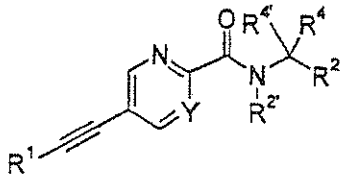
Positive allosteric modulators are compounds that do not directly activate receptors by themselves, but markedly potentiate agonist-stimulated responses, increase potency and maximum of efficacy. The binding of these compounds increase the affinity of a glutamate-site agonist at its extracellular N-terminal binding site. Positive allosteric modulation is thus an attractive mechanism for enhancing appropriate physiological receptor activation. There is a scarcity of selective positive allosteric modulators for the mGluR5 receptor. Conventional mGluR5 receptor modulators typically lack satisfactory aqueous solubility and exhibit poor oral bioavailability. Therefore, there remains a need for compounds that overcome these deficiencies and that effectively provide selective positive allosteric modulators for the mGluR5 receptor.

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

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

The present disclosure~~invention~~ 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 positive allosteric modulators for the mGluR5 receptor, such as schizophrenia, tuberous sclerosis, and cognition and to pharmaceutical compositions containing the compounds of formula I..

In a first aspect, there is provided a compound of formula



I

wherein

Y is N or C-R^3;

and R^3 is hydrogen, methyl, halogen or nitrile;

R^1 is phenyl or pyridinyl, which are optionally substituted by halogen, C_{1-4}-alkyl or C_{1-4}-alkoxy;

$R^2/R^{2'}$ are independently from each other hydrogen, C_{1-4}-alkyl or C_{1-4}-alkyl substituted by halogen,

or R^2 and $R^{2'}$ may form together with the N-atom to which they are attached a morpholine ring, a piperidine ring or an azetidine ring, which are unsubstituted or substituted one or more substituents selected from C_{1-4}-alkoxy, halogen, hydroxy or methyl;

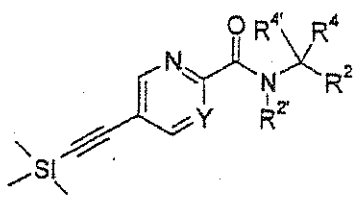
$R^4/R^{4'}$ are independently from each other hydrogen or C_{1-4}-alkyl,

or R^4 and $R^{4'}$ form together a C_{3-5}-cycloalkyl-, tetrahydrofuran- or an oxetane-ring;

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

In a second aspect, there is provided a process for preparation of a compound of formula I as described above, comprising the variants

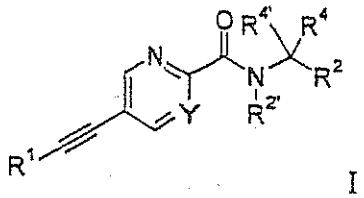
a) reacting a compound of formula



with a suitable compound of formula

R^1-hal 7

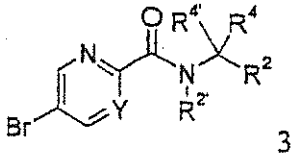
to form a compound of formula



I

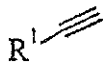
wherein the substituents are described above, or

b) reacting a compound of formula



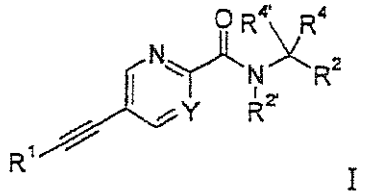
3

with a suitable compound of formula



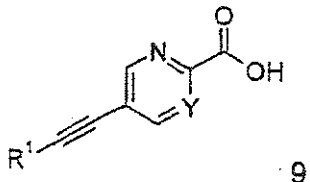
4

to form a compound of formula



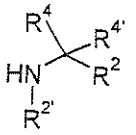
I

c) reacting a compound of formula



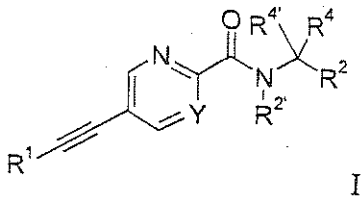
9

with a suitable compound of formula



2

to form a compound of formula



I

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

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

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

In a fifth aspect, there is provided the use of a compound as defined above for the manufacture of a medicament for the treatment of schizophrenia or cognitive diseases.

In a sixth aspect, there is provided a compound as defined above for the treatment of schizophrenia or cognitive diseases.

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 "lower alkyl" denotes a saturated, i.e. aliphatic hydrocarbon group including a straight or branched carbon chain with 1 – 4 carbon atoms. Examples for "alkyl" are methyl, ethyl, n-propyl, and isopropyl.

The term "lower alkyl substituted by halogen" denotes an alkyl group as defined above, wherein at least one hydrogen atom is replaced by halogen. Preferred is the group CF_3.

The term "alkoxy" denotes a group -O-R' wherein R' is lower alkyl as defined above.

The term "halogen" denotes fluoro, chloro, bromo or iodo.

The term "pharmaceutically acceptable salt" or "pharmaceutically acceptable acid addition salt" embraces salts with inorganic and organic acids, such as hydrochloric acid, nitric acid,