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(54) **Titre : UN METABOLITE D'ILOPERIDONE DESTINE A ETRE UTILISE DANS LE TRAITEMENT DE TROUBLES PSYCHIATRIQUES**
(54) **Title: AN ILOPERIDONE METABOLITE FOR USE IN THE TREATMENT OF PSYCHIATRIC DISORDERS**

(57) **Abrégé/Abstract:**
This invention relates to the treatment of disorders amenable to treatment with an atypical antipsychotic such as iloperidone. More specifically, R-P88, or a pharmaceutically acceptable salt thereof, or an ester of R-P88 or a pharmaceutically acceptable salt of such ester at a dose of 1 mg to 24 mg once per day for the treatment of a psychiatric disorder selected from a group consisting of: schizophrenia, schizoaffective disorder, bipolar disorder, depression, major depression, psychotic episodes, autism, autism spectrum disorder, fragile X syndrome, and pervasive development disorder.

Abstract

This invention relates to the treatment of disorders amenable to treatment with an atypical antipsychotic such as iloperidone. More specifically, R-P88, or a pharmaceutically acceptable salt thereof, or an ester of R-P88 or a pharmaceutically acceptable salt of such ester at a dose of 1 mg to 24 mg once per day for the treatment of a psychiatric disorder selected from a group consisting of: schizophrenia, schizoaffective disorder, bipolar disorder, depression, major depression, psychotic episodes, autism, autism spectrum disorder, fragile X syndrome, and pervasive development disorder.

AN ILOPERIDONE METABOLITE FOR USE IN THE TREATMENT OF PSYCHIATRIC DISORDERS

Field of the Invention

This invention is in the field of treatment of disorders amenable to treatment with an atypical antipsychotic such as iloperidone.

Background of the Invention

Iloperidone (1-[4-[3-[4-(6-flouro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl] ethanone) is disclosed in US Patent 5,364,866. Active metabolites of Iloperidone, e.g., S-P88 (also referred to as (S)-P-88-8891), are useful in the present invention. See, e.g., WO2003020707. In some cases, it may be advantageous to use iloperidone preferentially in patients with certain genotypes as disclosed, e.g., in WO2006039663.

Fanapt® iloperidone is currently approved in the United States for the acute treatment of schizophrenia. The recommended target dosage of Fanapt® tablets is 12 to 24 mg/day, administered b.i.d., i.e., twice per day. The target dosing range is achieved by daily dosage adjustments, alerting patients to symptoms of orthostatic hypotension. Fanapt® must be titrated slowly from a low starting dose to avoid orthostatic hypotension due to its alpha adrenergic blocking properties. The recommended starting dose for Fanapt® tablets is 1 mg taken twice daily. Increases to reach the target dose range of 6-12 mg twice daily, may be made with daily dosage adjustments to 2 mg twice daily, 4 mg twice daily, 6 mg twice daily, 8 mg twice daily, 10 mg twice daily, and 12 mg twice daily on days 2, 3, 4, 5, 6, and 7, respectively. The maximum recommended dose is 12 mg twice daily (24 mg/day).

Summary of the Invention

This invention relates to the treatment of disorders that are amenable to treatment with an atypical antipsychotic, in particular, iloperidone, that comprises administering to the patient R-P88 according to a dosing that is derived from the pharmacokinetics of R-P88 in the body.

In a particular illustrative embodiment, the invention provides a method of treating a patient suffering from a disorder amenable to treatment with iloperidone that comprises internally administering to the patient an effective amount of R-P88 once per day.

In another embodiment, the invention provides a method of treating a patient suffering from a disorder amenable to treatment with iloperidone that comprises internally administering to the patient an effective amount of R-P88

twice per day, wherein the effective amount is 3 to 9 mg twice daily (totaling 6 to 18 mg/day.

According to one aspect of the present invention, there is provided R-P88, or a pharmaceutically acceptable salt thereof, or an ester of R-P88 or a pharmaceutically acceptable salt of such ester at a dose of 1 mg to 24 mg once per day for the treatment of a psychiatric disorder selected from a group consisting of: schizophrenia, schizoaffective disorder, bipolar disorder, depression, major depression, psychotic episodes, autism, autism spectrum disorder, fragile X syndrome, and pervasive development disorder.

According to another aspect, there is provided R-P88, or a pharmaceutically acceptable salt thereof or an ester of R-P88 or a pharmaceutically acceptable salt of such ester for the treatment of a psychiatric disorder selected from a group consisting of: schizophrenia, schizoaffective disorder, bipolar disorder, depression, major depression, psychotic episodes, autism, autism spectrum disorder, fragile X syndrome, and pervasive development disorder at a dose of 1 mg to 24 mg, twice per day.

According to another aspect, there is provided a pharmaceutical composition comprising R-P88 or a pharmaceutically acceptable salt thereof, or an ester of R-P88 or a pharmaceutically acceptable salt of an ester of R-P88 as the sole or primary active ingredient, and a pharmaceutically acceptable carrier.

According to another aspect, there is provided a pharmaceutical composition comprising R-P88 or a pharmaceutically acceptable salt thereof, or

an ester thereof or a pharmaceutically acceptable salt of an ester thereof, for use in the treatment of a disorder amenable to treatment with iloperidone.

According to another aspect, there is provided R-P88 or a pharmaceutically acceptable salt thereof, or an ester thereof or a pharmaceutically acceptable salt of an ester thereof, for use in the manufacture of a medicament for use in the treatment of a disorder amenable to treatment with iloperidone.

According to one aspect of the invention, there is provided a R-P88, or a pharmaceutically acceptable salt thereof or an ester of R-P88 or a pharmaceutically acceptable salt of such ester for treatment of a psychiatric disorder selected from a group consisting of: schizophrenia, schizoaffective disorder, bipolar disorder, depression, major depression, psychotic episodes, autism, autism spectrum disorder, fragile X syndrome, and pervasive development disorder, titrated to final dose in accordance with the following increments:

1 mg once daily, 2 mg once daily, 4 mg once daily, 6 mg once daily, 8 mg once daily, 10 mg once daily, 12 mg once daily, to reach a maximum dose of 12 mg/day, or

2 mg once daily, 4 mg once daily, 8 mg once daily, 12 mg once daily, 16 mg once daily, 20 mg once daily, 24 mg once daily, to reach a maximum dose of 24 mg/day or

2 mg once daily, 4 mg once daily, 8 mg once daily, 12 mg once daily, to reach a maximum dose of 12 mg/day or

1 mg once daily, 4 mg once daily, 8 mg once daily, and 12 mg once daily, to reach a maximum dose of 12 mg/day, or

2 mg once daily, 6 mg once daily, and 12 mg once daily, to reach a maximum dose of 12 mg/day, or

4 mg once daily, 8 mg once daily, 16 mg once daily, and 24 mg once daily, to reach a maximum dose of 24 mg/day, or

8 mg once daily and 24 mg once daily, to reach a maximum dose of 24 mg/day.

According to another aspect of the invention, there is provided a R-P88, or a pharmaceutically acceptable salt thereof or an ester of R-P88 or a pharmaceutically acceptable salt of such ester for treatment of a psychiatric disorder selected from a group consisting of: schizophrenia, schizoaffective disorder, bipolar disorder, depression, major depression, psychotic episodes, autism, autism spectrum disorder, fragile X syndrome, and pervasive development disorder, titrated to final dose in accordance with the following dosing schedule:

1 mg *q.d.* on day 1, 2 mg *q.d.* on day 2, 4 mg *q.d.* on day 3, 6 mg *q.d.* on day 4, 8 mg *q.d.* on day 5, 10 mg *q.d.* on day 6, and 12 mg *q.d.* on day 7 and thereafter, or

2 mg *q.d.* on day 1, 4 mg *q.d.* on day 2, 8 mg *q.d.* on day 3, 12 mg *q.d.* on day 4, 16 mg *q.d.* on day 5, 20 mg *q.d.* on day 6, and 24 mg *q.d.* on day 7 and thereafter, or

2 mg *q.d.* on day 1 and 2, 4 mg *q.d.* on day 3 and 4, 8 mg *q.d.* on day 5 and 6, and 12 mg *q.d.* on day 7 and thereafter,

1 mg *q.d.* on day 1, 4 mg *q.d.* on day 2, 8 mg *q.d.* on day 3, and 12 mg *q.d.* on day 4 and thereafter, or

2 mg *q.d.* on day 1 and 2, 6 mg *q.d.* on day 3 and 4, and 12 mg *q.d.* on day 5 and thereafter, or

4 mg *q.d.* on day 1, 8 mg *q.d.* on day 2, 16 mg *q.d.* on day 3, and 24 mg *q.d.* on day 4 and thereafter, or

8 mg *q.d.* on day 1 and 2 and 24 mg *q.d.* on day 3 and thereafter.

According to yet another aspect of the invention, there is provided a R-P88, or a pharmaceutically acceptable salt thereof or an ester of R-P88 or a pharmaceutically acceptable salt of such ester for treatment of a psychiatric disorder selected from a group consisting of: schizophrenia, schizoaffective disorder, bipolar disorder, depression, major depression, psychotic episodes, autism, autism spectrum disorder, fragile X syndrome, and pervasive development disorder, titrated in accordance with the following increments:

1 mg twice daily, 2 mg twice daily, and 3 mg twice daily, to reach a maximum dose of 6 mg/day, or

1 mg twice daily, 2 mg twice daily, 3 mg twice daily, 4 mg twice daily, 5 mg twice daily and 6 mg twice daily, to reach a maximum dose of 12 mg/day, or

1 mg twice daily, 2 mg twice daily, 4 mg twice daily, 6 mg twice daily, 8 mg twice daily, to reach a maximum dose of 16 mg/day, or

1 mg twice daily, 4 mg twice daily, and 6 mg twice daily, to reach a maximum dose of 12 mg/day, or

2 mg twice daily and 6 mg twice daily, to reach a maximum dose of 12 mg/day.

According to still another aspect of the invention, there is provided a R-P88, or a pharmaceutically acceptable salt thereof or an ester of R-P88 or a pharmaceutically acceptable salt of such ester for treatment of a psychiatric disorder selected from a group consisting of: schizophrenia, schizoaffective disorder, bipolar disorder, depression, major depression, psychotic episodes, autism, autism spectrum disorder, fragile X syndrome, and pervasive development disorder, titrated in accordance with the following schedule:

1 mg b.i.d. on day 1, 2 mg b.i.d. on day 2, 3 mg b.i.d. on day 3 and thereafter or

1 mg b.i.d. on day 1, 2 mg b.i.d. on day 2, 3 mg b.i.d. on day 3, 4 mg b.i.d. on day 4, 5 mg b.i.d. on day 5, 6 mg b.i.d. on day 6 and thereafter or

1 mg b.i.d. on day 1, 2 mg b.i.d. on day 2, 4 mg b.i.d. on day 3, 6 mg b.i.d. on day 4, 8 mg b.i.d. on day 5 and thereafter.

According to one aspect of the invention, there is provided a pharmaceutical composition comprising R-P88 or a pharmaceutically acceptable salt thereof, or an ester of R-P88 or a pharmaceutically acceptable salt of an ester of R-P88 as the sole or primary active ingredient, and a pharmaceutically acceptable carrier, formulated for once daily administration at a dose of 12 mg.

The illustrative aspects of the present invention are designed to solve the problems herein described and other problems not discussed, which are discoverable by a skilled artisan.

Detailed Description of the Invention

There are three major metabolic pathways by which iloperidone is cleared in humans. Specifically, iloperidone is:

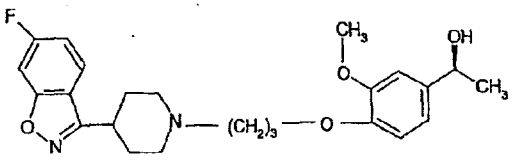
(1) converted to S-P88, which both (a) converts back to iloperidone, creating a dynamic equilibrium (P88 Iloperidone), and (b) is further metabolized and eliminated via the CYP2D6 pathway;

(2) metabolized via the CYP2D6 pathway to P95, which is then eliminated;

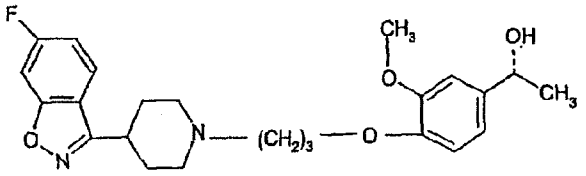
(3) metabolized via the CYP3A4 pathway to P89, which is then eliminated.

This invention relates to a method of treating a patient suffering from a disorder that is amenable to treatment with an antipsychotic, such as iloperidone, that comprises orally administering R-P88.

P88, by its chemical name, is known as 1-[4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanol and, alternatively, as 4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxy-□-methylbenzenemethanol. In humans, P-88 is found only in the S-enantiomeric form, which has the following structure:



However, P-88 can also be synthesized in its R enantiomeric form, which has the structure:



P88 and the S and R forms thereof are described in US Patent No. 7,977,356,

Although R-P88 is not found in humans, it has a receptor binding profile for relevant receptors that is similar to that of iloperidone and S-P88 in important ways and is therefore useful as an atypical antipsychotic.

In human plasma, *in vitro*, R-P88 converts back to iloperidone more slowly than does S-P88. This invention takes advantage of this unexpected finding by using R-P88 in place of iloperidone, or in place of racemic P88 or S-P88, in the treatment of conditions for which an atypical antipsychotic is indicated. Specifically, while iloperidone is administered twice per day at a maximum daily dose of 24 mg/day, R-P88 can be administered once per day or, at lower doses than iloperidone (or S-P88), twice per day

Thus, in an illustrative aspect of this invention, an effective amount of R-P88, or a salt or solvate thereof, is orally administered to a human suffering from a psychiatric disorder, e.g., schizophrenia, schizoaffective disorder, bipolar disorder (mania and/or depression), depression, major depression, psychotic

episodes, autism, autism spectrum disorder, fragile X syndrome , and pervasive developmental disorder. An effective amount is an amount that during the course of therapy will have a preventive or ameliorative effect on a psychiatric disorder, such as schizophrenia, or a symptom thereof, or of bipolar disorder. An effective amount, quantitatively, may vary depending upon, for example, the patient, the severity of the disorder or symptom being treated, and the route of administration.

It will be understood that the dosing protocol including the amount of R-P88 or salt or solvate thereof actually administered will be determined by a qualified healthcare professional in the light of the relevant circumstances including, for example, the condition to be treated, the chosen route of administration, the age, weight, and response of the individual patient, and the severity of the patient's symptoms. Patients should of course be monitored for possible adverse events, including, e.g., those adverse events associated with administration of iloperidone, e.g., QT prolongation and orthostatic hypotension.

q.d. Dosing Protocols

In an illustrative embodiment of the invention, the patient swallows a pharmaceutical composition comprising an effective amount of R-P88 once per day (*q.d.*), e.g., in an amount of 1 to 24 mg/day, 6 to 24 mg/day, 12 to 24 mg/day, 6 to 18 mg/day, or 6 to 12 mg/day, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 18, 20, 22, or 24 mg/day. At the initiation of treatment, the amount of R-P88 administered each day can be titrated upwards until a final dose, i.e., a maximum dose, is reached, similar to the way in which iloperidone is titrated

upon initiation of treatment. For example, a patient can be administered R-P88 once per day titrated in accordance with the following increments:

1 mg once daily, 2 mg once daily, 4 mg once daily, 6 mg once daily, 8 mg once daily, 10 mg once daily, 12 mg once daily, to reach a maximum, i.e., final, dose of 12 mg/day, or

2 mg once daily, 4 mg once daily, 8 mg once daily, 12 mg once daily, 16 mg once daily, 20 mg once daily, 24 mg once daily, to reach a maximum dose of 24 mg/day, or

2 mg once daily, 4 mg once daily, 8 mg once daily, 12 mg once daily, to reach a maximum dose of 12 mg/day.

In other illustrative *q.d.* dosing protocols of the invention, upward titration to a final dose may be made more quickly, e.g., more quickly than for iloperidone, or upward titration may be omitted entirely, with a final dose administered to a patient at the first administration. For example, in an illustrative embodiment of the invention, an abbreviated upward titration may include:

1 mg once daily, 4 mg once daily, 8 mg once daily, and 12 mg once daily, on days 1, 2, 3, and 4 to reach a maximum dose of 12 mg/day, or

2 mg once daily, 6 mg once daily, and 12 mg once daily, on days 1, 2, and 3 to reach a maximum dose of 12 mg/day, or

4 mg once daily, 8 mg once daily, 16 mg once daily, and 24 mg once daily, on days 1, 2, 3, and 4 to reach a maximum dose of 24 mg/day, or

8 mg once daily and 24 mg once daily, on days 1 and 2 to reach a maximum dose of 24 mg/day.

Thus, illustrative titration schedules for *q.d.* administration include, e.g.:

1 mg *q.d.* on day 1, 2 mg *q.d.*on day 2, 4 mg *q.d.*on day 3, 6 mg *q.d.*on day 4, 8 mg *q.d.*on day 5, 10 mg *q.d.*on day 6, and 12 mg *q.d.*on day 7 and thereafter, or

2 mg *q.d.*on day 1, 4 mg *q.d.*on day 2, 8 mg *q.d.*on day 3, 12 mg *q.d.*on day 4, 16 mg *q.d.*on day 5, 20 mg *q.d.*on day 6, and 24 mg *q.d.*on day 7 and thereafter, or

2 mg *q.d.*on days 1 and 2, 4 mg *q.d.*on days 3 and 4, 8 mg *q.d.*on days 5 and 6, and 12 mg *q.d.*on day 7 and thereafter,

1 mg *q.d.*on day 1, 4 mg *q.d.*on day 2, 8 mg *q.d.*on day 3, and 12 mg *q.d.*on day 4 and thereafter, or

2 mg *q.d.*on days 1 and 2, 6 mg *q.d.*on days 3 and 4, and 12 mg *q.d.*on day 5 and thereafter, or

4 mg *q.d.*on day 1, 8 mg *q.d.*on day 2, 16 mg *q.d.*on day 3, and 24 mg *q.d.*on day 4 and thereafter, or

8 mg *q.d.*on days 1 and 2 and 24 mg *q.d.*on day 3 and thereafter.

b.i.d. Dosing Protocols

In an illustrative embodiment of the invention, the patient swallows a pharmaceutical composition comprising an effective amount of R-P88 twice per day (*b.i.d.*) in the amount of 1 to 24 mg/day, e.g., 2 to 18 mg/day, e.g., 6 to 18 mg/day, e.g., 6 mg/day, 12 mg/day, 16 mg/day, or 18 mg/day. In such illustrative embodiment, at the initiation of treatment, the amount R-P88 administered each day can be titrated upwards until a final dose is reached. For example, a patient can be administered R-P88 once per day titrated in accordance with the following increments:

1 mg twice daily, 2 mg twice daily, and 3 mg twice daily, to reach a maximum dose of 6 mg/day, or

1 mg twice daily, 2 mg twice daily, 3 mg twice daily, 4 mg twice daily, 5 mg twice daily and 6 mg twice daily, to reach a maximum dose of 12 mg/day, or

1 mg twice daily, 2 mg twice daily, 4 mg twice daily, 6 mg twice daily, 8 mg twice daily, to reach a maximum dose of 16 mg/day, or

1 mg twice daily, 2 mg twice daily, 4 mg twice daily, 6 mg twice daily, 8 mg twice daily, 10 mg twice daily, and 12 mg twice daily, to reach a maximum dose of 24 mg/day.

In other illustrative *b.i.d.* dosing protocols of the invention, upward titration to a final dose may be made more quickly, e.g., more quickly than for iloperidone, or upward titration may be omitted entirely, with a final dose administered to a patient at the first administration. For example, in an illustrative embodiment of the invention, an abbreviated upward titration may include:

1 mg twice daily, 4 mg twice daily, and 6 mg twice daily, on days 1, 2, 3, and 4 to reach a maximum dose of 12 mg/day, or

2 mg twice daily and 6 mg twice daily, on days 1 and 2 to reach a maximum dose of 12 mg/day, or

1 mg twice daily, 4 mg twice daily, and 12 mg twice daily, on days 1, 2, and 3 to reach a maximum dose of 24 mg/day, or

2 mg twice daily, 6 mg twice daily, and 12 mg twice daily, on days 1, 2, and 3 to reach a maximum dose of 24 mg/day.

Thus, illustrative titration schedules for *b.i.d.* administration include, e.g.:

1 mg b.i.d. on day 1, 2 mg b.i.d. on day 2, 3 mg b.i.d. on day 3 and thereafter or

1 mg b.i.d. on day 1, 2 mg b.i.d. on day 2, 3 mg b.i.d. on day 3, 4 mg b.i.d. on day 4, 5 mg b.i.d. on day 5, 6 mg b.i.d. on day 6 and thereafter or

1 mg b.i.d. on day 1, 2 mg b.i.d. on day 2, 4 mg b.i.d. on day 3, 6 mg b.i.d. on day 4, 8 mg b.i.d. on day 5 and thereafter or

1 mg b.i.d. on day 1, 2 mg b.i.d. on day 2, 4 mg b.i.d. on day 3, 6 mg b.i.d. on day 4, 8 mg b.i.d. on day 5, 10 mg b.i.d. on day 6, 12 mg b.i.d. in day 7 and thereafter.

Pharmaceutical Compositions & Administration

For therapeutic or prophylactic use, R-P88 or a salt or solvate thereof will normally be administered as a pharmaceutical composition comprising R-P88 as the (or an) essential active pharmaceutical ingredient with a solid or liquid pharmaceutically acceptable carrier and, optionally, with pharmaceutically acceptable excipients employing standard and conventional techniques.

Pharmaceutical compositions useful in the practice of this invention include suitable dosage forms for oral administration. Thus, if a solid carrier is used, the preparation may be tableted, placed in a hard gelatin capsule in powder or pellet form, or in the form of a troche or lozenge. The solid carrier may contain conventional excipients such as binding agents, fillers, tableting lubricants, disintegrants, wetting agents and the like. The tablet may, if desired, be film coated by conventional techniques. If a liquid carrier is employed, the preparation may be in the form of a syrup, emulsion, soft gelatin capsule, sterile

vehicle for injection, an aqueous or non-aqueous liquid suspension, or may be a dry product for reconstitution with water or other suitable vehicle before use. Liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, wetting agents, non-aqueous vehicle (including edible oils), preservatives, as well as flavoring and/or coloring agents.

The pharmaceutical compositions may be prepared by conventional techniques appropriate to the desired preparation containing appropriate amounts of R-P88. *See*, for example, Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa., 17th edition, 1985.

Some examples of suitable carriers and diluents include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup, methyl cellulose, methyl- and propylhydroxybenzoates, talc, magnesium stearate and mineral oil. The formulations can additionally include lubricating agents, wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavoring agents. The compositions of the invention may be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient.

The compositions can be formulated in a unit dosage form. The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired prophylactic or therapeutic effect over the course of a treatment period, in association with the required pharmaceutical carrier. Such unit dosage form can be formulated with

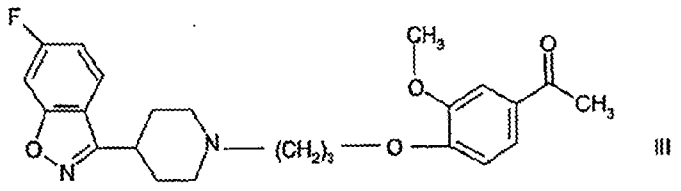
an amount of R-P88 required to administer R-P88 in accordance with any of the dosing protocols described in this specification or claims. For example, if a patient is being treated with R-P88, 6 mg/day b.i.d., each unit dosage form can comprise 6 mg of R-P88 and the patient would take one unit dose form in the morning and one in the afternoon or evening. Or, if a patient is being treated with R-P88, 12 mg/day b.i.d., each unit dosage form can comprise 6 mg of R-P88 and the patient would take two unit dosage forms in the morning and two in the afternoon or evening.

Methods for the administration of iloperidone directed toward, *inter alia*, eliminating or minimizing the prolongation of a corrected electrocardiographic QT (QTc) interval associated with increased concentrations of iloperidone or iloperidone derivatives are described in WO 2006/039663, WO 2008/121899, WO 2009/036056, WO 2009/036100, WO 2010/117931, WO 2010/117937, WO 2010/117941, WO 2010/117943, and WO2010/132866. Such methods can also be applied to R-P88 administered in accordance with the method of this invention.

The invention thus includes R-P88, as well as a pharmaceutical composition comprising R-P88, for the treatment of disorders that are amenable to treatment with an atypical antipsychotic in accordance with the dosing regiments generally and specifically described above.

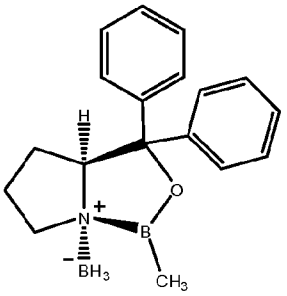
Synthesis

R-P88 can be synthesized by known methods, such as those disclosed in US Patent No. 7,977,356. As disclosed therein, R-P88 can be synthesized by the stereospecific reduction of iloperidone, which has formula III:



III

with an optically active borane complex of formula IV:

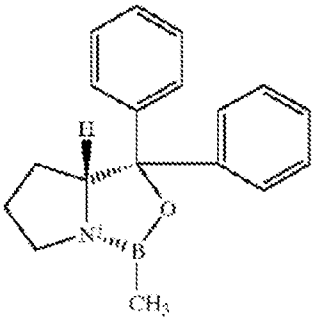


The reactions can be effected according to conventional methods. Working up the reaction mixtures and purification of the compounds thus obtained may be carried out in accordance with known procedures.

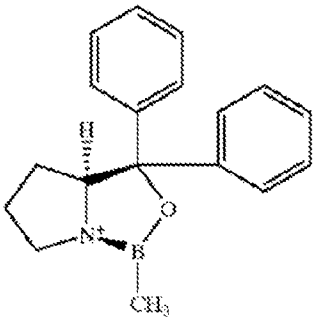
Acid addition salts may be produced from the free bases in known manner, and vice-versa. Suitable acid addition salts for use in accordance with the present invention include, for example, the hydrochloride.

The borane complexes used as starting materials can be produced from the corresponding compounds of formulas Va and Vb, according to known procedures.

Va



Vb



The starting materials of formulas Va and Vb are known.

Example

The aim of this study was to evaluate the potential conversion of (R)-P88 and (S)-P88 to iloperidone in human liver S9 fraction in the presence of NAD and NADP. A copy of the final report from this study, entitled, "InVitro Metabolism of (R)-P88 and (S)-P88 in Human Liver S9 Fraction," ("Final Report") is attached.

Three concentrations of (R)-P88 and (S)-P88 (1, 10 and 100 μM) were incubated with human liver S9 fractions in the presence of NAD and NADP. Under initial rate conditions, 13 concentrations of (R)-P88 and (S)-P88 (1 to 100 μM) were incubated with human liver S9 fractions to determine the Michaelis-Menten enzyme kinetic constants, Km and Vmax, for the formation of iloperidone.

The resultant data showed that S-P88 converted significantly more quickly to iloperidone than did R-P88. At some substrate concentrations, the

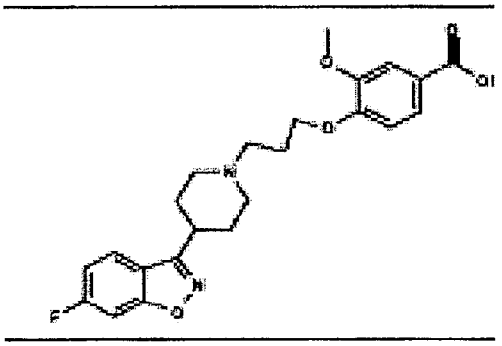
rate of R-P88 conversion to iloperidone was more than twice that of S-P88 to iloperidone. The data, which were statistically significant, are shown in the following table.

Substrate Conc. μ(μM)	**Mean Rate of Iloperidone Formation (pmol/min/mg protein)**		Difference Between Means	p value	95% Confidence Interval for Difference Between Means
	R-P88	**S-P88**			
1	**15.5**	**36.3**	20.8	<0.001	19.8 to 21.8
2	**29.8**	**62.1**	32.4	<0.001	23.5 to 41.2
4	**66.3**	**101**	34.9	0.002	22.3 to 47.6
6	**87.4**	**167**	79.9	<0.001	61.7 to 98.1
8	**126**	**183**	57.4	0.002	35.1 to 79.8
10	**158**	**271**	112	<0.001	104 to 121
12.5	**186**	**298**	112	<0.001	96.1 to 128
15	**211**	**340**	130	<0.001	117 to 143
20	**262**	**439**	176	<0.001	142 to 211
25	**307**	**553**	247	<0.001	207 to 287
50	**423**	**922**	499	<0.001	392 to 606
75	**491**	**1270**	776	<0.001	715 to 837
100	**521**	**1660**	1139	<0.001	954 to 1324

In addition, results of the experiments include that the conversion of (R)-P88 to iloperidone showed a slightly S-shaped direct plot and "hook"-shaped Eadie-Hofstee plot suggesting allosteric interactions.

In contrast, the conversion of (S)-P88 to iloperidone best fit a biphasic saturation enzyme model suggesting two enzymes contributing to the metabolism of (S)-P88, one high-affinity enzyme with normal saturation kinetics and one low affinity enzyme with linear (non-saturating) enzyme kinetics.

In addition, slower conversion of R-P88 to iloperidone is expected to result in decreased formation of P95, which has the following structure and chemical name:



4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxy-benzoic acid, and which has been implicated in episodes of orthostatic hypotension following initial administration of iloperidone.

R-P88 may form pharmaceutically acceptable salts. It may also form fatty acid esters, e.g., via the hydroxy group in the ethanolic moiety, and pharmaceutically acceptable salts thereof, such as described in US20070197595. This invention comprises use of such salts, esters, or salts of esters in place of or in addition to R-P88.

The foregoing description of various aspects of the invention has been presented for purposes of illustration and description. It is not intended to be exhaustive or to limit the invention to the precise form disclosed, and obviously, many modifications and variations are possible. Such modifications and variations that may be apparent to a person skilled in the art are intended to be included within the scope of the invention as defined by the accompanying claims.

Claims:

1. A pharmaceutical composition comprising R-P88 or a pharmaceutically acceptable salt thereof, or an ester of R-P88 or a pharmaceutically acceptable salt of an ester of R-P88 as the sole or primary active ingredient, and a pharmaceutically acceptable carrier, formulated for once daily administration at a dose of 12 mg.