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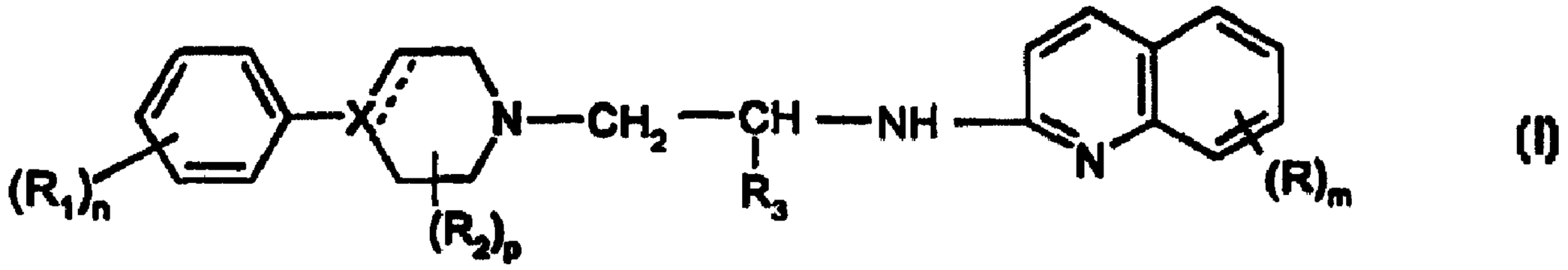
(54) Titre : DERIVES DE 2-AMINOQUINOLINE AYANT UNE ACTIVITE AGONISTE DU RECEPTEUR D4
(54) Title: 2-AMINOQUINOLINE DERIVATIVES HAVING D4-AGONISTIC ACTIVITY



(I)

(57) Abrégé/Abstract:
The present invention relates to a group of novel 2-aminoquinoline derivatives which are potent and selective agonists of the dopamine D4-receptor. The compounds have general formula (I) wherein $(R_1)_n$ represents 1 or 2 substituents, which can be the same or different, from the group C_{1-3}-alkyl or alkoxy, halogen, trifluoromethyl, nitro, amino, and mono- or dialkyl (C_{1-2})-amino, or two groups R_1 at adjacent carbon atoms together with the benzene ring may form the benzdioxane group or benzofuran group, X represents nitrogen or carbon, and the dotted line may represent a double bond, $(R_2)_p$ represents 0, 1 or 2 substituents, which can be the same or different, from the group methyl and ethyl, or $(R_2)_p$ is a methylene bridge or ethylene bridge, R_3 is hydrogen or methyl, and $(R)_m$ represents 0, 1, or 2 substituents, which can be the same or different and can be located at all available positions of the quinolyl group, from the group C_{1-3}-alkyl or alkoxy, halogen, trifluoromethyl, nitro, amino, and mono- or dialkyl (C_{1-2})-amino, on the understanding that R_1 cannot represent o-OCH_3 when X is nitrogen, $(R_2)_p$ and R_3 are hydrogen, m is 0 and n is 1.

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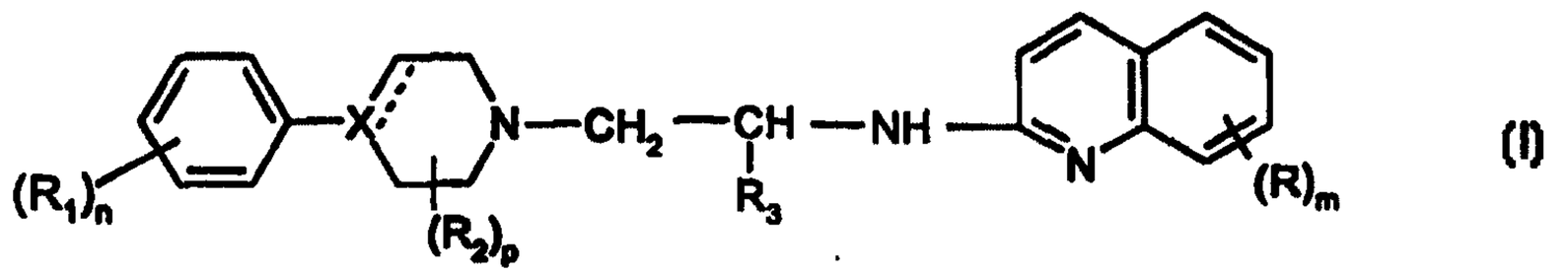
(54) Title: 2–AMINOQUINOLINE DERIVATIVES HAVING D4–AGONISTIC ACTIVITY



(I)

(57) Abstract

The present invention relates to a group of novel 2–aminoquinoline derivatives which are potent and selective agonists of the dopamine D4–receptor. The compounds have general formula (I) wherein $(R_1)_n$ represents 1 or 2 substituents, which can be the same or different, from the group C_{1-3}–alkyl or alkoxy, halogen, trifluoromethyl, nitro, amino, and mono– or dialkyl (C_{1-2})–amino, or two groups R_1 at adjacent carbon atoms together with the benzene ring may form the benzdioxane group or benzofuran group, X represents nitrogen or carbon, and the dotted line may represent a double bond, $(R_2)_p$ represents 0, 1 or 2 substituents, which can be the same or different, from the group methyl and ethyl, or $(R_2)_p$ is a methylene bridge or ethylene bridge, R_3 is hydrogen or methyl, and $(R)_m$ represents 0, 1, or 2 substituents, which can be the same or different and can be located at all available positions of the quinolyl group, from the group C_{1-3}–alkyl or alkoxy, halogen, trifluoromethyl, nitro, amino, and mono– or dialkyl (C_{1-2})–amino, on the understanding that R_1 cannot represent o–OCH_3 when X is nitrogen, $(R_2)_p$ and R_3 are hydrogen, m is 0 and n is 1.

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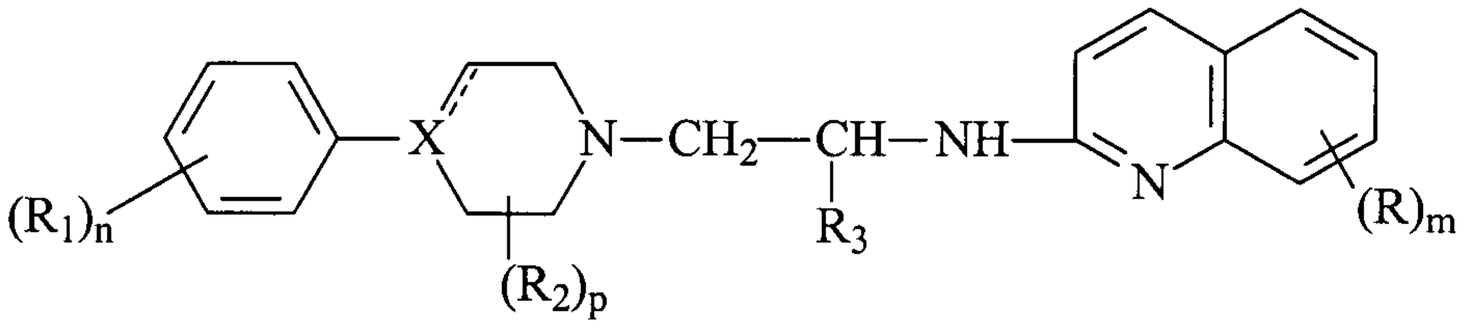
2-Aminoquinoline derivatives having D4-agonistic activity

The present invention relates to a group of novel 2-aminoquinoline derivatives, to a method for the preparation of these compounds, and to pharmaceutical compositions containing one or more of these compounds as an active component.

Canadian Patent Application No. 2,293,480, published after the priority date of the present invention, discloses 2-aminoalkylaminoquinolines as dopamine D_4 ligands. The compounds disclosed in the Examples of that patent application are either pyrimidine or pyridine derivatives, or are linked through a propylene bridge. These are structural features, which are not present in the structures of formula (I) of the present invention.

EP 0512755 relates to a group of piperazine derivatives having 5-HT_{1A} antagonistic activity. The nitrogen in the quinolyl-2-amino moiety of these compounds is substituted with a group $-CZR^3$, wherein Z is oxygen or sulphur, and R^3 represents lower alkyl, cycloalkyl, aryl, heteroaryl or substituted amino.

It has surprisingly been found that the compounds and salts thereof of the formula (I)



(I)

wherein

- $(R_1)_n$ represents 1 or 2 substituents, which can be the same or different, from the group C_{1-3}-alkyl or alkoxy, halogen, trifluoromethyl, nitro, amino, and mono- or dialkyl(C_{1-2})-amino, or two groups R_1 at adjacent carbon atoms together with the benzene ring may form the benzdioxane group or benzofuran group,

- X represents nitrogen or carbon, and the dotted line may represent a double bond,

- $(R_2)_p$ represents 0, 1 or 2 substituents, which can be the same or different, from the group methyl and ethyl, or $(R_2)_p$ is a methylene bridge or ethylene bridge,

- R_3 is hydrogen or methyl, and

- $(R)_m$ represents 0, 1 or 2 substituents, which can be the same or different and can be located at all available positions of the quinolyl group, from the group C_{1-3}-alkyl or alkoxy, halogen, trifluoromethyl, nitro, amino, and mono- or dialkyl(C_{1-2})-amino,

- on the understanding that R_1 cannot represent o-OCH_3 when X is nitrogen, $(R_2)_p$ and R_3 are hydrogen, and m is 0 and n is 1,

are potent and selective agonists of the dopamine D4-receptor.

According to one aspect of the present invention, there is provided a compound of formula (I) or a salt thereof

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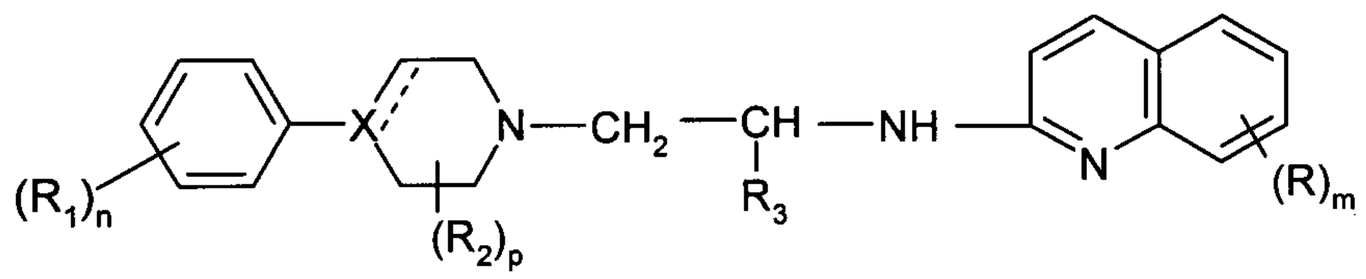
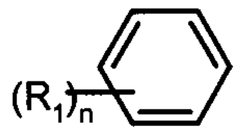


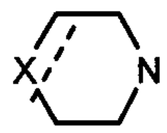
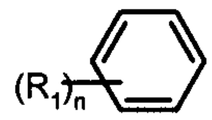
(I)

wherein the compound is

1-(2-[2-quinolyl]amino)-ethyl-4-(4-methoxyphenyl) piperazine

or the compound of formula (I), wherein $(R_2)_p$ and R_3 are hydrogen, and $(R)_m$,

 and  are as defined in a row of the following table:

$(R)_m$		
H	piperazine	benzofuran-7-yl
H	piperazine	1,4-benzodioxan-5-yl
H	piperazine	m-CF_3-phenyl
H	piperazine	p-Cl-phenyl
H	3,4-dehydropiperidine	p-CH_3O-phenyl
H	piperidine	p-CH_3O-phenyl
6-Cl	piperazine	p-CH_3O-phenyl
7-Cl	piperazine	p-CH_3O-phenyl
8-Cl	piperazine	p-CH_3O-phenyl
4-CH_3	piperazine	p-CH_3O-phenyl
8-OCH_3	piperazine	p-CH_3O-phenyl
5-Cl	piperazine	p-CH_3O-phenyl

Compounds having formula (I) wherein R, R_1 and X have the above meaning, m is 0 or 1, n is 1, and $(R_2)_p$ and R_3 represent hydrogen, and salts thereof are preferred.

Especially preferred are compounds wherein $(R_1)_n$ is p-OCH_3, and the remaining variables are as previously described, and salts thereof.

Of particular interest is the compound 1-(2-[2-quinolyl]amino)-ethyl-4-(4-methoxyphenyl) piperazine, and salts thereof.

Due to the potent and selective D4-agonistic activity the compounds according to the invention are suitable for use in the treatment of psychiatric disorders such as psychosis, anxiety, depression, attention deficits, memory disorders,neurological disorders such as Parkinson's disease and ischaemia and other CNS-diseases involving dopaminergic neurotransmission.

The affinity of the compounds of the invention for dopamine D4 receptors was determined using CHO-K1 cells which are stably transfected to express the human recombinant dopamine receptor, D4.2 subtype (Van Tol et al, Nature 350, 610, 1991) and using [3H]-Spiperone as the ligand. After incubation of a freshly prepared cellmembrane preparation with the [3H]-ligand, with or without addition of compounds of the invention, separation of bound and free ligand was performed by filtration over glassfiberfilters (Research Biochemicals International protocol, Catalog No. D-177). Radioactivity on the filter was measured by liquid scintillation counting. Results are expressed as IC50 values and transformed into inhibitory constants (Ki).

The dopamine D4 agonistic activity of compounds of the invention was determined by functional studies using CHO-K1 cells stably expressing the human dopamine D4.4 receptor (Van Tol, et al, Nature, 358, 149, 1992). These cells were fitted with a construct encoding a truncated form of alkaline phosphatase, causing it to get secreted by the cells. Expression of this secretable alkaline phosphatase (SeAP) is under direct control of cellular cyclic AMP (Berger et al, Gene, 66, 1, 1988). SeAP measurements were done with p-nitrophenylphosphate (pNPP) as the substrate using

colorimetric readout at 450 nm. Dopamine D4 agonist activity was determined by incubation of cells with prostaglandin PGE1 (1uM), with or without addition of compounds of the invention, and subsequent quantification of the concentration-dependant attenuation of dopamine D4 receptor mediated SeAP formation, yielding estimates of intrinsic activity and potency (pEC50 values). Quinpirole and dopamine were used as reference dopamine agonists.

Absence of dopamine D4 antagonistic activity was confirmed using the same assay, but co-incubating cells with prostaglandin PGE1 (1uM) and the standard agonist quinpirole (1uM), with or without addition of compounds of the invention. In this way, the antagonistic effect of compounds of the invention against agonist dependant attenuation of dopamine D4 receptor mediated stimulation of adenylate cyclase and subsequent SeAP formation was determined.

Dopamine D4 agonist properties and the absence of D4 antagonist properties of selected compounds of the invention were further confirmed using radioactive measurements of cAMP formation according to Salomon et al. (Anal Biochem, 58, 541, 1974) as modified by Weiss et al. (J Neurochem 45, 869, 1985).

The selectivity of the compounds of the invention with regard to the dopamine D2 receptor, was determined by measuring the affinity for dopamine D2 receptors using rat brain homogenates and [3H]-Spiperone as the ligand (Leysen et al, Biochem Pharmacol 27, 307, 1978). After incubation of a freshly prepared cellmembrane preparation with the [3H]-ligand, with or without addition of compounds of the invention, separation of bound and free ligand was performed by filtration over glassfiberfilters. Radioactivity on the filter was measured by liquid scintillation counting. Results are expressed as IC50 values and transformed into inhibitory constants (Ki).

The dopamine D2 (ant)agonistic activity of compounds of the invention was determined by functional studies based on radioactive measurements of cAMP formation according to Salomon et al. (Anal Biochem, 58,541, 1974) as modified by Weiss et al. (J Neurochem 45, 869, 1985), using CHO cells,

stably expressing human dopamine D2L receptors (Grandy et al, Proc Natl Acad Sci USA, 86, 9762, 1989).

Suitable acids with which the compounds can form pharmaceutically acceptable acid addition salts are for example hydrochloric acid, sulphuric acid, phosphoric acid, nitric acid, and organic acids such as citric acid, fumaric acid, maleic acid, tartaric acid, acetic acid, benzoic acid, p-toluene sulphonic acid, methane sulphonic acid and naphthalene sulphonic acid.

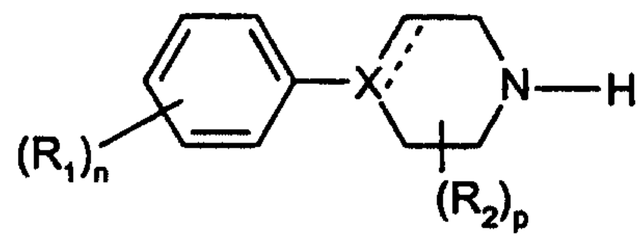
The compounds of the invention can be brought into forms suitable for administration by means of usual processes using auxiliary substances and/or liquid or solid carrier materials.

The compounds of the invention having formula (I) can be obtained according to methods known for the synthesis of structurally related compounds.

A suitable method for the preparation of the compounds having formula (I) is the following:

Step 1

Reaction of a compound having formula (II):

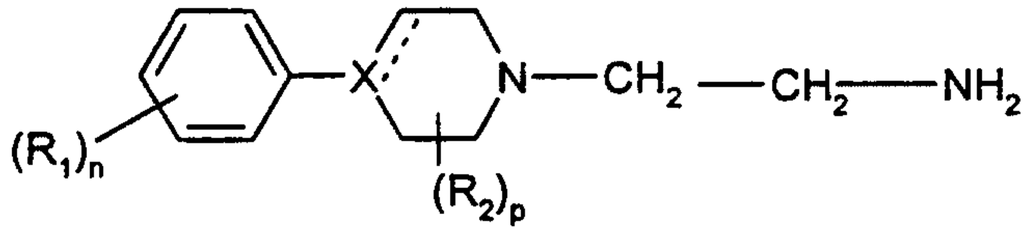


(II)

with chloroacetonitrile in a polar solvent such as acetonitrile in the presence of a base such as triethylamine.

Step 2

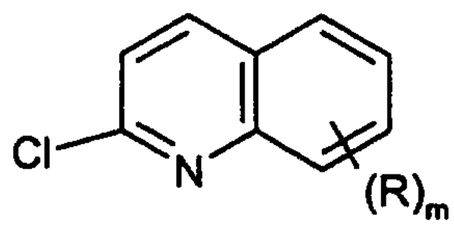
The obtained N-cyanomethyl derivative of the compound of formula (II) can be hydrogenated with a reducing agent such as lithium aluminium hydride in an aprotic solvent such as tetrahydrofuran to give the corresponding 2-aminoethyl derivative having formula (III):



(III)

Step 3:

The compound having formula (III) is then reacted with a suitable 2-chloroquinoline derivative of the formula (IV):



(IV)

in the presence of a base such as potassium carbonate in a polar aprotic solvent such as dimethylsulfoxide at 20 - 140°C, to give the desired compound having formula (I).

The preparation of the compounds of the present invention is illustrated with the following examples.

Example I

1-(2-[2-quinolyl]amino)-ethyl-4-(4-methoxyphenyl) piperazine .hydrochloride

Part A: To a solution of 19.2 g (100 mmol) of commercially available 4-methoxyphenyl piperazine in acetonitrile (300 ml), 12.1 g (120 mmol) of triethylamine and 7.6 g (100 mmol) of chloroacetonitrile were subsequently added. The reaction mixture was refluxed for 2 hrs, cooled to room temperature and concentrated *in vacuo*. To the residue dichloromethane (300 ml) and water (150 ml) were added, the water layer was further extracted with dichloromethane (50 ml), the combined organic layers were dried over sodiumsulphate and concentrated *in vacuo*. In this manner 18.5 g of 1-(cyanomethyl)-4-(4-methoxyphenyl) piperazine (80%) was obtained as a white solid.

Part B: To a solution of 18.5 g (80 mmol) of 1-(cyanomethyl)-4-(4-methoxyphenyl) piperazine in dry tetrahydrofuran (350 ml), heated to 40 °C, a quantity of 6.1 g (160 mmol, 2 equivalent) of lithium aluminium hydride was added in portions. Cooling of the reaction mixture was required to keep the temperature at about 40 °C during addition of the lithium aluminium hydride. After reflux for 1 hr, the mixture was cooled to room temperature and subsequent dropwise addition was carried out of 1). a mixture of water (6 ml) and tetrahydrofuran (40 ml), 2). a solution of sodium hydroxide in water (2N, 12 ml) and 3). water (12 ml). The reaction mixture was heated at 40 °C for 2 hrs. The precipitate obtained after cooling to room temperature was removed by filtration and washed with tetrahydrofuran (two times 25 ml). The filtrate was concentrated *in vacuo*. To the filtrate water (300 ml) and dichloromethane (150 ml) were added, the water layer was further extracted with dichloromethane (two times 100 ml) , the combined organic layers were dried over sodium sulphate and concentrated *in vacuo*. The product was purified applying flash-chromatography over silicagel using dichloromethane/methanol/ammonia 85:14:1 as the eluent. After concentration *in vacuo* a total of 9.4 g of 1-(2-aminoethyl)-4-(4-methoxyphenyl) piperazine (50% yield) was obtained as an oil, slowly solidifying at room temperature.

Part C: A solution of 9.4 g (40 mmol) of 1-(2-aminoethyl)-4-(4-methoxyphenyl) piperazine in dry dimethyl sulfoxide (30 ml) , 6.5 g (40 mmol) of commercially available 2-chloroquinoline and 6.1 g (44 mmol, 1.1 equivalent) of dry potassium carbonate were heated to 120 °C under nitrogen for 20 hrs. After cooling to room temperature water (150 ml) and dichloromethane (100 ml) were added. The water layer was further extracted with dichloromethane (two times 100 ml), the combined organic layers were washed with water (40 ml), dried over sodium sulphate and concentrated *in vacuo*. The product was purified applying flash-chromatography over silicagel using dichloromethane/methanol 95:5 as the eluent. After concentration *in vacuo* the residual oil was dissolved in absolute ethanol (80 ml), heated to 70°C and a solution of 1.46 g hydrochloride (40 mmol) in absolute ethanol (10 ml) was added. After stirring for 1/2 hr at 70°C, subsequent cooling and stirring at room temperate for 2 hrs, the resulting precipitate was collected by filtration, washed with hexane (two times 25 ml) and dried *in vacuo*. In this manner

10.2 g of 1-(2-[2-quinolyl]amino)-ethyl-4-(4-methoxyphenyl) piperazine.hydrochloride was obtained as a white solid (64% yield)

In an analogous manner the compounds having formula (I), wherein R_2 and R_3 are hydrogen listed below have been prepared:

Table

Example	$(R)_m$			Salt
II	H	piperazine	benzofuran-7-yl	2.fumarate
III	H	piperazine	1,4-benzodioxan-5-yl	fumarate
IV	H	piperazine	m-CF_3-phenyl	2.HCl
V	H	piperazine	p-Cl-phenyl	2.HCl
VI	H	3,4-dehydropiperidine	p-CH_3O-phenyl	base
VII	H	piperidine	p-CH_3O-phenyl	base
VIII	6-Cl	piperazine	p-CH_3O-phenyl	base
IX	7-Cl	piperazine	p-CH_3O-phenyl	base
X	8-Cl	piperazine	p-CH_3O-phenyl	base
XI	4-CH_3	piperazine	p-CH_3O-phenyl	base
XII	8-OCH_3	piperazine	p-CH_3O-phenyl	base
XIII	5-Cl	piperazine	p-CH_3O-phenyl	base

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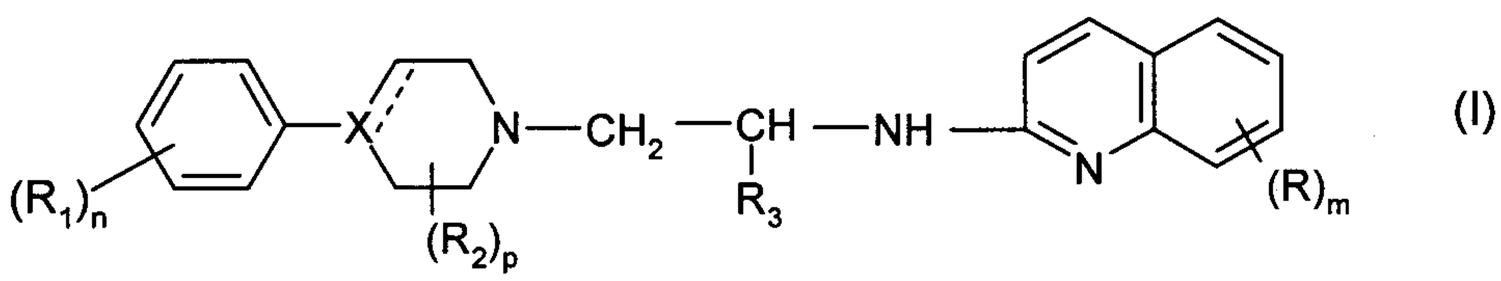
CLAIMS:

1. A compound of formula (I) or a salt thereof



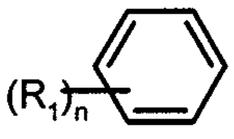
(I)

wherein the compound is

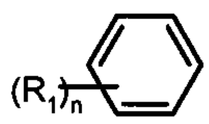
1-(2-[2-quinolyl]amino)-ethyl-4-(4-methoxyphenyl) piperazine

or the compound of formula (I), wherein $(R_2)_p$ and R_3 are hydrogen, and $(R)_m$,

and



are as defined in a row of the following table:

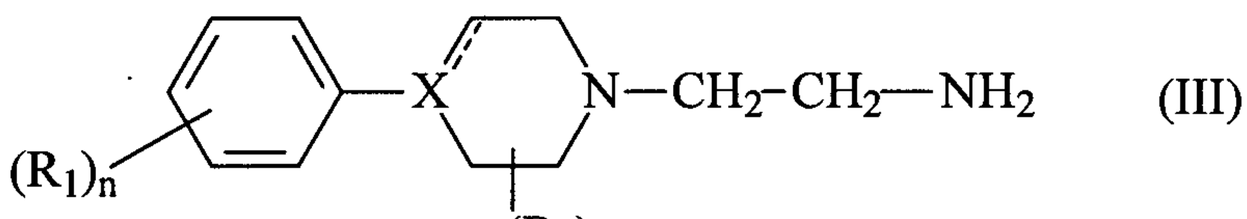
$(R)_m$		
H	piperazine	benzofuran-7-yl
H	piperazine	1,4-benzodioxan-5-yl
H	piperazine	m-CF_3-phenyl
H	piperazine	p-Cl-phenyl
H	3,4-dehydropiperidine	p-CH_3O-phenyl
H	piperidine	p-CH_3O-phenyl
6-Cl	piperazine	p-CH_3O-phenyl
7-Cl	piperazine	p-CH_3O-phenyl
8-Cl	piperazine	p-CH_3O-phenyl
4-CH_3	piperazine	p-CH_3O-phenyl
8-OCH_3	piperazine	p-CH_3O-phenyl
5-Cl	piperazine	p-CH_3O-phenyl

2. 1-(2-[2-Quinolyl]amino)-ethyl-4-(4-methoxyphenyl) piperazine or a salt thereof.

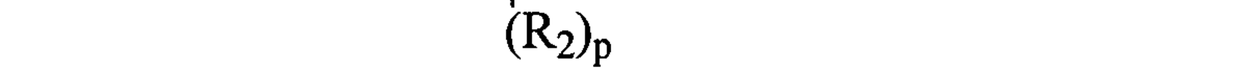
3. A pharmaceutical composition comprising a compound or salt as defined in claim 1 or 2 and a pharmaceutically acceptable carrier or diluent.

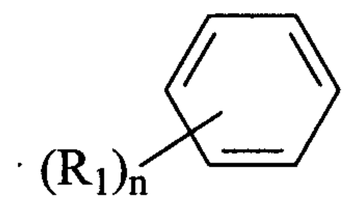
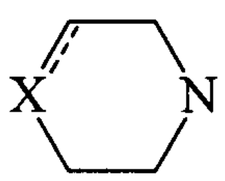
4. A method for preparing the pharmaceutical composition defined in claim 3, wherein the compound or salt as defined in claim 1 or 2 is admixed with the pharmaceutically acceptable carrier or diluent.

5. A method for preparation of the compound defined in claim 1, wherein R_3 is hydrogen comprising reacting a compound having formula (III)

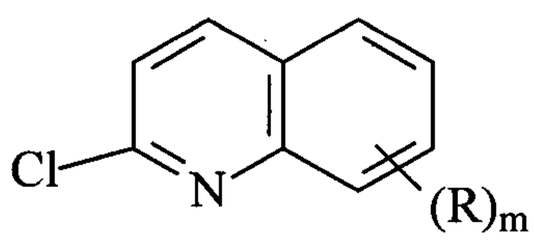


(III)



wherein $(R_2)_p$,  and 

are as defined for the compound of formula (I) in claim 1 with a compound of the formula (IV)



(IV)

wherein $(R)_m$ is as defined for the compound of formula (I) in claim 1.

6. A compound or salt as defined in claim 1 or 2 for treating a central nervous system disease involving dopaminergic neurotransmission.

7. A compound or salt as defined in claim 1 or 2 for treating a psychiatric disorder.

8. A compound or salt according to claim 7, wherein the psychiatric disorder is psychosis, anxiety, depression, an attention deficit or a memory disorder.

9. A compound or salt as defined in claim 1 or 2 for treating a neurological disorder.

10. A compound or salt according to claim 9, wherein the neurological disorder is Parkinson's disease or ischaemia.

11. Use of a compound or salt as defined in claim 1 or 2 for treating a central nervous system disease involving dopaminergic neurotransmission.

12. Use of a compound or salt as defined in claim 1 or 2 for treating a psychiatric disorder.

13. The use according to claim 12, wherein the psychiatric disorder is psychosis, anxiety, depression, an attention deficit or a memory disorder.

14. Use of a compound or salt as defined in claim 1 or 2 for treating a neurological disorder.

15. The use according to claim 14, wherein the neurological disorder is Parkinson's disease or ischaemia.

16. Use of a compound or salt as defined in claim 1 or 2 in preparation of a pharmaceutical composition for treating a central nervous system disease involving dopaminergic neurotransmission.

17. Use of a compound or salt as defined in claim 1 or 2 in preparation of a pharmaceutical composition for treating a psychiatric disorder.

18. The use according to claim 17, wherein the psychiatric disorder is psychosis, anxiety, depression, an attention deficit or a memory disorder.

19. Use of a compound or salt as defined in claim 1 or 2 in preparation of a pharmaceutical composition for treating a neurological disorder.

20. The use according to claim 19, wherein the neurological disorder is Parkinson's disease or ischaemia.

21. A pharmaceutical composition as defined in claim 3 for treating a central nervous system disease involving dopaminergic neurotransmission.

22. A pharmaceutical composition as defined in claim 3 for treating a psychiatric disorder.

23. A pharmaceutical composition according to claim 22, wherein the psychiatric disorder is psychosis, anxiety, depression, an attention deficit or a memory disorder.

24. A pharmaceutical composition as defined in claim 3 for treating a neurological disorder.

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25. A pharmaceutical composition according to claim 24, wherein the neurological disorder is Parkinson's disease or ischaemia.

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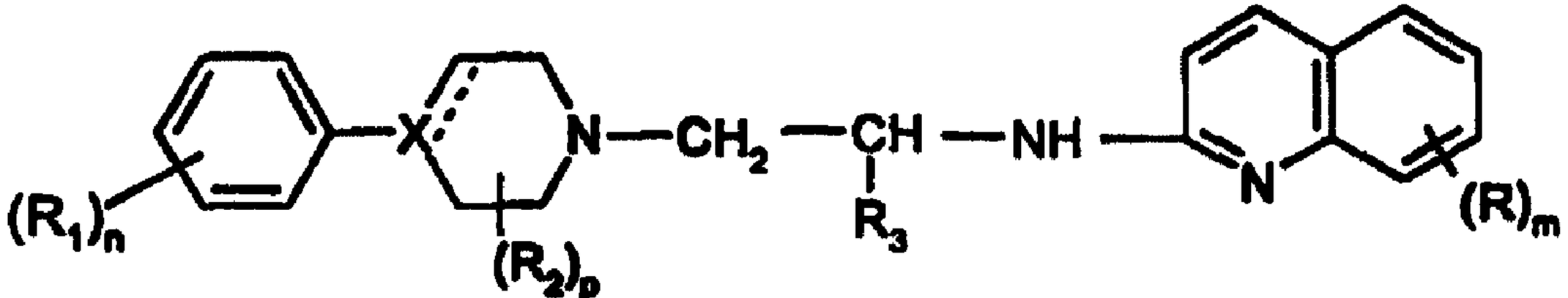

(I)