DESCRIPTION

Title of Invention

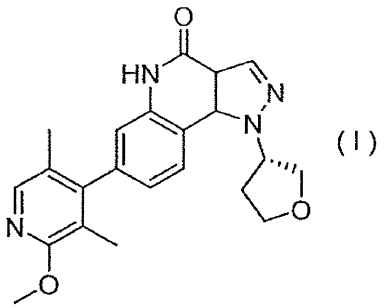
Dementia Therapeutic Agent Combining Pyrazoloquinoline Derivative and Memantine

Technical Field

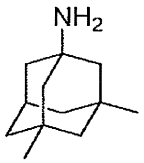
[0001] The present invention relates to a therapeutic agent for dementia combining a pyrazoloquinoline derivative having phosphodiesterase 9 (PDE9) inhibitory action or a pharmaceutically acceptable salt thereof, and memantine or a pharmaceutically acceptable salt thereof.

Background Art

[0002]



(I)



(II)

[0003] Pyrazoloquinoline derivatives represented by formula (I) (hereunder referred to as "compound (I)") have phosphodiesterase 9 (PDE9) inhibitory action, and are considered to have promising ameliorative effects on cognitive function in Alzheimer's disease (PTL 1).

[0004] Memantine, represented by formula (II) (hereunder referred to as "compound (II)") has an antagonistic effect on NMDA-type glutamate receptors, and it has been reported to improve cognitive function in moderate to severe Alzheimer's disease, while also exhibiting efficacy against peripheral symptoms such as agitation, irritability, aggression and behavioral disorder (BPSD: Behavioral and Psychological Symptoms of Dementia) (see NPLs 1 and 2).

[0005] Other Alzheimer's disease therapeutic agents that have been approved for application include the acetylcholine esterase inhibitors donepezil, galantamine and rivastigmine. Donepezil is indicated for mild to severe Alzheimer's disease, and has been reported to have, in addition to a cognitive function-ameliorating effect, also an effect against BPSD including agitation, anxiety, apathy, delusion, depression, disinhibition, hallucination, irritability, aberrant motor behavior and apathy (see NPLs 3, 4, 5, 6 and 7). Galantamine and rivastigmine are indicated for mild to moderate Alzheimer's disease (see NPLs 8 and 9).

Combined use of different acetylcholine esterase inhibitors is contraindicated, but any acetylcholine esterase inhibitor may be used in combination with memantine. According to the 2010 Dementia Disease Treatment Guidelines, acetylcholine esterase inhibitors are recommended for the core symptoms of Alzheimer's disease, with one of donepezil, galantamine or rivastigmine being selected first, and then switching to another acetylcholine esterase inhibitor if a problem arises in terms of effect or tolerance. When the effect of the acetylcholine esterase inhibitor is inadequate or a problem arises in terms of tolerance, combination with memantine or switching to memantine may be considered.

[0006] However, acetylcholine esterase inhibitors have digestive system side-effects. In cases where their use is precluded due to side-effects or tolerance, memantine may be selected for moderate to severe Alzheimer's disease patients, but at the current time no effective method of treatment exists for mild Alzheimer's disease patients. The combined use of acetylcholine esterase inhibitors with memantine is possible in patients that experience inadequate effects, but opinions are divided since some reports have indicated an effect by their combined use (see NPL 10) while other reports have indicated no effect (see NPL 11).

Citation List

Patent Literature

[0007] [PTL 1] US Patent No. 8563565

Non-Patent Literature

[0008] [NPL 1] Mecocci et al., Int J Geriatr Psychiatry, vol.24, p.532

[NPL 2] Grossberg et al., Dement Geriatr Cogn Disord, 2009, vol.27, p.164

[NPL 3] Homma et al., Dement. Geriatr. Cogn. Disord., 2000, vol.11, p.299

[NPL 4] Homma et al., Dement. Geriatr. Cogn. Disord., 2008, vol.25, p.399

[NPL 5] Mori et al., Ann. Neurol, vol.72, p.41 2012

[NPL 6] Holmes at al., Neurology, 2004, vol.63, p.214

[NPL 7] Gauthier et al., Int Psychogeriatr, 2002, vol.14, p.389

[NPL 8] Raskind et al., Neurology, 2000, vol.54, p.226

[NPL 9] Winblad et al., Neurology, 2007, vol.69, p.S14

[NPL 10] Lopez et al., J Neurol Neurosurg Psychiatry, 2009, vol.80, p.600

[NPL 11] Howard et al., New Eng J. Med., 2012, vol.366, p.893

Summary of Invention

Technical Problem

[0009] It is currently the case that no satisfactory method of treatment exists for

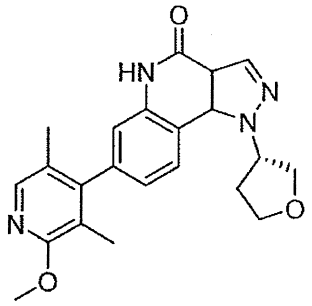
Alzheimer's disease, while an effective anti-dementia agent is also yet to be developed.

Solution to Problem

[0010] In order to solve this problem, the present inventors have carried out much ardent research using a scopolamine-induced cognitive impairment rat model, and as a result we have completed this invention upon finding that the combined use of compound (I) or a pharmaceutically acceptable salt thereof with compound (II) or a pharmaceutically acceptable salt thereof surprisingly exhibits an effect of inhibiting scopolamine-induced cognitive impairment, in doses that are ineffective with each alone.

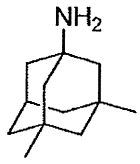
[0011] Specifically, the invention relates to the following <1> to <19.3>.

<1> A therapeutic agent for Alzheimer's disease for combined use of(S)-7-(2-methoxy-3,5-dimethylpyridin-4-yl)-1-(tetrahydrofuran-3-yl)-1H-pyrazolo[4,3-c]quinoline-4(5H)-one represented by formula (I):



(I)

or a pharmaceutically acceptable salt thereof, and memantine represented by formula (II):



(II)

or a pharmaceutically acceptable salt thereof.

<2> The therapeutic agent according to <1>, wherein the Alzheimer's disease is moderate or severe Alzheimer's disease.

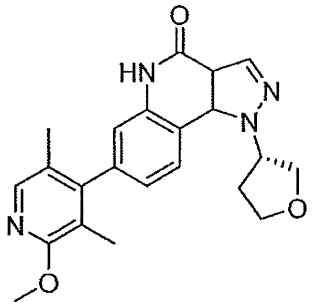
<3> The therapeutic agent according to <1> or <2>, wherein the memantine or pharmaceutically acceptable salt thereof is memantine hydrochloride.

<4> The therapeutic agent according to any one of <1> to <3>, wherein the (S)-7-(2-methoxy-3,5-dimethylpyridin-4-yl)-1-(tetrahydrofuran-3-yl)-1H-pyrazolo[4,3-c]quinoline-4(5H)-one or pharmaceutically acceptable salt thereof is (S)-7-(2-methoxy-3,5-dimethylpyridin-4-yl)-1-(tetrahydrofuran-3-yl)-1H-pyrazolo[4,3-c]qui

noline-4(5H)-one maleate.

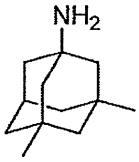
<5> A therapeutic agent for Alzheimer's disease for simultaneous or separate administration of

(S)-7-(2-methoxy-3,5-dimethylpyridin-4-yl)-1-(tetrahydrofuran-3-yl)-1H-pyrazolo[4,3-c]qui noline-4(5H)-one represented by formula (I):



(I)

or a pharmaceutically acceptable salt thereof, and memantine represented by formula (II):



(II)

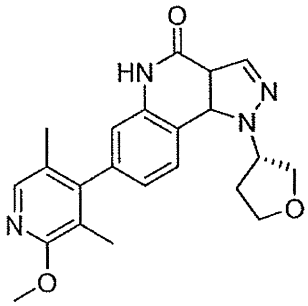
or a pharmaceutically acceptable salt thereof.

<6> The therapeutic agent according to <5>, wherein the Alzheimer's disease is moderate or severe Alzheimer's disease.

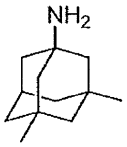
<7> The therapeutic agent according to <5> or <6>, wherein the memantine or pharmaceutically acceptable salt thereof is memantine hydrochloride.

<8> The therapeutic agent according to any one of <5> to <7>, wherein the (S)-7-(2-methoxy-3,5-dimethylpyridin-4-yl)-1-(tetrahydrofuran-3-yl)-1H-pyrazolo[4,3-c]qui noline-4(5H)-one or pharmaceutically acceptable salt thereof is (S)-7-(2-methoxy-3,5-dimethylpyridin-4-yl)-1-(tetrahydrofuran-3-yl)-1H-pyrazolo[4,3-c]qui noline-4(5H)-one maleate.

<9> A therapeutic agent for Alzheimer's disease, comprising (S)-7-(2-methoxy-3,5-dimethylpyridin-4-yl)-1-(tetrahydrofuran-3-yl)-1H-pyrazolo[4,3-c]qui noline-4(5H)-one represented by formula (I):


(I)

or a pharmaceutically acceptable salt thereof, and memantine represented by formula (II):


(II)

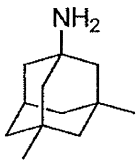
or a pharmaceutically acceptable salt thereof.

<10> The therapeutic agent according to <9>, wherein the Alzheimer's disease is moderate or severe Alzheimer's disease.

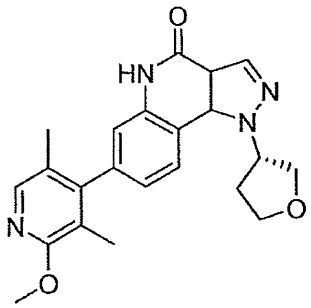
<11> The therapeutic agent according to <9> or <10>, wherein the memantine or pharmaceutically acceptable salt thereof is memantine hydrochloride.

<12> The therapeutic agent according to any one of <9> to <11>, wherein the (S)-7-(2-methoxy-3,5-dimethylpyridin-4-yl)-1-(tetrahydrofuran-3-yl)-1H-pyrazolo[4,3-c]quinoline-4(5H)-one or pharmaceutically acceptable salt thereof is (S)-7-(2-methoxy-3,5-dimethylpyridin-4-yl)-1-(tetrahydrofuran-3-yl)-1H-pyrazolo[4,3-c]quinoline-4(5H)-one maleate.

<13> Memantine represented by formula (II):


(II)

or a pharmaceutically acceptable salt thereof, for treatment of Alzheimer's disease by use in combination with (S)-7-(2-methoxy-3,5-dimethylpyridin-4-yl)-1-(tetrahydrofuran-3-yl)-1H-pyrazolo[4,3-c]quinoline-4(5H)-one represented by formula (I):



(I)

or a pharmaceutically acceptable salt thereof.

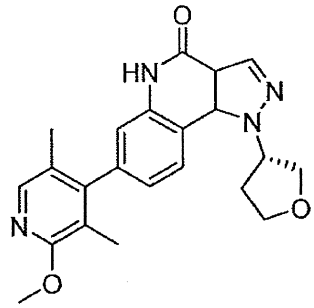
<13.1> Memantine or a pharmaceutically acceptable salt thereof according to <13>, wherein the Alzheimer's disease is moderate or severe Alzheimer's disease.

<13.2> Memantine or a pharmaceutically acceptable salt thereof according to <13> or <13.1>, wherein the memantine or pharmaceutically acceptable salt thereof is memantine hydrochloride.

<13.3> Memantine or a pharmaceutically acceptable salt thereof according to any one of <13> to <13.2>, wherein the (S)-7-(2-methoxy-3,5-dimethylpyridin-4-yl)-1-(tetrahydrofuran-3-yl)-1H-pyrazolo[4,3-c]quinoline-4(5H)-one or pharmaceutically acceptable salt thereof is (S)-7-(2-methoxy-3,5-dimethylpyridin-4-yl)-1-(tetrahydrofuran-3-yl)-1H-pyrazolo[4,3-c]quinoline-4(5H)-one maleate.

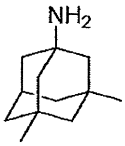
<14>

(S)-7-(2-methoxy-3,5-dimethylpyridin-4-yl)-1-(tetrahydrofuran-3-yl)-1H-pyrazolo[4,3-c]quinoline-4(5H)-one represented by formula (I):



(I)

or a pharmaceutically acceptable salt thereof, for treatment of Alzheimer's disease by use in combination with memantine represented by formula (II):



(II)

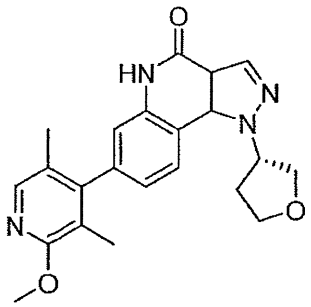
or a pharmaceutically acceptable salt thereof.

<14.1> A compound represented by formula (I) or a pharmaceutically acceptable salt thereof according to <14>, wherein the Alzheimer's disease is moderate or severe Alzheimer's disease.

<14.2> A compound represented by formula (I) or a pharmaceutically acceptable salt thereof according to <14> or <14.1>, wherein the memantine or pharmaceutically acceptable salt thereof is memantine hydrochloride.

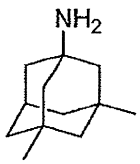
<14.3> A compound represented by formula (I) or a pharmaceutically acceptable salt thereof according to any one of <14> to <14.2>, wherein the (S)-7-(2-methoxy-3,5-dimethylpyridin-4-yl)-1-(tetrahydrofuran-3-yl)-1H-pyrazolo[4,3-c]quinoline-4(5H)-one or pharmaceutically acceptable salt thereof is (S)-7-(2-methoxy-3,5-dimethylpyridin-4-yl)-1-(tetrahydrofuran-3-yl)-1H-pyrazolo[4,3-c]quinoline-4(5H)-one maleate.

<15> A method for treating Alzheimer's disease, for combined use of (S)-7-(2-methoxy-3,5-dimethylpyridin-4-yl)-1-(tetrahydrofuran-3-yl)-1H-pyrazolo[4,3-c]quinoline-4(5H)-one represented by formula (I):



(I)

or a pharmaceutically acceptable salt thereof, and memantine represented by formula (II):



(II)

or a pharmaceutically acceptable salt thereof.

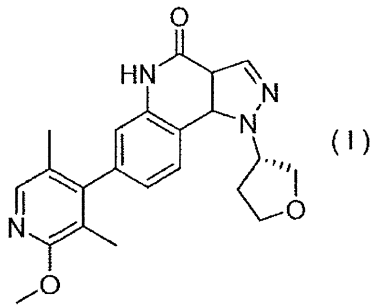
<15.1> The method according to <15>, wherein the Alzheimer's disease is moderate or

severe Alzheimer's disease.

<15.2> The method according to <15> or <15.1>, wherein the memantine or pharmaceutically acceptable salt thereof is memantine hydrochloride.

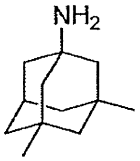
<15.3> The method according to any one of <15> to <15.2>, wherein the (S)-7-(2-methoxy-3,5-dimethylpyridin-4-yl)-1-(tetrahydrofuran-3-yl)-1H-pyrazolo[4,3-c]quinoline-4(5H)-one or pharmaceutically acceptable salt thereof is (S)-7-(2-methoxy-3,5-dimethylpyridin-4-yl)-1-(tetrahydrofuran-3-yl)-1H-pyrazolo[4,3-c]quinoline-4(5H)-one maleate.

<16> A pharmaceutical composition comprising (S)-7-(2-methoxy-3,5-dimethylpyridin-4-yl)-1-(tetrahydrofuran-3-yl)-1H-pyrazolo[4,3-c]quinoline-4(5H)-one represented by formula (I):



(I)

or a pharmaceutically acceptable salt thereof, memantine represented by formula (II):



(II)

or a pharmaceutically acceptable salt thereof, and an excipient.

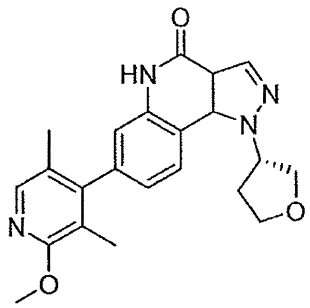
<16.1> The pharmaceutical composition according to <16>, wherein the memantine or pharmaceutically acceptable salt thereof is memantine hydrochloride.

<16.2> The pharmaceutical composition according to <16> or <16.1>, wherein the (S)-7-(2-methoxy-3,5-dimethylpyridin-4-yl)-1-(tetrahydrofuran-3-yl)-1H-pyrazolo[4,3-c]quinoline-4(5H)-one or pharmaceutically acceptable salt thereof is (S)-7-(2-methoxy-3,5-dimethylpyridin-4-yl)-1-(tetrahydrofuran-3-yl)-1H-pyrazolo[4,3-c]quinoline-4(5H)-one maleate.

<17> A kit comprising:

a pharmaceutical composition comprising

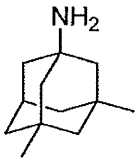
(S)-7-(2-methoxy-3,5-dimethylpyridin-4-yl)-1-(tetrahydrofuran-3-yl)-1H-pyrazolo[4,3-c]quinoline-4(5H)-one represented by formula (I):



(I)

or a pharmaceutically acceptable salt thereof, and an excipient, and

a pharmaceutical composition comprising memantine represented by formula (II):



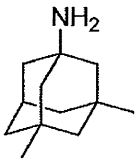
(II)

or a pharmaceutically acceptable salt thereof, and an excipient.

<17.1> The kit according to <17>, wherein the memantine or pharmaceutically acceptable salt thereof is memantine hydrochloride.

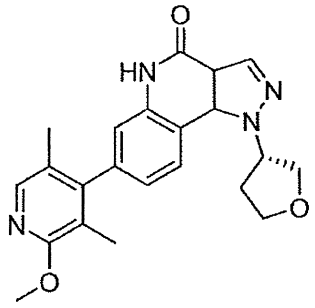
<17.2> The kit according to any one of <17> to <17.1>, wherein the (S)-7-(2-methoxy-3,5-dimethylpyridin-4-yl)-1-(tetrahydrofuran-3-yl)-1H-pyrazolo[4,3-c]quinoline-4(5H)-one or pharmaceutically acceptable salt thereof is a maleate.

<18> The use of memantine represented by formula (II):



(II)

or a pharmaceutically acceptable salt thereof, for production of a therapeutic agent for Alzheimer's disease by use in combination with (S)-7-(2-methoxy-3,5-dimethylpyridin-4-yl)-1-(tetrahydrofuran-3-yl)-1H-pyrazolo[4,3-c]quinoline-4(5H)-one represented by formula (I):



(I)

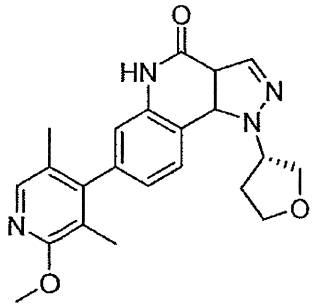
or a pharmaceutically acceptable salt thereof.

<18.1> The use of memantine or a pharmaceutically acceptable salt thereof according to <18>, wherein the Alzheimer's disease is moderate or severe Alzheimer's disease.

<18.2> The use of memantine or a pharmaceutically acceptable salt thereof according to <18> or <18.1>, wherein the memantine or pharmaceutically acceptable salt thereof is memantine hydrochloride.

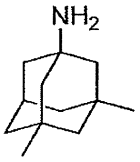
<18.3> The use of memantine or a pharmaceutically acceptable salt thereof according to any one of <18> to <18.2>, wherein the (S)-7-(2-methoxy-3,5-dimethylpyridin-4-yl)-1-(tetrahydrofuran-3-yl)-1H-pyrazolo[4,3-c]quinoline-4(5H)-one or pharmaceutically acceptable salt thereof is (S)-7-(2-methoxy-3,5-dimethylpyridin-4-yl)-1-(tetrahydrofuran-3-yl)-1H-pyrazolo[4,3-c]quinoline-4(5H)-one maleate.

<19> The use of (S)-7-(2-methoxy-3,5-dimethylpyridin-4-yl)-1-(tetrahydrofuran-3-yl)-1H-pyrazolo[4,3-c]quinoline-4(5H)-one represented by formula (I):



(I)

or a pharmaceutically acceptable salt thereof, for production of a therapeutic agent for Alzheimer's disease by use in combination with memantine represented by formula (II):



(II)

or a pharmaceutically acceptable salt thereof.

<19.1> The use of a compound represented by formula (I) or a pharmaceutically acceptable salt thereof according to <19>, wherein the Alzheimer's disease is moderate or severe Alzheimer's disease.

<19.2> The use of a compound represented by formula (I) or a pharmaceutically acceptable salt thereof according to <19> or <19.1>, wherein the memantine or pharmaceutically acceptable salt thereof is memantine hydrochloride.

<19.3> The use of a compound represented by formula (I) or a pharmaceutically acceptable salt thereof according to any one of <19> to <19.2>, wherein the (S)-7-(2-methoxy-3,5-dimethylpyridin-4-yl)-1-(tetrahydrofuran-3-yl)-1H-pyrazolo[4,3-c]quinoline-4(5H)-one or pharmaceutically acceptable salt thereof is (S)-7-(2-methoxy-3,5-dimethylpyridin-4-yl)-1-(tetrahydrofuran-3-yl)-1H-pyrazolo[4,3-c]quinoline-4(5H)-one maleate.

Advantageous Effects of Invention

[0012] The present invention provides a therapeutic agent for Alzheimer's disease, combining a pyrazoloquinoline derivative represented by formula (I) or a pharmaceutically acceptable salt thereof, which has a PDE9 inhibitory action, with memantine or a pharmaceutically acceptable salt thereof, which has an NMDA-type glutamate receptor antagonistic effect. The therapeutic agent using this combination exhibits a more notable ameliorative effect on cognitive function in animal models compared to their uses alone, and it has potential for use as a therapeutic agent for Alzheimer's disease.

Description of Embodiments

[0013] The present invention will now be explained in detail.

[0014] A "pharmaceutically acceptable salt" as referred to throughout the present specification is not particularly limited as long as it is a salt formed with the compound of the invention, and specific examples include acid addition salts such as inorganic acid salts, organic acid salts or acidic amino acid salts.

[0015] Unless otherwise specified, in the context of "pharmaceutically acceptable salt" as used herein, the number of acid molecules per one molecule of the compound in a formed

salt is not particularly limited as long as the salt is formed in an appropriate ratio. In one embodiment, the number of acid molecules per one molecule of the compound is about 0.1 to about 5; in another embodiment, the number of acid molecules per one molecule of the compound is about 0.5 to about 2; and in still another embodiment, the number of acid molecules per one molecule of the compound is about 0.5, about 1 or about 2.

[0016] Specific examples of an inorganic acid salt include hydrochloride, hydrobromide, sulfate, nitrate and phosphate, and specific examples of an organic acid salt include acetate, succinate, fumarate, maleate, tartrate, citrate, lactate, stearate, benzoate, methanesulfonate, p-toluenesulfonate and benzenesulfonate.

[0017] Specific examples of an acidic amino acid salt include aspartate and glutamate.

[0018]

[Formulation]

The pharmaceutical composition of the invention can be produced by mixing a pharmaceutically acceptable additive with compound (I) or a pharmaceutically acceptable salt thereof, and/or compound (II) or a pharmaceutically acceptable salt thereof. The pharmaceutical composition of the invention can be produced by a known method, such as the method described in the General Rules for Preparations of the Japanese Pharmacopoeia, 16th Edition.

The pharmaceutical composition of the invention can be appropriately administered to a patient according to the dosage form.

[0019] The dose of compound (I) or a pharmaceutically acceptable salt thereof and compound (II) or a pharmaceutically acceptable salt thereof according to the invention will vary depending on the severity of symptoms, the patient age, gender and body weight, the form of administration and type of salt, and the specific type of disease, and the like; but usually, in adult, about 30 μg to 10 g, in one embodiment 100 μg to 5 g, and in another embodiment 100 μg to 1 g is administered orally per day, in a single dose or in several divided doses; or about 30 μg to 1 g, in one embodiment 100 μg to 500 mg, and in another embodiment 100 μg to 300 mg is administered by injection per day, in a single dose or in several divided doses.

Examples

[0020] Compound (I) can be produced by the method described in PTL 1, for example.

[0021]

(Pharmacological Test Examples)

The present inventors confirmed the combined effects of compound (I) and memantine hydrochloride using the following animal model.

[0022]

[Test Example 1] Novel object recognition test using rats with scopolamine-induced cognitive impairment

Acetylcholine nervous system disorder has been reported in Alzheimer's disease (Whitehouse et al., Science, 1982, vol.215, p.1237), and scopolamine-administered animals are utilizable as an animal model for Alzheimer's disease. Scopolamine is a muscarine receptor inhibitor which blocks acetylcholine nervous system transmission. The acetylcholine nervous system is involved in memory and attention, and healthy humans or animals administered scopolamine exhibit dementia-like amnesia symptoms which are attenuated by drugs used for treatment of cognitive impairment in Alzheimer's disease (Snyder et al., Alzheimer's & Dementia 1(2005)126-135, Sambeth et al., European Journal of Pharmacology, vol.572(2007), pp.151-159).

[0023]

Materials and methods

6-week-old male Long Evans rats (Institute for Animal Reproduction) were subjected to the test. A habituation process to the experimental procedure was carried out once per day for 2 days prior to the test. In the habituation process, a vehicle was administered to the rats, and then the rats were placed in an empty test apparatus (40 cm × 30 cm × 45 cm height) and allowed to explore for 3 minutes, and after then placed in a waiting chamber (13 cm × 30 cm × 45 cm height) for about 1 minute, they were returned to the empty test apparatus again and left for 5 minutes.

An acquisition trial (T1) was carried out on the day of the test. Compound (I) was orally administered 2 hours before T1. Memantine hydrochloride was orally administered 1 hour before T1. Scopolamine (Wako Pure Chemical Industries, Ltd.) was subcutaneously administered 30 minutes before T1 at a dose of 0.7 mg/kg. In T1, the rats were habituated to the empty test apparatus for 3 minutes and then placed in the waiting chamber. After setting two identical objects in the test apparatus, the rats were returned into the test apparatus again and allowed to freely explore the two identical objects for 5 minutes. The rats were then returned into their rearing cages. After 2 hours, a retention trial (T2) was carried out. The rats were placed in the empty test apparatus for 3 minutes for habituation, and were then transferred into the waiting chamber. After setting an object used in T1 ("familiar" object)

and an object not used in T1 ("novel" object) in the test apparatus, the rats were again returned into the test apparatus and allowed to freely explore these objects for 3 minutes. The objects were wiped with a wet wipe impregnated with ethanol after each experiment so as to leave no trace of odor. The behaviors of the rats during T1 and T2 were recorded by a digital video camera, and the total exploration time for each object was manually measured using a stopwatch. Exploratory behavior was defined as the behavior in which the rat brings its nose within 2 cm of the object and directs its nose toward the object.

In the novel object recognition test, the percentage of exploration of the novel object in T2 is considered to be an index for amnesia, reflecting discrimination between the familiar object and the novel object. The percentage of exploration of the novel object was calculated by the following formula.

The percentage of exploration of the novel object (%) = N/(N + F) × 100

F: time spent in exploring the familiar object

N: time spent in exploring the novel object

Rats whose total time spent in exploring the objects during T1 or T2 was 10 seconds or less or rats whose percentage of the time spent in exploring either of the objects during T1 was not less than 70% or not more than 30% of the total exploration time were excluded from the data analysis.

The results were expressed as mean ± standard error. The difference between the normal control group untreated with scopolamine and the disease control group treated with scopolamine was analyzed by an unpaired t-test (significant difference: *). The difference between the disease control group and the single drug-treated group was analyzed by Dunnett-type multiple comparison test (significant difference: #). The difference between the combined treatment group and the single drug-treated group was analyzed by an unpaired t-test (significant difference: ※). A value of $p < 0.05$ was judged to be a statistically significant difference. Statistical analysis was conducted using GraphPad Prism version 5.04 or 6.02. The results are shown in Tables 1 to 4.

[0024] [Table 1]

Normal control group	Scopolamine-administered group		
	Disease control group	Compound (I) 0.3 mg/kg	Compound (I) 1 mg/kg
71.3 ±3.1	54.4 ±2.8*	58.7 ±3.2	59.9 ±3.4

[0025] [Table 2]

Normal control group	Scopolamine-administered group		
	Disease control group	Compound (I) 3.3 mg/kg	Compound (I) 10 mg/kg
73.8 ±3.0	53.3 ±2.2*	68.5 ±2.0#	68.5 ±1.6#

[0026] [Table 3]

Normal control group	Scopolamine-administered group		
	Disease control group	Memantine 3 mg/kg	Memantine 10 mg/kg
70.2 ±3.0	55.0 ±3.9*	68.9 ±4.0#	59.9 ±3.8

[0027] [Table 4]

Normal control group	Scopolamine-administered group		
	Disease control group	Memantine 1 mg/kg	Compound (I) 1 mg/kg and memantine 1 mg/kg
69.8 ±2.8	54.3 ±3.0*	58.1 ±2.4	69.0 ±2.0※

[0028]

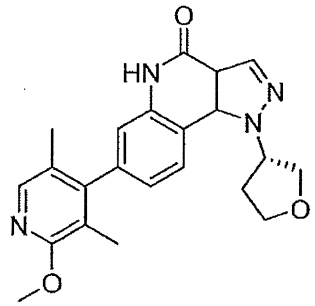
Results

In T2, the rats of the disease control group exhibited a significantly lower percentage of exploration of the novel object than the rats of the normal control group. This means that memory impairment was induced in the rats by scopolamine.

Compound (I) exhibited a significant ameliorative effect on the percentage of exploration of the novel object at 3.3 mg/kg (Table 2), but did not exhibit a significant effect at 1 mg/kg (Table 1). Memantine hydrochloride exhibited a significant ameliorative effect on the percentage of exploration of the novel object at 3 mg/kg (Table 3). While no significant ameliorative effect on the percentage of exploration of the novel object was exhibited with memantine hydrochloride (1 mg/kg) alone, the combined treatment group with compound (I) (1 mg/kg) and memantine hydrochloride (1 mg/kg) exhibited a significantly higher percentage of exploration of the novel object than the group treated with memantine hydrochloride (1 mg/kg) alone (Table 4). This result indicates an augmenting effect on cognitive function by compound (I) when in combination with memantine hydrochloride.

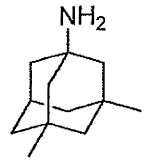
CLAIMS

1. A therapeutic agent for Alzheimer's disease for combined use of (S)-7-(2-methoxy-3,5-dimethylpyridin-4-yl)-1-(tetrahydrofuran-3-yl)-1H-pyrazolo[4,3-c]quinoline-4(5H)-one represented by formula (I):



(I)

or a pharmaceutically acceptable salt thereof, and memantine represented by formula (II):



(II)

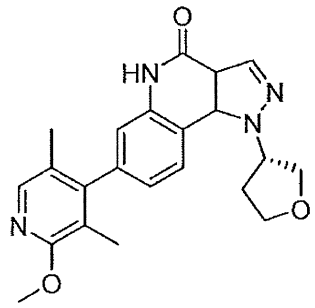
or a pharmaceutically acceptable salt thereof.

2. The therapeutic agent according to claim 1, wherein the Alzheimer's disease is moderate or severe Alzheimer's disease.

3. The therapeutic agent according to claim 1 or 2, wherein the memantine or pharmaceutically acceptable salt thereof is memantine hydrochloride.

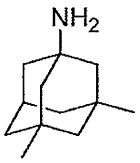
4. The therapeutic agent according to any one of claims 1 to 3, wherein the (S)-7-(2-methoxy-3,5-dimethylpyridin-4-yl)-1-(tetrahydrofuran-3-yl)-1H-pyrazolo[4,3-c]quinoline-4(5H)-one or pharmaceutically acceptable salt thereof is (S)-7-(2-methoxy-3,5-dimethylpyridin-4-yl)-1-(tetrahydrofuran-3-yl)-1H-pyrazolo[4,3-c]quinoline-4(5H)-one maleate.

5. A therapeutic agent for Alzheimer's disease for simultaneous or separate administration of (S)-7-(2-methoxy-3,5-dimethylpyridin-4-yl)-1-(tetrahydrofuran-3-yl)-1H-pyrazolo[4,3-c]quinoline-4(5H)-one represented by formula (I):



(I)

or a pharmaceutically acceptable salt thereof, and memantine represented by formula (II):



(II)

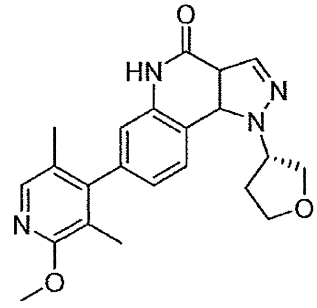
or a pharmaceutically acceptable salt thereof.

6. The therapeutic agent according to claim 5, wherein the Alzheimer's disease is moderate or severe Alzheimer's disease.

7. The therapeutic agent according to claim 5 or 6, wherein the memantine or pharmaceutically acceptable salt thereof is memantine hydrochloride.

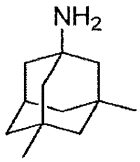
8. The therapeutic agent according to any one of claims 5 to 7, wherein the (S)-7-(2-methoxy-3,5-dimethylpyridin-4-yl)-1-(tetrahydrofuran-3-yl)-1H-pyrazolo[4,3-c]quinoline-4(5H)-one or pharmaceutically acceptable salt thereof is (S)-7-(2-methoxy-3,5-dimethylpyridin-4-yl)-1-(tetrahydrofuran-3-yl)-1H-pyrazolo[4,3-c]quinoline-4(5H)-one maleate.

9. A therapeutic agent for Alzheimer's disease, comprising (S)-7-(2-methoxy-3,5-dimethylpyridin-4-yl)-1-(tetrahydrofuran-3-yl)-1H-pyrazolo[4,3-c]quinoline-4(5H)-one represented by formula (I):



(I)

or a pharmaceutically acceptable salt thereof, and memantine represented by formula (II):



(II)

or a pharmaceutically acceptable salt thereof.

10. The therapeutic agent according to claim 9, wherein the Alzheimer's disease is moderate or severe Alzheimer's disease.

11. The therapeutic agent according to claim 9 or 10, wherein the memantine or pharmaceutically acceptable salt thereof is memantine hydrochloride.

12. The therapeutic agent according to any one of claims 9 to 11, wherein the (S)-7-(2-methoxy-3,5-dimethylpyridin-4-yl)-1-(tetrahydrofuran-3-yl)-1H-pyrazolo[4,3-c]quinoline-4(5H)-one or pharmaceutically acceptable salt thereof is (S)-7-(2-methoxy-3,5-dimethylpyridin-4-yl)-1-(tetrahydrofuran-3-yl)-1H-pyrazolo[4,3-c]quinoline-4(5H)-one maleate.