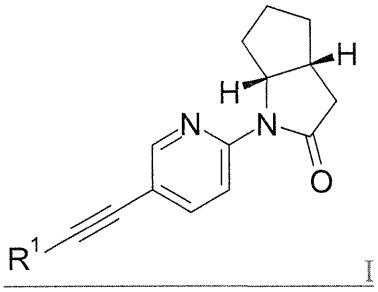
The present ~~invention~~ disclosure relates to compounds of formula I and to their pharmaceutically acceptable salts, to these compounds as pharmaceutically active substances, to the processes for their production as well as to the use in the treatment or prevention of disorders, relating to allosteric modulators for the mGluR5 receptor, such as schizophrenia and cognition and to pharmaceutical compositions containing the compounds of formula I.

In an aspect, there is provided ethynyl derivatives of formula I



I

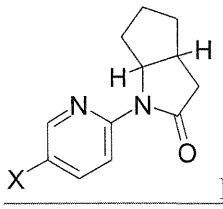
wherein

R^1 is phenyl, which is optionally substituted by 1-2 halogen atoms, selected from fluorine or chlorine;

or a pharmaceutically acceptable acid addition salt in enantiomerically pure form.

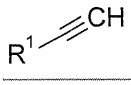
In another aspect, there is provided a process for preparation of a compound of formula I as defined herein, comprising the variants

a) reacting a compound of formula II



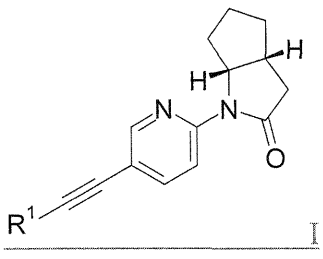
II

wherein X is a halogen atom selected from bromine or iodine, and where the compound of formula II is a racemic mixture or in enantiomerically pure form with a suitable aryl-acetylene of formula III



III

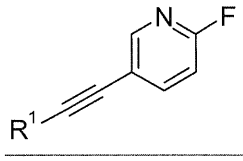
to form a compound of formula I



I

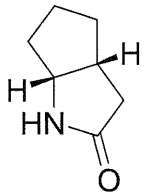
wherein the substituents are described above, or if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts or

b) reacting a compound of formula



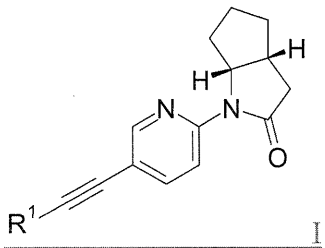
6

with a compound of formula



4

to a compound of formula



I

wherein the substituents are described herein, or if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts.

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

In another aspect, there is provided a pharmaceutical composition comprising at least one of the compounds as defined herein, as well as its pharmaceutically acceptable salt.

In another aspect, there is provided a compound as defined herein, when applicable as mixtures of enantiomers, diastereomers, or in enantiomerically pure form; as well as its pharmaceutically acceptable salt, for use as a medicament.

In another aspect, there is provided use of a compound as defined herein, as well as its pharmaceutically acceptable salt for the manufacture of a medicament for the treatment or prevention of diseases relating to allosteric modulators of $mGluR^5$ receptors.

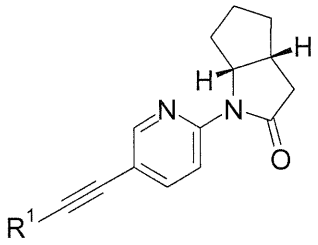
In another aspect, there is provided a compound as defined herein for the treatment or prevention of schizophrenia, cognitive diseases, fragile X syndrome or autism.

The following definitions of the general terms used in the present description apply irrespective of whether the terms in question appear alone or in combination.

As used herein, the term "halogen" denotes chlorine or fluorine.

The term "pharmaceutically acceptable salt" or "pharmaceutically acceptable acid addition salt" embraces salts with inorganic and organic acids, such as hydrochloric acid, nitric acid, sulfuric acid, phosphoric acid, citric acid, formic acid, fumaric acid, maleic acid, acetic acid, succinic acid, tartaric acid, methane-sulfonic acid, p-toluenesulfonic acid and the like.

One embodiment of the invention are compounds of formula I-A



I-A

wherein

R^1 is phenyl which is optionally substituted by 1-2 fluorine atoms;

or a pharmaceutically acceptable acid addition salt, in enantiomerically pure form with the absolute configuration as shown in formula I.

Compounds of formula I-A are the followings:

(3aR,6aR)-1-(5-(phenylethynyl)pyridin-2-yl)hexahydrocyclopenta[b]pyrrol-2(1H)-one

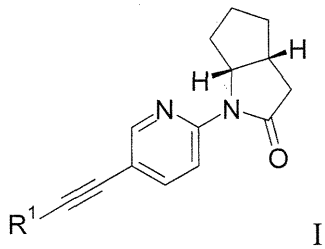
(3aR,6aR)-1-(5-((3-fluorophenyl)ethynyl)pyridin-2-yl)hexahydrocyclopenta[b]pyrrol-2(1H)-one

(3aR,6aR)-1-(5-((4-fluorophenyl)ethynyl)pyridin-2-yl)hexahydrocyclopenta[b]pyrrol-2(1H)-one

or

(3aR,6aR)-1-(5-((2,5-difluorophenyl)ethynyl)pyridin-2-yl)hexahydrocyclopenta[b]pyrrol-2(1H)-one.

The preparation of compounds of formula I of the present invention may be carried out in sequential or convergent synthetic routes. Syntheses of the compounds of the invention are shown in the following schemes 1 to 2. The skills required for carrying out the reaction and purification of the resulting products are known to those skilled in the art. The substituents and



I

wherein the substituents are described in claim 1, or if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts.

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

6. A pharmaceutical composition comprising at least one of the compounds according to any one of claims 1 to 3 as well as its pharmaceutically acceptable salt.

7. A compound of any one of claims 1 to 3, when applicable as mixtures of enantiomers, diastereomers, or in enantiomerically pure form; as well as its pharmaceutically acceptable salt, for use as a medicament.

8. The use of a compound according to any one of claims 1 to 3 as well as its pharmaceutically acceptable salt for the manufacture of a medicament for the treatment or prevention of diseases relating to allosteric modulators of $mGluR^5$ receptors.

~~9. The use of a compound according to claim 8 for the treatment or prevention of schizophrenia, cognitive diseases, fragile X syndrome or autism.~~

~~10~~9. A compound according to any one of claims 1 to 3 for the treatment or prevention of schizophrenia, cognitive diseases, fragile X syndrome or autism.

~~11. A method for the treatment of schizophrenia, cognitive diseases, fragile X syndrome or autism, which method comprises administering an effective amount of a compound as defined in any one of claims 1 to 3.~~