

[0006]

[Non Patent Literature 1]D. P. Taylor, Neuropeptides.
19 Suppl: 15-19, 1991

[Non Patent Literature 2]P. Seeman, Can. J. Psychiatry.
5 47: 27-38, 2002

[Non Patent Literature 3]C. J. Schmidt, Life Science.
56 (25): 2209-2222, 1995

SUMMARY OF INVENTION

10 PROBLEMS TO BE SOLVED BY THE INVENTION

[0007]

An object of the present invention is the provision of
novel compounds which have antagonist activity for
serotonin 5-HT_{2A} receptor with agonist activity for
15 serotonin 5-HT_{1A} receptor, and are useful for a medicament
for treating neuropsychiatric diseases.

MEANS OF SOLVING THE PROBLEMS

[0008]

20 The present inventors have extensively studied to
reach the above object, and then have found that a compound
of Formula (1) as below, or a pharmaceutically acceptable
salt thereof (hereinafter, also referred to as "the present
compound") has antagonist activity for serotonin 5-HT_{2A}
25 receptor together with agonist activity for serotonin 5-
HT_{1A}

manufacture of a medicament for treating mental disease or central nervous system disease.

[0034]

[Item 26] A compound according to any one of Items 1 to 18,
5 or a pharmaceutically acceptable salt thereof, for use in the treatment of mental disease or central nervous system disease.

[0035]

[Item 27] A medicament for treating mental disease or
10 central nervous system disease, comprising a compound according to any one of Items 1 to 18, or a pharmaceutically acceptable salt thereof, and at least one drug selected from the group consisting of antidepressant
15 supplements, dopamine receptor agonists, antiparkinsonian drugs, antiepileptic drugs, analgesic drugs, hormone preparations, antimigraine drugs, adrenaline β receptor antagonists, antimentia drugs, drugs for treating mood disorders, antiemetic drugs, sleep-inducing drugs, and
20 anticonvulsants.

[0036]

[Item 28] A medicament for treating mental disease or central nervous system disease, comprising a compound according to any one of Items 1 to 18, or a
25 pharmaceutically acceptable salt thereof, as an active ingredient, for combination use with at least one drug selected from the group consisting of antidepressant drugs,

anxiolytic drugs, antischizophrenic agents, dopamine supplements, dopamine receptor agonists, antiparkinsonian drugs, antiepileptic drugs, analgesic drugs, hormone preparations, antimigraine drugs, adrenaline β receptor antagonists, antidementia drugs, drugs for treating mood disorders, antiemetic drugs, sleep-inducing drugs, and anticonvulsants.

EFFECT OF THE INVENTION

10 [0037]

The present compound has antagonist activity for 5-HT_{2A} receptor and agonist activity for 5-HT_{1A} receptor. In a preferred embodiment, the present compound has a good metabolic stability, provides a long disappearance half-life (T_{1/2}) in human, and exhibits higher selectivities to these receptors than other GPCRs such as dopamine D₂ receptor (hereinafter, referred to as "D₂ receptor") and hERG channel. Thus, some preferred compounds of the present invention are useful as a medicament for treating

15

20 neuropsychiatric diseases, which has a long persistence effect in human body and high safety.

BRIEF DESCRIPTION OF DRAWINGS

agents, dopamine supplements, dopamine receptor agonist, antiparkinsonian drugs, antiepileptic drugs, analgesic drugs, hormone preparations, antimigraine agents, adrenaline β receptor antagonist, antidementia drugs, drugs
5 for treating mood disorders, antiemetic drugs, sleep-inducing drugs, and anticonvulsants. The concomitant drug is preferably anxiolytic drugs such as selective serotonin reuptake inhibitor.

[0164]

10 The administration interval of the present compound and its concomitant drug is not limited, *i.e.*, the concomitant drug may be administered to a subject patient at the same time as the present compound or at a suitable interval. Or, the present compound and its concomitant
15 drug can be formulated into a combination drug. The dose of the concomitant drug can be suitably determined based on the standard of the clinically-used dose thereof. The combination ratio of the present compound and its concomitant drug can be suitably determined based on its
20 subject patient, administration route, disease, pathology, and combinations thereof. For example, when the subject patient is a human being, the concomitant drug may be used in 0.01 to 100 parts by weight per part of the present compound. For the purpose of reducing side effects, an
25 antiemetic drug, a sleep-inducing drug, an anticonvulsant, etc. may be used in

153	658.75	16		193	755.52	27
154	45.09	58		194	46.48	40

[0330]

Test 3: Evaluation of antagonist activity for human 5-HT_{2A} receptor

Aequorin, Gα16 protein, and each receptor were transiently expressed in CHO-K1 cells (Chinese hamster ovary). The cells were cultured in a CO₂ incubator at 37°C overnight, seeded into a 384-well plate, and stood at room temperature for 2 or more hours. Each compound dissolved in DMSO was added thereto, and changes in luminescence were measured by FDSS/μCELL functional drug screening system (Hamamatsu Photonics K.K.). Antagonist activity was calculated from the following formula.

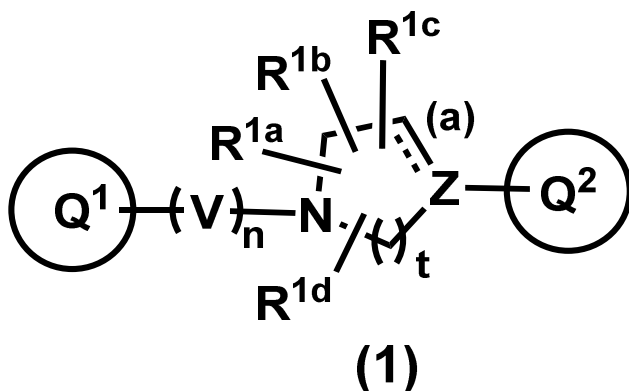
[0331]

Antagonist activity (%) = 100 × {(Luminescence of well in the presence of 1 nmol/L 5-HT - Luminescence of well containing solvent) - (Luminescence of well in the presence of test compound and 1 nmol/L 5-HT - Luminescence of well containing solvent)} / (Luminescence of well in the presence of 1 nmol/L 5-HT - Luminescence of well containing solvent)

The concentration of test compound in which 50% of antagonist activity was obtained was calculated as IC₅₀. The results are shown below.

CLAIMS

1. A compound of Formula (1):



5 wherein V is $\text{CR}^{\text{A}}\text{R}^{\text{B}}$;

n is 1 or 2;

Z is nitrogen atom, carbon atom, or $-\text{CR}^{\text{J}}-$;

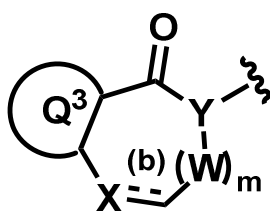
t is 1, 2, or 3;

10 the bond (a) accompanied with broken line is single bond or double bond;

R^{A} and R^{B} are each independent, where each symbol may be independently the same or different when each symbol exists plurally, and are hydrogen atom, C_{1-6} alkyl, C_{1-6} alkoxy, or C_{3-10} cycloalkyl (wherein the alkyl, the alkoxy, and the cycloalkyl moieties may be each independent and optionally substituted with the same or different 1 to 3 halogen atoms);

15 $\text{R}^{1\text{a}}$, $\text{R}^{1\text{b}}$, $\text{R}^{1\text{c}}$, and $\text{R}^{1\text{d}}$ are each independently hydrogen atom, halogen atom, or C_{1-6} alkyl optionally substituted with the same or different 1 to 3 halogen atoms;

20 Ring Q^1 is a group of the following Formula (2):



(2)

wherein Ring Q^3 is an optionally substituted 5- or 6-membered aromatic heterocyclic ring;

W is $CR^C R^D$;

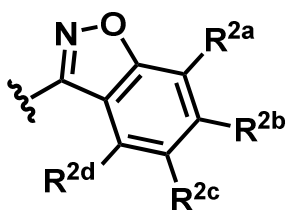
5 m is 0 or 1;

X is $-CR^E-$ or $-CR^F R^G-$;

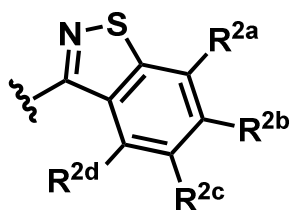
Y is nitrogen atom or $-CR^H-$;

the bond (b) accompanied with broken line is single bond or double bond;

10 Ring Q^2 is a group of the following Formula (3a) or (3b):



(3a)



(3b)

wherein R^{2a} , R^{2b} , R^{2c} , and R^{2d} are each independently hydrogen atom, halogen atom, cyano, C_{1-6} alkyl, C_{1-6} alkoxy (wherein the alkyl and the alkoxy moieties may be each independent and optionally substituted with the same or different 1 to 3 halogen atoms), or amino optionally substituted with the same or different 1 or 2 C_{1-6} alkyl;

20 R^C , R^D , R^E , R^F , R^G , R^H , and R^J are each independently hydrogen atom, C_{1-6} alkyl, C_{1-6} alkoxy, or C_{3-10} cycloalkyl (wherein the alkyl, the alkoxy, and the cycloalkyl moieties may be each independent and optionally substituted with the same or different 1 to 3 halogen atoms), provided that when R^F and R^G are C_{1-6} alkyl, then these groups may combine

together with the carbon atom to which they attach to form a 3- to 6-membered saturated carbocyclic ring;

provided that

(I) when Ring Q^3 is an optionally substituted 5-membered aromatic heterocyclic ring, then R^{2a} , R^{2b} , R^{2c} , and R^{2d} are hydrogen atom;

(II) when Ring Q^3 is an optionally substituted 6-membered aromatic heterocyclic ring, then m is 0;

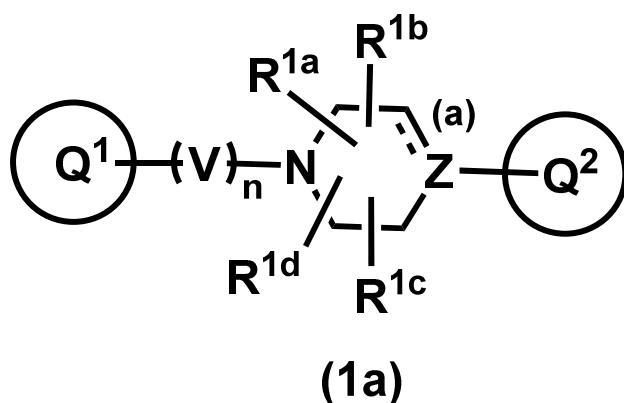
(III) when the bond (a) accompanied with broken line is double bond, then Z is carbon atom;

(IV) when the bond (b) accompanied with broken line is single bond, then X is $-CR^F R^G-$; and

(V) when the bond (b) accompanied with broken line is double bond, then X is $-CR^E-$, or a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1, wherein Ring Q^3 is a 5- or 6-membered aromatic heterocyclic ring optionally substituted with the same or different 1 to 3 groups selected from the group consisting of hydrogen atom, halogen atom, cyano, C_{1-6} alkyl, C_{3-10} cycloalkyl (wherein the alkyl and the cycloalkyl moieties may be each independent and optionally substituted with the same or different 1 to 3 halogen atoms), and C_{1-6} alkoxy (wherein the alkoxy moiety may be optionally substituted with the same or different 1 to 3 halogen atoms or 4- to 8-membered saturated heterocyclyl), or a pharmaceutically acceptable salt thereof.

3. The compound according to claim 1 or 2, wherein Formula (1) is Formula (1a):



wherein Q^1 , Q^2 , V , Z , n , R^{1a} , R^{1b} , R^{1c} , R^{1d} , and the bond (a) accompanied with broken line are as defined in the above, or a pharmaceutically acceptable salt thereof.

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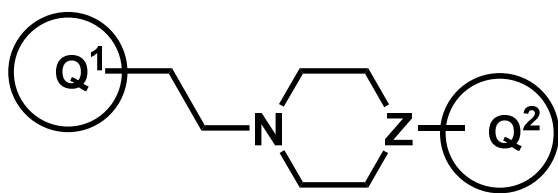
4. The compound according to any one of claims 1 to 3, wherein R^{1a} , R^{1b} , R^{1c} , and R^{1d} are hydrogen atom, or a pharmaceutically acceptable salt thereof.

10 5. The compound according to any one of claims 1 to 4, wherein both of R^A and R^B are hydrogen atom, or a pharmaceutically acceptable salt thereof.

6. The compound according to any one of claims 1 to 5,
15 wherein n is 2, or a pharmaceutically acceptable salt thereof.

7. The compound according to any one of claims 1 to 6,
wherein the bond (a) accompanied with broken line is single
20 bond, or a pharmaceutically acceptable salt thereof.

8. The compound according to claim 1 or 2, wherein Formula (1) is represented by the following Formula (1b):

**(1b)**

wherein Q^1 , Q^2 , and Z are as defined in the above, or a pharmaceutically acceptable salt thereof.

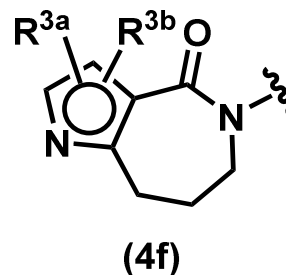
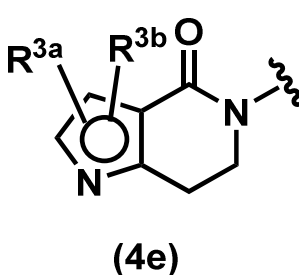
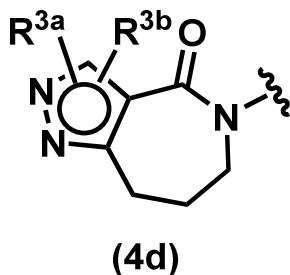
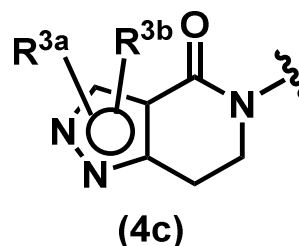
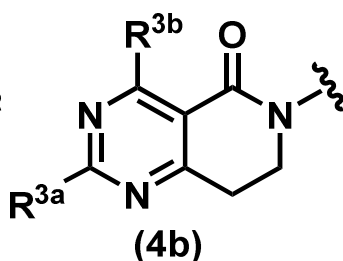
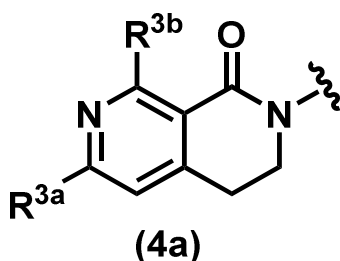
5 9. The compound according to any one of claims 1 to 8, wherein Z is nitrogen atom, or a pharmaceutically acceptable salt thereof.

10 10. The compound according to any one of claims 1 to 8, wherein Z is $-CH-$, or a pharmaceutically acceptable salt thereof.

15 11. The compound according to any one of claims 1 to 10, wherein Y is nitrogen atom, or a pharmaceutically acceptable salt thereof.

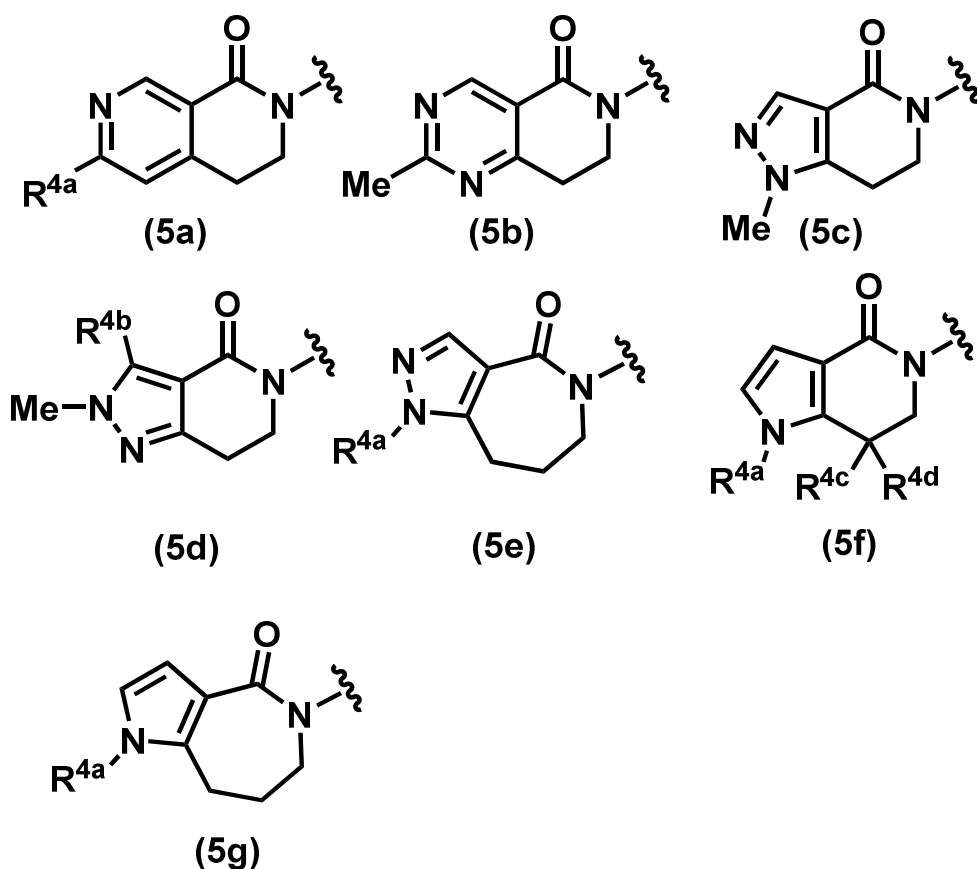
20 12. The compound according to any one of claims 1 to 11, wherein the bond (b) accompanied with broken line is single bond and X is $-CH_2-$, or a pharmaceutically acceptable salt thereof.

13. The compound according to any one of claims 1 to 12, wherein Ring Q^1 is any one of the following Formula (4a), (4b), (4c), (4d), (4e), or (4f):



wherein R^{3a} and R^{3b} are each independently hydrogen atom, halogen atom, cyano, C_{1-6} alkyl, C_{1-6} alkoxy (wherein the alkyl and the alkoxy moieties may be each independent and optionally substituted with the same or different 1 to 3 halogen atoms), or amino optionally substituted with the same or different 1 to 2 C_{1-6} alkyl, or a pharmaceutically acceptable salt thereof.

14. The compound according to any one of claims 1 to 12, wherein Ring Q^1 is any one of the following Formula (5a), (5b), (5c), (5d), (5e), (5f), or (5g):



wherein R^{4a} is C_{1-6} alkyl or C_{1-6} alkoxy,

R^{4b} is hydrogen atom or C_{1-6} alkyl,

R^{4c} and R^{4d} are each independently hydrogen atom or C_{1-6} alkyl, provided that when one of R^{4c} or R^{4d} is hydrogen atom, then the other is C_{1-6} alkyl, or alternatively, R^{4c} and R^{4d} may combine together with the carbon atom to which they attach to form a 3- to 6-membered saturated carbocyclic ring, or a pharmaceutically acceptable salt thereof.

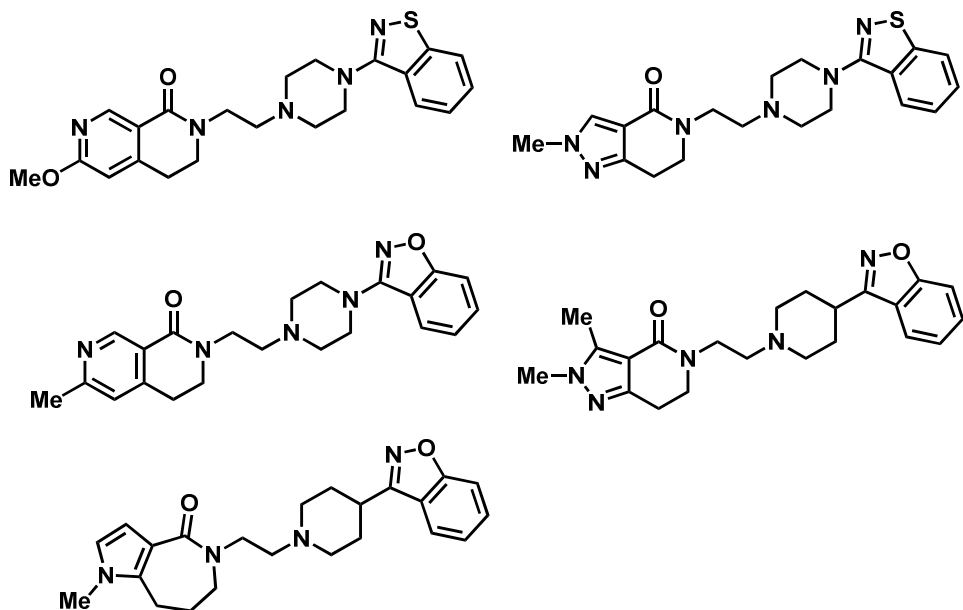
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15. The compound according to any one of claims 1 to 14, wherein Ring Q^2 is a group of Formula (3a), or a pharmaceutically acceptable salt thereof.

15 16. The compound according to any one of claims 1 to 14, wherein Ring Q^2 is a group of Formula (3b), or a pharmaceutically acceptable salt thereof.

17. The compound according to any one of claims 1 to 16, wherein R^{2a} , R^{2b} , R^{2c} , and R^{2d} are hydrogen atom, or a pharmaceutically acceptable salt thereof.

18. The compound according to claim 1, which is represented by any one of the following formulae:



or a pharmaceutically acceptable salt thereof.

19. A drug comprising a compound according to any one of claims 1 to 18, or a pharmaceutically acceptable salt thereof, as an active ingredient.

20. A medicament for treating mental disease or central nervous system disease, comprising a compound according to any one of claims 1 to 18, or a pharmaceutically acceptable salt thereof, as an active ingredient.

21. The medicament according to claim 20, wherein the mental disease or central nervous system disease is organic, including symptomatic, mental disorders; mental and behavioural disorders due to psychoactive substance use;

schizophrenia, schizotypal disorders, and delusional disorders; mood [affective] disorders; neurotic disorders, stress-related disorders, and somatoform disorders; nonorganic sleep disorders; sexual dysfunction, not caused
5 by organic disorder or disease; pervasive developmental disorders; behavioural and emotional disorders with onset usually occurring in childhood and adolescence; extrapyramidal and movement disorders; other degenerative diseases of nervous system; or sleep disorders.

10

22. The medicament according to claim 20, wherein the mental disease or central nervous system disease is schizophrenia, positive symptoms of schizophrenia, negative symptoms of schizophrenia, bipolar disorders with psychotic
15 features, depressive disorders with psychotic features, psychopathic symptoms associated with dementia, psychopathic symptoms associated with Alzheimer's disease, psychopathic symptoms associated with dementia with Lewy bodies, psychopathic symptoms associated with Parkinson's
20 disease with dementia, psychopathic symptoms associated with Parkinson's disease, or irritation, agitation, or aggression associated with Alzheimer's disease.

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23. The medicament according to claim 20, wherein the mental disease or central nervous system disease is schizophrenia, psychopathic symptoms associated with dementia, psychopathic symptoms associated with Alzheimer's
disease, psychopathic symptoms associated with dementia with Lewy bodies, or irritation, agitation, or aggression
30 associated with Alzheimer's disease.

24. A method for treating mental disease or central nervous system disease, comprising administering a

therapeutically effective amount of a compound according to any one of claims 1 to 18, or a pharmaceutically acceptable salt thereof, to a patient in need thereof.

- 5 25. Use of a compound according to any one of claims 1 to 18, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating mental disease or central nervous system disease.
- 10 26. A compound according to any one of claims 1 to 18, or a pharmaceutically acceptable salt thereof, for use in the treatment of mental disease or central nervous system disease.
- 15 27. A medicament for treating mental disease or central nervous system disease, comprising a compound according to any one of claims 1 to 18, or a pharmaceutically acceptable salt thereof, and at least one drug selected from the group consisting of antidepressant drugs, anxiolytic drugs,
20 antischizophrenic agents, dopamine supplements, dopamine receptor agonists, antiparkinsonian drugs, antiepileptic drugs, analgesic drugs, hormone preparations, antimigraine drugs, adrenaline β receptor antagonists, antidementia drugs, drugs for treating mood disorders, antiemetic drugs,
25 sleep-inducing drugs, and anticonvulsants.
28. A medicament for treating mental disease or central nervous system disease, comprising a compound according to any one of claims 1 to 18, or a pharmaceutically acceptable
30 salt thereof, as an active ingredient, for combination use with at least one drug selected from the group consisting of antidepressant drugs, anxiolytic drugs, antischizophrenic agents, dopamine supplements, dopamine

receptor agonists, antiparkinsonian drugs, antiepileptic drugs, analgesic drugs, hormone preparations, antimigraine drugs, adrenaline β receptor antagonists, antidementia drugs, drugs for treating mood disorders, antiemetic drugs, 5 sleep-inducing drugs, and anticonvulsants.