Tetrahydroquinoline derivatives for treating post-traumatic stress disorders

The present invention concerns the use of tetrahydroquinoline derivatives for the preparation of a medicament for preventing or treating post-traumatic stress disorders, as well as said tetrahydroquinoline derivatives for the prevention or the treatment of a post-traumatic stress disorder.

Human anxiety is a set of complex and interrelated forms of abnormal emotional reactions to particular environmental conditions. Human anxiety has been subdivided into five subtypes of anxiety disorders on the basis of differences in clinical expression and neurobiological substrate; these subtypes include: generalized anxiety disorders (GAD), panic anxiety disorders (PADs), phobic anxieties (PHOBs), obsessive-compulsive disorders (OCDs) and post-traumatic stress disorders (hereafter abbreviated PTSDs).

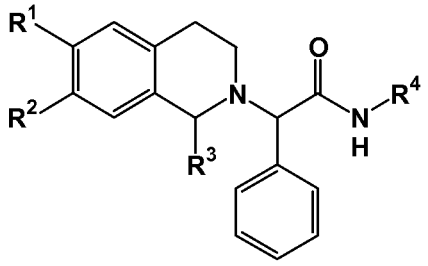
Orexin receptor antagonists are a novel type of nervous system or psychotropic drugs that decrease alertness and promote sleep. Their mode of action in animals and humans involves blockade of orexin receptors in the brain and modulation of sleep and arousal systems. Orexin receptor antagonists are currently developed for use in the treatment of sleep disorders and insomnias.

WO 01/68609 and WO 2005/118548 disclose that certain tetrahydroquinoline derivatives, including the compounds of formula I described below, are orexin receptor antagonists and can be used for the treatment of anxiety in general. However, US 2007/0160538 A1 discloses the use of orexin receptor antagonists (including the compounds of formula I mentioned below) for the treatment of several types of anxiety, but specifically excluding stress-related anxieties (and notably PTSDs).

It was now surprisingly discovered that, despite the teaching of US 2007/0160538 A1, the orexin receptor antagonists of formula I hereafter can be used for the preparation of a medicament, and are suitable, for the prevention or treatment of PTSDs.

Various embodiments of the invention are presented hereafter:

i) According to this invention, the compounds of formula I



I

wherein

R^1 and R^2 each independently represent $(C_1\text{-}C_4)$alkoxy,

R^3 represents aryl-$(C_1\text{-}C_4)$alkyl or heteroaryl-$(C_1\text{-}C_4)$alkyl, and

R^4 represents hydrogen or $(C_1\text{-}C_4)$alkyl,

or the pharmaceutically acceptable salts of said compounds of formula I, can be used for the preparation of a medicament, and are suitable, for the prevention or treatment of a PTSD.

The following paragraphs provide definitions of the various chemical moieties for the compounds according to the invention and are intended to apply uniformly throughout the specification and claims, unless an otherwise expressly set out definition provides a broader or narrower definition:

- The term "alkyl", used alone or in combination, refers to a saturated straight or branched chain alkyl group, containing from one to four carbon atoms. Representative examples of alkyl groups include methyl, ethyl, propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl and *tert*-butyl. The term "$(C_x\text{-}C_y)$alkyl" (x and y being two different integers) refers to a straight or branched chain alkyl group containing x to y carbon atoms.

- The term "alkoxy", used alone or in combination, refers to a saturated straight or branched chain alkoxy group, containing from one to four carbon atoms. Representative examples of alkoxy groups include methoxy, ethoxy, propoxy, *iso*-propoxy, *n*-butoxy, *iso*-butoxy, *sec*-butoxy and *tert*-butoxy. The term

"(C_x-C_y)alkoxy" (x and y being two different integers) refers to a straight or branched chain alkoxy group containing x to y carbon atoms.

- The term "halogen" refers to fluorine, chlorine, bromine or iodine, preferably to fluorine or chlorine.

- The term "aryl" refers to a phenyl group, which may be substituted one to three times by substituents each independently selected from the group consisting of halogen, alkyl, alkoxy, trifluoromethyl and trifluoromethoxy. Representative examples of aryl include, but are not limited to, phenyl, 4-trifluoromethyl-phenyl, 2-fluoro-phenyl, 3-fluoro-phenyl, 4-fluoro-phenyl, 2-chloro-phenyl, 3-chloro-phenyl, 4-chloro-phenyl, 2-methyl-phenyl, 3-methyl-phenyl, 4-methyl-phenyl, 2-methoxy-phenyl, 3-methoxy-phenyl and 4-methoxy-phenyl.

- The term aryl-(C_x-C_y)alkyl (x and y being two different integers) refers to a (C_x-C_y)alkyl group as previously defined in which one hydrogen atom has been replaced by an aryl group as previously defined. Representative examples of aryl-(C_1-C_4)alkyl groups include, but are not limited to, benzyl, 2-phenyl-ethyl and 2-(4-trifluoromethyl-phenyl)-ethyl.

- The term heteroaryl, alone or in combination, means a 5- to 10-membered monocyclic or bicyclic aromatic ring containing 1, 2 or 3 heteroatoms selected from oxygen, nitrogen and sulphur which may be the same or different. A heteroaryl group can be unsubstituted or substituted with up to three substituents independently selected from halogen, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, trifluoromethyl or trifluoromethoxy. Examples of such heteroaryl groups are pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, quinolinyl, isoquinolinyl, thienyl, thiazolyl, isothiazolyl, furyl, imidazolyl, pyrazolyl, pyrrolyl, indazolyl, indolyl, isoindolyl, benzimidazolyl, isoxazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, quinoxalinyl, phthalazinyl, cinnolinyl, isobenzofuranyl. A preferred heteroaryl group is pyridyl, which might be unsubstituted or substituted once with methyl, ethyl or methoxy.

- The term heteroaryl-(C_x-C_y)alkyl (x and y being two different integers) refers to a (C_x-C_y)alkyl group as previously defined in which one hydrogen atom has been replaced by a heteroaryl group as previously defined. Representative examples of heteroaryl-(C_1-C_4)alkyl groups include, but are not limited to, 2-(pyridin-3-yl)-ethyl

optionally substituted once on the pyridine ring with methyl, methoxy, chlorine or trifluoromethyl.

- The term "pharmaceutically acceptable salts" refers to non-toxic, inorganic or organic acid and/or base addition salts. Reference can be made to "Salt selection for basic drugs", *Int. J. Pharm.* (1986), **33**, 201-217.

ii) According to a preferred embodiment of this invention, the compounds of formula I as defined in embodiment i) above, or their pharmaceutically acceptable salts, will be such that R^1 represents methoxy or ethoxy (and preferably methoxy).

iii) According to another preferred embodiment of this invention, the compounds of formula I as defined in embodiment i) or ii) above, or their pharmaceutically acceptable salts, will be such that R^2 represents methoxy or ethoxy (and preferably methoxy).

iv) According to one variant of the invention, the compounds of formula I as defined in embodiment i), ii) or iii) above, or their pharmaceutically acceptable salts, will be such that R^3 represents aryl-(C_1-C_4)alkyl.

v) According to one subvariant of embodiment variant iv) above, the compounds of formula I as defined in embodiment iv) above, or their pharmaceutically acceptable salts, will be such that R^3 represents 4-trifluoromethyl-phenyl-methyl, 2-(4-trifluoromethyl-phenyl)-ethyl or 3-(4-trifluoromethyl-phenyl)-propyl (and especially 2-(4-trifluoromethyl-phenyl)-ethyl).

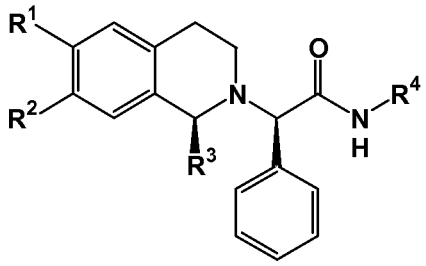
vi) According to another variant of the invention, the compounds of formula I as defined in embodiment i), ii) or iii) above, or their pharmaceutically acceptable salts, will be such that R^3 represents heteroaryl-(C_1-C_4)alkyl.

vii) According to one subvariant of embodiment variant vi) above, the compounds of formula I as defined in embodiment vi) above, or their pharmaceutically acceptable salts, will be such that R^3 represents (4-trifluoromethyl-3-pyridyl)-methyl, 2-(4-trifluoromethyl-3-pyridyl)-ethyl or 3-(4-trifluoromethyl-3-pyridyl)-propyl (and especially 2-(4-trifluoromethyl-3-pyridyl)-ethyl).

viii) According a further preferred embodiment of this invention, the compounds of formula I as defined in one of embodiments i) to vii) above, or their pharmaceutically

acceptable salts, will preferably be such that R^4 represents (C_1-C_4)alkyl (more preferably (C_1-C_3)alkyl, notably methyl or ethyl and in particular methyl).

ix) In a general manner, the compounds of formula I according to any one of embodiments i) to viii) used or suitable for the prevention or treatment of PTSDs, or their pharmaceutically acceptable salts, will be such that the configuration of the carbon atom bearing the phenyl group is (*R*) and that the configuration of the carbon atom bearing the radical R^3 is (*S*), that is, the compounds of formula I will have the configuration I*a* depicted below



I*a*

x) According to a particularly preferred variant of embodiments i) to v) and viii) or ix), the compound of formula I used or suitable for the prevention or treatment of PTSDs, or its pharmaceutically acceptable salt, will be 2-{6,7-dimethoxy-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-3,4-dihydro-1*H*-isoquinolin-2-yl}-*N*-methyl-2-phenyl-acetamide or one of its pharmaceutically acceptable salts.

xi) According to a preferred subembodiment of embodiment x), the compound of formula I used or suitable for the prevention or treatment of PTSDs, or its pharmaceutically acceptable salt, will be (*R*)-2-{(*S*)-6,7-dimethoxy-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-3,4-dihydro-1*H*-isoquinolin-2-yl}-*N*-methyl-2-phenyl-acetamide or one of its pharmaceutically acceptable salts (and especially (*R*)-2-{(*S*)-6,7-dimethoxy-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-3,4-dihydro-1*H*-isoquinolin-2-yl}-*N*-methyl-2-phenyl-acetamide hydrochloride).

xii) Another embodiment of this invention relates to a method of treating a patient affected by a PTSD, said method comprising the administration of a compound of formula I as defined in embodiment i) above, or a pharmaceutically acceptable salt thereof, in an amount sufficient to treat said PTSD.

xiii) Yet another embodiment of this invention relates to a method of reducing the symptoms of a patient affected by a PTSD, said method comprising the administration of a compound of formula I as defined in embodiment i) above, or a pharmaceutically acceptable salt thereof, in an amount sufficient to reduce the symptoms of the PTSD in said patient.

xiv) A further embodiment of this invention relates to a method of preventing, in a patient susceptible to be affected by a PTSD, the occurrence of the PTSD said method comprising the administration of a compound of formula I as defined in embodiment i) above, or a pharmaceutically acceptable salt thereof, in an amount sufficient to prevent the occurrence of the PTSD in said patient.

xv) Yet a further embodiment of this invention relates to a method of reducing, in a patient susceptible to be affected by a PTSD (that is, a person having been subject to traumatic stress), the symptoms of the PTSD, said method comprising the administration of a compound of formula I as defined in embodiment i) above, or a pharmaceutically acceptable salt thereof, in an amount sufficient to reduce the symptoms of the PTSD in said patient.

Concerning the methods corresponding to embodiments xii) to xv) above, the preferences mentioned regarding the compounds of formula I and their pharmaceutically acceptable salts in embodiments i) to xi) above are applicable *mutatis mutandis* to said methods.

The compounds of formula I and their pharmaceutically acceptable salts can be prepared by methods known to one skilled in the art (see e.g. WO 01/68609 and WO 2005/118548).

The compounds of formula I and their pharmaceutically acceptable salts can be used as medicaments for the prevention or treatment of PTSDs, e.g. in the form of pharmaceutical compositions for enteral or parenteral administration.

The production of the pharmaceutical compositions can be effected in a manner which will be familiar to any person skilled in the art (see for example Remington, The Science and Practice of Pharmacy, 21st Edition (2005), Part 5, "Pharmaceutical Manufacturing" [published by Lippincott Williams & Wilkins]) by bringing the described compounds of formula I or their pharmaceutically acceptable salts, optionally in combination with other

therapeutically valuable substances, into a galenical administration form together with suitable, non-toxic, inert, therapeutically compatible solid or liquid carrier materials and, if desired, usual pharmaceutical adjuvants.

The dose of a compound or pharmaceutically acceptable salt according to the present invention, to be provided for the treatment of PTSDs, varies according to the administration method, the age and body weight of the subject to be treated as well as the state of the latter, and will be finally decided by the attending doctor. As an indication, the amount of a compound of formula I contemplated to be given to the patient to reduce or eliminate the symptoms of PTSDs, either preventively or curatively, is from 1 mg to 1000 mg per day (i.e. from 0.015 to 15 mg/kg body weight per day), particularly from 5 mg to 500 mg per day (i.e. 0.075 to 7.5 mg/kg per day) and more particularly from 10 mg to 200 mg per day (i.e. 0.15 to 3 mg/kg per day).

Particular embodiments of the invention are described in the following Example, which serves to illustrate the invention in more detail without limiting its scope in any way.

Pharmacological properties of the invention compounds

Effect of a compound of formula I on fear-potentiated startle response in rats

Experimental methods:

The compounds of formula I can be administered to the animal in order to assess their effects on emotional reactivity. A decrease in reactivity, relative to the absence of the test agents, indicates that the administered compound reduces fear and anxiety. As used herein, a "control mammal" can be an untreated mammal (i.e. an animal receiving no agents or not the same combinations to be assessed), and/or a trained control mammal (i.e. a mammal that undergoes training to demonstrate a learned behaviour).

Signs of decreased emotional reactivity to acoustic stimuli have been discovered in an animal model of fear potentiated acoustic startle. Anxiolytic-like activity - as assessed by decreased acoustic startle reactivity - was observed one hour after treatment with a compound of the formula I compared to vehicle (PEG400) control treatment and to active treatment with diazepam given orally. This was observed in the Fischer F344 strain of

laboratory rats characterized by a particular degree of emotional reactivity. In human medicine, increased acoustic startle reactivity has been observed in patients suffering from PTSD anxiety compared to healthy subjects (Exaggerated acoustic startle reflex in Gulf War veterans with posttraumatic stress disorder, *Am. J. Psychiatry* (1996), **153**(1), 64-68).

In the fear-potentiated startle procedure in rats, a neutral stimulus such as light is repetitively paired with an aversive stimulus such as mild foot shock. When an animal is presented with loud acoustic stimuli, enhanced startle responses are elicited when the startle stimulus is preceded by the light (a classically conditioned increase in fear). Benzodiazepine anxiolytics attenuate the response enhancement. Startle response was recorded by using auditory startle chambers. After a 95-dB habituation session in the dark, 10 randomly alternating acoustic stimuli of 90, 95, or 105 dB (50-ms duration) were given in the presence or absence of light. Startle response amplitudes for each trial type were averaged for each rat across the entire test session.

Results:

The results obtained after performing the test described above on four groups of rats:

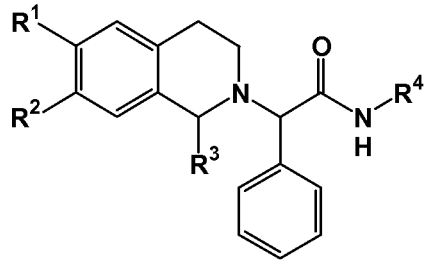
- a first group of 12 rats (called "control 1" in Figure 1) that have been treated with the vehicle only,
- a second group of 12 rats (called "Compound A" in Figure 1) that have received oral treatment by 107 mg/kg of (*R*)-2-{(*S*)-6,7-dimethoxy-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-3,4-dihydro-1*H*-isoquinolin-2-yl}-*N*-methyl-2-phenyl-acetamide hydrochloride,
- a third group of 16 rats (called "control 2" in Figure 1) that have been treated with the vehicle only, and
- a fourth group of 12 rats (called "Diazepam" in Figure 1), that have received oral treatment by 3 mg/kg diazepam,

have been summarised in Figure 1.

As one can see, oral treatment by (*R*)-2-{(*S*)-6,7-dimethoxy-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-3,4-dihydro-1*H*-isoquinolin-2-yl}-*N*-methyl-2-phenyl-acetamide hydrochloride (compound A, to be compared with rats of the group "control 1"), like oral treatment by diazepam (to be compared with rats of the group "control 2"), reduces in a significant manner the startle response amplitude in Fischer F344 rats.

Claims

1. Use of a compound of formula I



I

wherein

R^1 and R^2 each independently represent $(C_1\text{-}C_4)$alkoxy,

R^3 represents aryl-$(C_1\text{-}C_4)$alkyl or heteroaryl-$(C_1\text{-}C_4)$alkyl, and

R^4 represents hydrogen or $(C_1\text{-}C_4)$alkyl,

or of a pharmaceutically acceptable salt of said compound of formula I, for the preparation of a medicament for the prevention or treatment of a post-traumatic stress disorder.

2. Use according to claim 1, wherein the compound of formula I or its pharmaceutically acceptable salt is such that R^1 represents methoxy or ethoxy.

3. Use according to claim 1 or 2, wherein the compound of formula I or its pharmaceutically acceptable salt is such that R^2 represents methoxy or ethoxy.

4. Use according to one of claims 1 to 3, wherein the compound of formula I or its pharmaceutically acceptable salt is such that R^3 represents aryl-$(C_1\text{-}C_4)$alkyl.

5. Use according to claim 4, wherein the compound of formula I or its pharmaceutically acceptable salt is such that R^3 represents 2-(4-trifluoromethyl-phenyl)-ethyl.

6. Use according to one of claims 1 to 3, wherein the compound of formula I or its pharmaceutically acceptable salt is such that R^3 represents heteroaryl-$(C_1\text{-}C_4)$alkyl.

7. Use according to one of claims 1 to 6, wherein the compound of formula I or its pharmaceutically acceptable salt is such that R^4 represents (C_1-C_4)alkyl.

8. Use according to claim 7, wherein the compound of formula I or its pharmaceutically acceptable salt is such that R^4 represents methyl.

9. Use according to claim 1, wherein the compound of formula I or its pharmaceutically acceptable salt is 2-{6,7-dimethoxy-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-3,4-dihydro-1*H*-isoquinolin-2-yl}-*N*-methyl-2-phenyl-acetamide or one of its pharmaceutically acceptable salts.

10. Use according to claim 9, wherein the compound of formula I or its pharmaceutically acceptable salt is (*R*)-2-{(*S*)-6,7-dimethoxy-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-3,4-dihydro-1*H*-isoquinolin-2-yl}-*N*-methyl-2-phenyl-acetamide or one of its pharmaceutically acceptable salts.

11. Use according to claim 10, wherein (*R*)-2-{(*S*)-6,7-dimethoxy-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-3,4-dihydro-1*H*-isoquinolin-2-yl}-*N*-methyl-2-phenyl-acetamide hydrochloride is used.

12. A compound of formula I as described in any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof, for the prevention or treatment of a post-traumatic stress disorder.