

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
18 May 2012 (18.05.2012)

(10) International Publication Number
WO 2012/063513 A1

(51) International Patent Classification:

C07D 41/12 (2006.01) *A61K 31/506* (2006.01)
A61K 31/343 (2006.01) *A61K 45/00* (2006.01)
A61K 31/4545 (2006.01) *A61P 25/00* (2006.01)
A61K 31/495 (2006.01) *A61P 43/00* (2006.01)
A61K 31/496 (2006.01)

(21) International Application Number:

PCT/JP2011/062314

(22) International Filing Date:

24 May 2011 (24.05.2011)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

61/411,081 8 November 2010 (08.11.2010) US
2011-033453 18 February 2011 (18.02.2011) JP

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))
- as to non-prejudicial disclosures or exceptions to lack of novelty (Rule 4.17(v))

Published:

- with international search report (Art. 21(3))



WO 2012/063513 A1

(54) Title: METHOD OF TREATMENT FOR MENTAL DISORDERS

(57) Abstract: The invention relates to a medicament or a method for treating mental disorders, in detail, ADHD comprising lurasidone, or a combination of lurasidone and a D4 receptor agonist.

DESCRIPTION

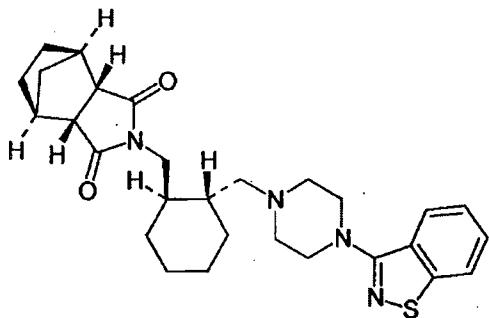
METHOD OF TREATMENT FOR MENTAL DISORDERS

5 TECHNICAL FIELD

[0001] The invention relates to a method for treating mental disorders, in more detail, a novel method for treating ADHD.

10 BACKGROUND ART

[0002] Lurasidone [chemical name: (3a*R*,4*S*,7*R*,7a*S*)-2-*{(1R,2R)-2-[4-(1,2-benzisothiazol-3-yl)piperazin-1-yl-methyl]cyclohexylmethyl}hexahydro-4,7-methano-2*H*-isoindole-1,3-dione] of the following formula is a compound having a pharmacological activity as an antipsychotic agent, which is characteristic of a high affinity for dopamine D₂, serotonin 5-HT_{1A}, 5-HT_{2A}, 5-HT₇, and noradrenaline α_{2C} receptors, and characteristic of minimal to no affinity for histamine H₁ and muscarinic M₁ receptors. Lurasidone possesses antipsychotic effects, antidepressant- or anxiolytic-like effects, and pharmacological profiles with potentially-reduced liability for extrapyramidal and CNS depressant side effects, which is expected to be used for the treatment of schizophrenia and bipolar disorder (Patent Reference 1, Non-patent Reference 1).*



[0003] Dopamine D₄ receptors are one of subtypes of dopamine receptors, which are known as a target in the treatment of schizophrenia or Parkinson's disease.

5 [0004] Attention deficit/hyperactivity disorder (ADHD) is one of developmental disorders, which is characterized by inattention, hyperactivity, and impulsiveness. The symptom includes difficulty in concentrating, overactivity, and inattention. Generally, the symptom is observed in 10 children who are 7 year-old or younger. In addition, the symptom includes inattention-predominant type which is not dominant in overactivity. The incidence rate up to school-age is 1 - 6 %, and the rate of boys is higher than that of girls. ADHD had been thought to be a disease in children 15 and be naturally improved in adults because the cases of hyperactivity decrease with aging. But, currently it is thought that adults can suffer from ADHD.

As a drug therapy for ADHD, central stimulants are used in order to raise patient's arousal level, and 20 methylphenidate hydrochloride is mainly used in America and a sustained preparation of methylphenidate has been

approved in Japan as a medicament for treating ADHD in childhood. In addition, atomoxetine hydrochloride which is a noradrenaline reuptake inhibitor is also acceptable in Japan, but the applied patients thereof are limited to children. Thus, there is no medicament therefor for adults in Japan. In America, methylphenidate is acceptable for adults, but, it is indicated that methylphenidate has the same side-effect as psychostimulants such as amphetamine, methamphetamine, and cocaine.

[0005] 10 Risperidone, which is one of serotonin/dopamine antagonists (SDAs), has been reported in connection with ADHD (Non-patent Reference 2). However, there has not been any study about the improvement of attention function in ADHD using risperidone.

15 On the other hand, there is a report about the relationship between dopamine D₄ agonist and ADHD (Non-patent References 3 and 4).

PRIOR ART

20 [Patent Reference]

[0006]

[Patent Reference 1] JP 5(1993)-17440 A (US 5532372 A)

[Non-patent Reference]

[0007]

25 [Non-patent Reference 1] Exp Opin Invest Drugs 18(11):

1715-1726 (2009)

[Non-patent Reference 2] Neuropsychiatric Disease and Treatment 2008; 4(1) 203-207.

5 [Non-patent Reference 3] Behav Pharmacol. 2008 Dec; 19(8): 765-76.

[Non-patent Reference 4] Neuropharmacology. 2003 Mar; 44(4): 473-81.

DISCLOSURE OF INVENTION

10 (Problem to Be Solved by the Invention)

[0008] The purpose of the present invention is to provide a novel medicament for treating ADHD and a novel method therefor. In particular, the purpose is to provide a medicament and a method useful for treating attention 15 function/impulsiveness in ADHD.

(Means to Solve the Problem)

[0009] The present inventors have extensively studied to reach the above object and then has found that lurasidone 20 or a pharmaceutically acceptable acid addition salt thereof of the present invention, as well as a combination of lurasidone or a pharmaceutically acceptable acid addition salt thereof and a D₄ receptor agonist of the present invention exhibit the desired therapeutic effect increasing 25 attention function and suppressing impulsiveness caused by

ADHD in primates model of ADHD. Based upon the new findings, the present invention has been completed.

[0010] One embodiment of the present invention is directed to a method for treating ADHD which comprises administering a therapeutically effective amount of lurasidone or a pharmaceutically acceptable acid addition salt thereof to a mammal in need thereof.

[0011] One embodiment of the present invention is directed to the above method wherein treating ADHD is improving attention function in ADHD, i.e. a method for improving attention function in ADHD which comprises administering a therapeutically effective amount of lurasidone or a pharmaceutically acceptable acid addition salt thereof to a mammal in need thereof.

[0012] One embodiment of the present invention is directed to the above method which further comprises administering an additional psychotropic drug as a combination drug. The additional psychotropic drug used as a combination drug is preferably a D_4 receptor agonist, and the embodiment thereof is a method for treating ADHD which comprises administering a therapeutically effective amount of lurasidone or a pharmaceutically acceptable acid addition salt thereof and a therapeutically effective amount of a D_4 receptor agonist to a mammal in need thereof; in particular, the method for improving attention

function in ADHD.

The D₄ receptor agonist used herein is preferably one or more medicaments selected from the group consisting of PD-168077, ABT-724, ABT-670, F-15063, A-412997, FAUC-327, 5 Ro-10-5824, CP-226269, PIP-3EA, FAUC-299, FAUC-316, FAUC-179, FAUC-356, FAUC-312, A-369508, and pharmaceutically acceptable salts thereof; more preferably one or more medicaments selected from the group consisting of PD-168077, ABT-724, ABT-670, F-15063, A-412997, FAUC-327, Ro-10-5824, 10 CP-226269, PIP-3EA, and pharmaceutically acceptable salts thereof; and even more preferably one or more medicaments selected from the group consisting of PD-168077, ABT-724, ABT-670, F-15063, and pharmaceutically acceptable salts thereof.

15 [0013] Additional embodiment of the present invention is directed to a method for improving attention function in schizophrenia and/or bipolar disorder which comprises administering a therapeutically effective amount of lurasidone or a pharmaceutically acceptable acid addition salt thereof and a therapeutically effective amount of a D₄ receptor agonist to a mammal in need thereof.

20 [0014] Additional embodiment of the present invention is directed to a pharmaceutical product for treating ADHD which comprises lurasidone or a pharmaceutically acceptable acid addition salt thereof. In addition, the

pharmaceutical product wherein treating ADHD is improving attention function in ADHD is also an embodiment of the present invention.

In addition, one embodiment of the invention is directed to a pharmaceutical product for treating ADHD which comprises lurasidone or a pharmaceutically acceptable acid addition salt thereof and a D₄ receptor agonist. In addition, the pharmaceutical product wherein treating ADHD is improving attention function in ADHD is also an embodiment of the present invention.

[0015] Additional embodiment of the present invention is directed to a kit for treating ADHD which comprises lurasidone or a pharmaceutically acceptable acid addition salt thereof. In addition, the kit wherein treating ADHD is improving attention function in ADHD is also an embodiment of the present invention.

In addition, one embodiment of the invention is directed to a kit for treating ADHD which comprises lurasidone or a pharmaceutically acceptable acid addition salt thereof and a D₄ receptor agonist. In addition, the kit wherein treating ADHD is improving attention function in ADHD is also an embodiment of the present invention.

[0016] Additional embodiment of the present invention is directed to use of lurasidone or a pharmaceutically acceptable acid addition salt thereof in the manufacture of

a pharmaceutical composition for treating ADHD. In addition, the use wherein treating ADHD is improving attention function in ADHD is also an embodiment of the present invention.

5 In addition, one embodiment of the invention is directed to use of lurasidone or a pharmaceutically acceptable acid addition salt thereof and a D₄ receptor agonist in the manufacture of a pharmaceutical composition for treating ADHD. In addition, the use wherein treating 10 ADHD is improving attention function in ADHD is also an embodiment of the present invention.

Additional embodiment of the present invention is directed to a pharmaceutical composition comprising lurasidone or a pharmaceutically acceptable acid addition salt thereof for use in the treatment of ADHD. In addition, 15 the pharmaceutical composition wherein the treatment of ADHD is improvement of attention function in ADHD is also an embodiment of the present invention.

In addition, one embodiment of the invention is 20 directed to a pharmaceutical composition comprising lurasidone or a pharmaceutically acceptable acid addition salt thereof and a D₄ receptor agonist for use in the treatment of ADHD. In addition, the pharmaceutical composition wherein the treatment of ADHD is improvement of 25 attention function in ADHD is also an embodiment of the

present invention.

[0017] Additional embodiment of the present invention is directed to use of lurasidone or a pharmaceutically acceptable acid addition salt thereof in the manufacture of a pharmaceutical composition for treating ADHD which is administered in combination with a D₄ receptor agonist. In addition, the use wherein treating ADHD is improving attention function in ADHD is also an embodiment of the present invention.

[0018] Additional embodiment of the present invention is directed to use of a D₄ receptor agonist for potentiating the efficacy of lurasidone or a pharmaceutically acceptable acid addition salt thereof for treating ADHD. In addition, the use wherein treating ADHD is improving attention function in ADHD is also an embodiment of the present invention.

Additional embodiment of the present invention is directed to use of lurasidone or a pharmaceutically acceptable acid addition salt thereof for potentiating the efficacy of a D₄ receptor agonist for treating ADHD. In addition, the use wherein treating ADHD is improving attention function in ADHD is also an embodiment of the present invention.

[0019] Additional embodiment of the present invention is directed to a medicament for treating ADHD which comprises

lurasidone or a pharmaceutically acceptable acid addition salt thereof. In addition, the medicament wherein treating ADHD is improving attention function in ADHD is also an embodiment of the present invention.

5 In addition, one embodiment of the invention is directed to a medicament for treating ADHD which comprises lurasidone or a pharmaceutically acceptable acid addition salt thereof and a D₄ receptor agonist. In addition, the medicament wherein treating ADHD is improving attention 10 function in ADHD is also an embodiment of the present invention.

In addition, one embodiment of the invention is directed to a medicament for treating ADHD which comprises lurasidone or a pharmaceutically acceptable acid addition salt thereof for the administration in combination with a D₄ receptor agonist. In addition, the medicament wherein treating ADHD is improving attention function in ADHD is 15 also an embodiment of the present invention.

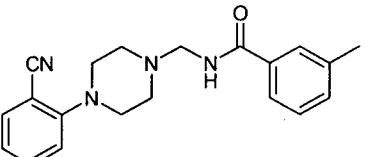
In addition, one embodiment of the invention is 20 directed to a medicament for treating ADHD which comprises a D₄ receptor agonist for the administration in combination with lurasidone or a pharmaceutically acceptable acid addition salt thereof. In addition, the medicament wherein treating ADHD is improving attention function in ADHD is 25 also an embodiment of the present invention.

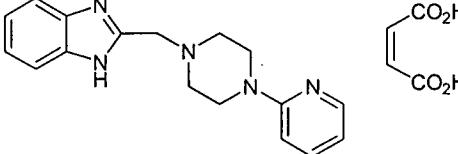
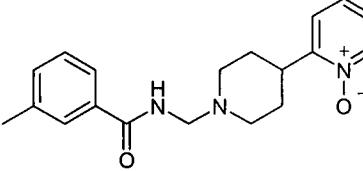
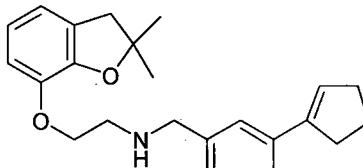
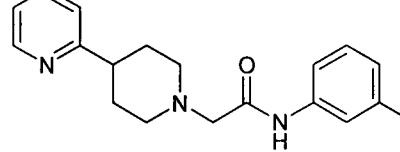
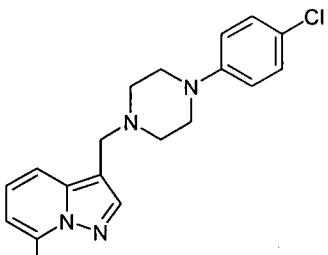
[0020] The improvement of attention function in ADHD of the present invention includes improvement of attention deficit, hyperactivity disorder, etc., in more detail, improvement of impairment in a continuous concentration, improvement of a diminished rapid-reaction, improvement of a reduced activity, etc.

[0021] Preferably, the D₄ receptor agonist used herein includes, but is not limited thereto, the compounds listed in the following table and pharmaceutically acceptable acid 10 addition salts thereof. More preferable D₄ receptor agonist includes PD-168077, ABT-724, ABT-670, F-15063, A-412997, FAUC-327, Ro-10-5824, CP-226269, PIP-3EA, and pharmaceutically acceptable acid addition salts thereof, and even more preferably, PD-168077, ABT-724, ABT-670, F-15 15 063, and pharmaceutically acceptable acid addition salts.

The D₄ receptor agonist of the present invention may be used in a combination of two or more D₄ receptor agonists.

20 [Table 1]

Drug Name [CAS Reg. No.]	Compound Name (Structure)	Reference
PD-168077 [190383-31-4]	N-[4-(2-Cyanophenyl)-piperazin-1-ylmethyl]-3-methylbenzamide 	WO 2002041894

Drug Name [CAS Reg. No.]	Compound Name (Structure)	Reference
ABT-724 [474417-17-9]	2-[4-(2-Pyridyl)piperazin-1-ylmethyl]-1H-benzimidazole maleate 	WO 2003/076431 WO 2002/088093
ABT-670	3-Methyl-N-[4-(1-oxido-pyridin-2-yl)piperidin-1-ylmethyl]benzamide 	WO 2003/099266
F-15063 [680203-70-7] [680203-72-9 (fumarate)]	N-[3-(1-Cyclopenten-1-yl)benzyl]-N-[2-(2,2-dimethyl-2,3-dihydro-1-benzofuran-7-yloxy)ethyl]amine 	WO 2007/104872 WO 2004/035561
A-412997 [630116-49-3]	N-(3-Methylphenyl)-2-[4-(2-pyridyl)piperidin-1-yl]-acetamide 	US 2003/229094 WO 2003/099266
FAUC-327	3-[4-(4-Chlorophenyl)-piperazin-1-ylmethyl]-pyrazolo[1,5-a]pyridine-7-carbonitrile 	Bioorganic & Medicinal Chemistry Letters 12 (2002) 633-636

Drug Name [CAS Reg. No.]	Compound Name (Structure)	Reference
Ro-10-5824 [189744-46-5]	2-Methyl-5-(4-phenyl-1,2,3,6-tetrahydropyridin-1-ylmethyl)pyrimidine-4-amine 	WO 1997/013759
CP-226269	5-Fluoro-2-[4-(2-pyridyl)piperazin-1-ylmethyl]-1H-indole 	US 2006/172995 US 7235661
PIP-3EA	2-[4-(2-Methoxyphenyl)piperazin-1-ylmethyl]-imidazo[1,2-a]pyridine 	J. Med. Chem. 2006, 49, 3938-3947
FAUC-299 [313972-96-2]	2-(4-Phenylpiperazin-1-ylmethyl)-1H-indole-5-carbonitrile 	J. Med. Chem. 2000, 43, 4563-4569
FAUC-316 [313973-04-5]	2-[4-(4-Fluorophenyl)piperazin-1-ylmethyl]-1H-indole-5-carbonitrile 	J. Med. Chem. 2000, 43, 4563-4569

Drug Name [CAS Reg. No.]	Compound Name (Structure)	Reference
FAUC-179	1-Phenyl-4-[2-phenyl-4,5-dihydro-1H-imidazol-4(R)-ylmethyl]piperazine hydrochloride 	Bioorganic & Medicinal Chemistry Letters 11 (2001) 2533-2536
FAUC-356	1-(4-Ethynyl-1H-pyrrol-2-ylmethyl)-4-phenylpiperazine 	Bioorganic & Medicinal Chemistry Letters 12 (2002) 1937-1940
FAUC-312	2-Phenyl-4(R)-(4-phenylpiperazin-1-ylmethyl)-1,4,5,6-tetrahydropyrimidine 	Bioorganic & Medicinal Chemistry Letters 13 (2003) 851-854
A-369508	2-[4-(2-Cyanophenyl)-piperazin-1-yl]-N-(3-methylphenyl)acetamide 	US 2003/229094 WO 2003/099266

(Effect of the Invention)

[0022] Lurasidone or a pharmaceutically acceptable acid addition salt thereof of the present invention is useful

5 for treating ADHD, in particular, for improving attention function in ADHD. In addition, the effect of lurasidone or a pharmaceutically acceptable acid addition salt thereof can be enhanced by administering lurasidone or a

pharmaceutically acceptable acid addition salt thereof in combination with a D₄ receptor agonist.

Further, the present invention can be also effective for improving a behavior disorder such as inhibition of aggression in ADHD; in more detail, effective for aggression against self and/or others, hostility, hyperactivity, severe impulsiveness, etc.

In addition, the present invention can be also effective for improving attention function in a patient suffering from schizophrenia and/or bipolar disorder.

BRIEF DESCRIPTION OF DRAWINGS

[0023]

Fig. 1 depicts a marmoset, acryl boxes with a piece of Baumkuchen, a cage and the test pattern in EXAMPLE 1.

Fig. 2 shows the variation of the correct % between both results of the ORD test wherein one was carried out before the oral administration of haloperidol and the other was carried out 2 hours after the administration. The dot in the figure shows the variation of the correct % in each individual marmoset and the bar graph indicates the average value in each treated group.

Fig. 3 shows the variation of the correct % between both results of the ORD test wherein one was carried out before the oral administration of clozapine and the other

was carried out 2 hours after the administration. The dot in the figure shows the variation of the correct % in each individual marmoset and the bar graph indicates the average value in each treated group.

5 Fig. 4 shows the variation of the correct % between both results of the ORD test wherein one was carried out before the oral administration of risperidone and the other was carried out 2 hours after the administration. The dot in the figure shows the variation of the correct % in each 10 individual marmoset and the bar graph indicates the average value in each treated group.

Fig. 5 shows the variation of the correct % between both results of the ORD test wherein one was carried out before the oral administration of olanzapine and the other 15 was carried out 2 hours after the administration. The dot in the figure shows the variation of the correct % in each individual marmoset and the bar graph indicates the average value in each treated group.

Fig. 6 shows the variation of the correct % between 20 both results of the ORD test wherein one was carried out before the oral administration of lurasidone hydrochloride and the other was carried out 2 hours after the administration. The dot in the figure shows the variation of the correct % in each individual marmoset and the bar graph indicates the average 25 value in each treated group.

Note that "Lurasidone (mg/kg, p.o.)" shown in Fig. 6-8 means the dose of lurasidone hydrochloride.

Fig. 7 shows the variation of the correct % in single administration of L-745,870 or in the combined 5 administration with lurasidone hydrochloride (10 mg/kg, p.o.). The dot in the figure shows the variation of the correct % in each individual marmoset and the bar graph indicates the average value in each treated group.

Fig. 8 shows the variation of the correct % in single 10 administration of Ro 10-5824 or in the combined administration with lurasidone hydrochloride (3 mg/kg, p.o.). The dot in the figure shows the variation of the correct % in each individual marmoset and the bar graph indicates the average value in each treated group.

15

BEST MODE FOR CARRYING OUT THE INVENTION

[0024] Lurasidone may be used in form of the free base, optionally in form of its pharmaceutically acceptable acid addition salt and/or optionally in form of the hydrate and/or solvate thereof. Suitable acid addition salts 20 include, for example, those of the acids selected from succinic acid, hydrobromic acid, acetic acid, fumaric acid, maleic acid, methanesulphonic acid, lactic acid, phosphoric acid, hydrochloric acid, sulphuric acid, tartaric acid and 25 citric acid. Mixtures of the above-mentioned acid addition

salts may also be used. Amongst the aforementioned acid addition salts, the hydrochloride and the hydrobromide, particularly the hydrochloride, are preferred.

[0025] The present invention includes prodrugs of lurasidone or a pharmaceutically acceptable acid addition salt thereof and a D₄ receptor agonist. In general, such prodrugs are functional derivatives of the compounds of this invention which are readily convertible *in vivo* into the required compound.

10 The exemplified prodrugs of the invention, but are not limited to, include the following types:

Phosphate ester prodrug for hydroxyl or amine group of the parent drug.

15 Carbonate or carbamate prodrug for carboxyl, hydroxyl or amine group of the parent drug.

Amide prodrug for carboxylic acid or amine group of the parent drug.

Amino acid-attached prodrug for carboxylic acid or amine group of the parent drug.

20 Oxime prodrug for ketone, amidine or guanidine group of the parent drug.

The prodrugs of the invention can be prepared, for example, by means disclosed in *Nature Reviews Drug Discovery* 7; 255 - 270 (2008); or *Journal of Medicinal Chemistry* 2005, 48 (16), 5305-5320.

[0026] The term "therapeutically effective amount" shall mean the amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by a 5 researcher or clinician.

The terms "treating" and "treatment" used herein include any treatment of the disease (e.g. improvement of the symptoms, relief of the symptoms, arrest of the development of the symptoms, etc.) as well as any 10 prevention of the disease (e.g. prevention of the onset and/or progression of the disease).

[0027] As used herein, the term "pharmaceutical product" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any 15 product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

[0028] The term "ADHD" used herein means attention deficit/hyperactivity disorder, in more detail, one of 20 developmental disorders, which is characterized by inattention, hyperactivity, and impulsiveness. The symptom includes difficulty in concentrating, overactivity, and inattention.

In addition, the improvement of ADHD includes 25 inhibition of aggression, and the specific behavior

disorder of aggression includes aggression against self and/or others, hostility, hyperactivity, severe impulsiveness, etc.

The improvement of impairment in a continuous concentration, the improvement of a diminished rapid-reaction, and the improvement of a reduced activity, which are examples of the improvement of attention function in ADHD of the present invention, can be evaluated by visual/perceptual seeking and/or systematic/continuous listening as a marker of the improvement.

[0029] In the combination of the present invention, lurasidone or a pharmaceutically acceptable acid addition salt thereof and a D₄ receptor agonist may be administered separately or together in one pharmaceutical composition. In addition, the administration of one element of the combination of the present invention may be prior to, concurrent with, or subsequent to the administration of the other element of the combination. These ingredients may be formulated into a single dosage form or two separate ones.

[0030] Lurasidone and a D₄ receptor agonist of the present invention can be easily reacted with a pharmaceutically acceptable acid to form a salt thereof. The acid includes an inorganic acid such as hydrochloric acid, sulphuric acid, phosphoric acid, and hydrobromic acid; and an organic acid such as oxalic acid, maleic acid,

fumaric acid, malic acid, tartaric acid, citric acid, and benzoic acid. A preferable salt of lurasidone includes the hydrochloride thereof.

[0031] The active ingredients of the present invention (lurasidone or a pharmaceutically acceptable acid addition salt thereof, or the combination of lurasidone or a pharmaceutically acceptable acid addition salt thereof and a D₄ receptor agonist) may be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous or subcutaneous injection, or implant), buccal, nasal, vaginal, rectal, sublingual, or topical (e.g., ocular eyedrop) routes of administration and may be formulated alone or together, in suitable dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles appropriate for each route of administration.

[0032] Lurasidone and a pharmaceutically acceptable acid addition salt thereof of the present active compound can be orally administered in a needed amount suitable for the active ingredient, as a generally-used dosage form such as tablet, capsules, syrup, and suspension, or parenterally administered as an injection form such as solution, emulsion, suspension and patch.

The above-mentioned drug form can be prepared by formulating the active compound with conventional additives

such as carrier, excipient, binder, and stabilizer. In the case of injections, for example, acceptable buffer, solubilizer, isotonic agent and pH adjuster can be also used.

5 [0033]

The dosage of the active ingredients of the present invention is not limited, but it can vary depending upon dosage amount of each active ingredient, frequency of administration, administration form, condition of a patient 10 suffering from the disease. For example, lurasidone or a pharmaceutically acceptable acid addition salt thereof of the present invention can be orally administered in a dosage of 1 - 200 mg, preferably 20 - 160 mg, per day for an adult, and once to several times a day. The D₄ receptor 15 agonist can be orally administered in a dosage of 1 - 600 mg per day for an adult, and once to several times a day.

When these active ingredients are prepared in a single dosage form, the D₄ receptor agonist is generally contained in 0.1 to 10 parts, preferably 0.3 to 3 parts, by weight 20 per one part by weight of lurasidone or a pharmaceutically acceptable acid addition salt thereof. And, the drug combination may include the sum of the ingredients in 0.1 - 70 % (w/w) in the preparation, but not limited thereto.

25 EXAMPLE

[0034] Hereinafter, the present invention is further illustrated by Examples, but should not be construed to be limited thereto.

[0035]

5 Example 1

(Method)

ORD test (object retrieval with detour test) is already reported as a method for evaluating executive function (attention function/impulsiveness) in primates.

10 The present inventors have found that the method is useful as a model experiment for evaluating ADHD, then carried out the following test according to the method.

Male and female common marmosets having body weights of 250 - 450 g were used. Haloperidol, clozapine, 15 olanzapine, risperidone, and lurasidone hydrochloride were separately suspended in 0.5 % methylcellulose (MC), and then each suspension was orally administered in a dose of 5 mL/kg to the marmosets. On the other hand, L-745,870 which is a D₄ antagonist, and Ro 10-5824 which is a D₄ agonist 20 were separately dissolved in saline, and then each solution was intramuscularly administered to the femoris area in a dose of 0.5 mL/kg.

[0036] According to the method described in the literature (*Psychopharmacology* (2008) 196: 643-648) which 25 was partially modified, the ORD test was carried out as

follows (see Fig. 1).

(Training for ORD test)

Clear acrylic cubic boxes (dimensions: 4 cm x 4 cm x 4 cm) with one open side are set as the thick frames shown in Fig. 1. In each of the boxes, 0.3 - 0.5 g of Baumkuchen as a food reward is placed at the point of each triangle in Fig. 1. The marmoset can reach out from the cage (shown as dotted line region) to obtain the reward placed in the acrylic box. Fig. 1 is a view from the directly above. Amongst the situations between each direction of the box and each position of the reward, 5 patterns (line of sight, left outside, left inside, right outside, and right inside) are defined as "easy task", and the other 2 patterns (left deep, and right deep) are defined as "difficult task". It is recorded as "correct" when the test animal can obtain the reward in one trial, while it is recorded as "incorrect" when the animal can obtain the reward in the second trial or later.

[0037] The ORD test is carried out in the order described in the following table without any interval between each trial, which is referred to as "one series". The marmoset is made to be trained with the one series once a day.

[Table 2]

Trial number	Position of the reward	Level	Trial number	Position of the reward	Level
1	Line of sight	Easy	10	Left outside	Easy
2	Line of sight	Easy	11	Left inside	Easy
3	Right outside	Easy	12	Left deep	Difficult
4	Right deep	Difficult	13	Left deep	Difficult
5	Right outside	Easy	14	Right deep	Difficult
6	Right inside	Easy	15	Left deep	Difficult
7	Right deep	Difficult	16	Right deep	Difficult
8	Left outside	Easy	17	Line of sight	Easy
9	Left deep	Difficult			

[0038] The marmosets were trained with the ORD test at least 10 times, and then the trained marmosets were used in 5 the following main test.

The main ORD test was carried out as follows.

[0039] (1) The ORD test is carried out before administering each test drug (former value). Hereinafter, the ORD test is done in one series containing the 17 trials 10 corresponding to the above-mentioned training.

(2) Two hours after administering each test drug, the same ORD test is carried out again (latter value). In case of the combined administration, the first drug (lurasidone hydrochloride) is administered; one hour later, the second drug (the D₄ antagonist or D₄ agonist) is administered; and then the ORD test is done one hour after the second drug is 15 administered.

(3) The variation of correct % in the Difficult task is calculated according to the following formula in order

to evaluate the effect of each drug. For example, in case that the "correct count" in the before-administration test (former value) is 3 and the "correct count" in the after-administration test (latter value) is 5, the "correct %" is
5 calculated to rise in 25 % ($= (5-3) / 8 \times 100 \%$) based on the fact that the trial count of the difficult task in each series is 8.

The variation of the correct % =

10 {the difference between the both correct counts in
the difficult task (latter value - former value)} /
8 x 100

(4) The amount of Baumkuchen is $0.5 \text{ g} \times 17 = 8.5 \text{ g}$ in one series. The marmoset can be tested at most 2 sets per day, i.e. it has been confirmed that the marmoset can take
15 at most 17 g of Baumkuchen per day, but, all the test marmosets cannot be satisfied with 17 g of Baumkuchen.

(5) In case that a marmoset treated with the drug is used again, the marmoset is given in 2 week-drug-holidays, and before the test it is confirmed that the previous
20 medication will not affect the test.

(6) 5 to 6 marmosets were used per one test group. When a marmoset(s) suffered from vomiting or cataleptic akinesia induced by the drug and then the ORD test with the marmoset(s) could not be done, the data of the marmoset(s)
25 were excluded. And, when the test for one drug is done

over 2 days, the solvent test (control group) is done in both the days. Thereby, in some cases, the control group can include the data using at most 12 animals (6 animals x 2 times).

5 [0040]

(Result 1)

As shown in Fig. 2 to 5, haloperidol, clozapine, risperidone and olanzapine in each single administration decreased the correct % of the ORD test in a dose-dependent manner. On the other hand, lurazidone hydrochloride increased the correct % of the ORD test in a dose-dependent manner as shown in Fig. 6. Namely, it was indicated that lurazidone hydrochloride in single administration can improve attention function in ADHD and suppress impulsiveness.

15 [0041]

(Result 2)

Although the single intramuscular administration of L-745,870 which is a D₄ antagonist (10 mg/kg) had no effects on the ORD score as shown in Fig.7, the combined administration of L-745,870 (3 mg/kg, i.m.) with lurazidone hydrochloride (10 mg/kg, p.o.) decreased the correct % which was increased by the administration of lurazidone hydrochloride. It seems that lurazidone failed to decrease the ORD score because of its weak D₄ antagonistic actions

in contrast to the strong D₄/D₂ receptor antagonistic actions of SDAs (serotonin dopamine antagonists) other than lurasidone.

[0042]

5 (Result 3)

As shown in Fig. 8, the single administration of Ro 10-5824 which is a D₄ agonist increased the ORD score in a dose dependent manner. Also, when the administration of lurasidone hydrochloride (3 mg/kg, p.o.) which had no 10 effects on the correct % was combined with the administration of Ro 10-5824 (0.3 mg/kg, i.m.) which is also had no effects on the correct %, the ORD score was significantly increased. These results suggest that the application of lurasidone as a combination drug with D₄ 15 agonist could enhance the therapeutic effects in ADHD therapy. Also, these results suggest a possibility that a compound having both SDA action and D₄ agonist action could be a medicament for treating ADHD. Among deficits in 20 attention function which are the symptoms of ADHD, in particular, such medication is expected to improve continuous concentration, rapid-reaction and visual/perceptual seeking.

[0043]

Example 2

25 According to the five-choice serial reaction time task

test (5-CSRT test) which is based on the procedure described in *Neuropharmacology*. 2006 Aug; 51(2): 238-50. Epub 2006 May 6. or *Brain Res Cogn Brain Res*. 2004 Apr; 19(2): 123-3, it is possible to evaluate the effect of the compounds or the combination drugs of the present invention for improving deficits in attention function which are the symptoms of ADHD, in particular, continuous concentration, rapid-reaction and visual/perceptual seeking.

5 (Animals)

10 Common marmosets (male / female, 250 - 450 g weight) are used.

(Induction of cognitive impairment)

15 Transient cognitive impairment is induced in the marmosets by the intramuscular administration of ketamine hydrochloride (1.0 - 3.0 mg/kg). 15 min after the administration, the 5-CSRT test is initiated.

(Drugs, preparation and administration methods)

20 A suspension of 0.5 % lurasidone hydrochloride in methylcellulose (MC) is orally administrated to the marmosets (0.1 - 30 mg/kg). On the other hand, L-745,870 which is a D₄ antagonist and Ro 10-5824 which is a D₄ agonist are dissolved in saline, and intramuscularly administrated to the femoris area in a dose of 0.1 - 10 mg/kg and 0.1 - 3 mg/kg, respectively. These drugs are 25 administrated 1 - 2 hours prior to the ketamine

administration.

(5-CSRT test)

The 5-CSRT test is performed according to the following procedure which is made by partially modifying that of the above reference (*Neuropharmacology*. 2006 Aug; 51(2): 238-50. Epub 2006 May 6.).

A system called CANTAB (Cambridge Neuropsychological Test Automated Battery) in which computerized tasks can be presented on a personal computer and a food reward is given 10 for a correct answer, is employed. A piece of Baumkuchen (0.1 - 0.3 g) is given to each individual through the CNTAB device as a food reward for the correct answer. The marmosets reach out from the cage, answer the tasks provided by CANTAB device, and make actions to obtain the 15 food reward.

In the tasks of the 5-CSRT test, white lined circles having a diameter of 3 cm are presented at each vertex of an equilateral pentagon of 10 cm on a side, and only one of the 5 circles is lighted to yellow inside the white line 20 for a period of 0.2 to 1.0 sec, then the yellow signal is blacked out. And, the marmosets can touch the lighting circle, and will be given the reward for the correct answer if they touch the lighting circle in the lighting period or within 15 sec after the extinction. Each task is loaded in 25 every 5 sec, and the numbers of correct answers, wrong

answers and omission, and time to respond to the task are recorded to evaluate the effect of drugs. The tasks consist of up to 30 tasks and up to 10 min of the total test period.

5 [0044]

Example 3

Suitably designed clinical tests for evaluating deficits in attention function in ADHD include Continuous Performance Test (CPT) (Reference URL1), Test of Variables 10 of Attention (T.O.V.A) (Reference URL2). Alternatively, the improvement of deficits in attention function in ADHD by the compound and the combination drug of the present invention can be confirmed using NIH Test of Attention (Reference URL2) operated in NIDCD (National institute on 15 deafness and other communication disorders) of the NIH (National institute of health) and a clinical test based on new CPT (Reference URL3) which is a modified CPT test.

Reference URL1

ClinicalTrials.gov Identifier: NCT00546910

20 <http://clinicaltrials.gov/ct2/show/NCT00546910>

Reference URL2

ClinicalTrials.gov Identifier: NCT00776737

<http://clinicaltrials.gov/ct2/show/NCT00776737>

Reference URL3

25 ClinicalTrials.gov Identifier: NCT00646464

<http://clinicaltrials.gov/ct2/show/NCT00646464>

[0045]

Example 4

The improvement of deficits in attention function in
5 ADHD by the compound and the combination drug of the
present invention can be confirmed using clinical tests
based on the procedures described in Reference 1 and
Reference 2 as suitably designed clinical test for
evaluating deficits in attention function in ADHD.

10 Reference 1: *Rinsho Seishin Yakuri*, vol. 12, issue. 9, Page
1957-1964 (2009.09)

Reference 2: *Rinsho Seishin Yakuri*, Vol. 12, issue 9, Page
1965-1977 (2009.09)

Specifically, for example, by comparing the total
15 score of ADHD RS-IV (ADHD Rating Scale-IV, Japanese edition
(clinician version)) before and after the administration of
the compound or combintion drug of the present invention
for a certain period (e.g., but not limited to, 8 weeks) to
6 to 18 years old patients fulfilling the diagnostic
20 criteria of ADHD based on DSM-IV (*Diagnostic and
Statistical Manual of Mental Disorders*, 4th. Edition), the
improvement of deficits in attention function which are the
symptoms of ADHD can be confirmed (Reference 1, Page 1958-
1960).

25 In the tests described above, conditiones such as

patients, administration period, dose, and methods for assessment can be appropriately modified. For example, evaluation according to scores of Inattention Subscale of ADHD RS-IV consisting of 9 terms, evaluation according to 5 scores of Hyperactivity-Impulsiveness Subscale consisting of 9 terms, and/or evaluation according to ADHD generalized severity (CGI-ADHD-S) can be employed besides the total scores of ADHD RS-IV. Furthermore, other tests described in Reference 1 and Reference 2, and tests described in 10 reference literatures in these References as well as tests with appropriately modified conditions of above tests can also be employed.

[0046]

Example 5

15 According to the Y-maze test with juvenile stroke-prone spontaneously hypertensive rats (SHRSP), it is possible to evaluate the effect of lurasidone hydrochloride on attention function with spontaneous Alternation Behavior as an index of attention or concentration (Behav Brain 20 Funct. 2005 Jul 15;1:9). Moreover, the effects of lurasidone hydrochloride on hyperactivity, which is one of core symptoms in ADHD, can be confirmed by the total number of the Arm Entries in a Y-maze test.

[0047]

25 (Y-maze test with SHRSP rats)

Methods:

For the estimation of inattentive behavior, male juvenile SHRSP rats as an ADHD model and WKY rats as a reference (4 weeks old, n=8-10/group) are used. These 5 animals are commercially available from Charles River Laboratories Japan, inc. or Hoshino Laboratory animals, inc. Lurasidone hydrochloride (e.g. 0.01, 0.03, 0.1, 0.3, 1, 3 and 10 mg/kg; produced by Dainippon Sumitomo Pharma Co., Ltd.) is dissolved in 0.5% methylcellulose and 0.2% Tween 10 80, and is administrated intraperitoneally in a volume of 1 ml/kg, 30 minutes before the evaluation.

The method of Y-maze test was already reported elsewhere (Behav Pharmacol. 2002 Feb;13(1):1-13). The "Arm Entry" means the entry of all four paws into one arm. The 15 "Alternation Behavior", which is actual alternations, means the consecutive Arm Entries into three different arms. The test is carried out for 8 minutes in one session and the total number that a rat performs the Arm Entry is counted. The "Maximum Alternations" means the total number of the 20 Arm Entries minus two. An index of attention is calculated as a percentage of the Alternation Behavior, as described below.

A percentage of Alternation Behavior =
(the total number of the Alternation Behavior) / (the 25 Maximum Alternations) x 100

[0048]

Results:

The increased number of total Arm Entries and the decreased percentage of Alternation Behavior were observed 5 in the SHRSP rats compared to the WKY rats, indicating hyperactivity and inattention behavior in the SHRSP, respectively. After the administration of 0.1, 0.3 or 1.0 mg/kg of lurasidone hydrochloride, the Alternation Behavior was improved in the SHRSP rats, with a statistical 10 significance at 0.3 (p=0.0124) mg/kg. Furthermore the SHRSP to which lurasidone hydrochloride was given in a dose of 0.1, 0.3 or 1.0 mg/kg showed the decreased number of total Arm Entries with a statistical significance at 0.3 (p=0.0096) and 1 (p=0.0047) mg/kg, suggesting attenuated 15 hyperactivity in the SHRSP. Thus, it is concluded that lurasidone hydrochloride improved inattention behavior and hyperactivity in SHRSP.

[Table 3]

Table 3: Inattention

Animal species	Dose (mg/kg)	% of Alternation Behavior mean \pm SE
WKY	0	82 \pm 3
SHRSP	0	61 \pm 2
SHRSP	0.1	70 \pm 5
SHRSP	0.3	75 \pm 2 *
SHRSP	1.0	72 \pm 2

*: P<0.05

[Table 4]

Table 4: Hyperactivity

Animal species	Dose (mg/kg)	Total Arm Entries mean \pm SE
WKY	0	20 \pm 1
SHRSP	0	27 \pm 1
SHRSP	0.1	24 \pm 1
SHRSP	0.3	22 \pm 2 *
SHRSP	1.0	21 \pm 1 *

*: P<0.05

[0049]

Example 6

The elevated-plus maze with SHRSP makes it possible to
 5 estimate the effects of lurasidone hydrochloride on
 impulsivity, which is one of main symptoms of ADHD (Behav
 Brain Funct. 2005 Jul 15;1:9). In particular, it is
 possible to confirm the effect of lurasidone hydrochloride
 on impulsivity by measuring the spending time on open arms
 10 and/or the number of the entry into open arm in an
 elevated-plus maze. WKY rats are available as a normal
 animal.

[0050]

(Elevated plus maze in SHRSP rats)

15 Methods:

The spending time on open arms in an elevated plus
 maze can be used as an index of impulsive-like behavior
 according to the method described previously (Behav
 Pharmacol. 2002 Feb;13(1):1-13). For the estimation of
 20 impulsivity, male juvenile SHRSP rats as an ADHD model and

WKY rats as a reference (5 weeks old, n=8-10/group) are used. These animals are commercially available from Charles River Laboratories Japan, inc. or Hoshino Laboratory animals, inc. Lurasidone hydrochloride (e.g. 5 0.01, 0.03, 0.1, 0.3, 1, 3 and 10 mg/kg; produced by Dainippon Sumitomo Pharma Co., Ltd.) is dissolved in 0.5% methylcellulose and 0.2% Tween 80, and is administrated intraperitoneally in a volume of 1 ml/kg, 30 minutes before the evaluation. A plus maze with two open and close arms 10 (50 cm x 10 cm) is elevated 50 cm above a floor. After the administration of lurasidone hydrochloride, SHRSP or WKY rat is placed in the center area and allowed to enter each arm freely for a 10 min session. Analysis is performed with a video tracking software, EthoVision[®] XT (Noldus 15 Information Technology), in which the "Arm Entry" means an entry of a body center.

[0051]

There is no significant difference in the spending time on closed arms between SHRSP and WKY, while SHRSP 20 spends for a longer time on open arms. They indicate impulsive behavior and/or less anxiety in SHRSP. The decrease of time which SHRSP spends on open arms of an elevated-plus maze indicates the improvement of impulsivity by the compound. Thus, the ameliorating effect of 25 lurasidone hydrochloride on impulsivity can be evaluated.

CLAIMS

1. A method for treating ADHD which comprises administering a therapeutically effective amount of lurasidone or a pharmaceutically acceptable acid addition salt thereof to a mammal in need thereof.

2. The method of claim 1 wherein treating ADHD is improving attention function in ADHD.

10

3. A method for treating ADHD which comprises administering a therapeutically effective amount of lurasidone or a pharmaceutically acceptable acid addition salt thereof and a therapeutically effective amount of a D₄ receptor agonist to a mammal in need thereof.

4. The method of claim 3 wherein treating ADHD is improving attention function in ADHD.

20 5. The method of claim 3 or 4 wherein the D₄ receptor agonist is one or more medicaments selected from the group consisting of PD-168077, ABT-724, ABT-670, F-15063, A-412997, FAUC-327, Ro-10-5824, CP-226269, PIP-3EA, FAUC-299, FAUC-316, FAUC-179, FAUC-356, FAUC-312, A-369508, and 25 pharmaceutically acceptable salts thereof.

6. A pharmaceutical product for treating ADHD which comprises lurasidone or a pharmaceutically acceptable acid addition salt thereof.

5

7. A pharmaceutical product for treating ADHD which comprises lurasidone or a pharmaceutically acceptable acid addition salt thereof and a D₄ receptor agonist.

10 8. Use of lurasidone or a pharmaceutically acceptable acid addition salt thereof in the manufacture of a pharmaceutical composition for treating ADHD.

15 9. Use of lurasidone or a pharmaceutically acceptable acid addition salt thereof and a D₄ receptor agonist in the manufacture of a pharmaceutical composition for treating ADHD.

20 10. A medicament for treating ADHD comprising lurasidone or a pharmaceutically acceptable acid addition salt thereof.

11. A medicament for treating ADHD comprising lurasidone or a pharmaceutically acceptable acid addition salt thereof and a D₄ receptor agonist.

Fig. 1

Marmoset

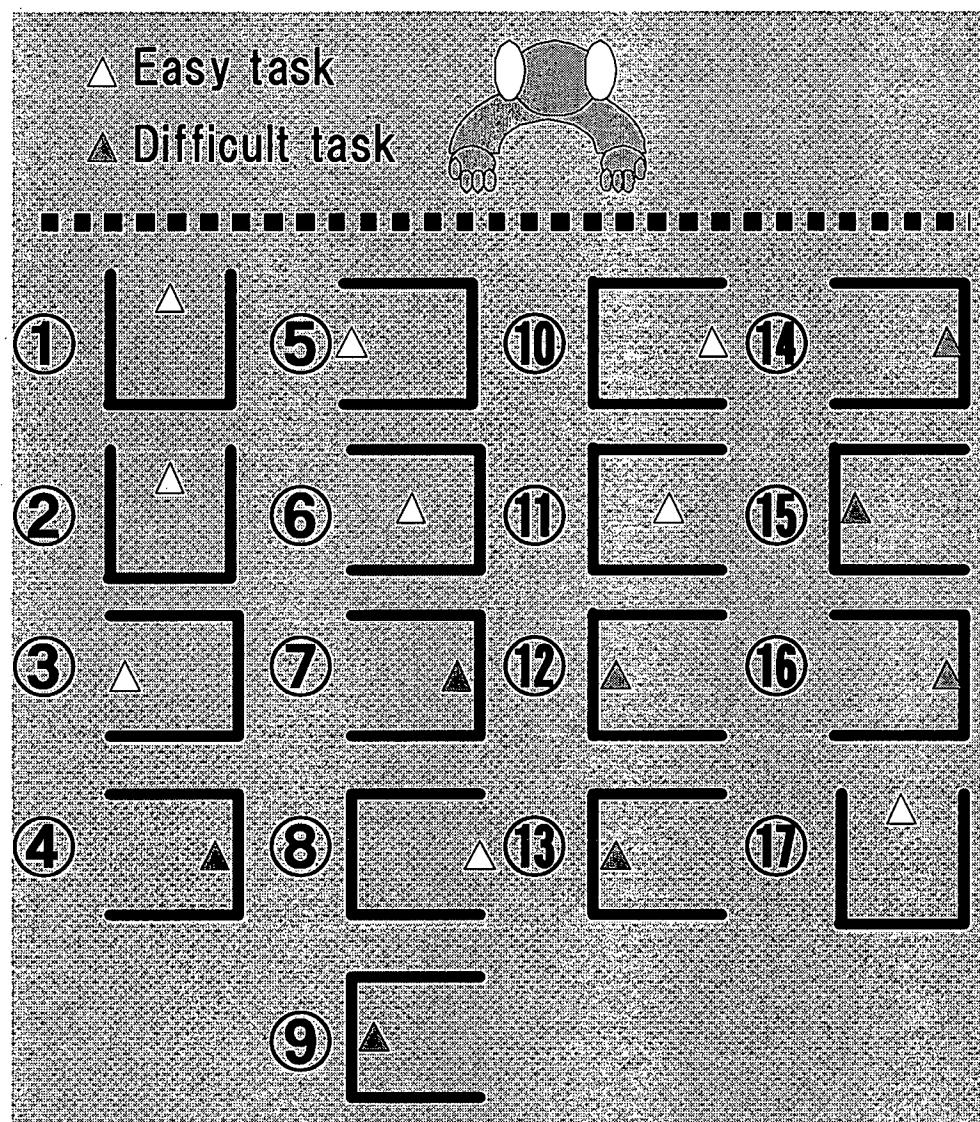
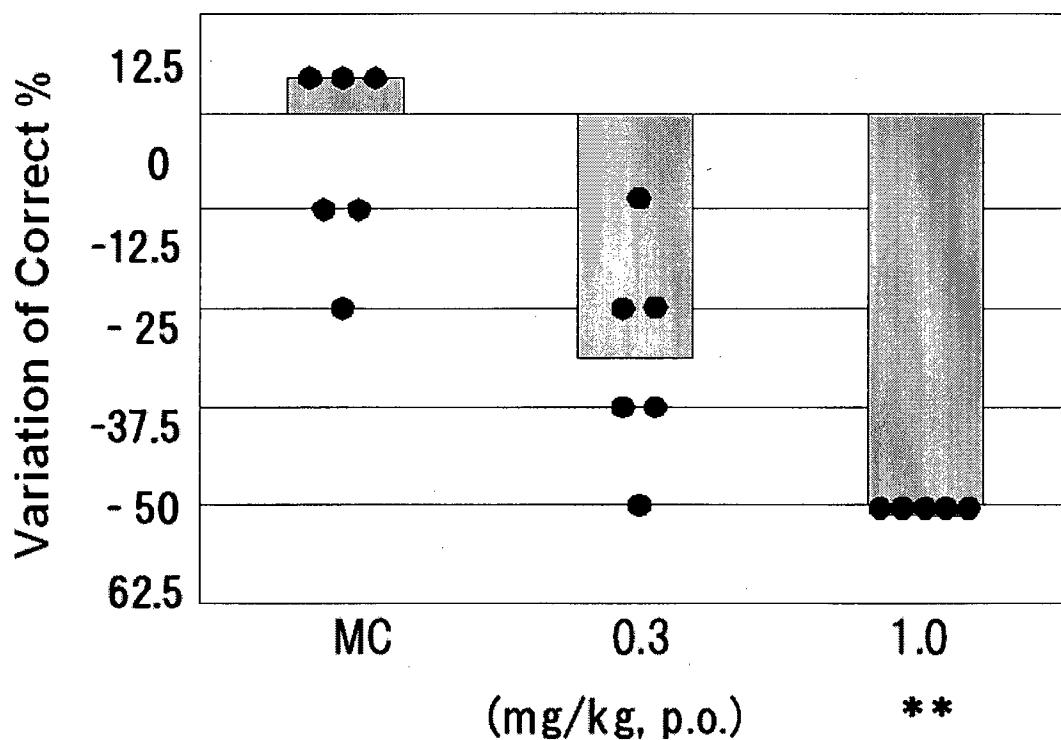


Fig. 2

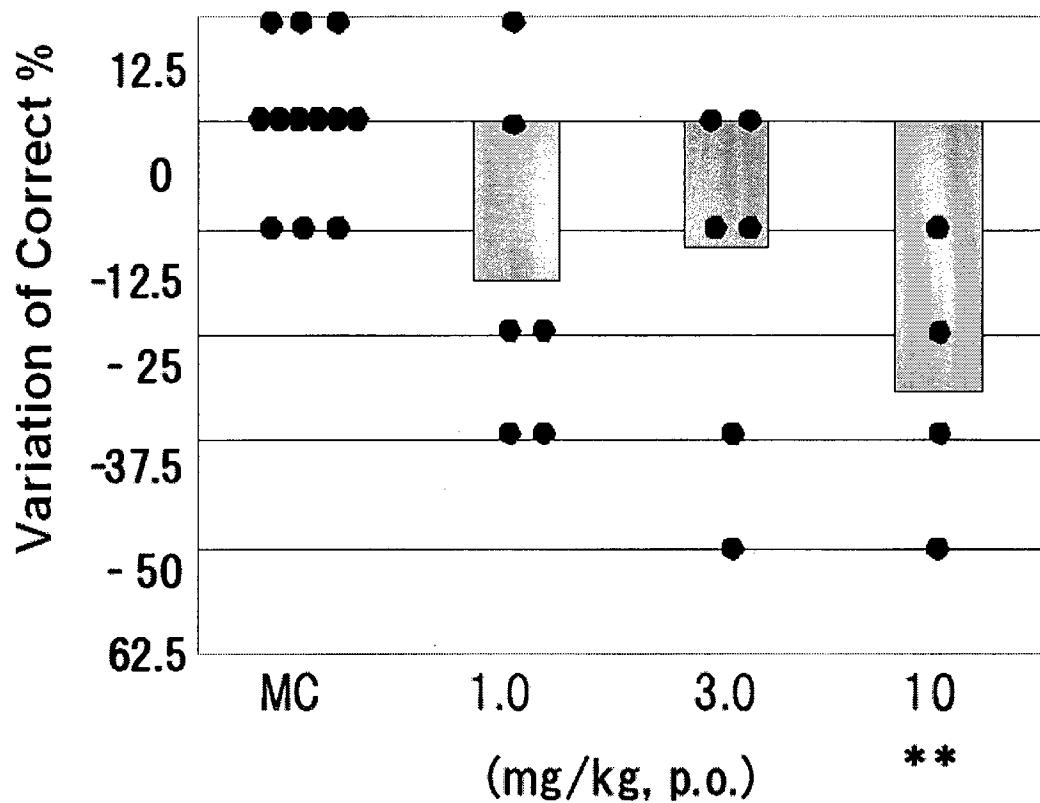
Haloperidol



Non-parametric Dunnet's test
** : P<0.01

Fig. 3

Clozapine



Non-parametric Dunnet's test

** : $P < 0.01$

Fig. 4

Risperidone

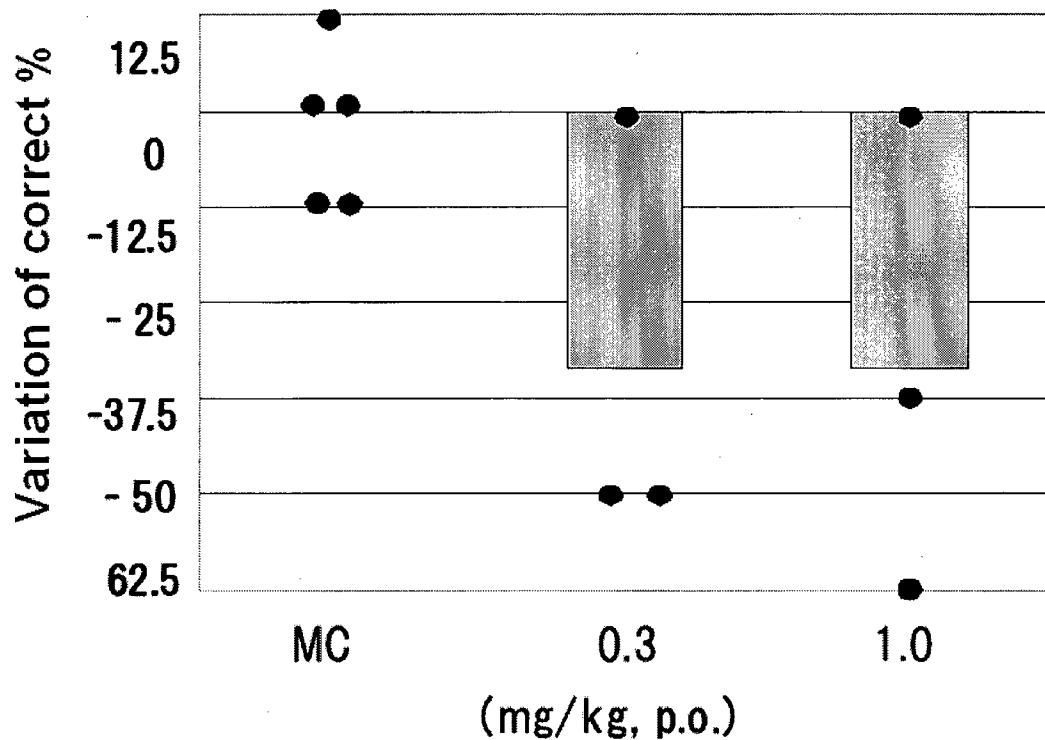
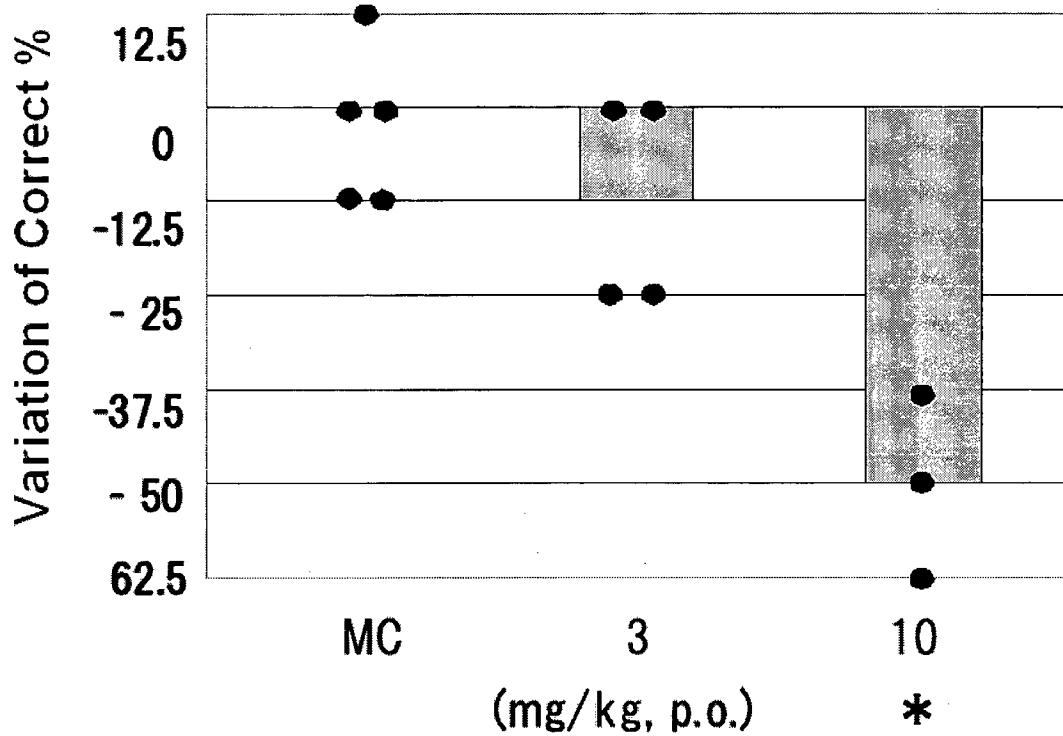


Fig. 5

Olanzapine



Non-parametric Dunnet's test

* : $P < 0.05$

Fig. 6

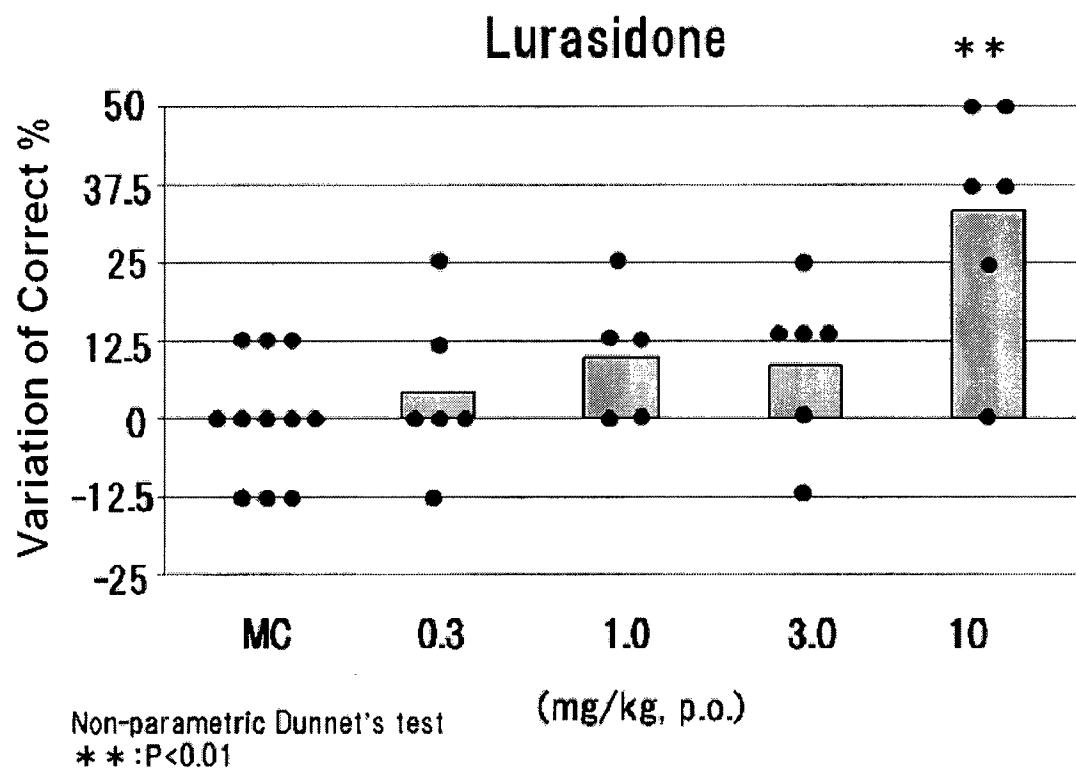


Fig. 7

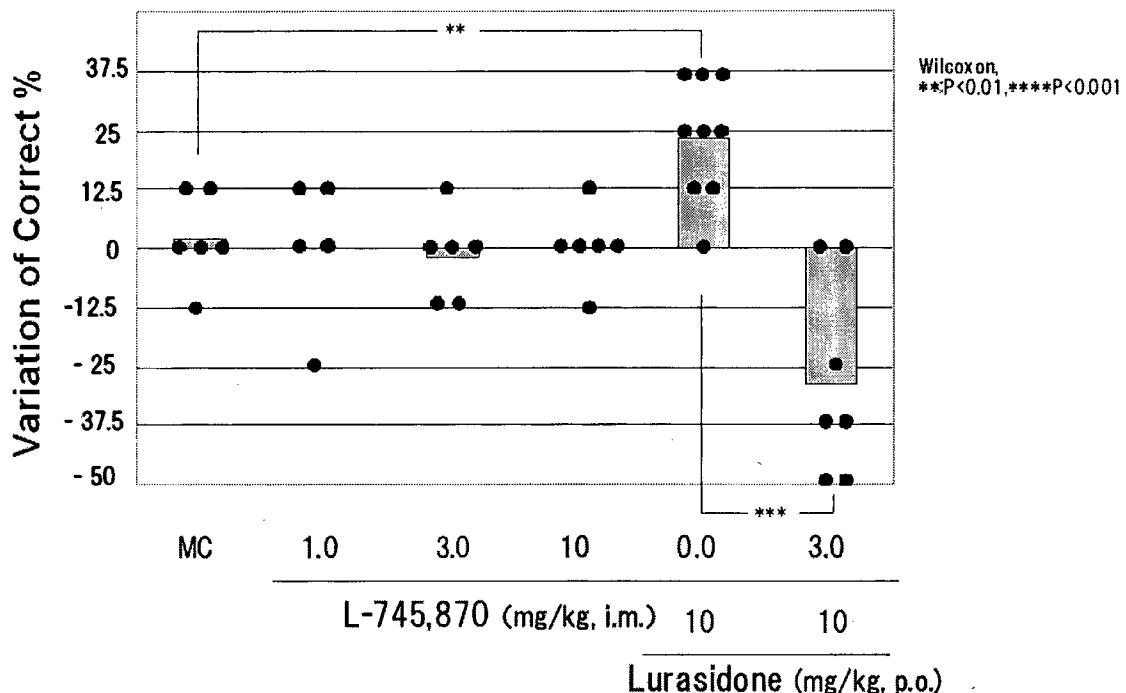
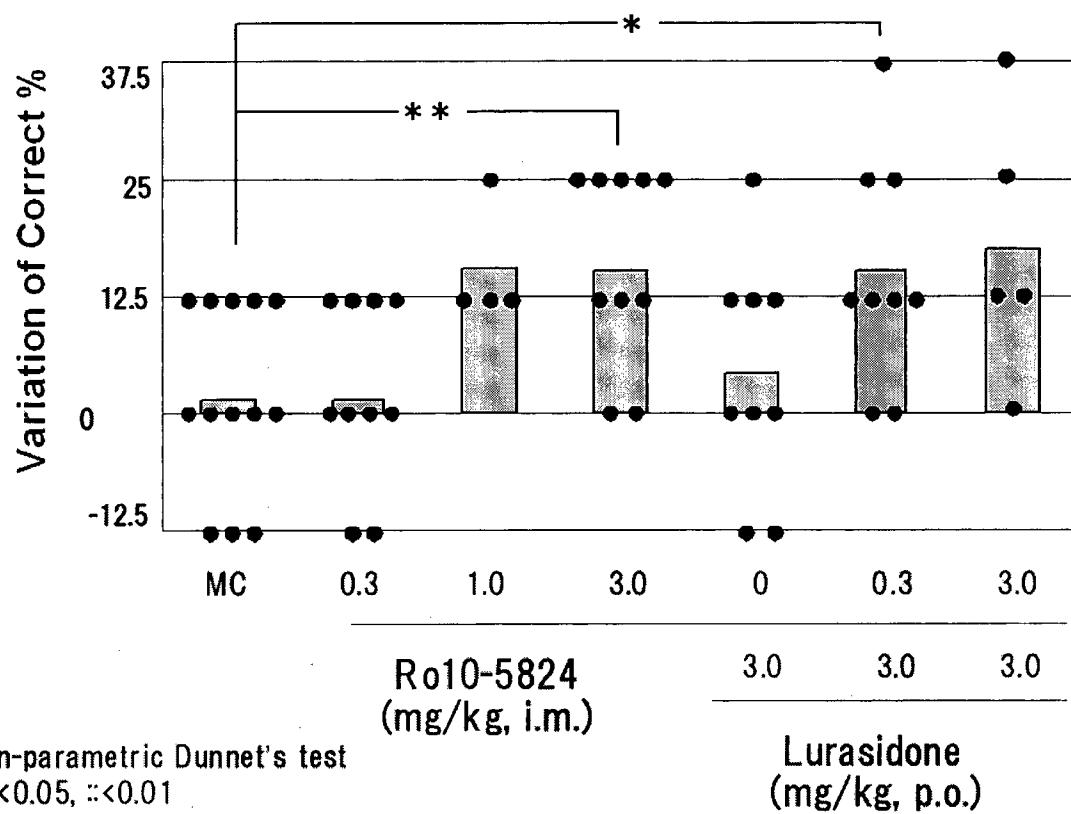


Fig. 8



INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2011/062314

A. CLASSIFICATION OF SUBJECT MATTER

Int.Cl. See extra sheet

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int.Cl. C07D417/12, A61K31/343, A61K31/4545, A61K31/495, A61K31/496, A61K31/506, A61K45/00, A61P25/00, A61P43/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Published examined utility model applications of Japan 1922-1996

Published unexamined utility model applications of Japan 1971-2011

Registered utility model specifications of Japan 1996-2011

Published registered utility model applications of Japan 1994-2011

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAPLUS/REGISTRY (STN), JSTPlus/JMEDPlus/JST7580 (JDreamII)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2004/113333 A1 (Sumitomo Pharmaceuticals Co., Ltd) 2004.12.29, & EP 1637530 A1 & US 2006/142276 A1 & US 2008/255148 A1 Claims 1-12, page 1, line 8-18	6-11
Y	WO 2004/017973 A1 (Sumitomo Pharmaceuticals Co., Ltd) 2004.03.04, & EP 1535616 A1 & US 2006/025422 A1 & EP 1944030 A1 & EP 1535616 B1 Claims 1-19, page 1, line 12-17	6-11
Y	WO 2008/124030 A1 (Merck & Co., Inc.) 2008.10.16, & EP 2144905 A1 Claims 1-20, page 6, line 32- page 8, line 7	6-11

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:

“A” document defining the general state of the art which is not considered to be of particular relevance

“E” earlier application or patent but published on or after the international filing date

“L” document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

“O” document referring to an oral disclosure, use, exhibition or other means

“P” document published prior to the international filing date but later than the priority date claimed

“T” later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

“X” document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

“Y” document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

“&” document member of the same patent family

Date of the actual completion of the international search

16.06.2011

Date of mailing of the international search report

28.06.2011

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INTERNATIONAL SEARCH REPORT

International application No. PCT/JP2011/062314
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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	POWELL, S.B. et al, RO-10-5824 is a selective dopamine D4 receptor agonist that increases novel object exploration in C57 mice, <i>Neuropharmacology</i> , 2003, Vol.44, No.4, p.473-481 Abstract, page 470 right column line 34-46	7, 9, 11
A	RUTTEN, K. et al., Selective PDE inhibitors rolipram and sildenafil improve object retrieval performance in adult cynomolgus macaques, <i>Psychopharmacology</i> , 2008, Vol.196, p.643-8 The whole document, page 644 left column line 11-15	6-11
A	RUSSELL, V.A. et al., Animal models of attention-deficit hyperactivity disorder, <i>Behavioral and Brain Functions</i> , 2005, 1: 9 The whole document	6-11
A	WO 2007/124757 A2 (H. Lundbeck A/S) 2007.11.08, & EP 2026793 A2 & JP 2009-535367 A Claims 11, 27, 30, 41, 44	6-11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2011/062314

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: 1–5
because they relate to subject matter not required to be searched by this Authority, namely:
The subject matter of claims 1–5 relates to a method for treatment of the human body by therapy, which does not require an international search by the International Searching Authority in accordance with PCT Article 17(2)(a)(i) and [Rule 39.1(IV)].
2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP2011/062314

CLASSIFICATION OF SUBJECT MATTER

C07D417/12 (2006. 01) i, A61K31/343 (2006. 01) i, A61K31/4545 (2006. 01) i,
A61K31/495 (2006. 01) i, A61K31/496 (2006. 01) i, A61K31/506 (2006. 01) i,
A61K45/00 (2006. 01) i, A61P25/00 (2006. 01) i, A61P43/00 (2006. 01) i