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(54) **PHARMACEUTICAL FORMULATIONS CONTAINING DOPAMINE RECEPTOR LIGANDS**

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(57) **ABSTRACT**

The present invention relates to stable and bioavailable immediate release formulations comprising dopamine receptor ligands. Methods of treating various disorders by administering the formulations are also described.

5 Claims, No Drawings

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PHARMACEUTICAL FORMULATIONS CONTAINING DOPAMINE RECEPTOR LIGANDS

Matter enclosed in heavy brackets [ ] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue; a claim printed with strikethrough indicates that the claim was canceled, disclaimed, or held invalid by a prior post-patent action or proceeding.

REFERENCE TO RELATED APPLICATIONS

More than one reissue application has been filed for the reissue of U.S. Pat. No. 9,056,846. The reissue application numbers are 16/384,264 (the present application) filed on Apr. 15, 2019 and 15/598,971 filed on May 18, 2017 (now U.S. Pat. No. RE47,350).

This *is an* application *for reissue of U.S. Pat. No. 9,056,846, and is a continuation application of U.S. Ser. No. 15/598,971, filed May 18, 2017, which issued as U.S. Pat. No. RE47,350 on Apr. 16, 2019, and which is also a reissue application of U.S. application Ser. No. 13/653,576, filed Oct. 17, 2012, which issued as U.S. Pat. No. 9,056,846 on Jun. 16, 2015, and which* is a continuation of U.S. application Ser. No. 12/504,149 filed on Jul. 16, 2009*, which issued as U.S. Pat. No. 9,056,845 on Jun. 16, 2015,* and claims the benefit of U.S. Provisional Application No. 61/081,052, filed Jul. 16, 2008, all of which **[**is**]** *are* incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates to stable and bioavailable immediate release formulations comprising dopamine receptor ligands. Methods of treating various disorders by administering the formulations are also described.

BACKGROUND OF THE INVENTION

Solid oral drug compositions or preparations have various release profiles such as an immediate release profile as referenced by FDA guidelines ("Dissolution Testing of Immediate Release Solid Oral Dosage Forms", issued August/1997, Section IV-A) or an extended release profile as referenced by FDA Guidelines ("Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/InVivo Correlations", Food and Drug Administration, CDER, September 1997, Page 17). In the dissolution testing guideline for immediate release profiles, materials which dissolve at least 80% in the first 30 to 60 minutes in solution qualify as immediate release profiles. Therefore, immediate release solid dosage forms permit the release of most or all of the active ingredient over a short period of time, such as 60 minutes or less, and make rapid absorption of the drug possible.

Additional advantages of immediate release formulations include increased flexibility in drug administration by allowing the target drug to be administered either as multiples of lower strength formulations or as one higher strength formulation.

Food and Drug Administration guidelines (see, e.g., ICH Guideline Q3B, Revision 2, July 2006) provide limits for the amount of degradation product(s) that may be present in pharmaceutical formulations.

Maximum Daily Dose	Degradation Product Threshold
<10 mg	1.0% or 50 μg TDI, whichever is lower
10 mg-100 mg	0.5% or 200 μg TDI, whichever is lower
>100 mg-2 g	0.2% or 3 mg TDI, whichever is lower

TDI: Total daily intake

If the amount of degradation products exceeds the above thresholds, additional safety and toxicity studies may be required in accordance with the guidelines. To avoid the need for additional testing, it is therefore important to develop dosage forms that are stable over extended periods of time, and contain amounts of degradation product(s) within the FDA guidelines.

There is a need for stable dosage forms containing these compounds which comply with FDA degradation product guidelines. Applicants have now developed stable and bioavailable immediate release formulations containing (thio)-carbamoyl-cyclohexane derivatives. These formulations are disclosed herein.

SUMMARY OF THE INVENTION

In one embodiment, the present invention relates to (thio)-carbamoyl-cyclohexane derivatives, such as cariprazine (trans-1{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-3,3-dimethyl-urea) and pharmaceutically acceptable salts thereof, e.g., cariprazine hydrochloride that can be formulated into immediate release dosage forms in which the dosage forms have advantageous stability profiles and wherein the dosage forms preferably release the drug rapidly and are bioavailable.

In another embodiment, stable and bioavailable formulations comprising cariprazine or pharmaceutically acceptable salts thereof are described in which the amount of hydrolysis degradation product is less than about 1% w/w.

In yet another embodiment, stable and bioavailable formulations comprising cariprazine hydrochloride are described in which the amount of hydrolysis degradation product is less than about 1% w/w.

In additional embodiments, formulations containing from about 0.05 mg to about 15 mg cariprazine or pharmaceutically acceptable salts thereof are described wherein a single dose administration of the formulation provides an in vivo plasma profile comprising (i) a mean C_{max} of less than about 26.3 ng/mL, (ii) a mean $AUC_{0-\infty}$ of more than about 2 ng·hr/mL and (iii) a mean T_{max} of about 3 or more hours.

In another embodiment, a pharmaceutical formulation is described comprising:

(a) between about 0.5% and about 15% of trans-1{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-3,3-dimethyl-urea hydrochloride,

(b) between about 5% and about 95% of lactose monohydrate,

(c) between 0% and about 10% of talc,

(d) between 0% and about 5% of colloidal silicon dioxide,

(e) between 0% and about 15% of sodium starch glycolate,

(f) between 0% and about 15% of hydroxypropyl cellulose, and

(g) between about 0.1% and about 3% of magnesium stearate.

In yet another embodiment, a pharmaceutical formulation is described comprising:

(a) between about 0.5% and about 15% of trans-1{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-3,3-dimethyl-urea hydrochloride,

(b) between about 0.1% and about 20% of sodium carbonate,

(c) between 0% and about 10% of talc,

(d) between 0% and about 5% of colloidal silicon dioxide,

(e) between 0% and about 15% of sodium starch glycolate,

(f) between about 5% and about 95% of microcrystalline cellulose, and

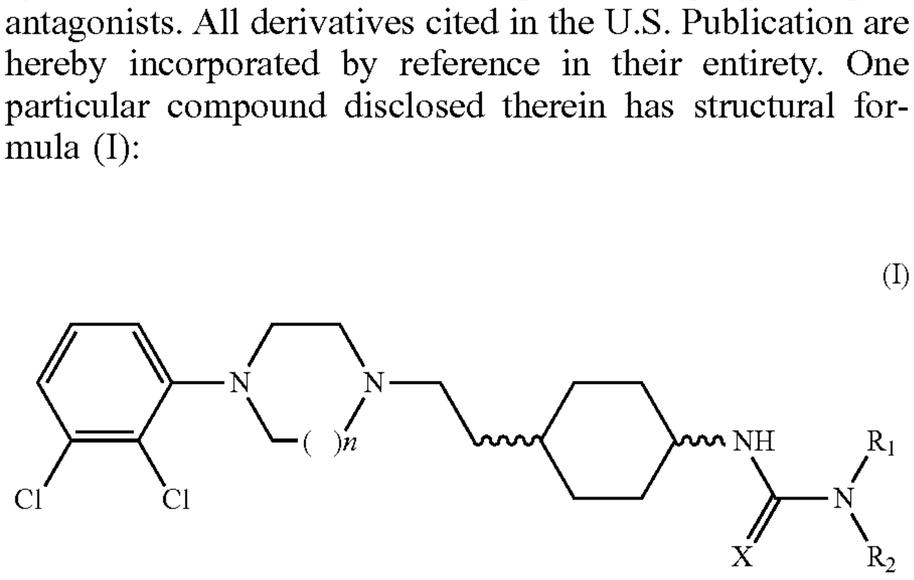
(g) between about 0.1% and about 3% of magnesium stearate.

In further embodiments, formulations comprising cariprazine hydrochloride are described in which the formulation releases the active ingredient at a rate of more than about 80% within about the first 60 minutes following administration of the formulation to a patient in need thereof.

In yet other embodiments, methods of treating conditions that require modulation of a dopamine receptor comprising administering to a patient in need thereof an effective amount of a formulation comprising cariprazine or pharmaceutically acceptable salts thereof are described in which the amount of hydrolysis degradation product is less than about 1% w/w.

DETAILED DESCRIPTION OF THE INVENTION

One embodiment of the present invention comprises trans-1{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-3,3-dimethyl-urea, or a pharmaceutically acceptable salt thereof, wherein the formulation comprises less than about 1% w/w trans-4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl-amine, or a pharmaceutically acceptable salt thereof. U.S. Patent Publication No. 2006/0229297 discloses (thio)-carbamoyl-cyclohexane derivatives as dopamine D_3/D_2 receptor antagonists. All derivatives cited in the U.S. Publication are hereby incorporated by reference in their entirety. One particular compound disclosed therein has structural formula (I):



wherein

R_1 and R_2 are each, independently, hydrogen, alkyl, alkenyl, aryl, cycloalkyl or aroyl,

or R_1 and R_2 form a heterocyclic ring with the adjacent nitrogen atom;

X is O or S;

n is 1 or 2;

and/or geometric isomers and/or stereoisomers and/or diastereomers and/or salts and/or hydrates and/or solvates thereof.

Compounds of formula (I) are orally active and very potent dopamine D_3/D_2 receptor antagonists, which bind with significantly higher potency to D_3 than D_2 receptors.

The compounds of formula (I) have been found to be hydrolytically unstable. For example, trans-1{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-3,3-dimethyl-urea hydrochloride (cariprazine hydrochloride) undergoes hydrolytic cleavage of the amide bond to form trans-4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl-amine dihydrochloride (De-BOC). Applicants have found that compounds of formula (I) undergo hydrolytic degradation when formulated with commonly used excipients (e.g., anhydrous dicalcium phosphate, microcrystalline cellulose containing 5% water). The formation of a degradation product such as De-BOC in a pharmaceutical formulation is detrimental to activity. Moreover, if the amount of degradation product exceeds FDA guidelines, additional safety and toxicology testing must be undertaken. Thus, it is important that stable and bioavailable formulations containing, for example, cariprazine and its salts, be developed, in which the amount of degradation product present falls within accepted FDA guidelines.

The preparation of stable and bioavailable dosage forms containing compounds of formula (I) is; however, not straightforward. For example, the use of low-moisture grade microcrystalline cellulose (e.g., Avicel PH 112), moisture absorbing/adsorbing agents (e.g., magnesium oxide) or chelating agents (e.g., ethylenediamaintetraacetic acid "EDTA") does not provide formulations with enhanced stability toward hydrolytic degradation product formation.

Applicants have surprisingly found that stable and bioavailable immediate release dosage forms comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof (e.g., cariprazine hydrochloride) can be prepared. The formulations exhibit enhanced stability with respect to degradation product formation, are highly bioavailable and release the active ingredient in the stomach environment, e.g. at pH 1-4.

In one aspect, stable formulations of the present invention may be prepared by controlling the solid-state microenvironmental pH of the formulation. Thus, in one embodiment, the present invention relates to pharmaceutical formulations (e.g., solid oral dosage forms) comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a compound that modulates the pH environment of the solid formulation (e.g., an alkaline or acidic buffering agent). Suitable buffering agents include, for example, organic compounds (e.g., triethylamine, arginine, diethanolamine, and meglumine), carbonates (e.g., sodium carbonate, lithium carbonate, potassium carbonate, magnesium carbonate) and bicarbonates (e.g., sodium bicarbonate, lithium bicarbonate, potassium bicarbonate, magnesium bicarbonate). An exemplary formulation comprises a compound of formula (I), or a pharmaceutically acceptable salt thereof (e.g., cariprazine hydrochloride), and sodium carbonate. In certain embodiments, the amount of the buffering agent (e.g., sodium carbonate) is between about 0.1% and about 50% w/w, for example, between about 1% and about 15% w/w. Suitable ratios of the compound of formula (I), or a pharmaceutically acceptable salt thereof to the buffering agent are, e.g., from about 1.2 to about 12.8. In certain embodiments, the microenvironmental pH of the formulation is more than about 6, for example, more than about 8, more than about 9, more than about 10.

Without wishing to be bound by theory, Applicants believe that raising the solid state microenvironmental pH of the formulation enhances stability of the active agent toward degradation by reducing ionization of the weakly basic drug and thereby inhibiting hydrolysis.

In another aspect, stable formulations may be prepared by formulating a compound of formula (I), or a pharmaceutically acceptable salt thereof, with an excipient having a low water activity (i.e., an excipient that has a low amount of free water that may be released to effect hydrolytic degradation of the active ingredient). Applicants surprisingly found that the total amount of water present within an excipient is not the controlling factor regarding hydrolytic degradation. Rather, it is the amount of water present within an excipient that is available to be released that is the controlling factor in reducing hydrolytic degradation. For example, cariprazine hydrochloride formulations containing Avicel PH 102 (a microcrystalline cellulose containing about 5% water) in the absence of a buffering agent (e.g., sodium carbonate) show substantial formation of De-Boc after storage at 1 month at 40° C. and 75% Relative Humidity (RH). In contrast, cariprazine hydrochloride formulations containing lactose monohydrate with about 5% water show non-detectable levels of De-Boc after storage for 6 months under similar storage conditions.

Thus, in another embodiment, the present invention relates to pharmaceutical formulations (e.g., solid oral dosage forms) comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, and an excipient selected from lactose monohydrate, pregelatinized starch (e.g., Starch 1500), mannitol, and dicalcium phosphate dihydrate. An exemplary formulation comprises a compound of formula (I), or a pharmaceutically acceptable salt thereof (e.g. cariprazine hydrochloride), and lactose monohydrate. A further exemplary formulation comprises a compound of formula (I), or a pharmaceutically acceptable salt thereof and dicalcium phosphate dihydrate. A further exemplary formulation comprises a compound of formula (I), or a pharmaceutically acceptable salt thereof and mannitol.

In certain embodiments of the compound of formula (I), when R_1 and/or R_2 represent alkyl, the alkyl moiety is a substituted or unsubstituted saturated hydrocarbon radical which may be straight-chain or branched-chain and contains about 1 to about 6 carbon atoms (e.g., 1 to 4 carbon atoms), and is optionally substituted with one or more C_{1-6} alkoxycarbonyl, aryl (e.g., phenyl) or (C_{1-6} alkoxycarbonyl)-C_{1-6} alkyl groups, or combinations thereof.

In additional embodiments, R_1 and R_2 form a heterocyclic ring with the adjacent nitrogen atom, which may be a saturated or unsaturated, optionally substituted, monocyclic or bicyclic ring, which may contain further heteroatoms selected from O, N, or S. For example, the heterocyclic ring can be pyrrolidine, piperazine, piperidine or morpholine.

In additional embodiments, when R_1 and/or R_2 represent alkenyl, the alkenyl moiety may have 2 to 7 carbon atoms and 1 to 3 double bonds.

In additional embodiments, when R_1 and/or R_2 represent aryl, the aryl moiety may be selected from an optionally substituted mono-, bi- or tricyclic aryl, such as, but not limited to, phenyl, naphthyl, fluorononyl, or anthraquinonyl group (e.g., phenyl or naphthyl). The aryl moiety may be substituted with one or more C_{1-6} alkoxy, trifluoro-C_{1-6} alkoxy, C_{1-6} alkoxycarbonyl, C_{1-6} alkanoyl, aryl, C_{1-6} alkylthio, halogen, cyano groups or combinations thereof.

In additional embodiments, when R_1 and/or R_2 represent cycloalkyl, the cycloalkyl moiety may be selected from an optionally substituted mono-, bi- or tricyclic cycloalkyl group, such as cyclohexyl or adamantyl.

In additional embodiments, when R_1 and/or R_2 represent aroyl the aryl moiety therein is as defined above, e.g., phenyl.

In exemplary embodiments, the compound of formula (I) is trans-1{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-3,3-dimethyl-urea, or a pharmaceutically acceptable salt thereof, for example, trans-1{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-3,3-dimethyl-urea hydrochloride

In additional embodiments, the present invention relates to formulations comprising trans-1{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-3,3-dimethyl-urea, or a pharmaceutically acceptable salt thereof in which the amount of De-BOC present is less than about 1% w/w, such as less than about 0.5% w/w. For example, in accordance with FDA guidelines, the amount of De-Boc present is less than 1% w/w (for dosage forms containing up to about 5 mg active agent), less than about 0.5% w/w (for dosage forms containing from about 5.1 mg to about 10 mg active agent), less than about 0.5% w/w (for dosage forms containing from about 10.1 mg to about 40 mg active agent).

Exemplary cariprazine hydrochloride formulations are set forth in Tables 1 and 2.

TABLE 1

Formulations Containing Lactose Monohydrate

Ingredient	Function	Range (% w/w)	Preferred Range (% w/w)	1st Exemplary Amount (% w/w)	2nd Exemplary Amount (% w/w)
Lactose monohydrate	Filler	5-95	75-95	89.0	85.9
Cariprazine hydrochloride	Active	0.5-15	0.8-4	0.8	3.9
Talc USP	Glidant	0-10	0-5	2.5	1.0
Collodial silicon dioxide	Glidant	0-5	0-2	1.0	2.5
Sodium starch glycolate	Disintegrant	0-15	2-8	4.0	4.0
Hydroxypropyl cellulose	Binder	0-15	2-8	2.0	2.0
Magnesium stearate	Lubricant	0.1-3.0	0.25-2.0	0.7	0.7
Total (Core Tablets)		100.0	100.0	100.0	100.0
Opadry Coating	Film	1-10	2-5	3.0	3.0
Total (Coated Tablets)				103.0	103.0

TABLE 2

Formulations Containing Sodium Carbonate

Ingredient	Function	Range (% w/w)	Preferred Range (% w/w)	Exemplaty Amount (% w/w)
Microcrystalline cellulose (Avicel PH102)	Filler	5-95	75-95	86.2
Cariprazine hydrochloride	Active	0.5-15	0.8-4	0.8
Talc USP	Glidant	0-10	0-5	3.0
Collodial silicon dioxide	Glidant	0-5	0-2	1.0
Sodium starch glycolate	Disintegrant	0-15	2-8	3.0
Magnesium stearate	Binder	0.1-3.0	0.25-2.0	1.0

TABLE 2-continued

Formulations Containing Sodium Carbonate				
Ingredient	Function	Range (% w/w)	Preferred Range (% w/w)	Exemplaty Amount (% w/w)
Sodium carbonate	pH Modifier	0.1-20	5-10	5.0
Total (Core Tablets)		100.0	100.0	100.0
Opadry	Film Coating	1-10	3.0	3.0
Total (Coated Tablets)			103.0	103.0

The plasma concentration of the immediate release formulations of the present invention have a time of maximum plasma concentration (T_{max}) in human patients ranging from between about 3 to about 6 hours, and an in vitro release rate of more than about 80% in about 60 minutes, more preferably in about 30 minutes.

The pharmaceutical formulations of the present invention allow for modification of the C_{max} by changing the strength of the formulation without substantially affecting the T_{max}, of the drug. The immediate release formulations described in the present invention provide the desired T_{max} without compromising the initial peak (C_{max}).

In a further aspect, the present invention relates to a formulation comprising from about 0.05 mg to about 15 mg trans-1{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-3,3-dimethyl-urea, or a pharmaceutically acceptable salt thereof, wherein the single dose administration of formulation provides an in vivo plasma profile comprising (i) a mean C_{max} of less than about 26.3 ng/mL, (ii) a mean $AUC_{0-\infty}$ of more than about 2 ng·hr/mL and (iii) a mean T_{max} of about 3 or more hours. For example, the formulation provides an in vivo plasma profile comprising (i) a mean C_{max} of less than about 22.5 ng/mL, (ii) a mean $AUC_{0-\infty}$ of more than about 3 ng·hr/mL and (iii) a mean T_{max} of about 3 or more hours.

In one embodiment, the formulation comprises about 0.1 mg trans-1{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]cyclohexyl}-3,3-dimethyl-urea, or a pharmaceutically acceptable salt thereof, wherein the single dose administration of formulation provides an in vivo plasma profile comprising (i) a mean C_{max} of less than about 0.2 ng/mL, (ii) a mean $AUC_{0-\infty}$ of more than about 2 ng·hr/mL and (iii) a mean T_{max} of about 3 or more hours. For example, the formulation provides an in vivo plasma profile comprising (i) a mean C_{max} of less than about 0.2 ng/mL, (ii) a mean $AUC_{0-\infty}$ of more than about 3 ng·hr/mL and (iii) a mean T_{max} of about 3 or more hours.

In one embodiment, the formulation comprises about 0.25 mg trans-1{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-3,3-dimethyl-urea, or a pharmaceutically acceptable salt thereof, wherein the single dose administration of formulation provides an in vivo plasma profile comprising (i) a mean C_{max} of less than about 0.5 ng/mL, (ii) a mean $AUC_{0-\infty}$ of more than about 5 ng·hr/mL and (iii) a mean T_{max} of about 3 or more hours. For example, the formulation provides an in vivo plasma profile comprising (i) a mean C_{max} of less than about 0.4 ng/mL, (ii) a mean $AUC_{0-\infty}$ of more than about 7 ng·hr/mL and (iii) a mean T_{max} of about 3 or more hours.

In one embodiment, the formulation comprises about 0.5 mg trans-1{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-3,3-dimethyl-urea, or a pharmaceutically acceptable salt thereof, wherein the single dose administration of formulation provides an in vivo plasma profile comprising (i) a mean C_{max} of less than about 0.9 ng/mL, (ii) a mean $AUC_{0-\infty}$ of more than about 10 ng·hr/mL and (iii) a mean T_{max} of about 3 or more hours. For example, the formulation provides an in vivo plasma profile comprising (i) a mean C_{max} of less than about 0.8 ng/mL, (ii) a mean $AUC_{0-\infty}$ of more than about 15 ng·hr/mL and (iii) a mean T_{max} of about 3 or more hours.

In one embodiment, the formulation comprises about 1 mg trans-1{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-3,3-dimethyl-urea, or a pharmaceutically acceptable salt thereof, wherein the single dose administration of formulation provides an in vivo plasma profile comprising (i) a mean C_{max} of less than about 1.8 ng/mL, (ii) a mean $AUC_{0-\infty}$ of more than about 20 ng·hr/mL and (iii) a mean T_{max} of about 3 or more hours. For example, the formulation provides an in vivo plasma profile comprising (i) a mean C_{max} of less than about 1.5 ng/mL, (ii) a mean $AUC_{0-\infty}$ of more than about 30 ng·hr/mL and (iii) a mean T_{max} of about 3 or more hours.

In one embodiment, the formulation comprises about 1.5 mg trans-1{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-3,3-dimethyl-urea, or a pharmaceutically acceptable salt thereof, wherein the single dose administration of formulation provides an in vivo plasma profile comprising (i) a mean C_{max} of less than about 2.7 ng/mL, (ii) a mean $AUC_{0-\infty}$ of more than about 30 ng·hr/mL and (iii) a mean T_{max} of about 3 or more hours. For example, the formulation provides an in vivo plasma profile comprising (i) a mean C_{max} of less than about 2.3 ng/mL, (ii) a mean $AUC_{0-\infty}$ of more than about 45 ng·hr/mL and (iii) a mean T_{max} of about 3 or more hours.

In one embodiment, the formulation comprises about 2 mg trans-1{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-3,3-dimethyl-urea, or a pharmaceutically acceptable salt thereof, wherein the single dose administration of formulation provides an in vivo plasma profile comprising (i) a mean C_{max} of less than about 3.5 ng/mL, (ii) a mean $AUC_{0-\infty}$ of more than about 40 ng·hr/mL and (iii) a mean T_{max} of about 3 or more hours. For example, the formulation provides an in vivo plasma profile comprising (i) a mean C_{max} of less than about 3.0 ng/mL, (ii) a mean $AUC_{0-\infty}$ of more than about 60 ng·hr/mL and (iii) a mean T_{max} of about 3 or more hours.

In one embodiment, the formulation comprises about 2.5 mg trans-1{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-3,3-dimethyl-urea, or a pharmaceutically acceptable salt thereof, wherein the single dose administration of formulation provides an in vivo plasma profile comprising (i) a mean C_{max} of less than about 4.4 ng/mL, (ii) a mean $AUC_{0-\infty}$ of more than about 50 ng·hr/mL and (iii) a mean T_{max} of about 3 or more hours. For example, the formulation provides an in vivo plasma profile comprising (i) a mean C_{max} of less than about 3.8 ng/mL, (ii) a mean $AUC_{0-\infty}$ of more than about 75 ng·hr/mL and (iii) a mean T_{max} of about 3 or more hours.

In one embodiment, the formulation comprises about 3 mg trans-1{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-3,3-dimethyl-urea, or a pharmaceutically acceptable salt thereof, wherein the single dose administration of formulation provides an in vivo plasma profile comprising (i) a mean C_{max} of less than about 5.3 ng/mL, (ii) a mean $AUC_{0-\infty}$ of more than about 60 ng·hr/mL and (iii) a

mean T_{max} of about 3 or more hours. For example, the formulation provides an in vivo plasma profile comprising (i) a mean C_{max} of less than about 4.5 ng/mL, (ii) a mean $AUC_{0-\infty}$ of more than about 90 ng·hr/mL and (iii) a mean T_{max} of about 3 or more hours.

In one embodiment, the formulation comprises about 4.5 mg trans-1{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-3,3-dimethyl-urea, or a pharmaceutically acceptable salt thereof, wherein the single dose administration of formulation provides an in vivo plasma profile comprising (i) a mean C_{max} of less than about 7.9 ng/mL, (ii) a mean $AUC_{0-\infty}$ of more than about 90 ng·hr/mL and (iii) a mean T_{max} of about 3 or more hours. For example, the formulation provides an in vivo plasma profile comprising (i) a mean C_{max} of less than about 6.8 ng/mL, (ii) a mean $AUC_{0-\infty}$ of more than about 135 ng·hr/mL and (iii) a mean T_{max} of about 3 or more hours.

In one embodiment, the formulation comprises about 5 mg trans-1{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-3,3-dimethyl-urea, or a pharmaceutically acceptable salt thereof, wherein the single dose administration of formulation provides an in vivo plasma profile comprising (i) a mean C_{max} of less than about 8.8 ng/mL, (ii) a mean $AUC_{0-\infty}$ of more than about 100 ng·hr/mL and (iii) a mean T_{max} of about 3 or more hours. For example, the formulation provides an in vivo plasma profile comprising (i) a mean C_{max} of less than about 7.5 ng/mL, (ii) a mean $AUC_{0-\infty}$ of more than about 150 ng·hr/mL and (iii) a mean T_{max} of about 3 or more hours.

In one embodiment, the formulation comprises about 6 mg trans-1{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-3,3-dimethyl-urea, or a pharmaceutically acceptable salt thereof, wherein the single dose administration of formulation provides an in vivo plasma profile comprising (i) a mean C_{max} of less than about 10.5 ng/mL, (ii) a mean $AUC_{0-\infty}$ of more than about 120 ng·hr/mL and (iii) a mean T_{max} of about 3 or more hours. For example, the formulation provides an in vivo plasma profile comprising (i) a mean C_{max} of less than about 9.0 ng/mL, (ii) a mean $AUC_{0-\infty}$ of more than about 180 ng·hr/mL and (iii) a mean T_{max} of about 3 or more hours.

In one embodiment, the formulation comprises about 7.5 mg trans-1{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-3,3-dimethyl-urea, or a pharmaceutically acceptable salt thereof, wherein the single dose administration of formulation provides an in vivo plasma profile comprising (i) a mean C_{max} of less than about 13.2 ng/mL, (ii) a mean $AUC_{0-\infty}$ of more than about 150 ng·hr/mL and (iii) a mean T_{max} of about 3 or more hours. For example, the formulation provides an in vivo plasma profile comprising (i) a mean C_{max} of less than about 11.3 ng/mL, (ii) a mean $AUC_{0-\infty}$ of more than about 225 ng·hr/mL and (iii) a mean T_{max} of about 3 or more hours.

In one embodiment, the formulation comprises about 9 mg trans-1{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-3,3-dimethyl-urea, or a pharmaceutically acceptable salt thereof, wherein the single dose administration of formulation provides an in vivo plasma profile comprising (i) a mean C_{max} of less than about 15.8 ng/mL, (ii) a mean $AUC_{0-\infty}$ of more than about 180 ng·hr/mL and (iii) a mean T_{max} of about 3 or more hours. For example, the formulation provides an in vivo plasma profile comprising (i) a mean C_{max} of less than about 13.5 ng/mL, (ii) a mean $AUC_{0-\infty}$ of more than about 270 ng·hr/mL and (iii) a mean T_{ma} of about 3 or more hours.

In one embodiment, the formulation comprises about 12.5 mg trans-1{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-3,3-dimethyl-urea, or a pharmaceutically acceptable salt thereof, wherein the single dose administration of formulation provides an in vivo plasma profile comprising (i) a mean C_{max} of less than about 21.9 ng/mL, (ii) a mean $AUC_{0-\infty}$ of more than about 250 ng·hr/mL and (iii) a mean T_{max} of about 3 or more hours. For example, the formulation provides an in vivo plasma profile comprising (i) a mean C_{max} of less than about 18.8 ng/mL, (ii) a mean $AUC_{0-\infty}$ of more than about 375 ng·hr/mL and (iii) a mean T_{max} of about 3 or more hours.

In one embodiment, the formulation comprises about 15 mg trans-1{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-3,3-dimethyl-urea, or a pharmaceutically acceptable salt thereof, wherein the single dose administration of formulation provides an in vivo plasma profile comprising (i) a mean C_{max} of less than about 26.3 ng/mL, (ii) a mean $AUC_{0-\infty}$ of more than about 300 ng·hr/mL and (iii) a mean T_{max} of about 3 or more hours. For example, the formulation provides an in vivo plasma profile comprising (i) a mean C_{max} of less than about 22.5 ng/mL, (ii) a mean $AUC_{0-\infty}$ of more than about 450 ng·hr/mL and (iii) a mean T_{max} of about 3 or more hours.

Pharmaceutically acceptable salts include those obtained by reacting the main compound, functioning as a base with an inorganic or organic acid to form a salt, for example, salts of hydrochloric acid, sulfuric acid, phosphoric acid, methane sulfonic acid, camphor sulfonic acid, oxalic acid, maleic acid, succinic acid, citric acid, formic acid, hydrobromic acid, benzoic acid, tartaric acid, fumaric acid, salicylic acid, mandelic acid, and carbonic acid. Pharmaceutically acceptable salts also include those in which the main compound functions as an acid and is reacted with an appropriate base to form, e.g., sodium, potassium, calcium, magnesium, ammonium, and choline salts. Those skilled in the art will further recognize that acid addition salts may be prepared by reaction of the compounds with the appropriate inorganic or organic acid via any of a number of known methods. Alternatively, alkali and alkaline earth metal salts can be prepared by reacting the compounds of the invention with the appropriate base via a variety of known methods.

The following are further examples of acid salts that can be obtained by reaction with inorganic or organic acids: acetates, adipates, alginates, citrates, aspartates, benzoates, benzenesulfonates, bisulfates, butyrates, camphorates, digluconates, cyclopentanepropionates, dodecylsulfates, ethanesulfonates, glucoheptanoates, glycerophosphates, hemisulfates, heptanoates, hexanoates, fumarates, hydrobromides, hydroiodides, 2-hydroxy-ethanesulfonates, lactates, maleates, methanesulfonates, nicotinates, 2-naphthalenesulfonates, oxalates, palmoates, pectinates, persulfates, 3-phenylpropionates, picrates, pivalates, propionates, succinates, tartrates, thiocyanates, tosylates, mesylates and undecanoates.

For example, the pharmaceutically acceptable salt can be a hydrochloride salt, a hydrobromide salt or a mesylate salt. In one embodiment, the pharmaceutically acceptable salt is a hydrochloride salt.

In another embodiment, the formulations of the present invention contain trans-1{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-3,3-dimethyl-urea hydrochloride.

In yet another embodiment, the present invention relates to a formulation comprising from about 0.05 mg to about 15 mg trans-1{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-3,3-dimethyl-urea hydrochloride, about 0.1 mg, about 0.25 mg, about 0.5 mg, about 1 mg, about 1.5 mg, about 2 mg, about 2.5 mg, about 3 mg, about 4.5 mg,

about 5 mg, about 6 mg, about 7.5 mg, about 9 mg, about 12.5 mg, or about 15 mg. In other embodiments, the formulation is administered in an amount which ranges between any two of the dosage amounts.

In yet another embodiment, the present invention relates to a formulation comprising from about 0.05 mg to about 15 mg trans-1{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-3,3-dimethyl-urea hydrochloride wherein the single dose administration of the formulation provides an in vivo plasma profile comprising (i) a mean C_{max} of less than about 26.3 ng/mL, (ii) a mean $AUC_{0-\infty}$ of more than about 2 ng·hr/mL and (iii) a mean T_{max} of about 3 or more hours. For example, the formulation provides an in vivo plasma profile comprising (i) a mean C_{max} of less than about 22.5 ng/mL, (ii) a mean $AUC_{0-\infty}$ of more than about 3 ng·hr/mL and (iii) a mean T_{max} of about 3 or more hours.

Some of the compounds useful in the formulations described herein may exist in different polymorphic forms. As known in the art, polymorphism is an ability of a compound to crystallize as more than one distinct crystalline or "polymorphic" species. The use of such polymorphs is within the scope of the present invention.

Some of the compounds useful in the formulations described herein may exist in different solvate forms. Solvates of the compounds of the invention may also form when solvent molecules are incorporated into the crystalline lattice structure of the compound molecule during the crystallization process. For example, suitable solvates include hydrates, e.g., monohydrates, dihydrates, sesquihydrates, and hemihydrates. The use of such solvates is within the scope of the present invention.

Dosage Forms

Numerous standard references are available that describe procedures for preparing various formulations suitable for administering the compounds according to the invention. Examples of potential formulations and preparations are contained, for example, in the Handbook of Pharmaceutical Excipients, American Pharmaceutical Association (current edition); Pharmaceutical Dosage Forms: Tablets (Lieberman, Lachman and Schwartz, editors) current edition, published by Marcel Dekker, Inc., as well as Remington's Pharmaceutical Sciences (Arthur Osol, editor), 1553-1593 (current edition).

The mode of administration and dosage forms is closely related to the therapeutic amounts of the compounds or formulations which are desirable and efficacious for the given treatment application.

Suitable dosage forms include, but are not limited to oral, rectal, sub-lingual, mucosal, nasal, ophthalmic, subcutaneous, intramuscular, intravenous, transdermal, spinal, intrathecal, intra-articular, intra-arterial, sub-arachinoid, bronchial, lymphatic, and intra-uterille administration, and other dosage forms for systemic delivery of active ingredients. Formulations suitable for oral administration are preferred (e.g., tablets, capsules).

To prepare such pharmaceutical dosage forms, the active ingredient, is typically mixed with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration.

In preparing the formulations in oral dosage form, any of the usual pharmaceutical media may be employed. Thus, for liquid oral preparations, such as, for example, suspensions, elixirs and solutions, suitable carriers and additives include water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like. For solid oral preparations such as, for example, powders, capsules and tablets, suitable carriers and additives include starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like. Suitable carriesrs and additives include, for example, sucrose, mannitol, polyethylene glycol, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, sodium lauryl sulphate, chremophor, tweens, spans, pluronics, microcrystalline cellulose, calcium phosphate, talc, fumed silica, hydroxypropyl methyl cellulose, wax, and fatty acids, etc.

Due to their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form. If desired, tablets may be sugar coated or enteric coated by standard techniques.

For parenteral formulations, the carrier will usually comprise sterile water, though other ingredients, for example, ingredients that aid solubility or for preservation, may be included. Injectable solutions may also be prepared in which case appropriate stabilizing agents may be employed.

In some applications, it may be advantageous to utilize the active agent in a "vectorized" form, such as by encapsulation of the active agent in a liposome or other encapsulant medium, or by fixation of the active agent, e.g., by covalent bonding, chelation, or associative coordination, on a suitable biomolecule, such as those selected from proteins, lipoproteins, glycoproteins, and polysaccharides.

Treatment methods of the present invention using formulations suitable for oral administration may be presented as discrete units such as capsules, cachets, tablets, or lozenges, each comprising a predetermined amount of the active ingredient as a powder or granules. Optionally, a suspension in an aqueous liquor or a non-aqueous liquid may be employed, such as a syrup, an elixir, an emulsion, or a draught.

A tablet may be made by compression or molding, or wet granulation, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine, with the active compound being in a free-flowing form such as a powder or granules which optionally is mixed with, for example, a binder, disintegrant, lubricant, inert diluent, surface active agent, or discharging agent. Molded tablets comprised of a mixture of the powdered active compound with a suitable carrier may be made by molding in a suitable machine.

A syrup may be made by adding the active compound to a concentrated aqueous solution of a sugar, for example sucrose, to which may also be added any accessory ingredient(s). Such accessory ingredient(s) may include flavorings, suitable preservative, agents to retard crystallization of the sugar, and agents to increase the solubility of any other ingredient, such as a polyhydroxy alcohol, for example glycerol or sorbitol.

Formulations suitable for parenteral administration usually comprise a sterile aqueous preparation of the active compound, which preferably is isotonic with the blood of the recipient (e.g., physiological saline solution). Such formulations may include suspending agents and thickening agents and liposomes or other microparticulate systems which are designed to target the compound to blood components or one or more organs. The formulations may be presented in unit-dose or multi-dose form.

Parenteral administration may comprise any suitable form of systemic delivery or delivery directly to the CNS. Administration may for example be intravenous, intra-arterial, intrathecal, intramuscular, subcutaneous, intramuscular, intra-abdominal (e.g., intraperitoneal), etc., and may be

effected by infusion pumps (external or implantable) or any other suitable means appropriate to the desired administration modality.

Nasal and other mucosal spray formulations (e.g. inhalable forms) can comprise purified aqueous solutions of the active compounds with preservative agents and isotonic agents. Such formulations are preferably adjusted to a pH and isotonic state compatible with the nasal or other mucous membranes. Alternatively, they can be in the form of finely divided solid powders suspended in a gas carrier. Such formulations may be delivered by any suitable means or method, e.g., by nebulizer, atomizer, metered dose inhaler, or the like.

Formulations for rectal administration may be presented as a suppository with a suitable carrier such as cocoa butter, hydrogenated fats, or hydrogenated fatty carboxylic acids.

Transdermal formulations may be prepared by incorporating the active agent in a thixotropic or gelatinous carrier such as a cellulosic medium, e.g., methyl cellulose or hydroxyethyl cellulose, with the resulting formulation then being packed in a transdermal device adapted to be secured in dermal contact with the skin of a wearer.

In addition to the aforementioned ingredients, formulations of this invention may further include one or more accessory ingredient(s) selected from diluents, buffers, flavoring agents, binders, disintegrants, surface active agents, thickeners, lubricants, preservatives (including antioxidants), and the like.

Dosages

The active ingredient present in the formulation can normally be administered in a combined daily dosage regimen (for an adult patient) of, for example, between about 0.05 mg and about 50 mg, between about 0.1 mg and about 20 mg, between about 0.1 mg and about 15 mg, between about 0.1 mg and about 12.5 mg.

In certain embodiments, the pharmaceutical formulation includes about 0.05 mg, about 0.1 mg, about 0.2 mg, about 0.25 mg, about 0.3 mg, about 0.4 mg, about 0.5 mg, about 0.75 mg, about 1 mg, about 1.5 mg, about 2 mg, about 2.5 mg, about 3 mg, about 3.5 mg, about 4 mg, about 4.5 mg, about 5 mg, about 5.5 mg, about 6 mg, about 6.5 mg, about 7 mg, about 7.5 mg, about 8 mg, about 8.5 mg, about 9 mg, about 9.5 mg, about 10 mg, about 10.5 mg, about 11 mg, about 11.5 mg, about 12.0 mg, about 12.5 mg, about 13.0 mg, about 13.5 mg, about 14.0 mg, about 14.5 mg or about 15.0 mg of active ingredient, such as trans-1{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-3,3-dimethyl-urea, or pharmaceutically acceptable salt thereof (e.g., trans-1{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-3,3-dimethyl-urea hydrochloride).

For example, the pharmaceutical formulation includes about 0.1 mg, about 0.25 mg, about 0.5 mg, about 1 mg, about 1.5 mg, about 2 mg, about 2.5 mg, about 3 mg, about 5 mg, about 6 mg, about 7.5 mg, about 9 mg, about 12.5 mg or about 15.0 mg of active ingredient, such as trans-1{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-3,3-dimethyl-urea, or pharmaceutically acceptable salt thereof (e.g., trans-1{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-3,3-dimethyl-urea hydrochloride).

In yet further embodiments, the active ingredient (e.g., trans-1{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-3,3-dimethyl-urea, or a pharmaceutically acceptable salt thereof), is present in the formulation in an amount which ranges between any two of these dosage amounts (e.g., between about 0.1 mg and about 15 mg, between about 0.5 mg and about 12.5 mg, between about 1.5 mg and about 6 mg, between about 6 mg and about 12.5 mg).

The desired dose may be administered as one or more daily sub dose(s) administered at appropriate time intervals throughout the day, or alternatively, in a single dose, for example, for morning or evening administration. For example, the daily dosage may be divided into one, into two, into three, or into four divided daily doses.

The duration of the treatment may be decades, years, months, weeks, or days, as long as the benefits persist.

Methods of Treatment

The present invention further provides methods for treating conditions that requires modulation of a dopamine receptor, particularly, a dopamine D_3 and/or D_2 receptor. In further embodiments, the present invention provides methods for treating a condition that requires modulation of a dopamine D3 and/or D_2 receptor utilizing one or more formulations of the present invention.

Dysfunction of the dopaminergic neurotransmitter system is involved in the pathology of several neuropsychiatric and neurodegenerative disorders, such as schizophrenia, drug abuse and Parkinson's disease, respectively. The effect of dopamine is mediated via at least five distinct dopamine receptors belonging to the D_1-(D_1, D_5) or the D_2-(D_2, D_3, D_4) families. D_3 receptors have been shown to have characteristic distribution in the cerebral dopaminergic systems. Namely, high densities were found in certain limbic structures, such as nucleus accumbens and islands of Calleja. Therefore, preferential targeting of the D_3 receptors may be a promising approach for more selective modulation of dopaminergic functions and consequently for successful therapeutic intervention in several abnormalities, such as schizophrenia, emotional or cognitive dysfunctions and addiction (see, e.g., Sokoloff, P. et al.: Nature, 1990, 347, 146; Schwartz, J. C., et al.: Clin. Neuropharmacol. 1993, 16, 295; Levant, B.: Pharmacol. Rev. 1997, 49, 231), addiction (see, e.g., Pilla, C. et al.: Nature 1999, 400, 371) and Parkinson's disease (see, e.g., Levant, B. et al.: CNS Drugs 1999, 12, 391) or pain (see, e.g., Levant, B. et al.: Neurosci. Lett. 2001, 303, 9).

The dopamine D_2 receptors are widely distributed in the brain and are known to be involved in numerous physiological functions and pathological states. D_2 antagonists are widely used drugs as antipsychotics, for example. However, it is also well known that massive antagonism of the D_2 receptors leads to unwanted side-effects such as extrapyramidal motor symptoms, psychomotor sedation or cognitive disturbances. These side effects seriously restrict the therapeutic utilization of D_2 antagonist compounds. (Wong A. H. C. et al., Neurosci. Biobehav. Rev., 27, 269, 2003)

In a further aspect, the present invention provides methods for treating conditions which require preferential modulation of dopamine D_3 and/or D_2 receptors, for example psychoses (e.g. schizophrenia, schizo-affective disorders), cognitive impairment accompanying schizophrenia, mild-to-moderate cognitive deficits, dementia, psychotic states associated with dementia, psychotic depression, mania, acute mania, paranoid and delusional disorders, dyskinetic disorders such as Parkinson's disease, neuroleptic induced parkinsonism, tardive dyskinesia, eating disorders (e.g. bulimia nervosa), attention deficit disorders, hyperactivity disorders in children, depression, anxiety, sexual dysfunction, sleep disorders, emesis, aggression, autism and drug abuse, which comprises administering to a subject in need thereof an effective amount of a compound and/or formulation of the present invention.

A preferred use for D_3/D_2 antagonists with D_3 preference according to the present invention is in the treatment of schizophrenia, schizo-affective disorders, cognitive impairment accompanying schizophrenia, mild-to-moderate cognitive deficits, dementia, psychotic states associated with dementia, psychotic depression, mania, paranoid and delusional disorders, dyskinetic disorders such as Parkinson's disease, neuroleptic induced parkinsonism, depression, anxiety, drug abuse (e.g. cocaine abuse).

The particular combination of the two receptor-actions described above allows the simultaneous manifestation of the beneficial actions of both the D_3 antagonism (e.g. cognitive enhancer effect, inhibition of extrapyramidal motor symptoms, inhibitory action on drug abuse) and the D_2 antagonism (e.g. antipsychotic effect). Furthermore, the same combination surprisingly results in canceling out the disadvantageous features of D_2 antagonism (e.g. extrapyramidal symptoms, psychomotor sedation, cognitive disturbances).

In exemplary embodiments, the present invention relates to methods of treating schizophrenia (e.g., positive symptoms of schizophrenia, negative symptoms of schizophrenia). In another embodiment, the present invention relates to methods of treating cognitive defects associated with schizophrenia.

In another embodiment, the present invention relates to methods of treating acute mania.

In yet another embodiment, the present invention relates to methods of treating bipolar disorder.

DEFINITIONS

The term "pharmaceutically acceptable" means biologically or pharmacologically compatible for in vivo use in animals or humans, and preferably means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans.

The term "schizophrenia" is intended to include the group of mental disorders characterized by disruptions in thinking and perception, and includes schizophrenia (and all its subtypes; paranoid, catatonic, disorganized, residual, undifferentiated) and other psychotic disorders (as per Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition, Washington, D.C. (1994): American Psychiatric Association, or The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines, Geneva (1992): World Health Organization) such as schizophreniform and schizoaffective disorders, brief psychotic disorder, etc.

In a clinical evaluation, schizophrenia is commonly marked by "positive symptoms" such as hallucinations (especially auditory hallucination which are usually experienced as voices), disorganized thought processes and delusions as well as "negative symptoms" which include affective flattening, alogia, avolition, and anhedonia.

The term "the negative symptoms of schizophrenia" refer to a class of symptoms of schizophrenia which can be considered to reflect a 'loss' in functional, directed thought or activity. Negative symptoms of schizophrenia are well known in the art, and include affective flattening (characterized by, for example, an immobile and/or unresponsive facial expression, poor eye contact and reduced body language), alogia ('poverty of speech' or brief, laconic and/or empty replies), avolition (characterized by a reduced or absent ability to initiate and carry out goal-directed activities), anhedonia (loss of interest or pleasure), asocialty (reduced social drive and interaction), apathy and other negative symptoms known to those of skill in the art. The negative symptoms of schizophrenia may be assessed using any methodology known in the art including, but not limited to, the Brief Psychiatric Rating Scale (BPRS), and the Positive and Negative Symptom Scale (PANSS). The BPRS and PANSS have subscales or factors that can be used to measure negative symptoms. Other scales have been designed to address specifically negative symptoms: For example the Scale for the Assessment of Negative Symptoms (SANS), the Negative Symptoms Assessment (NSA) and the Schedule for the Deficit Syndrome (SDS). Subscales of the BPRS and PANSS may also be used to assess positive symptoms, although methods for specifically assessing positive symptoms are also available (e.g., the Scale for the Assessment of Positive Symptoms, or SAPS).

The terms "cognitive impairment associated with schizophrenia" and "cognitive defects associated with schizophrenia" refers to cognitive deficits in schizophrenia patients. Cognitive impairment in schizophrenia is a core feature of the illness (i.e. not a result of treatment or clinical symptoms). Cognitive deficits include, but are not limited to deficits of attention/vigilance, working memory, verbal learning and memory, visuospatial memory, reasoning/problem solving and social cognition. There are numerous neuropsychological tests used to measure cognitive deficits in schizophrenia, such as the Wisconsin Card Sorting Test (WCST).

The terms "treat," "treatment," and "treating" refer to one or more of the following: relieving or alleviating at least one symptom of a disorder in a subject; relieving or alleviating the intensity and/or duration of a manifestation of a disorder experienced by a subject; and arresting, delaying the onset (i.e., the period prior to clinical manifestation of a disorder) and/or reducing the risk of developing or worsening a disorder.

An "effective amount" means the amount of a formulation according to the invention that, when administered to a patient for treating a state, disorder or condition is sufficient to effect such treatment. The "effective amount" will vary depending on the active ingredient, the state, disorder, or condition to be treated and its severity, and the age, weight, physical condition and responsiveness of the mammal to be treated.

The term "therapeutically effective" applied to dose or amount refers to that quantity of a compound or pharmaceutical formulation that is sufficient to result in a desired activity upon administration to a mammal in need thereof. As used herein with respect to the pharmaceutical formulations comprising trans-1{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-3,3-dimethyl-urea, or a pharmaceutically acceptable salt thereof, e.g., trans-1{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-3,3-dimethyl-urea hydrochloride, the term "therapeutically effective amount/dose" refers to the amount/dose of the compound that, when combined, is sufficient to produce an effective response upon administration to a mammal.

A subject or patient in whom administration of the therapeutic compound is an effective therapeutic regimen for a disease or disorder is preferably a human, but can be any animal, including a laboratory animal in the context of a trial or screening or activity experiment. Thus, as can be readily appreciated by one of ordinary skill in the art, the methods, compounds and formulations of the present invention are particularly suited to administration to any animal, particularly a mammal, and including, but by no means limited to,

humans, domestic animals, such as feline or canine subjects, farm animals, such as but not limited to bovine, equine, caprine, ovine, and porcine subjects, wild animals (whether in the wild or in a zoological garden), research animals, such as mice, rats, rabbits, goats, sheep, pigs, dogs, cats, etc., avian species, such as chickens, turkeys, songbirds, etc., i.e., for veterinary medical use.

The term "about" or "approximately" means within an acceptable error range for the particular value as determined by one of ordinary skill in the art, which will depend in part on how the value is measured or determined, i.e., the limitations of the measurement system. For example, "about" can mean within 1 or more than 1 standard deviations, per practice in the art. Alternatively, "about" with respect to the formulations can mean plus or minus a range of up to 20%, preferably up to 10%, more preferably up to 5%.

The pharmacokinetic parameters described herein include area under the plasma concentration-time curve (AUC_{0-t} and $AUC_{0-\infty}$), maximum plasma concentration (C_{max}), time of maximum plasma concentration (T_{max}) and terminal elimination half-life ($T_{1/2}$). The time of maximum concentration, T_{max}, is determined as the time corresponding to C_{max}. Area under the plasma concentration-time curve up to the time corresponding to the last measurable concentration (AUC_{0-t}) is calculated by numerical integration using the linear trapezoidal rule as follows:

$$AUC_{0-t} = \sum_{i=2}^{n} 0.5 \cdot (C_i + C_{i-1}) \cdot (t_i - t_{i-1}) \quad \text{Eq. 1}$$

where C_i is the plasma memantine concentrations at the corresponding sampling time point t_i and n is the number of time points up to and including the last quantifiable concentration.

The terminal half-life ($T_{1/2}$) is calculated using the following equation:

$$T_{1/2} = \frac{0.693}{\lambda_z} \quad \text{Eq. 2}$$

where λ_z is the terminal elimination rate constant.

The area under the plasma concentration-time curve from time zero to infinity is calculated according to the following equation:

$$AUC_{0-\infty} = AUC_{0-t} + \frac{C_{last}}{\lambda_z} \quad \text{Eq. 3}$$

where C_{last} is the last measurable concentration.

EXAMPLES

The following examples are merely illustrative of the present invention and should not be construed as limiting the scope of the invention in any way as many variations and equivalents that are encompassed by the present invention will become apparent to those skilled in the art upon reading the present disclosure.

Avicel PH102 is a microcrystalline cellulose that may be obtained from FMC Biopolymer (Philadelphia, Pa.). Avicel PH 112 is a low moisture microcrystalline cellulose that may be obtained from FMC Biopolymer (Philadelphia, Pa.). Aerosil 200VV is a fumed silica that may be obtained from Evonik Industries/Degussa (Parsippany, N.J.). Prosolv SMC C90 is a microcrystalline cellulose that may be obtained from JRS Pharma (Paterson, N.Y.). Starch 1500 and Starcap 1500 are co-processed starches that may be obtained from Colorcon (West Point, Pa.). Starlac (a mixture of 85% lactose monohydrate and 15% maize starch) may be obtained from Roquette Pharma (Keokuk, Iowa). Syloid 63FP is a silica gel that may be obtained from Davison Chemical Division of W. R. Grace & Co. (Baltimore, Md.).

Dissolution rates were measured using a USP Apparatus II (paddle) with 500 ml of 0.01N HCl containing 0.25% polysorbate 80.

Example 1

Preparation of a Capsule Formulations Containing Cariprazine Hydrochloride

Example 1A

Capsules containing cariprazine hydrochloride and anhydrous calcium hydrogen phosphate were prepared according to Table 3.

TABLE 3

Composition of Capsule Formulations

	Amount (% w/w)		
Ingredient	Capsule I (0.5 mg)*	Capsule II (2.5 mg)*	Capsule III (12.5 mg)*
Cariprazine hydrochloride	0.5	2.7	13.6
Microcrystalline cellulose	59.5	58.2	51.7
Calcium hydrogen phosphate, anhydrous	40.0	39.1	34.7
Total	100.0	100.0	100.0

*amount of cariprazine free base

The microcrystalline cellulose (Avicel PH 102) and anhydrous calcium hydrogen phosphate were sieved together through a sieve of 0.80 mm. The final powder was blended for 2 minutes in a high-shear mixer. The empty capsule shells were filled with the powder mixture using a manual capsule filling machine. The bulk filled capsules were then manually packaged into glass vials.

The stability of the capsule formulations (at 40° C. and 75% RH) is shown in Table 4.

TABLE 4

Formulation Stability

	Amount of De-BOC (% w/w)		
Time	Capsule I	Capsule II	Capsule III
Initial	<0.02	<0.02	<0.02
1 Month	0.089	<0.02	<0.02
2 Months	0.160	0.064	<0.02
3 Months	0.199	0.076	<0.02
6 Months	Not Determined	0.100	<0.02

High levels of an additional degradation product were observed at 3 months for Capsule I.

Example 1B

Capsules containing cariprazine hydrochloride and pregelatinized starch were prepared according to Table 5:

TABLE 5

Composition of Capsule Formulations

Ingredient	Amount (% w/w) Capsule I (0.5 mg)*	Capsule II (1.5 mg)*	Capsule III (6.0 mg)*
Cariprazine hydrochloride	0.545	1.635	6.54
Pregelatinized Starch	98.455	97.365	92.46
Magnesium stearate	1.000	1.000	1.000
Total	100.0	100.0	100.0

*amount of cariprazine free base

The pregelatinized starch and cariprazine were sieved through a #20 sieve and mixed in a V-shell blender for 20 minutes by 5 step geometric mixing using an Intensifier bar in the final step. The magnesium stearate was sieved through #20 screen, added and the blend mixed for further 2 minutes. The final blend was then filled into capsules using a MG2 Futura Encapsulation machine. The capsules were packed into HDPE bottles and induction sealed.

The stability of the capsule formulations (at 40° C. and 75% RH) in a HDPE bottle, induction sealed with no dessicant is shown in Table 6.

TABLE 6

Formulation Stability

Time	Amount of De-BOC (% w/w) Capsule I	Capsule II	Capsule III
Initial	Not Detected	Not Detected	Not Detected
1 Month	Not Detected	Not Detected	Not Detected
2 Months	0.061	0.070	Not Detected
3 Months	0.093	0.075	Not Detected
6 Months	0.159	0.106	Not Detected

Not detected means <0.05% w/w or below the limit of quantitation.

The dissolution rates for Capsules II and III is shown in Table 7.

TABLE 7

Dissolution Rates

Time (mins)	% Dissolved Capsule II	Capsule III
0	0	0
15	97	97
20	97	98
45	95	99
60	97	99

Example 1C

Capsules containing cariprazine hydrochloride, Starlac (a combination of 85% lactose monohydrate and 15% starch) were prepared according to Table 8.

TABLE 8

Composition of Capsule Formulation

Ingredient	Amount (% w/w) Capsule I (0.5 mg)*
Cariprazine hydrochloride	0.545
Lactose monohydrate, starch (Starlac)	98.455
Magnesium stearate	1.000
Total	100.0

*amount of cariprazine free base

The Starlac and cariprazine were sieved through a #20 sieve and mixed in a V-shell blender for 20 minutes by 5 step geometric mixing using an Intensifier bar in the final step. The magnesium stearate was sieved through #20 screen, added and the blend mixed for further 2 minutes. The final blend was then filled into capsules using a MG2 Futura Encapsulation machine. The capsules were packed into HDPE bottles and induction sealed.

The stability of the capsule formulations (at 40° C. and 75% RH)) in a HDPE bottle, induction sealed with no dessicant is shown in Table 9.

TABLE 9

Formulation Stability

Time	Amount of De-BOC (% w/w) Capsule I
Initial	Not Detected
2 weeks	Not Detected
1 Month	Not Detected
2 Months	Not Detected
3 Months	Not Detected

Example 1D

Capsules containing cariprazine hydrochloride and mannitol were prepared according to Table 10:

TABLE 10

Composition of Capsule Formulation

Ingredient	Amount (% w/w) Capsule 1(0.5 mg)*
Cariprazine hydrochloride	0.545
Mannitol	98.455
Magnesium stearate	1.000
Total	100.0

*amount of cariprazine free base

The mannitol and cariprazine were sieved through a #20 sieve and mixed in a V-shell blender for 20 minutes by 5 step geometric mixing using an Intensifier bar in the final step. The magnesium stearate was sieved through #20 screen, added and the blend mixed for further 2 minutes. The final blend was then filled into capsules using a MG2 Futura

Encapsulation machine. The capsules were packed into HDPE bottles and induction sealed.

The stability of the capsule formulations (at 40° C. and 75% RH) in a HDPE bottle, induction sealed with no dessicant is shown in Table 11.

TABLE 11

Formulation Stability

Time	Amount of De-BOC (% w/w) Capsule I
Initial	Not Detected
2 weeks	Not Detected
1 Month	Not Detected
2 Months	Not Detected
3 Months	0.105

Example 1E

Capsules containing cariprazine hydrochloride and lactose monohydrate were prepared according to Table 12:

TABLE 12

Composition of Capsule Formulation

Ingredient	Amount (% w/w) Capsule I (0.5 mg)*
Cariprazine hydrochloride	0.545
Lactose monohydrate	98.455
Magnesium stearate	1.000
Total	100.0

*amount of cariprazine free base

The lactose monohydrate and cariprazine were sieved through a #20 sieve and mixed in a V-shell blender for 20 minutes by 5 step geometric mixing using an Intensifier bar in the final step. The magnesium stearate was sieved through #20 screen, added and the blend mixed for further 2 minutes. The final blend was then filled into capsules using a MG2 Futura Encapsulation machine. The capsules were packed into HDPE bottles and induction sealed.

The stability of the capsule formulations (at 40° C. and 75% RH) in a HDPE bottle, induction sealed with no dessicant is shown in Table 13.

TABLE 13

Formulation Stability

Time	Amount of De-BOC (% w/w) Capsule I
Initial	Not Detected
2 weeks	Not Detected
1 Month	Not Detected
2 Months	Not Detected
3 Months	0.124

Example 1F

Capsules containing cariprazine hydrochloride, Starcap 1500 (a mixture of co-processed corn starch and pregelatinized starch) were prepared according to Table 14:

TABLE 14

Composition of Capsule Formulation

Ingredient	Amount (% w/w) Capsule I (0.5 mg)*
Cariprazine hydrochloride	0.545
Corn starch, pregelatinized starch (Starcap 1500)	98.455
Magnesium stearate	1.000
Total	100.0

*amount of cariprazine free base

The Starcap1500 and cariprazine were sieved through a #20 sieve and mixed in a V-shell blender for 20 minutes by 5 step geometric mixing using an Intensifier bar in the final step. The magnesium stearate was sieved through #20 screen, added and the blend mixed for further 2 minutes. The final blend was then filled into capsules using a MG2 Futura Encapsulation machine. The capsules were packed into HDPE bottles and induction sealed.

The stability of the capsule formulations (at 40° C. and 75% RH) in a HDPE bottle, induction sealed with no dessicant is shown in Table 15.

TABLE 15

Formulation Stability

Time	Amount of De-BOC (% w/w) Capsule I
Initial	Not Detected
2 weeks	Not Detected
1 Month	Not Detected
2 Months	0.08
3 Months	0.118

Example 2

Preparation of a Stable Tablet Formulations Containing Cariprazine

Example 2A

Tablet formulations containing cariprazine hydrochloride and lactose monohydrate were prepared as shown in Table 16.

TABLE 16

Tablet Formulations

Ingredient	Function	Amount (% w/w)	Amount (mg/tablet) Tablet I 0.5 mg*	Tablet II 2.0 mg*	Tablet III 2.5 mg*
Lactose monohydrate	Filler	88.971	62.28	249.12	311.4
Cariprazine hydrochloride	Active	0.779	0.545	2.18	2.725
Talc USP	Glidant	2.5	1.75	7.0	8.75
Collodial silicon dioxide	Glidant	1.0	0.7	2.8	3.5

TABLE 16-continued

Tablet Formulations

Ingredient	Function	Amount (% w/w)	Amount (mg/tablet) Tablet I 0.5 mg*	Tablet II 2.0 mg*	Tablet III 2.5 mg*
Sodium starch glycolate	Dis-integrant	4.0	2.8	11.2	14.0
Hydroxypropyl cellulose	Binder	2.0	1.4	5.6	7.0
Magnesium stearate	Lubricant	0.75	0.525	2.1	2.625
Total		100.00	70	280	350

*amount of cariprazine free base

All ingredients except the magnesium stearate were sieved through a #20 sieve and mixed in a V-shell blender for 10 minutes. Mixing was continued for a further 10 minutes using an Intensifier bar in the final step. The magnesium stearate was sieved through #20 screen, added and the blend mixed for further 2 minutes. The final blend was then compressed into tablets using a Korsch PH106 compression machine. The tablets were packed into HDPE bottles and induction sealed.

The stability of the tablet formulations (at 40° C. and 75% RH) in a HDPE bottle, induction sealed with no dessicant is shown in Table 17.

TABLE 17

Formulation Stability

Time	Amount of De-BOC (% w/w) Tablet I	Tablet II	Tablet III
Initial	0.07	Not Detected	0.06
1 Month	0.05	Not Detected	Not Detected
2 Months	0.08	Not Detected	0.05
3 Months	0.06	Not Detected	0.07
6 Months	0.08	Not Detected	0.08

The dissolution rates for Tablet I after storage at 40° C. and 75% RH in a HDPE bottle, induction sealed with no dessicant is shown in Table 18.

TABLE 18

Dissolution Rates

Time (mins)	% Released Initial	1 Month	2 Months	3 Months	6 Months
0	0	0	0	0	0
5	60	65	62	68	67
10	88	87	84	93	98
15	91	89	87	96	100
30	90	90	89	97	104
45	92	91	90	98	100
60	92	91	90	98	100

The dissolution rates for Tablet II after storage at 40° C. and 75% RH in a HDPE bottle, induction sealed with no dessicant is shown in Table 19.

TABLE 19

Dissolution Rates

Time (mins)	% Released Initial	1 Month	2 Months	3 Months	6 Months
0	0	0	0	0	0
15	90	89	86	92	88
30	95	94	96	96	91
45	97	96	97	97	92
60	98	97	98	99	93

The dissolution rates for in Tablet III after storage at 40° C. and 75% RH in a HDPE bottle, induction sealed with no dessicant is shown in Table 20.

TABLE 20

Dissolution Rates

Time (mins)	% Released Initial	1 Month	2 Months	3 Months	6 Months
0	0	0	0	0	0
5	64	75	68	76	77
10	86	93	89	92	90
15	91	97	93	96	94
30	97	100	97	99	95
45	98	101	98	100	96
60	99	102	100	100	96

Example 2B

Tablet formulations containing cariprazine hydrochloride and lactose monohydrate were prepared as shown in Table 21.

TABLE 21

Tablet Formulations

Ingredient	Function	Amount (% w/w)	Amount (mg/tablet) Tablet I 2.5 mg*	Tablet II 12.5 mg*
Lactose monohydrate	Filler	85.855	60.098	300.49
Cariprazine hydrochloride	Active	3.895	2.727	13.635
Talc USP	Glidant	1.0	0.7	3.5
Collodial silicon dioxide	Glidant	2.5	1.75	8.75
Sodium starch glycolate	Disintegrant	4.0	2.8	14.0
Hydroxypropyl cellulose	Binder	2.0	1.4	7.0
Magnesium stearate	Lubricant	0.75	0.525	2.625
Total		100.00	70	350

*amount of cariprazine free base

All ingredients except the magnesium stearate were sieved through a #20 sieve and mixed in a V-shell blender for 10 minutes. Mixing was continued for a further 10 minutes using an Intensifier bar in the final step. The magnesium stearate was sieved through #20 screen, added and the blend mixed for further 2 minutes. The final blend was then compressed into tablets using a Korsch PH106 compression machine. The tablets were packed into HDPE bottles and induction sealed.

The stability of the tablet formulations (at 40° C. and 75% RH) in a HDPE bottle, induction sealed with no dessicant is shown in Table 22.

TABLE 22

Formulation Stability

Time	Amount of De-BOC (% w/w) Tablet I	Tablet II
Initial	0.0265	Not Detected
1 Month	0.02	Not Detected
2 Months	Not Detected	Not Detected
3 Months	Not Detected	Not Detected
6 Months	Not Detected	Not Detected

The dissolution rates for Tablet I after storage at 40° C. and 75% RH in a HDPE bottle, induction sealed with no dessicant is shown in Table 23.

TABLE 23

Dissolution Rates

Time	% Released				
(mins)	Initial	1 Month	2 Months	3 Months	6 Months
0	0	0	0	0	0
5	67	61	58	59	Not tested
10	95	90	89	91	Not tested
15	99	95	94	95	96
30	101	97	96	96	101
45	102	98	96	97	101
60	103	98	97	98	102

The dissolution rates for Tablet II after storage at 40° C. and 75% RH in a HDPE bottle, induction sealed with no dessicant is shown in Table 24.

TABLE 24

Dissolution Rates

Time	% Released				
(mins)	Initial	1 Month	2 Months	3 Months	6 Months
0	0	0	0	0	0
5	57	68	55	57	Not tested
10	93	89	83	86	Not tested
15	101	93	91	92	97
30	105	97	96	96	101
45	107	98	98	97	101
60	108	99	99	98	102

Example 2C

Tablets containing cariprazine hydrochloride and sodium carbonate as a buffering agent were prepared according to Table 25:

TABLE 25

Tablet Formulations

Ingredient	Function	Amount (% w/w)
Microcrystalline cellulose (Avicel PH102)	Filler	86.221
Cariprazine hydrochloride	Active	0.779
Talc USP	Glidant	3.000
Collodial silicon dioxide	Glidant	1.000
Sodium starch glycolate	Disintegrant	3.000
Magnesium stearate	Lubricant	1.000
Sodium carbonate	pH modifier	5.000
Total		100.000

All ingredients except the magnesium stearate were sieved through a #20 sieve and mixed in a V-shell blender for 15 minutes. The magnesium stearate was sieved through #20 screen, added and the blend mixed for further 2 minutes. The final blend was then compressed into tablets using a Korsch PH106 compression machine. The tablets were packed into HDPE bottles and induction sealed.

The stability of the tablet formulations (at 40° C. and 75% RH) in a HDPE bottle, induction sealed with no dessicant is shown in Table 26.

TABLE 26

Formulation Stability

Time	Amount of De-BOC (% w/w)
Initial	Not Detected
2 Weeks	Not Detected
1 Month	0.090
2 Months	0.102
3 Months	0.176
6 Months	0.165

The amount of De-BOC present in formulations containing differing amounts of sodium carbonate (stored for 3 months at 40° C., 75% RH in sealed 60 cc HDPE bottles with no desiccant) is shown in Table 27. Slurries were prepared by taking a tablet and dispersing it in the correct volume of deionized water needed to prepare a suspension containing 2% solids. The pH of the slurry was then measured using pH meter.

TABLE 27

Formulation Stability

Amount of Sodium Carbonate (% w/w)	pH (2% slurry)	Amount of De-Boc after 3 months at 40 C./75% RH (% w/w)
1.0	10.4	0.36
5.0	10.9	0.17
10.0	11.1	0.14

Example 3

Comparison Examples

Additional tablets containing cariprazine hydrochloride and other excipients were prepared according to Table 28:

TABLE 28

Tablet Formulations

Ingredient (% w/w)	Tablet 1	Tablet 2	Tablet 3	Tablet 4	Tablet 5	Tablet 6	Tablet 7	Tablet 8	Tablet 9	Tablet 10	Tablet 11
Cariprazine hydrochloride	0.779	0.779	0.779	0.779	0.779	0.779	0.779	0.779	0.779	0.779	0.779
Talc USP	3.000	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
Sodium starch glycolate	5.000	5.0	0.5	0.5	3.0	0.5	3.0	0.5	0.5	3.0	3.0
Magnesium stearate	1.000	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Aerosil 200VV	0.700	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Prosolv SMCC90	89.521	—	—	—	—	—	—	—	—		—
Avicel PH102	—	89.221	62.721	62.721	81.221	93.721	88.721	—	—	91.121	91.201
Starch 1500	—	—	31	—	—		—	—	93.721	—	—
Dicalcium phosphate dihydrate	—	—	—	31.0	—	—	—	—	—	—	—
Magnesium oxide	—	—	—	—	10.0	—	—	—	—	—	—
Syloid 63FP	—	—	—	—	—	—	2.5	—	—	—	—
Butylated Hydroxyanisol	—	—	—	—	—	—	—	—	—	—	0.01
Butylated Hydroxytoluene	—	—	—	—	—	—	—	—	—	—	0.01
EDTA	—	—	—	—	—	—	—	—	—	0.1	—
Avicel PH112 (Low Moisture)	—	—	—	—	—	—	—	93.721	—	—	—
Total	100	100	100	100	100	100	100	100	100	100	100

All ingredients except the magnesium stearate were sieved through a #20 sieve and mixed in a V-shell blender for 15 minutes. The magnesium stearate was sieved through #20 screen, added and the blend mixed for further 2 minutes. The final blend was then compressed into tablets using a Korsch PH106 compression machine. The tablets were packed into HDPE bottles and induction sealed.

The stability of the tablet formulations described in Table 29 (stored at 40° C. and 75% RH in 60 cc HDPE bottles, induction sealed with no dessicant) is shown in Table 29.

TABLE 29

Formulation Stability

Amount of De-BOC (% w/w)

Time	Tablet 1	Tablet 2	Tablet 3	Tablet 4	Tablet 5	Tablet 6	Tablet 7	Tablet 8	Tablet 9	Tablet 10	Tablet 11
Initial	0.058	0.052	ND	ND	ND	ND	ND	ND	ND	ND	ND
2 Weeks	0.344	0.273	0.119	0.194	0.136	0.196	0.069	0.102	0.076	0.095	0.093
1 Month	0.617	0.483	0.192	0.342	0.350	0.749	0.139	0.369	0.36	0.245	0.226
2 Months	1.318	0.925	0.720	0.799	0.464	1.411	0.312	0.512	0.496	0.500	0.474
3 Months	2.66	1.765	Not Tested	Not Tested	Not Tested	Not Tested	Not Tested	0.755	0.760	Not Tested	Not Tested

As can be seen from Table 30, the amount of De-Boc present in each of these tablet formulations at 2 months is greater than for the capsule and tablet formulations of the present invention described in Examples 1 and 2.

Example 4

A Double-Blind Placebo Controlled Single Dose Study Conducted in Healthy Male Volunteers

A double-blind, placebo controlled single dose study of the pharmacokinetic parameters of cariprazine (capsules) in healthy male volunteers was conducted. The design of the study is shown in Table 30.

TABLE 30

Study Design

Group	Number of Subjects Receiving Active Drug	Period	Dose (mg)	Condition	Wash-Out Interval Before Period 2	PK Blood Sampling
I	6	1	1	Fasted		0-168 h
II	6	1	2.5	Fasted		0-336 h

TABLE 30-continued

Study Design

Group	Number of Subjects Receiving Active Drug	Period	Dose (mg)	Condition	Wash-Out Interval Before Period 2	PK Blood Sampling
I	6	2	2	Fasted	~2 weeks	0-672 h
II	6	2	1.5	Fasted	~4 weeks	0-336 h
III	6	1	0.5	Fasted		0-168 h

The composition of the capsules is given below in Table 31.

TABLE 31

Capsule Composition

Ingredient	Amount (mg) 0.5 mg Capsule	2.5 mg Capsule	12.5 mg Capsule
Cariprazine hydrochloride	0.543	2.713	13.563
Microcrystalline cellulose	59.457	58.177	51.690
Calcium hydrogen phosphate, anhydrous	40.00	39.110	34.747

The mean pharmacokinetic parameters observed after administration of a single dose of 0.5 to 2.5 mg cariprazine are shown below in Table 32.

TABLE 32

Mean Pharmacokinetic Parameters

Treatment Group	Period	Dose (mg)	C_{max}, (ng/mL)	AUC_{0-168}, (ng/mL * h)	T_{max}, (h)	$T_{1/2}$ (h)
III	1	0.5	0.14	14.09	6	216.7
I	1	1	0.76	35.36	3	185.3
II	2	1.5	1.19	46.66	3	129.9
I	2	2	2.53	95.33	3	130.0
II	1	2.5	2.50	97.46	4	138.5

Mean maximum plasma concentrations (C_{max}) were generally obtained within about 3 to about 6 hours of dosing. T_{max}, values are about 3 to about 6 hours.

The pharmacokinetics of trans-1{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-3,3-dimethylurea hydrochloride over the single-dose range of 0.5 mg to 2.5 mg suggest approximate dose proportionality of exposure relative to mean AUC. Linear calculated pharmacokinetic parameters (based on the 2.0 mg data (Table 35, 80% of AUClast, Treatment I) for dosages greater than 2.0 mg and on the 0.5 mg data for dosages lower than 0.5 mg (Table 33) are shown in Table 33.

TABLE 33

Linear Calculated Pharmacokinetic Parameters

Dose (mg)	Mean C_{max} (ng/mL)	Mean AUC_{0-168} (ng/mL * h)
0.1	0.03	2.82
0.25	0.09	1.05
3	3.80	96.8
4.5	5.70	145.2
5	6.33	161.4
6	7.60	193.6
7.5	9.50	242.1
9	11.39	290.4
12.5	15.83	403.5
15	18.99	484.2

One skilled in the art with the benefit of this disclosure may readily determine pharmacokinetic parameters for any specific dosage of cariprazine used in a formulation.

Example 5

A Single-Center, Randomized, Open-Label, Parallel-Group Single-Dose Study

The objectives of this study were (i) to assess the effect of food on the oral bioavailability of cariprazine (2-mg tablet), (ii) to assess the effect of gender on the oral bioavailability of cariprazine after a single oral dose (2-mg tablet), and (iii) to evaluate the pharmacokinetics of cariprazine and its metabolites after an oral dose (2-mg tablet).

Methodology

This clinical study was conducted as a single-center, randomized, open-label, parallel-group single-dose study. A total of 42 healthy male and female patients aged 18-45 years were selected, with an approximate male-to-female ratio of 1:1.

Dosing occurred in two treatment sessions (Treatment 1 and Treatment 2) separated by 5 to 7 days. The subjects were randomized with ~1:1 male-female ratio to receive one of the following two treatments:

Treatment 1:

Single oral dose of one 2-mg cariprazine tablet under fasted conditions (12 female, 11 male subjects)

Treatment 2:

Single oral dose of one 2-mg cariprazine tablet under fed conditions (10 female, 9 male subjects)

Subjects were given the study drug with 240 mL of water in the clinic under fed/fasted conditions at 0800 hours on Day 1. Subjects taking Treatment 1 underwent a 10-hour overnight fast before dosing on Day 1 and continued fasting for an additional 4 hours postdose. Subjects taking Treatment 2 underwent a 10-hour overnight fast before eating a US Food and Drug Administration standardized high-fat breakfast at 0730 hours on Dosing Day 1.

This study was 30 days in duration (Day −1 through the last pharmacokinetic (PK) blood sample collection on Day 29).

Patient Evaluations

Vital Signs/Adverse Event Assessment

Heart rate and blood pressure were measure in the supine position (the subject lying down for at least 5 minutes prior to testing) on the same arm throughout the study and before any corresponding blood sample was collected. In addition to the Screening and End-of-Study measurements, vital signs (BP and pulse) were measured at:

Day 1: (0.0 (predose), 2, 4, 8 and 12 hours postdose)
Day 2: 25 hours after Day 1 dose administration
Day 3: 48 hours after Day 1 dose administration
Day 5: 96 hours after Day 1 dose administration

Blood Sampling

Blood sampling was performed at the following times to determine cariprazine plasma concentrations:

0.0 (predose), 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, 168, 336, 504 and 672 hours postdose.

The mean pharmacokinetic parameters observed during the study are presented in Table 34.

TABLE 34

Mean Pharmacokinetic Parameters

Treatment Group	C_{max} (ng/mL)	AUC_{last} (ng · h/mL)	AUC∞-obs (ng · h/mL)	Tmax (h)	T½ (h)
Treatment 1 (Fasted)	1.99	80.69	89.87	4.91	202.60

TABLE 34-continued

Mean Pharmacokinetic Parameters					
Treatment Group	C_{max} (ng/mL)	AUC_{last} (ng · h/mL)	AUC∞-obs (ng · h/mL)	Tmax (h)	T½ (h)
Treatment 1 (Fed)	1.72	89.22	96.96	9.21	198.33

Example 6

A Multiple Dose Study Conducted in Healthy Male Volunteers

Thirty-two healthy male subjects (mean age=24.9 years) were randomized into 4 groups (I-IV). In each group, 2 subjects received placebo and 6 subjects received one of the following treatments:

(I) 7 doses of 0.5 mg cariprazine administered every other day;

(II) 14 doses of 0.5 mg cariprazine every day;

(III) 2 doses of 0.5 mg cariprazine followed by 12 doses of 1.0 mg cariprazine every day; and

(IV) 21 doses of 1.0 mg cariprazine every day.

Plasma samples were analyzed for cariprazine by a validated LC-MS/MS assay (Internal Standards: deuterated compounds; Sample preparation: Liquid-liquid extraction after alkalization; Sample Volume: 1 mL; Calibration Range: 0.05-25 ng/mL; Inonization: +ESI with MRM mode).

The design of the study is shown below in Table 35.

TABLE 35

Study Design								
						PK Blood Sampling		
Group	Number of Subjects Receiving Active Drug	Frequency of dosing	Dose, mg	Days	Condition	PK Profile After First Dose	Predose Samples	PK Profile After Last Dose
I	6	once every other day	0.5	1, 3, 5, 7, 9, 11, 13	Fasted	0-48 h	Days 3, 5, 7, 9, 11	0-3 weeks
II	6	once daily	0.5	1-14	Fasted	0-24 h	Days 2, 3, 4, 5, 7, 9, 11, 13	0-9 weeks
III	6	once daily	0.5/1	1-2 (0.5 mg) 3-14 (1 mg)	Fasted	0-24 h	Days 2, 3, 4, 5, 7, 9, 11, 13	0-9 weeks
IV	6	once daily	1	1-21	Fasted	0-24 h	Days 2, 3, 5, 8, 11, 14, 16, 18, 19, 20	0-9 weeks

The mean pharmacokinetic parameters observed are shown below in Table 36.

TABLE 36

Mean Pharmacokinetic Parameters			
Treatment Group	C_{max}, ng/mL	t_{max}, h	$AUC_{0-\tau}$, ng/mL * h
I	1.034 (22.3)	4 (3-6)	32.9 (21.6)
II	1.418 (18.0)	3.5 (2-4)	25.0 (22.8)

TABLE 36-continued

Mean Pharmacokinetic Parameters			
Treatment Group	C_{max}, ng/mL	t_{max}, h	$AUC_{0-\tau}$, ng/mL * h
III	3.193 (25.9)	4 (2-4)	53.6 (30.6)
IV	3.897 (18.9)	(2-3)	56.8 (18.1)

The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and the accompanying figures. Such modifications are intended to fall within the scope of the appended claims. It is further to be understood that all values are approximate, and are provided for description.

We claim:

[1. A method of treating a condition selected from the group consisting of schizophrenia, bipolar disorder, acute mania, and depression, the method comprising administering to a patient in need thereof a solid oral pharmaceutical formulation comprising from about 0.05 to about 9 mg trans-1{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-3,3-dimethyl-urea, or a pharmaceutically acceptable salt thereof, and an excipient having low water activity selected from the group consisting of pregelatinized starch, mannitol, anhydrous calcium hydrogen phosphate, and mixtures thereof, wherein the formulation provides an in vivo plasma profile comprising a mean C_{max} of less than about 26.3 ng/mL, a mean AUC_0-∞ of more than about 2 ng·hr/mL and a mean T_{max} of about 3 or more hours, wherein the formulation has a dissolution rate of more than about 80% within about the first 60 minutes following administration of the composition to the patient; and wherein the formulation has a pH in the range of about 9.0 to about 12.0.**]**

[2. The method of claim **1**, wherein the formulation comprises about 1.5 mg trans-1{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-3,3-dimethyl-urea, or a pharmaceutically acceptable salt thereof, and provides an in vivo plasma profile comprising a mean C_{max} of less than about 2.7 ng/mL and a mean T_{max} of about 3 or more hours.**]**

[3. The method of claim 1, wherein the formulation comprises about 3 mg trans-1{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-3,3-dimethyl-urea, or a pharmaceutically acceptable salt thereof, and provides an in vivo plasma profile comprising a mean C_{max} of less than about 5.3 ng/mL and a mean T_{max} of about 3 or more hours.]

[4. The method of claim 1, wherein the formulation comprises about 4.5 mg trans-1{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-3,3-dimethyl-urea, or a pharmaceutically acceptable salt thereof, and provides an in vivo plasma profile comprising a mean C_{max} of less than about 7.9 ng/mL and a mean T_{max} of about 3 or more hours.]

[5. The method of claim 1, wherein the formulation comprises about 6 mg trans-I{4-[2-[4-(2,3-dichlorophenyl)-piperazin-I-yl]-ethyl]-cyclohexyl}-3,3-dimethyl-urea, or a pharmaceutically acceptable salt thereof, and provides an in vivo plasma profile comprising a mean C_{max} of less than about 10.5 ng/mL and a mean T_{max} of about 3 or more hours.]

[6. The method of claim 1, wherein the formulation comprises about 9 mg trans-I{4-[2-[4-(2,3-dichlorophenyl)-piperazin-I-yl]-ethyl]-cyclohexyl}-3,3-dimethyl-urea, or a pharmaceutically acceptable salt thereof, and provides an in vivo plasma profile comprising a mean AUC_0-∞ of more than about 180 ng·hr/mL and a mean T_{max} of about 3 or more hours.]

[7. The method of claim 1, wherein the formulation comprises about 0.5 mg trans-I{4-[2-[4-(2,3-dichlorophenyl)-piperazin-I-yl]-ethyl]-cyclohexyl}-3,3-dimethyl-urea, or a pharmaceutically acceptable salt thereof, and provides an in vivo plasma profile comprising a mean C_{max} of less than about 0.9 ng/mL and a mean T_{max} of about 3 or more hours.]

[8. The method of claim 1, wherein the excipient comprises pregelatinized starch.]

[9. The method of claim 1, wherein the excipient comprises mannitol.]

[10. The method of claim 1, wherein the excipient comprises anhydrous calcium hydrogen phosphate.]

11. A method of treating a condition selected from the group consisting of schizophrenia, bipolar disorder, acute mania, and depression, the method comprising administering to a patient in need thereof a solid oral pharmaceutical formulation comprising about 1.5 mg, about 3 mg, about 4.5 mg, or about 6 mg, of trans-1 {4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-3,3-dimethyl-urea, or a pharmaceutically acceptable salt thereof, and a pregelatinized starch.

12. The method of claim 11, wherein the solid oral pharmaceutical formulation comprises about 1.5 mg trans-1 {4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-3,3-dimethyl-urea, or a pharmaceutically acceptable salt thereof.

13. The method of claim 11, wherein the solid oral pharmaceutical formulation comprises about 3.0 mg trans-1 {4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-3,3-dimethyl-urea, or a pharmaceutically acceptable salt thereof.

14. The method of claim 11, wherein the solid oral pharmaceutical formulation comprises about 4.5 mg trans-1 {4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-3,3-dimethyl-urea, or a pharmaceutically acceptable salt thereof.

15. The method of claim 11, wherein the solid oral pharmaceutical formulation comprises about 6.0 mg trans-1 {4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-3,3-dimethyl-urea, or a pharmaceutically acceptable salt thereof.

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