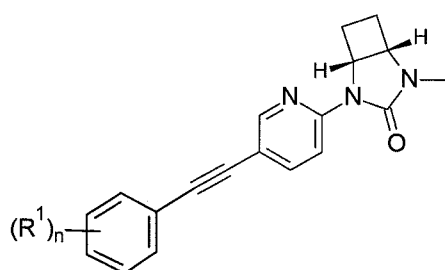


Fragile-X syndrome, autism spectrum disorders, Parkinson's disease, and gastro esophageal reflux disease (GERD)

Objects of the embodiments disclosed herein are compounds of formula I and their pharmaceutically acceptable salts, the above-mentioned compounds as pharmaceutically active substances and their production. Further objects of the embodiments disclosed herein are medicaments based on a compound in accordance with the disclosure and their manufacture as well as the use of the compounds in the control or prevention of mGluR5 receptor (NAM) mediated disorders, which are anxiety and pain, depression, Fragile-X syndrome, autism spectrum disorders, Parkinson's disease, and gastro-esophageal reflux disease (GERD, and, respectively, for the production of corresponding medicaments.

Compounds of the present disclosure have been generically described in reference 1 (WO2011128279) as positive allosteric modulators of the mGluR5 receptor. Most similar exemplified compounds are linked to a 5- or 6-membered ring. Surprisingly it has been found that compounds having a smaller ring size, a 4-membered ring, and with the absolute stereochemistry of the bicyclic ring (1R,5S), are highly potent mGluR5 antagonists, which have a completely opposite pharmacology to that described in WO2011128279 for positive allosteric modulators.

In one aspect, there is provided a compound of formula I



wherein

R¹ is hydrogen or F;

n is 1 or 2

or a pharmaceutically acceptable acid addition salt thereof.

In another aspect, there is provided compounds of formula I, for example the following:

(1S,5R)-2-methyl-4-(5-(phenylethynyl)pyridin-2-yl)-2,4-diazabicyclo[3.2.0]heptan-3-one

(1R,5S)-2-(5-((4-fluorophenyl)ethynyl)pyridin-2-yl)-4-methyl-2,4-diazabicyclo[3.2.0] heptan-3-one

(1R,5S)-2-(5-((3-fluorophenyl)ethynyl)pyridin-2-yl)-4-methyl-2,4-diazabicyclo[3.2.0] heptan-3-one or

5 (1R,5S)-2-(5-((2,5-difluorophenyl)ethynyl)pyridin-2-yl)-4-methyl-2,4-diazabicyclo[3.2.0] heptan-3-one.

In another aspect, there is provided a compound selected from the group consisting of (-)-(1R,5S)-2-methyl-4-(5-(phenylethynyl)pyridin-2-yl)-2,4-diazabicyclo [3.2.0]heptan-3-one;

10 (+)-(1S,5R)-2-[5-(3-fluoro-phenylethynyl)-pyridin-2-yl]-4-methyl-2,4-diazabicyclo[3.2.0] heptan-3-one;

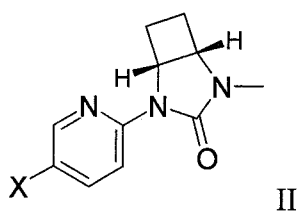
(+)-(1S,5R)-2-[5-(4-fluoro-phenylethynyl)-pyridin-2-yl]-4-methyl-2,4-diazabicyclo[3.2.0]heptan-3-one; and

(+)-(1S,5R)-2-[5-(2,5-difluoro-phenyl-ethynyl)-pyridin-2-yl]-4-methyl-2,4-diazabicyclo[3.2.0]heptan-3-one.

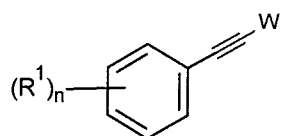
In another aspect, there is provided a compound as defined herein for use as therapeutically active substance.

In another aspect, there is provided a process for preparation of a compound of formula I as defined herein, comprising the variant

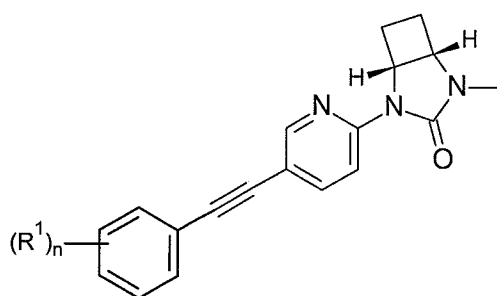
20 reacting a compound of formula II



wherein X is a halogen atom selected from bromine or iodine with a suitable aryl-acetylene of formula III



25 aryldialkylsilyl-group to form a compound of formula I



I

wherein the substituent R^1 is described above, in enantiomerically pure form with the absolute stereochemistry as drawn in formula I or by using II in racemic form followed by chiral separation of I to yield the optically pure enantiomer; and

- 5 if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts.

In another aspect, there is provided a pharmaceutical composition comprising a compound as defined herein and a therapeutically active carrier.

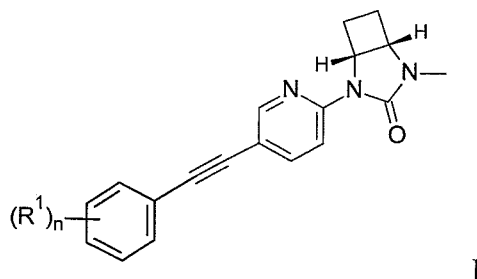
- 10 In another aspect, there is provided use of a compound as defined herein for the manufacture of a medicament for the treatment of anxiety and pain, depression, Parkinson's disease, and gastro-esophageal reflux disease (GERD).

In another aspect, there is provided a compound as defined herein for use in the treatment of anxiety and pain, depression, Parkinson's disease, and gastro-esophageal reflux disease (GERD).

- 15 The main difference between positive- and negative allosteric modulators can be seen in figure 1. An mGluR5 positive allosteric modulator (PAM) leads to increased receptor activity (Ca^{2+} mobilisation) in presence of a fixed concentration of glutamate whereas an allosteric antagonist (negative allosteric modulator, NAM) leads to a reduction of receptor activation. The affinity for the receptor in Figure 1 is ca. 10^{-7} M for the PAM and between 10^{-7} M and 10^{-8} M for the NAM. These values can also be measured using a binding assay to displace a radioligand (= MPEP) see assay description.
- 20

Claims

1. A compound of formula I



wherein

R¹ is hydrogen or F;

n is 1 or 2

or a pharmaceutically acceptable acid addition salt thereof.

2. A compound selected from the group consisting of

(1S,5R)-2-methyl-4-(5-(phenylethynyl)pyridin-2-yl)-2,4-diazabicyclo[3.2.0]heptan-3-one

(1R,5S)-2-(5-((4-fluorophenyl)ethynyl)pyridin-2-yl)-4-methyl-2,4-diazabicyclo[3.2.0]heptan-3-one

(1R,5S)-2-(5-((3-fluorophenyl)ethynyl)pyridin-2-yl)-4-methyl-2,4-diazabicyclo[3.2.0]heptan-3-one and

(1R,5S)-2-(5-((2,5-difluorophenyl)ethynyl)pyridin-2-yl)-4-methyl-2,4-diazabicyclo[3.2.0]heptan-3-one.

3. A compound selected from the group consisting of

(-)-(1R,5S)-2-methyl-4-(5-(phenylethynyl)pyridin-2-yl)-2,4-diazabicyclo [3.2.0]heptan-3-one;

(+)-(1S,5R)-2-[5-(3-fluoro-phenylethynyl)-pyridin-2-yl]-4-methyl-2,4-diazabicyclo[3.2.0]heptan-3-one;

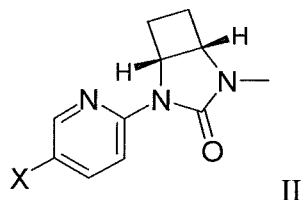
(+)-(1S,5R)-2-[5-(4-fluoro-phenylethynyl)-pyridin-2-yl]-4-methyl-2,4-diazabicyclo[3.2.0]heptan-3-one; and

(+)-(1S,5R)-2-[5-(2,5-difluoro-phenyl-ethynyl)-pyridin-2-yl]-4-methyl-2,4-diazabicyclo[3.2.0]heptan-3-one.

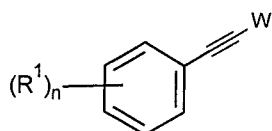
4. A compound according to any one of claims 1 to 3 for use as therapeutically active substance.

5. A process for preparation of a compound of formula I according to any one of claims 1 to 3, comprising the variant

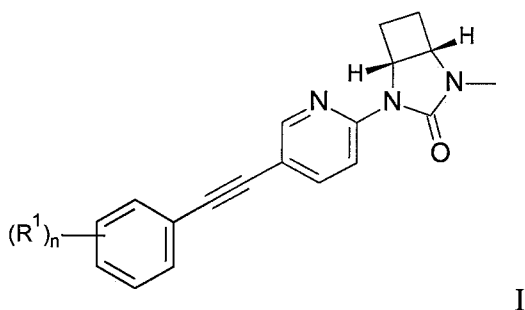
reacting a compound of formula II



wherein X is a halogen atom selected from bromine or iodine
with a suitable aryl-acetylene of formula III



to form a compound of formula I



wherein the substituent R^1 is described above, in enantiomerically pure form with the absolute stereochemistry as drawn in formula I or by using II in racemic form followed by chiral separation of I to yield the optically pure enantiomer; and
if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts.

6. A pharmaceutical composition comprising a compound in accordance with any one of claims 1 to 3 and a therapeutically active carrier.
7. The use of a compound as claimed in any one of claims 1 to 3 for the manufacture of a medicament for the treatment of anxiety and pain, depression, Parkinson's disease, and gastro-esophageal reflux disease (GERD).
8. A compound according to any one of claims 1 to 3 for use in the treatment of anxiety and pain, depression, Parkinson's disease, and gastro-esophageal reflux disease (GERD).