DESCRIPTION

Title of Invention

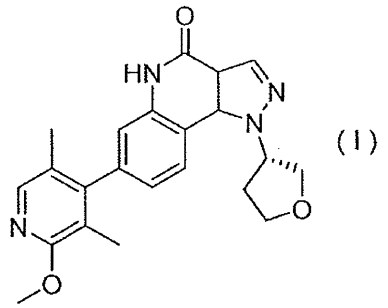
Dementia Therapeutic Agent Combining Pyrazoloquinoline Derivative and Donepezil

Technical Field

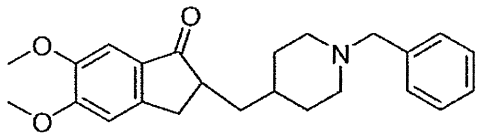
[0001] The present invention relates to a therapeutic agent for dementia combining a pyrazoloquinoline derivative having phosphodiesterase 9 (PDE9) inhibitory action or a pharmaceutically acceptable salt thereof, and donepezil or a pharmaceutically acceptable salt thereof.

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] Donepezil, represented by formula (II) (hereunder referred to as "compound (II)") has acetylcholine esterase-inhibitory action, and has been reported to exhibit an effect against Alzheimer's disease and Lewy body dementia (see NPLs 1, 2 and 3).

[0005] In addition, the acetylcholine esterase inhibitors galantamine and rivastigmine and the NMDA receptor antagonist memantine have been approved as therapeutic agents for Alzheimer's disease. 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 peripheral symptoms such as agitation, anxiety, apathy, delusion, depression, disinhibition, hallucination, irritability, aberrant motor behavior and apathy (BPSD: Behavioral and Psychological Symptoms of Dementia) (see NPLs 4 and 5). Galantamine and rivastigmine are indicated for mild to moderate Alzheimer's disease (see NPLs 6 and 7). Memantine has been reported to have efficacy for ameliorating cognitive function, and for

BPSD (agitation, irritability, aggression and behavioral disorder) in moderate to severe 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] Acetylcholine esterase inhibitors, however, have been reported to have digestive system side-effects, and to aggravate Parkinson's symptoms (see NPL 10). In cases where acetylcholine esterase inhibitors cannot be used due to side-effects or tolerance, memantine may be selected if the patient has moderate to severe Alzheimer's disease, but at the current time no effective method of treatment exists for other 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 11) while other reports have indicated no effect (see NPL 12).

Citation List

Patent Literature

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

Non-Patent Literature

[0008] [NPL 1] Homma et al., Dement. Geriatr. Cogn. Disord., 2000, vol.11, p.299

[NPL 2] Homma et al., Dement. Geriatr. Cogn. Disord., 2008, vol.25, p.399

[NPL 3] Mori et al., Ann. Neurol, vol.72, p.41 2012

[NPL 4] Holmes at al., Neurology, 2004, vol.63, p.214

[NPL 5] Gauthier et al., Int Psychogeriatr, 2002, vol.14, p.389

[NPL 6] Raskind et al., Neurology, 2000, vol.54, p.226

[NPL 7] Winblad et al., Neurology, 2007, vol.69, p.S14

[NPL 8] Mecocci et al., Int J Geriatr Psychiatry, vol.24, p.532

[NPL 9] Grossberg et al., Dement Geriatr Cogn Disord, 2009, vol.27, p.164

[NPL 10] Bourke et al., Ann. Pharmacother., 1998, vol.32, p.610

[NPL 11] Lopez et al., J Neurol Neurosurg Psychiatry, 2009, vol.80, p.600

[NPL 12] 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 or Lewy body dementia, while an effective anti-dementia agent is also yet to be developed.

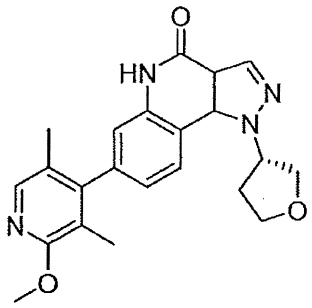
Solution to Problem

[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>.

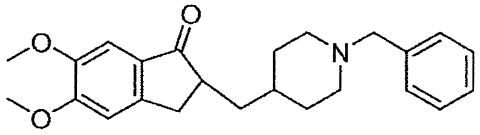
<1> A therapeutic agent for Alzheimer's disease or Lewy body dementia, for combined use of

(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 donepezil represented by formula (II):



(II)

or a pharmaceutically acceptable salt thereof.

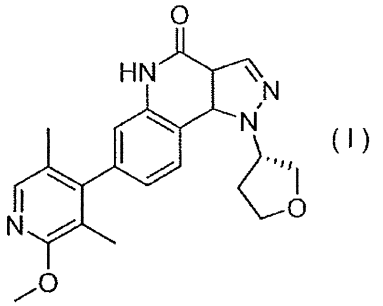
<2> The therapeutic agent according to <1>, wherein the donepezil or pharmaceutically acceptable salt thereof is donepezil hydrochloride.

<3> The therapeutic agent according to <1> or <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.

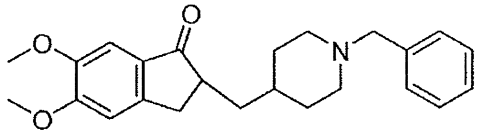
<4> The therapeutic agent according to any one of <1> to <3>, wherein the Alzheimer's disease is mild, moderate or severe Alzheimer's disease.

<5> A therapeutic agent for Alzheimer's disease or Lewy body dementia 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 donepezil represented by formula (II):



(II)

or a pharmaceutically acceptable salt thereof.

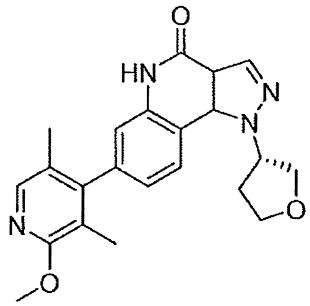
<6> The therapeutic agent according to <5>, wherein the donepezil or pharmaceutically acceptable salt thereof is donepezil hydrochloride.

<7> The therapeutic agent according to <5> or <6>, 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.

<8> The therapeutic agent according to any one of <5> to <7>, wherein the Alzheimer's disease is mild, moderate or severe Alzheimer's disease.

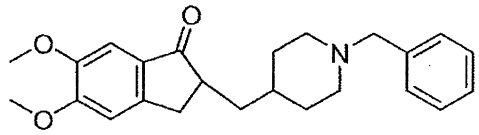
<9> A therapeutic agent for Alzheimer's disease or Lewy body dementia, comprising (S)-7-(2-methoxy-3,5-dimethylpyridin-4-yl)-1-(tetrahydrofuran-3-yl)-1H-pyrazolo[4,3-c]qui

noline-4(5H)-one represented by formula (I):



(I)

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



(II)

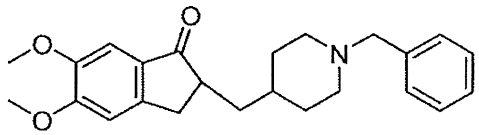
or a pharmaceutically acceptable salt thereof.

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

<11> The therapeutic agent according to <9> or <10>, 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.

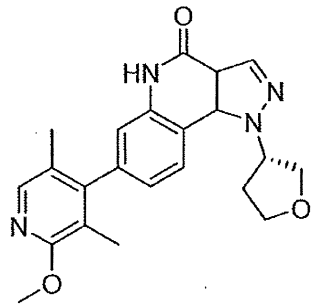
<12> The therapeutic agent according to any one of <9> to <11>, wherein the Alzheimer's disease is mild, moderate or severe Alzheimer's disease.

<13> Donepezil represented by formula (II):



(II)

or a pharmaceutically acceptable salt thereof, for treatment of Alzheimer's disease or Lewy body dementia 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.

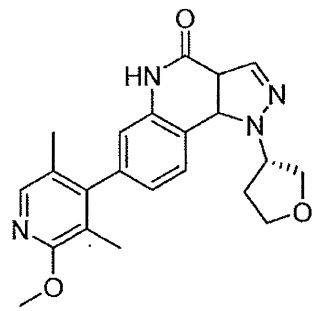
<13.1> Donepezil or a pharmaceutically acceptable salt thereof according to <13>, wherein the donepezil or pharmaceutically acceptable salt thereof is donepezil hydrochloride.

<13.2> Donepezil or a pharmaceutically acceptable salt thereof according to <13> or <13.1>, 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.

<13.3> Donepezil or a pharmaceutically acceptable salt thereof according to any one of <13> to <13.2>, wherein the Alzheimer's disease is mild, moderate or severe Alzheimer's disease.

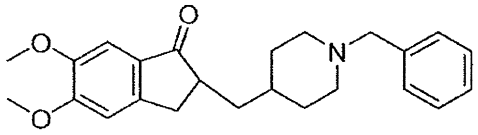
<14>

(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 or Lewy body dementia by use in combination with donepezil represented by formula (II):



(II)

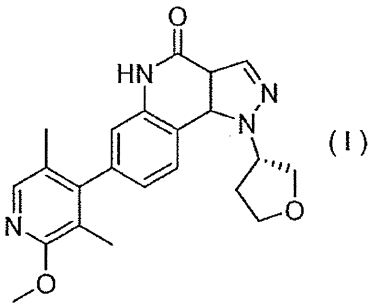
or a pharmaceutically acceptable salt thereof.

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

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

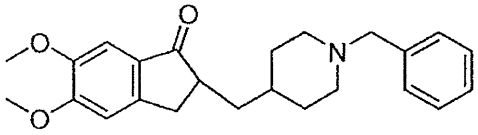
<14.3> A compound represented by formula (I) or a pharmaceutically acceptable salt thereof according to any one of <14> to <14.2>, wherein the Alzheimer's disease is mild, moderate or severe Alzheimer's disease.

<15> A method for treating Alzheimer's disease or Lewy body dementia 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 donepezil represented by formula (II):



(II)

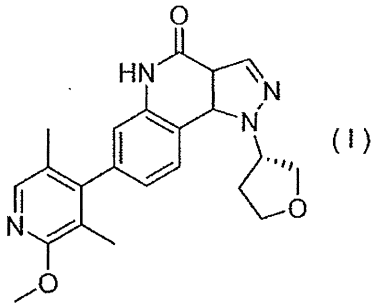
or a pharmaceutically acceptable salt thereof.

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

<15.2> The method according to <15> or <15.1>, 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.

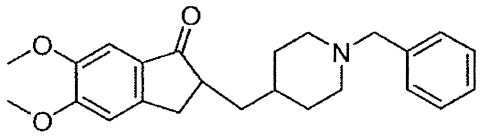
<15.3> The method according to any one of <15> to <15.2>, wherein the Alzheimer's disease is mild, moderate or severe Alzheimer's disease.

<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, donepezil represented by formula (II):



(II)

or a pharmaceutically acceptable salt thereof,

and an excipient.

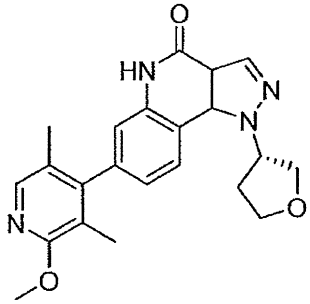
<16.1> The pharmaceutical composition according to <16>, wherein the donepezil or pharmaceutically acceptable salt thereof is donepezil hydrochloride.

<16.2> The medical 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]qui

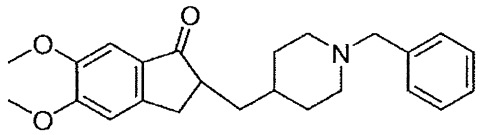
noline-4(5H)-one represented by formula (I):



(I)

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

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



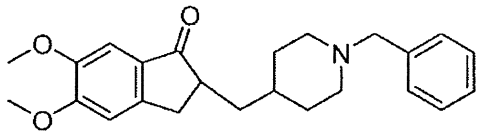
(II)

or a pharmaceutically acceptable salt thereof, and an excipient.

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

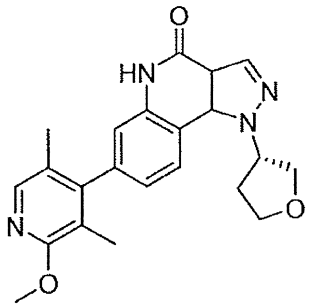
<17.2> The kit according to <17> or <17.1>, wherein the (S)-7-(2-methoxy-3,5-dimethylpyridin-4-yl)-1-(tetrahydrofuran-3-yl)-1H-pyrazolo[4,3-c]quinoline-4(5H)-one or pharmaceutically acceptable salt thereof is (S)-7-(2-methoxy-3,5-dimethylpyridin-4-yl)-1-(tetrahydrofuran-3-yl)-1H-pyrazolo[4,3-c]quinoline-4(5H)-one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

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



(II)

or a pharmaceutically acceptable salt thereof, for production of a therapeutic agent for Alzheimer's disease or Lewy body dementia 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)

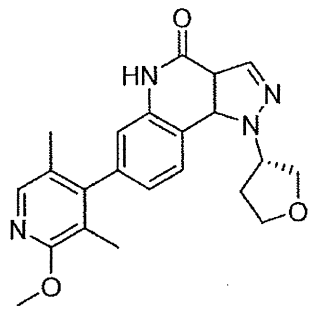
or a pharmaceutically acceptable salt thereof.

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

<18.2> The use of donepezil or a pharmaceutically acceptable salt thereof according to <18> or <18.1>, 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.

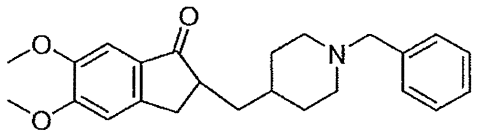
<18.3> The use of donepezil or a pharmaceutically acceptable salt thereof according to any one of <18> to <18.2>, wherein the Alzheimer's disease is mild, moderate or severe Alzheimer's disease.

<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 or Lewy body dementia by use in combination with donepezil 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 donepezil or pharmaceutically acceptable salt thereof is donepezil hydrochloride.

<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 (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.

<19.3> 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 Alzheimer's disease is mild, moderate or severe Alzheimer's disease.

Advantageous Effects of Invention

[0012] The present invention provides a therapeutic agent for Alzheimer's disease and Lewy body dementia, combining a pyrazoloquinoline derivative represented by formula (I) having PDE9 inhibitory action, or a pharmaceutically acceptable salt thereof, and donepezil having acetylcholine esterase inhibitory action, or a pharmaceutically acceptable salt thereof. 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 and Lewy body dementia.

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 donepezil

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 and Lewy body dementia (Whitehouse et al., Science, 1982, vol.215, p.1237, Shimada et al., Neurology, vol.73, p.273, 2009, Tiraboschi et al., Neurology 54(2000) 407-411, Perry et. al., NeuroReport, vol.5, pp.747-749(1994)), and scopolamine-administered animals are utilizable as an animal model for Alzheimer's disease and Lewy body dementia. 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 and Lewy body dementia (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. Donepezil 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 (%) = $N/(N + F) \times 100$

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 Dunnett-type multiple comparison 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 5.

[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	Donepezil 0.03 mg/kg
71.1 ±3.3	55.0 ±2.3*	62.7 ±3.6

[0027] [Table 4]

Normal control group	Scopolamine-administered group		
	Disease control group	Donepezil 0.1 mg/kg	Donepezil 0.3 mg/kg
71.5 ±4.8	53.9 ±2.7*	66.2 ±4.0	70.4 ±4.8#

[0028] [Table 5]

Normal control group	Scopolamine-administered group			
	Disease control group	Donepezil 0.03 mg/kg	Compound (I) 1 mg/kg	Donepezil 0.03 mg/kg and Compound (I) 1 mg/kg
76.4 ±2.3	54.8 ±3.8*	57.8 ±4.0	64.9 ±2.2	73.1 ±2.3 ※

[0029]

Results

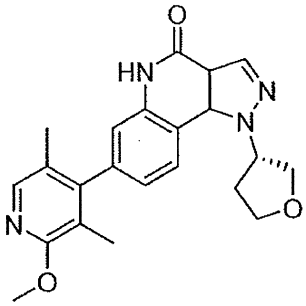
In T2, the rats of the disease control group exhibited a significantly lower percentage of exploration of the novel object than the rats of the normal control group. This means that memory impairment was induced in the rats by scopolamine.

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). Donepezil hydrochloride exhibited a significant ameliorative effect on the percentage of exploration of the novel object at 0.3 mg/kg (Table 4), but did not exhibit a significant effect at 0.03 mg/kg (Table 3). When the effects of compound (I) and donepezil hydrochloride alone were compared with the effect of their use in combination, in doses that are ineffective with each alone, it was found that the combined treatment group with compound (I) (1 mg/kg) and donepezil hydrochloride (0.03 mg/kg) exhibited a significantly

higher percentage of exploration of the novel object than the donepezil hydrochloride (0.03 mg/kg) single drug-treated group (Table 5). This result indicates an augmenting effect on cognitive function by compound (I) when in combination with donepezil hydrochloride.

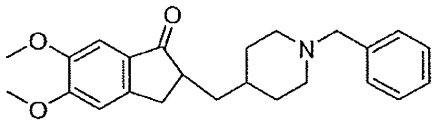
CLAIMS

1. A therapeutic agent for Alzheimer's disease or Lewy body dementia 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 donepezil represented by formula (II):



(II)

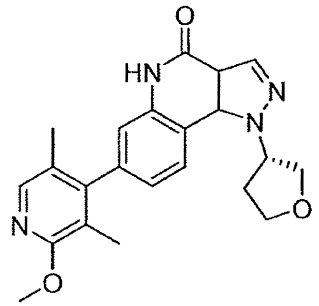
or a pharmaceutically acceptable salt thereof.

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

3. The therapeutic agent according to claim 1 or 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.

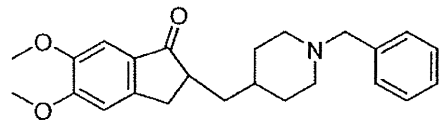
4. The therapeutic agent according to any one of claims 1 to 3, wherein the Alzheimer's disease is mild, moderate or severe Alzheimer's disease.

5. A therapeutic agent for Alzheimer's disease or Lewy body dementia 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 donepezil represented by formula (II):



(II)

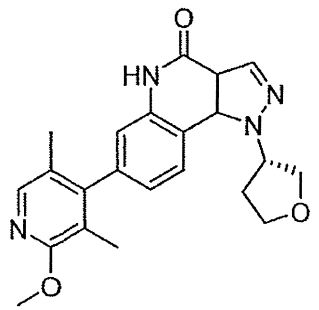
or a pharmaceutically acceptable salt thereof.

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

7. The therapeutic agent according to claim 5 or 6, 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.

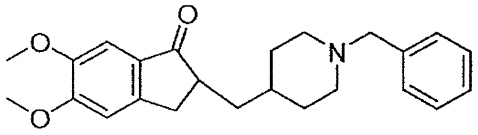
8. The therapeutic agent according to any one of claims 5 to 7, wherein the Alzheimer's disease is mild, moderate or severe Alzheimer's disease.

9. A therapeutic agent for Alzheimer's disease or Lewy body dementia, 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 donepezil represented by formula (II):


(II)

or a pharmaceutically acceptable salt thereof.

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

11. The therapeutic agent according to claim 9 or 10, 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.

12. The therapeutic agent according to any one of claims 9 to 11, wherein the Alzheimer's disease is mild, moderate or severe Alzheimer's disease.