

20 A method for treating psychosis comprising administering an effective amount of the cycloalkane derivative of any one of Terms 1-4 or an acid addition salt thereof to a mammal in need thereof.

[0013]

Term 7

Use of the cycloalkane derivative of any one of Terms 1-4 or an acid addition salt thereof in preparation of an antipsychotic agent.

5 BEST MODE FOR CARRYING OUT THE INVENTION

[0014] Hereinafter, the functional groups used herein are illustrated.

The lower alkylene group used in Z and E, or used as a bridge in case that R³ and R⁴, or R⁴ and R⁵ are connected
10 together to form a ring, is, for example, C₁₋₆ alkylene group, and preferably C₁₋₃ alkylene group, including methylene, ethylene, trimethylene, etc. The more preferable alkylene is methylene.

[0015] The lower alkenylene group used in Z is, for
15 example, C₂₋₆ alkenylene group, and preferably C₂₋₃ alkenylene group, including vinylene, propenylene, etc. The more preferable alkenylene is vinylene.

[0016] The aromatic hydrocarbon group used in Ar and Ar²
20 is, for example, aromatic hydrocarbon group having 6 to 14 carbon atoms, and preferably having 6 to 10 carbon atoms, including phenyl, naphthyl, etc. The more preferable aromatic hydrocarbon group is phenyl.

The aromatic heterocyclyl group used in Ar and Ar²
includes, for example, monocyclic aromatic heterocyclyl
25 group, and bicyclic aromatic heterocyclyl group.

The monocyclic aromatic heterocyclyl group includes, for example, an aromatic ring group having not more than 6 carbon atoms and including 1 to 4 heteroatoms selected independently from nitrogen atom, oxygen atom or sulfur atom, and for example, pyridyl, pyrimidinyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, furyl, imidazolyl, etc. are exemplified.

The bicyclic aromatic heterocyclyl group includes, for example, a bicyclic group having not more than 10 carbon atoms and including 1 to 5 heteroatoms selected independently from nitrogen atom, oxygen atom or sulfur atom, wherein the heteroatoms may be contained in only one ring, in both rings, or in lapped site of both rings. The examples thereof include a fused benzologue ring such as benzisoxazolyl, benzofuryl, quinolyl, isoquinolyl, indolyl, indazolyl, indolinyl, oxoindolinyl, tetrahydroquinolyl, dihydroquinolonyl, tetrahydroquinolonyl, benzimidazolyl, and benzoxazolyl; azaindolyl; naphthyridinyl; pteridinyl; thienofuranyl; imidazothiophenyl; imidazofuranyl; benzisothiazolyl; etc. The preferable Ar includes benzoyl, benzisoxazolyl, indazolyl, indolyl, indolinyl, and benzisothiazolyl.

[0017] The lower alkyl group used herein is, for example, C₁₋₆ alkyl group, and preferably C₁₋₄ alkyl group, including methyl, ethyl, propyl, 2-propyl, butyl, etc. The more

preferable alkyl is methyl and ethyl.

[0018] The lower cycloalkyl group used herein is, for example, C₃₋₆ cycloalkyl group, and preferably C₃₋₄ cycloalkyl group, including cyclopropyl, cyclobutyl, etc.

5 The more preferable cycloalkyl is cyclopropyl.

[0019] The lower alkyl group substituted with one or more hydroxy groups include, for example, hydroxymethyl group, 2-hydroxyethyl group, 2-hydroxy-2-propyl group, etc.

10 The lower cycloalkyl group substituted with one or more hydroxy groups include, for example, 2-hydroxycyclopropyl group, 3-hydroxycyclobutyl group, etc.

The lower alkyl group substituted with one or more fluorine atoms include, for example, trifluoromethyl group, 2-fluoroethyl group, etc.

15 The lower cycloalkyl group substituted with one or more fluorine atoms include, for example, 2-fluorocyclopropyl group, 3-fluorocyclobutyl group, etc.

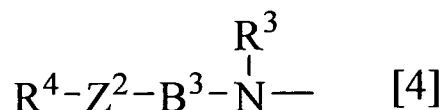
[0020] The lower alkoxy group used herein is, for example, C₁₋₆ alkoxy group, and preferably C₁₋₄ alkoxy group, including methoxy, ethoxy, propoxy, 2-propoxy, butoxy, methylenedioxy, etc. The more preferable lower alkoxy group is methoxy.

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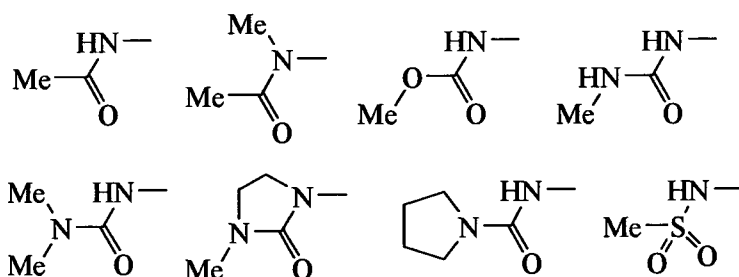
[0021] The halogen atom used herein includes, for example, fluorine, chlorine, bromine, and iodine. The preferable halogen is fluorine and chlorine.

25

[0022] The group according to formula [4]:



includes, for example, the following groups:



5 [0023] R^1 and R^2 which are the substituents in formula [3] each may be connected to any carbon atoms of which the ring in formula [3] is composed. R^1 and R^2 may be connected to the same carbon atom, if possible. In case that E is a lower alkylene, R^1 and R^2 each may be connected to the carbon atoms of which the lower alkylene is composed.

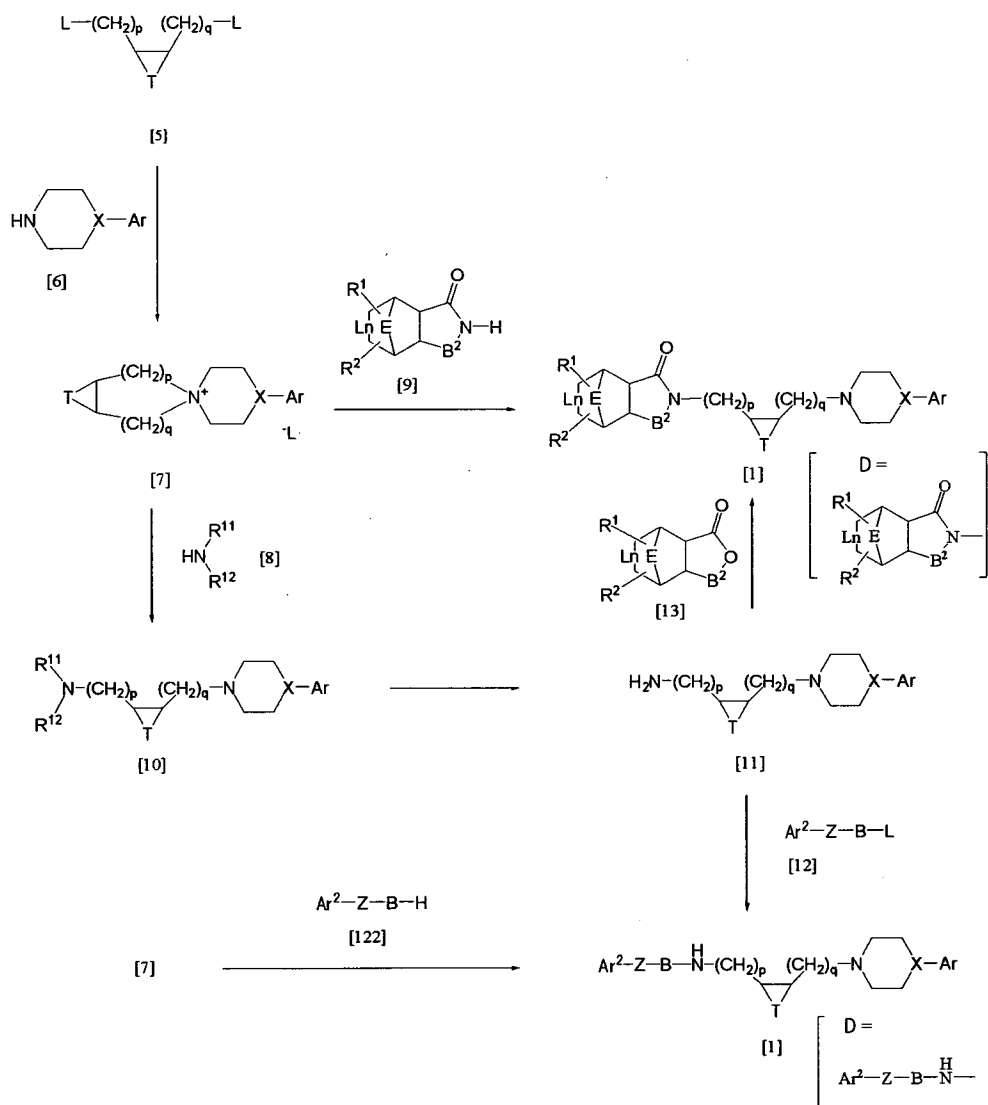
[0024] The acid additive salt used herein includes an addition salt with a pharmaceutically acceptable inorganic acid or organic acid. The salt with an inorganic acid includes, for example, hydrochloride, hydrobromide, 10 hydroiodide, sulfate, nitrate, phosphate, etc. and preferably hydrochloride. The salt with an organic acid includes, for example, acetate, oxalate, citrate, malate, tartrate, maleate, fumarate, etc.

[0025] The compound of formula [1] includes any possible 20 stereoisomer(s) and/or optical isomer(s). The compound of

the present invention may include a mixture of the isomers and an isolated isomer thereof.

[0026] The present compounds [1] can be prepared, for example, by the method shown in the following schemes.

5 Scheme a)



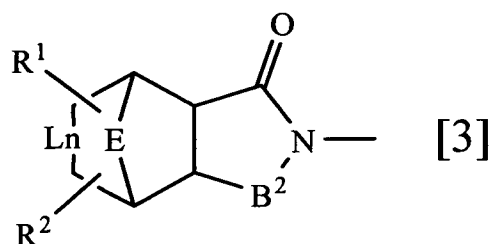
Wherein $p, q, R^1, R^2, D, T, X, Z, B, B^2, E, L_n, Ar$ and Ar^2 are as defined above. R^{11} and R^{12} mean a substituent or a functional group which independently or collectively can

act as a protective group and be removed by means of a general chemical procedure to transform the protected amino group to the corresponding free amino group. The compound of formula [8] includes, for example, dibenzylamine, diallylamine, phthalimide, etc.

L denotes a leaving group. The leaving group used herein includes, for example, a halogen atom, an alkylsulfonyloxy, and an arylsulfonyloxy. The alkylsulfonyloxy includes, for example, methanesulfonyloxy, etc. The arylsulfonyloxy includes, for example, p-toluenesulfonyloxy, benzenesulfonyloxy, etc.

[0027] The starting compound in Scheme a) is a known compound or can be prepared by the following methods described in some references. For example, the process of the compound of formula [6] is disclosed in JP-63(1988)-83085 A, *J. Med. Chem.*, 28, 761-769, (1985). And the process of the compound of formula [5] is disclosed in JP-5(1993)-17440 A.

[0028] In case that D denotes the substituent of formula [3]:



the compound of formula [1] can be prepared by reacting the

compound of formula [7] and the compound of formula [9] in the presence of a base and an optional catalyst. The solvent used in the reaction includes, for example, an aromatic solvent such as toluene, xylene, and chlorobenzene.

5 The reaction temperature may be around the boiling point of the reaction solvent. The catalyst used in the reaction includes, for example, a crown ether such as dibenzo-18-crown-6-ether. The amount of the catalyst may be used in the range of 0.1 to 10 % per the compound of formula [7] by
10 weight. The amount of the compound of formula [9] may be used in the range of 1 to 1.5 moles per 1 mole of the compound of formula [7].

[0029] The compound of formula [7] can be prepared by reacting the compound of formula [5] and the compound of
15 formula [6] in the presence of a base. The solvent used in the reaction includes, for example, an alcohol, acetonitrile, dimethylformamide, etc. The reaction temperature may be around the boiling point of the reaction solvent. The base used in the reaction includes, for
20 example, potassium carbonate, sodium carbonate, etc. The amount of the base may be used in the range of 0.5 to 2 moles per 1 mole of the compound of formula [5]. The amount of the compound of [6] may be used in the range of 1 to 1.5 moles per 1 mole of the compound of formula [5].
25 The alcohol mentioned above includes, for example, methanol,

ethanol, propanol, 2-propanol, butanol, etc.

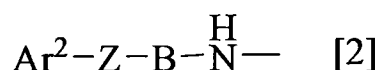
[0030] In addition, the compound of formula [1] can be also prepared by reacting the compound of formula [11] and the compound of formula [13]. The solvent used in the
5 reaction includes, for example, pyridine, toluene, xylene, chlorobenzene, etc. The reaction temperature may be around the boiling point of the reaction solvent.

The compound of formula [11] can be obtained by the deprotection of the compound of formula [10] through a
10 conventional method, for example, the method described in "*Protective group in Organic Synthesis, Theodora W. Greene, John Wiley & Sons*".

[0031] The compound of formula [10] can be prepared by reacting the compound of formula [7] and the compound of
15 formula [8] optionally in the presence of a base and/or a catalyst. It is possible to use an alkaline metal salt or alkaline earth metal salt of the compound of formula [8], instead of the combination of the compound of formula [8] and a base. The solvent used in the reaction includes, for
20 example, an aromatic solvent such as toluene, xylene, and chlorobenzene; and an aprotic polar solvent such as dimethylsulfoxide and dimethylformamide. The reaction temperature may be around the boiling point of the reaction solvent. The catalyst used in the reaction includes, for
25 example, a crown ether such as dibenzo-18-crown-6-ether.

The amount of the catalyst may be used in the range of 0.1 to 10 % per the compound of formula [7] by weight. The amount of the compound of formula [8] may be used in the range of 1 to 1.5 moles per 1 mole of the compound of formula [7]. The base used in the reaction includes, for example, an inorganic base such as potassium carbonate and sodium carbonate.

[0032] In case that D denotes the substituent of formula [2]:



10

the compound of formula [1] can be prepared by reacting the compound of formula [11] and the compound of formula [12] in the presence of a base and an optional catalyst. The solvent used in the reaction includes, for example, an aprotic polar solvent such as dimethylsulfoxide and dimethylformamide; and a halogen solvent such as chloroform and dichloromethane. The reaction temperature may be around the boiling point of the reaction solvent. The catalyst used in the reaction includes, for example, N,N-dimethylaminopyridine. The amount of the catalyst may be used in the range of 0.1 to 10 % per the compound of formula [11] by weight. The amount of the compound of formula [12] may be used in the range of 1 to 1.5 moles per 1 mole of the compound of formula [11]. The base used in

15

20

the reaction includes, for example, an inorganic base such as potassium carbonate and sodium carbonate; and a tert-amine such as triethylamine and Hunig's base.

[0033] In addition, the compound of formula [1] can be prepared by reacting the compound of formula [7] and the compound of formula [122] in the presence of a base and an optional catalyst. The solvent used in the reaction includes, for example, an aromatic solvent such as toluene, xylene, and chlorobenzene. The reaction temperature may be around the boiling point of the reaction solvent. The catalyst used in the reaction includes, for example, a crown ether such as dibenzo-18-crown-6-ether. The amount of the catalyst may be used in the range of 0.1 to 10 % per the compound of formula [7] by weight. The amount of the compound of formula [122] may be used in the range of 1 to 1.5 moles per 1 mole of the compound of formula [7].

[0034] In case that R^1 , R^2 , Ar and Ar^2 are unstable at each reaction step in the preparation process, these functional groups may be protected through a conventional method, for example, the method described in "*Protective group in Organic Synthesis, Theodora W. Greene, John Wiley & Sons*", and each protective group can be cleaved after each reaction is completed.

[0035] The protective group for hydroxy group includes, for example, benzyl group, tetrahydropyranyl group, acetyl

group, etc. The protective group for amino group includes, for example, benzyl group, tert-butoxycarbonyl group, trifluoroacetyl group, etc. The group that can be easily transformed to amino group, for example, nitro group or the like can be used instead of a protected amino group.

The protective group for carboxyl group, or the functional group that can be easily transformed to carboxyl group includes tert-butyl group, trialkylsilyl group, alkoxycarbonyl group, carbamoyl group, nitrile group, etc.

[0036] In case that the compound of formula [1] is optically divided, it can be done as follows. The compound of formula [1] is dissolved in an inert solvent (e.g. acetonitrile, an alcohol, etc.), and then an optically active acid (e.g. L-tartaric acid, D-tartaric acid, D-camphoric acid, L-mandelic acid, L-pyroglutamic acid, D-10-camphorsulfonic acid, D-quinic acid, L-malic acid, dibenzoyl-L-tartaric acid, etc., and preferably L-tartaric acid or D-tartaric acid) is added to the solution to form a salt thereof. The temperature to form the salt can be chosen from the range of room temperature to boiling point of the used solvent. It is preferable to heat the solution around the boiling point of the used solvent temporarily in order to enhance its chiral purity. In addition, it is possible to enhance the yield of the salt by optionally cooling the precipitated salt before the filtering process.

The amount of the optically active acid (dividing agent) is suitably 0.5 to 2.0 moles per one mole of the substance, preferably around the equivalent thereof. It is also possible to obtain a highly pure optically-active salt by optionally re-crystallizing the initially-obtained crystal in a solvent suitable for crystallization such as an alcohol. If necessary, the optically active compound of formula [1] can be obtained as a free form by conventionally treating the obtained salt with a base.

[0037] The present compound can be administered orally or parenterally in the medical use. Namely, the compound can be orally administered as a generally-used dosage form such as powder, granule, tablet, capsules, syrup, and suspension, or parenterally administered as an injection form such as solution, emulsion, and suspension thereof. And it can be rectally administered as a suppository. Furthermore, it can be intravesically administered as a solution. The above-mentioned drug form can be prepared by formulating the present compound with conventional additives such as carrier, excipient, binder, stabilizer, and diluent. In the case of injections, for example, acceptable buffer, solubilizer, and isotonic agent can be also used. In the case of the above-mentioned oral formulation or suppository, the present compound may be contained preferably in 0.1 - 70 % (w/w) per the

composition. The dosage and the frequency of administration depend on various conditions such as target disease, symptom, age and body weight of a subject, type of formulation, and manner of administration. In general, the present compound can be administered in a dosage of 0.1 - 2000 mg, preferably 1 - 200 mg per a day for an adult, and once to several times (e.g. twice to 4 times) a day.

[0038] The compounds of the invention are useful for treating psychosis, in more detail as follows.

The compounds of the invention exhibit high affinity for one or plural subtypes of various receptors, for example, dopaminergic receptor such as dopamine D₁ receptor, dopamine D₂ receptor, dopamine D₃ receptor and dopamine D₄ receptor; serotonergic receptor such as serotonin 5-HT_{1A} and serotonin 5-HT₂; and noradrenergic receptor such as α 1 noradrenergic receptor and α 2 noradrenergic receptor.

It has been well known that D2 receptor antagonistic action in a subtype of dopaminergic receptor is strongly correlated with psychotic effect (see: e.g. Seeman, *Pharmacol. Rev.*, 32, 229 (1981)). And also, it has been reported that 5-HT₂ receptor antagonistic action in a subtype of serotonergic receptor is useful for antipsychotic effect (see: e.g. Janssen et al., *J. Pharm. Exper. Ther.*, 244, 685 (1988)). Especially, D2 receptor antagonistic action can control positive symptoms of

schizophrenia (e.g. hallucination, delusion), while 5-HT₂ receptor antagonistic action can contribute to improve negative symptoms of schizophrenia (e.g. indifference, social withdrawal). In addition, it has been suggested
5 that 5-HT₂ receptor antagonistic action can decrease some side effects in the extrapyramidal tract which often arises in a maintenance therapy of schizophrenia using D2 receptor antagonist.

In addition, it has been recently suggested that D4
10 antagonistic action which is one of other dopaminergic receptor subtypes does not cause the side effects in the extrapyramidal tract which often arise in a maintenance therapy of schizophrenia (see, e.g. Seeman et al., *Nature*, 350, 610 (1991); Seeman et al., *Nature*, 358, 149 (1992)).

15 Further, it has been reported that antagonistic action of 5-HT_{1A} receptor which is a subtype of other serotonergic receptors is correlated with antianxiety (see: e.g. Titeler, *Biochem. Pharmacol.*, 36, 3265 (1987)).

Accordingly, the compounds of the invention have
20 psychotropic actions such as antipsychotic action, antianxiety, and antidepressive action, which are useful, for example, as a medicament for treating schizophrenia, senile insanity psychosis, bipolar disorder, neurosis, senile dementia and associated symptoms thereof, etc.

EXAMPLE

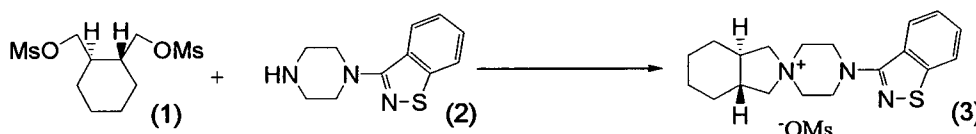
[0039]

Example 1

N-{ [(1*R*,2*R*)-2-{ [4-(1,2-benzisothiazol-3-yl)piperazin-1-yl]-methyl}cyclohexyl]methyl}-1,3-benzodioxole-5-carboxamide
5 [Compound (6)]

[0040]

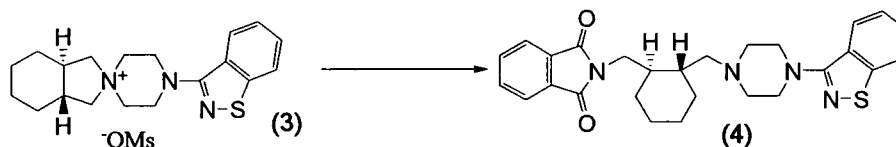
(A) Synthesis of Compound (3)



10 A mixture of (1*R*,2*R*)-cyclohexane-1,2-diyl dimethanedimethanesulfonate (1) (11.7 g, 38.9 mmol), 3-(piperazin-1-yl)-1,2-benzisothiazole (2) (7.76 g, 35.4 mmol), potassium carbonate (4.9 g, 35.4 mmol) and acetonitrile (200 ml) was refluxed for 20 hours. The mixture was filtrated at the
15 hot state thereof, and the filtrate was concentrated to give Compound (3) (12 g, 28.3 mmol, yield: 80%).

[0041]

(B) Synthesis of Compound (4)



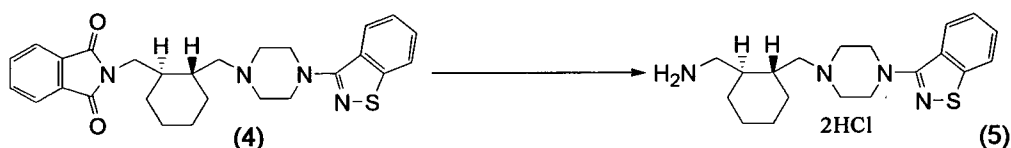
20 A mixture of Compound (3) (12 g, 28.3 mmol), potassium phthalimide (8.9 g, 48.1 mmol) and dimethylformamide (200

ml) was heated at 150°C for 15 hours, and then ethyl acetate and saturated aqueous sodium bicarbonate were added to the mixture. The organic layer was washed with aqueous sodium bicarbonate and brine, dried and concentrated in vacuo to give 2-[[[(1R,2R)-2-[[4-(1,2-benzisothiazol-3-yl)piperazin-1-yl]methyl]cyclohexyl]methyl]-1*H*-isoindole-1,3(2*H*)-dione [Compound (4)] (12.3 g, 26.0 mmol, yield: 92%).

MS (ESI+) (M+1, %); 475 (100).

10 [0042]

(C) Synthesis of Compound (5)



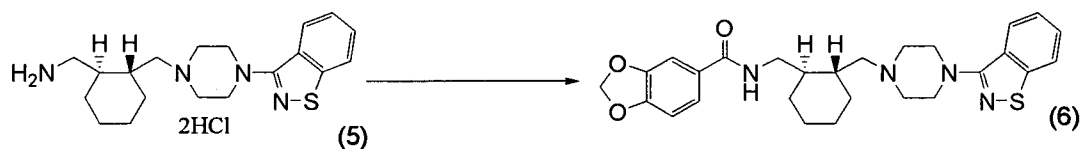
A mixture of Compound (4) (15 g, 28.3 mmol, crude), aqueous hydrazine (10 ml) and ethanol (300 ml) was refluxed for 30 minutes. The mixture was filtrated, and the filtrate was concentrated to give Compound (5) as a free base. The compound was treated with hydrochloric acid to give 1-[[[(1R,2R)-2-[[4-(1,2-benzisothiazol-3-yl)piperazin-1-yl]methyl]cyclohexyl]methanamine dihydrochloride [Compound (5)] (10.8 g, 26 mmol, yield: 92%).

20

MS (ESI+) (M+1, %); 345 (100).

[0043]

(D) Synthesis of Compound (6)



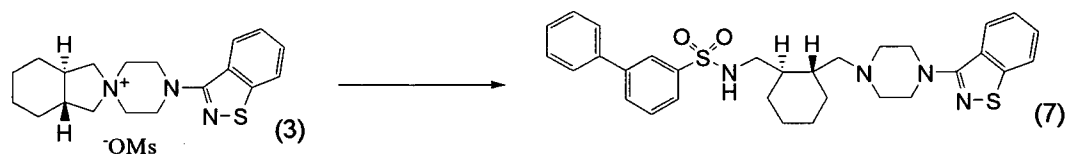
A mixture of Compound (5) (70 mg, 0.2 mmol), triethylamine (20 μ l, 0.24 mmol), piperonyl chloride (47 mg, 0.26 mmol) and chloroform (3 ml) was stirred at room temperature for 7 hours, and then ethyl acetate and saturated aqueous sodium bicarbonate were added to the mixture. The organic layer was washed with aqueous sodium bicarbonate and brine, dried and concentrated. The resulting residue was purified by a silica gel chromatography to give *N*-{[(1*R*,2*R*)-2-{[4-(1,2-benzisothiazol-3-yl)piperazin-1-yl]methyl}cyclohexyl]methyl}-1,3-benzodioxole-5-carboxamide [Compound (6)] (93 mg, 0.19 mmol, yield: 93%).

MS (ESI+) ($M+1$, %); 493 (100), $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 7.86 (m, 2H), 7.40 (brm, 4H), 6.80 (dd, 1H, $J = 9.0, 6.0$ Hz), 5.98 (s, 2H), 3.67 (m, 4H), 3.56 (m, 2H), 3.47 (m, 4H), 2.85 (m, 1H), 2.65 (m, 1H), 1.73 (m, 4H), 1.24 (brm, 6H).

[0044]

Example 2

Synthesis of *N*-{[(1*R*,2*R*)-2-{[4-(1,2-benzisothiazol-3-yl)piperazin-1-yl]methyl}cyclohexyl]methyl}biphenyl-3-sulfonamide (7)



A mixture of Compound (3) (130 mg, 0.3 mmol) which is a synthetic intermediate in the above Example 1, 3-phenylbenzenesulfonyl amide (75 mg, 0.4 mmol), potassium carbonate (54 mg, 0.4 mmol), 18-crown-6-ether (5 mg, 18 μ mol) and acetonitrile (2 ml) was refluxed for 15 hours, and then ethyl acetate and saturated aqueous sodium bicarbonate were added to the mixture. The organic layer was washed with aqueous sodium bicarbonate and brine, dried and concentrated in vacuo. The resulting residue was purified by a silica gel chromatography to give N-([(1R,2R)-2-{[4-(1,2-benzisothiazol-3-yl)piperazin-1-yl]-methyl}cyclohexyl)methyl]biphenyl-3-sulfonamide [Compound (7)] (35 mg, 67 μ mol, yield: 17%).

MS (ESI+) (M+1, %); 561 (100), $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 8.10 (m, 1H), 7.84 (m, 3H), 7.75 (m, 1H), 7.58 (m, 3H), 7.50 (m, 1H), 7.43 (m, 1H), 7.38 (m, 2H), 7.34 (m, 1H), 3.65 (m, 3H), 3.48 (m, 5H), 3.07 (dd, 1H, $J = 12.0, 5.0$ Hz), 2.70 (brm, 3H), 1.62 (brm, 4H), 1.36 (m, 2H), 1.23 (m, 3H), 1.04 (m, 1H).

[0045]

Example 3

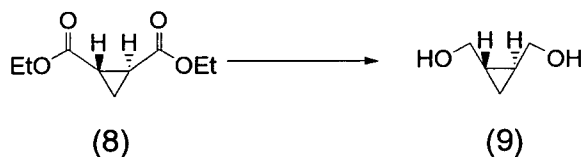
N-([(1S,2S)-2-{[4-(1,2-benzisothiazol-3-yl)piperazin-1-yl]-

methyl}cyclopropyl]methyl}-1,3-benzodioxole-5-carboxamide

[Compound (14)]

[0046]

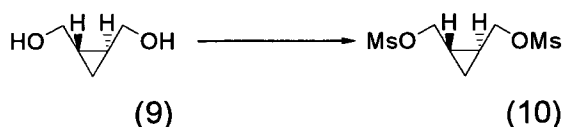
(A) Synthesis of Compound (9)



A mixture of diethyl cyclopropane-dicarboxylate (8) (6.5 g, 34.9 mmol) and tetrahydrofuran (24 ml) was added dropwise at ice temperature to a mixture of lithium aluminium hydride (2.4 g, 62.8 mmol) and tetrahydrofuran 10 (50 ml). The mixture was stirred at room temperature for 2 hours and then cooled. Water (44 ml) and Celite (22 g) were added to the mixture in order, and the mixture was filtrated. The filtrate was washed with brine, dried, and concentrated in vacuo to give (1*S*,2*S*)-cyclopropane-1,2- 15 dioldimethanol [Compound (9)] (1.36 g, 11.3 mmol, yield: 32%).

[0047]

(B) Synthesis of Compound (10)

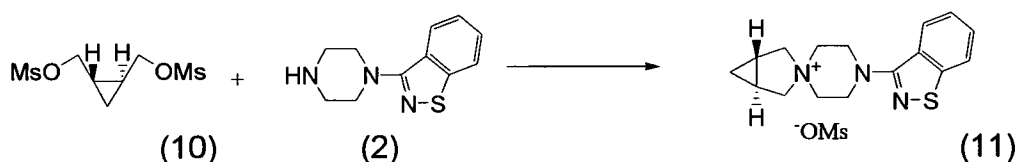


To a mixture of Compound (9) (1.36 g, 11.3 mmol), triethylamine (6.9 ml, 56.5 mmol) and chloroform (40 ml) was added methanesulfonyl chloride (4.1 g, 36.1 mmol)

dropwise in ice temperature. The mixture was stirred at room temperature for two days, and then saturated aqueous sodium bicarbonate and ethyl acetate were added to the mixture. The organic layer was washed with aqueous sodium bicarbonate and brine, dried and concentrated in vacuo to give (1*S*,2*S*)-cyclopropane-1,2-diylldimethanediyl dimethanesulfonate [Compound (10)] (2.9 g, 11.2 mmol, yield: 99%).

[0048]

(C) Synthesis of Compound (11)



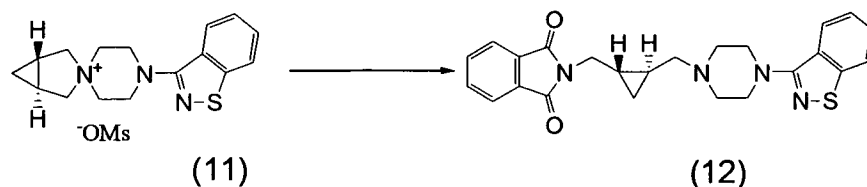
10

A mixture of Compound (10) (2.9 g, 11.2 mmol), 3-(piperazin-1-yl)-1,2-benzisothiazole (2) (1.9 g, 8.9 mmol), potassium carbonate (1.2 g, 8.9 mmol) and acetonitrile (50 ml) was refluxed for 20 minutes. The mixture was filtrated at the hot state thereof, and the filtrate was concentrated to give Compound (11) (4.2 g, 11.0 mmol, yield: 98%).

15

[0049]

(D) Synthesis of Compound (12)



20

A mixture of Compound (11) (4.2 g, 11.0 mmol), potassium phthalimide (3.5 g, 18.9 mmol) and dimethyl-

formamide (40 ml) was heated at 180°C for 4 hours, and then ethyl acetate and saturated aqueous sodium bicarbonate were added to the mixture. The organic layer was washed with aqueous sodium bicarbonate and brine, dried and concentrated in vacuo to give 2-[[[(1*S*,2*S*)-2-[[4-(1,2-benzisothiazol-3-yl)piperazin-1-yl]methyl]cyclopropyl]-methyl]-1*H*-isoindole-1,3(2*H*)-dione [Compound (12)] (3.4 g, 7.8 mmol, yield: 71%).

MS (ESI+) (M+1, %); 433 (100).

10 [0050]

(E) Synthesis of Compound (13)

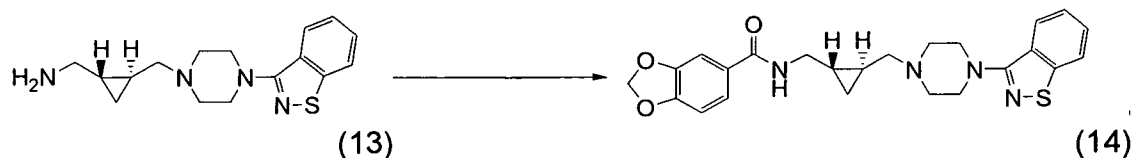


A mixture of Compound (12) (3.4 g, 7.8 mmol), aqueous hydrazine (12 ml) and ethanol (30 ml) was refluxed for 2 hours. The mixture was filtrated, and the filtrate was concentrated to give 1-[[[(1*S*,2*S*)-2-[[4-(1,2-benzisothiazol-3-yl)piperazin-1-yl]methyl]cyclopropyl]methanamine [Compound (13)] (2.1 g, 7.0 mmol, yield: 91%).

MS (ESI+) (M+1, %); 303 (100).

20 [0051]

(F) Synthesis of Compound (14)



A mixture of Compound (13) (24 mg, 78 μ mol), triethylamine (350 μ l), piperonyl chloride (29 mg, 0.15 mmol) and chloroform (3 ml) was stirred at room temperature for 7 hours, and then ethyl acetate and saturated aqueous sodium bicarbonate were added to the mixture. The organic layer was washed with aqueous sodium bicarbonate and brine, dried and concentrated in vacuo. The resulting residue was purified by a silica gel chromatography to give N-
 10 {[(1*S*,2*S*)-2-{{4-(1,2-benzisothiazol-3-yl)piperazin-1-yl}-methyl}cyclopropyl]methyl}-1,3-benzodioxole-5-carboxamide [Compound (14)] (32 mg, 72 μ mol, yield: 91%).

MS (ESI+) ($M+1$, %); 451 (100), $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 7.84 (dd, 2H, $J = 15.0, 6.0$ Hz), 7.47 (t, 1H, $J = 7.5$ Hz),
 15 7.34 (m, 4H), 6.80 (d, 1H, $J = 6.0$ Hz), 5.97 (s, 2H), 3.57 (m, 4H), 3.36 (m, 2H), 2.77 (m, 4H), 2.55 (dd, 1H, $J = 12.0, 6.0$ Hz), 2.28 (dd, 1H, $J = 12.0, 6.0$ Hz), 0.99 (m, 2H), 0.60 (dt, 1H, $J = 9.0, 6.0$ Hz), 0.47 (dt, 1H, $J = 9.0, 6.0$ Hz).

[0052]

Example 4

N-{{[(1*S*,2*S*)-2-{{4-(1,2-benzisothiazol-3-yl)piperazin-1-yl}-methyl}cyclopentyl]methyl}-1,3-benzodioxole-5-carboxamide

[Compound (21)]

[0053]

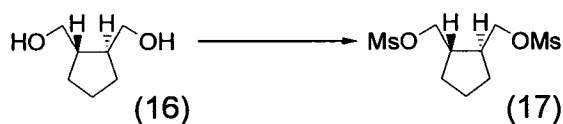
(A) Synthesis of Compound (16)



5 A mixture of cyclopentane-dicarboxylic acid (15) (2.0 g, 12.6 mmol) and tetrahydrofuran (20 ml) was added dropwise at room temperature to a mixture of lithium aluminium hydride (1.4 g, 38.0 mmol) and tetrahydrofuran (40 ml). The mixture was stirred at 70°C for 8 hours and
10 then cooled. Water (30 ml) and Celite (25 g) were added to the mixture in order, and the mixture was filtrated. The filtrate was washed with brine, dried, and concentrated in vacuo to give (1S,2S)-cyclopentane-1,2-diylldimethanol [Compound (16)] (1.6 g, 12.6 mmol, quantitative).

15 [0054]

(B) Synthesis of Compound (17)

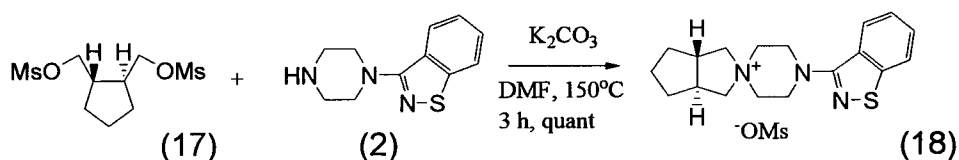


To a mixture of Compound (16) (1.6 g, 12.6 mmol), triethylamine (8.0 ml, 64.5 mmol) and chloroform (20 ml)
20 was added methanesulfonyl chloride (4.7 g, 41.3 mmol) dropwise in ice temperature. The mixture was stirred at room temperature for 3 days, and then saturated aqueous

sodium bicarbonate and ethyl acetate were added to the mixture. The organic layer was washed with aqueous sodium bicarbonate and brine, dried and concentrated in vacuo to give (1*S*,2*S*)-cyclopentane-1,2-diylldimethanediyl dimethane-5 sulfonate [Compound (17)] (3.6 g, 12.6 mmol, quantitative).

[0055]

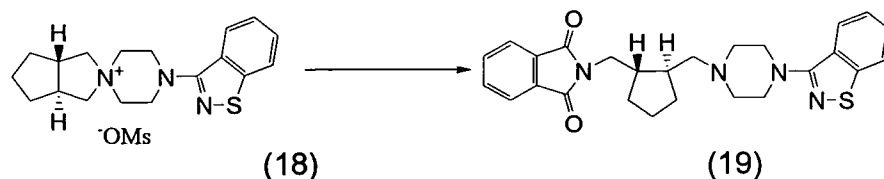
(C) Synthesis of Compound (18)



A mixture of Compound (17) (2.0 g, 6.7 mmol), 3-(piperazin-1-yl)-1,2-benzisothiazole (2) (1.4 g, 6.4 mmol), potassium carbonate (0.8 g, 6.5 mmol) and dimethylformamide (10 ml) was stirred at 150°C for 3 hours. The mixture was filtrated at the hot state thereof, and the filtrate was concentrated to give Compound (18) (2.7 g, 6.7 mmol, quantitative).

[0056]

(D) Synthesis of Compound (19)



A mixture of Compound (18) (2.4 g, 6.0 mmol),
20 potassium phthalimide (1.3 g, 7.2 mmol) and dimethyl-
formamide (30 ml) was refluxed for 4 hours, and then ethyl

acetate and saturated aqueous sodium bicarbonate were added to the mixture. The organic layer was washed with aqueous sodium bicarbonate and brine, dried and concentrated in vacuo. The resulting residue was purified by a silica gel chromatography to give 2-[[[(1*S*,2*S*)-2-[[4-(1,2-benzisothiazol-3-yl)piperazin-1-yl]methyl]cyclopentyl]methyl]-1*H*-isoindole-1,3(2*H*)-dione [Compound (19)] (2.2 g, 4.8 mmol, yield: 81%).

MS (ESI+) (*M*+1, %); 461 (100).

10 [0057]

(E) Synthesis of Compound (20)



A mixture of Compound (19) (2.2 g, 4.8 mmol), aqueous hydrazine (2 ml) and ethanol (60 ml) was refluxed for 2 hours, and then filtrated. Ethyl acetate and water were added to the filtrate. The organic layer was washed with brine, dried and concentrated in vacuo to give 1-[[[(1*S*,2*S*)-2-[[4-(1,2-benzisothiazol-3-yl)piperazin-1-yl]methyl]cyclopentyl]methyl]methanamine [Compound (20)] (0.7 g, 2.2 mmol, yield: 46%).

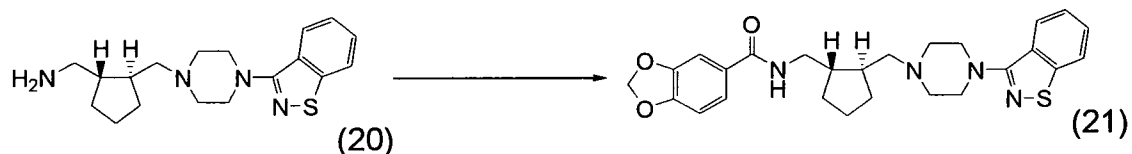
20

MS (ESI+) (*M*+1, %); 331 (100).

[0058]

(F) Synthesis of Compound (21)

Synthesis of *N*-{[(1*S*,2*S*)-2-{[4-(1,2-benzisothiazol-3-yl)-piperazin-1-yl]methyl}cyclopentyl]methyl}-1,3-benzodioxole-5-carboxamide (21)



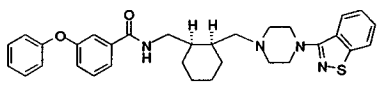
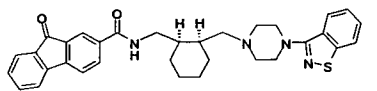
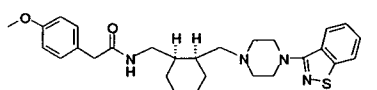
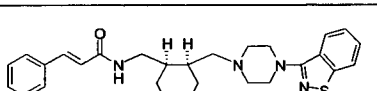
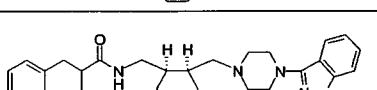
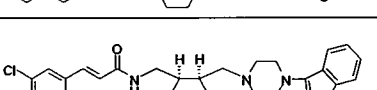
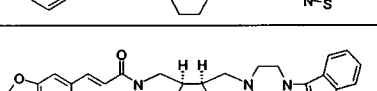
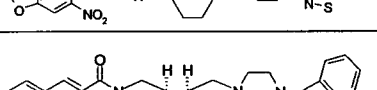
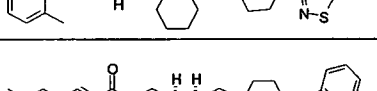
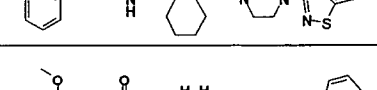
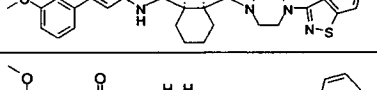
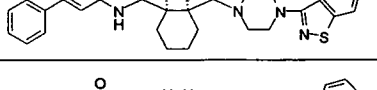
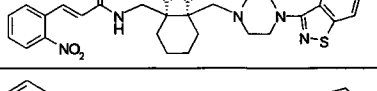
5 A mixture of 1-[(1*S*,2*S*)-2-{[4-(1,2-benzisothiazol-3-yl)piperazin-1-yl]methyl}cyclopentyl]methanamine (20) (28 mg, 84 μ mol), triethylamine (200 μ l), piperonyl chloride (29 mg, 0.15 mmol) and chloroform was stirred at room temperature for 7 hours, and then ethyl acetate and
10 saturated aqueous sodium bicarbonate were added to the mixture. The organic layer was washed with aqueous sodium bicarbonate and brine, dried and concentrated in vacuo. The resulting residue was purified by a silica gel chromatography to give *N*-{[(1*S*,2*S*)-2-{[4-(1,2-benz-
15 isothiazol-3-yl)piperazin-1-yl]methyl}cyclopentyl]methyl}-1,3-benzodioxole-5-carboxamide (21) (34 mg, 71 μ mol, yield: 85%).

MS (ESI+) (*M*+1, %); 479 (100), ¹H-NMR (300 MHz, CDCl₃) δ 7.85 (m, 2H), 7.48 (m, 1H), 7.34 (brm, 3H), 7.15 (m, 1H),
20 3.79 (m, 1H), 3.67 (1H, m), 3.56 (m, 5H), 3.51 (s, 2H), 3.39 (m, 1H), 2.87 (m, 2H), 2.66 (m, 1H), 2.44 (m, 1H), 1.82 (m, 3H), 1.56 (m, 3H), 1.28 (brm, 2H).

[0059]

Examples 5 - 243

The following compounds were prepared according to the processes in Examples 1 to 4.

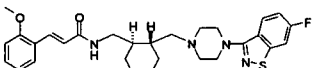
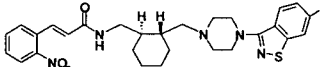
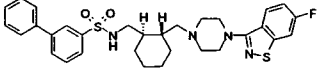
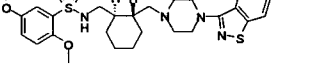
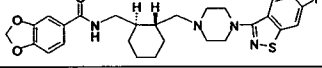
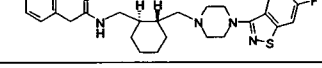
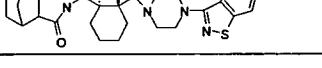
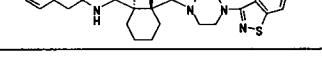
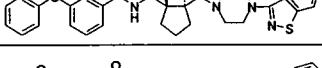
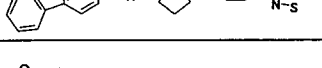
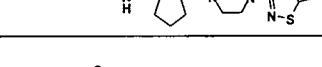
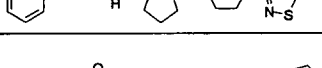
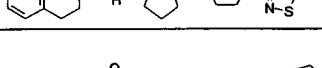
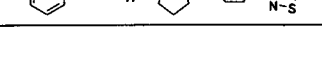
Example No.	Structure	Molecular Weight	MS (ESI+) (M+1, peak intension)
5		540.73	541 (100)
6		550.73	551 (100)
7		492.69	493 (100)
8		474.67	475 (100)
9		502.73	503 (100)
10		509.12	510 (100)
11		563.68	564 (100)
12		488.70	489 (100)
13		488.70	489 (100)
14		534.73	535 (100)
15		504.70	505 (100)
16		519.67	520 (100)
17		560.79	561 (100)

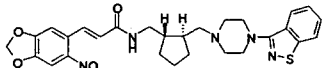
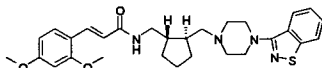
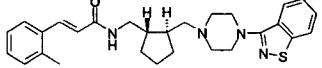
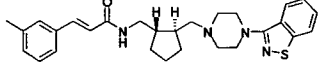
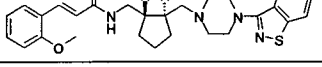
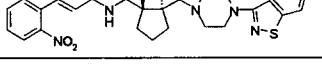
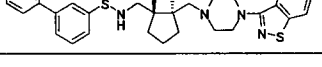
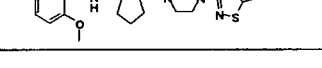
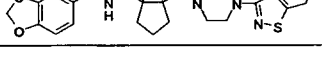
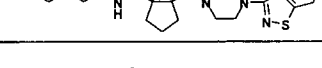
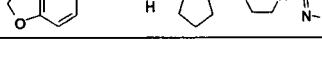
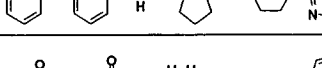
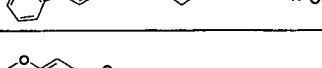
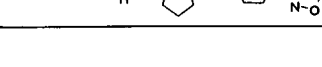
Example No.	Structure	Molecular Weight	MS (ESI+) (M+1, peak intension)
18		544.74	545 (100)
19		492.65	493 (100)
20		497.11	498 (100)
21		518.68	519 (100)
22		540.73	541 (100)
23		550.73	551 (100)
24		492.69	493 (100)
25		474.67	475 (100)
26		502.73	503 (100)
27		509.12	510 (100)
28		563.68	564 (100)
29		488.70	489 (100)
30		488.70	489 (100)
31		534.73	535 (100)
32		504.70	505 (100)

Example No.	Structure	Molecular Weight	MS (ESI+) (M+1, peak intension)
33		519.67	520 (100)
34		560.79	561 (100)
35		544.74	545 (100)
36		492.65	493 (100)
37		497.11	498 (100)
38		518.68	519 (100)
39		519.67	520 (100)
40		543.56	544 (100)
41		534.73	535 (100)
42		534.73	535 (100)
43		504.70	505 (100)
44		492.66	493 (100)
45		553.57	554 (100)
46		510.65	511 (100)
47		510.65	511 (100)

Example No.	Structure	Molecular Weight	MS (ESI+) (M+1, peak intensity)
48		542.67	543 (100)
49		554.12	555 (100)
50		558.67	559 (100)
51		597.58	598 (100)
52		534.73	535 (100)
53		540.73	541 (100)
54		550.73	551 (100)
55		492.69	493 (100)
56		474.67	475 (100)
57		502.73	503 (100)
58		509.12	510 (100)
59		563.68	564 (100)
60		488.70	489 (100)
61		488.70	489 (100)
62		534.73	535 (100)

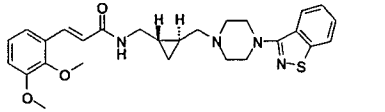
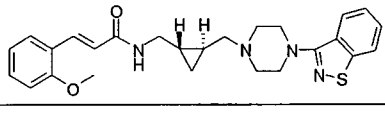
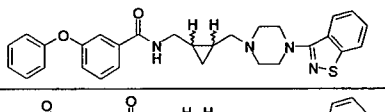
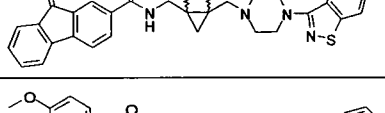
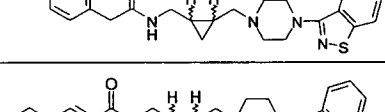
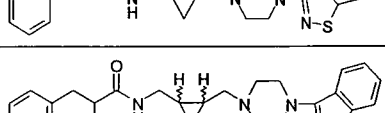
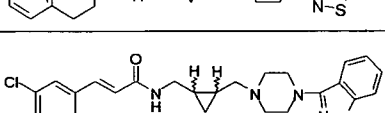
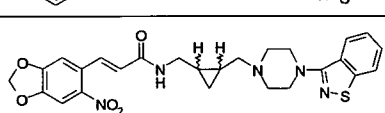
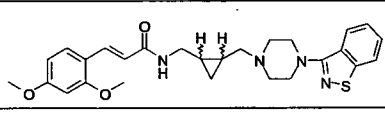
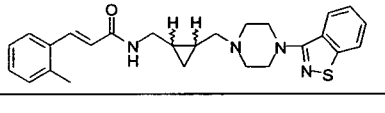
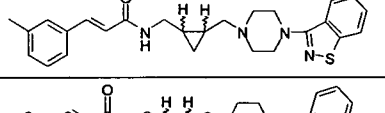
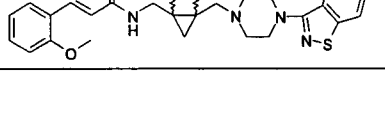
Example No.	Structure	Molecular Weight	MS (ESI+) (M+1, peak intensity)
63		504.70	505 (100)
64		519.67	520 (100)
65		560.79	561 (100)
66		544.74	545 (100)
67		492.65	493 (100)
68		497.11	498 (100)
69		518.68	519 (100)
70		558.72	559 (100)
71		492.66	493 (100)
72		520.72	521 (100)
73		527.11	528 (100)
74		581.67	582 (100)
75		506.69	507 (100)
76		506.69	507 (100)
77		552.72	553 (100)

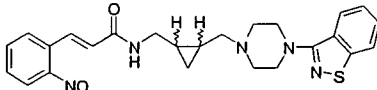
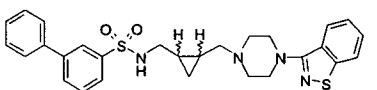
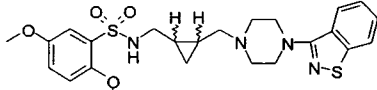
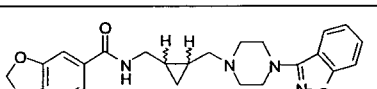
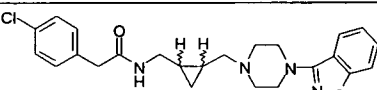
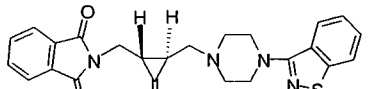
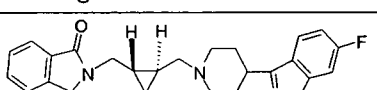
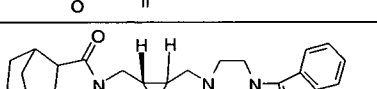
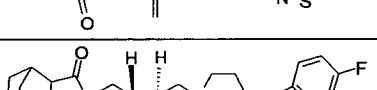
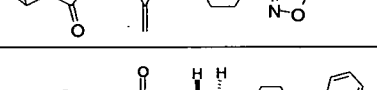
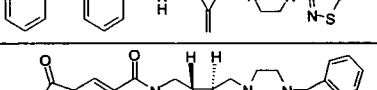
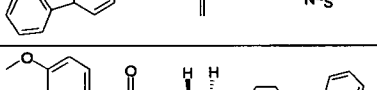
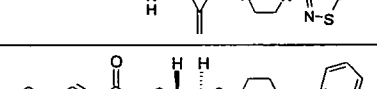
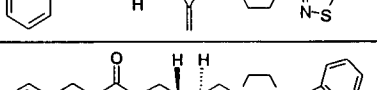
Example No.	Structure	Molecular Weight	MS (ESI+) (M+1, peak intension)
78		522.69	523 (100)
79		537.66	538 (100)
80		578.78	579 (100)
81		562.73	563 (100)
82		510.64	511 (100)
83		515.10	516 (100)
84		536.67	537 (100)
85		510.68	511 (100)
86		515.10	516 (100)
87		526.71	527 (100)
88		536.70	537 (100)
89		478.66	479 (100)
90		460.65	461 (100)
91		488.70	489 (100)
92		495.09	496 (100)

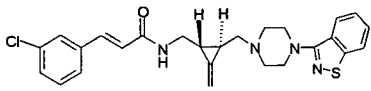
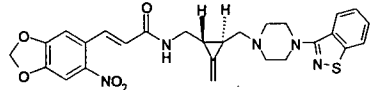
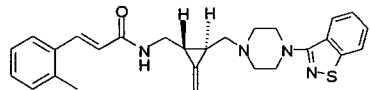
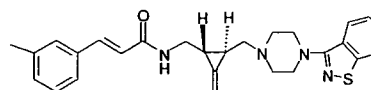
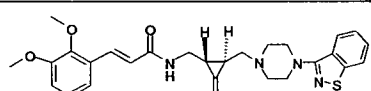
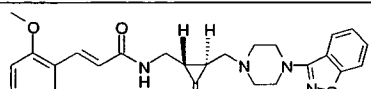
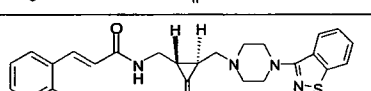
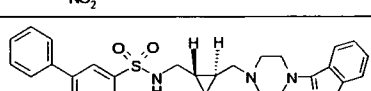
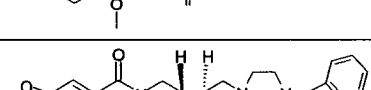
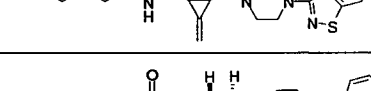
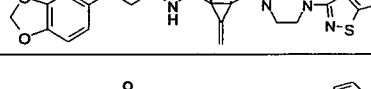
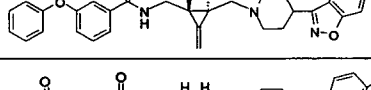
Example No.	Structure	Molecular Weight	MS (ESI+) (M+1, peak intension)
93		549.65	550 (100)
94		520.70	521 (100)
95		474.67	475 (100)
96		474.67	475 (100)
97		520.70	521 (100)
98		490.67	491 (100)
99		505.64	506 (100)
100		546.76	547 (100)
101		530.71	531 (100)
102		478.62	479 (100)
103		483.08	484 (100)
104		504.66	505 (100)
105		527.64	528 (100)
106		537.64	538 (100)
107		479.60	480 (100)

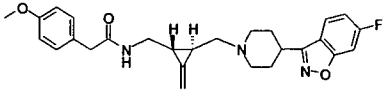
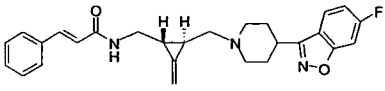
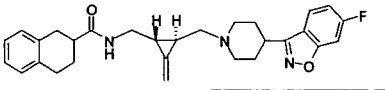
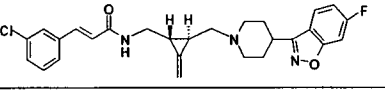
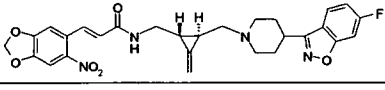
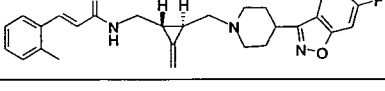
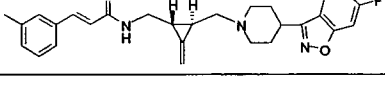
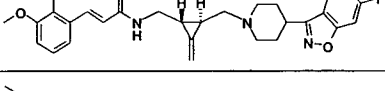
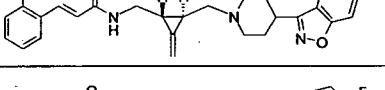
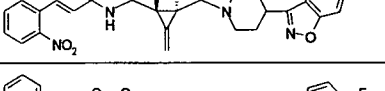
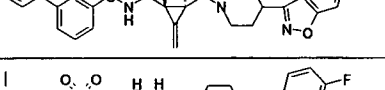
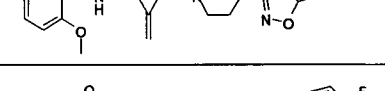
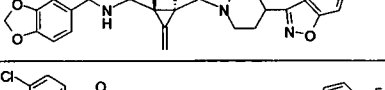
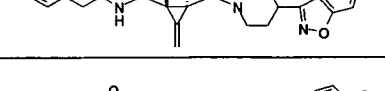
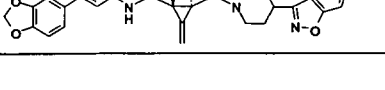
Example No.	Structure	Molecular Weight	MS (ESI+) (M+1, peak intension)
108		461.58	462 (100)
109		489.64	490 (100)
110		496.03	497 (100)
111		550.59	551 (100)
112		475.61	476 (100)
113		475.61	476 (100)
114		521.64	522 (100)
115		491.61	492 (100)
116		506.58	507 (100)
117		547.70	548 (100)
118		531.65	532 (100)
119		479.56	480 (100)
120		484.02	485 (100)
121		505.59	506 (100)
122		518.70	519 (100)

Example No.	Structure	Molecular Weight	MS (ESI+) (M+1, peak intension)
123		502.66	503 (100)
124		450.56	451 (100)
125		455.03	456 (100)
126		476.60	477 (100)
127		477.59	478 (100)
128		498.65	499 (100)
129		508.65	509 (100)
130		450.61	451 (100)
131		432.59	433 (100)
132		460.65	461 (100)
133		467.04	468 (100)
134		521.60	522 (100)
135		492.65	493 (100)
136		446.62	447 (100)
137		446.62	447 (100)

Example No.	Structure	Molecular Weight	MS (ESI+) (M+1, peak intensity)
138		492.65	493 (100)
139		462.62	463 (100)
140		498.65	499 (100)
141		508.65	509 (100)
142		450.61	451 (100)
143		432.59	433 (100)
144		460.65	461 (100)
145		467.04	468 (100)
146		521.60	522 (100)
147		492.65	493 (100)
148		446.62	447 (100)
149		446.62	447 (100)
150		492.65	493 (100)
151		462.62	463 (100)

Example No.	Structure	Molecular Weight	MS (ESI+) (M+1, peak intension)
152		477.59	478 (100)
153		518.70	519 (100)
154		502.66	503 (100)
155		450.56	451 (100)
156		455.03	456 (100)
157		444.56	445 (100)
158		445.50	446 (100)
159		462.62	463 (100)
160		463.56	464 (100)
161		510.66	511 (100)
162		520.66	521 (100)
163		462.62	463 (100)
164		444.60	445 (100)
165		472.66	473 (100)

Example No.	Structure	Molecular Weight	MS (ESI+) (M+1, peak intension)
166		479.05	480 (100)
167		533.61	534 (100)
168		458.63	459 (100)
169		458.63	459 (100)
170		504.66	505 (100)
171		474.63	475 (100)
172		489.60	490 (100)
173		530.72	531 (100)
174		514.67	515 (100)
175		462.57	463 (100)
176		467.04	468 (100)
177		488.61	489 (100)
178		511.60	512 (100)
179		521.60	522 (100)

Example No.	Structure	Molecular Weight	MS (ESI+) (M+1, peak intensification)
180		463.56	464 (100)
181		445.54	446 (100)
182		473.60	474 (100)
183		479.99	480 (100)
184		534.55	535 (100)
185		459.57	460 (100)
186		459.57	460 (100)
187		505.59	506 (100)
188		475.57	476 (100)
189		490.54	491 (100)
190		531.65	532 (100)
191		515.61	516 (100)
192		463.51	464 (100)
193		467.98	468 (100)
194		489.55	490 (100)

Example No.	Structure	Molecular Weight	MS (ESI+) (M+1, peak intension)
195		541.67	542 (100)
196		551.67	552 (100)
197		493.63	494 (100)
198		475.61	476 (100)
199		503.67	504 (100)
200		510.06	511 (100)
201		564.62	565 (100)
202		489.64	490 (100)
203		489.64	490 (100)
204		535.66	536 (100)
205		505.64	506 (100)
206		520.61	521 (100)
207		561.72	562 (100)
208		545.68	546 (100)
209		493.58	494 (100)

Example No.	Structure	Molecular Weight	MS (ESI+) (M+1, peak intension)
210		498.05	499 (100)
211		519.62	520 (100)
212		475.57	476 (100)
213		493.63	494 (100)
214		541.67	532 (100)
215		551.67	552 (100)
216		475.61	476 (100)
217		510.06	511 (100)
218		564.62	565 (100)
219		489.64	490 (100)
220		535.66	536 (100)
221		493.58	494 (100)
222		519.62	520 (100)
223		475.64	476 (100)

Example No.	Structure	Molecular Weight	MS (ESI+) (M+1, peak intension)
224		510.08	511 (100)
225		493.63	494 (100)
226		502.64	503 (100)
227		506.60	507 (100)
228		590.74	591 (100)
229		490.63	491 (100)
230		540.69	541 (100)
231		550.68	551 (100)
232		474.63	475 (100)
233		509.07	510 (100)
234		563.63	564 (100)
235		488.65	489 (100)
236		488.65	489 (100)
237		534.68	535 (100)

Example No.	Structure	Molecular Weight	MS (ESI+) (M+1, peak intensity)
238		504.65	505 (100)
239		519.62	520 (100)
240		560.74	561 (100)
241		544.69	545 (100)
242		492.60	493 (100)
243		497.06	498 (100)

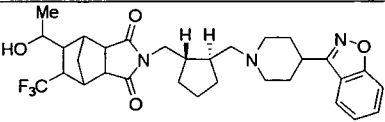
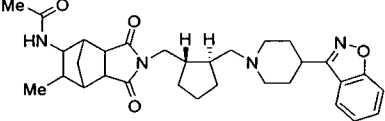
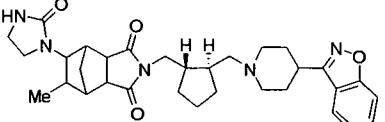
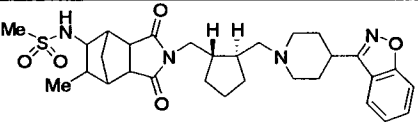
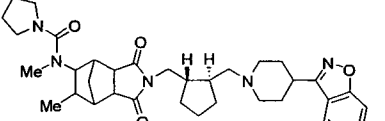
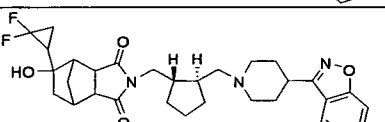
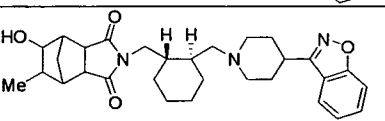
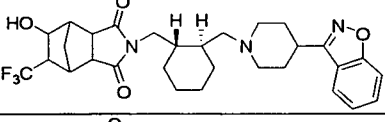
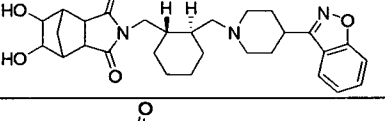
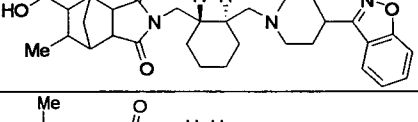
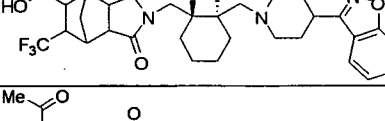
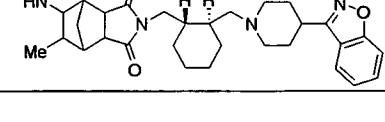
[0060]

Examples 244 - 343

The following compounds can be prepared in a similar manner.

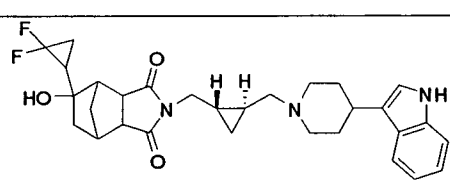
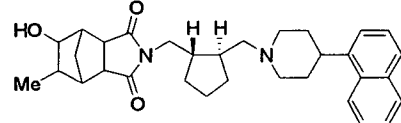
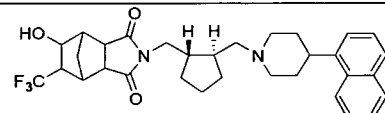
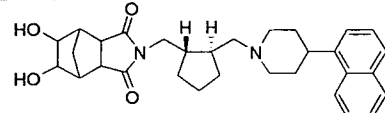
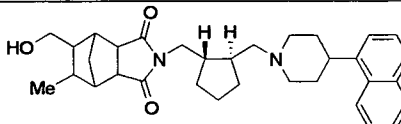
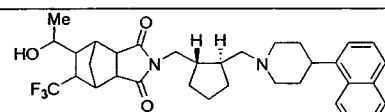
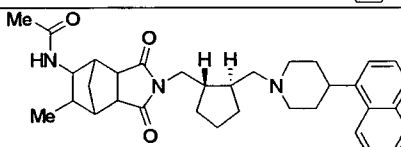
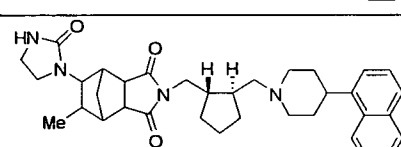
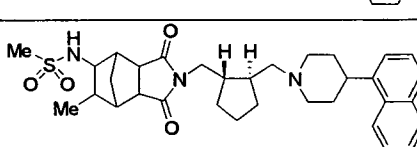
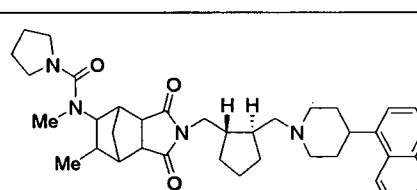
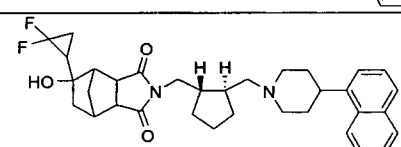
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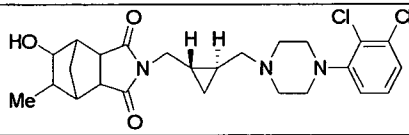
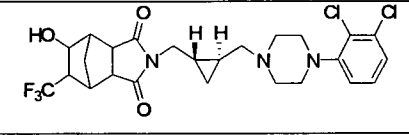
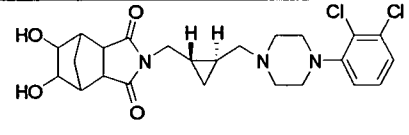
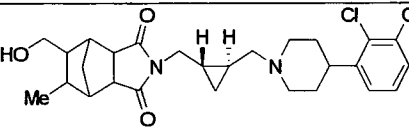
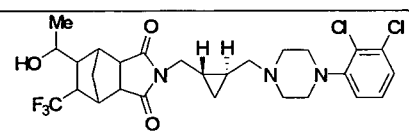
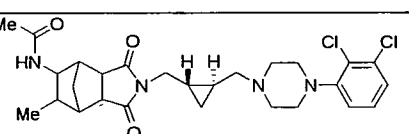
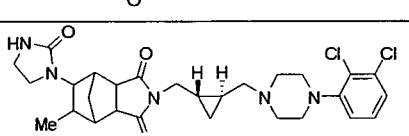
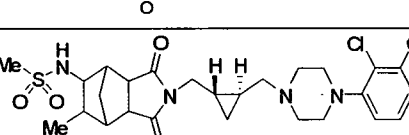
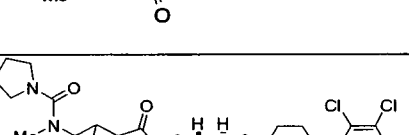
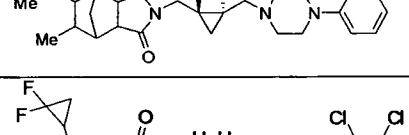
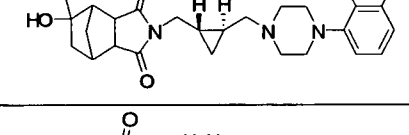
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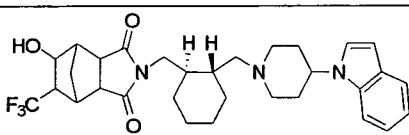
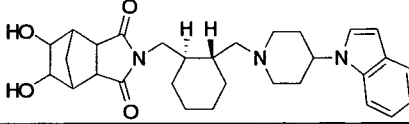
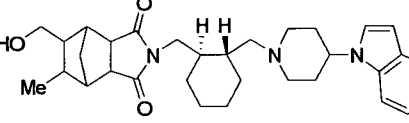
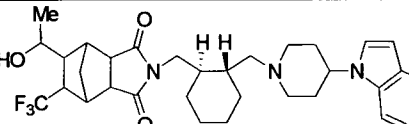
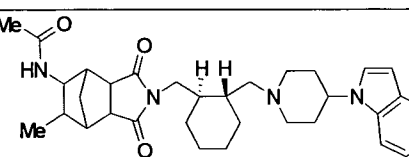
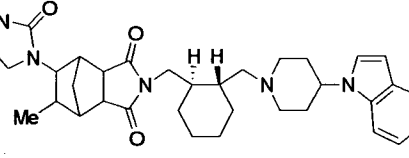
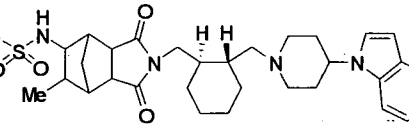
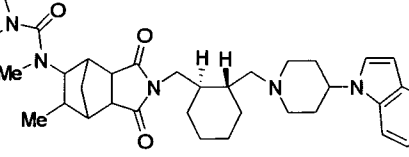
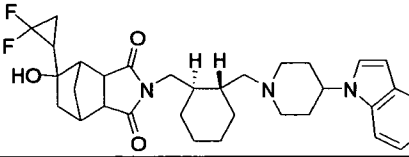
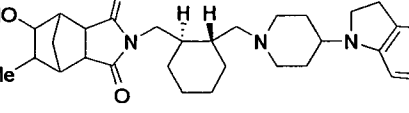
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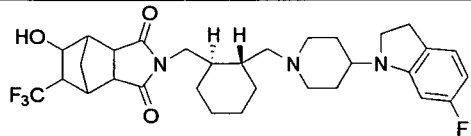
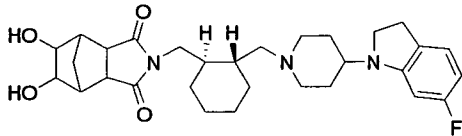
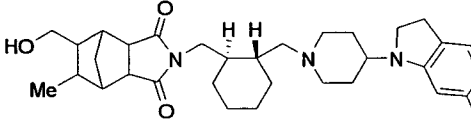
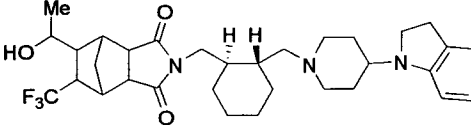
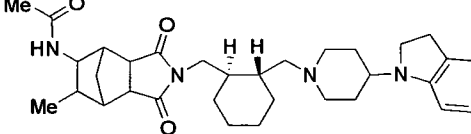
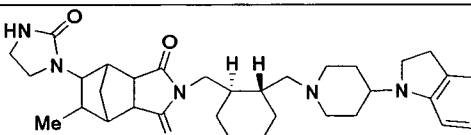
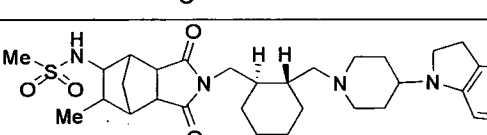
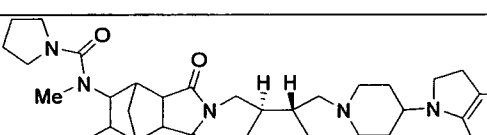
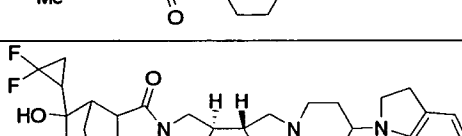
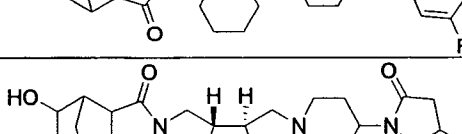
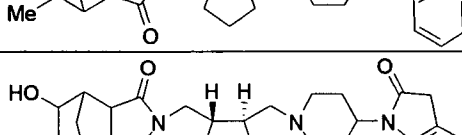
Example No.	Structure
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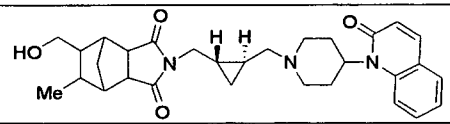
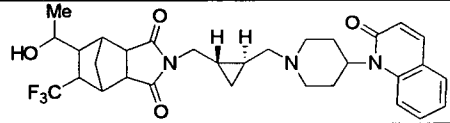
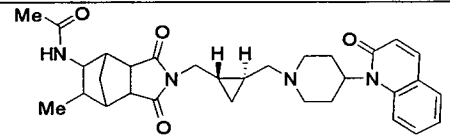
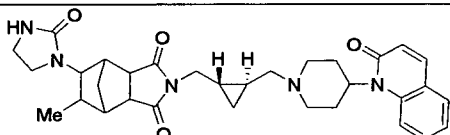
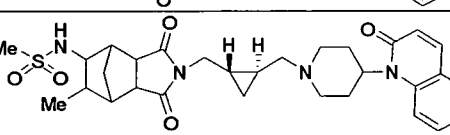
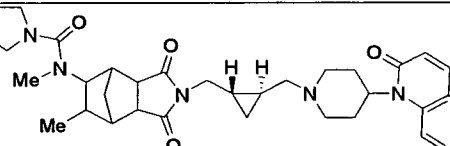
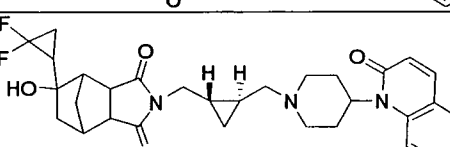
Example No.	Structure
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Example No.	Structure
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[0061]

Experiment 1

<Method>

5 (1) Antipsychotic action (Anti D2 activity) (*in vitro*)

In general, there is clinically some correlation between antipsychotic action and antagonistic action for dopamine D2 receptor. The experimental method used herein is a binding assay for D2 receptor which is one of the

10 tests evaluating D2 receptor action *in vitro*. According to

the known method (e.g. *Japan. J. Pharmacol.*, 53, 321-329 (1990)), the above-captioned experiment was carried out using [3H] spiperone, i.e., the binding amount of [3H] spiperone to the preparation cell membrane expressing human D2 receptor was measured, and then the binding inhibitory rate by the test compound (100 nM) was measured/calculated. The results are shown in the following table.

Example No.	Binding inhibitory rate (%) for D2 receptor (100 nM)	Example No.	Binding inhibitory rate (%) for D2 receptor (100 nM)
13	92	87	93
14	92	100	91
15	93	101	94
16	94	102	95
21	91	104	92
32	91	137	95
33	90	139	91
36	92	185	92
37	90	190	92
44	91	192	90
60	91	200	92
62	91	221	93
64	92	222	93
67	90	223	94
69	91	225	94
82	94	239	95
83	94	240	85
84	95	241	95
85	91	242	95
86	94	243	94

(2) Antipsychotic action (*in vivo*)

The anti-methamphetamine test which is a typical *in vivo* test for evaluating antipsychotic action in the clinical study was carried out as follows. The test substance was intraperitoneally administered to a male rat, and 30 minutes later methamphetamine (1 mg/kg) was intraperitoneally administered to the male rat. Ten minutes after completing the administrations, the movement of the rat was measured with Supermex for 90 minutes, and the dose for 50% inhibition: ED₅₀ value was calculated. The result was shown in the table below.

Example No.	Antidopaminergic action ED ₅₀ (mg/kg)
87	4.5
200	0.24

[0063]

(3) Side effects

The cataleptic action which is a typical central nervous system side-effect of antipsychotic agents in the clinical study was evaluated as follows. The test substance was intraperitoneally administered to a male rat. One hour later, the rat was made to hold on a pole three times which is horizontally set at a height of 9 cm. When the rat retained the unnatural stretched pose for 30 seconds even one time out of three times, the rat was evaluated as cataleptic positive. The dose for inducing

50% the rats to the catalepsy: ED₅₀ value was calculated.

The result was shown in the table below.

Example No.	Cataleptic ED ₅₀ (mg/kg)
87	>135
200	>7.2

[0064]

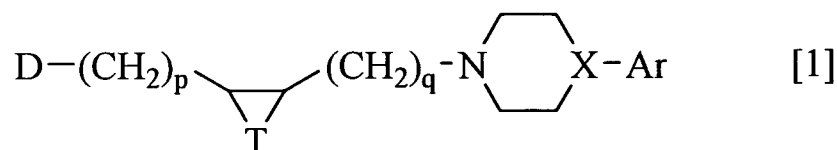
5 (Effect of the Invention)

The compounds of the present invention and acid additive salts thereof exhibited a potent psychotropic action. Especially, it has become clear that the compounds of the present invention and acid additive salts thereof exhibit an excellent effect for improving a broad spectrum of schizophrenia such as positive symptom, negative symptom, and cognitive dysfunction, while never almost causing abnormal electrocardiogram, weight gain, etc., thus are very safe medicaments.

10

CLAIMS

1. A cycloalkane derivative of formula [1]:

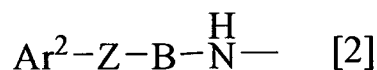


5 wherein

p and q are independently 1 or 2;

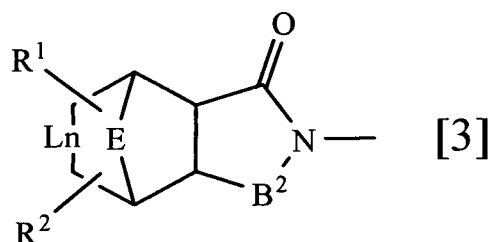
T is $-(\text{CH}_2)_n-$ wherein n is 1 to 4, or $-\text{C}(=\text{CH}_2)-$;

D is the group of formula [2]:



10 wherein Ar^2 is an aromatic heterocyclyl group or an aromatic carbocyclyl group wherein the aromatic heterocyclyl group and the aromatic carbocyclyl group may be substituted with 1 or 2 substituents selected independently from the group consisting of nitro group,
 15 cyano group, halogen atom, lower alkyl group, lower alkoxy group, trifluoromethyl group, trifluoromethoxy group and phenoxy group, and further the lower alkyl group, the alkoxy group and the phenoxy group may be substituted with one or more halogen atoms which are the same or different;
 20 B is carbonyl group or sulfonyl group,
 Z is single bond, lower alkylene, lower alkenylene, or ethynylene,

the group of formula [3]:



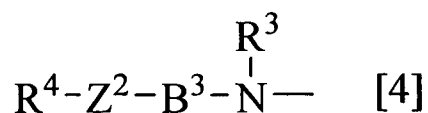
wherein B² is carbonyl group or sulfonyl group;

Ln is single or double bond;

5 E is lower alkylene which may be optionally substituted with one or two lower alkyl groups which are the same or different, oxygen atom, or two hydrogen atoms which are attached at the both ends (i.e., E is not a bridge);

10 R¹ and R² are independently hydrogen atom, hydroxy, lower alkyl group, or lower cycloalkyl group, which may be independently connected to any one of the carbon atoms which compose the ring of formula [3], or R¹ and R² may be connected to the same carbon atom if possible, wherein the
15 lower alkyl group and the lower cycloalkyl group may be substituted with one or more substituents selected independently from the group consisting of hydroxy group and fluorine atom, or

the group of formula [4]:



wherein B³ is carbonyl group or sulfonyl group;

Z² is single bond, oxygen atom, or -NR⁵-;

R³, R⁴ and R⁵ are independently hydrogen atom or lower alkyl, or R³ and R⁴, or R⁴ and R⁵ may be connected together
 5 directly or via lower alkylene to form a ring;

X is N, CH or C(OH); and

Ar is aromatic heterocyclyl group, aromatic hydrocarbon group, benzoyl, or phenoxy, wherein the aromatic heterocyclyl group, the aromatic hydrocarbon group,
 10 the benzoyl, and the phenoxy may be substituted with one or more substituents selected independently from the group consisting of lower alkyl, lower alkoxy and halogen atom;

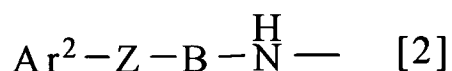
provided that Ar is not benzisothiazolyl group when D is the substituent of formula [3],
 15 or an acid additive salt thereof.

2. The cycloalkane derivative of claim 1
 wherein

p and q are 1,

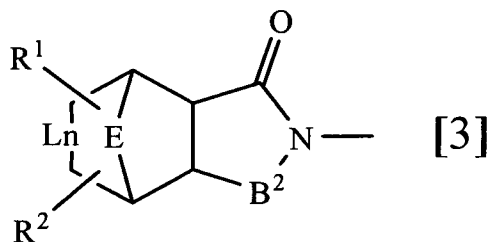
20 T is -(CH₂)_n- wherein n is 1 to 4,

D is the group of formula [2]:



wherein Ar² and B are defined as claim 1, and Z is single bond, methylene, vinylene or ethynylene, or

the group of formula [3]:



wherein B^2 , E, R^1 , R^2 and Ln are defined as claim 1, and

X is N or CH,

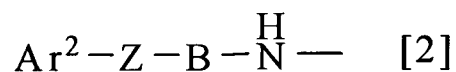
5 or an acid additive salt thereof.

3. The cycloalkane derivative of claim 2

wherein

T is $-(CH_2)_n-$ wherein n is 3 or 4,

10 D is the group of formula [2]:



wherein Ar^2 and B are defined as claim 2, and Z is single bond, methylene or vinylene,

or an acid additive salt thereof.

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4. The cycloalkane derivative of claim 2 or 3 wherein Z is single bond or vinylene, or an acid additive salt thereof.