# PHARMACEUTICAL COMPOSITIONS AND METHOD FOR TREATING SCHIZOPHRENIA

## FIELD OF THE INVENTION

The present invention relates to use of (thio)-carbamoyl-cyclohexane derivatives, particularly trans-4-{2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl}-N,N-dimethylcarbamoyl-cyclohexylamine and pharmaceutically acceptable salts thereof in the manufacture of a medicament for the treatment of schizophrenia. Furthermore, the present invention relates to the treatment of schizophrenia through the administration of (thio)-carbamoyl cyclohexane derivatives, particularly trans-4-{2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl}-N,N-dimethylcarbamoyl-cyclohexylamine and pharmaceutically acceptable salts thereof.

## BACKGROUND OF THE INVENTION

Schizophrenia is a lifelong disabling psychiatric disorder with a reported worldwide prevalence of about 1%, including 3.2 million Americans (see, e.g., National Institute of Mental Health, Schizophrenia, http://www.nimh.nih.gov/healthinformation/schizophreniamenu.cfm 2006; Mueser and McGurk, Lancet 2004;363:2063-72, 2004). The disorder usually manifests during adolescence or in young adulthood; the cardinal symptoms fall into three domains — positive symptoms, such as delusions and hallucinations, negative symptoms, such as lack of drive and social withdrawal, and cognitive symptoms, such as problems with attention and memory. These lead to social and occupational dysfunction, which inevitably have a profound effect on the family and the place of the affected individual in wider society. In addition to psychiatric symptoms, patients with schizophrenia are at greater risk for medical comorbidities than the general population.

Drug treatment with dopamine antagonists is the cornerstone of schizophrenia management both during the acute as well as the residual phase. Current guidelines recommend atypical antipsychotics, including risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole, as first-line treatment for schizophrenia. These drugs can be

uniformly characterized by their dual mode of action: in addition to antagonism of the dopamine $D_2$ receptor, they are also potent inhibitors at the serotonin 5-$HT_{2A}$ receptor.

Although an improvement over the classical neuroleptics, atypical antipsychotics still have shortcomings in the effective management of the disease. In particular, these drugs are associated with a high incidence of side effects (eg extrapyramidal symptoms [EPSs] at high dose, sedation, cardiovascular effects such as QTc prolongation, hematologic alterations, effects on sexual function, weight gain, metabolic abnormalities). Furthermore, treatment resistance remains high with 10% to30% of patients having little or no response to currently available antipsychotic medications, and up to an additional 30% of patients having only partial treatment response (see, e.g., Lehman *et al.*, *Am. J. Psychiatry*,161(2 Suppl), 1-56, 2004). This has led to the common clinical practice of experimental use of high doses of atypicals, antipsychotic polypharmacy, and augmentation with other psychotropic drugs (see, e.g., Zink *et al., Eur. Psychiatry*, 19:56-58, 2004; Stahl and Grady, *Curr. Med. Chem.*, 11, 313-27, 2004).

According to the American Psychiatric Association guidelines for the treatment of schizophrenia, 60 % to 70 % of patients relapse within 1 year without maintenance treatment and almost 90% relapse within 2 years (see, e.g., Lehman *et al.*, *Am. J. Psychiatry*, 161(2 Suppl), 1-56, 2004).

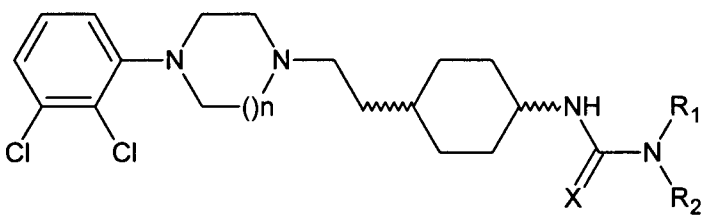
Overall, a significant unmet medical need in the treatment of schizophrenia still exists and much effort is being made to identify and develop improved antipsychotic agents.

In this search, the $D_3$ dopamine receptor has emerged as a possible target for antipsychotic drug treatment. This strategy is based on the brain distribution and suggested role of $D_3$ receptors, which have the highest density in the ventral striatum (see, e.g., Gurevich and Joyce, *Neuropsychopharmacology*, 20, 60-80, 1999), one of the core areas in the disease pathology. Dopamine $D_3$ receptors appear to participate in regulation of motor activity (see, e.g., Shafer and Levant, *Psychopharmacology* (Berl), 135, 1-1, 1998) and cognitive function (see, e.g., Ukai *et al., Eur. J. Pharmacol.*, 324, 147-51, 1997; Smith et al., *Pharmacol. Biochem. Behav.*, 63, 201-11, 1999). Selective antagonists of the receptor modulated or even abolished motor disturbances (catalepsy) induced by $D_2$ antagonists (see, e.g., Millan *et al., Eur. J. Pharmacol.*, 321, R7-9, 1997; Gyertyán *et al.*, [abstract]. *Int. J.*

*Neuropsychopharmacol.*, 5 Suppl. 1, 174, 2002) in rodent models and did not cause motor side effects or increase prolactin levels when given alone (see, e.g., Reavill *et al., A. J. Pharmacol. Exp. Ther.*, 294, 1154-65, 2000; Millan *et al., J. Pharmacol. Exp. Ther.*, 293, 1063-73, 2000). This suggests greatly reduced extrapyramidal side effect liability. $D_3$ antagonists were shown to improve cognitive deficiencies caused by various agents in rodents (see, e.g., Sigala *et al., Eur. J. Pharmacol.*, 336, 107-12, 1997; Laszy *et al., Psychopharmacology* (Berl), 179, 567-75, 2005) and primates, suggesting the possibility of a promising approach to the treatment of cognitive disturbances in schizophrenia. Dopamine $D_3$ receptor antagonists increase the motor activity of animals in habituated environments (see, e.g., Waters *et al., J. Neural. Transm. Gen. Sect.*, 98, 39-55, 1994; Sautel *et al., J. Pharmacol. Exp. Ther.*, 275, 1239-46, 1995; Gyertyán and Sághy, Behav. *Pharmacol.*, 15, 253-62, 2004). This activating effect may prove to be beneficial against the negative symptoms of the disease.

However, the lack of effect of selective $D_3$ antagonists in various animal models used so far to assess (human) antipsychotic action suggests that "pure" $D_3$ antagonists alone may not have sufficiently robust antipsychotic effects to justify clinical development. It has been shown that approximately 60 % to 80 % occupancy of dopamine $D_2$ receptors is necessary to achieve an antipsychotic action in the clinic (see, e.g., Nyberg *et al., Br. J. Psychiatry. Suppl.*, (29), 40-4, May 1996; Seeman, *Clin. Neurosci. Res.*, 1, 53-60, 2001). This latter phenomenon provides the basis for the view that $D_2$ antagonism is essential for antipsychotic action. Therefore, it is considered that addition of $D_3$ antagonism to $D_2$ antagonism may offer distinct advantages over the existing antipsychotics in the treatment of schizophrenia, namely no EPSs, cognitive enhancing potential, and augmented effect on negative symptoms.

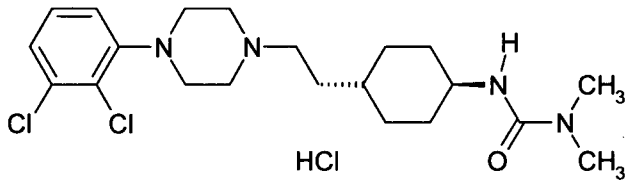
U.S. Patent Publication No. 2006/0229297 discloses (thio)-carbamoyl-cyclohexane derivatives that are $D_3$ and $D_2$ dopamine receptor subtype preferring ligands, having the formula (I):




(I)

wherein $R_1$, $R_2$, X, and n are as defined therein.

Hungarian Patent Application No. P0700339 discloses salts of trans-4-{2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl}-N,N-dimethylcarbamoyl-cyclohexylamine. One particular compound disclosed therein is trans-4-{2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl}-N,N-dimethylcarbamoyl-cyclohexylamine hydrochloride, which is also known as trans-1{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-3,3-dimethyl-urea hydrochloride, the structural formula for which is shown below:




These (thio)-carbamoyl-cyclohexane derivatives 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 $D_3$ receptor antagonism is about one order of magnitude greater than the $D_2$ receptor antagonism, which is believed to counteract some of the extrapyramidal side effects produced by $D_2$ receptor antagonists. In addition to the increased relative affinity for dopamine $D_3$ to $D_2$, e.g. trans-4-{2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl}-N,N-dimethylcarbamoyl-cyclohexylamine hydrochloride has a low potency at other receptor sites such as the 5-$HT_{2C}$, histamine $H_1$, and adrenergic receptor sites, which suggest a lower potential for side effects such as EPSs and body weight gain.

Thus, there is an existing and continual need for effective treatments for the symptoms of schizophrenia and cognitive effects associated with schizophrenia, without some of the side effects associated with traditional treatments.

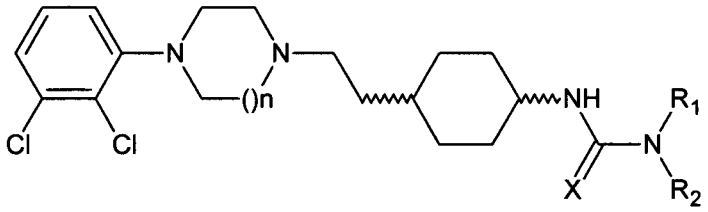
## SUMMARY OF THE INVENTION

The present invention relates to use of (thio)-carbamoyl-cyclohexane derivatives of formula (I), particularly trans-4-{2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl}-N,N-dimethylcarbamoyl-cyclohexylamine and pharmaceutically acceptable salts thereof in the

manufacture of a medicament for the treatment of schizophrenia. Furthermore the present invention relates to the treatment of schizophrenia through the administration of (thio)-carbamoyl cyclohexane derivatives of formula (I), particularly trans-4-{2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl}-N,N-dimethylcarbamoyl-cyclohexylamine and pharmaceutically acceptable salts thereof.

## DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to use of (thio)-carbamoyl-cyclohexane derivatives of formula (I)




(I)

wherein

$R_1$ and $R_2$ are each, independently hydrogen, alkyl, alkenyl, aryl, cycloalkyl, 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 and/or polymorphs thereof in the manufacture of a medicament for the treatment of schizophrenia.

In certain embodiments, 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 (particularly, 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.

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 of the claimed compounds 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.

In one embodiment, the pharmaceutically acceptable salt is a hydrochloride salt.

Some of the compounds useful in the present invention can 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. A polymorph is a solid crystalline phase of a compound with at least two different arrangements or polymorphic forms of that compound molecule in the solid state. Polymorphic forms of any given compound are defined by the same chemical formula or composition and are as distinct in chemical structure as crystalline structures of two different chemical compounds. The use of such polymorphs is within the scope of the present invention.

Some of the compounds useful in the present invention can 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.

Furthermore, the present invention particularly relates to the use of trans-4-{2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl}-N,N-dimethylcarbamoyl-cyclohexylamine and pharmaceutically acceptable salts thereof, more particularly to the use of trans-4-{2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl}-N,N-dimethylcarbamoyl-cyclohexylamine hydrochloride in the manufacture of a medicament for the treatment of schizophrenia.

Furthermore, the present invention relates to a method of treating schizophrenia by administering to a patient in need thereof, a therapeutically effective amount of a compound of formula (I) and/or geometric isomers and/or stereoisomers and/or diastereomers and/or salts and/or hydrates and/or solvates and/or polymorphs thereof as the active ingredient. Furthermore, the present invention particularly relates to a method of treating schizophrenia by administering to a patient in need thereof a therapeutically effective amount of trans-4-{2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl}-N,N-dimethylcarbamoyl-cyclohexylamine or a pharmaceutically acceptable salt thereof, more particularly a therapeutically effective amount of trans-4-{2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl}-N,N-dimethylcarbamoyl-cyclohexylamine hydrchloride, as active ingredient.

In certain embodiments, the active ingredient is administered in an amount of about 0.1 mg, about 0.2 mg, about 0.3 mg, about 0.4 mg, about 0.5 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, or about 12 mg. In yet further embodiments, the active ingredient is administered in an amount which ranges between any two of these dosage amounts. For example, in one embodiment, the active ingredient is administered in an amount from about 1.5 mg to about 4.5 mg. In another embodiment, the active ingredient is administered in an amount from about 6 mg to about 12 mg. In yet another embodiment, the active ingredient is administered in an amount from about 0.5 mg to about 12 mg

In exemplary embodiments, the active ingredient is administered in an amount of about 0.5 mg, about 1.0 mg, about 1.5 mg, about 3 mg, about 4.5 mg, about 6 mg, about 9 mg or about 12 mg, for example, in an amount of about 1.5 mg, about 3 mg, about 4.5 mg, about 6 mg, about 9 mg or about 12 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.

In one embodiment, the present invention relates to a method of treating schizophrenia by administering to a patient in need thereof about 0.5 mg trans-4-{2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl}-N,N-dimethylcarbamoyl-cyclohexylamine or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention relates to a method of treating schizophrenia by administering to a patient in need thereof about 1.0 mg trans-4-{2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl}-N,N-dimethylcarbamoyl-cyclohexylamine or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention relates to a method of treating schizophrenia by administering to a patient in need thereof about 1.5 mg trans-4-{2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl}-N,N-dimethylcarbamoyl-cyclohexylamine or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention relates to a method of treating schizophrenia by administering to a patient in need thereof about 3 mg trans-4-{2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl}-N,N-dimethylcarbamoyl-cyclohexylamine or a pharmaceutically acceptable salt thereof.

In a further embodiment, the present invention relates to a method of treating schizophrenia by administering to a patient in need thereof about 4.5 mg trans-4-{2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl}-N,N-dimethylcarbamoyl-cyclohexylamine or a pharmaceutically acceptable salt thereof.

In yet another embodiment, the present invention relates to a method of treating schizophrenia by administering to a patient in need thereof about 6 mg trans-4-{2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl}-N,N-dimethylcarbamoyl-cyclohexylamine or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention relates to a method of treating schizophrenia by administering to a patient in need thereof about 9 mg trans-4-{2-[4-(2,3-

dichlorophenyl)-piperazin-1-yl]-ethyl}-N,N-dimethylcarbamoyl-cyclohexylamine or a pharmaceutically acceptable salt thereof.

In yet another embodiment, the present invention relates to a method of treating schizophrenia by administering to a patient in need thereof about 12 mg trans-4-{2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl}-N,N-dimethylcarbamoyl-cyclohexylamine or a pharmaceutically acceptable salt thereof.

In additional embodiments, the active ingredient administered is trans-4-{2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl}-N,N-dimethylcarbamoyl-cyclohexylamine hydrochloride.

In one embodiment, the active ingredient is administered in one or two divided daily doses.

In one embodiment, the administration of the active ingredient provides therapeutic effects in the treatment of cognitive symptoms of schizophrenia. In another embodiment, the administration of the active ingredient provides therapeutic effects in the treatment of positive symptoms of schizophrenia. In a further embodiment, the administration of the active ingredient provides therapeutic effects in the treatment of negative symptoms of schizophrenia.

In other embodiments, the administration provides therapeutic effects in the treatment of affective symptoms of schizophrenia, residual symptoms of schizophrenia, or schizophreniform disorder.

The compounds of formula (I) can be administered alone or as an active ingredient of a pharmaceutical composition.

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 compositions 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.

To prepare such pharmaceutical dosage forms, the active ingredient, is intimately admixed 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 compositions 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. 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 containing 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.

The formulations of the present invention can have immediate release, sustained release, delayed-onset release or any other release profile known to one skilled in the art.

In one embodiment of the present invention, trans-4-{2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl}-N,N-dimethylcarbamoyl-cyclohexylamine or a pharmaceutically acceptable salt thereof is administered as an adjunctive treatment to one or more additional therapeutic agents (e.g., antipsychotics, antidepressants). In another embodiment, trans-4-{2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl}-N,N-dimethylcarbamoyl-cyclohexylamine or a pharmaceutically acceptable salt thereof may be co-administered as a combination therapy with one or more one or more additional therapeutic agents (e.g., antipsychotics, antidepressants).

The antipsychotic may be an atypical or a typical antipsychotic, preferably an atypical antipsychotic. Examples of atypical antipsychotics include, but are not limited to, olanzapine, clozapine, risperidone, sertindole, quetiapine, aripiprazole, ziprasidone, and surmontil, Examples of typical antipsychotics include, but are not limited to: acepromazine, benperidol, bromazepam, bromperidol, chlorpromazine, chlorprothixene, clotiapine, cyamemazine, diazepam, dixyrazine, droperidol, flupentixol, fluphenazine, fluspirilene, haloperidol, heptaminol, isopropamide iodide, levomepromazine, levosulpiride, loxapine, melperone, mesoridazine, molindone, oxypertine, oxyprothepine, penfluridol, perazine, periciazine, perphenazine, pimozide, pipamperone, pipotiazine, prochlorperazine, promazine, promethazine, prothipendyl, pyridoxine, sulpiride, sultopride, tetrabenazine, thioproperazine, thioridazine, tiapride, tiotixene, trifluoperazine, triflupromazine, trihexyphenidyl, and zuclopenthixol.

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 term "cognitive deficits 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:

(a) relieving or alleviating at least one symptom of a disorder in a subject, including for example, allergic and inflammatory disorders, such as asthma and COPD;

(b) relieving or alleviating the intensity and/or duration of a manifestation of a disorder experienced by a subject including, but not limited to, those that are in response to a given stimulus (e.g., pressure, tissue injury, cold temperature, etc.);

(c) 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 an active ingredient that, when administered to a patient (e.g., a mammal) for treating a disease (i.e., schizophrenia), is sufficient to effect such treatment for the disease, or an amount that is sufficient for modulating a dopamine receptor (e.g., the dopamine $D_2$ and/or dopamine $D_3$ receptor) to achieve the objectives of the invention. The "effective amount" will vary depending on the compound, the disease and its severity and the age, weight, responsiveness, etc., of the patient to be treated.

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 compositions 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 compositions can mean plus or minus a range of up to 20%, preferably up to 10%, more preferably up to 5%. Alternatively, particularly with respect to biological systems or processes, the term can mean within an order of magnitude, preferably within 5-fold, and more preferably within 2-fold, of a value. Where particular values are described in the application and claims, unless otherwise stated the term "about" means within an acceptable error range for the particular value.

## EXAMPLES

The following example is 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.

### EXAMPLE 1

This clinical study will be conducted as a multicenter, randomized, double-blind, placebo-controlled, parallel-group, flexible-dose study. A total of approximately 375 inpatients patients will be selected using criteria that includes patients who (i) currently meet or have met in the past the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)* criteria for schizophrenia (295.30 Paranoid Type, 295.10 Disorganized Type, 295.20 Catatonic Type, or 295.90 Undifferentiated Type) based on the Structured Clinical Interview for DSM-IV (SCID), (ii) have a PANSS total score $\geq$ 70 and $\leq$ 120 at Visit 1 and at Visit 2, (iii) have a score $\geq$ 4 (moderate) on item P1 (delusions) or P3 (hallucinatory behavior) of the PANSS at Visit 1 and at Visit 2, and (iv) have a score $\geq$ 4 (moderate) on item P2 (conceptual disorganization) or P6 (suspiciousness/persecution) of the PANSS at Visit 1 and at Visit 2.

This study will be 10 weeks in duration; 6-weeks double-blind treatment and 4-weeks safety follow-up. A no-drug washout period of up to 7 days will precede randomization. Patients will be hospitalized during the screening phase. Patients will remain hospitalized for a minimum of 21 days following randomization and initiation of double-blind medication. The evaluation schedule is shown in Table 1.

**Table 1: Evaluation Schedule**

| | Screening | Baseline | Double-Blind Phase | | | | | | Safety Follow-up | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Visit 1 | Visit 2 | Visit 3 | Visit 4 | Visit 5[1] | Visit 6[1] | Visit 7[1] | Visit 8[2] | Visit 9 | Visit 10 |
| End of Study Week | –1 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 8 | 10 |
| Days | up to –7 | 0 | 7 | 14 | 21 | 28 | 35 | 42 | 56 | 70 |

Patients who meet all eligibility criteria at Visit 1 will enter a no-drug washout period of up to 7 days. Following the wash-out period, patients who meet all eligibility criteria will be assigned a randomization number at Visit 2 and dispensed the corresponding blister pack of double-blind study medication for Week 1 of double-blind treatment.

All patients meeting the eligibility criteria will be randomized (1:1:1) to one of three treatment groups:

(I) placebo,

(II) 1.5 - 4.5 mg trans-4-{2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl}-N,N-dimethylcarbamoyl-cyclohexylamine hydrochloride, or

(III) 6 - 12 mg trans-4-{2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl}-N,N-dimethylcarbamoyl-cyclohexylamine hydrochloride.

Patients will be supplied with identically appearing capsules containing 1.5 mg, 3.0 mg, or 6.0 mg of trans-4-{2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl}-N,N-dimethylcarbamoyl-cyclohexylamine hydrochloride or placebo.

All study drugs will be dispensed in blister packs, one for each week. Each card will contain 30 capsules arranged in 10 columns and 3 rows, adequate for the 7 days of the week plus 3 extra days. The configuration of the blister pack is provided in Table 2. All study drugs will be administered as a single daily dose at bedtime. The dosing can be switched to morning if there are tolerability problems; however, any switch must allow at least 24 hours between two consecutive doses.

**Table 2: Double Blind Study Dosing Regimen**

| **Treatment Group 1: 1.5-4.5 mg** | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **Day 1** | **Day 2** | **Day 3** | **Day 4** | **Day 5** | **Day 6** | **Day 7** | **Day 8** | **Days 9-14** | **Days 15-42** |
| Row 1 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 |
| Row 2 | 0 | 0 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 |
| Row 3 | 0 | 0 | 0 | 0 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 |
| **Treatment Group 2 : 6-12 mg** | | | | | | | | | | |
| | **Day 1** | **Day 2** | **Day 3** | **Day 4** | **Day 5** | **Day 6** | **Day 7** | **Day 8** | **Days 9-14** | **Days 15-42** |
| Row 1 | 1.5 | 1.5 | 3 | 3 | 3 | 3 | 3 | 3 | 6 | 6 |
| Row 2 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 3 | 3 | 3 |
| Row 3 | 0 | 0 | 0 | 0 | 3 | 3 | 3 | 3 | 3 | 3 |
| **Treatment Group 3: Placebo** | | | | | | | | | | |
| | **Day 1** | **Day 2** | **Day 3** | **Day 4** | **Day 5** | **Day 6** | **Day 7** | **Day 8** | **Days 9-14** | **Days 15-42** |
| Row 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Row 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Row 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

On day 1 and day 2, all patients will be administered one capsule from row 1 of the blister pack. On day 3, the dose can be increased to two capsules (rows 1 and 2), if response is not adequate and there are no tolerability problems. Starting on day 5, the dose can be increased by one capsule to a maximum of three capsules (rows 1, 2, and 3) depending on response and tolerability. For patients randomized to Group II (1.5-4.5 mg trans-4-{2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl}-N,N-dimethylcarbamoyl-cyclohexylamine hydrochloride), the maximum dose of 4.5 mg can be reached by day 5, whereas for patients randomized to Group III (6-12 mg trans-4-{2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl}-N,N-dimethylcarbamoyl-cyclohexylamine hydrochloride), the maximum dose of 12 mg can be reached by Day 9. Any dose increases will be done in increments of one capsule.

Evaluations, to be conducted using established ratings methods, include:

| Visit | Day | Evaluation |
|---|---|---|
| 1 | up to -7 | SCI-PANSS |
| 2 | 0 | SCI-PANSS, CGI-S, CDSS |
| 3 | 7 | SCI-PANSS, CGI-S, CGI-I |
| 4 | 14 | SCI-PANSS, CGI-S, CGI-I |
| 5 | 21 | SCI-PANSS, CGI-S, CGI-I, CDSS |
| 6 | 28 | SCI-PANSS, CGI-S, CGI-I |
| 7 | 35 | SCI-PANSS, CGI-S, CGI-I |
| 8 | 42 | SCI-PANSS, CGI-S, CGI-I, CDSS |

PANSS Total Score (see, e.g., Kay et al., Schizophr. Bull., 13, 261-76, 1987)
CGI-S: Clinical Global Impressions - Severity (see, e.g., Guy ECDEU Assessment Manual for Psychopharmacology. Rockville, Md: US Department of Health, Education, and Welfare, 218-22, Publication ADM 76-338, 1976)
CGI-I: Clinical Global Impressions - Improvement (see, e.g., Guy ECDEU Assessment Manual for Psychopharmacology. Rockville, Md: US Department of Health, Education, and Welfare, 218-22, Publication ADM 76-338, 1976)
CDSS: Calgary Depression Scale for Schizophrenia (see, e.g., Addington et al., Schizophr. Res., 19, 205-12, 1996)

Blood samples will be collected on days 14, 21, 28, 35, 42, 56, and 70.

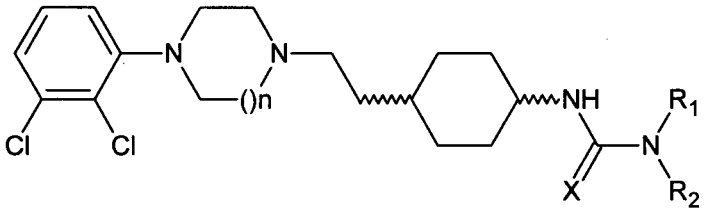
It is anticipated that the aforementioned treatment regime with trans-4-{2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl}-N,N-dimethylcarbamoyl-cyclohexylamine hydrochloride will show significant effectiveness in the treatment of schizophrenia, when compared to patients treated with placebo.

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.

The entire disclosures of all applications, patents and publications, cited above and below, are hereby incorporated by reference in their entirety.

**Claims:**

1. A method of treating schizophrenia comprising administering to a patient in need thereof a therapeutically effective amount of a (thio)-carbamoyl-cyclohexane derivative of formula (I)



(I)

wherein

$R_1$ and $R_2$ are each, independently hydrogen, alkyl, alkenyl, aryl, cycloalkyl, 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 and/or polymorphs thereof.

2. The method according to claim 1, wherein the compound of formula (I) is trans-4-{2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl}-N,N-dimethylcarbamoyl-cyclohexylamine and/or salts and/or hydrates and/or solvates and/or polymorphs thereof.

3. The method according to claim 1, wherein the compound of formula (I) is trans-4-{2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl}-N,N-dimethylcarbamoyl-cyclohexylamine hydrochloride and/or hydrates and/or solvates and/or polymorphs thereof.

4. The method according to claim 4 wherein the therapeutically effective amount of a compound of formula (I) is about 0.1 to 12 mg.

5. The method according to claim 4 wherein the therapeutically effective amount of a compound of formula (I) is about 0.5 mg.

6. The method according to claim 4 wherein the therapeutically effective amount of a compound of formula (I) is about 1.0 mg.

7. The method according to claim 4 wherein the therapeutically effective amount of a compound of formula (I) is about 1.5 mg.

8. The method according to claim 4 wherein the therapeutically effective amount of a compound of formula (I) is about 3 mg.

9. The method according to claim 4 wherein the therapeutically effective amount of a compound of formula (I) is about 4.5 mg.

10. The method according to claim 4 wherein the therapeutically effective amount of a compound of formula (I) is about 6 mg.

11. The method according to claim 4 wherein the therapeutically effective amount of a compound of formula (I) is about 9 mg.

12. The method according to claim 4 wherein the therapeutically effective amount of a compound of formula (I) is about 12 mg.

13. The method according to any one of claims 4-12, wherein a compound of formula (I) is administered in one, two, three or four divided daily doses.

14. The method according to any one of claims 4-13, wherein a compound of formula (I) provides therapeutic effects in the treatment of cognitive symptoms of schizophrenia.

15. The method according to any one of claims 4-13, wherein a compound of formula (I) provides therapeutic effects in the treatment of negative symptoms of schizophrenia.

16. The method according to any one of claims 4-13, wherein a compound of formula (I) provides therapeutic effects in the treatment of positive symptoms of schizophrenia.

17. The method according to any one of claims 4-13, wherein a compound of formula (I) provides therapeutic effects in the treatment of affective and residual symptoms of schizophrenia.

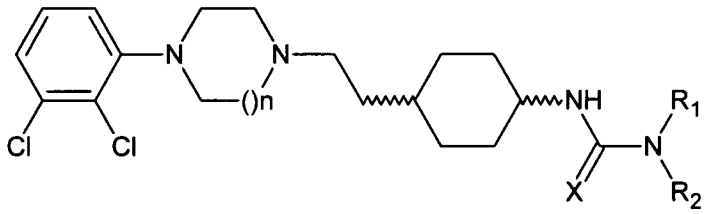
18. The method according to any one of claims 4-13, wherein a compound of formula (I) provides therapeutic effects in the treatment of secondary social and occupational dysfunctions of schizophrenia.

19. The method according to any one of claims 4-13, wherein a compound of formula (I) provides therapeutic effects in the treatment of schizophreniform disorder and schizoaffective disorders.

20. The method according to any one of claims 4-19, wherein a compound of formula (I) is administered as an adjunctive treatment to one or more additional therapeutic agents.

21. The method according to any one of claims 4-19, wherein a compound of formula (I) is co-administered as a combination therapy with one or more one or more additional therapeutic agents.

22. The use of (thio)-carbamoyl-cyclohexane derivatives of formula (I)




(I)

wherein

$R_1$ and $R_2$ are each, independently hydrogen, alkyl, alkenyl, aryl, cycloalkyl, 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 and/or polymorphs thereof in a therapeutically effective amount in the manufacture of a medicament for the treatment of schizophrenia.

23. The use according to claim 22 characterized by that the compound of formula (I) is trans-4-{2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl}-N,N-dimethylcarbamoyl-

cyclohexylamine and/or salts and/or hydrates and/or solvates and/or polymorphs thereof.

24. The use according to claim 22 characterized by that the compound of formula (I) is trans-4-{2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl}-N,N-dimethylcarbamoyl-cyclohexylamine hydrochloride and/or hydrates and/or solvates and/or polymorphs thereof.

25. The use according to any one of the claims 22-24 characterized by that the therapeutically effective amount of a compound of formula (I) is about 0.1 to 12 mg.

26. The use according to claim 25 characterized by that the therapeutically effective amount of a compound of formula (I) is about 0.5 mg.

27. The use according to claim 25 characterized by that the therapeutically effective amount of a compound of formula (I) is about 1.0 mg.

28. The use according to claim 25 characterized by that the therapeutically effective amount of a compound of formula (I) is about 1.5 mg.

29. The use according to claim 25 characterized by that the therapeutically effective amount of a compound of formula (I) is about 3.0 mg.

30. The use according to claim 25 characterized by that the therapeutically effective amount of a compound of formula (I) is about 4.5 mg.

31. The use according to claim 25 characterized by that the therapeutically effective amount of a compound of formula (I) is about 6 mg.

32. The use according to claim 25 characterized by that the therapeutically effective amount of a compound of formula (I) is about 9 mg.

33. The use according to claim 25 characterized by that the therapeutically effective amount of a compound of formula (I) is about 12 mg.

34. The use according to any one of claims 25-33 characterized by that the therapeutically effective amount of a compound of formula (I) is divided into one, two, three or four daily doses.

35. The use according to any one of claims 25-34 characterized by that it is for the treatment of cognitive symptoms of schizophrenia.

36. The use according to any one of claims 25-34 characterized by that it is for the treatment of negative symptoms of schizophrenia.

37. The use according to any one of claims 25-34 characterized by that it is for the treatment of positive symptoms of schizophrenia.

38. The use according to any one of claims 25-34 characterized by that it is for the treatment of cognitive symptoms of schizophrenia.

39. The use according to any one of claims 25-34 characterized by that it is for the treatment of affective and residual symptoms of schizophrenia.

40. The use according to any one of claims 25-34 characterized by that it is for the treatment of secondary social and occupational dysfunctions of schizophrenia.

41. The use according to any one of claims 25-34 characterized by that it is for the treatment of schizophreniform disorder and schizoaffective disorders.