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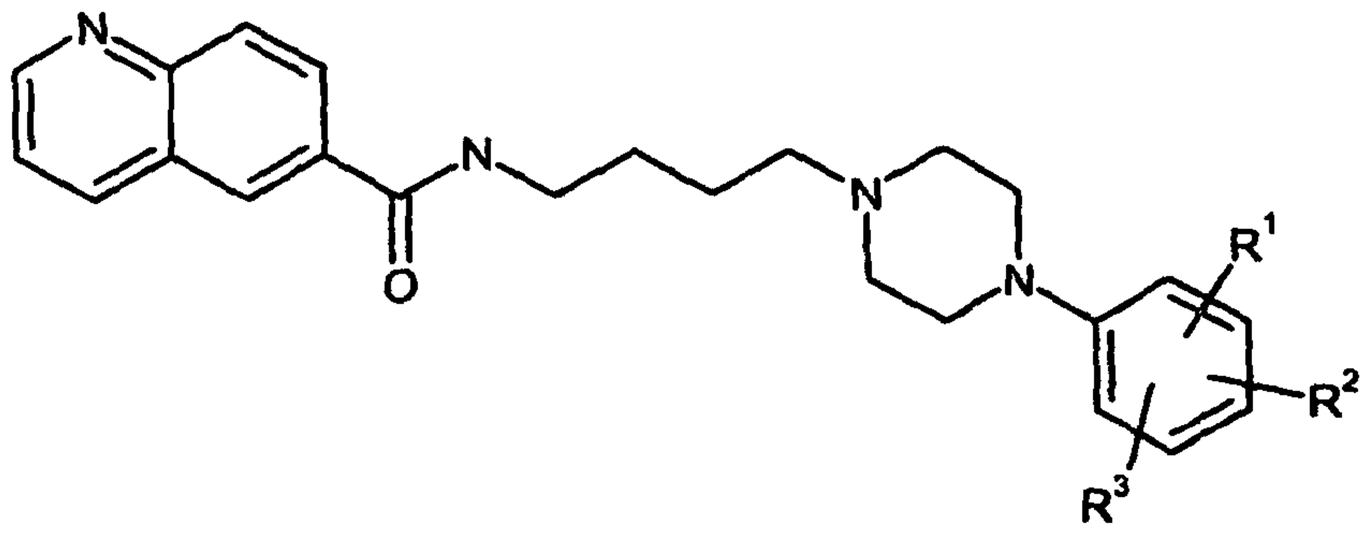
(54) Titre : DERIVES D'ARYLPIPERAZINE UTILES POUR LE TRAITEMENT DE TROUBLES NEUROPSYCHIATRIQUES
(54) Title: ARYL PIPERAZINE DERIVATIVES USEFUL FOR THE TREATMENT OF NEUROPSYCHIATRIC DISORDERS



(I)

(57) Abrégé/Abstract:
This invention provides novel aryl piperazine derivatives represented by Formula (I) having medical utility, in particular as modulators of dopamine and serotonin receptors, preferably the D_3, $5HT_{1A}$ and $5\text{-}HT_{2A}$ receptor subtypes, and in particular useful for the treatment of neuropsychiatric disorders, incl. schizophrenia.

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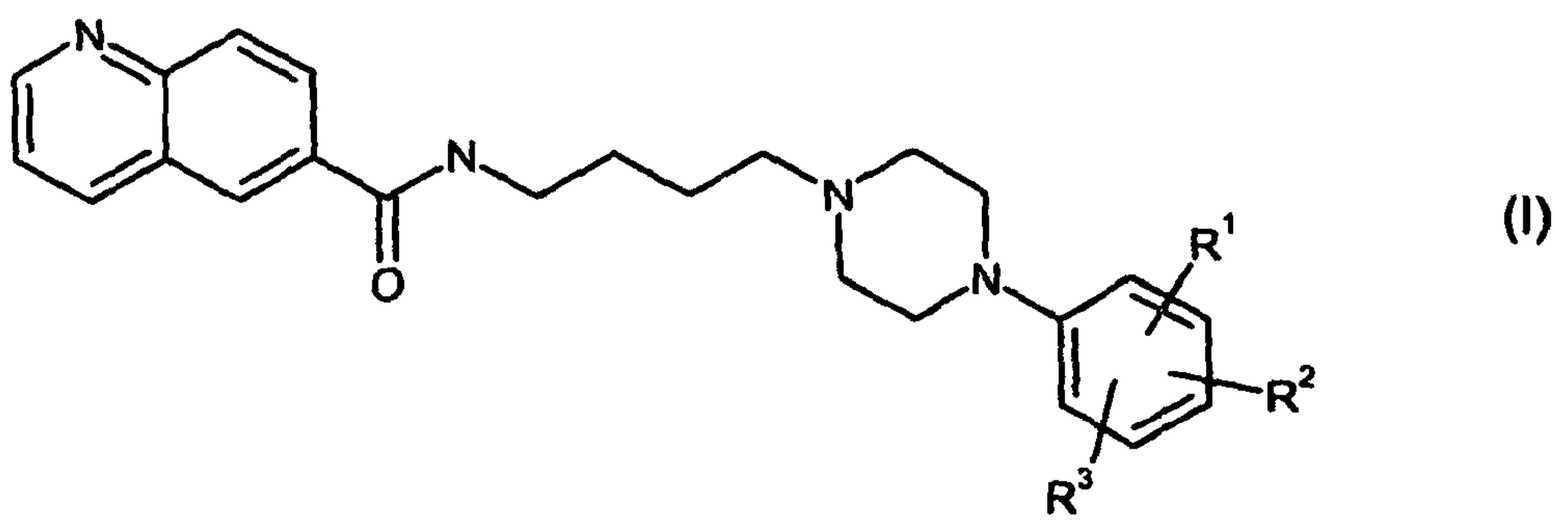
(54) **Title:** ARYL PIPERAZINE DERIVATIVES USEFUL FOR THE TREATMENT OF NEUROPSYCHIATRY DISORDERS



(I)

(57) **Abstract:** This invention provides novel aryl piperazine derivatives represented by Formula (I) having medical utility, in particular as modulators of dopamine and serotonin receptors, preferably the D_3, $5HT_{1A}$ and $5\text{-}HT_{2A}$ receptor subtypes, and in particular useful for the treatment of neuropsychiatric disorders, incl. schizophrenia.

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ARYL PIPERAZINE DERIVATIVES USEFUL FOR THE TREATMENT OF NEUROPSYCHIATRIC DISORDERS

TECHNICAL FIELD

This invention provides novel aryl piperazine derivatives having medical utility, in particular as modulators of dopamine and serotonin receptors, preferably the D_3, $5HT_{1A}$ and $5\text{-}HT_{2A}$ receptor subtypes, and in particular useful for the treatment of neuropsychiatric disorders, incl. schizophrenia.

BACKGROUND ART

Dopamine is involved in several important functions, excitatory and inhibitory, via dopaminergic receptors in the central and peripherical nervous system. Dopamine receptors were originally classified into two main groups: D_1 and D_2. The five currently cloned dopamine receptors fall into these classes. Thus, the D_1-like receptors include D_1 and D_5, while the D_2-like receptors include D_2, D_3 and D_4.

The dopamine receptors, and in particular the D_2-like receptors, are recognised as potential therapeutic targets for various neurological and psychiatric disorders, in particular psychotic disorders, incl. schizophrenia. Other therapeutic indications associated with the dopamine receptors include depression, Parkinson's disease, Huntington's disease, movement disorders such as dystonia, anxiety, restlessness, obsessive-compulsive disorders, mania, geriatric disorders, dementia, sexual dysfunction, musculo-skeletal pain symptoms, e.g. pain associated with fibromyalgia, substance abuse (cocaine abuse and addiction), abuse liability and withdrawal symptoms in drug addicts, and sleep disorders.

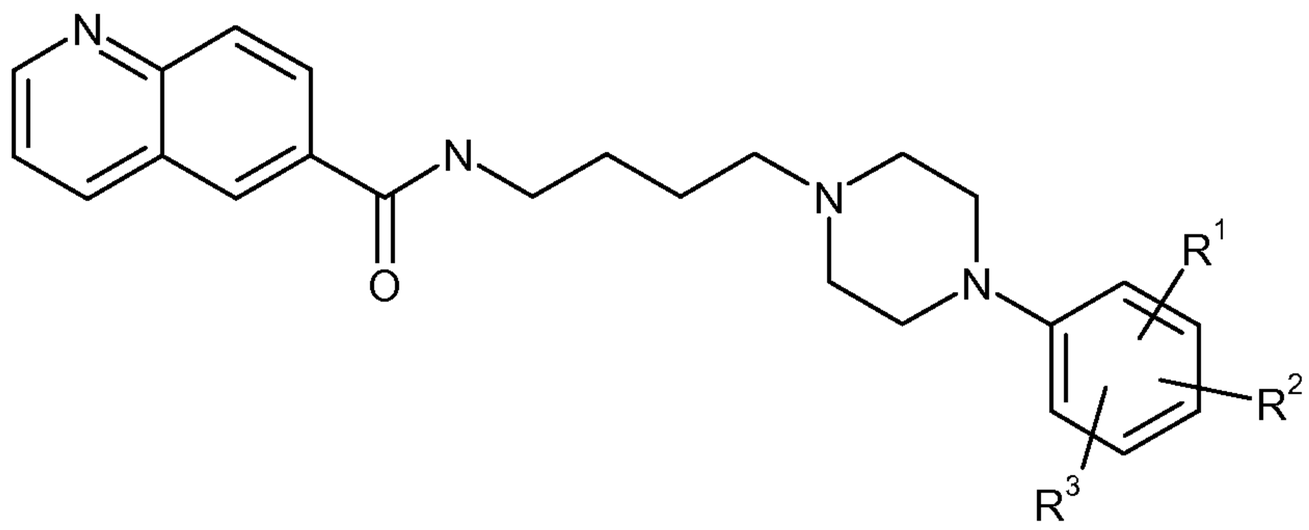
Still other therapeutic indications include eating disorders such as overeating, compulsive overeating, inability to regulate eating, bulimia and Binge-eating disorder.

Also the compounds of the invention may be useful for the treatment of abuse liability and withdrawal symptoms caused by termination of use of addictive substances. Such addictive substances include nicotine containing products such as tobacco, opioids such as heroin, cocaine and morphine, cannabis, benzodiazepines, benzodiazepine-like drugs, and alcohol. Withdrawal from addictive substances is in general a traumatic experience characterised by anxiety and frustration, anger, anxiety, difficulties in concentrating, restlessness, decreased heart rate and increased appetite and weight gain.

Finally receptor selective ligands find use as diagnostic tools in diagnostic methods, and in particular for *in vivo* receptor imaging (neuroimaging).

CLAIMS:

1. An aryl piperazine derivative represented by Formula I



(I)

an enantiomer thereof or a mixture of its enantiomers, or a pharmaceutically acceptable salt thereof, wherein R^1, R^2 and R^3, independently of each other, represent hydrogen, methyl, hydroxy, methoxy, halo, trifluoromethyl, cyano or carboxy.

2. The aryl piperazine derivative of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1, R^2 and R^3, independently of each other, represent hydrogen, methyl, hydroxy, methoxy, halo or trifluoromethyl.

3. The aryl piperazine derivative of claims 1, or a pharmaceutically acceptable salt thereof, wherein R^1, R^2 and R^3, independently of each other, represent hydrogen, halo, hydroxy or trifluoromethyl.

4. The aryl piperazine derivative of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1, R^2 and R^3, independently of each other, represent hydrogen, fluoro, chloro, bromo or trifluoromethyl.

5. The aryl piperazine derivative of claim 1, or a pharmaceutically acceptable salt thereof, wherein

one of R^1, R^2 and R^3, represents hydrogen or hydroxy; and

the two others of R^1, R^2 and R^3, independently of each other, represent methyl, methoxy, halo, trifluoromethyl, cyano or carboxy.

6. The aryl piperazine derivative of claim 1, or a pharmaceutically acceptable salt thereof, wherein

two of R^1, R^2 and R^3, represents hydrogen; and

the last one of R^1, R^2 and R^3 represent methyl, hydroxy, methoxy, halo, trifluoromethyl, cyano or carboxy.

7. The aryl piperazine derivative of claim 1, which is

N-(4-(4-Phenylpiperazin-1-yl)butyl)quinoline-6-carboxamide; or

Quinoline-6-carboxylic acid {4-[4-(2,3-difluoro-phenyl)-piperazin-1-yl]-butyl}-amide;

an enantiomer thereof or a mixture of its enantiomers, or a pharmaceutically acceptable salt thereof.

8. A pharmaceutical composition comprising a therapeutically effective amount of an aryl piperazine derivative of any one of claims 1-7, or a pharmaceutically-acceptable addition salt thereof, or a prodrug thereof, together with at least one pharmaceutically acceptable carrier or diluent.

9. The aryl piperazine derivative of any one of claims 1-7, or a pharmaceutically acceptable salt thereof, or a prodrug thereof, for use as a medicament.

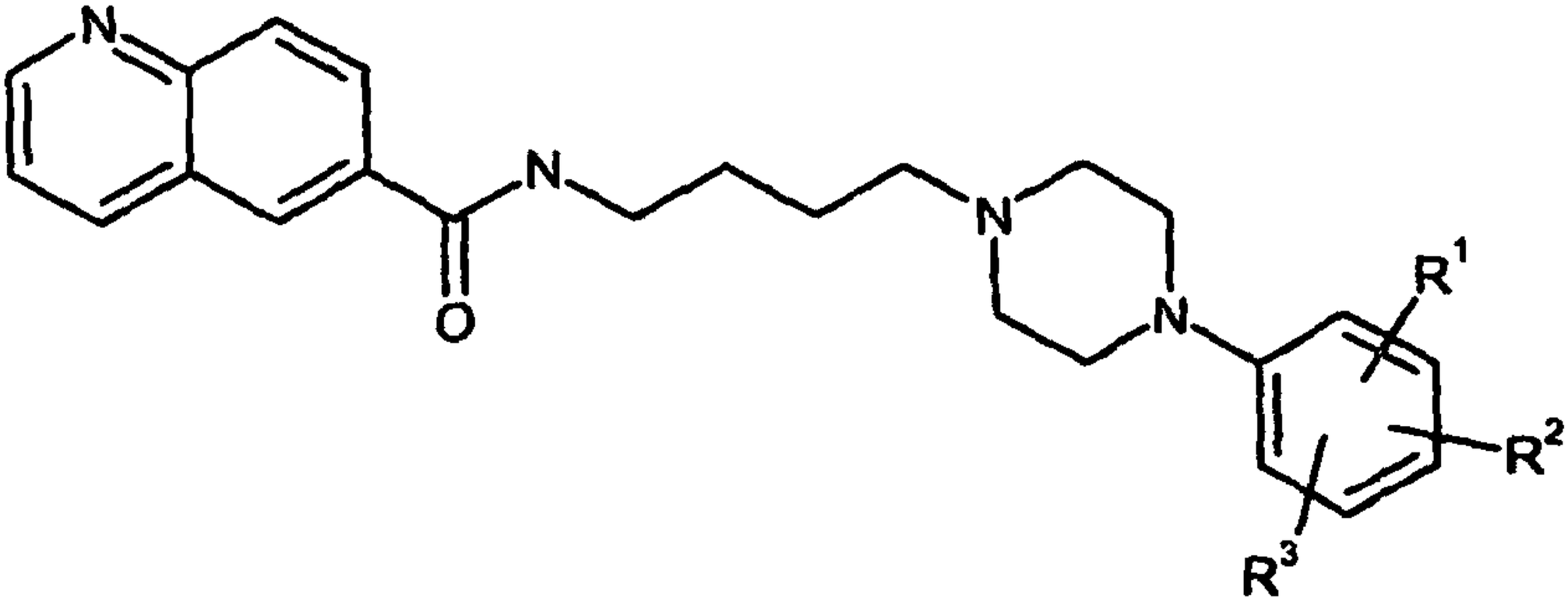
10. Use of the aryl piperazine derivative of any one of claims 1-7, or a pharmaceutically acceptable salt thereof, or a prodrug thereof, for the manufacture of a pharmaceutical composition.

11. Use of the aryl piperazine derivative of any one of claims 1-7, or a pharmaceutically acceptable salt thereof, for the manufacture of a pharmaceutical composition for the treatment, prevention or alleviation of a disease or a disorder or a condition of a mammal, including a human, which disease, disorder or condition is responsive to modulation of the dopamine and serotonin receptors.

12. The use according to claim 11, wherein the disease or a disorder or a condition is a neurological or psychiatric disorders, in particular psychotic disorders, schizophrenia, depression, Parkinson's disease, Huntington's disease, movement disorders, dystonia, anxiety, restlessness, obsessive-compulsive disorders, mania, geriatric disorders, dementia, sexual dysfunction, musculo-skeletal pain symptoms, pain associated with fibromyalgia, sleep disorders, substance abuse or addiction, and abuse liability and withdrawal symptoms in drug addicts, cocaine abuse or addiction.

13. The use according to claim 12, wherein the disease or a disorder or a condition is a neurological or psychiatric disorder, in particular a psychotic disorder, preferably schizophrenia.

14. A method of diagnosis, treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disorder, disease or condition is responsive to modulation of the dopamine and serotonin receptors, in particular the D_3, D_2-like and 5-HT_2 receptor subtypes, preferably the dopamine D_3 receptor subtype and/or the D_3/5-HT_{1A} or D_3/5-HT_{2A} receptor sybtypes, which method comprises the step of administering to such a living animal body in need thereof, a therapeutically effective amount of an aryl piperazine derivative according to any one of claims 1-7, a pharmaceutically acceptable salt thereof, or a prodrug thereof.



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