Chromatography (HPLC). The peak areas and retention times of the samples were extracted at the same wavelength used for the calibration.

The solubility is calculated using the following equation:

$S = (A - b) / a$ (x 10 for the sample diluted 1/10)

Where S is the solubility in µg/mL; A is the peak area of the sample; a is the slope and b is the intercept of the calibration curve. Since this method is not optimal for values well below 1 µg/ml, the value (<1) is given for compounds where no substance peak is detected at the maximal dilution, which means the actual solubility is well below 1 µg/mL.
In the case of reference compound 106, the compound was equilibrated for 24 h in 0.05 M phosphate buffer (pH 6.5) using a procedure identical to that performed with the LYSA assay. The amount of solute present was then directly determined using manual conventional HPLC analytics.

Spontaneous glutathione (GSH) addition assay:

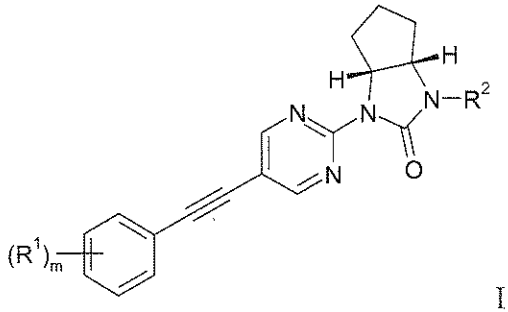
10µM of test substance dissolved in pH 7.4 phosphate buffer was incubated with 5mM GSH (glutathione) for 24 hours at room temperature. The samples were then analyzed using a mass spectrometer to determine whether adducts between glutathione and the drug had been formed. Samples for which the mass of a covalent adduct was clearly detected (M+307) are indicated as FLAG (positive). Compounds for which no adduct was detected are designated NO FLAG (negative).

Compounds of formula I are distinguished by having valuable therapeutic properties. They can be used in the treatment or prevention of disorders, relating to allosteric modulators for the mGluR5 receptor.

The most preferred indications for compounds which are allosteric modulators are schizophrenia and cognition.

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 one aspect, there is provided ethynyl derivatives of formula I



I

wherein

R^1 is hydrogen or halogen;

R^2 is C_{1-3}-alkyl or $-(CH_2)_n$-O-CH_3;

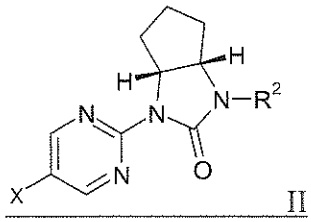
n is 2 or 3;

m is 1 or 2;

or a pharmaceutically acceptable acid addition salt, a racemic mixture, or its corresponding enantiomer and/or optical isomer and/or stereoisomer thereof.

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

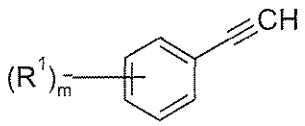
reacting a compound of formula II



II

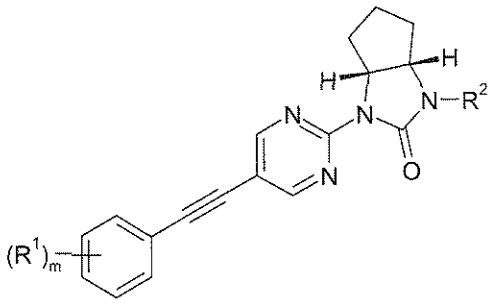
wherein X is a halogen atom selected from bromine or iodine

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.

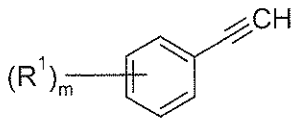
In another aspect, there is provided a compound as defined herein for use as therapeutically active substance.

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.

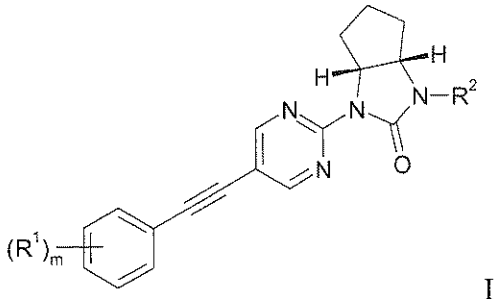
In another aspect, there is provided use of a compound as defined herein as well as its pharmaceutically acceptable salt for the manufacture of a medicament for the treatment or prevention of a disease relating to allosteric modulators of $mGluR^5$ receptors, wherein said disease is selected from the group consisting of schizophrenia, cognitive diseases, fragile X syndrome and autism.

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.



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.

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 a diseases relating to allosteric modulators of $mGluR^5$ receptors, wherein said disease is selected from the group consisting of ~~:~~

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