(THIO)CARBAMOYL-CYCLOHEXANE DERIVATIVES AS D3/D2 RECEPTOR ANTAGONISTS

Field of the invention

The present invention relates to new D_3 and D_2 dopamine receptor subtype preferring ligands of formula (I) and/or geometric isomers and/or stereoisomers and/or diastereomers and/or salts and/or hydrates and/or solvates thereof, to the processes for producing the same, to pharmacological compositions containing the same and to their use in therapy and/or prevention of a condition which requires modulation of dopamine receptors.

Description of the prior art

Cyclohexane derivatives are described in patent application WO 99/67206 useful in the therapy for the treatment of pain.

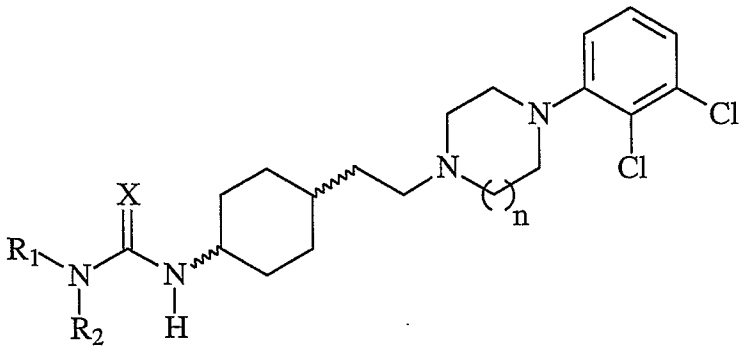
The compounds mentioned in the above publications are not declared or even not suggested having activity on the dopamine D_3 and/or D_2 receptors.

Summary of the invention

Surprisingly it was found that in contrast to the known above mentioned structurally analogous compounds the new derivatives of formula (I) of the present invention have high or very high affinity for dopamine D_3 receptors and moderate to high affinity to dopamine D_2 receptors always in such a combination that the D_3 affinity is 5 to 200 fold higher than the D_2 affinity. In addition, the compounds have even higher selectivity over other receptors, such as alpha-1 receptors. The dual (i.e. D_3 and D_2) receptor functional antagonism coupled in the above mentioned particular proportion is especially important as it allows the simultaneous manifestation of the beneficial effects of modulation of *both* the D_3 and D_2 receptors, however, *without* the appearance of the known disadvantages of each individual receptor action.

This type of new molecules belonging to the structure of formula (I) will be referred further on in this application as "D_3/D_2 ligands with D_3 preference".

The invention relates to new cyclohexane derivatives having (thio)carbamoyl side chain of formula (I):



(I)

wherein

R_1 and R_2 represent independently a substituent selected from hydrogen, alkyl, aryl, alkenyl, cycloalkyl, aroyl, or R_1 and R_2 may form a heterocyclic ring with the adjacent nitrogen atom;

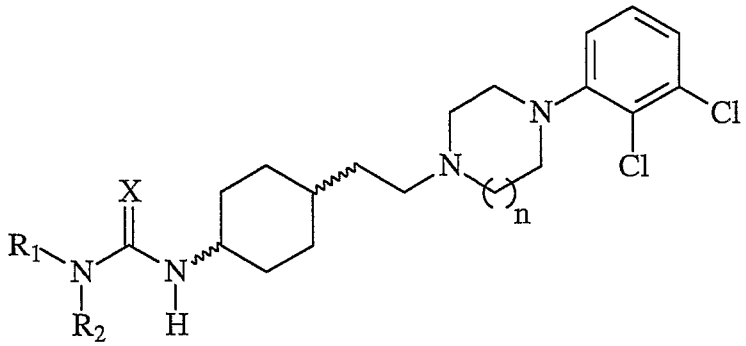
X represents an oxygen or sulphur atom;

n is an integer of 1 to 2,

and/or geometric isomers and/or stereoisomers and/or diastereomers and/or salts and/or hydrates and/or solvates thereof, to the processes for producing the same, to pharmacological compositions containing the same and to their use in therapy and/or prevention of pathological conditions which require the modulation of dopamine receptors such as psychoses (e.g. schizophrenia, schizo-affective disorders, etc.), drug (e.g. alcohol, cocaine and nicotine, opioids, etc.) abuse, cognitive impairment accompanying schizophrenia, mild-to-moderate cognitive deficits, dementia, psychotic states associated with dementia, eating disorders (e.g. bulimia nervosa, etc.), attention deficit disorders, hyperactivity disorders in children, psychotic depression, mania, paranoid and delusional disorders, dyskinetic disorders (e.g. Parkinson's disease, neuroleptic induced parkinsonism, tardive dyskinesias) anxiety, sexual dysfunction, sleep disorders, emesis, aggression, autism.

Detailed description of the invention

The invention relates to new cyclohexane derivatives having (thio)carbamoyl side chain of formula (I):



(I)

wherein

R_1 and R_2 represent independently a substituent selected from hydrogen, alkyl, alkenyl, aryl, cycloalkyl, aroyl, or R_1 and R_2 may form a heterocyclic ring with the adjacent nitrogen atom;

X represents an oxygen or sulphur atom;

n is an integer of 1 to 2,

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

When R_1 and/or R_2 represent alkyl, the alkyl moiety may contain 1 to 6 carbon atoms with straight or branched chain optionally substituted with one or more C_{1-6} alkoxycarbonyl, aryl, preferably phenyl or (C_{1-6} alkoxycarbonyl)-C_{1-6} alkyl group.

R_1 and R_2 may form a heterocyclic ring with the adjacent nitrogen atom, which may be saturated or unsaturated optionally substituted monocyclic or bicyclic ring, which may contain further heteroatoms selected from O, N, or S. The heterocyclic group is preferably pyrrolidinyl.

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.

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 phenyl, naphthyl, fluorenonyl, or antraquinonyl group, preferably 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 or cyano. The aryl is as defined above.

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.

When R_1 and/or R_2 represent aroyl the aryl moiety therein is as defined above, preferably phenyl.

The invention relates also to the salts of compounds of formula (I) formed with acids.

Both organic and inorganic acids can be used for the formation of acid addition salts. Suitable inorganic acids can be for example hydrochloric acid, sulfuric acid, nitric acid and phosphoric acid. Representatives of monovalent organic acids can be for example formic acid, acetic acid, propionic acid, and different butyric acids, valeric acids and capric acids. Representatives of bivalent organic acids can be for example oxalic acid, malonic acid, maleic acid, fumaric acid and succinic acid. Other organic acids can also be used, such as hydroxy acids for example citric acid, tartaric acid, or aromatic carboxylic acids for example benzoic acid or salicylic acid, as well as aliphatic and aromatic sulfonic acids for example methanesulfonic acid, naphtalenesulfonic acid and p-toluenesulfonic acid. Especially valuable group of the acid addition salts is in which the acid component itself is physiologically acceptable and does not have therapeutical effect in the applied dose or it does not have unfavourable influence on the effect of the active ingredient. These acid addition salts are pharmaceutically acceptable acid addition salts. The reason why acid addition salts, which do not belong to the pharmaceutically acceptable acid addition salts belong to the present invention is, that in given case they can be advantageous in the purification and isolation of the desired compounds.

Solvates and/or hydrates of compounds of formula (I) are also included within the scope of the invention.

The compounds of formula (I) exist in the form of *cis* and *trans* isomers with respect to the configuration of the cyclohexane ring. These and their mixtures are likewise within the scope of the present inention. The compounds of the invention are preferably in *trans* configuration.

Certain compounds of formula (I) when the compound contains C_{2-7} alkenyl group can exist in the form of *cis*- and/or *trans*- isomers. These are likewise within the scope of the present invention including all such isomers and the mixtures thereof.

Certain compounds of formula (I) can exist as stereoisomers and diastereomers, too. These and the mixtures thereof are likewise within the scope of the present invention.

As the invention relates also to the salts of compounds of formula (I) formed with acids, especially the salts formed with pharmaceutically acceptable acids, the meaning of compound of formula (I) is either the free base or the salt even if it is not referred separately.

Preferred compounds of the invention are those compounds of formula (I), wherein

R_1 and R_2 represent independently

hydrogen, or

C_{1-6} alkyl, with straight or branched chain optionally substituted with one or more C_{1-6} alkoxycarbonyl, aryl, or (C_{1-6} alkoxycarbonyl)-C_{1-6} alkyl group, or R_1 and R_2 may form a heterocyclic ring with the adjacent nitrogen atom, which may be saturated or unsaturated optionally substituted monocyclic or bicyclic ring, which may contain further heteroatoms selected from O, N, or S, or

C_{2-7} alkenyl with 1 to 3 double bond, or

a mono-, bi- or tricyclic aryl, preferably phenyl or naphthyl optionally sustituted 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 or cyano, or

an optionally substituted mono-, bi- or tricyclic cycloalkyl group, or

aroyl group;

X represents oxygen or sulphur atom;

n is an integer of 1 to 2,

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

Particularly preferred compounds of the invention are those compounds of formula (I), wherein

R_1 and R_2 represent independently

hydrogen, or

C_{1-6} alkyl, with straight or branched chain and optionally substituted with one or more C_{1-6} alkoxycarbonyl, phenyl or (C_{1-6} alkoxycarbonyl)-C_{1-6} alkyl group or R_1 and R_2 may form a heterocyclic ring with the adjacent nitogen atom, preferably pyrrolidinyl ring, or

C_{2-7} alkenyl with 1 double bond, or

phenyl or naphthyl group optionally sustituted 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 or cyano, or

cyclohexyl or adamantyl group, or

benzoyl group;

X represents oxygen or sulphur atom;

n is an integer of 1 to 2,

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

The most prominent compounds of the invention are those compounds of formula (I), wherein

R_1 and R_2 represent independently

hydrogen, or

C_{1-6} alkyl with straight or branched chain optionallly substituted with C_{1-6} alkoxycarbonyl, or phenyl or R_1 and R_2 form a pyrrolidinyl ring;

allyl;

phenyl optionally substituted with one or more C_{1-6} alkoxy, cyano or C_{1-6} alkanoyl;

cyclohexyl;

X represents oxygen or sulphur;

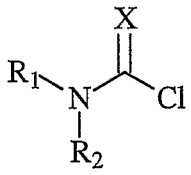
n is 1,

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

The invention also relates to the pharmaceutical compositions containing the compounds of formula (I) as active ingredient.

Further subject of the present invention is the pharmaceutical manufacture of medicaments containing compounds of formula (I), as well as the process of treatments and/or prevention with these compounds, which means administering to a mammal to be treated - including human - effective amount/amounts of compounds of formula (I) of the present invention as such or as medicament.

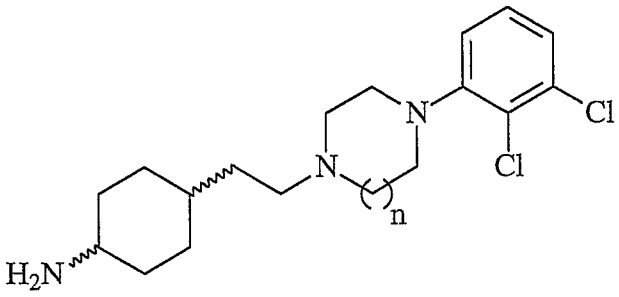
The present invention also provides a process (Method A) for preparing compounds of formula (I) by forming an amide bond between a (thio)carbamoylchoride of formula (II)):



(II)

wherein R_1, R_2 and X is as described above for the formula (I);

and an amine of formula (III):



(III)

wherein the meaning of n is as described above for the formula (I),

or derivatives thereof.

The amide bond formation may be carried out by known methods, preferably by suspending or dissolving the appropriate amine (III) or a salt thereof in a suitable solvent (e.g. tetrahydrofurane, dimethylformamide or chlorinated hydrocarbons or hydrocarbons) and reacting it with the appropriate (thio)carbamoylchloride (II) in the presence of a base (e.g. triethylamine). The reaction can be carried out advantageously between –10 °C and 60 °C. The reactions are followed by thin layer

chromatography. The necessary reaction time is about 6-60 h. The work-up of the reaction mixture can be carried out by different methods. The products can be purified, e.g. by crystallization or by column chromatography.

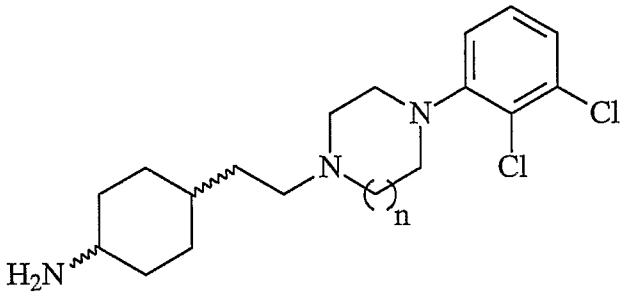
Another process (Method B) for preparing the compounds of formula (I) by forming an amide bond between the iso(thio)cyanate of formula (IV):

$$R_1—N=C=X$$

(IV)

wherein the meaning of R_1 and X is as described above for the formula (I),

and an amine of formula (III):



(III)

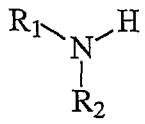
wherein the meaning of n is as described above for the formula (I),

or derivatives thereof

The amide bond formation may be carried out by known methods, preferably by suspending or dissolving the appropriate amine (III) or a salt thereof in a suitable solvent (e.g. tetrahydrofurane, dimethylformamide or chlorinated hydrocarbons or hydrocarbons) and reacting it with the appropriate iso(thio)cyanates (IV) if necessary in the presence of a base (e.g. triethylamine). The reaction can be carried out advantageously between 5 °C and 50 °C. The reactions are followed by thin layer chromatography. The necessary reaction time is about 6-10 h. The work-up of the reaction mixture can be carried out by different methods. The products can be purified, e.g. by crystallization or by column chromatography.

Method B may be carried out also by using automated parallel synthesis.

Another process (Method C) for preparing compounds of formula (I) is transforming in situ an amine of formula (III) to iso(thio)cyanate derivative and reacting the latter with an amine of formula (V):



(V)

wherein R_1 and R_2 are as described above for the formula (I),

or derivatives thereof.

The above reaction may be carried out by known methods. The transformation of amine (III) to iso(thio)cyanate derivative may be carried out in situ in an aprotic solvent (e.g. tetrahydrofurane, chlorinated hydrocarbons) by the use of an appropriate (thio)carbonic acid derivative (e.g. phosgene, triphosgene, thiophosgene) in the presence of a base (e.g. triethylamine), advantageously between –5 °C and room temperature. To the thus obtained solution or suspension an appropriate amine of (V), wherein R_1 and R_2 are as described above, is added in the form of base or salt formed with organic or inorganic acid. The necessary reaction time is between 2-24 hours. The work-up of the reaction mixture can be carried out by different methods. The products can be purified, e.g. by crystallization or by column chromatography.

The obtained (thio)ureas of formula (I) can be transformed into the salts thereof with acids and/or liberated the (thio)ureas of formula (I) from the obtained acid addition salts by treatment with a base, and/or can be separated the *cis*- and/or *trans*-isomers and/or the stereoisomers and/or diastereomers and/or can be transformed into hydrates and/or solvates thereof.

The (thio)carbamoylchlorides of formula (II) and iso(thio)cyanates of formula (IV) and the amines of formula (V), wherein R_1, R_2 and X are as defined above, are either commercially available or can be synthesized by different known methods.

The synthesis of amine of formula (III), wherein n=1 is described e.g. in WO 03/029233 or Bioorg. Med. Chem. Lett.; EN; 7; 18; **1997**; 2403-2408.

The amines of formula (III), wherein n=2, are new compounds and are also included within the scope of the present invention.

The new amines of formula (III), wherein n=2 are synthesized by conventional known methods mentioned above.

The compounds of formula (I) can also be prepared by automated parallel synthesis.

The separatrion of *cis*- and *trans* isomers either of compounds of formula (I) or of formula (III) or the protected derivatives of the latter is carried out by conventional methods, e.g. by chromatography and/or crystallitation, or the *cis* and *trans* isomers of formula (I) can be prepared from the pure *cis* or *trans* precursor.

The compounds of formula (I) of the present invention, in contrast to known antipsychotics, have been found to exhibit high affinity for dopamine D_3 receptors, less activity toward D_2 receptors and much less affinity to aderenergic alpha-1 receptors, and are expected to be useful in the treatment of disease states and/or prevention the same in which dopamine D_3 and/or D_2 receptors are involved in the disease pathology and thus their modulation is required.

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 (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 (Pilla, C. et al.: Nature **1999**, 400, 371) and Parkinson's disease (Levant, B. et al.: CNS Drugs **1999,** 12, 391) or pain (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. **2003,** 27, 269.).

The present invention provides novel compounds of formula (I) and/or geometric isomers and/or stereoisomers and/or diastereomers and/or salts and/or hydrates and/or solvates thereof which have high (less than 10 nM) or very high (less than 1 nM) affinity to dopamine D_3 receptors and – simultaneously – have moderate (between 50 and 200 nM) to high (between 1 and 10 nM) affinity to D_2 receptors always in such combination that the D_3 affinity is 5 to 200 fold higher than the D_2 affinity.

In a further aspect of the present invention it provides a method of 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, 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 of formula (I) and/or geometric isomers and/or stereoisomers and/or diastereomers and/or salts and/or hydrates and/or solvates thereof.

The invention also provides the use 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 thereof in the manufacture of a medicament for the treatment of conditions which require modulation of dopamine receptors especially that of dopamine D_3 and/or D_2 receptors.

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 cancelling out the disadvantageous features of D_2 antagonism (e.g. extrapyramidal symptoms, psychomotor sedation, cognitive disturbances).

For use in medicine, the compounds of formula (I) of the present invention and/or geometric isomers and/or stereoisomers and/or diastereomers and/or physiologically acceptable salts and/or hydrates and/or solvates thereof are usually administered as a standard pharmaceutical composition. The present invention therefore provides in a further aspect pharmaceutical compositions comprising a new compound of formula (I) and/or geometric isomers and/or stereoisomers and/or diastereomers and/or physiologically acceptable salts and/or hydrates and/or solvates thereof and physiologically acceptable carriers.

The compounds of formula (I) of the present invention and/or geometric isomers and/or stereoisomers and/or diastereomers and/or physiologically acceptable salts and/or hydrates and/or solvates thereof may be administered by any convenient method, for example by oral, parental, buccal, sublingual, nasal, rectal or transdermal administration and the pharmaceutical compositions adapted accordingly.

The compounds of formula (I) of the present invention and/or geometric isomers and/or stereoisomers and/or diastereomers and/or physiologically acceptable salts and/or hydrates and/or solvates thereof which are active when given orally can be formulated as liquids or solids, for example syrups, suspensions or emulsions, tablets, capsules and lozenges.

A liquid formulation of the compounds of formula (I) of the present invention and/or geometric isomers and/or stereoisomers and/or diastereomers and/or physiologically acceptable salts and/or hydrates and/or solvates thereof generally

consists of a suspension or solution of the compound of formula (I) and/or geometric isomers and/or stereoisomers and/or diastereomers and/or salts and/or hydrates and/or solvates thereof in a suitable liquid carrier(s) for example an aqueous solvent, such as water, ethanol or glycerine, or a non-aqueous solvent, such as polyethylene glycol or an oil. The formulation may also contain a suspending agent, preservative, flavouring or colouring agent.

A composition in the solid form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose, cellulose etc.

A composition in the solid form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatine capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatine capsule.

Typical parenteral compositions consist of a solution or suspesion of the compound of formula (I) of the present invention and/or geometric isomers and/or stereoisomers and/or diastereomers and/or physiologically acceptable salts and/or hydrates and/or solvates thereof in a steril aqueous carrier or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

Compositions of the present invention for nasal administration containing a compound of formula (I) and/or geometric isomers and/or stereoisomers and/or diastereomers and/or physiologically acceptable salts and/or hydrates and/or solvates thereof may conveniently be formulated as aerosols, drops, gels and powders. Aerosol formulations of the present invention typically comprise a solution or fine suspension of the compound of formula (I) and/or geometric isomers and/or stereoisomers and/or diastereomers and/or physiologically acceptable salts and/or hydrates and/or solvates thereof in a physiologically acceptable aqueous or non-aqueous solvent and are usually presented in a single or multidose quantities in steril form is a sealed container, which can take the form of a cartridge or refill for use with an atomising device. Alternatively, the sealed container may be a unitary dispensing

device, such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve which is intended for disposal once the contents of the container have been exhausted. Where the dosage form comprises an aerosol dispenser, it will contain a propellant which can be a compressed gas, such as compressed air or an organic propellant, such as a fluorochlorohydrocarbon. The aerosol dosages form can also take the form af a pump-atomiser. Compositions of the present invention containing a compound of formula (I) and/or geometric isomers and/or stereoisomers and/or diastereomers and/or physiologically acceptable salts and/or hydrates and/or solvates thereof suitable for buccal or sublingual administration include tablets, lozenges and pastilles, wherein the active ingredient is formulated with a carrier, such as sugar and acacia, tragacanth, or gelatine and glycerin etc.

Compositions of the present invention containing a compound of formula (I) and/or geometric isomers and/or stereoisomers and/or diastereomers and/or physiologically acceptable salts and/or hydrates and/or solvates thereof for rectal administration are conveniently in the form of suppositories containing a conventional supposiory base, such as cocoa butter.

Compositions of the present invention containing a compound of formula (I) and/or geometric isomers and/or stereoisomers and/or diastereomers and/or physiologically acceptable salts and/or hydrates and/or solvates thereof for transdermal administration include ointments, gels and patches.

The compositions of the present invention containing a compound of formula (I) and/or geometric isomers and/or stereoisomers and/or diastereomers and/or physiologically acceptable salts and/or hydrates and/or solvates thereof are preferably in the unit dose form, such as tablet, capsule or ampoule.

Each dosage unit of the present invention for oral administration contains preferably from 1 to 250 mg of a compound of formula (I) and/or geometric isomers and/or stereoisomers and/or diastereomers and/or physiologically acceptable salts and/or hydrates and/or solvates thereof calculated as a free base.

Each dosage unit of the present invention for parenteral administration contains preferably from 0.1 to 2 mg of a compound of formula (I) and/or geometric isomers and/or stereoisomers and/or diastereomers and/or physiologically acceptable salts and/or hydrates and/or solvates thereof calculated as a free base.

The physiologically acceptable compounds formula (I) of the present invention and/or geometric isomers and/or stereoisomers and/or diastereomers and/or physiologically acceptable salts and/or hydrates and/or solvates thereof can normally be administered in a daily dosage regimen (for an adult patient) of, for example, an oral dose between 1 mg and 500 mg, preferably between 10 mg and 400 mg, e.g. between 10 mg and 250 mg or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 100 mg, preferably between 0.1 mg and 50 mg, e.g. between 1 and 25 mg of the compound of formula (I) and/or geometric isomers and/or stereoisomers and/or diastereomers and/or physiologically acceptable salts and/or hydrates and/or solvates thereof calculated as the free base. The compounds of the present invention can be administered 1 to 4 times per day. The compounds of the present invention can suitably be administered for a period of continous therapy, for example for a week or more.

Biological test methods

Receptor binding assays

1. D_3 receptor binding

Binding assays were carried out on rat recombinant D_3 receptors (expressed in Sf9 cells) according to the supplier instruction (Packard BioScience, BioSignal Packard Inc. Cat. No. 6110139, Technical Data Sheet) using [^{3}H]-spiperone (0.85 nM) as ligand and haloperidol (10 μM) for determination of non-specific binding.

2. D_2 receptor binding

D_2 receptor binding assay was carried out as described by Creese et al. (European Journal of Pharmacology **60**:55-66, 1979) on rat brain striatal membrane preparation using [^{3}H]-spiperone (0.6 nM) as ligand. The non-specific binding was determined in the presence of 1 μM (+)-butaclamol.

3. Alpha-1 receptor binding

Alpha-1 receptor binding study was performed according to the method described by Greengrass and Bremmer (European Journal of Pharmacology **55**:323-326, 1979) on rat brain cortical membrane preparation using [^{3}H]-prasosin (0.5 nM) as ligand. The non-specific binding was determined in the presence of 10 μM phentolamine.

D_3 and D_2 and alpha-1 receptor binding data of selected compounds of the invention are listed in the Table hereinbelow.

Compound	D3 IC-50 (nM)	D2 IC-50 (nM)	Alfa-1 IC-50 (nM)
1	+++	++	>200
2	++++	+	>200
4	++++	++	>200
5	++++	++	>200
6	++++	++	>200
7	+++	++	>200
8	++++	++	>200
9	++++	+++	>200
11	++++	++	>200
12	++++	++	>200
15	++++	++	>200
20	+++	++	>200
22	++++	++	>200
23	++++	++	>200
24	++++	++	>200
29	+++	++	>200
33	++++	++	>200

Compound	D3 IC-50 (nM)	D2 IC-50 (nM)	Alfa-1 IC-50 (nM)
35	++++	++	>200
36	++++	++	>200
38	++++	++	>200
39	++++	++	>200
40	++++	+	>200
41	++++	+	>200
42	++++	++	>200
Haloperidol	+	++	+++
Aripiprazole	+++	+++	>200
Risperidone	++	++	+++
Olanzapine	+	+	++

+: IC-50 is between 50 and 200 nM

++: IC-50 is between 10 and 50 nM

+++: IC-50 is between 1 and 10 nM

++++: IC-50 is less than 1 nM

>200: IC-50 value is higher than 200 nM

The most prominent side effects of the first generation antipsychotic compounds (e.g. chlorpromazine and haloperidol) are the extrapyramidal symptoms such as pseudoparkinsonism and tardive dyskinesia and the orthostatic hypotension. The former two are the result of massive blockade of D_2 receptors in the basal ganglia whereas the latter is the consequence of antagonism of alpha-1 receptors.

Compounds in the above Table are highly or very highly potent ligands at D_3 receptors (IC-50 values are less than 1 nM or between 1 and 10 nM, respectively) and moderately to highly potent ligands at dopamine D_2 receptors showing 5 to 200 fold selectivity (selectivity: IC-50 for D_2 divided by IC-50 for D_3) over D_2 receptors. However, coupling the high or very high D_3 affinity to the moderate to high D_2 affinity

in this particular proportion allows to preserve the beneficial (e.g. antipsychotic) actions of a D_2 antagonist while – at the same time – impedes (by the D_3 antagonism) the appearance of the disadvantageous consequences of massive D_2 receptor blockade like extrapyramidal symptoms or cognitive disturbances. It is therefore anticipated that no or greatly diminished adverse effects related to D_2 receptors will occur in the course of therapeutical application of compounds of the present invention. In addition, the compounds have very low or practically no affinity to adrenergic alpha-1 receptors (IC-50 higher than 200 nM for each compound) and thus have extremely high D_3/alpha-1 selectivity (ranging from several hundred-fold to several thousand fold). From the very low or no affinity of the compounds to adrenergic alpha-1 receptors the lack of cardiovascular side effects (e.g. orthostatic hypotension) is anticipated.

The invention is further illustrated by the following non-limiting examples.

The structure of all intermediates and end products were elucidated by IR, NMR and MS spectroscopy.

Example 1

1-(2,3-dichlorophenyl)-[1,4]diazepine (starting material)

2.25 g (10 mmol) 1-bromo-2,3-dichloro-benzene was dissolved in dry toluene (50 ml), 2.3 (11 mmol) of [1,4]diazepine-1-carboxylic acid tert-butylester was added followed by 0.2 g BINAP (2,2-bis(diphenylphosphino)-1,1'-binaphtyl), 85 mg tris(dibenzylideneacetone)dipalladium(0) and 1.2 g (12mmol) sodium-tert-butoxyde. The reaction mixture was refluxed for eight hours and filtered. The organic layer was washed with water, dried and evaporated in vacuo. The residue was purified by chromatography and deprotected at 10 °C using 20 ml ethylacetate saturated with gaseous hydrochloric acid, the precipitate was filtered giving 2.1 g (yield: 75 %) hydrochloride salt of the title compound, melting at 182-3 °C.

Example 2

***Trans*-N-{4-[2-[4-(2,3-dichloro-phenyl)-hexahydro-[1,4]diazepin-1-yl]-ethyl]-cyclohexyl}-carbamic acid tert-butylester** (intermediate)

0.7 g (2.5 mmol) of 1-(2,3-dichlorophenyl)-[1,4]diazepine hydrochloride and 0.6 g (2.5 mmol) of *trans*-2-{1-[4-(N-tert-butyloxycarbonyl)amino]cyclohexyl}-acetaldehyde were dissolved in dichloroethane (35 ml), 0.35 ml (2.5 mmol) triethylamine was added, then 0.79 g (3.7 mmol) sodium triacetoxyborohydride was added portionswise and the reaction mixture was stirred for 20 hours at ambient temperature, then 20 % potassium carbonate solution in water (20 ml) was added. The organic layer was separated, dried and evaporated to dryness in vacuo. The precipitate was recrystallized from acetonitrile to give the title compound 1.0 g (yield: 85.8 %), m.p.: 95-8 °C.

Example 3

***Trans*-4-[2-[4-(2,3-dichloro-phenyl)-hexahydro-[1,4]diazepin-1-yl]-ethyl]-cyclohexylamine** (intermediate)

0.93 g (2.1 mmol) *trans*-N-{4-[2-[4-(2,3-dichloro-phenyl)-hexahydro-[1,4]diazepin-1-yl]-ethyl]-cyclohexyl}-carbamic acid tert-butylester was deprotected at 10 °C using 15 ml ethylacetate saturated with gaseous hydrochloric acid, after 4 hours the precipitate was filtered giving 0.91 g (yield: 98 %) dihydrochloride salt of the title compound, melting at 260-6 °C.

Method A

***Trans*-1-{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-3,3-dimethyl-urea** (compound 1)

1.39g (3 mmol) trans-4-{2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl}-cyclohexyl-amine trihydrochloride was suspended in dichloromethane (100 ml), triethylamine (2.1 ml, 15 mmol) was added followed by 0.30 ml (3.3 mmol) N,N-dimethylcarbamoylchloride. The reaction mixture was stirred for 48 hours at room

temperature, filtered. The filtrate was washed with water (2 x 20 ml), dried and evaporated in vacuo. Recrystallizing from methanol gave the title compound (0.83 g, 65 %), melting at 212-4 °C.

Method B

***Trans*-1-{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-3-ethyl-urea** (compound 2)

0.56g (1.2 mmol) trans-4-{2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl}-cyclohexyl-amine was dissolved in dry dichloromethane (20 ml), ethylisocyanate (0.1 ml, 1.3 mmol) was added and the reaction mixture was stirred at room temperature for 4 hours. The solvent was removed *in vacuo.* The residue was stirred with water, the precipitate was filtered, giving the title compound (0.33 g, 65 %). Melting point: 235-8 °C.

Method C

***Trans*-1-{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-3,3-dimethyl-urea** (compound 1)

0.56g (1.2 mmol) trans-4-{2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl}-cyclohexyl-amine trihydrochloride was suspended in dry dichloromethane (50 ml), triethylamine 0.77 ml, 6 mmol) was added and 0.13g (0.44 mmol) triphosgene dissolved in dichloromethane was dropped in. After one hour stirring at room temperature dimetilamine hydrochloride (0.49 g, 6 mmol) followed by triethylamine (0.84 ml, 6 mmol) was added and the stirring was continued for 20 hours. The mixture was filtered, the filtrate washed with water, dried and evaporated in vacuo. Recrystallizing the product from methanol gave the title compound (0.27 g, 52 %). Melting point: 212-4 °C.

Applying one of the above procedures the following compounds were prepared:

trans-1-{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-3-methyl-urea (compound 3), melting point: 210-4 °C;

trans-1-{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-3-propyl-urea (compound 4), melting point: 218-20 °C;

trans-1-{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-3-isopropyl-urea (compound 5), melting point: 227-30 °C;

trans-1-{4-[2-[4-(2,3-dichlorophenyl)-hexahydro[1,4]diazepin-1-yl]-ethyl]-cyclohexyl}-3-ethyl-urea (compound 6), melting point: 115-8 °C;

trans-1-{4-[2-[4-(2,3-dichlorophenyl)-hexahydro[1,4]diazepin-1-yl]-ethyl]-cyclohexyl}-3,3-dimethyl-urea (compound 7), melting point: 168-72 °C;

trans-N-{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-pyrrolidine-1-carboxamide (compound 8), melting point: 201-3 °C;

trans-N-{4-[2-[4-(2,3-dichlorophenyl)-hexahydro[1,4]diazepin-1-yl]-ethyl]-cyclohexyl}-pyrrolidine-1-carboxamide (compound 9*);*

trans-1-{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-3,3-diethyl-urea (compound 10), melting point: 171-3 °C;

trans-1-{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-3-ethyl-3-methyl-urea (compound 11), melting point: 195-8 °C;

trans-1-{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-3-methyl-3-propyl-urea (compound 12), melting point: 137-9 °C;

trans-1-{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-urea (compound 13), melting point: 215-7 °C;

trans-N-{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-piperazine-1-carboxamide (compound 14), melting point: 293-6 °C;

trans-N-{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-4-methyl-piperazine-1-carboxamide (compound 15), melting point: 166-8 °C;

trans-N-{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-morpholine-4-carboxamide (compound 16), melting point: 201-3 °C;

trans-N-{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-piperidine-1-carboxamide (compound 17), melting point: 188-90 °C;

trans-N-{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-4-hydroxy-piperidine-1-carboxamide (compound 18), melting point: 178-80 °C.

Automated parallel synthesis (general procedure)

0.1 mmol of *trans*-4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexylamine was dissolved in 1 ml of dichloromethane, and 0.1 mmol of the appropriate isocyanate or isothiocyanate compound was added. The mixture was vigorously shaken for 12 hours. The solvent was evaporated in vacuo. 1 ml of n-hexane was added to the remaining solid and the mixture was vigorously shaken for 20 minutes.The solvent was decanted from the solid residue, and the solid was dried in vacuo.

Applying the above procedures the following compounds were prepared:

compound	mol weight	k'	Purity (HPLC Area%)	Iupac
19	505,49	5,768	99,4	*trans*-1-(4-{2-[4-(2,3-Dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-3-(2-methoxy-phenyl)-urea
20	505,49	5,807	95,59	*trans*-1-(4-{2-[4-(2,3-Dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-3-(3-methoxy-phenyl)-urea
21	439,43	4,816	96,25	*trans*-1-Allyl-3-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-urea
22	535,52	5,901	99,52	*trans*-1-(4-{2-[4-(2,3-Dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-3-(2,4-dimethoxy-phenyl)-urea
23	519,52	6,092	98,37	*trans*-1-(4-{2-[4-(2,3-Dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-3-(2-ethoxy-phenyl)-urea
24	455,48	6,123	95,02	*trans*-1-Butyl-3-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-urea
25	559,46	6,619	94,62	*trans*-1-(4-{2-[4-(2,3-Dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-3-(4-trifluoromethoxy-phenyl)-urea
26	533,59	6,324	99,43	*trans*-1-Adamantan-1-yl-3-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-urea
27	521,56	5,976	88,03	*trans*-1-(4-{2-[4-(2,3-Dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-3-(4-methylsulfanyl-phenyl)-urea

compound	mol weight	k'	Purity (HPLC Area%)	Iupac
28	551,56	6,441	85,42	*trans*-1-Biphenyl-2-yl-3-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-urea
29	513,51	5,354	99,3	*trans*-2-[3-(4-{2-[4-(2,3-Dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-ureido]-3-methyl-butyric acid methyl ester
30	533,50	6,161	96,32	*trans*-2-[3-(4-{2-[4-(2,3-Dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-ureido]-benzoic acid methyl ester
31	500,48	5,704	93,41	*trans*-1-(3-Cyano-phenyl)-3-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-urea
32	565,55	5,694	93,74	*trans*-1-(4-{2-[4-(2,3-Dichloro-phenyl)-piperazin-1-yl]-ethyl}cyclohexyl)-3-(3,4,5-trimethoxy-phenyl)-urea
33	481,51	5,591	99	*trans*-1-Cyclohexyl-3-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-urea
34	441,45	5,121	96,93	*trans*-1-(4-{2-[4-(2,3-Dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-3-propyl-urea
35	491,53	5,689	98,53	*trans*-1-(4-{2-[4-(2,3-Dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-3-phenyl-thiourea
36	549,65	6,852	95,94	*trans*-1-Adamantan-1-yl-3-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-thiourea

compound	mol weight	k'	Purity (HPLC Area%)	Iupac
37	487,50	5,951	99	*trans*-1-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-3-ethoxycarbonyl-thiourea
38	471,54	5,634	97,03	*trans*-1-tert-Butyl-3-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-thiourea
39	505,56	5,909	99	*trans*-1-Benzyl-3-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-thiourea
40	521,56	5,77	94,24	*trans*-1-(4-{2-[4-(2,3-Dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-3-(2-methoxy-phenyl)-thiourea
41	471,54	5,786	99	*trans*-1-Butyl-3-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-thiourea
42	457,51	5,387	96,79	*trans*-1-(4-{2-[4-(2,3-Dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-3-propyl-thiourea
43	519,54	6,459	97,68	*trans*-1-Benzoyl-3-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-thiourea
44	501,52	5,382	96,17	*trans*-[3-(4-{2-[4-(2,3-Dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-thioureido]-acetic acid ethyl ester
45	443,49	5,007	99	*trans*-1-(4-{2-[4-(2,3-Dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-3-ethyl-thiourea

compound	mol weight	k'	Purity (HPLC Area%)	Iupac
46	541,59	6,401	96,26	*trans*-1-(4-{2-[4-(2,3-Dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-3-naphthalen-1-yl-thiourea
47	455,48	5,143	94,98	*trans*-1-tert-Butyl-3-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-urea
48	475,47	5,481	95,69	*trans*-1-(4-{2-[4-(2,3-Dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-3-phenyl-urea
49	489,49	5,491	94,42	*trans*-1-Benzyl-3-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-urea
50	505,49	5,666	90,78	*trans*-1-(4-{2-[4-(2,3-Dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-3-(4-methoxy-phenyl)-urea
51	485,46	4,754	97,78	*trans*-[3-(4-{2-[4-(2,3-Dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-ureido]-acetic acid ethyl ester

The LC/MS analysis were performed using an HP 1100 binary gradient system, controlled by ChemStation software. HP diode array detector was used to acquire UV spectra at λ = 210 nm. Analytical chromatographic experiments were made on Discovery C_{16}-Amide, 5 cm X 4.6 mm X 5 µm column with a flow rate of 0.8 ml/min for qualification (purity, capacity factor). All experiments were performed using HP MSD single quadruple mass spectrometer equipped with an electrospray ionisation source to determine the molecular mass.

[$k' = t_R - t_0 / t_0$ t_R = retention time

t_0 = eluent retention time]

k'= capacity factor

The A eluent was water containing 0.1% TFA (Sigma, Germany), the B eluent was 95% acetonitrile (Merck, Germany) containing 0.1% TFA and 5% A eluent. Gradient elution was used, starting with 100% A eluent and processing to 100% B eluent over a periode of 15 minutes.

Pharmaceutical formulations

a) Intravenous injection

Compound of formula (I)	1-40 mg
Buffer	to pH ca 7
Solvent/complexing agent	to 100 ml

b) Bolus injenction

Compound of formula (I)	1-40 mg
Buffer	to pH ca 7
Co-solvent	to 5 ml

Buffer: suitable buffers include citrate, phosphate, sodium hydroxide/hydrochloric acid.

Solvent: typically water but may also include cyclodextrins (1-100 mg) and co-solvents, such as propylene glycol, polyethylene glycol and alcohol.

c) Tablet

Compound of formula (I)	1-40 mg
Diluent/Filter(may also include cyclodextrins)	50-250 mg
Binder	5-25 mg
Disintegrant (may also include cyclodextrins)	5-50 mg
Lubricant	1-5 mg
Cyclodextrin	1-100 mg

Diluent: e.g. mycrocrystalline cellulose, lactose starch.

Binder: e.g. polyvinylpyrrolidone, hydroxypropylmethylcellulose.

Disintegrant: e.g. sodium starch glycolate, crospovidone.

Lubricant: e.g. magnesium stearate, sodium stearyl fumarate

d) Oral suspension

Compound of formula (I)	1-40 mg
Suspending agent	0.1-10 mg
Diluent	20-60 mg
Preservative	0.01-1.0 mg
Buffer	to pH ca 5-8
Co-solvent	0-40 mg
Flavour	0.01-1.0 mg
Colourant	0.001-0.1 mg

Suspending agent:e.g. xanthan gum, mycrocrystalline cellulose.

Diluent: e.g. sorbitol solution, tipically water.

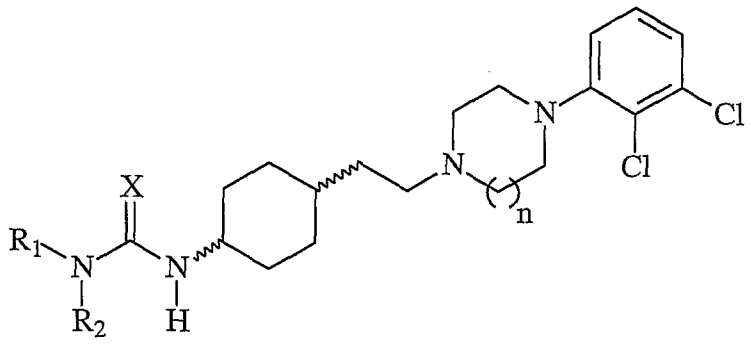
Preservative: e.g. sodium benzoate.

Buffer: e.g. citrate.

Co-solvent: e.g. alcohol, propylene glycol, polyethylene glycol, cyclodextrin.

What we claim:

1. A compound of formula (I):



(I)

wherein

R_1 and R_2 represent independently a substituent selected from hydrogen, alkyl, alkenyl, aryl, cycloalkyl, aroyl, or R_1 and R_2 may form a heterocyclic ring with the adjacent nitrogen atom;

X represents an oxygen or sulphur atom;

n is an integer of 1 to 2,

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

2. A compound as claimed in claim 1,

wherein

R_1 and R_2 represent independently

hydrogen, or

C_{1-6} alkyl, with straight or branched chain optionally substituted with one or more C_{1-6} alkoxycarbonyl, aryl, or (C_{1-6} alkoxycarbonyl)-C_{1-6} alkyl group, or R_1 and R_2 may form a heterocyclic ring with the adjacent nitrogen atom, which may be saturated or unsaturated optionally substituted monocyclic or bicyclic ring, which may contain further heteroatoms selected from O, N, or S, or

C_{2-7} alkenyl with 1 to 3 double bond, or

a mono-, bi- or tricyclic aryl, preferably phenyl or naphthyl optionally sustituted 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 or cyano, or

an optionally substituted mono-, bi- or tricyclic cycloalkyl group, or

aroyl group;

X represents oxygen or sulphur atom;

n is an integer of 1 to 2,

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

3. A compound as claimed in claims 1 and 2,

wherein

R_1 and R_2 represent independently

hydrogen, or

C_{1-6} alkyl, with straight or branched chain optionally substituted with one or more C_{1-6} alkoxycarbonyl, phenyl or (C_{1-6} alkoxycarbonyl)-C_{1-6} alkyl group or R_1 and R_2 may form a heterocyclic ring with the adjacent nitogen atom, which may be unsaturated optionally by C_{1-6} alkyl or hydroxy substituted monocyclic ring, which may contain further heteroatoms selected from O or N, or

C_{2-7} alkenyl with 1 double bond, or

phenyl or naphthyl group optionally sustituted 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 or cyano, or

cyclohexyl or adamantyl group, or

benzoyl group;

X represents oxygen or sulphur atom;

n is an integer of 1 to 2,

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

4. A compound as claimed in any of claims 1 to 3,

wherein

R_1 and R_2 represent independently

hydrogen, or

C_{1-6} alkyl with straight or branched chain optionallly substituted with C_{1-6} alkoxycarbonyl, or phenyl or R_1 and R_2 form an optionally by C_{1-6} alkyl or hydroxy substituted pyrrolidine, piperazine, piperidine or morpholine ring;

allyl;

phenyl optionally substituted with one or more C_{1-6} alkoxy, cyano or C_{1-6} alkanoyl;

cyclohexyl;

X represents oxygen or sulphur;

n is 1,

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

5. A compound selected from

trans-1-{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-3-methyl-urea,

trans-1-{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-3-propyl-urea,

trans-1-{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-3-isopropyl-urea,

trans-1-{4-[2-[4-(2,3-dichlorophenyl)-hexahydro[1,4]diazepin-1-yl]-ethyl]-cyclohexyl}-3-ethyl-urea,

trans-1-{4-[2-[4-(2,3-dichlorophenyl)-hexahydro[1,4]diazepin-1-yl]-ethyl]-cyclohexyl}-3,3-dimethyl-urea,

trans-N-{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-pyrrolidine-1-carboxamide,

trans-N-{4-[2-[4-(2,3-dichlorophenyl)-hexahydro[1,4]diazepin-1-yl]-ethyl]-cyclohexyl}-pyrrolidine-1-carboxamide,

trans-1-{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-3,3-diethyl-urea;

trans-1-{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-3-ethyl-3-methyl-urea;

trans-1-{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-3-methyl-3-propyl-urea;

trans-1-{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-urea;

trans-N-{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-piperazine-1-carboxamide;

trans-N-{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-4-methyl-piperazine-1-carboxamide;

trans-N-{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-morpholine-4-carboxamide;

trans-N-{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-piperidine-1-carboxamide;

trans-N-{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-4-hydroxy-piperidine-1-carboxamide;

trans-1-{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-3,3-dimethyl-urea,

trans-1-{4-[2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl}-3-ethyl-urea,

trans-1-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-3-(2-methoxy-phenyl)-urea,

trans-1-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-3-(3-methoxy-phenyl)-urea,

trans-1-allyl-3-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]- ethyl}-cyclohexyl)-urea,

trans-1-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-3-(2,4-dimethoxy-phenyl)-urea,

trans-1-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-3-(2-ethoxy-phenyl)-urea,

trans-1-butyl-3-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-urea,

trans-1-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-3-(4-trifluoromethoxy-phenyl)-urea,

trans-1-adamantan-1-yl-3-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-urea,

trans-1-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-3-(4-methylsulfanyl-phenyl)-urea,

trans-1-biphenyl-2-yl-3-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-urea

trans-2-[3-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-ureido]-3-methyl-butyric acid methyl ester,

trans-2-[3-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-ureido]-benzoic acid methyl ester,

trans-1-(3-cyano-phenyl)-3-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-urea,

trans-1-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}cyclohexyl)-3-(3,4,5-trimethoxy-phenyl)-urea,

trans-1-cyclohexyl-3-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-urea,

trans-1-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-3-propyl-urea,

trans-1-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-3-phenyl-thiourea,

trans-1-adamantan-1-yl-3-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-thiourea,

trans-1-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-3-ethoxycarbonyl-thiourea,

trans-1-tert-butyl-3-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-thiourea,

trans-1-benzyl-3-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-thiourea,

trans-1-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-3-(2-methoxy-phenyl)-thiourea,

trans-1-butyl-3-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-thiourea,

trans-1-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-3-propyl-thiourea,

trans-1-benzoyl-3-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-thiourea,

trans-[3-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-thioureido]-acetic acid ethyl este,r

trans-1-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-3-ethyl-thiourea,

trans-1-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-3-naphthalen-1-yl-thiourea,

trans-1-tert-butyl-3-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-urea,

trans-1-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-3-phenyl-urea,

trans-1-benzyl-3-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-urea,

trans-1-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-3-(4-methoxy-phenyl)-urea,

trans-[3-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-ureido]-acetic acid ethyl ester,

trans-1-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-3-(2-methoxy-phenyl)-urea,

trans-1-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-3-(3-methoxy-phenyl)-urea,

trans-1-allyl-3-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-urea,

trans-1-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-3-(2,4-dimethoxy-phenyl)-urea,

trans-1-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-3-(2-ethoxy-phenyl)-urea,

trans-1-butyl-3-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-urea,

trans-1-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-3-(4-trifluoromethoxy-phenyl)-urea,

trans-1-adamantan-1-yl-3-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-urea,

trans-1-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-3-(4-methylthio-phenyl)-urea,

trans-1-biphenyl-2-yl-3-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-urea,

trans-2-[3-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-ureido]-3-methyl-butyric acid methyl ester,

trans-2-[3-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-ureido]-benzoic acid methyl ester,

trans-1-(3-cyano-phenyl)-3-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-urea,

trans-1-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}cyclohexyl)-3-(3,4,5-trimethoxy-phenyl)-urea,

trans-1-cyclohexyl-3-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-urea

trans-1-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-3-phenyl-thiourea,

trans-1-adamantan-1-yl-3-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-thiourea,

trans-1-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-3-ethoxycarbonyl-thiourea,

trans-1-tert-butyl-3-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-thiourea,

trans-1-benzyl-3-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-thiourea,

trans-1-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-3-(2-methoxy-phenyl)-thiourea,

trans-1-butyl-3-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-thiourea,

trans-1-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-3-propyl-thiourea,

trans-1-benzoyl-3-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-thiourea,

trans-[3-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-thioureido]-acetic acid ethyl ester,

trans-1-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-3-ethyl-thiourea,

trans-1-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-3-naphthalen-1-yl-thiourea,

trans-1-tert-butyl-3-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-urea,

trans-1-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-3-phenyl-urea,

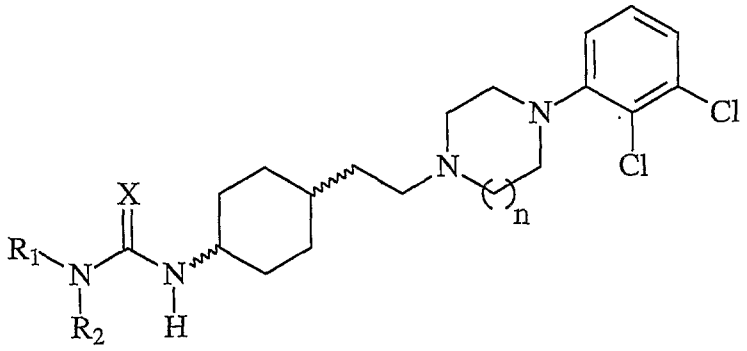
trans-1-benzyl-3-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-urea,

trans-1-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-3-(4-methoxy-phenyl)-urea,

trans-[3-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-ureido]-acetic acid ethyl ester,

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

6. A process for preparing a compound of formula (I):



(I)

wherein

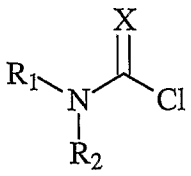
R_1 and R_2 represent independently a substituent selected from hydrogen, alkyl, alkenyl, aryl, cycloalkyl, aroyl, or R_1 and R_2 may form a heterocyclic ring with the adjacent nitrogen atom;

X represents an oxygen or sulphur atom;

n is an integer of 1 to 2,

and/or geometric isomers and/or stereoisomers and/or diastereomers and/or salts and/or hydrates and/or solvates thereof, which comprises:

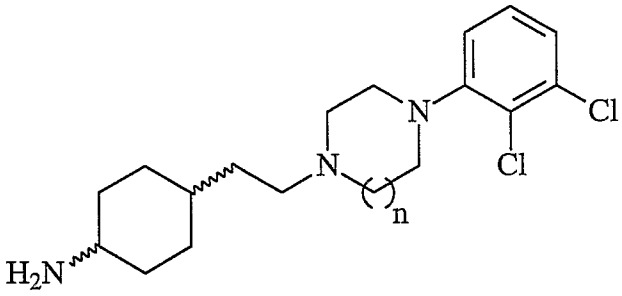
a) by forming an amide bond between a (thio)carbamoylchoride of formula (II):



(II)

wherein R_1, R_2 and X is as described above for the formula (I);

and an amine of formula (III):



(III)

wherein the meaning of n is as described above for the formula (I),

or derivatives thereof, or

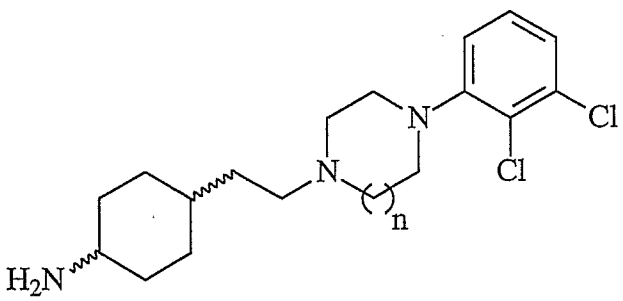
b) by forming an amide bond between the iso(thio)cyanate of formula (IV):

$$R_1—N=C=X$$

(IV)

wherein the meaning of R_1 and X is as described above for the formula (I),

and an amine of formula (III):

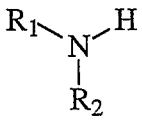


(III)

wherein the meaning of n is as described above for the formula (I),

or derivatives thereof, or

c) transforming in situ an amine of formula (III) to iso(thio)cyanate derivative and reacting the latter with an amine of formula (V):



(V)

wherein R_1 and R_2 are as described above for the formula (I),

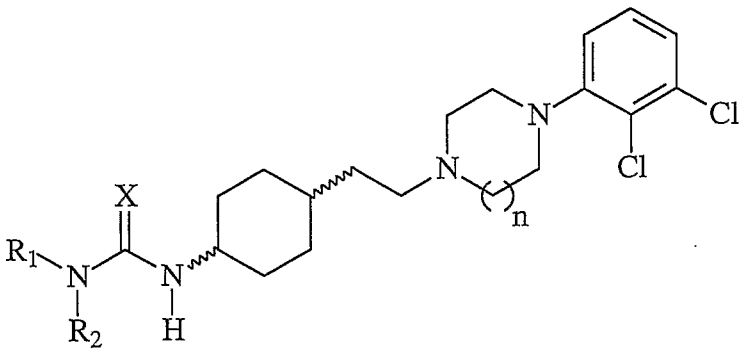
or derivatives thereof, and

interconverting one compound (I) obtained by any of method a) to c), wherein R_1, R_2, X and n are as defined for compound (I) to a different compound of formula (I) wherein R_1, R_2, X and n are as defined for compound (I);

where appropriate, separating the enantiomers and/or diastereomers, and/or *cis*- and/or *trans*- isomers of compounds of formula (I), or intermediates thereto wherein R_1, R_2, X and n are as defined defined for compound (I) by conventional methods;

and optionally thereafter forming salts and/or hydrates and/or solvates.

7. A process according to claim 6 for preparing a compound of the general formula (I):



(I)

wherein

R_1 and R_2 represent independently

hydrogen, or

C_{1-6} alkyl, with straight or branched chain and optionally substituted with one or more C_{1-6} alkoxycarbonyl, aryl, or (C_{1-6} alkoxycarbonyl)-C_{1-6} alkyl group, or R_1 and R_2 may form a heterocyclic ring with the adjacent nitrogen atom, which may be saturated or unsaturated optionally substituted monocyclic or bicyclic ring, which may contain further heteroatoms selected from O, N, or S, or

C_{2-7} alkenyl with 1 to 3 double bond, or

a mono-, bi- or tricyclic aryl, preferably phenyl or naphthyl optionally sustituted 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 or cyano, or

an optionally substituted mono-, bi- or tricyclic cycloalkyl group, or

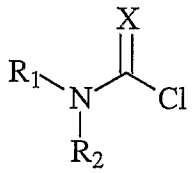
aroyl group;

X represents oxygen or sulphur atom;

n is an integer of 1 to 2,

and/or geometric isomers and/or stereoisomers and/or diastereomers and/or salts and/or hydrates and/or solvates thereof, which comprises:

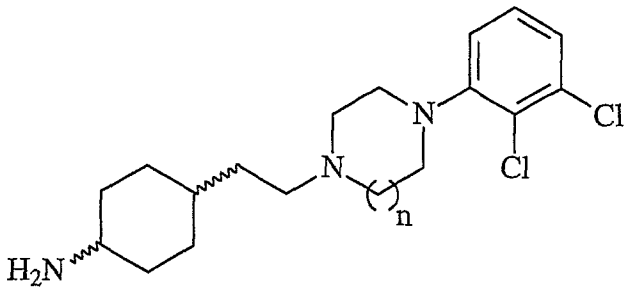
a) by forming an amide bond between a (thio)carbamoylchoride of formula (II):



(II)

wherein R_1, R_2 and X is as described above for the formula (I);

and an amine of formula (III):



(III)

wherein the meaning of n is as described above for the formula (I),

or derivatives thereof, or

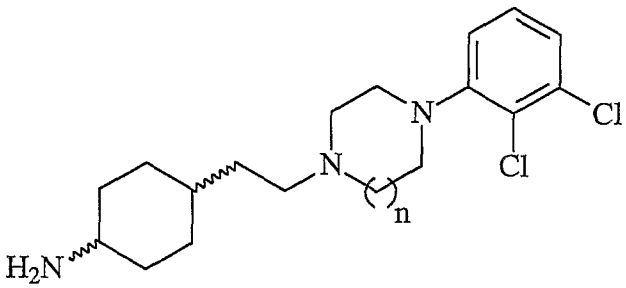
b) by forming an amide bond between the iso(thio)cyanate of formula (IV):

$$R_1—N=C=X$$

(IV)

wherein the meaning of R_1 and X is as described above for the formula (I),

and an amine of formula (III):

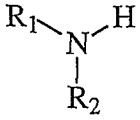


(III)

wherein the meaning of n is as described above for the formula (I),

or derivatives thereof, or

c) transforming in situ an amine of formula (III) to iso(thio)cyanate derivative and reacting the latter with an amine of formula (V):



(V)

wherein R_1 and R_2 are as described above for the formula (I),

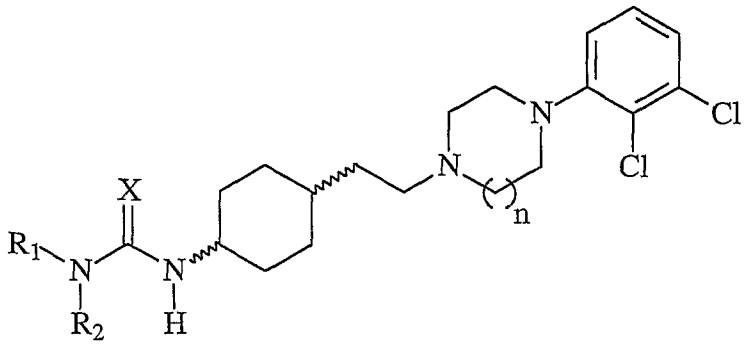
or derivatives thereof, and

interconverting one compound (I) obtained by any of method a) to c), wherein R_1, R_2, X and n are as defined for compound (I) to a different compound of formula (I) wherein R_1, R_2, X and n are as defined for compound (I);

where appropriate, separating the enantiomers and/or diastereomers, and/or *cis-* and/or *trans-* isomers of compounds of formula (I), or intermediates thereto wherein R_1, R_2, X and n are as defined defined for compound (I) by conventional methods;

and optionally thereafter forming salts and/or hydrates and/or solvates.

8. A process according to claims 6 and 7 for preparing a compound of the general formula (I):



(I)

wherein

R_1 and R_2 represent independently

hydrogen, or

C_{1-6} alkyl, with straight or branched chain and optionally substituted with one or more C_{1-6} alkoxycarbonyl, phenyl or (C_{1-6} alkoxycarbonyl)-C_{1-6} alkyl group or R_1 and R_2 may form a heterocyclic ring with the adjacent nitogen atom, which may be unsaturated optionally by C_{1-6} alkyl or hydroxy substituted monocyclic ring, which may contain further heteroatoms selected from O or N, or

C_{2-7} alkenyl with 1 double bond, or

phenyl or naphthyl group optionally sustituted 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 or cyano, or

cyclohexyl or adamantyl group, or

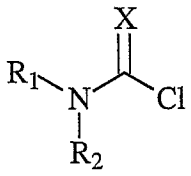
benzoyl group;

X represents oxygen or sulphur atom;

n is an integer of 1 to 2,

and/or geometric isomers and/or stereoisomers and/or diastereomers and/or salts and/or hydrates and/or solvates thereof, which comprises:

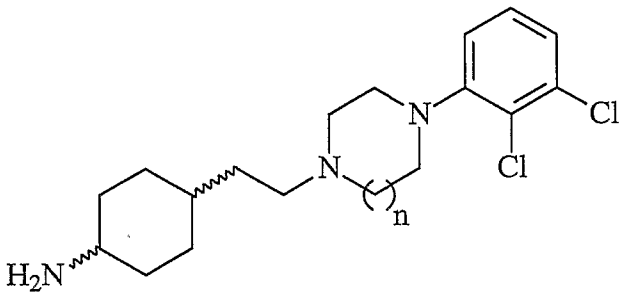
a) by forming an amide bond between a (thio)carbamoylchoride of formula (II):



(II)

wherein R_1, R_2 and X is as described above for the formula (I);

and an amine of formula (III):

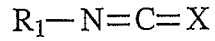


(III)

wherein the meaning of n is as described above for the formula (I),

or derivatives thereof, or

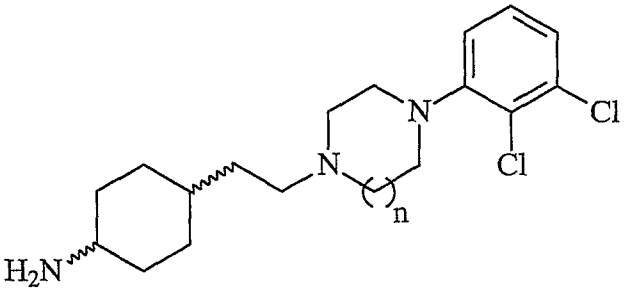
b) by forming an amide bond between the iso(thio)cyanate of formula (IV):



(IV)

wherein the meaning of R_1 and X is as described above for the formula (I),

and an amine of formula (III):

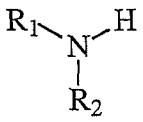


(III)

wherein the meaning of n is as described above for the formula (I),

or derivatives thereof, or

c) transforming in situ an amine of formula (III) to iso(thio)cyanate derivative and reacting the latter with an amine of formula (V):



(V)

wherein R_1 and R_2 are as described above for the formula (I),

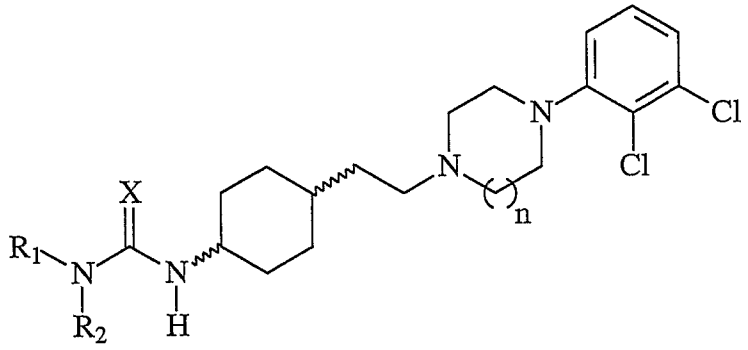
or derivatives thereof, and

interconverting one compound (I) obtained by any of method a) to c), wherein R_1, R_2, X and n are as defined for compound (I) to a different compound of formula (I) wherein R_1, R_2, X and n are as defined for compound (I);

where appropriate, separating the enantiomers and/or diastereomers, and/or *cis-* and/or *trans-* isomers of compounds of formula (I), or intermediates thereto wherein R_1, R_2, X and n are as defined defined for compound (I) by conventional methods;

and optionally thereafter forming salts and/or hydrates and/or solvates.

9. A process according to any of claims 6 to 7 for preparing a compound of the general formula (I):



(I)

wherein

R_1 and R_2 represent independently

hydrogen, or

C_{1-6} alkyl with straight or branched chain optionallly substituted with C_{1-6} alkoxycarbonyl, or phenyl or R_1 and R_2 form an optionally by C_{1-6} alkyl or hydroxy substituted pyrrolidine, piperazine, piperidine or morpholine ring;

allyl;

phenyl optionally substituted with one or more C_{1-6} alkoxy, cyano or C_{1-6} alkanoyl;

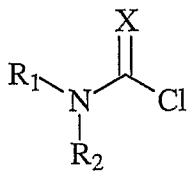
cyclohexyl;

X represents oxygen or sulphur;

n is 1,

and/or geometric isomers and/or stereoisomers and/or diastereomers and/or salts and/or hydrates and/or solvates thereof, which comprises:

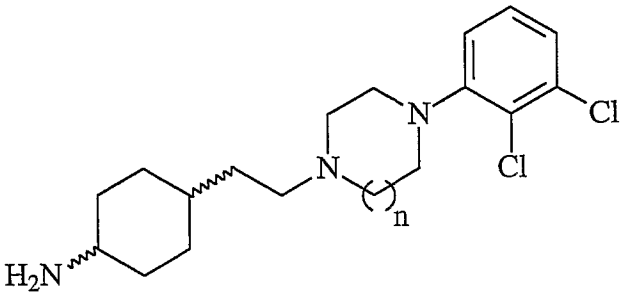
a) by forming an amide bond between a (thio)carbamoylchoride of formula (II):



(II)

wherein R_1, R_2 and X is as described above for the formula (I);

and an amine of formula (III):



(III)

wherein the meaning of n is as described above for the formula (I),

or derivatives thereof, or

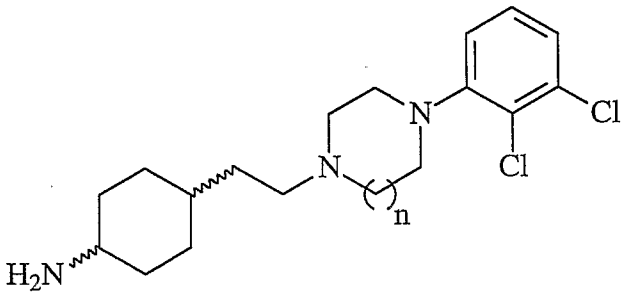
b) by forming an amide bond between the iso(thio)cyanate of formula (IV):

$$R_1—N=C=X$$

(IV)

wherein the meaning of R_1 and X is as described above for the formula (I),

and an amine of formula (III):

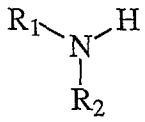


(III)

wherein the meaning of n is as described above for the formula (I),

or derivatives thereof, or

c) transforming in situ an amine of formula (III) to iso(thio)cyanate derivative and reacting the latter with an amine of formula (V):



(V)

wherein R_1 and R_2 are as described above for the formula (I),

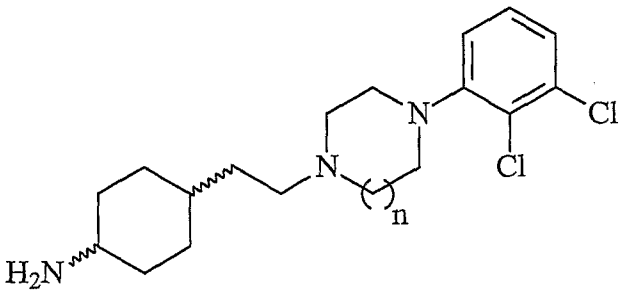
or derivatives thereof, and

interconverting one compound (I) obtained by any of method a) to c), wherein R_1, R_2, X and n are as defined for compound (I) to a different compound of formula (I) wherein R_1, R_2, X and n are as defined for compound (I);

where appropriate, separating the enantiomers and/or diastereomers, and/or *cis*- and/or *trans*- isomers of compounds of formula (I), or intermediates thereto wherein R_1, R_2, X and n are as defined defined for compound (I) by conventional methods;

and optionally thereafter forming salts and/or hydrates and/or solvates.

10. An amine of formula (III):



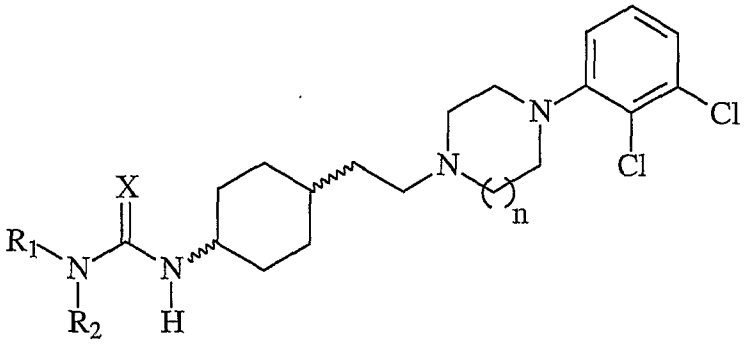
(III)

wherein

n is 2,

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

11. A pharmaceutical composition comprising a compound of formula (I):



(I)

wherein

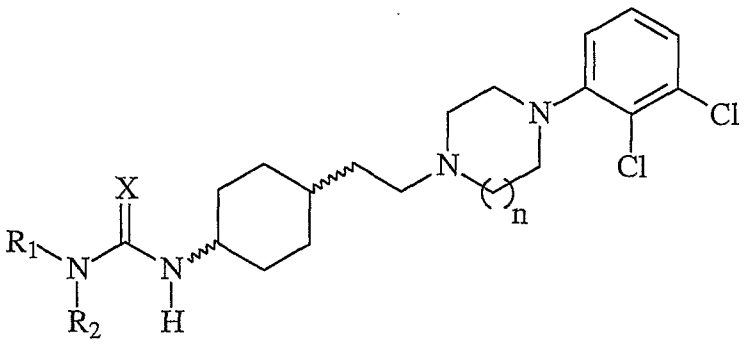
R_1 and R_2 represent independently a substituent selected from hydrogen, alkyl, alkenyl, aryl, cycloalkyl, aroyl, or R_1 and R_2 may form a heterocyclic ring with the adjacent nitrogen atom;

X represents an oxygen or sulphur atom;

n is an integer of from 1 to 2,

and/or geometric isomers and/or stereoisomers and/or diastereomers and/or physiologically acceptable salts and/or hydrates and/or solvates thereof and physiologically acceptable carrier(s) therefore.

12. A pharmaceutical composition comprising a compound of formula (I)



(I)

as claimed in claim 11,

wherein

R_1 and R_2 represent independently

hydrogen, or

C_{1-6} alkyl, with straight or branched chain optionally substituted with one or more C_{1-6} alkoxycarbonyl, aryl, or (C_{1-6} alkoxycarbonyl)-C_{1-6} alkyl group, or R_1 and R_2 may form a heterocyclic ring, which may be saturated or unsaturated optionally substituted monocyclic or bicyclic ring, which may contain further heteroatoms selected from O, N, or S, or

C_{2-7} alkenyl with 1 to 3 double bond, or

a mono-, bi- or tricyclic aryl optionally sustituted 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 or cyano, or

an optionally substituted mono-, bi- or tricyclic cycloalkyl group, or

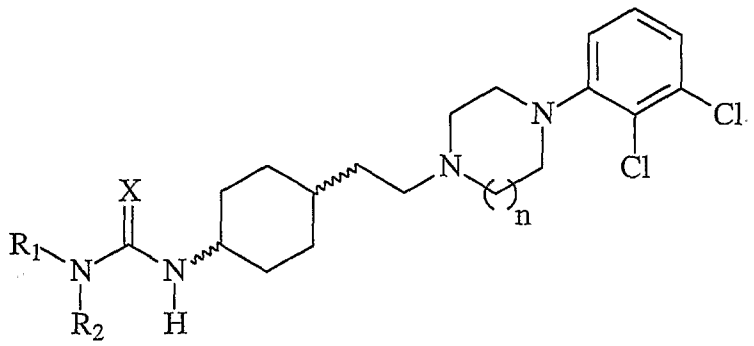
aroyl group;

X represents oxygen or sulphur atom;

n is an integer of 1 to 2,

and/or geometric isomers and/or stereoisomers and/or diastereomers and/or physiologically acceptable salts and/or hydrates and/or solvates thereof and physiologically acceptable carrier(s) therefore.

13. A pharmaceutical composition comprising a compound of formula (I)



(I)

as claimed in claims 11 and 12,

wherein

R_1 and R_2 represent independently

hydrogen, or

C_{1-6} alkyl, with straight or branched chain optionally substituted with one or more C_{1-6} alkoxycarbonyl, phenyl or (C_{1-6} alkoxycarbonyl)-C_{1-6} alkyl group, or R_1 and R_2 may form a heterocyclic ring with the adjacent nitrogen atom, which may be unsaturated optionally by C_{1-6} alkyl or hydroxy substituted monocyclic ring, which may contain further heteroatoms selected from O or N, or

C_{2-7} alkenyl with one double bond, or

phenyl or naphthyl group optionally sustituted 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 or cyano, or

cyclohexyl or adamantyl group, or

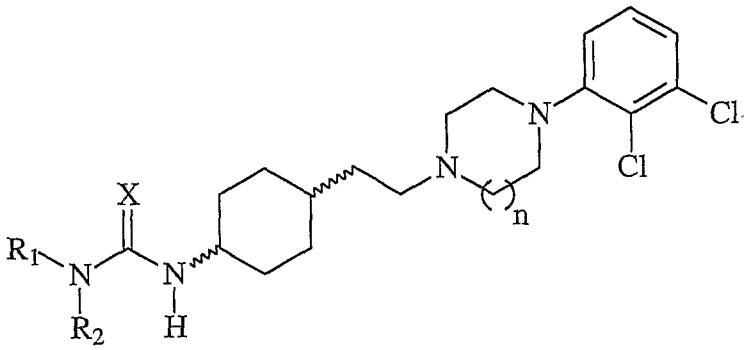
benzoyl group;

X represents oxygen or sulphur atom;

n is an integer of 1 to 2,

and/or geometric isomers and/or stereoisomers and/or diastereomers and/or physiologically acceptable salts and/or hydrates and/or solvates thereof and physiologically acceptable carrier(s) therefore.

14. A pharmaceutical composition comprising a compound of formula (I)



(I)

as claimed in any of claims 11 to 13,

wherein

R_1 and R_2 represent independently

hydrogen, or

C_{1-6} alkyl with straight or branched chain optionallly substituted with C_{1-6} alkoxycarbonyl, or phenyl or R_1 and R_2 form an optionally by C_{1-6} alkyl or hydroxy substituted pyrrolidine, piperazine, piperidine or morpholine ring;

allyl;

phenyl optionally substituted with one or more C_{1-6} alkoxy, cyano or C_{1-6} alkanoyl;

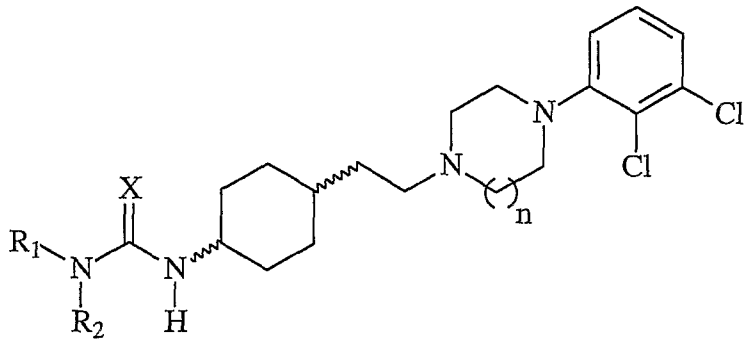
cyclohexyl;

X represents oxygen or sulphur;

n is 1,

and/or geometric isomers and/or stereoisomers and/or diastereomers and/or physiologically acceptable salts and/or hydrates and/or solvates thereof and physiologically acceptable carrier(s) therefore.

15. The use of a compound of formula (I)



(I)

wherein

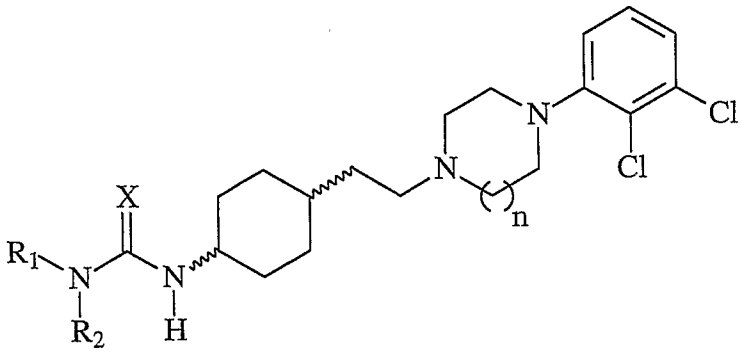
R_1 and R_2 represent independently a substituent selected from hydrogen, alkyl, alkenyl, aryl, cycloalkyl, aroyl, or R_1 and R_2 may form a heterocyclic ring with the adjacent nitrogen atom;

X represents an oxygen or sulphur atom;

n is an integer of 1 to 2,

and/or geometric isomers and/or stereoisomers and/or diastereomers and/or physiologically acceptable salts and/or hydrates and/or solvates thereof in the manufacture of a medicament for the treatment and/or prevention of a condition which requires modulation of dopamine receptor(s).

16. The use of a compound of formula (I)



(I)

as claimed in claim 15,

wherein

R_1 and R_2 represent independently

hydrogen, or

C_{1-6} alkyl, with straight or branched chain optionally substituted with one or more C_{1-6} alkoxycarbonyl, aryl, or(C_{1-6} alkoxycarbonyl)-C_{1-6} alkyl group, or R_1 and R_2 may form a heterocyclic ring with the adjacent nitrogen atom, which may be saturated or unsaturated optionally substituted monocyclic or bicyclic ring, which may contain further heteroatoms selected from O, N, or S, or

C_{2-7} alkenyl with 1 to 3 double bond, or

a mono-, bi- or tricyclic aryl, optionally sustituted 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 or cyano, or

an optionally substituted mono-, bi- or tricyclic cycloalkyl group, or

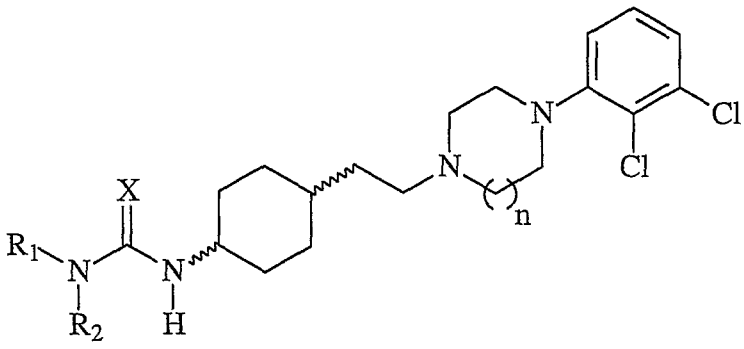
aroyl group;

X represents oxygen or sulphur atom;

n is an integer of 1 to 2,

and/or geometric isomers and/or stereoisomers and/or diastereomers and/or physiologically acceptable salts and/or hydrates and/or solvates thereof in the manufacture of a medicament for the treatment and/or prevention of a condition which requires modulation of dopamine receptor(s).

17. The use of a compound of formula (I)



(I)

as claimed in claims 15 and 16,

wherein

R_1 and R_2 represent independently

hydrogen, or

C_{1-6} alkyl, with straight or branched chain optionally substituted with one or more C_{1-6} alkoxycarbonyl, phenyl or (C_{1-6} alkoxycarbonyl)-C_{1-6} alkyl group, or R_1 and R_2 may form a heterocyclic ring with the adjacent nitrogen atom, which may be unsaturated optionally by C_{1-6} alkyl or hydroxy substituted monocyclic ring, which may contain further heteroatoms selected from O or N, or

C_{2-7} alkenyl with 1 double bond, or

phenyl or naphthyl group optionally sustituted 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 or cyano, or

cyclohexyl or adamantyl group, or

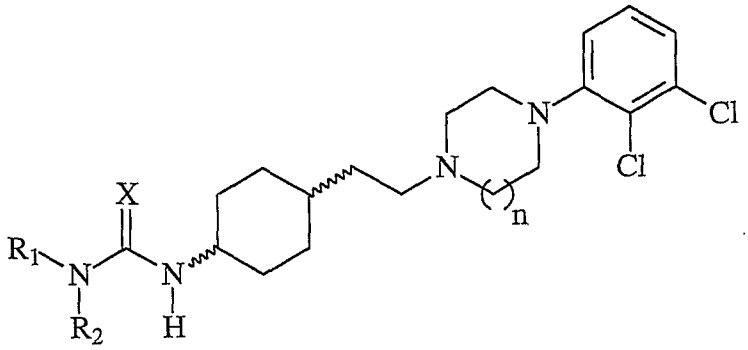
benzoyl group;

X represents oxygen or sulphur atom;

n is an integer of 1 to 2,

and/or geometric isomers and/or stereoisomers and/or diastereomers and/or physiologically acceptable salts and/or hydrates and/or solvates thereof in the manufacture of a medicament for the treatment and/or prevention of a condition which requires modulation of dopamine receptor(s).

18. The use of a compound of formula (I)



(I)

as claimed in any of claims 15 to 17,

wherein

R_1 and R_2 represent independently

hydrogen, or

C_{1-6} alkyl with straight or branched chain optionallly substituted with C_{1-6} alkoxycarbonyl, or phenyl or R_1 and R_2 form an optionally by C_{1-6} alkyl or hydroxy substituted pyrrolidine, piperazine, piperidine or morpholine ring;

allyl;

phenyl optionally substituted with one or more C_{1-6} alkoxy, cyano or C_{1-6} alkanoyl;

cyclohexyl;

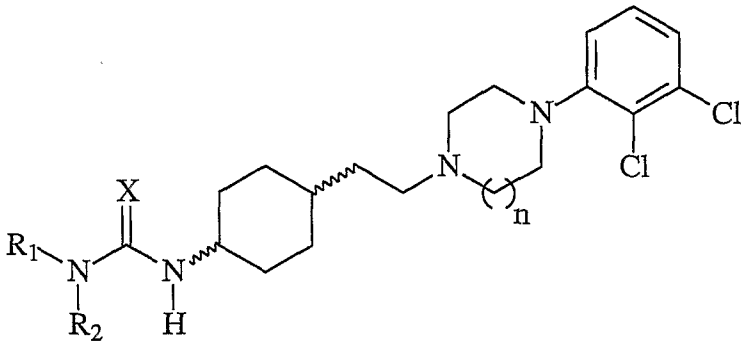
X represents oxygen or sulphur;

n is 1,

and/or geometric isomers and/or stereoisomers and/or diastereomers and/or physiologically acceptable salts and/or hydrates and/or solvates thereof in the manufacture of a medicament for the treatment and/or prevention of a condition which requires modulation of dopamine receptor(s).

19. The use according to any claims of 15 to 18, wherein the dopamine receptor is a dopamine D_3 and/or D_2 receptor.

20. A method of treating and/or preventing a condition which requires modulation of dopamine receptor(s) which comprises administering to a subject in need thereof an effective amount of a compound of formula (I)



(I)

wherein

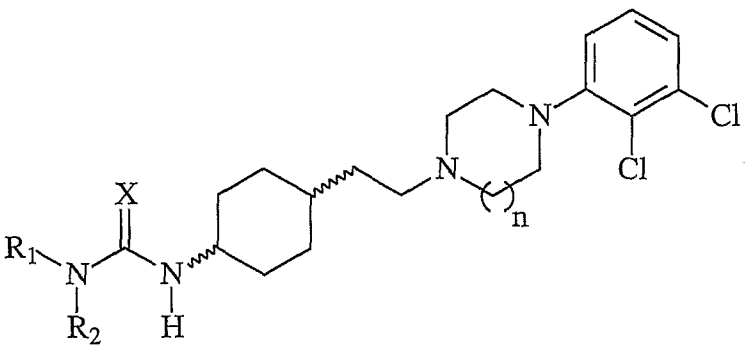
R_1 and R_2 represent independently a substituent selected from hydrogen, alkyl, alkenyl, aryl, cycloalkyl, aroyl, or R_1 and R_2 may form a heterocyclic ring with the adjacent nitrogen atom;

X represents an oxygen or sulphur atom;

n is an integer of 1 to 2,

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

21. A method of treating and/or preventing a condition which requires modulation of dopamine receptor(s) which comprises administering to a subject in need thereof an effective amount of a compound of formula (I)



(I)

as claimed in claim 20,

wherein

R_1 and R_2 represent independently

hydrogen, or

C_{1-6} alkyl, with straight or branched chain optionally substituted with one or more C_{1-6} alkoxycarbonyl, aryl, or (C_{1-6} alkoxycarbonyl)-C_{1-6} alkyl group, or R_1 and R_2 may form a heterocyclic ring, which may be saturated or unsaturated optionally substituted monocyclic or bicyclic ring, which may contain further heteroatoms selected from O, N, or S, or

C_{2-7} alkenyl with 1 to 3 double bond, or

a mono-, bi- or tricyclic aryl optionally sustituted 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 or cyano, or

an optionally substituted mono-, bi- or tricyclic cycloalkyl group, or

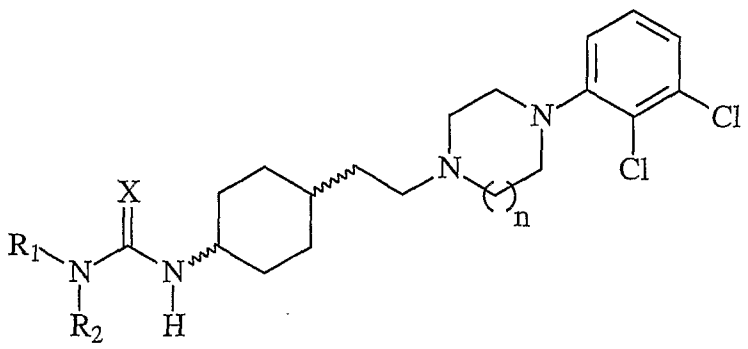
aroyl group;

X represents oxygen or sulphur atom;

n is an integer of 1 to 2,

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

22. A method of treating and/or preventing a condition which requires modulation of dopamine receptor(s) which comprises administering to a subject in need thereof an effective amount of a compound of formula (I)



(I)

as claimed in claims 20 and 21,

wherein

R_1 and R_2 represent independently

hydrogen, or

C_{1-6} alkyl, with straight or branched chain optionally substituted with one or more C_{1-6} alkoxycarbonyl, phenyl or (C_{1-6} alkoxycarbonyl)-C_{1-6} alkyl group. R_1 and R_2 may optionally form a heterocyclic ring, which may be unsaturated optionally by C_{1-6} alkyl or hydroxy substituted monocyclic ring, which may contain further heteroatoms selected from O or N, or

C_{2-7} alkenyl with 1 double bond, or

phenyl or naphthyl group optionally sustituted 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 or cyano, or

cyclohexyl or adamantyl group, or

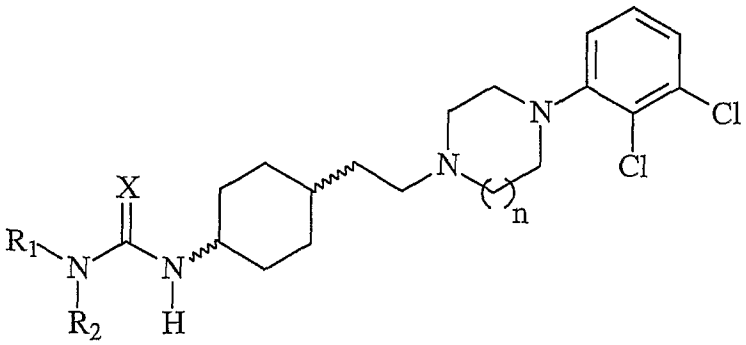
benzoyl group;

X represents oxygen or sulphur atom;

n is an integer of 1 to 2,

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

23. A method of treating and/or preventing a condition which requires modulation of dopamine receptor(s) which comprises administering to a subject in need thereof an effective amount of a compound of formula (I)



(I)

as claimed in any claims of 20 to22,

wherein

R_1 and R_2 represent independently

hydrogen, or

C_{1-6} alkyl with straight or branched chain optionallly substituted with C_{1-6} alkoxycarbonyl, or phenyl or R_1 and R_2 form a an optionally by C_{1-6} alkyl or hydroxy substituted pyrrolidine, piperazine, piperidine or morpholine ring;

allyl;

phenyl optionally substituted with one or more C_{1-6} alkoxy, cyano or C_{1-6} alkanoyl;

cyclohexyl;

X represents oxygen or sulphur;

n is 1,

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

24. The method according to any of claims 15 to 18, wherein the dopamine receptor is a dopamine D_3 and/or D_2 receptor.