

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.

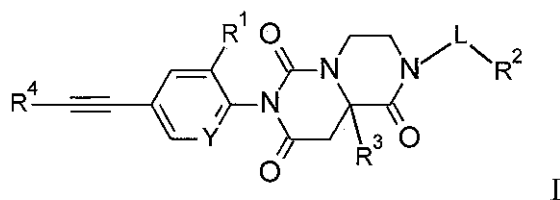
Other proposed effects of mGluR4 PAM's can be expected for the treatment of emesis, obsessive compulsive disorder and autism.

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 type 2 diabetes.

The present 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 and diabetes type 2 and to pharmaceutical compositions containing the compounds of formula I.

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



wherein

R<sup>1</sup> is hydrogen, F or Cl;

L is a bond or C<sub>1-7</sub>-alkylene;

R<sup>2</sup> is -(CH<sub>2</sub>)<sub>n</sub>O-C<sub>1-7</sub>-alkyl, C<sub>1-7</sub>-alkyl substituted by halogen, -(CH<sub>2</sub>)<sub>n</sub>C(O)O-C<sub>1-7</sub>-alkyl, phenyl substituted by C<sub>1-7</sub>-alkyl or halogen, or is a 5 or 6-membered heteroaryl group, selected from pyridinyl, pyrimidinyl, pyridazinyl, thiazolyl, imidazolyl, pyrazolyl or triazolyl, which are optionally substituted by C<sub>1-7</sub>-alkyl, halogen, C<sub>1-7</sub>-alkoxy, =O, benzyloxy,

cycloalkyloxy, hydroxy, cyano, C<sub>1-7</sub>-alkyl substituted by halogen, or by
$$-(\text{CH}_2)_n\text{O}-\text{C}_{1-7}\text{-alkyl};$$

$n$  is 1, 2 or 3;

$R^3$  is hydrogen, C<sub>1-7</sub>-alkyl or  $-(CH_2)_nO-C_{1-7}$ -alkyl;

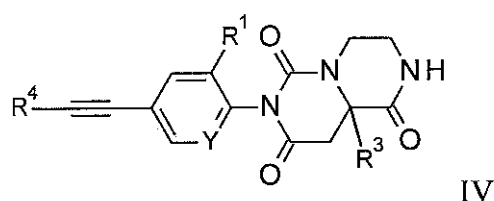
R<sup>4</sup> is phenyl, pyridinyl or pyrimidinyl, optionally substituted by F;

Y is CF or CCl;

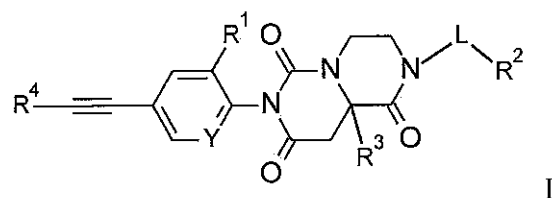
or a pharmaceutically acceptable salt or acid addition salt, a racemic mixture, or its corresponding enantiomer and/or optical isomer and/or stereoisomers thereof.

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

a) reacting a compound of formula IV



with a compound of formula  $\text{XLR}^2$ , wherein X is halogen,  
to a compound of formula I



and, 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 present disclosure also relates to a method for the treatment or prophylaxis of Parkinson's disease, anxiety, emesis, obsessive compulsive disorder, 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 disclosure includes all racemic mixtures, all their corresponding enantiomers and/or optical isomers.

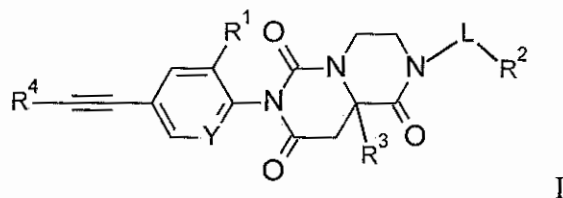
The following definitions of the general terms used in the present description apply irrespective of whether the terms in question appear alone or in combination.

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-

# Claims

1. A compound of formula I



wherein

$R^1$  is hydrogen, F or Cl;

L is a bond or  $C_{1-7}$ -alkylene;

$R^2$  is  $-(CH_2)_nO-C_{1-7}$ -alkyl,  $C_{1-7}$ -alkyl substituted by halogen,  $-(CH_2)_nC(O)O-C_{1-7}$ -alkyl, phenyl substituted by  $C_{1-7}$ -alkyl or halogen, or is a 5 or 6-membered heteroaryl group, selected from pyridinyl, pyrimidinyl, pyridazinyl, thiazolyl, imidazolyl, pyrazolyl or triazolyl, which are optionally substituted by  $C_{1-7}$ -alkyl, halogen,  $C_{1-7}$ -alkoxy,  $=O$ , benzyloxy, cycloalkyloxy, hydroxy, cyano,  $C_{1-7}$ -alkyl substituted by halogen, or by  $-(CH_2)_nO-C_{1-7}$ -alkyl;  
n is 1, 2 or 3;

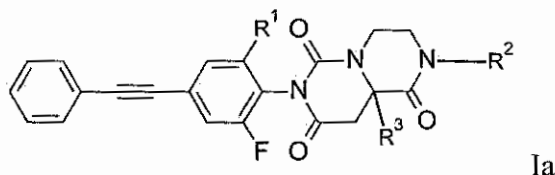
$R^3$  is hydrogen,  $C_{1-7}$ -alkyl or  $-(CH_2)_nO-C_{1-7}$ -alkyl;

$R^4$  is phenyl, pyridinyl or pyrimidinyl, optionally substituted by F;

Y is CF or CCl;

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

2. A compound of formula Ia according to claim 1,



wherein

$R^1$  is F or Cl;

$R^2$  is  $-(CH_2)_nO-C_{1-7}\text{-alkyl}$ ,  $C_{1-7}\text{-alkyl}$  substituted by halogen or  $-(CH_2)_nC(O)O-C_{1-7}\text{-alkyl}$ ,

$N$  is 1, 2 or 3;

$R^3$  hydrogen,  $C_{1-7}\text{-alkyl}$  or  $-(CH_2)_nO-C_{1-7}\text{-alkyl}$ ;

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

3. A compound of formula Ia according to claims 1 and 2, wherein the compounds are:

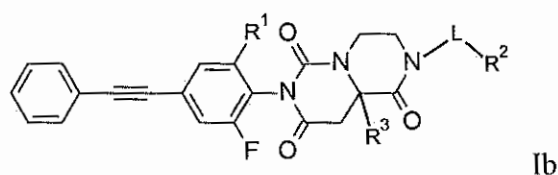
(9a*S*)-7-[2,6-difluoro-4-(2-phenylethynyl)phenyl]-2-(2-methoxyethyl)-9a-methyl-4,9-dihydro-3H-pyrazino[1,2-*c*]pyrimidine-1,6,8-trione

(9a*S*)-7-[2,6-difluoro-4-(2-phenylethynyl)phenyl]-2-(3-methoxypropyl)-9a-methyl-4,9-dihydro-3H-pyrazino[1,2-*c*]pyrimidine-1,6,8-trione

(9a*S*)-7-[2,6-difluoro-4-(2-phenylethynyl)phenyl]-9a-methyl-2-(2,2,2-trifluoroethyl)-4,9-dihydro-3H-pyrazino[1,2-*c*]pyrimidine-1,6,8-trione or

Ethyl 4-[(9a*S*)-7-[2,6-difluoro-4-(2-phenylethynyl)phenyl]-9a-methyl-1,6,8-trioxo-4,9-dihydro-3H-pyrazino[1,2-*c*]pyrimidin-2-yl]butanoate.

4. A compound of formula Ib according to claim 1



wherein

$R^1$  is F or Cl;

$L$  is  $C_{1-7}\text{-alkylene}$ ;

$R^2$  is phenyl substituted by  $C_{1-7}\text{-alkyl}$  or by halogen;

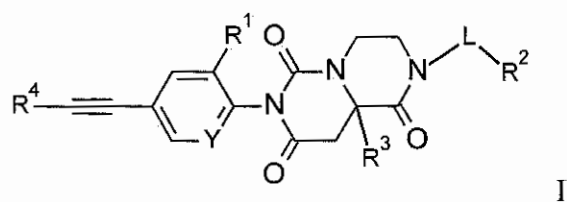
$R^3$  hydrogen,  $C_{1-7}\text{-alkyl}$  or  $-(CH_2)_nO-C_{1-7}\text{-alkyl}$ ;

$n$  is 1, 2 or 3;

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

5. A compound of formula Ib according to claims 1 and 4, wherein the compounds are  
 (9aRS)-7-[2,6-difluoro-4-(2-phenylethynyl)phenyl]-9a-methyl-2-(m-tolylmethyl)-4,9-dihydro-3H-pyrazino[1,2-c]pyrimidine-1,6,8-trione  
 (9aRS)-7-[2,6-difluoro-4-(2-phenylethynyl)phenyl]-9a-methyl-2-(p-tolylmethyl)-4,9-dihydro-3H-pyrazino[1,2-c]pyrimidine-1,6,8-trione  
 (9aRS)-7-[2,6-difluoro-4-(2-phenylethynyl)phenyl]-9a-methyl-2-(o-tolylmethyl)-4,9-dihydro-3H-pyrazino[1,2-c]pyrimidine-1,6,8-trione  
 (9aRS)-7-[2,6-difluoro-4-(2-phenylethynyl)phenyl]-2-[(2,6-dimethylphenyl)methyl]-9a-methyl-4,9-dihydro-3H-pyrazino[1,2-c]pyrimidine-1,6,8-trione  
 (9aRS)-2-[(2-chlorophenyl)methyl]-7-[2,6-difluoro-4-(2-phenylethynyl)phenyl]-9a-methyl-4,9-dihydro-3H-pyrazino[1,2-c]pyrimidine-1,6,8-trione  
 (9aRS)-2-[(3-chlorophenyl)methyl]-7-[2,6-difluoro-4-(2-phenylethynyl)phenyl]-9a-methyl-4,9-dihydro-3H-pyrazino[1,2-c]pyrimidine-1,6,8-trione  
 (9aS)-7-[2,6-difluoro-4-(2-phenylethynyl)phenyl]-2-[(2-fluorophenyl)methyl]-9a-methyl-4,9-dihydro-3H-pyrazino[1,2-c]pyrimidine-1,6,8-trione  
 (9aS)-7-[2,6-difluoro-4-(2-phenylethynyl)phenyl]-2-[(3-fluorophenyl)methyl]-9a-methyl-4,9-dihydro-3H-pyrazino[1,2-c]pyrimidine-1,6,8-trione or  
 (9aS)-7-[2,6-difluoro-4-(2-phenylethynyl)phenyl]-2-[(4-fluorophenyl)methyl]-9a-methyl-4,9-dihydro-3H-pyrazino[1,2-c]pyrimidine-1,6,8-trione.

6. A compound of formula Ic according to claim 1



wherein

R<sup>1</sup> is hydrogen, F or Cl;

L is a bond or C<sub>1-7</sub>-alkylene;

R<sup>2</sup> is a 5 or 6-membered heteroaryl group, selected from pyridinyl, pyrimidinyl, pyridazinyl, thiazolyl, imidazolyl, pyrazolyl or triazolyl, which are optionally substituted by C<sub>1-7</sub>-alkyl, halogen, C<sub>1-7</sub>-alkoxy, =O, benzyloxy, cycloalkyloxy,

hydroxy, cyano, C<sub>1-7</sub>-alkyl substituted by halogen, or by

-(CH<sub>2</sub>)<sub>n</sub>O-C<sub>1-7</sub>-alkyl;

n is 1, 2 or 3;

R<sup>3</sup> is hydrogen, C<sub>1-7</sub>-alkyl or -(CH<sub>2</sub>)<sub>n</sub>O-C<sub>1-7</sub>-alkyl;

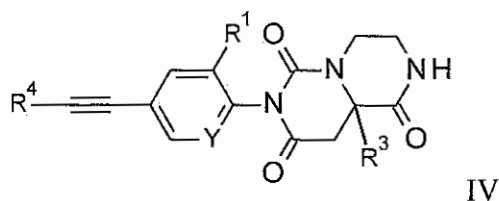
R<sup>4</sup> is phenyl, pyridinyl or pyrimidinyl, optionally substituted by F;

Y is CF or CCl;

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

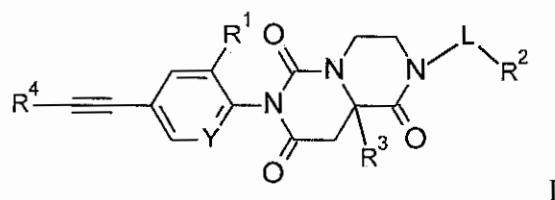
7. A compound of formula Ic according to claims 1 and 6, wherein the compounds are  
 (9aRS)-7-[2,6-difluoro-4-(2-phenylethynyl)phenyl]-2-(3-pyridyl)-3,4,9,9a-tetrahydropyrazino[1,2-c]pyrimidine-1,6,8-trione  
 (9aRS)-7-[2,6-difluoro-4-(2-phenylethynyl)phenyl]-2-pyrimidin-4-yl-3,4,9,9a-tetrahydropyrazino[1,2-c]pyrimidine-1,6,8-trione  
 (9aRS)-7-[2,6-difluoro-4-(2-phenylethynyl)phenyl]-2-(2-pyridyl)-3,4,9,9a-tetrahydropyrazino[1,2-c]pyrimidine-1,6,8-trione  
 (9aRS)-7-[2,6-difluoro-4-(2-phenylethynyl)phenyl]-9a-methyl-2-(2-pyridyl)-4,9-dihydro-3H-pyrazino[1,2-c]pyrimidine-1,6,8-trione  
 (9aS)-7-[2,6-difluoro-4-(2-phenylethynyl)phenyl]-9a-methyl-2-(2-pyridyl)-4,9-dihydro-3H-pyrazino[1,2-c]pyrimidine-1,6,8-trione  
 (9aRS)-7-[2,6-difluoro-4-(2-phenylethynyl)phenyl]-9a-methyl-2-(3-pyridyl)-4,9-dihydro-3H-pyrazino[1,2-c]pyrimidine-1,6,8-trione  
 (9aS)-7-[2,6-difluoro-4-(2-phenylethynyl)phenyl]-9a-methyl-2-(3-pyridyl)-4,9-dihydro-3H-pyrazino[1,2-c]pyrimidine-1,6,8-trione  
 (9aRS)-7-[2,6-difluoro-4-(2-phenylethynyl)phenyl]-9a-methyl-2-(3-pyridyl)-4,9-dihydro-3H-pyrazino[1,2-c]pyrimidine-1,6,8-trione  
 (9aS)-7-[2,6-difluoro-4-(2-phenylethynyl)phenyl]-9a-methyl-2-(3-pyridyl)-4,9-dihydro-3H-pyrazino[1,2-c]pyrimidine-1,6,8-trione  
 (9aRS)-7-[2,6-difluoro-4-(2-phenylethynyl)phenyl]-9a-methyl-2-(6-methyl-2-pyridyl)-4,9-dihydro-3H-pyrazino[1,2-c]pyrimidine-1,6,8-trione

a) reacting a compound of formula IV



with a compound of formula  $\text{XLR}^2$ , wherein X is halogen,

to a compound of formula I



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

9. A compound of formula I according to any one of claims 1 - 7 for use as therapeutically active substances.

10. A compound of formula I according to any one of claims 1- 7 for use in the treatment of Parkinson's disease, anxiety, emesis, obsessive compulsive disorder, autism, neuroprotection, cancer, depression and diabetes type 2.

11. A pharmaceutical composition comprising a compound of formula I as claimed in any one of claim 1 - 7 and pharmaceutically acceptable excipients.

12. The use of a compound of formula I according to any one of claims 1 - 7 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.