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 and autism.

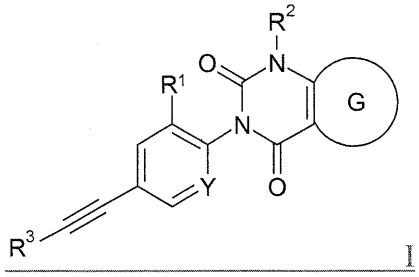
Compounds of formula I are distinguished by having valuable therapeutic properties. They can be used in the treatment or prevention of disorders, relating to allosteric modulators for the mGluR4 receptor.

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

SUMMARY

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 mGluR4 receptor, such as Parkinson's disease, anxiety, emesis, obsessive compulsive disorder, autism, neuroprotection, cancer, depression and diabetes type 2 and to pharmaceutical compositions containing the compounds of formula I~~.~~.

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



I

wherein

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

G is a 5 or 6-membered aromatic or heteroaromatic ring containing 0, 1, 2 or 3 heteroatoms, selected from the group consisting of phenyl, pyridinyl with different N-positions, imidazolyl, pyrazinyl, pyrimidinyl, thiophenyl, thiazolyl, pyrazolyl or thiadiazolyl, which are optionally substituted by 1, 2 or 3 substituents, selected from the group consisting of halogen, lower alkyl, lower

alkoxy, lower alkoxy substituted by halogen or NRR';

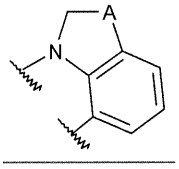
R and R' are independently from each other hydrogen or lower alkyl, or may form together with the N atom to which they are attached a five or six membered saturated heterocyclic group which may contain an additional oxygen, NH, or N-lower alkyl group;

R^1 is hydrogen, halogen or lower alkyl substituted by halogen;

$R^{1'}$ is hydrogen, halogen or lower alkyl substituted by halogen;

R^2 is hydrogen, lower alkyl, lower alkoxyalkyl, cycloalkyl or heterocycloalkyl;

or R^2 may form together with the closest carbon atom in group G a group

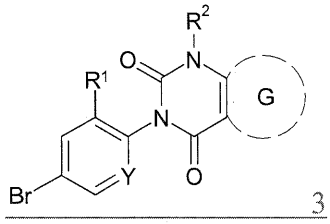


for A being $-CH_2-$, $-CH_2CH_2$, or $-C(CH_3)_2-$,

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

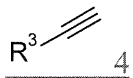
or a pharmaceutically acceptable salt or acid addition salt, a racemic mixture, or its corresponding enantiomer and/or optical isomer and/or stereoisomer thereof.

In a second aspect, there is provided a process for the manufacture of a compound of formula I as defined herein, in which the process comprises reacting a compound of formula 3



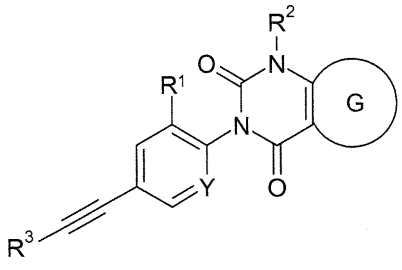
3

with a compound of formula 4



4

to form a compound of formula I



I

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

In a third aspect, there is provided a compound of formula I as defined herein for use as therapeutically active substances.

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

In a sixth aspect, there is provided the 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.

A further object of the embodiments disclosed herein~~present invention~~ is a method for the treatment or prophylaxis of Parkinson's disease, anxiety, emesis, obsessive compulsive disorder, autism, neuroprotection, cancer, depression and diabetes type 2, 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.

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.

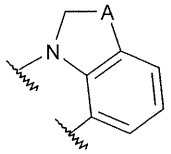
As used herein, the term "lower alkyl" denotes a saturated straight- or branched-chain group containing from 1 to 7 carbon atoms, for example, methyl, ethyl, propyl, isopropyl, n-butyl, i-butyl, 2-butyl, t-butyl and the like. Preferred alkyl groups are groups with 1 - 4 carbon atoms.

As used herein, the term "lower alkoxy" denotes a lower alkyl group as defined above, which is linked with an O atom.

3-[2,6-Difluoro-4-(2-phenylethynyl)phenyl]-1,8-dimethyl-pyrido[3,2-d]pyrimidine-2,4-dione
6-[2,6-Difluoro-4-(2-phenylethynyl)phenyl]-4-methyl-[1,2,5]thiadiazolo[3,4-d]pyrimidine-5,7-dione
6-[2,6-Difluoro-4-(2-phenylethynyl)phenyl]-4-isopropyl-[1,2,5]thiadiazolo[3,4-d]pyrimidine-5,7-dione
3-[2-Chloro-4-(2-phenylethynyl)phenyl]-1,5-dimethyl-quinazoline-2,4-dione
3-[2-Chloro-4-(2-phenylethynyl)phenyl]-1-(2-methoxyethyl)quinazoline-2,4-dione
6-[2-Chloro-4-(2-phenylethynyl)phenyl]-4-methyl-2-morpholino-thiazolo[4,5-d]pyrimidine-5,7-dione
6-(2-Chloro-4-phenylethynyl-phenyl)-4-methyl-4H-thiazolo[4,5-d]pyrimidine-5,7-dione
3-[2-Chloro-4-(2-phenylethynyl)phenyl]-1-cyclobutyl-quinazoline-2,4-dione
3-[2-Chloro-4-(2-phenylethynyl)phenyl]-8-isopropyl-1-methyl-quinazoline-2,4-dione
8-Chloro-3-[2,6-difluoro-4-(2-phenylethynyl)phenyl]-1-methyl-pyrido[3,2-d]pyrimidine-2,4-dione
5-[2,6-Difluoro-4-(2-phenylethynyl)phenyl]-2,7-dimethyl-pyrazolo[3,4-d]pyrimidine-4,6-dione
5-[2,6-Difluoro-4-(2-phenylethynyl)phenyl]-1,7-dimethyl-pyrazolo[3,4-d]pyrimidine-4,6-dione
5-[2,6-Difluoro-4-(2-phenylethynyl)phenyl]-7-isopropyl-2H-pyrazolo[3,4-d]pyrimidine-4,6-dione
3-[2-Chloro-4-(2-phenylethynyl)phenyl]-8-methoxy-1-methyl-quinazoline-2,4-dione
3-[2,6-Difluoro-4-(2-phenylethynyl)phenyl]-1-(oxetan-3-yl)quinazoline-2,4-dione
6-[2-Chloro-4-(2-phenylethynyl)phenyl]-4-methyl-thiazolo[5,4-d]pyrimidine-5,7-dione
3-[2,6-Difluoro-4-(2-phenylethynyl)phenyl]-1-isopropyl-pteridine-2,4-dione
1-[2,6-Difluoro-4-(2-phenylethynyl)phenyl]-3,7-dimethyl-purine-2,6-dione
3-[2,6-Difluoro-4-(2-phenylethynyl)phenyl]-8-methoxy-1-methyl-quinazoline-2,4-dione
3-[2-Fluoro-4-(2-phenylethynyl)-6-(trifluoromethyl)phenyl]-1-isopropyl-quinazoline-2,4-dione
or
8-(2,2-Difluoroethoxy)-3-[2,6-difluoro-4-(2-phenylethynyl)phenyl]-1-methyl-quinazoline-2,4-dione.

4. A compound of formula IB according to claim 1

or R^2 may form together with the closest carbon atom in group G a group



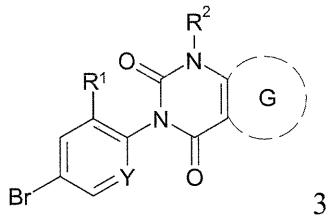
for A being $-CH_2-$, $-CH_2CH_2$, or $-C(CH_3)_2-$,

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

9. A compound of formula ID according to claim 8, wherein the compound is 6-[3-Chloro-5-[2-(3-pyridyl)ethynyl]-2-pyridyl]-4-isopropyl-2-methyl-pyrazolo[4,3-d]pyrimidine-5,7-dione.

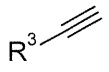
10. A process for the manufacture of a compound of formula I as defined in any one of claims 1 to 9, in which the process comprises

reacting a compound of formula 3



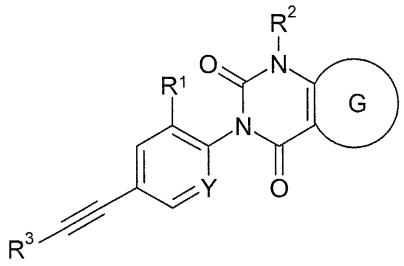
3

with a compound of formula 4



4

to form a compound of formula I



I

wherein the substituents are described in claim 1, or

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

11. A compound of formula I according to any one of claims 1 - 9 for use as therapeutically

active substances.

12.A compound of formula I according to any one of claims 1- 9 for use in the treatment of Parkinson's disease, anxiety, emesis, obsessive compulsive disorder, autism, neuroprotection, cancer, depression and diabetes type 2.

13. A pharmaceutical composition comprising a compound of formula I as claimed in any one of claim 1 - 9 and pharmaceutically acceptable excipients.

14. The use of a compound of formula I according to any one of claims 1 - 9 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,

~~15. A method for the treatment of Parkinson's disease, anxiety, emesis, obsessive compulsive disorder, autism, neuroprotection, cancer, depression and diabetes type 2, which method comprises administering an effective amount of a compound of formula I as claimed in any one of claims 1 - 9.~~

~~16. The invention as hereinbefore described.~~