PTO-1390 (Rev. 02-2005)
Approved for use through 03/31/2007. OMB 0651-0021
U. S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A SUBMISSION UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	U.S. APPLICATION NO. (If known, see 37 CFR 1.5)
0020-5041PUS2	10/525021 NEW

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PT/JP2003/010490	20 August 2003	22 August 2002

TITLE OF INVENTION: AGENT FOR TREATMENT OF SCHIZOPHRENIA

APPLICANT(S) FOR DO/EO/US: Mitsutaka NAKAMURA; Masaaki OGASA; and Shunsuke SAMI

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [x] This is a **FIRST** submission of items concerning a submission under 35 U.S.C. 371.
2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a submission under 35 U.S.C. 371.
3. [x] This is an express request to begin national examination procedures (35 U.S.C. 371 (f)). The submission must include items (5), (6), (9) and (21) indicated below.
4. [x] The US has been elected (Article 31).
5. [x] A copy of the International Application as filed (35 U.S.C. 371 (c)(2))
   a. [ ] is attached hereto (required only if not communicated by the International Bureau).
   b. [x] has been communicated by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [x] An English language translation of the International Application as filed (35 U.S.C. 371 (c)(2)).
   a. [x] is attached hereto.
   b. [ ] has been previously submitted under 35 U.S.C. 154(d)(4).
7. [x] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. [ ] are attached hereto (required only if not communicated by the International Bureau).
   b. [ ] have been communicated by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [x] have not been made and will not be made.
8. [ ] An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. [x] An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. [ ] An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

Items 11 to 20 below concern document(s) or information included:

11. [x] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [x] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [x] A preliminary amendment.
14. [ ] An Application Data Sheet under 37 CFR 1.76.
15. [ ] A substitute specification.
16. [ ] A power of attorney and/or change of address letter.
17. [ ] A computer-readable form of the sequence listing in accordance with PCT Rule 13*ter*.2 and 37 CFR 1.821 - 1.825.
18. [ ] A second copy of the published International Application under 35 U.S.C. 154(d)(4).
19. [ ] A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
20. [x] Other items or information: PCT/IB/308; PCT/IB/304; PCT/IB/332; PCT/IPEA/409; Translation of Provisional Application No. 60/404,927; Drawing - One (1) Sheet

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10/525021 NEW	PT/JP2003/010490	0020-5041PUS2

The following fees have been submitted	CALCULATIONS	PTO USE ONLY
21. [x] Basic national fee $300	$ 300.00	
22. [x] Examination fee		
If International preliminary examination report prepared by USPTO and all claims satisfy provisions of PCT Article 33(1)-(4) $100		
All other situations $200	$ 200.00	
23. [x] Search fee		
Search fee (37 CFR 1.445(a)(2)) has been paid on the international application to the USPTO as an International Searching Authority $100		
International Search Report prepared and provided to the Office $400		
All other situations $500	$ 500.00	
TOTAL OF 21, 22 and 23 =	$ 1,000.00	
[ ] Additional fee for specification and drawings filed in paper over 100 sheets (excluding sequence listing or computer program listing filed in an electronic medium). The fee is **$250** for each additional 50 sheets of paper or fraction thereof.		

Total Sheets	Extra sheets	Number of each additional 50 or fraction thereof (round up to a whole number	RATE
23 - 100 =	/50 =		x **$250.00**

Surcharge of **$130.00** for furnishing the oath or declaration later than 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).					$	
CLAIMS	NUMBER FILED	NUMBER EXTRA		RATE		
Total claims	32 - 20 =	12	x	50.00	$ 600.00	
Independent claims	3 - 3 =		x		$ 0.00	
MULTIPLE DEPENDENT CLAIM(s) (if applicable)			+	360.00	$ 360.00	
TOTAL OF ABOVE CALCULATIONS =					$ 1,960.00	
[ ] Applicant claims small entity status. See 37 CFR 1.27. Fees above are reduced by ½.					$	
SUBTOTAL =					$ 1,960.00	
Processing fee of **$130.00** for furnishing the English translation later than 30 months from the earliest claimed priority date (37 CFR 1.492 (f)). +					$	
TOTAL NATIONAL FEE =					$ 1,960.00	
Fee for recording the enclosed assignment (37 CFR 1.21 (h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +					$ 40.00	
TOTAL FEES ENCLOSED =					$ 2,000.00	
					Amount to be refunded:	$
					Amount to be charged:	$

a. [x] A check in the amount of $ 2,000.00 to cover the above fees is enclosed.

b. [ ] Please charge my Deposit Account No. _____ in the amount of $ _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [x] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 02-2448. A duplicate copy of this sheet is enclosed.

d. [ ] Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b)) must be filed and granted to restore the International Application to pending status.

SEND ALL CORRESPONDENCE TO:

February 18, 2005

CUSTOMER NUMBER: 02292

/clb

SIGNATURE: _____

Mark J. Nuell

NAME

36,623

REGISTRATION NUMBER

DESCRIPTION

AGENT FOR TREATMENT OF SCHIZOPHRENIA

TECHNICAL FIELD

The present invention relates to a novel method for treatment of schizophrenia and a novel therapeutic agent used therein. More particularly, the present invention relates to a method for improving schizophrenia without being accompanied by extrapyramidal symptoms by orally administering a prescribed dose of a specific bicycloheptane-dicarboximide derivative once a day, and a therapeutic agent used in said method.

BACKGROUND ART

Schizophrenia (split personality) is a kind of endogenous psychosis, and it is developed mainly during adolescence, and after a chronic course, the personality of patient is progressively decayed, and some of patients may culminate in a mental decay. The symptoms of this disease are, for example, positive symptoms often observed during the early stage of the disease such as hallucination, delusion, etc., or negative symptoms such as apathy and withdrawal, or cognitive dysfunction such as impairments of concentration and learning abilities, etc. Moreover, there are other symptoms such as depression, anxiety, etc. as related symptoms thereof.

Medication is mainly employed in the treatment of schizophrenia, but the treatment of schizophrenia should be continued for a long time, and even though schizophrenia is once healed, there is a large risk of reoccurring of schizophrenia after drug withdrawal so that it is necessary to continue the medication forever. Therefore, any side effects of medication may always be serious problems, and based on

this perspective, it has been desired to develop a medicine being suitable for prolonged medication.

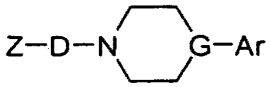
The agents for treatment of schizophrenia are various medicaments such as ones classified in the category of antipsychotic, for example, phenothiazine derivatives (e.g., chlorpromazine, methoxy-promazine, etc.), thioxanthin derivatives having a similar structure to phenothiazine (e.g., chlorprothixene, flupentixol, etc.), benzamide derivatives (e.g., sulpiride, sultopride, etc.), thienodiazepine derivatives (e.g., clotiazepam, etizolam, etc.), and further butyrophenone derivatives (e.g., haloperidol, triperidol, etc.), diphenylbutylamine derivatives (e.g., pimozide, etc.), etc.

However, phenothiazine derivatives, phenothiazine analogues, and butyrophenone derivatives may cause serious side effects of extrapyramidal symptoms showing parkinsonism such as the stiff gait of skeletal muscles, tremor of muscles, lack of facial expression, salivation, etc. Further, diphenylbutylamine derivatives may cause extrapyramidal symptoms in addition to insomnia. In addition, these conventional antipsychotics may be effective on only some of symptoms among positive symptoms, negative symptoms, cognitive dysfunctions of schizophrenia, and there has been no drug being effective on all of these symptoms.

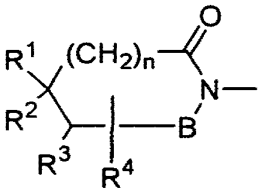
Therefore, it has been desired to develop a safe medicament which exhibits an excellent effect on various schizophrenia as an antipsychotic without causing side effects such as extrapyramidal symptoms.

On the other hand, it has been known that the imide derivative of the following formula, which was found by the co-workers of the present inventors, may be useful as an antipsychotic (c.f., neuroleptic agent, antiaxiety, etc.), especially as an agent for treatment of schizophrenia, senile insanity, manic depressive psychoses, and

nervous breakdown (USP 5,532,372).



wherein Z is



;

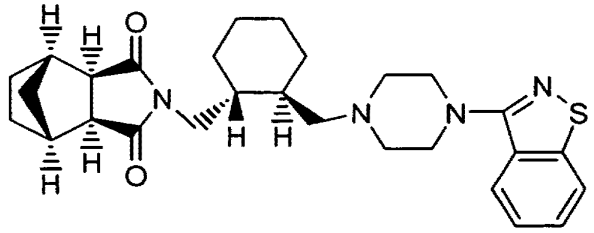
D is a group of the formula: $-(CH_2)_p-A-(CH_2)_q-$,

Gは  or  , etc., and

Ar is an aromatic group, or an aromatic heterocyclic group, etc.

DISCLOSURE OF INVENTION

The present inventor has intensively studied on a series of imide derivatives with respect to many aspects including a use and a dose thereof in order to find a novel agent for treatment of schizophrenia, which may exhibit an excellent effect in the treatment of schizophrenia and have no side effect such as extrapyramidal symptoms, which are often observed in many conventional antipsychotics, and can safely be administered for a long time. As a result, the present inventors have found that (1R,2S,3R,4S)-N-[(1R,2R)-2-[4-(1,2-benzoisothiazol-3-yl)-1-piperazinylmethyl]-1-cyclohexylmethyl]-2,3-bicyclo[2.2.1]heptane-dicarboximide of the following formula:



(1)

or a pharmaceutically acceptable salt thereof such as a hydrochloride

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