mGluR4 modulators were also shown to exert anti-depressive actions (*Neuropharmacology, 46(2), 151-9, 2004).*

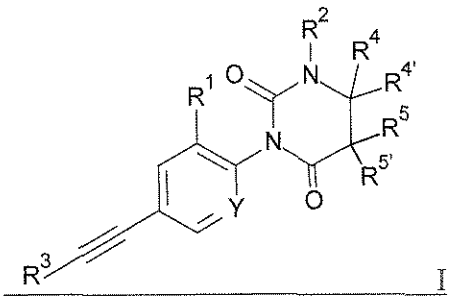
In addition, mGluR4 modulators were also shown to be involved in glucagon secretion inhibition (*Diabetes, 53(4), 998-1006, 2004)*. Therefore, orthosteric or positive allosteric modulators of mGluR4 have potential for the treatment of type 2 diabetes through its hypoglycemic effect.

Moreover, mGluR4 was shown to be expressed in prostate cancer cell-line (*Anticancer Res. 29(1), 371-7, 2009)* or colorectal carcinoma (*Cli. Cancer Research, 11(9)3288-95, 2005).* mGluR4 modulators may therefore have also potential role for the treatment of cancers.

Other proposed effects of mGluR4 PAM's can be expected for the treatment of emesis, obsessive compulsive disorder, anorexia and autism.

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 mGluR4 receptor.

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



I

wherein

Y is N or C-$R^{1'}$;

$R^{1'}$ is hydrogen or F;

R^1 is hydrogen, halogen or C_{1-7}-alkyl substituted by halogen;

R^2 is hydrogen or C_{1-7}-alkyl;

or R^2 forms together with R^4 a 6 membered heterocyclic ring containing

$-CH_2-CH_2-O-CH_2-$ or $-CH_2-CH_2-NR-C(O)-$;

R is hydrogen, C_{1-7}-alkyl, phenyl or benzyl;

R^3 is phenyl or pyridinyl, wherein the N atom in the pyridinyl group may be in different positions;

$R^{4'}$ is hydrogen, C_{1-7}-alkyl or C_{1-7}-alkoxyalkyl;

R^4 is hydrogen, C_{1-7}-alkyl, phenyl optionally substituted by halogen or C_{1-7}-alkoxy, or is cycloalkyl, or is pyridinyl optionally substituted by halogen, C_{1-7}-alkyl, C_{1-7}-alkoxy or =O, or is pyrimidinyl optionally substituted by C_{1-7}-alkyl, C_{1-7}-alkoxy or =O, or is 1- C_{1-7}-alkyl-pyridinyl, or is pyrazinyl, or is pyridazinyl optionally substituted by C_{1-7}-alkyl, C_{1-7}-alkoxy or =O, *or is* 1-methylpyrrolo[2,3-b]pyridine-5-yl, or is 6-imidazo[1,2-b]pyridazin-6-yl;

or R^4 forms together with $R^{4'}$ a 4, 5 or 6 membered heterocyclic ring containing $-(CH_2)_5-$, $-CH_2-CH_2-O-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-CH_2-$, $-CH_2-O-CH_2-CH_2-$ or $CH_2-CH_2-CH_2-O-CH_2$;

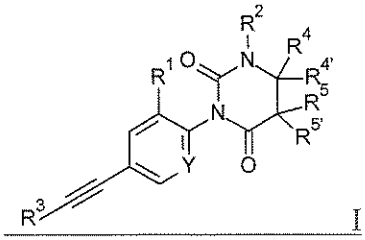
R^5 and $R^{5'}$ are hydrogen or C_{1-7}-alkyl;

or R^4 forms together with R^5 a saturated 5- membered ring containing $-CH_2-CH_2-CH_2-$;

or a pharmaceutically acceptable salt or 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 the manufacture of a compound of formula I as defined herein, which process comprises

a) alkylating 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 of formula I as defined herein for use as therapeutically active substances.

In another aspect, there is provided a compound of formula I as defined herein for use in the treatment of Parkinson's disease, anxiety, emesis, obsessive compulsive disorder, autism, neuroprotection, cancer, depression and diabetes type 2.

In another aspect, there is provided a pharmaceutical composition comprising a compound of formula I as defined herein and pharmaceutically acceptable excipients.

In another aspect, there is provided use of a compound of formula I as defined herein for the preparation of a medicament for the treatment of Parkinson's disease, anxiety, emesis, obsessive compulsive disorder, autism, neuroprotection, cancer, depression and diabetes type 2.

The most preferred indications for compounds which are allosteric modulators for the mGluR4 receptor are Parkinson's disease, anxiety, emesis, obsessive compulsive disorder, anorexia, autism, neuroprotection, cancer, depression and type 2 diabetes.

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 their use in the treatment or prevention of disorders, relating to allosteric modulators for the mGluR4 receptor, such as Parkinson's disease, anxiety, emesis, obsessive compulsive disorder, autism, neuroprotection, cancer, depression and diabetes typ 2 and to pharmaceutical compositions containing the compounds of formula I.

A further object of the ~~present invention~~embodiments disclosed herein is a method for the treatment or prophylaxis of Parkinson's disease, anxiety, emesis, obsessive compulsive disorder, anorexia, autism, neuroprotection, cancer, depression and type 2 diabetes , which method comprises administering an effective amount of a compound of formula I to a mammal in need.

Furthermore, the ~~invention~~ disclosure includes all racemic mixtures, all their corresponding enantiomers and/or optical isomers, or analogues containing isotopes of hydrogen, fluorine, carbon, oxygen or nitrogen.

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.