

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.

In addition, in *British Journal of Pharmacology* (2013), 169, 1824-1839 agonists of mGluR4 may further be used in the treatment of positive, negative and cognitive symptoms of schizophrenia.

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, schizophrenia 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 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, anorexia, autism, neuroprotection, cancer, depression, schizophrenia and diabetes type 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, autism, neuroprotection, cancer, depression, schizophrenia 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.

In one aspect, there is provided the compounds

3-[2,6-difluoro-4-(2-phenylethynyl)phenyl]-1-isopropyl-imidazolidine-2,4-dione

(5RS)-3-[2,6-difluoro-4-(2-phenylethynyl)phenyl]-1-isopropyl-5-methyl-imidazolidine-2,4-dione

3-[2,6-difluoro-4-(2-phenylethynyl)phenyl]-1-isopropyl-5,5-dimethyl-imidazolidine-2,4-dione

3-[2,6-difluoro-4-(2-phenylethynyl)phenyl]-5,5-dimethyl-1-phenyl-imidazolidine-2,4-dione

1-tert-butyl-3-[2,6-difluoro-4-(2-phenylethynyl)phenyl]imidazolidine-2,4-dione

1-cyclopropyl-3-[2,6-difluoro-4-(2-phenylethynyl)phenyl]imidazolidine-2,4-dione

7-[2,6-difluoro-4-(2-phenylethynyl)phenyl]-5-isopropyl-2-oxa-5,7-diazaspiro[3.4]octane-6,8-

5 dione

(5RS,8aRS)-2-[2,6-difluoro-4-(2-phenylethynyl)phenyl]-5-methyl-5,6,8,8a-

tetrahydroimidazo[5,1-c][1,4]oxazine-1,3-dione

(3aRS)-2-[2,6-difluoro-4-(2-phenylethynyl)phenyl]-3a,4-dihydroimidazo[1,5-a]indole-1,3-dione

(3aRS)-2-[2,6-difluoro-4-(2-phenylethynyl)phenyl]-4,5-dihydro-3aH-imidazo[1,5-a]quinoline-

10 1,3-dione

(10aRS)-2-[2,6-difluoro-4-(2-phenylethynyl)phenyl]-10,10a-dihydro-5H-imidazo[1,5-

b]isoquinoline-1,3-dione

(5RS,8aRS)-2-[2-chloro-4-(2-phenylethynyl)phenyl]-5-methyl-6,7,8,8a-tetrahydro-5H-

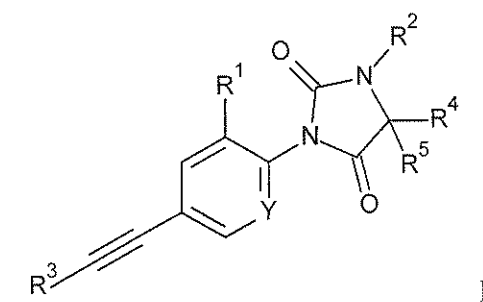
imidazo[1,5-a]pyridine-1,3-dione and

15 (5RS,8aRS)-2-[2-chloro-6-fluoro-4-[2-(3-pyridyl)ethynyl]phenyl]-5-methyl-6,7,8,8a-tetrahydro-

5H-imidazo[1,5-a]pyridine-1,3-dione

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

encompassed by formula I



20

wherein

Y is C-R^{1'};

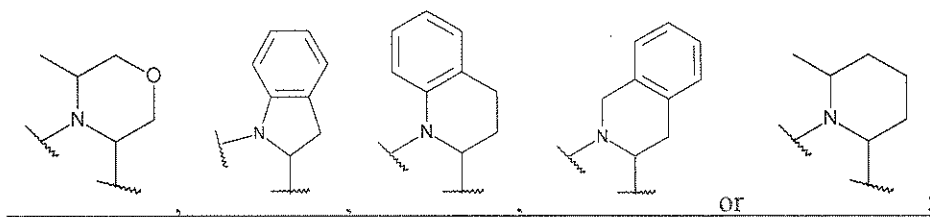
R^{1'} is hydrogen or halogen;

R¹ is hydrogen or halogen;

25 R² is hydrogen, C₁₋₇-alkyl or phenyl;

R⁴ is hydrogen or C₁₋₇ alkyl;

or R² and R⁴ may form together with the corresponding atoms, to which they are attached the
following rings



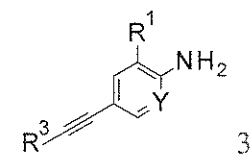
R^5 is hydrogen or C_{1-7} -alkyl; and if R^2 and R^4 form a ring as described above, than R^5 is hydrogen; or

R^4 and R^5 may form together with the C-atom to which they are attached a heterocycloalkyl ring;

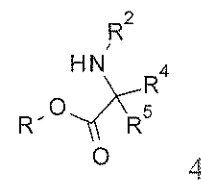
R^3 is phenyl or pyridinyl, wherein the N atom in the pyridinyl group may be in different positions.

In another aspect, there is provided the preparation of a compound as defined herein, which process comprises

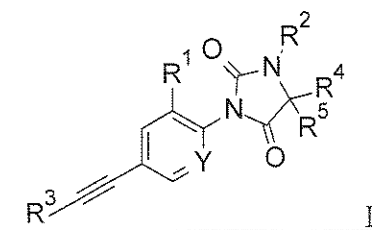
10 reacting a compound of formula 3



with a compound of formula 4



15 wherein R is methyl, ethyl or hydrogen, and the other substituents are described above, with triphosgene or carbonyldiimidazole (CDI), in the presence or absence of a base, selected from triethylamine, and in a solvent, selected from toluene or dioxane, to a compound of formula



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

In another aspect, there is provided the compounds

3-[2,6-difluoro-4-(2-phenylethynyl)phenyl]-1-isopropyl-imidazolidine-2,4-dione

(5RS)-3-[2,6-difluoro-4-(2-phenylethynyl)phenyl]-1-isopropyl-5-methyl-imidazolidine-2,4-dione

5 3-[2,6-difluoro-4-(2-phenylethynyl)phenyl]-1-isopropyl-5,5-dimethyl-imidazolidine-2,4-dione

3-[2,6-difluoro-4-(2-phenylethynyl)phenyl]-5,5-dimethyl-1-phenyl-imidazolidine-2,4-dione

1-tert-butyl-3-[2,6-difluoro-4-(2-phenylethynyl)phenyl]imidazolidine-2,4-dione

1-cyclopropyl-3-[2,6-difluoro-4-(2-phenylethynyl)phenyl]imidazolidine-2,4-dione

7-[2,6-difluoro-4-(2-phenylethynyl)phenyl]-5-isopropyl-2-oxa-5,7-diazaspiro[3.4]octane-6,8-

10 dione

(5RS,8aRS)-2-[2,6-difluoro-4-(2-phenylethynyl)phenyl]-5-methyl-5,6,8,8a-

tetrahydroimidazo[5,1-c][1,4]oxazine-1,3-dione

(3aRS)-2-[2,6-difluoro-4-(2-phenylethynyl)phenyl]-3a,4-dihydroimidazo[1,5-a]indole-1,3-dione

(3aRS)-2-[2,6-difluoro-4-(2-phenylethynyl)phenyl]-4,5-dihydro-3aH-imidazo[1,5-a]quinoline-

15 1,3-dione

(10aRS)-2-[2,6-difluoro-4-(2-phenylethynyl)phenyl]-10,10a-dihydro-5H-imidazo[1,5-

b]isoquinoline-1,3-dione

(5RS,8aRS)-2-[2-chloro-4-(2-phenylethynyl)phenyl]-5-methyl-6,7,8,8a-tetrahydro-5H-

imidazo[1,5-a]pyridine-1,3-dione and

20 (5RS,8aRS)-2-[2-chloro-6-fluoro-4-[2-(3-pyridyl)ethynyl]phenyl]-5-methyl-6,7,8,8a-tetrahydro-

5H-imidazo[1,5-a]pyridine-1,3-dione

as defined above for use as therapeutically active substances.

In another aspect, there is provided the compounds

3-[2,6-difluoro-4-(2-phenylethynyl)phenyl]-1-isopropyl-imidazolidine-2,4-dione

25 (5RS)-3-[2,6-difluoro-4-(2-phenylethynyl)phenyl]-1-isopropyl-5-methyl-imidazolidine-2,4-dione

3-[2,6-difluoro-4-(2-phenylethynyl)phenyl]-1-isopropyl-5,5-dimethyl-imidazolidine-2,4-dione

3-[2,6-difluoro-4-(2-phenylethynyl)phenyl]-5,5-dimethyl-1-phenyl-imidazolidine-2,4-dione

1-tert-butyl-3-[2,6-difluoro-4-(2-phenylethynyl)phenyl]imidazolidine-2,4-dione

30 1-cyclopropyl-3-[2,6-difluoro-4-(2-phenylethynyl)phenyl]imidazolidine-2,4-dione

7-[2,6-difluoro-4-(2-phenylethynyl)phenyl]-5-isopropyl-2-oxa-5,7-diazaspiro[3.4]octane-6,8-

dione

(5RS,8aRS)-2-[2,6-difluoro-4-(2-phenylethynyl)phenyl]-5-methyl-5,6,8,8a-

tetrahydroimidazo[5,1-c][1,4]oxazine-1,3-dione

(3aRS)-2-[2,6-difluoro-4-(2-phenylethynyl)phenyl]-3a,4-dihydroimidazo[1,5-a]indole-1,3-dione

(3aRS)-2-[2,6-difluoro-4-(2-phenylethynyl)phenyl]-4,5-dihydro-3aH-imidazo[1,5-a]quinoline-1,3-dione

(10aRS)-2-[2,6-difluoro-4-(2-phenylethynyl)phenyl]-10,10a-dihydro-5H-imidazo[1,5-

5 b]isoquinoline-1,3-dione

(5RS,8aRS)-2-[2-chloro-4-(2-phenylethynyl)phenyl]-5-methyl-6,7,8,8a-tetrahydro-5H-imidazo[1,5-a]pyridine-1,3-dione and

(5RS,8aRS)-2-[2-chloro-6-fluoro-4-[2-(3-pyridyl)ethynyl]phenyl]-5-methyl-6,7,8,8a-tetrahydro-5H-imidazo[1,5-a]pyridine-1,3-dione

10 as defined above for use in the treatment of Parkinson's disease, anxiety, emesis, obsessive compulsive disorder, autism, neuroprotection, cancer, depression, schizophrenia and diabetes type 2.

In another aspect, there is provided a pharmaceutical composition comprising a compound

15 3-[2,6-difluoro-4-(2-phenylethynyl)phenyl]-1-isopropyl-imidazolidine-2,4-dione

(5RS)-3-[2,6-difluoro-4-(2-phenylethynyl)phenyl]-1-isopropyl-5-methyl-imidazolidine-2,4-dione

3-[2,6-difluoro-4-(2-phenylethynyl)phenyl]-1-isopropyl-5,5-dimethyl-imidazolidine-2,4-dione

3-[2,6-difluoro-4-(2-phenylethynyl)phenyl]-5,5-dimethyl-1-phenyl-imidazolidine-2,4-dione

20 1-tert-butyl-3-[2,6-difluoro-4-(2-phenylethynyl)phenyl]imidazolidine-2,4-dione

1-cyclopropyl-3-[2,6-difluoro-4-(2-phenylethynyl)phenyl]imidazolidine-2,4-dione

7-[2,6-difluoro-4-(2-phenylethynyl)phenyl]-5-isopropyl-2-oxa-5,7-diazaspiro[3.4]octane-6,8-dione

(5RS,8aRS)-2-[2,6-difluoro-4-(2-phenylethynyl)phenyl]-5-methyl-5,6,8,8a-

25 tetrahydroimidazo[5,1-c][1,4]oxazine-1,3-dione

(3aRS)-2-[2,6-difluoro-4-(2-phenylethynyl)phenyl]-3a,4-dihydroimidazo[1,5-a]indole-1,3-dione

(3aRS)-2-[2,6-difluoro-4-(2-phenylethynyl)phenyl]-4,5-dihydro-3aH-imidazo[1,5-a]quinoline-1,3-dione

(10aRS)-2-[2,6-difluoro-4-(2-phenylethynyl)phenyl]-10,10a-dihydro-5H-imidazo[1,5-

30 b]isoquinoline-1,3-dione

(5RS,8aRS)-2-[2-chloro-4-(2-phenylethynyl)phenyl]-5-methyl-6,7,8,8a-tetrahydro-5H-imidazo[1,5-a]pyridine-1,3-dione and

(5RS,8aRS)-2-[2-chloro-6-fluoro-4-[2-(3-pyridyl)ethynyl]phenyl]-5-methyl-6,7,8,8a-tetrahydro-5H-imidazo[1,5-a]pyridine-1,3-dione

as defined above and pharmaceutically acceptable excipients.

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.

5 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.