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For two-character codes and other abbreviations, refer to "Guidance Notes on Codes and Abbreviations" in each periodically published PCT Gazette.

(54) Title: THERAPEUTIC AGENT FOR SCHIZOPHRENIA

(57) Abstract: Provided are a novel method for treatment of schizophrenia and a therapeutic agent used therein. The compound (1R,2S,3R,4S)-N-[(1R,2R)-2-[4-(1,2-benzoisothiazol-3-yl)-1-piperazinylmethyl]-1-cyclohexylmethyl]-2,3-bicyclo[2.2.1]heptanedicarboximide or a pharmaceutically acceptable salt thereof (for example, hydrochloride) as an active compound is orally administered to a schizophrenic patient in a daily dose of 5 mg to 120 mg once per day. According to this method, wide-ranging symptoms of schizophrenia, especially positive symptoms and negative symptoms, can be relieved without extrapyramidal adverse drug reactions.

Specification

THERAPEUTIC AGENT FOR 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 extrapyramidal adverse drug reactions by orally administering a prescribed dose of a specific bicycloheptanedicarboximide derivative once per day, and a therapeutic agent used in said method.

Background Art

Schizophrenia (split personality disorder) is a type of endogenous psychosis, developed mainly during adolescence. Over time, the personality of a patient progressively breaks down, culminating in mental decay in some patients. 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 associated symptoms thereof.

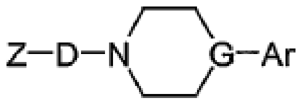
Medication is mainly employed in the treatment of schizophrenia, but the treatment of schizophrenia must be continued for a long time, and even after temporary recovery, there is a large risk of recurrence of schizophrenia after drug withdrawal, making it necessary to continue the medication forever. Therefore, adverse drug reactions are serious problems, and from this perspective, it has been desired to develop a medicine suitable for prolonged administration.

Numerous therapeutic agents for schizophrenia have been used, such as various medicaments classified in the category of antipsychotics, for example, phenothiazine derivatives (e.g., chlorpromazine, methoxypromazine, 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.

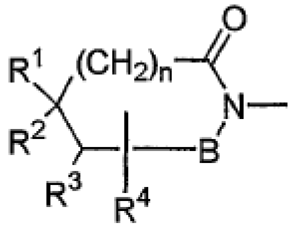
However, phenothiazine derivatives, phenothiazine analogues, butyrophenone derivatives and the like cause serious adverse drug reactions including extrapyramidal syndrome exhibiting parkinsonism such as stiffness of skeletal muscles, muscle tremor, lack of facial expression, salivation, etc. Further, diphenylbutylamine derivatives may cause extrapyramidal syndrome in addition to insomnia. In addition, these conventional antipsychotics may be effective on only some of the symptoms of schizophrenia among positive symptoms, negative symptoms, and cognitive dysfunctions, and there is no drug effective on all of these symptoms.

Therefore, it has been desired to develop a safe medicament that exhibits various excellent effects on schizophrenia as an antipsychotic without adverse drug reactions such as extrapyramidal syndrome.

On the other hand, it has been known that imide derivatives of the following formula, which was found by colleagues of the present inventors, may be useful as antipsychotics (neuroleptic agents, antianxiety agents), especially as agents for treatment of schizophrenia, senile psychosis, bipolar disorder, and neurosis (US Patent No. 5,532,372).



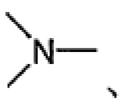
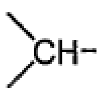
Here, Z is a group having the formula:


;

D is a group having the formula:

$$-(CH_2)_p-A-(CH_2)_q-$$
;

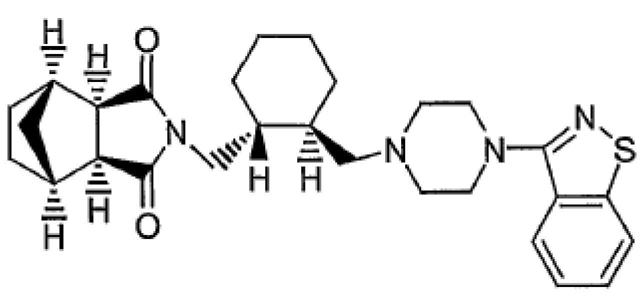
G is:

 or  , etc.;

and Ar is an aromatic group, aromatic heterocycle group, etc.

Summary of the Invention

The present inventors have intensively studied a series of imide derivatives with respect to many aspects including uses and doses thereof in order to find a novel agent for treatment of schizophrenia which is capable of exhibiting an excellent effect in the treatment of schizophrenia without adverse drug reactions such as extrapyramidal syndrome often observed in many conventional antipsychotics, and which can safely be administered for a long time. As a result, the present inventors 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]heptanedicarboximide represented by the following formula:



(1)

or a pharmaceutically acceptable salt thereof such as a hydrochloride thereof is effective for relieving the wide-ranging symptoms of schizophrenia, and may treat schizophrenia very safely without extrapyramidal adverse

Namely, the present invention provides a method for treatment of schizophrenia without extrapyramidal adverse drug reactions by oral administration of a prescribed amount of (1R,2S,3R,4S)-N-[(1R,2R)-2-[4-(1,2-benzoisothiazol-3-yl)-1-piperazinylmethyl]-1-cyclohexylmethyl]-2,3-bicyclo[2.2.1]heptanedicarboximide of the above formula (1) or a pharmaceutically acceptable salt thereof once per day, and further provides a therapeutic agent used in said method.

Brief Description of the Drawings

FIG. 1 is a graph showing the change with time in scores of the Brief Psychiatric Rating Scale (BPRS), which is an index of effect on schizophrenia, of the active compound of the present invention, (1R,2S,3R,4S)-N-[(1R,2R)-2-[4-(1,2-benzoisothiazol-3-yl)-1-piperazinylmethyl]-1-cyclohexylmethyl]-2,3-bicyclo[2.2.1]heptanedicarboximide hydrochloride, and placebo in a double blind clinical trial.

Detailed Description of the Invention

As shown in experiments described hereinafter, when a prescribed dose of (1R,2S,3R,4S)-N-[(1R,2R)-2-[4-(1,2-benzoisothiazol-3-yl)-1-piperazinylmethyl]-1-cyclohexylmethyl]-2,3-bicyclo[2.2.1]heptanedicarboximide hydrochloride was orally administered once per day for 6 weeks to patients with schizophrenia in the acute exacerbation phase, the present inventors found that excellent effects on wide-ranging symptoms were obtained, and surprisingly, almost none of the extrapyramidal adverse drug reactions observed in conventional antipsychotics were observed. In particular, abnormal electrocardiogram related to sudden death was not seen. Hence, the present inventors found this compound may be very safely used in the treatment of schizophrenia.

Namely, the present invention provides a novel method for treatment of schizophrenia that improves wide-ranging symptoms of schizophrenia including positive symptoms, negative symptoms, and cognitive dysfunction, especially positive symptoms and negative symptoms, without extrapyramidal adverse drug reactions, the method comprising orally administering a prescribed dose of (1R,2S,3R,4S)-N-[(1R,2R)-2-[4-(1,2-benzoisothiazol-3-yl)-1-piperazinylmethyl]-1-cyclohexylmethyl]-2,3-bicyclo[2.2.1]heptanedicarboximide of the above formula (1) or a pharmaceutically acceptable salt thereof, especially a hydrochloride thereof, to a schizophrenic patient once per day.

The present invention also provides a novel agent for such treatment of schizophrenia.

According to the present invention, excellent improvement effects on the wide-ranging symptoms of schizophrenia may be obtained by orally administering (1R,2S,3R,4S)-N-[(1R,2R)-2-[4-(1,2-benzoisothiazol-3-yl)-1-piperazinylmethyl]-1-cyclohexylmethyl]-2,3-bicyclo[2.2.1]-heptanedicarboximide or a pharmaceutically acceptable salt thereof, for example, a hydrochloride, at a daily dose of 5 mg to 120 mg, preferably at a daily dose of 10 mg to 100 mg, more preferably at a daily dose of 20 mg to 80 mg, once per day. Further, in the therapeutic method of the present invention, adverse drug reactions such as extrapyramidal adverse drug reactions such as parkinsonism, dyskinesia, akathisia, etc., abnormal electrocardiogram, and hepatic dysfunction are hardly observed, and hence, the present method may be very safely used and is suitable for a prolonged treatment.

Furthermore, when the present method is applied to a patient with schizophrenia in the chronic phase, the above active compound must be administered to said patient for a long time at a dose as low as possible, and in such a case, the daily dose of the active compound is in the range of 5 mg to 80 mg, preferably in the range of 5 mg to 60 mg, more preferably in the range of 10 mg to 40 mg, and it is orally administered once per day.

The therapeutic agent used in the method for treatment of schizophrenia of the present invention is in the

acceptable salt thereof, especially (1R,2S,3R,4S)-N-[(1R,2R)-2-[4-(1,2-benzoisothiazol-3-yl)-1-piperazinylmethyl]-1-cyclohexylmethyl]-2,3-bicyclo[2.2.1]heptanedicarboximide hydrochloride, in an amount of 5 mg to 120 mg, preferably in an amount of 10 mg to 100 mg, more preferably in an amount of 20 mg to 80 mg, per dosage unit. Examples of the oral preparation include tablets, granules, fine granules, powders, capsules, syrups, etc. These preparations should be in the form of a preparation for administration once per day.

The above preparations may be prepared by a conventional method by using a conventional pharmaceutically acceptable carrier usually used in the preparation of a conventional pharmaceutical formulation, for example, excipients such as lactose, white sugar, glucose, starch, calcium carbonate, kaolin, talc, crystalline cellulose, silicic acid, etc., binders such as water, ethanol, gelatin, carboxymethylcellulose, shellac, methylcellulose, gum arabic, tragacanth powder, polyvinylpyrrolidone, etc., disintegrating agents such as sodium alginate, agar powder, laminaria powder, sodium hydrogen carbonate, polyoxyethylenesorbitan fatty acid esters, sodium laurylsulfate, stearic acid monoglyceride, etc., and lubricants such as purified talc, stearate, boric acid powder, polyethyleneglycol, etc.

Experiments

The method for treatment of the present invention and the effects thereof are illustrated in more detail by experiments described hereinafter.

The active compound SM-13496 used in the experiments is (1R,2S,3R,4S)-N-[(1R,2R)-2-[4-(1,2-benzoisothiazol-3-yl)-1-piperazinylmethyl]-1-cyclohexylmethyl]-2,3-bicyclo[2.2.1]heptanedicarboximide hydrochloride, and the meanings of the abbreviations used in the experiments are as follows.

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th ed.
CGI-S: Clinical Global Impressions scale-Severity of Illness
CGI-I: Clinical Global Impressions scale-Improvement
AIMS: Abnormal Involuntary Movement Scale
EPS: Extrapyramidal symptoms
LOCF: Last Observation Carried Forward (LOCF Analysis: a method of using last not-missing data in cases of dropouts)
BAS: Barnes Akathisia Scale
SAS: Simpson-Angust Rating Scale (rating scale for extrapyramidal adverse drug reactions)
PANSS: Positive and Negative Syndrome Scale (rating scale for positive/negative symptoms)

Experiment 1

Early Phase II Clinical Trial

(1) Test method

According to the outline shown in Table 1 below, a placebo-controlled double blind study was conducted on 149 patients with schizophrenia in the acute exacerbation phase at 15 study centers in the U.S. Efficacy and safety were studied when SM-13496 at a dose of 40 mg or 120 mg or a placebo was orally administered once per day for 6 weeks after placebo washout.

Table 1

Name of Clinical Trial	Double-blind, randomized, fixed-dose, placebo-controlled, parallel-group, 6-week efficacy, safety, and tolerability study of two dose levels of SM-13496 in patients with

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