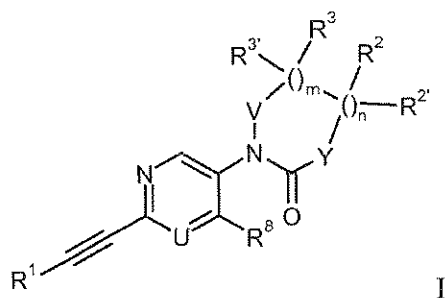


ETHYNYL DERIVATIVES AS MGLUR5 ALLOSTERIC MODULATORS

The present invention relates to ethynyl derivatives of formula I



wherein

U is N or CH,

5 R⁸ is hydrogen, halogen, lower alkyl or lower alkoxy;

Y is -N(R⁴)-, -O- or -C(R⁵R^{5'})-;

wherein R⁴ is hydrogen or lower alkyl and R⁵/R^{5'} are independently hydrogen, hydroxy, lower alkyl or lower alkoxy;

V is -N(R⁶)- or -C(R⁷R^{7'}),

10 wherein R⁶ is hydrogen or lower alkyl and R⁷/R^{7'} are independently from each other hydrogen, lower alkyl, CH₂-lower alkoxy or may form together with the carbon atom to which they are attached a C₃-C₆-cycloalkyl;

R¹ is phenyl or heteroaryl, which are optionally substituted by halogen, lower alkyl or lower alkoxy;

15 m is 0 or 1; in case m is 1,

R³/R^{3'} are independently from each other hydrogen, lower alkyl, CH₂-lower alkoxy or may form together with the carbon atom to which they are attached a C₃-C₆-cycloalkyl;

n is 0 or 1; in case n is 1,

R²/R^{2'} are independently from each other hydrogen, lower alkyl, CH₂-lower alkoxy or may form together with the carbon atom to which they are attached a C₃-C₆-cycloalkyl;

20

or if m is 1 and n is 0, R³ and R⁷ may form together with the carbon atoms to which they are attached a C₄₋₆-cycloalkyl;

or if m is 1 and n is 1, R² and R³ or R³ and R⁷ may form together with the carbon atoms to which they are attached a C₄₋₆-cycloalkyl;

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

It has now surprisingly been found that the compounds of general formula I are
5 allosteric modulators of the metabotropic glutamate receptor subtype 5 (mGluR5).

In the central nervous system (CNS) the transmission of stimuli takes place by the interaction of a neurotransmitter, which is sent out by a neuron, with a neuroreceptor.

Glutamate is the major excitatory neurotransmitter in the brain and plays a unique role in a variety of central nervous system (CNS) functions. The glutamate-dependent stimulus
10 receptors are divided into two main groups. The first main group, namely the ionotropic receptors, forms ligand-controlled ion channels. The metabotropic glutamate receptors (mGluR) belong to the second main group and, furthermore, belong to the family of G-protein coupled receptors.

At present, eight different members of these mGluR are known and of these some even
15 have sub-types. According to their sequence homology, signal transduction mechanisms and agonist selectivity, these eight receptors can be sub-divided into three sub-groups:

mGluR1 and mGluR5 belong to group I, mGluR2 and mGluR3 belong to group II and mGluR4, mGluR6, mGluR7 and mGluR8 belong to group III.

Ligands of metabotropic glutamate receptors belonging to the first group can be used for
20 the treatment or prevention of acute and/or chronic neurological disorders such as psychosis, epilepsy, schizophrenia, Alzheimer's disease, cognitive disorders and memory deficits, as well as chronic and acute pain.

Other treatable indications in this connection are restricted brain function caused by bypass operations or transplants, poor blood supply to the brain, spinal cord injuries, head injuries,
25 hypoxia caused by pregnancy, cardiac arrest and hypoglycaemia. Further treatable indications are ischemia, Huntington's chorea, amyotrophic lateral sclerosis (ALS), dementia caused by AIDS, eye injuries, retinopathy, idiopathic parkinsonism or parkinsonism caused by medicaments as well as conditions which lead to glutamate-deficiency functions, such as e.g. muscle spasms, convulsions, migraine, urinary incontinence, nicotine addiction, opiate
30 addiction, anxiety, vomiting, dyskinesia and depressions.

Disorders mediated full or in part by mGluR5 are for example acute, traumatic and chronic degenerative processes of the nervous system, such as Alzheimer's disease, senile dementia, Parkinson's disease, Huntington's chorea, amyotrophic lateral sclerosis and multiple sclerosis,

psychiatric diseases such as schizophrenia and anxiety, depression, pain and drug dependency (*Expert Opin. Ther. Patents* (2002), 12, (12)).

A new avenue for developing selective modulators is to identify compounds which act through allosteric mechanism, modulating the receptor by binding to a site different from the highly conserved orthosteric binding site. Allosteric modulators of mGluR5 have emerged recently as novel pharmaceutical entities offering this attractive alternative. Allosteric modulators have been described, for example in WO2008/151184, WO2006/048771, WO2006/129199 and WO2005/044797 and in *Molecular Pharmacology*, 40, 333 – 336, 1991; *The Journal of Pharmacology and Experimental Therapeutics*, Vol 313, No. 1, 199-206, 2005;

In recent years there have been significant advantages in understanding the pathophysiology of several disorders of brain development, suggesting that protein synthesis at synapses is triggered by activation of group I metabotropic glutamate receptors. Such disorders include fragile X syndrome, autism, idiopathic autism, tuberous sclerosis complex disorder, neurofibromatosis type 1 or Rett syndrome (*Annu. Rev. Med.*, 2011, 62, 31.1 – 31.19 and *Neuroscience* 156, 2008, 203-215).

Described in the prior art are positive allosteric modulators. They 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 increases the affinity of a glutamate-site agonist at its extracellular N-terminal binding site. Allosteric modulation is thus an attractive mechanism for enhancing appropriate physiological receptor activation. There is a scarcity of selective allosteric modulators for the mGluR5 receptor. Conventional mGluR5 receptor modulators typically lack satisfactory aqueous solubility and exhibit poor oral bioavailability.

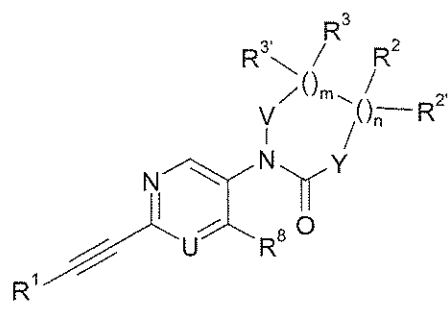
Therefore, there remains a need for compounds that overcome these deficiencies and that effectively provide selective allosteric modulators for the mGluR5 receptor.

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

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

The present disclosure relates to compounds of formula I and to their pharmaceutically acceptable salts, in cases where this applies to mixtures of enantiomers or diastereomers or their enantiomerically or diastereomerically pure forms, 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 mGluR5 receptor, such as schizophrenia, cognition, fragile X syndrome or autism, and to pharmaceutical compositions containing the compounds of formula I.

In a first aspect, there is provided ethynyl derivatives of formula I



wherein

U is N or CH,

R⁸ is hydrogen, halogen, C₁₋₄-alkyl or C₁₋₄-alkoxy;

Y is -N(R⁴)-, -O- or -C(R⁵R^{5'})-;

wherein R⁴ is hydrogen or C₁₋₄-alkyl and R⁵/R^{5'} are independently hydrogen, hydroxy, C₁₋₄-alkyl or C₁₋₄-alkoxy;

V is -N(R⁶)- or -C(R⁷R^{7'}),

wherein R⁶ is hydrogen or C₁₋₄-alkyl and R⁷/R^{7'} are independently from each other hydrogen, C₁₋₄-alkyl, CH₂-C₁₋₄alkoxy or may form together with the carbon atom to which they are attached a C₃-C₆-cycloalkyl;

R¹ is phenyl or heteroaryl, which are optionally substituted by halogen, C₁₋₄-alkyl or C₁₋₄-alkoxy;

m is 1,

R³/R^{3'} are independently from each other hydrogen, C₁₋₄-alkyl, CH₂-C₁₋₄alkoxy or may

form together with the carbon atom to which they are attached a C₃-C₆-cycloalkyl;

n is 0 or 1; in case n is 1,

R²/R^{2'} are independently from each other hydrogen, C₁₋₄-alkyl, CH₂-C₁₋₄alkoxy or may form together with the carbon atom to which they are attached a C₃-C₆-cycloalkyl;

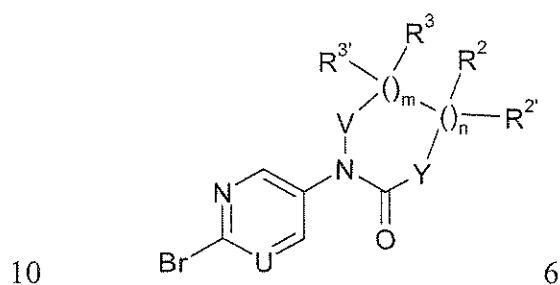
or if m is 1 and n is 0, R³ and R⁷ may form together with the carbon atoms to which they are attached a C₄₋₆-cycloalkyl;

or if m is 1 and n is 1, R² and R³ or R³ and R⁷ may form together with the carbon atoms to which they are attached a C₄₋₆-cycloalkyl;

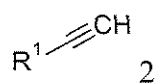
5 or to a pharmaceutically acceptable acid addition salt, to a racemic mixture, or to its corresponding enantiomer and/or optical isomer and/or stereoisomer thereof.

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

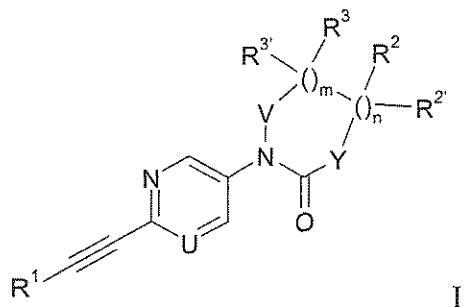
a) reacting a compound of formula



with a suitable aryl-acetylene of formula

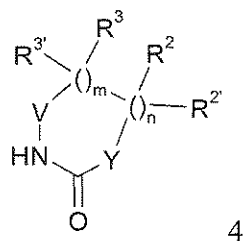


to a compound of formula

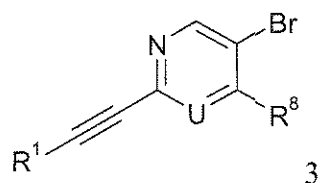


15 wherein the substituents are described above, or

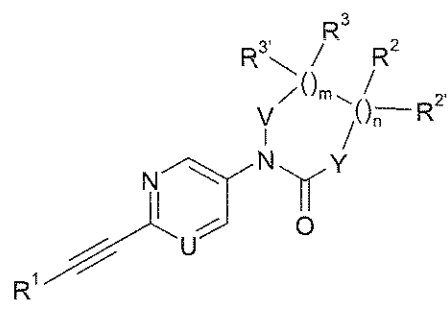
b) reacting a compound of formula



with a suitable compound of formula



to a compound of formula



5 wherein the substituents are described above, and,
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.

10 In a fourth aspect, there is provided a pharmaceutical composition comprising at least one of the compounds as defined above as well as its pharmaceutically acceptable salt.

In a fifth aspect, there is provided a compound as defined above, when applicable as mixtures of enantiomers, diastereomers, or in enantiomerically pure form; as well as its pharmaceutically acceptable salt, for use as a medicament.

15 In a sixth aspect, there is provided use of a compound as defined above as well as its pharmaceutically acceptable salt for the manufacture of a medicament for the treatment or prevention of schizophrenia, cognitive diseases, fragile X syndrome or autism.

In a seventh aspect, there is provided a compound as defined above for use in the treatment or prevention of schizophrenia, cognitive diseases, fragile X syndrome or autism.

20 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.

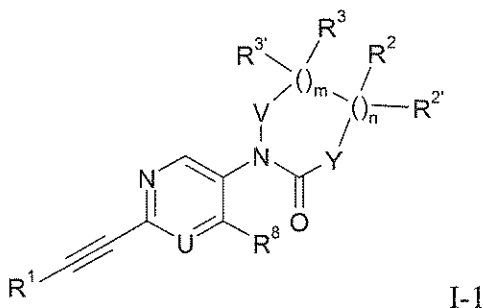
25 The term "alkoxy" denotes a group -O-R' wherein R' is lower alkyl as defined above.
The term "ethynyl" denotes the group -C≡C-.

The term "cycloalkyl" denotes a saturated carbon ring, containing from 3 to 6 carbon ring atoms, for example cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

The term "heteroaryl" denotes a 5 or 6-membered aromatic ring, containing at least one N, O or S-heteroatom, for example pyridinyl, pyrimidinyl, pyrazolyl, pyridazinyl, imidazolyl, triazolyl, thienyl or pyrazinyl.

The term "pharmaceutically acceptable salt" or "pharmaceutically acceptable acid addition salt" embraces salts with inorganic and organic acids, such as hydrochloric acid, nitric acid, sulfuric acid, phosphoric acid, citric acid, formic acid, fumaric acid, maleic acid, acetic acid, succinic acid, tartaric acid, methane-sulfonic acid, p-toluenesulfonic acid and the like.

One embodiment of the invention are compounds of formula



wherein

U is N or CH;

R⁸ is hydrogen;

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Y is CH₂, O, -N(CH₃)- or -N(CH₂CH₃)-;

V is CH₂, -NH- or -N(CH₃)-;

R¹ is phenyl or pyridinyl, which are optionally substituted by halogen;

m is 0 or 1; in case m is 1,

5 R³/R^{3'} are independently from each other hydrogen or lower alkyl,

n is 1;

R²/R^{2'} are independently from each other hydrogen or lower alkyl;

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

10 compounds

4,4-Dimethyl-1-(6-phenylethynyl-pyridin-3-yl)-pyrrolidin-2-one

6,6-Dimethyl-3-(6-phenylethynyl-pyridin-3-yl)-[1,3]oxazinan-2-one

3,4,4-Trimethyl-1-(6-phenylethynyl-pyridin-3-yl)-imidazolidin-2-one

1-[6-(4-Fluoro-phenylethynyl)-pyridin-3-yl]-3,4,4-trimethyl-imidazolidin-2-one

15 1-[6-(3-Fluoro-phenylethynyl)-pyridin-3-yl]-3,4,4-trimethyl-imidazolidin-2-one

3,4,4-Trimethyl-1-(6-pyridin-3-ylethynyl-pyridin-3-yl)-imidazolidin-2-one

1-[6-(3-Fluoro-phenylethynyl)-pyridin-3-yl]-4,4-dimethyl-pyrrolidin-2-one

5,5-Dimethyl-2-(6-phenylethynyl-pyridin-3-yl)-pyrazolidin-3-one

4,4-Dimethyl-1-(6-phenylethynyl-pyrimidin-3-yl)-pyrrolidin-2-one

20 3,4,4-Trimethyl-1-(2-phenylethynyl-pyrimidin-5-yl)-imidazolidin-2-one

3-Ethyl-4,4-dimethyl-1-(2-phenylethynyl-pyrimidin-5-yl)-imidazolidin-2-one

1,5,5-Trimethyl-2-(6-phenylethynyl-pyridin-3-yl)-pyrazolidin-3-one

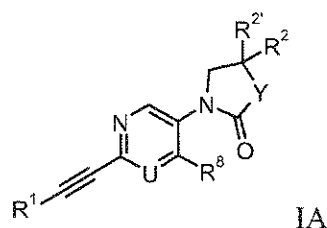
2-[6-(3-Fluoro-phenylethynyl)-pyridin-3-yl]-1,5,5-trimethyl-pyrazolidin-3-one

2-[6-(2,5-Difluoro-phenylethynyl)-pyridin-3-yl]-1,5,5-trimethyl-pyrazolidin-3-one

25 2-[6-(3-Fluoro-phenylethynyl)-pyridin-3-yl]-5,5-dimethyl-pyrazolidin-3-one or

2-[6-(2,5-Difluoro-phenylethynyl)-pyridin-3-yl]-5,5-dimethyl-pyrazolidin-3-one.

One further embodiment of the invention are compounds of formula



30 wherein

U is N or CH,

R⁸ is hydrogen, halogen, lower alkyl or lower alkoxy;

Y is -N(R⁴)-, O or -C(R⁵R⁵)-;

wherein R⁴ is hydrogen or lower alkyl and R⁵/R⁵' are independently hydrogen, hydroxy,

lower alkyl or lower alkoxy;

R¹ is phenyl or heteroaryl, which are optionally substituted by halogen, lower alkyl or lower alkoxy;

R²/R²' are independently from each other hydrogen, lower alkyl, CH₂-lower alkoxy or may form together with the carbon atom to which they are attached a C₃-C₆-cycloalkyl;

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

Examples of compounds of formula IA are the followings:

4,4-dimethyl-1-(6-phenylethynyl-pyridin-3-yl)-pyrrolidin-2-one

3,4,4-trimethyl-1-(6-phenylethynyl-pyridin-3-yl)-imidazolidin-2-one

1-[6-(4-fluoro-phenylethynyl)-pyridin-3-yl]-3,4,4-trimethyl-imidazolidin-2-one

1-[6-(3-fluoro-phenylethynyl)-pyridin-3-yl]-3,4,4-trimethyl-imidazolidin-2-one

3,4,4-trimethyl-1-(6-pyridin-3-ylethynyl-pyridin-3-yl)-imidazolidin-2-one

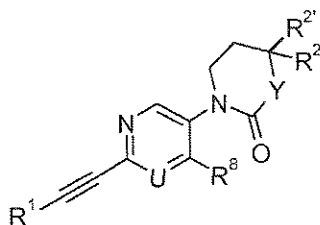
1-[6-(3-fluoro-phenylethynyl)-pyridin-3-yl]-4,4-dimethyl-pyrrolidin-2-one

4,4-dimethyl-1-(6-phenylethynyl-pyrimidin-3-yl)-pyrrolidin-2-one

3,4,4-Trimethyl-1-(2-phenylethynyl-pyrimidin-5-yl)-imidazolidin-2-one or

3-Ethyl-4,4-dimethyl-1-(2-phenylethynyl-pyrimidin-5-yl)-imidazolidin-2-one.

A further embodiment of the invention are compounds of formula



IB

wherein

U is N or CH,

R⁸ is hydrogen, halogen, lower alkyl or lower alkoxy;

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Y is $-N(R^4)-$, O or $-C(R^5R^{5'})-$;

wherein R^4 is hydrogen or lower alkyl and $R^5/R^{5'}$ are independently hydrogen, hydroxy, lower alkyl or lower alkoxy;

R^1 is phenyl or heteroaryl, which are optionally substituted by halogen, lower alkyl or lower alkoxy;

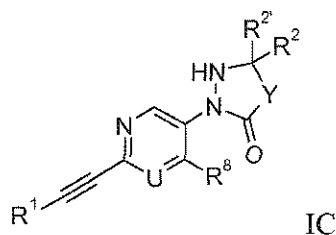
$R^2/R^{2'}$ are independently from each other hydrogen, lower alkyl, CH_2 -lower alkoxy or may form together with the carbon atom to which they are attached a C_3 - C_6 -cycloalkyl;

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

Specific examples from compounds of formula IB is the following:

6,6-dimethyl-3-(6-phenylethynyl-pyridin-3-yl)-[1,3]oxazinan-2-one.

A further embodiment of the invention are compounds of formula



wherein

U is N or CH,

R^8 is hydrogen, halogen, lower alkyl or lower alkoxy;

Y is $-N(R^4)-$, O or $-C(R^5R^{5'})-$;

wherein R^4 is hydrogen or lower alkyl and $R^5/R^{5'}$ are independently hydrogen, hydroxy, lower alkyl or lower alkoxy;

R^1 is phenyl or heteroaryl, which are optionally substituted by halogen, lower alkyl or lower alkoxy;

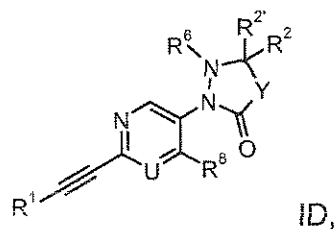
$R^2/R^{2'}$ are independently from each other hydrogen, lower alkyl, CH_2 -lower alkoxy or may form together with the carbon atom to which they are attached a C_3 - C_6 -cycloalkyl;

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

Examples from compounds of formula IC is the following:

5,5-dimethyl-2-(6-phenylethynyl-pyridin-3-yl)-pyrazolidin-3-one.

One further embodiment of the invention are compounds of formula



wherein

- 5 U is N or CH,
 R⁸ is hydrogen, halogen, lower alkyl or lower alkoxy;
 Y is -N(R⁴)-, -O- or -C(R⁵R^{5'})-;
 wherein R⁴ is hydrogen or lower alkyl and R⁵/R^{5'} are independently hydrogen, hydroxy,
 lower alkyl or lower alkoxy;
 10 R⁶ is hydrogen or lower alkyl
 R¹ is phenyl or heteroaryl, which are optionally substituted by halogen, lower alkyl or lower
 alkoxy;
 R²/R^{2'} are independently from each other hydrogen, lower alkyl, CH₂-lower alkoxy or may form
 together with the carbon atom to which they are attached a C₃-C₆-cycloalkyl;
 15 or a pharmaceutically acceptable acid addition salt, a racemic mixture, or its corresponding
 enantiomer and/or optical isomer and/or stereoisomer thereof.

Examples of compounds of formula I-D are

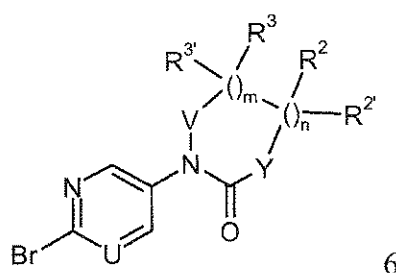
- 1,5,5-Trimethyl-2-(6-phenylethynyl-pyridin-3-yl)-pyrazolidin-3-one
 2-[6-(3-Fluoro-phenylethynyl)-pyridin-3-yl]-1,5,5-trimethyl-pyrazolidin-3-one
 20 2-[6-(2,5-Difluoro-phenylethynyl)-pyridin-3-yl]-1,5,5-trimethyl-pyrazolidin-3-one
 2-[6-(3-Fluoro-phenylethynyl)-pyridin-3-yl]-5,5-dimethyl-pyrazolidin-3-one or
 2-[6-(2,5-Difluoro-phenylethynyl)-pyridin-3-yl]-5,5-dimethyl-pyrazolidin-3-one.

- The preparation of compounds of formula I of the present invention may be carried out in
 25 sequential or convergent synthetic routes. Syntheses of the compounds of the invention are
 shown in the following schemes 1 and 2. The skills required for carrying out the reaction and
 purification of the resulting products are known to those skilled in the art. The substituents and
 indices used in the following description of the processes have the significance given herein
 before.

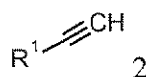
The compounds of formula I can be manufactured by the methods given below, by the methods given in the examples or by analogous methods. Appropriate reaction conditions for the individual reaction steps are known to a person skilled in the art. The reaction sequence is not limited to the one displayed in the schemes, however, depending on the starting materials and their respective reactivity the sequence of reaction steps can be freely altered. Starting materials are either commercially available or can be prepared by methods analogous to the methods given below, by methods described in references cited in the description or in the examples, or by methods known in the art.

The present compounds of formula I and their pharmaceutically acceptable salts may be prepared by methods, known in the art, for example by the process variant described below, which process comprises

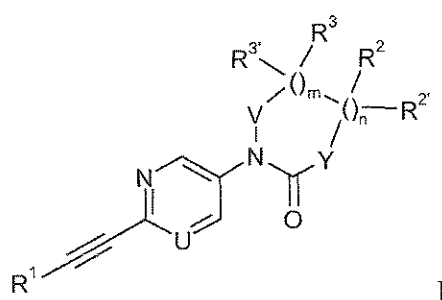
a) reacting a compound of formula



with a suitable aryl-acetylene of formula

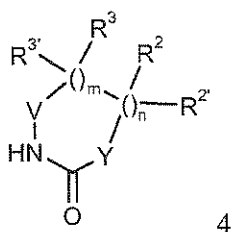


to a compound of formula



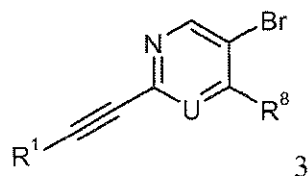
wherein the substituents are described above, or

b) reacting a compound of formula

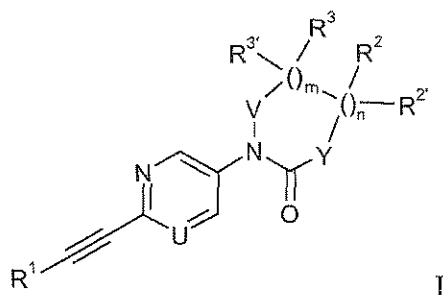


-10-

with a suitable compound of formula



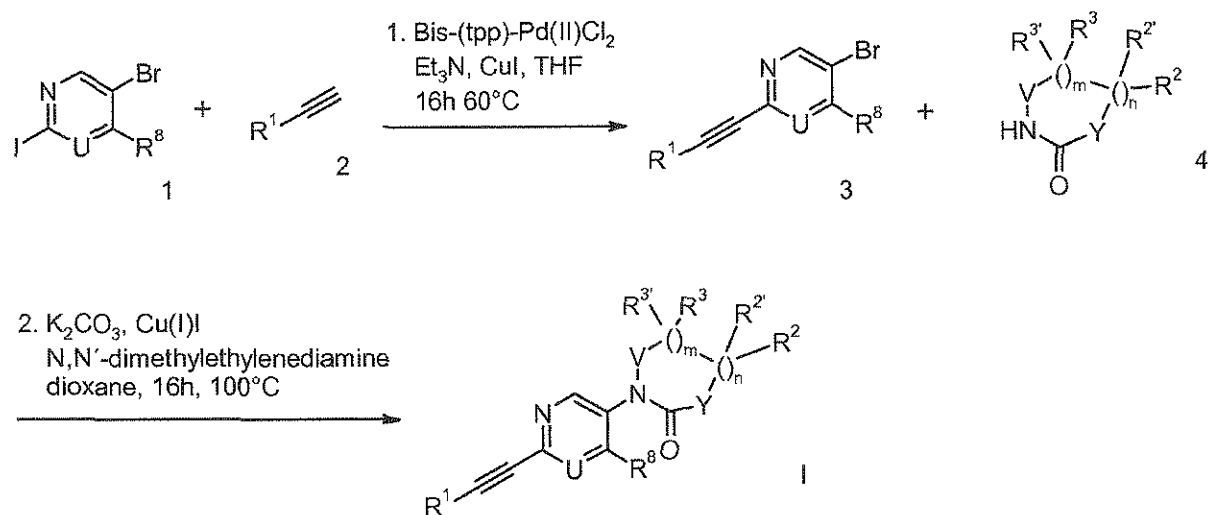
to a compound of formula



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

The preparation of compounds of formula I is further described in more detail in schemes 1 and
10 2 and in examples 1 – 16.

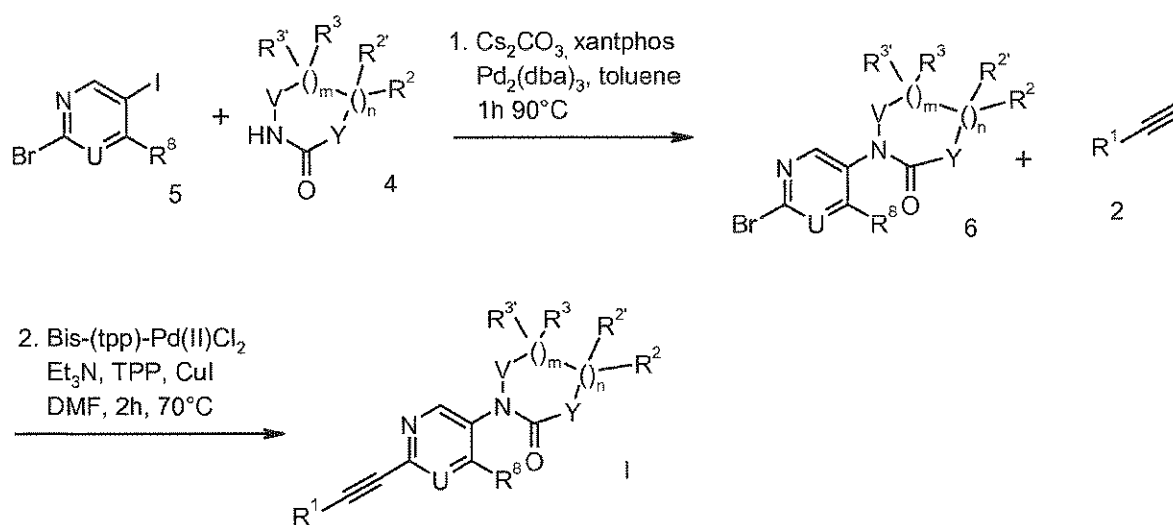
Scheme 1



An ethynyl-pyridine or ethynyl-pyrimidine compound of formula I can be obtained for example by Sonogashira coupling of an appropriate 5-bromo-2-iodo-pyridine or pyrimidine 1

with an appropriately substituted arylacetylene **2** to yield the corresponding 5-bromo-2-ethynylpyridine or pyrimidine derivatives **3**. Substitution of **3** with an appropriate lactam, cyclic carbamate, cyclic urea or pyrazolidin-3-one derivative **4** in presence of a base such as potassium carbonate and using copper(I)iodide and N,N'-dimethylethylenediamine in a solvent like dioxane yields the desired ethynyl-pyridine or ethynyl-pyrimidine compound of formula **I**.

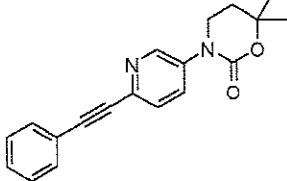
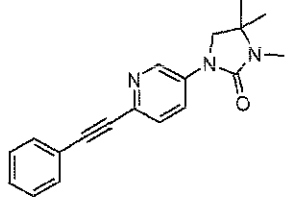
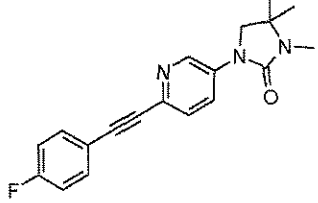
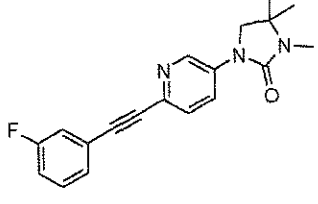
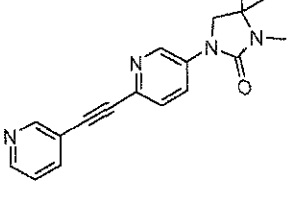
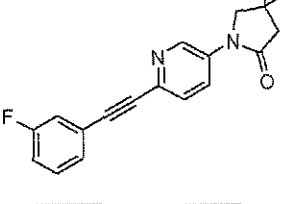
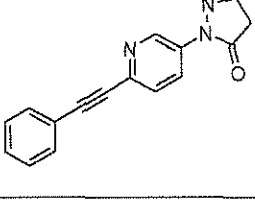
Scheme 2

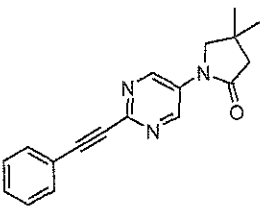
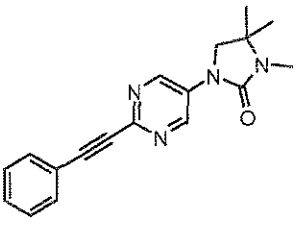
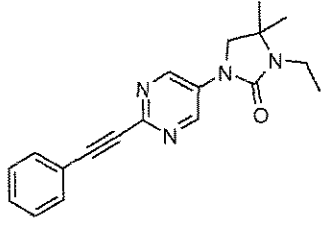
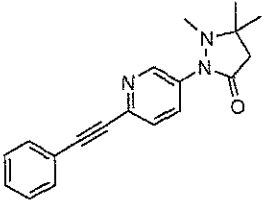
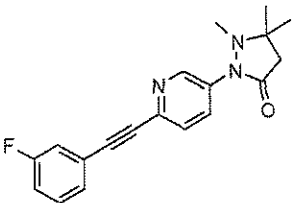
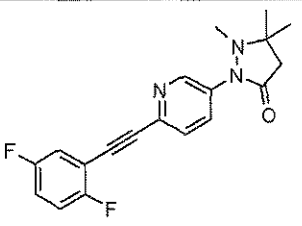
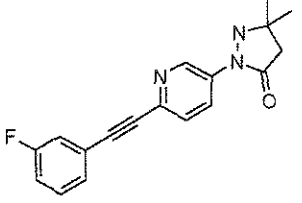


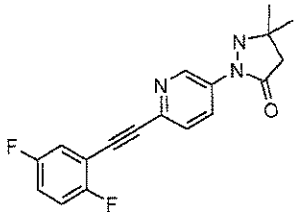
An ethynyl-pyridine or ethynyl-pyrimidine compound of formula **I** can be obtained for example by substitution of 2-bromo-5-iodo-pyridine or pyrimidine **5** with an appropriate lactam, cyclic carbamate, cyclic urea or pyrazolidin-3-one derivative **4** in presence of a base such as cesium carbonate and using xantphos and $\text{Pd}_2(\text{dba})_3$ in a solvent like toluene yielding the desired 2-bromo-pyridine or pyrimidine derivatives **6**. Sonogashira coupling of **6** with an appropriately substituted arylacetylene **2** yields ethynyl-pyridine or ethynyl-pyrimidine compound of formula **I**.

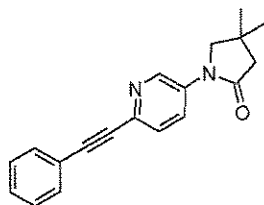
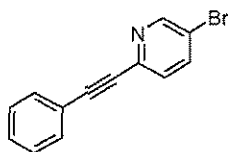
List of Examples:

Ex.	Structure	Name	EC ₅₀ (nM) mGlu5PAM	Eff. (%)
1		4,4-Dimethyl-1-(6-phenylethynyl-pyridin-3-yl)-pyrrolidin-2-one	49	75

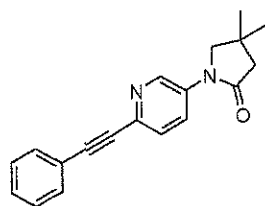
2		6,6-Dimethyl-3-(6-phenylethynyl-pyridin-3-yl)-[1,3]oxazinan-2-one	96	85
3		3,4,4-Trimethyl-1-(6-phenylethynyl-pyridin-3-yl)-imidazolidin-2-one	15	45
4		1-[6-(4-Fluorophenylethynyl)-pyridin-3-yl]-3,4,4-trimethylimidazolidin-2-one	50	44
5		1-[6-(3-Fluorophenylethynyl)-pyridin-3-yl]-3,4,4-trimethylimidazolidin-2-one	19	42
6		3,4,4-Trimethyl-1-(6-pyridin-3-ylethynyl-pyridin-3-yl)-imidazolidin-2-one	241	36
7		1-[6-(3-Fluorophenylethynyl)-pyridin-3-yl]-4,4-dimethylpyrrolidin-2-one	39	62
8		5,5-Dimethyl-2-(6-phenylethynyl-pyridin-3-yl)-pyrazolidin-3-one	62	56

9		4,4-Dimethyl-1-(6-phenylethynyl-pyrimidin-3-yl)-pyrrolidin-2-one	36	39
10		3,4,4-Trimethyl-1-(2-phenylethynyl-pyrimidin-5-yl)-imidazolidin-2-one	-	-
11		3-Ethyl-4,4-dimethyl-1-(2-phenylethynyl-pyrimidin-5-yl)-imidazolidin-2-one	79	52
12		1,5,5-Trimethyl-2-(6-phenylethynyl-pyridin-3-yl)-pyrazolidin-3-one	40	66
13		2-[6-(3-Fluorophenylethynyl)-pyridin-3-yl]-1,5,5-trimethyl-pyrazolidin-3-one	38	63
14		2-[6-(2,5-Difluorophenylethynyl)-pyridin-3-yl]-1,5,5-trimethyl-pyrazolidin-3-one	53	57
15		2-[6-(3-Fluorophenylethynyl)-pyridin-3-yl]-5,5-dimethyl-pyrazolidin-3-one	68	38

16		2-[6-(2,5-Difluoro-phenylethynyl)-pyridin-3-yl]-5,5-dimethyl-pyrrolidin-3-one	40	41
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Experimental Section:**Example 1****5 4,4-Dimethyl-1-(6-phenylethynyl-pyridin-3-yl)-pyrrolidin-2-one**Step 1: 5-Bromo-2-phenylethynyl-pyridine

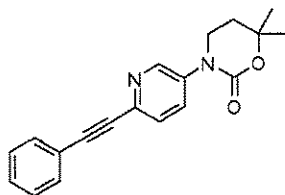
Bis-(triphenylphosphine)-palladium(II)dichloride (62 mg, 0.088 mmol, 0.05 equiv.) was dissolved in 5 ml THF. (500 mg, 1.76 mmol) 5-Bromo-2-iodopyridine and phenylacetylene (216 mg, 2.11 mmol, 1.2 equiv.) were added at room temperature. Triethylamine (0.74 ml, 5.28 mmol, 3 equiv.) and copper(I)iodide (10 mg, 0.053 mmol, 0.03 equiv.) were added and the mixture was stirred for 16 hours at 60°C. The reaction mixture was evaporated to dryness and loaded directly to a silica gel column. The crude product was purified by flash chromatography on a silica gel column eluting with a heptane:ethyl acetate gradient 100:0 to 90:10. The desired 5-bromo-2-phenylethynyl-pyridine (354 mg, 78 % yield) was obtained as a light yellow solid, MS: m/e = 258.0/259.9 (M+H⁺).

Step 2: 4,4-Dimethyl-1-(6-phenylethynyl-pyridin-3-yl)-pyrrolidin-2-one

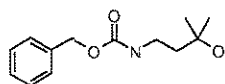
To a suspension of 5-bromo-2-phenylethynyl-pyridine (*Example 1, step 1*) (40 mg, 0.155 mmol), 4,4-dimethylpyrrolidine-2-one (21 mg, 0.186 mmol, 1.2 equiv.), potassium carbonate (64 mg, 0.465 mmol, 3 equiv.) and N,N'-dimethylethylenediamine (1.4 mg, 0.015 mmol, 0.1 equiv.) in 1 ml of dioxane was added under argon atmosphere copper(I)iodide (3 mg, 0.015 mmol, 0.1 equiv.). The mixture was stirred overnight at 100°C. The reaction mixture was cooled and extracted with saturated NaHCO₃ solution and two times with ethyl acetate. The organic layers were extracted with brine, combined, dried over sodium sulfate and evaporated to dryness. The crude product was purified by flash chromatography on a silica gel column eluting with a heptane:ethyl acetate gradient 100:0 to 30:70. The desired 4,4-dimethyl-1-(6-phenylethynyl-pyridin-3-yl)-pyrrolidin-2-one (30 mg, 67 % yield) was obtained as a white solid, MS: m/e = 291.1 (M+H⁺).

Example 2

6,6-Dimethyl-3-(6-phenylethynyl-pyridin-3-yl)-[1,3]oxazinan-2-one

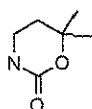


Step 1: (3-Hydroxy-3-methyl-butyl)-carbamic acid benzyl ester



(10 g, 42.1 mmol) Methyl 3-(benzyloxycarbonylamino)propanoate (CAS 54755-77-0) was dissolved in THF (150 ml) and cooled to 0-5 °C. 3N Methylmagnesium bromide in THF (56.2 ml, 120 mmol, 4 equiv.) was added drop wise and the mixture stirred for 1 hour at 0-5 °C. The reaction mixture was extracted with saturated NH₄Cl solution and two times with EtOAc. The organic layers were dried over Na₂SO₄ and evaporated to dryness. The desired (3-hydroxy-3-methyl-butyl)-carbamic acid benzyl ester (11.6 g, quant.) was obtained as a colorless oil, MS: m/e = 238.1 (M+H⁺) and used in the next step without further purification.

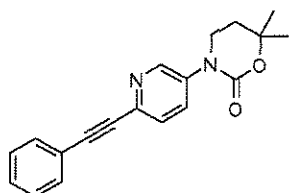
Step 2: 6,6-dimethyl-[1,3]oxazinan-2-one



(11.6 g, 48.9 mmol) (3-Hydroxy-3-methyl-butyl)-carbamic acid benzyl ester (*Example 72, step 1*) was dissolved in THF (250 ml) and sodium hydride (60%, 5.2 g, 108 mmol, 2.2 equiv.) was added in portions. The mixture was stirred for 3 hours at room temperature. 5ml saturated NaHCO_3 solution was added carefully and the mixture was evaporated with isolate to dryness.

- 5 The crude product was purified by flash chromatography by directly loading the residue onto a silica gel column and eluting with an ethyl acetate:methanol gradient 100:0 to 90:10. The desired 6,6-dimethyl-[1,3]oxazinan-2-one (3.2 g, 51 % yield) was obtained as a yellow solid, MS: $m/e = 130.1$ ($M+H^+$).

10 Step 3: 6,6-Dimethyl-3-(6-phenylethynyl-pyridin-3-yl)-[1,3]oxazinan-2-one

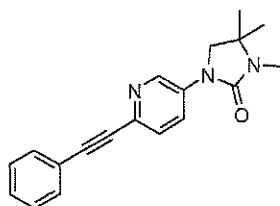


The title compound was obtained as a white solid, MS: $m/e = 307.2$ ($M+H^+$), using chemistry similar to that described in Example 1, step 2 from 5-bromo-2-phenylethynyl-pyridine (*Example 1, step 1*) and 6,6-dimethyl-[1,3]oxazinan-2-one (*Example 2, step 2*).

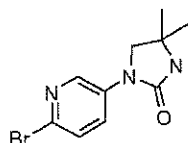
15

Example 3

3,4,4-Trimethyl-1-(6-phenylethynyl-pyridin-3-yl)-imidazolidin-2-one



Step 1: 1-(6-Bromo-pyridin-3-yl)-4,4-dimethyl-imidazolidin-2-one

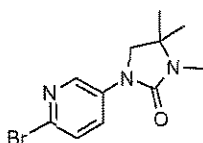


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To a suspension of 2-bromo-5-iodopyridine (1.0 g, 3.52 mmol), 4,4-dimethyl-imidazolidin-2-one (*CAS 24572-33-6*) (400 mg, 3.52 mmol, 1.0 equiv.), cesium carbonate (1.72 g, 5.28 mmol, 1.5 equiv.), and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (xantphos) (82 mg, 0.141 mmol, 0.04 equiv.) in 10ml of toluene was added under argon atmosphere

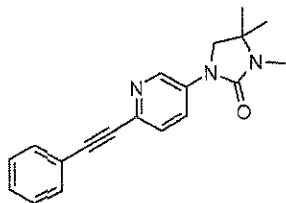
tris(dibenzylideneacetone)dipalladium(0) chloroform adduct ($\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$) (73 mg, 0.07 mmol, 0.02 equiv.). The mixture was stirred for 1 hour at 100°C. The mixture was directly loaded on a 50 g silicagel column and was eluted with an heptane:ethyl acetate gradient 100:0 to 0:100 and an ethyl acetate:methanol gradient 100:0 to 80:20. The desired 1-(6-bromo-pyridin-3-yl)-4,4-dimethyl-imidazolidin-2-one (810 mg, 85 % yield) was obtained as a light yellow solid, MS: $m/e = 207.1/272.1$ ($\text{M}+\text{H}^+$).

Step 2: 1-(6-Bromo-pyridin-3-yl)-3,4,4-trimethyl-imidazolidin-2-one



(810 mg, 3.0 mmol) 1-(6-Bromo-pyridin-3-yl)-4,4-dimethyl-imidazolidin-2-one (*Example 3, step 1*) was dissolved in DMF (8 ml) and cooled to 0-5°C. Iodomethane (640 mg, 280 μl , 4.5 mmol, 1.5 equiv.) and NaH (60%) (156 mg, 3.9 mmol, 1.3 equiv.) were added and the mixture was stirred for 2 hours at 0-5°C. The reaction mixture was treated with sat. NaHCO_3 solution and extracted two times with EtOAc. The organic layers were extracted with water and brine, dried over Na_2SO_4 and evaporated to dryness. The crude product was purified by flash chromatography on a silica gel column eluting with a heptane:ethyl acetate gradient 100:0 to 0:100. The desired 1-(6-bromo-pyridin-3-yl)-3,4,4-trimethyl-imidazolidin-2-one (800 mg, 94 % yield) was obtained as a yellow solid, MS: $m/e = 284.1/286.0$ ($\text{M}+\text{H}^+$).

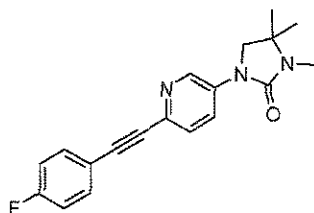
Step 3: 3,4,4-Trimethyl-1-(6-phenylethynyl-pyridin-3-yl)-imidazolidin-2-one



Bis-(triphenylphosphine)-palladium(II)dichloride (6 mg, 8.5 μmol , 0.03 equiv.) was dissolved in 1 ml DMF. (80 mg, 282 μmol) 1-(6-Bromo-pyridin-3-yl)-3,4,4-trimethyl-imidazolidin-2-one (*Example 3, step 2*) and phenylacetylene (58 mg, 563 μmol , 2 equiv.) were added at room temperature. Triethylamine (118 μl , 0.845 mmol, 3 equiv.), triphenylphosphine (4.4 mg, 16.9 μmol , 0.06 equiv.) and copper(I)iodide (1.6 mg, 8.45 μmol , 0.03 equiv.) were added and the mixture was stirred for 4 hours at 90°C. The reaction mixture was evaporated to dryness with isolute® and the crude product was purified by flash chromatography by directly loading the

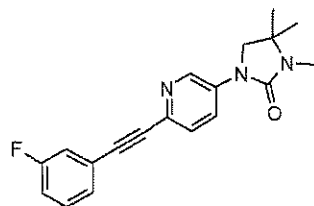
solid onto a silica gel column and eluting with an ethyl acetate:heptane gradient 0:100 to 100:0. The desired 3,4,4-trimethyl-1-(6-phenylethynyl-pyridin-3-yl)-imidazolidin-2-one (52 mg, 61 % yield) was obtained as a yellow solid, MS: $m/e = 306.2$ ($M+H^+$).

5

Example 4**1-[6-(4-Fluoro-phenylethynyl)-pyridin-3-yl]-3,4,4-trimethyl-imidazolidin-2-one**

The title compound was obtained as a yellow solid, MS: $m/e = 324.2$ ($M+H^+$), using chemistry similar to that described in Example 3, step 3 from 1-(6-bromo-pyridin-3-yl)-3,4,4-trimethyl-imidazolidin-2-one (Example 3, step 2) and 4-fluorophenylacetylene.

10

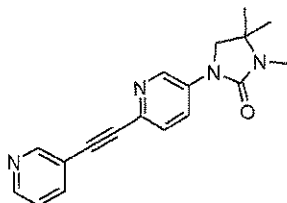
Example 5**1-[6-(3-Fluoro-phenylethynyl)-pyridin-3-yl]-3,4,4-trimethyl-imidazolidin-2-one**

The title compound was obtained as a yellow solid, MS: $m/e = 324.2$ ($M+H^+$), using chemistry similar to that described in Example 3, step 3 from 1-(6-bromo-pyridin-3-yl)-3,4,4-trimethyl-imidazolidin-2-one (Example 3, step 2) and 3-fluorophenylacetylene.

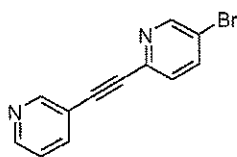
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Example 6**3,4,4-Trimethyl-1-(6-pyridin-3-ylethynyl-pyridin-3-yl)-imidazolidin-2-one**

20



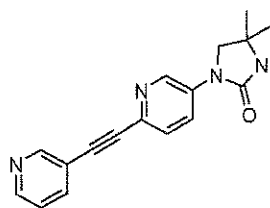
Step 1: 5-Bromo-2-pyridin-3-ylethynyl-pyridine



The title compound was obtained as a yellow solid, MS: $m/e = 259.0/260.9$ ($M+H^+$), using chemistry similar to that described in Example 1, step 1 from 5-bromo-2-iodopyridine and 3-ethynylpyridine.

5

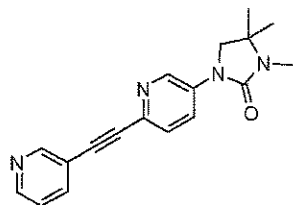
Step 2: 4,4-Dimethyl-1-(6-pyridin-3-ylethynyl-pyridin-3-yl)-imidazolidin-2-one



The title compound was obtained as a white solid, MS: $m/e = 293.1$ ($M+H^+$), using chemistry similar to that described in Example 1, step 2 from 5-bromo-2-(3-ethynylphenyl)pyridine (Example 6, step 1) and 4,4-dimethyl-imidazolidin-2-one (CAS 24572-33-6).

10

Step 3: 3,4,4-Trimethyl-1-(6-pyridin-3-ylethynyl-pyridin-3-yl)-imidazolidin-2-one

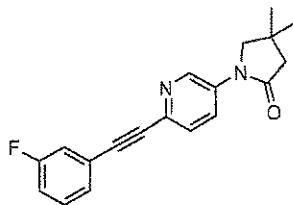


The title compound was obtained as a white solid, MS: $m/e = 307.2$ ($M+H^+$), using chemistry similar to that described in Example 3, step 2 from 4,4-dimethyl-1-(6-(3-ethynylphenyl)pyridin-3-yl)-imidazolidin-2-one (Example 6, step 2) and iodomethane.

15

Example 7

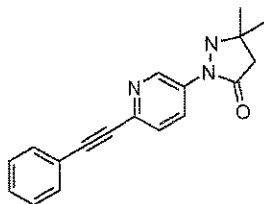
1-[6-(3-Fluorophenylethynyl)-pyridin-3-yl]-4,4-dimethyl-pyrrolidin-2-one



20

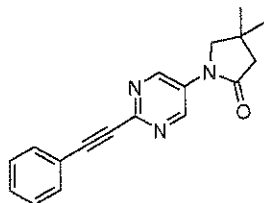
The title compound was obtained as a white solid, MS: $m/e = 309.1$ ($M+H^+$), using chemistry similar to that described in Example 1, step 1 and step 2 from 5-bromo-2-iodopyridine, 3-fluorophenylacetylene and 4,4-dimethylpyrrolidine-2-one.

5

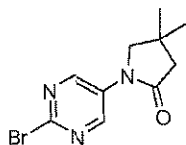
Example 8**5,5-Dimethyl-2-(6-phenylethynyl-pyridin-3-yl)-pyrazolidin-3-one**

The title compound was obtained as a white solid, MS: $m/e = 292.1$ ($M+H^+$), using chemistry similar to that described in Example 1, step 2 from 5-bromo-2-phenylethynyl-pyridine (*Example 1, step 1*) and 5,5-dimethyl-pyrazolidin-3-one (CAS 42953-82-2).

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Example 9**4,4-Dimethyl-1-(6-phenylethynyl-pyrimidin-3-yl)-pyrrolidin-2-one**

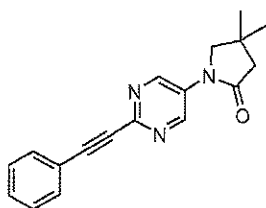
15 Step 1: 1-(2-Bromo-pyrimidin-5-yl)-4,4-dimethyl-pyrrolidin-2-one



The title compound was obtained as a light yellow solid, MS: $m/e = 270.1/272.1$ ($M+H^+$), using chemistry similar to that described in Example 3, step 1 from 2-bromo-5-iodopyrimidine and 4,4-dimethylpyrrolidine-2-one.

20

Step 2: 4,4-Dimethyl-1-(6-phenylethynyl-pyrimidin-3-yl)-pyrrolidin-2-one

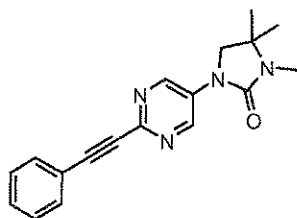


The title compound was obtained as a light brown solid, MS: $m/e = 292.3$ ($M+H^+$), using chemistry similar to that described in Example 1, step 3 from 1-(2-bromo-pyrimidin-5-yl)-4,4-dimethyl-pyrrolidin-2-one (*Example 9, step 1*) and phenylacetylene.

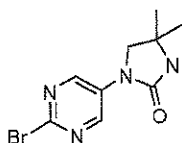
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Example 10

3,4,4-Trimethyl-1-(2-phenylethynyl-pyrimidin-5-yl)-imidazolidin-2-one



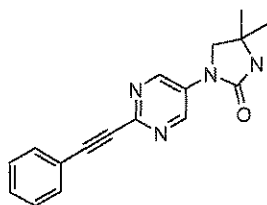
Step 1: 1-(2-Bromo-pyrimidin-5-yl)-4,4-dimethyl-imidazolidin-2-one



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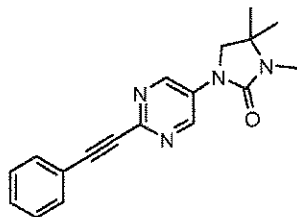
The title compound was obtained as a white solid, MS: $m/e = 271.2/273.1$ ($M+H^+$), using chemistry similar to that described in Example 3, step 1 from 2-bromo-5-iodopyrimidine and 4,4-dimethyl-imidazolidin-2-one (*CAS 24572-33-6*).

15 Step 2: 4,4-Dimethyl-1-(2-phenylethynyl-pyrimidin-5-yl)-imidazolidin-2-one

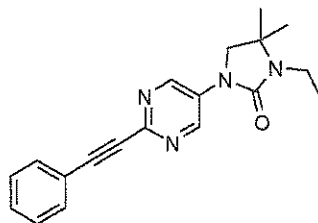


The title compound was obtained as a white solid, MS: $m/e = 293.0$ ($M+H^+$), using chemistry similar to that described in Example 3, step 3 from 1-(2-bromo-pyrimidin-5-yl)-4,4-dimethyl-imidazolidin-2-one (*Example 10, step 1*) and phenylacetylene.

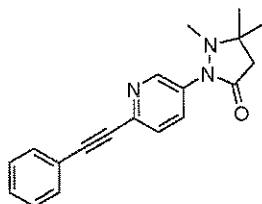
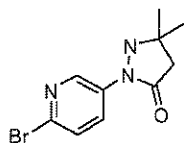
20

Step 2: 3,4,4-Trimethyl-1-(2-phenylethynyl-pyrimidin-5-yl)-imidazolidin-2-one

The title compound was obtained as a white solid, MS: $m/e = 307.2$ ($M+H^+$), using chemistry similar to that described in Example 3, step 2 from 4,4-dimethyl-1-(2-phenylethynyl-pyrimidin-5-yl)-imidazolidin-2-one (*Example 10, step 2*) and iodomethane.

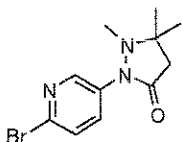
Example 11**3-Ethyl-4,4-dimethyl-1-(2-phenylethynyl-pyrimidin-5-yl)-imidazolidin-2-one**

The title compound was obtained as a light yellow solid, MS: $m/e = 321.4$ ($M+H^+$), using chemistry similar to that described in Example 3, step 2 from 4,4-dimethyl-1-(2-phenylethynyl-pyrimidin-5-yl)-imidazolidin-2-one (*Example 10, step 2*) and iodoethane.

Example 12**1,5,5-Trimethyl-2-(6-phenylethynyl-pyridin-3-yl)-pyrazolidin-3-one**Step 1: 2-(6-Bromo-pyridin-3-yl)-5,5-dimethyl-pyrazolidin-3-one

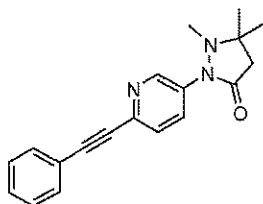
The title compound was obtained as a yellow oil, MS: $m/e = 270.3/272.3$ ($M+H^+$), using chemistry similar to that described in Example 3, step 1 from 2-bromo-5-iodopyridine and 5,5-dimethyl-pyrazolidin-3-one (CAS 42953-82-2) by using dioxane instead of toluene as solvent.

5 Step 2: 2-(6-Bromo-pyridin-3-yl)-1,5,5-trimethyl-pyrazolidin-3-one



A suspension of 2-(6-bromo-pyridin-3-yl)-5,5-dimethyl-pyrazolidin-3-one (Example 12, step 1) (800 mg, 2.96 mmol) and formic acid (0.57 ml, 14.8 mmol, 5 equiv.) in water (8 ml) was heated to 100°C. At this temperature formaldehyde (36% in water) (1.13 ml, 14.8 mmol, 5 equiv.) was added drop wise. The mixture was stirred overnight at 100°C. The reaction mixture was cooled and basified carefully with 2N NaOH and extracted two times with a small amount of dichloromethane. The organic layers were loaded directly on a silica gel column and the crude product was purified by flash chromatography eluting with a heptane:ethyl acetate gradient 100:0 to 0:100. The desired 2-(6-bromo-pyridin-3-yl)-1,5,5-trimethyl-pyrazolidin-3-one (380 mg, 45 % yield) was obtained as a colorless oil, MS: $m/e = 284.3/286.3$ ($M+H^+$).

Step 3: 1,5,5-Trimethyl-2-(6-phenylethynyl-pyridin-3-yl)-pyrazolidin-3-one

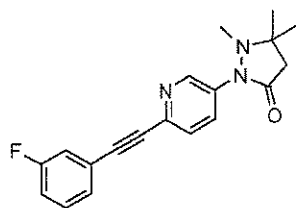


The title compound was obtained as a yellow oil, MS: $m/e = 306.5$ ($M+H^+$), using chemistry similar to that described in Example 3, step 3 from 2-(6-bromo-pyridin-3-yl)-1,5,5-trimethyl-pyrazolidin-3-one (Example 12, step 2) and phenylacetylene.

Example 13

2-[6-(3-Fluoro-phenylethynyl)-pyridin-3-yl]-1,5,5-trimethyl-pyrazolidin-3-one

-24-

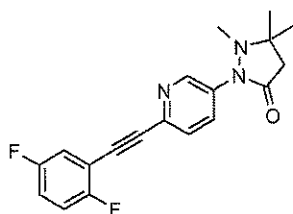


The title compound was obtained as a yellow oil, MS: $m/e = 324.4$ ($M+H^+$), using chemistry similar to that described in Example 3, step 3 from 2-(6-bromo-pyridin-3-yl)-1,5,5-trimethyl-pyrazolidin-3-one (Example 12, step 2) and 3-fluorophenylacetylene.

5

Example 14

2-[6-(2,5-Difluoro-phenylethynyl)-pyridin-3-yl]-1,5,5-trimethyl-pyrazolidin-3-one

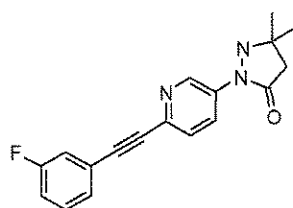


The title compound was obtained as a yellow solid, MS: $m/e = 342.4$ ($M+H^+$), using chemistry similar to that described in Example 3, step 3 from 2-(6-bromo-pyridin-3-yl)-1,5,5-trimethyl-pyrazolidin-3-one (Example 12, step 2) and 2,5-difluorophenylacetylene.

10

Example 15

2-[6-(3-Fluoro-phenylethynyl)-pyridin-3-yl]-5,5-dimethyl-pyrazolidin-3-one



15

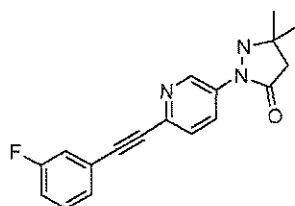
The title compound was obtained as a brown oil, MS: $m/e = 310.4$ ($M+H^+$), using chemistry similar to that described in Example 3, step 3 from 2-(6-bromo-pyridin-3-yl)-5,5-dimethyl-pyrazolidin-3-one (Example 12, step 1) and 3-fluorophenylacetylene.

20

Example 16

2-[6-(2,5-Difluoro-phenylethynyl)-pyridin-3-yl]-5,5-dimethyl-pyrazolidin-3-one

-25-



The title compound was obtained as a light yellow solid, MS: $m/c = 328.4$ ($M+H^+$), using chemistry similar to that described in Example 3, step 3 from 2-(6-bromo-pyridin-3-yl)-5,5-dimethyl-pyrazolidin-3-one (*Example 12, step 1*) and 2,5-difluorophenylacetylene.

5

Biological Assay and Data:

Intracellular Ca^{2+} mobilization assay

A monoclonal HEK-293 cell line stably transfected with a cDNA encoding for the human mGlu5a receptor was generated; for the work with mGlu5 Positive Allosteric Modulators (PAMs), a cell line with low receptor expression levels and low constitutive receptor activity was selected to allow the differentiation of agonistic versus PAM activity. Cells were cultured according to standard protocols (Freshney, 2000) in Dulbecco's Modified Eagle Medium with high glucose supplemented with 1 mM glutamine, 10% (vol/vol) heat-inactivated bovine calf serum, Penicillin/Streptomycin, 50 μ g/ml hygromycin and 15 μ g/ml blasticidin (all cell culture reagents and antibiotics from Invitrogen, Basel, Switzerland).

About 24 hrs before an experiment, 5×10^4 cells/well were seeded in poly-D-lysine coated, black/clear-bottomed 96-well plates. The cells were loaded with 2.5 μ M Fluo-4AM in loading buffer (1xHBSS, 20 mM HEPES) for 1 hr at 37°C and washed five times with loading buffer. The cells were transferred into a Functional Drug Screening System 7000 (Hamamatsu, Paris, France), and 11 half logarithmic serial dilutions of test compound at 37°C were added and the cells were incubated for 10-30 min. with on-line recording of fluorescence. Following this pre-incubation step, the agonist L-glutamate was added to the cells at a concentration corresponding to EC_{20} (typically around 80 μ M) with on-line recording of fluorescence; in order to account for day-to-day variations in the responsiveness of cells, the EC_{20} of glutamate was determined immediately ahead of each experiment by recording of a full dose-response curve of glutamate.

Responses were measured as peak increase in fluorescence minus basal (i.e. fluorescence without addition of L-glutamate), normalized to the maximal stimulatory effect obtained with saturating concentrations of L-glutamate. Graphs were plotted with the % maximal stimulatory

using XLfit, a curve fitting program that iteratively plots the data using Levenburg Marquardt algorithm. The single site competition analysis equation used was $y = A + ((B-A)/(1+((x/C)^D)))$, where y is the % maximal stimulatory effect, A is the minimum y, B is the maximum y, C is the EC_{50} , x is the log10 of the concentration of the competing compound and D is the slope of the curve (the Hill Coefficient). From these curves the EC_{50} (concentration at which half maximal stimulation was achieved), the Hill coefficient as well as the maximal response in % of the maximal stimulatory effect obtained with saturating concentrations of L-glutamate were calculated.

Positive signals obtained during the pre-incubation with the PAM test compounds (i.e. before application of an EC_{20} concentration of L-glutamate) were indicative of an agonistic activity, the absence of such signals were demonstrating the lack of agonistic activities. A depression of the signal observed after addition of the EC_{20} concentration of L-glutamate was indicative of an inhibitory activity of the test compound.

In the list of examples above are shown the corresponding results for compounds which all have $EC_{50} < 250$ nM..

The compounds of formula (I) and pharmaceutically acceptable salts thereof can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. However, the administration can also be effected rectally, e.g. in the form of suppositories, or parenterally, e.g. in the form of injection solutions.

The compounds of formula (I) and pharmaceutically acceptable salts thereof can be processed with pharmaceutically inert, inorganic or organic carriers for the production of pharmaceutical preparations. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts and the like can be used, for example, as such carriers for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carriers for soft gelatine capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like; depending on the nature of the active substance no carriers are, however, usually required in the case of soft gelatine capsules. Suitable carriers for the production of solutions and syrups are, for example, water, polyols, sucrose, invert sugar, glucose and the like. Adjuvants, such as alcohols, polyols, glycerol, vegetable oils and the like, can be used for aqueous injection solutions of water-soluble salts of compounds of

formula (I), but as a rule are not necessary. Suitable carriers for suppositories are, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like.

In addition, the pharmaceutical preparations can contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the
5 osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

As mentioned earlier, medicaments containing a compound of formula (I) or pharmaceutically acceptable salts thereof and a therapeutically inert excipient are also an object of the present invention, as is a process for the production of such medicaments which comprises
10 bringing one or more compounds of formula I or pharmaceutically acceptable salts thereof and, if desired, one or more other therapeutically valuable substances into a galenical dosage form together with one or more therapeutically inert carriers.

As further mentioned earlier, the use of the compounds of formula (I) for the preparation of medicaments useful in the prevention and/or the treatment of the above recited diseases is also an
15 object of the present invention.

The dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, the effective dosage for oral or parenteral administration is between 0.01-20 mg/kg/day, with a dosage of 0.1-10 mg/ kg/day being preferred for all of the indications described. The daily dosage for an adult human being
20 weighing 70 kg accordingly lies between 0.7-1400 mg per day, preferably between 7 and 700 mg per day.

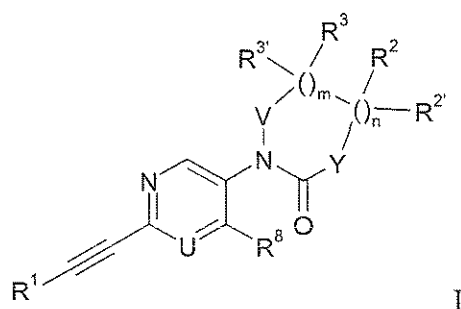
Pharmaceutical compositions comprising compounds of the invention:

Tablets of the following composition are produced in a conventional manner:

	<u>mg/Tablet</u>	
	Active ingredient	100
5	Powdered, lactose	95
	White corn starch	35
	Polyvinylpyrrolidone	8
	Na carboxymethylstarch	10
	Magnesium stearate	2
10	Tablet weight	<u>250</u>

Claims

1. Ethynyl derivatives of formula I



I

5 wherein

U is N or CH,

R⁸ is hydrogen, halogen, C₁₋₄-alkyl or C₁₋₄-alkoxy;

Y is -N(R⁴)-, -O- or -C(R⁵R^{5'})-;

wherein R⁴ is hydrogen or C₁₋₄-alkyl and R⁵/R^{5'} are independently hydrogen, hydroxy,
10 C₁₋₄-alkyl or C₁₋₄-alkoxy;

V is -N(R⁶)- or -C(R⁷R^{7'}),

wherein R⁶ is hydrogen or C₁₋₄-alkyl and R⁷/R^{7'} are independently from each other
hydrogen, C₁₋₄-alkyl, CH₂- C₁₋₄alkoxy or may form together with the carbon atom to
which they are attached a C₃-C₆-cycloalkyl;

15 R¹ is phenyl or heteroaryl, which are optionally substituted by halogen, C₁₋₄-alkyl or C₁₋₄-
alkoxy;

m is 1,

R³/R^{3'} are independently from each other hydrogen, C₁₋₄-alkyl, CH₂- C₁₋₄alkoxy or may form
together with the carbon atom to which they are attached a C₃-C₆-cycloalkyl;

20 n is 0 or 1; in case n is 1,

R²/R^{2'} are independently from each other hydrogen, C₁₋₄-alkyl, CH₂- C₁₋₄alkoxy or may form
together with the carbon atom to which they are attached a C₃-C₆-cycloalkyl;

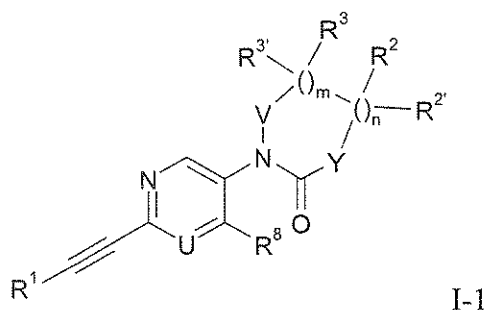
or if m is 1 and n is 0, R³ and R⁷ may form together with the carbon atoms to which they are
attached a C₄₋₆-cycloalkyl;

25 or if m is 1 and n is 1, R² and R³ or R³ and R⁷ may form together with the carbon atoms to
which they are attached a C₄₋₆-cycloalkyl;

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

2. Ethynyl derivatives of formula I-1 according to claim 1

5



wherein

U is N or CH;

R⁸ is hydrogen;

10 Y is CH₂, O, -N(CH₃)- or -N(CH₂CH₃)-;

V is CH₂, -NH- or -N(CH₃)-;

R¹ is phenyl or pyridinyl, which are optionally substituted by halogen;

m is 1,

R³/R^{3'} are independently from each other hydrogen or C₁₋₄-alkyl,

15 n is 0 or 1; in case n is 1;

R²/R^{2'} are independently from each other hydrogen or C₁₋₄-alkyl;

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

20 3. Ethynyl derivatives of formula I-1 according to claims 1 or 2, which compounds are

4,4-Dimethyl-1-(6-phenylethynyl-pyridin-3-yl)-pyrrolidin-2-one

6,6-Dimethyl-3-(6-phenylethynyl-pyridin-3-yl)-[1,3]oxazinan-2-one

3,4,4-Trimethyl-1-(6-phenylethynyl-pyridin-3-yl)-imidazolidin-2-one

1-[6-(4-Fluoro-phenylethynyl)-pyridin-3-yl]-3,4,4-trimethyl-imidazolidin-2-one

25 1-[6-(3-Fluoro-phenylethynyl)-pyridin-3-yl]-3,4,4-trimethyl-imidazolidin-2-one

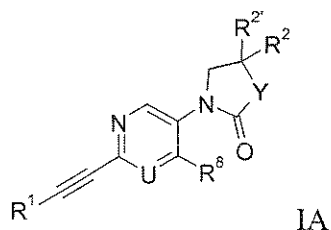
3,4,4-Trimethyl-1-(6-pyridin-3-ylethynyl-pyridin-3-yl)-imidazolidin-2-one

1-[6-(3-Fluoro-phenylethynyl)-pyridin-3-yl]-4,4-dimethyl-pyrrolidin-2-one

5,5-Dimethyl-2-(6-phenylethynyl-pyridin-3-yl)-pyrazolidin-3-one

4,4-Dimethyl-1-(6-phenylethynyl-pyrimidin-3-yl)-pyrrolidin-2-one
 3,4,4-Trimethyl-1-(2-phenylethynyl-pyrimidin-5-yl)-imidazolidin-2-one
 3-Ethyl-4,4-dimethyl-1-(2-phenylethynyl-pyrimidin-5-yl)-imidazolidin-2-one
 1,5,5-Trimethyl-2-(6-phenylethynyl-pyridin-3-yl)-pyrazolidin-3-one
 5 2-[6-(3-Fluoro-phenylethynyl)-pyridin-3-yl]-1,5,5-trimethyl-pyrazolidin-3-one
 2-[6-(2,5-Difluoro-phenylethynyl)-pyridin-3-yl]-1,5,5-trimethyl-pyrazolidin-3-one
 2-[6-(3-Fluoro-phenylethynyl)-pyridin-3-yl]-5,5-dimethyl-pyrazolidin-3-one or
 2-[6-(2,5-Difluoro-phenylethynyl)-pyridin-3-yl]-5,5-dimethyl-pyrazolidin-3-one.

10 4. Ethynyl derivatives of formula IA according to claim 1,



wherein

U is N or CH,

R⁸ is hydrogen, halogen, C₁₋₄-alkyl or C₁₋₄-alkoxy;

15 Y is -N(R⁴)-, O or -C(R⁵R^{5'})-;

wherein R⁴ is hydrogen or C₁₋₄-alkyl and R⁵/R^{5'} are independently hydrogen, hydroxy, C₁₋₄-alkyl or C₁₋₄-alkoxy;

R¹ is phenyl or heteroaryl, which are optionally substituted by halogen, C₁₋₄-alkyl or C₁₋₄-alkoxy;

20 R²/R^{2'} are independently from each other hydrogen, C₁₋₄-alkyl, CH₂-C₁₋₄alkoxy or may form together with the carbon atom to which they are attached a C₃-C₆-cycloalkyl;
 or a pharmaceutically acceptable acid addition salt, a racemic mixture, or its corresponding enantiomer and/or optical isomer and/or stereoisomer thereof.

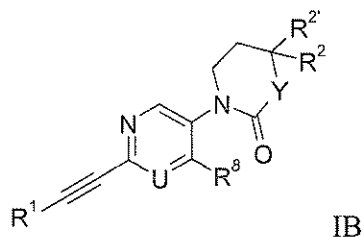
25 5. Ethynyl derivatives of formula IA according to claims 1 or 4, which compounds are:

4,4-dimethyl-1-(6-phenylethynyl-pyridin-3-yl)-pyrrolidin-2-one
 3,4,4-trimethyl-1-(6-phenylethynyl-pyridin-3-yl)-imidazolidin-2-one
 1-[6-(4-fluoro-phenylethynyl)-pyridin-3-yl]-3,4,4-trimethyl-imidazolidin-2-one
 1-[6-(3-fluoro-phenylethynyl)-pyridin-3-yl]-3,4,4-trimethyl-imidazolidin-2-one
 30 3,4,4-trimethyl-1-(6-pyridin-3-ylethynyl-pyridin-3-yl)-imidazolidin-2-one

1-[6-(3-fluoro-phenylethynyl)-pyridin-3-yl]-4,4-dimethyl-pyrrolidin-2-one
 4,4-dimethyl-1-(6-phenylethynyl-pyrimidin-3-yl)-pyrrolidin-2-one
 3,4,4-Trimethyl-1-(2-phenylethynyl-pyrimidin-5-yl)-imidazolidin-2-one or
 3-Ethyl-4,4-dimethyl-1-(2-phenylethynyl-pyrimidin-5-yl)-imidazolidin-2-one.

5

6. Ethynyl derivatives of formula according to claim 1,



wherein

U is N or CH,

10 R⁸ is hydrogen, halogen, C₁₋₄-alkyl or C₁₋₄-alkoxy;

Y is -N(R⁴)-, O or -C(R⁵R^{5'})-;

wherein R⁴ is hydrogen or C₁₋₄-alkyl and R⁵/R^{5'} are independently hydrogen, hydroxy, C₁₋₄-alkyl or C₁₋₄-alkoxy;

R¹ is phenyl or heteroaryl, which are optionally substituted by halogen, C₁₋₄-alkyl or C₁₋₄-alkoxy;

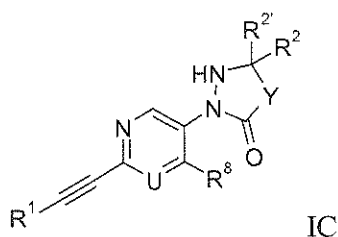
15

R²/R^{2'} are independently from each other hydrogen, C₁₋₄-alkyl, CH₂- C₁₋₄-alkoxy or may form together with the carbon atom to which they are attached a C₃-C₆-cycloalkyl;
 or a pharmaceutically acceptable acid addition salt, a racemic mixture, or its corresponding enantiomer and/or optical isomer and/or stereoisomer thereof.

20

7. Ethynyl derivatives of formula IB according to claims 1 and 6, which compound is 6,6-dimethyl-3-(6-phenylethynyl-pyridin-3-yl)-[1,3]oxazinan-2-one.

8. Ethynyl derivatives of formula IC according to claim 1,



25

wherein

U is N or CH,

R⁸ is hydrogen, halogen, C₁₋₄-alkyl or C₁₋₄-alkoxy;

Y is -N(R⁴)-, O or -C(R⁵R^{5'})-;

wherein R⁴ is hydrogen or C₁₋₄-alkyl and R⁵/R^{5'} are independently hydrogen, hydroxy, C₁₋₄-alkyl or C₁₋₄-alkoxy;

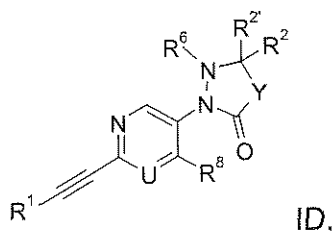
R¹ is phenyl or heteroaryl, which are optionally substituted by halogen, C₁₋₄-alkyl or C₁₋₄-alkoxy;

R²/R^{2'} are independently from each other hydrogen, C₁₋₄-alkyl, CH₂-C₁₋₄-alkoxy or may form together with the carbon atom to which they are attached a C₃-C₆-cycloalkyl;

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

9. Ethynyl derivatives of formula IC according to claims 1 and 8, which compound is 5,5-dimethyl-2-(6-phenylethynyl-pyridin-3-yl)-pyrazolidin-3-one.

10. Ethynyl derivatives of formula ID according to claim 1,



wherein

U is N or CH,

R⁸ is hydrogen, halogen, C₁₋₄-alkyl or C₁₋₄-alkoxy;

Y is -N(R⁴)-, -O- or -C(R⁵R^{5'})-;

wherein R⁴ is hydrogen or C₁₋₄-alkyl and R⁵/R^{5'} are independently hydrogen, hydroxy, C₁₋₄-alkyl or C₁₋₄-alkoxy;

R⁶ is hydrogen or C₁₋₄-alkyl

R¹ is phenyl or heteroaryl, which are optionally substituted by halogen, C₁₋₄-alkyl or C₁₋₄-alkoxy;

R²/R^{2'} are independently from each other hydrogen, C₁₋₄-alkyl, CH₂-C₁₋₄-alkoxy or may form together with the carbon atom to which they are attached a C₃-C₆-cycloalkyl;

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

11. Ethynyl derivatives of formula ID according to claims 1 and 10, wherein the compounds are

1,5,5-Trimethyl-2-(6-phenylethynyl-pyridin-3-yl)-pyrazolidin-3-one

5 2-[6-(3-Fluoro-phenylethynyl)-pyridin-3-yl]-1,5,5-trimethyl-pyrazolidin-3-one

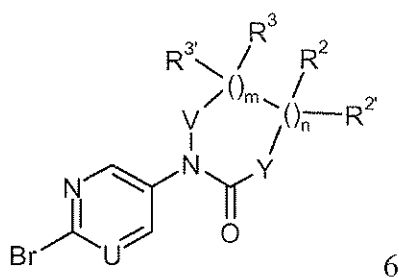
2-[6-(2,5-Difluoro-phenylethynyl)-pyridin-3-yl]-1,5,5-trimethyl-pyrazolidin-3-one

2-[6-(3-Fluoro-phenylethynyl)-pyridin-3-yl]-5,5-dimethyl-pyrazolidin-3-one or

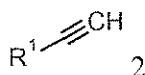
2-[6-(2,5-Difluoro-phenylethynyl)-pyridin-3-yl]-5,5-dimethyl-pyrazolidin-3-one.

10 12. A process for preparation of a compound of formula I as described in claim 1,
comprising the variants

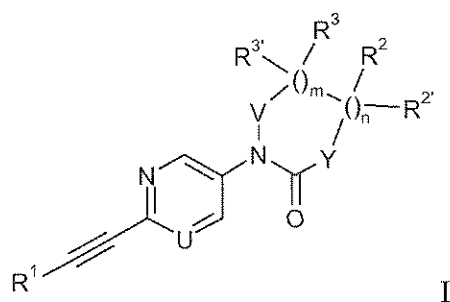
a) reacting a compound of formula



with a suitable aryl-acetylene of formula

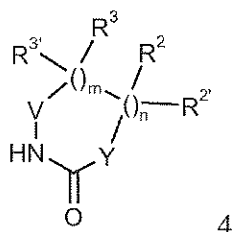


to a compound of formula

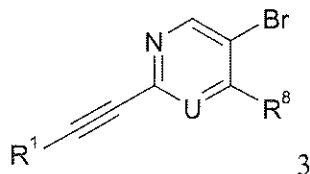


wherein the substituents are described in claim 1, or

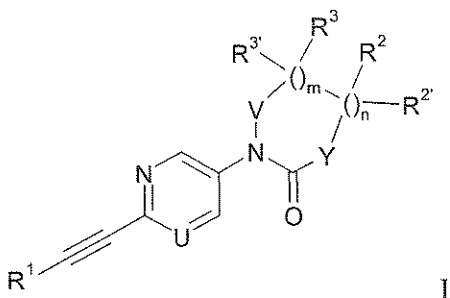
b) reacting a compound of formula



with a suitable compound of formula



to a compound of formula



5 wherein the substituents are described in claim 1, and,

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

13. A compound according to any one of claims 1 to 11 for use as therapeutically active substance.

10 14. A pharmaceutical composition comprising at least one of the compounds according to any one of claims 1 to 11 as well as its pharmaceutically acceptable salt.

15. A compound of any one of claims 1 –11, when applicable as mixtures of enantiomers, diastereomers, or in enantiomerically pure form; as well as its pharmaceutically acceptable salt, for use as a medicament.

15 16. The use of a compound according to any one of claims 1 to 11 as well as its pharmaceutically acceptable salt for the manufacture of a medicament for the treatment or prevention of schizophrenia, cognitive diseases, fragile X syndrome or autism.

17. The use of a compound according to claim 16 for the treatment or prevention of schizophrenia, cognitive diseases, fragile X syndrome or autism.

20 18. A compound according to any one of claims 1 to 11 for use in the treatment or prevention of schizophrenia, cognitive diseases, fragile X syndrome or autism.