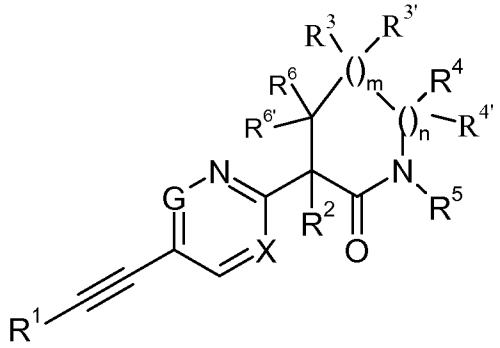
# ETHYNYL DERIVATIVES AS POSITIVE ALLOSTERIC MODULATORS OF THE MGLUR5

The present invention relates to ethynyl derivatives of formula I



I

wherein

X is N or C-R, wherein R is hydrogen or halogen;

G is N or CH;

with the proviso that maximum one of G or X can be nitrogen;

$R^1$ is phenyl or pyridinyl, which are optionally substituted by halogen;

$R^2$ is hydrogen, lower alkyl, hydroxy, lower alkoxy or C(O)O-benzyl;

$R^3$,$R^{3'}$, $R^4$, $R^{4'}$, $R^6$, $R^{6'}$ are independently from each other hydrogen or lower alkyl;

or $R^6$ and $R^4$ may form together with the carbon atom to which they are attached a $C_{4-6}$-cycloalkyl ring, if m is 0 and n is 1 or 2;

$R^5$ is hydrogen or lower alkyl;

n is 0, 1 or 2;

m is 0 or 1; with the proviso that n and m are not simultaneously 0;

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 positive allosteric modulators (PAM) 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 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 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 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, 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 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 site different from the highly conserved orthosteric binding site. Positive allosteric modulators of mGluR5 have emerged recently as novel pharmaceutical entities offering this attractive alternative. Positive 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;*

Positive allosteric modulators 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 increase the affinity of a glutamate-site agonist at its extracellular N-terminal binding site. Positive allosteric modulation is thus an attractive mechanism for enhancing appropriate physiological receptor activation. There is a scarcity of selective positive 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 positive 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 positive allosteric modulators for the mGluR5 receptor.

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

The present invention 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 positive allosteric modulators for the mGluR5 receptor, such as schizophrenia, tuberous sclerosis, and cognition and to pharmaceutical compositions containing the compounds of formula I..

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.

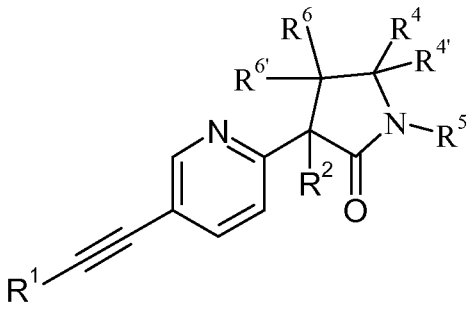
As used herein, the term "lower alkyl" denotes a saturated, i.e. aliphatic hydrocarbon group including a straight or branched carbon chain with 1 – 4 carbon atoms. Examples for “alkyl” are methyl, ethyl, n-propyl, and isopropyl.

The term “alkoxy” denotes a group -O-R’ wherein R’ is lower alkyl as defined above.

The term “halogen” denotes fluoro, chloro, bromo or iodo.

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 IA



IA

wherein

$R^1$ is phenyl or pyridinyl, which are optionally substituted by halogen;

$R^2$ is hydrogen, lower alkyl, hydroxy, lower alkoxy or C(O)O-benzyl;

$R^4$, $R^{4'}$, $R^6$, $R^{6'}$ are independently from each other hydrogen or lower alkyl;

or $R^6$ and $R^4$ may form together with the carbon atom to which they are attached a $C_{4-6}$-cycloalkyl ring;

$R^5$ is 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.

Examples from this group of compounds are

(RS)-1,5,5-trimethyl-3-(5-(phenylethynyl)pyridin-2-yl)pyrrolidin-2-one

(RS)-1,5,5-trimethyl-3-(5-(pyridin-3-ylethynyl)pyridin-2-yl)pyrrolidin-2-one

(RS)-3-(5-((3-chlorophenyl)ethynyl)pyridin-2-yl)-1,5,5-trimethylpyrrolidin-2-one

(RS)-3-(5-((3-fluorophenyl)ethynyl)pyridin-2-yl)-1,5,5-trimethylpyrrolidin-2-one

(RS)-3-hydroxy-1,5,5-trimethyl-3-(5-(phenylethynyl)pyridin-2-yl)pyrrolidin-2-one

(RS)-3-methoxy-1,5,5-trimethyl-3-(5-(phenylethynyl)pyridin-2-yl)pyrrolidin-2-one

(RS)-1,3,5,5-tetramethyl-3-(5-(phenylethynyl)pyridin-2-yl)pyrrolidin-2-one

(3RS,3aSR,6aSR)-1-methyl-3-(5-phenylethynyl-pyridin-2-yl)-hexahydro-cyclopenta[b]pyrrol-2-one

(3R,3aS,6aS) or (3S,3aR,6aR)-1-methyl-3-(5-phenylethynyl-pyridin-2-yl)-hexahydro-cyclopenta[b]pyrrol-2-one

(3RS,3aSR,6aSR)-3-[5-(4-fluoro-phenylethynyl)-pyridin-2-yl]-1-methyl-hexahydro-cyclopenta[b]pyrrol-2-one

(3RS,3aSR,6aSR)-3-[5-(3-fluoro-phenylethynyl)-pyridin-2-yl]-1-methyl-hexahydro-cyclopenta[b]pyrrol-2-one

(3R,3aS,6aS) or (3S,3aR,6aR)-3-[5-(3-fluoro-phenylethynyl)-pyridin-2-yl]-1-methyl-hexahydro-cyclopenta[b]pyrrol-2-one

(3S,3aR,6aR) or (3R,3aS,6aS)-3-[5-(3-fluoro-phenylethynyl)-pyridin-2-yl]-1-methyl-hexahydro-cyclopenta[b]pyrrol-2-one

(3RS,6SR,7SR)-1-methyl-3-(5-phenylethynyl-pyridin-2-yl)-octahydro-indol-2-one

(3SR,6SR,7SR)-1-methyl-3-(5-phenylethynyl-pyridin-2-yl)-octahydro-indol-2-one

(3R,6S,7S)-1-methyl-3-(5-phenylethynyl-pyridin-2-yl)-octahydro-indol-2-one and (3S,6R,7R)-1-Methyl-3-(5-phenylethynyl-pyridin-2-yl)-octahydro-indol-2-one

(3RS,6SR,7SR)-3-[5-(3-fluoro-phenylethynyl)-pyridin-2-yl]-1-methyl-octahydro-indol-2-one

(3SR,6SR,7SR)-3-[5-(3-fluoro-phenylethynyl)-pyridin-2-yl]-1-methyl-octahydro-indol-2-one

(3R,6S,7S)-3-[5-(3-fluoro-phenylethynyl)-pyridin-2-yl]-1-methyl-octahydro-indol-2-one

(3S,6R,7R)-3-[5-(3-fluoro-phenylethynyl)-pyridin-2-yl]-1-methyl-octahydro-indol-2-one

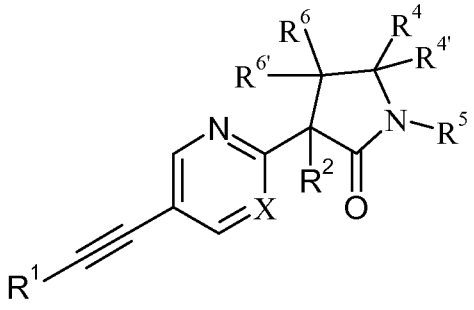
(3R,6S,7S)-3-[5-(4-fluoro-phenylethynyl)-pyridin-2-yl]-1-methyl-octahydro-indol-2-one

(3S,6R,7R)-3-[5-(4-fluoro-phenylethynyl)-pyridin-2-yl]-1-methyl-octahydro-indol-2-one

(RS)-3-[5-(2-chloro-pyridin-4-ylethynyl)-pyridin-2-yl]-1,5,5-trimethyl-pyrrolidin-2-one

(S) or (R)-3-[5-(2-chloro-pyridin-4-ylethynyl)-pyridin-2-yl]-1,5,5-trimethyl-pyrrolidin-2-one or (R) or (S)-3-[5-(2-chloro-pyridin-4-ylethynyl)-pyridin-2-yl]-1,5,5-trimethyl-pyrrolidin-2-one.

One embodiment of the invention are compounds of formula IB



IB

wherein

X is N or C-R, wherein R is halogen;

$R^1$ is phenyl or pyridinyl, which are optionally substituted by halogen;

$R^2$ is hydrogen, lower alkyl, hydroxy, lower alkoxy or C(O)O-benzyl;

$R^4$, $R^{4'}$, $R^6$, $R^{6'}$ are independently from each other hydrogen or lower alkyl;

or $R^6$ and $R^4$ may form together with the carbon atom to which they are attached a $C_{4-6}$-cycloalkyl ring,;

$R^5$ is 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.

Examples from this group of compounds are

(RS)-benzyl 1,5,5-trimethyl-2-oxo-3-(5-(phenylethynyl)pyrimidin-2-yl)pyrrolidine-3-carboxylate

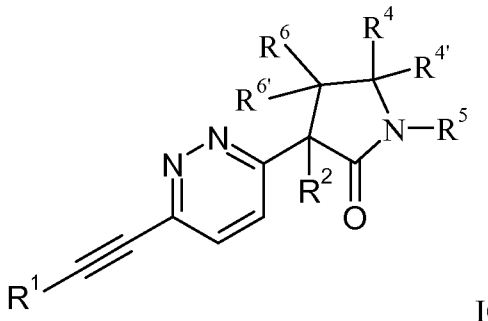
(RS)-1,5,5-trimethyl-3-(5-(phenylethynyl)pyrimidin-2-yl)pyrrolidin-2-one

(RS)-3-(5-((3-fluorophenyl)ethynyl)pyrimidin-2-yl)-1,5,5-trimethylpyrrolidin-2-one

(RS)-3-(5-((4-fluorophenyl)ethynyl)pyrimidin-2-yl)-1,5,5-trimethylpyrrolidin-2-one or

(3RS,3aSR,6aSR)-1-methyl-3-(5-phenylethynyl-pyrimidin-2-yl)-hexahydro-cyclopenta[b]pyrrol-2-one.

One embodiment of the invention are compounds of formula IC



IC

wherein

$R^1$ is phenyl or pyridinyl, which are optionally substituted by halogen;

$R^2$ is hydrogen, lower alkyl, hydroxy, lower alkoxy or C(O)O-benzyl;

$R^4$, $R^{4'}$, $R^6$, $R^{6'}$ are independently from each other hydrogen or lower alkyl;

or $R^6$ and $R^4$ may form together with the carbon atom to which they are attached a $C_{4-6}$-cycloalkyl ring;

$R^5$ is 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.

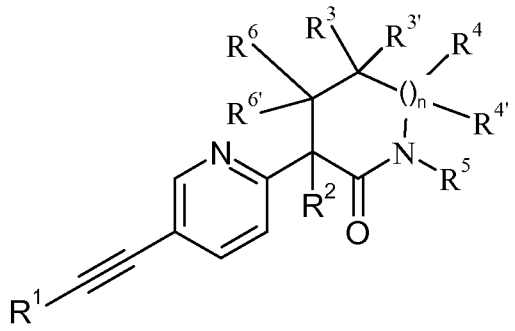
Examples from this group of compounds are

(RS)-3-(6-((3-fluorophenyl)ethynyl)pyridazin-3-yl)-1,5,5-trimethylpyrrolidin-2-one

(RS)-3-(6-((4-fluorophenyl)ethynyl)pyridazin-3-yl)-1,5,5-trimethylpyrrolidin-2-one or

(RS)-3-(6-(phenylethynyl)pyridazin-3-yl)-1,5,5-trimethylpyrrolidin-2-one.

One embodiment of the invention are compounds of formula ID



ID

wherein

$R^1$ is phenyl or pyridinyl, which are optionally substituted by halogen;

$R^2$ is hydrogen, lower alkyl, hydroxy, lower alkoxy or C(O)O-benzyl;

$R^3$,$R^{3'}$, $R^4$, $R^{4'}$, $R^6$, $R^{6'}$ are independently from each other hydrogen or lower alkyl;

$R^5$ is hydrogen or lower alkyl;

n is 1 or 2;

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

Examples from this group of compounds are

(RS)-1,6,6-trimethyl-3-(5-(phenylethynyl)pyridin-2-yl)piperidin-2-one

(RS)-3-(5-((3-fluorophenyl)ethynyl)pyridin-2-yl)-1,6,6-trimethylpiperidin-2-one

(RS)-3-(5-((4-fluorophenyl)ethynyl)pyridin-2-yl)-1,6,6-trimethylpiperidin-2-one

(RS)-1-methyl-3-(5-phenylethynyl-pyridin-2-yl)-azepan-2-one

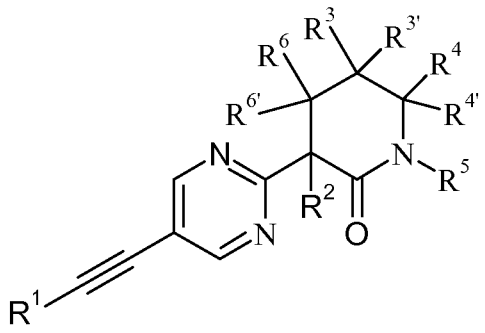
(RS)-3-[5-(4-fluoro-phenylethynyl)-pyridin-2-yl]-1-methyl-azepan-2-one

(RS)-3-[5-(3-fluoro-phenylethynyl)-pyridin-2-yl]-1-methyl-azepan-2-one

(S or R)-1-methyl-3-(5-phenylethynyl-pyridin-2-yl)-azepan-2-one or

(R or S)-1-methyl-3-(5-phenylethynyl-pyridin-2-yl)-azepan-2-one.

One embodiment of the invention are compounds of formula IE



IE

wherein

$R^1$ is phenyl or pyridinyl, which are optionally substituted by halogen;

$R^2$ is hydrogen, lower alkyl, hydroxy, lower alkoxy or C(O)O-benzyl;

$R^3$,$R^{3'}$, $R^4$, $R^{4'}$, $R^6$, $R^{6'}$ are independently from each other hydrogen or lower alkyl;

$R^5$ is 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.

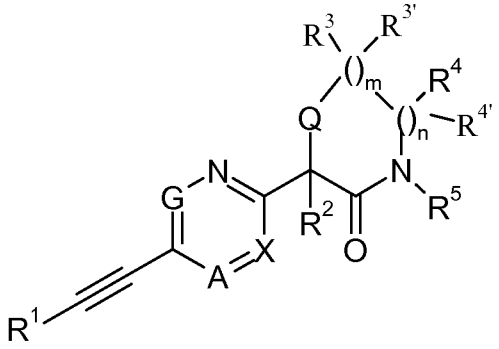
Examples from this group of compounds are

(RS)-1,6,6-trimethyl-3-(5-(phenylethynyl)pyrimidin-2-yl)piperidin-2-one

(RS)-3-(5-((4-fluorophenyl)ethynyl)pyrimidin-2-yl)-1,6,6-trimethylpiperidin-2-one or

(RS)-3-(5-((3-fluorophenyl)ethynyl)pyrimidin-2-yl)-1,6,6-trimethylpiperidin-2-one.

A further embodiment of the invention are compounds of formula



I-1

wherein

X is N or C-R, wherein R is hydrogen, methyl or halogen;

G and A are independently N or CH;

with the proviso that maximum one of G, A or X can be nitrogen;

Q is O, N-$R^9$ or -$CR^6R^{6'}$-;

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

$R^2$ is hydrogen, lower alkyl, hydroxy, lower alkoxy, C(O)O-benzyl, C(O)O-lower alkyl or $CONR^7R^8$;

$R^3$,$R^{3'}$, $R^4$, $R^{4'}$, $R^6$, $R^{6'}$ are independently from each other hydrogen, lower alkyl, alkoxy, hydroxy or $CH_2$-lower alkoxy;
or $R^3$ and $R^4$ may form together with the carbon atom to which they are attached a $C_{4-6}$-cycloalkyl ring;

$R^5$ is hydrogen, lower alkyl, or may form together with $R^4$ a $C_3$-$C_6$-cycloalkyl;

$R^7$, $R^8$ are independently hydrogen, lower alkyl, or $R^7$ can form with $R^8$ a $C_3$-$C_6$-cycloalkyl ring;

$R^9$ is hydrogen or lower alkyl;

n is 0, 1 or 2;

m is 0 or 1;

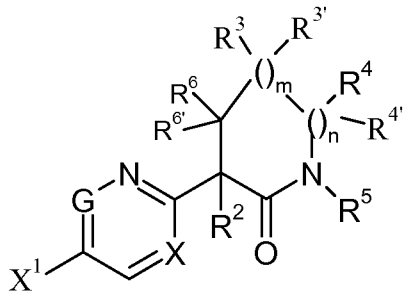
or a pharmaceutically acceptable acid addition salt, a racemic mixture, or its corresponding enantiomer and/or optical isomer and/or stereoisomer thereof.

The preparation of compounds of formula I of the present invention may be carried out in sequential or convergent synthetic routes. Syntheses of the compounds of the invention are shown in the following scheme 1. 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 variants described below, which process comprises

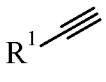
a) reacting a compound of formula



3

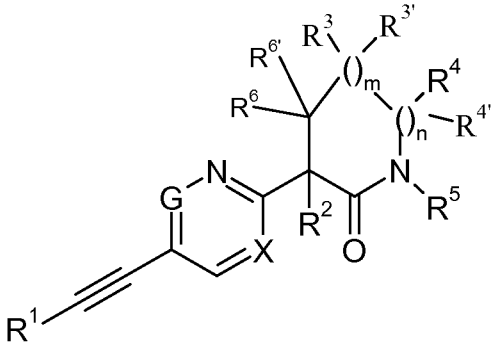
wherein $X^1$ is halogen

with a compound of formula



4

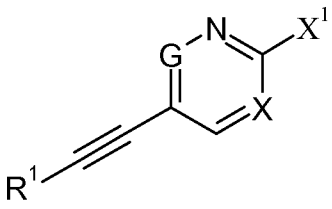
to a compound of formula



I

wherein the definitions are as described above or

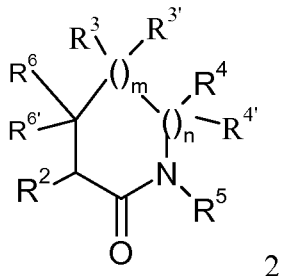
b) reacting a compound of formula



5

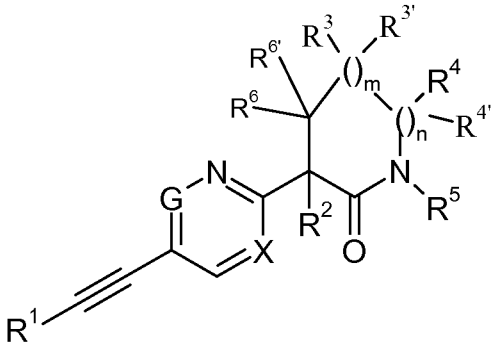
wherein $X^1$ is halogen

with a compound of formula



2

to form a compound of formula

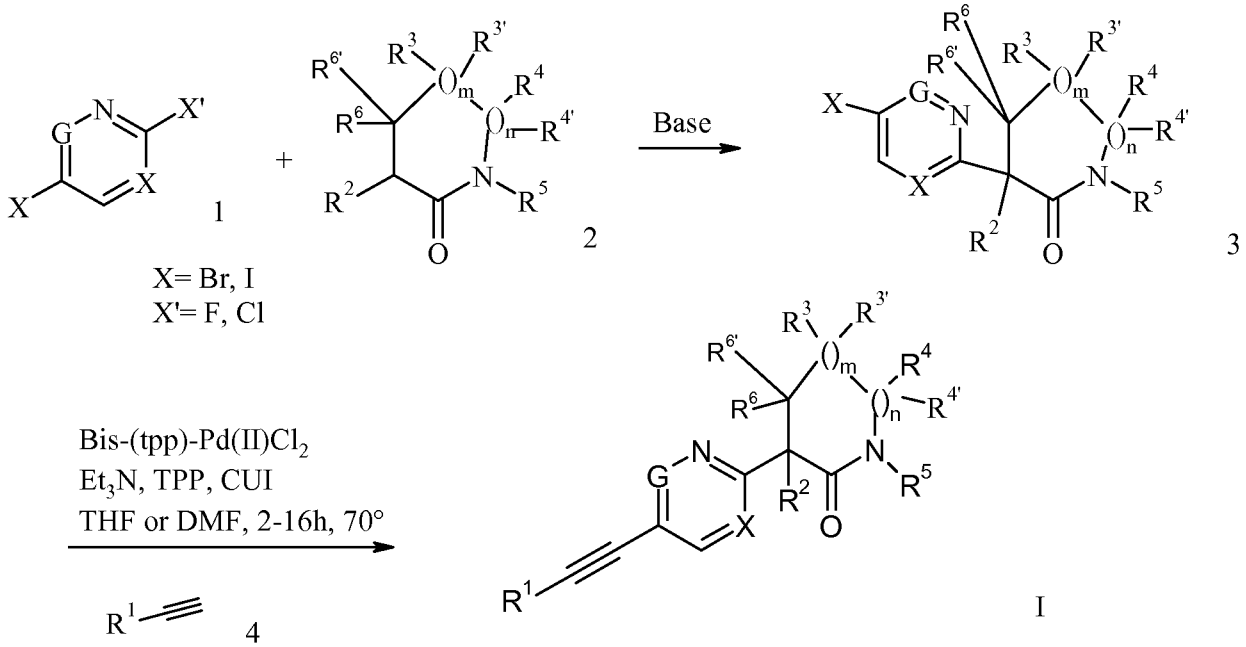


I

wherein the definitions are as described above, or, 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 to 4 and in examples 1 – 46.

Scheme 1




1 2 3

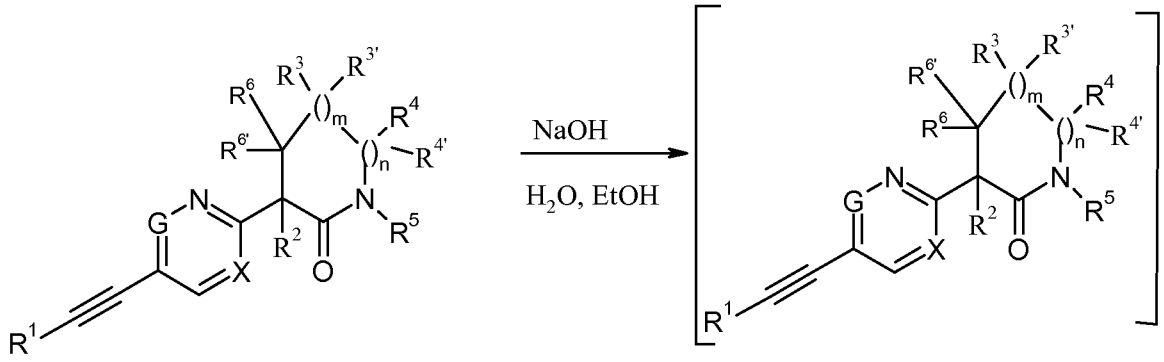
X= Br, I
X'= F, Cl

4 I

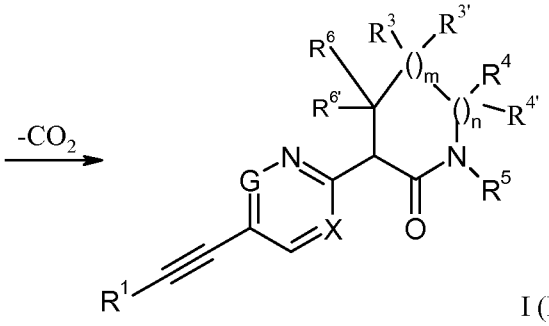
An acetylenic compound of formula **I** can be obtained for example by reaction of a para-dihalo disubstituted heterocyclic derivative **1** with an appropriately substituted cyclic amide **2** in

the presence of a strong base such as sodium hydride, sodium hexamethyldisilylamide (NaHMDS), lithium diisopropylamide (LDA), or in an inert solvent like toluene, DMF, DMSO or THF; or sodium alkoxide in a corresponding alcohol as solvent to form the corresponding 3-heteroaryl lactam derivatives **3**. Sonogashira coupling of the lactams **3** with an appropriately substituted arylacetylene **4** yield the desired ethynyl compounds of general formula **I** (scheme 1).

Scheme 2



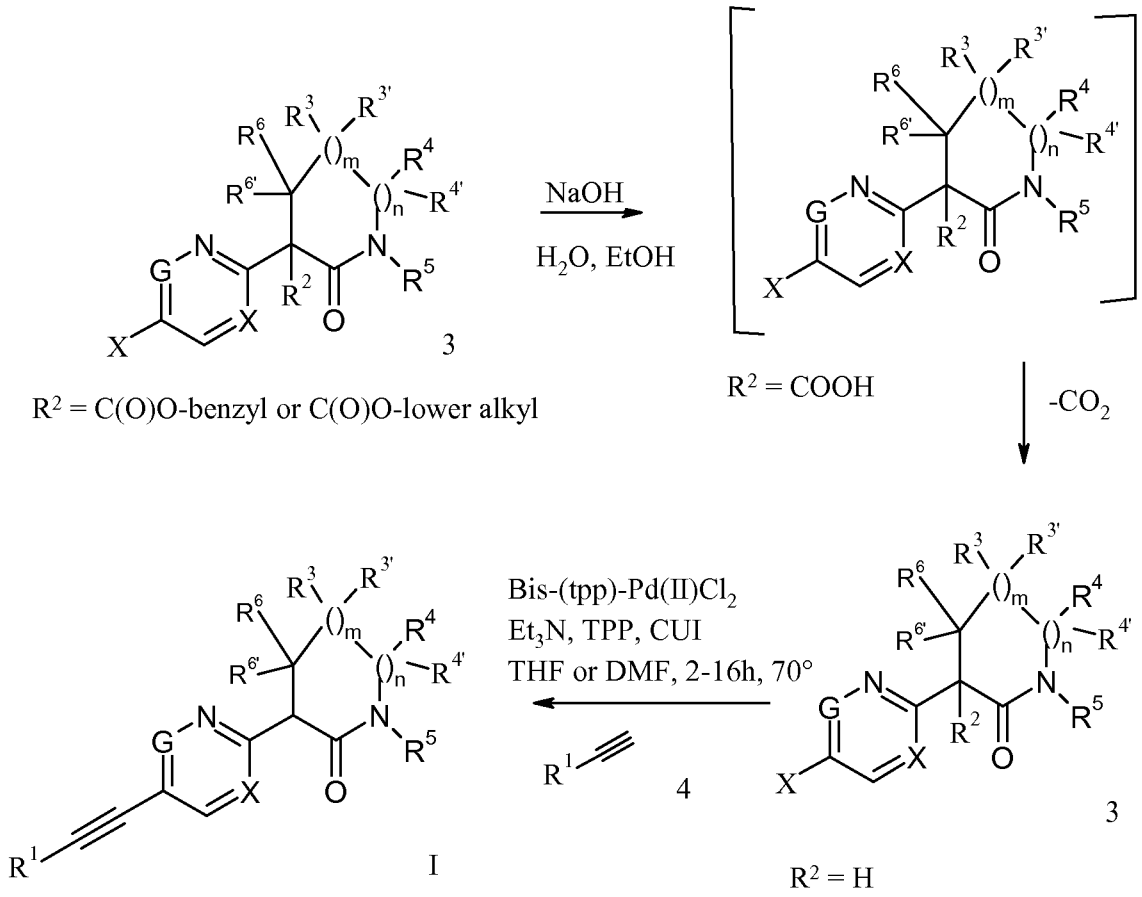

I ($R^2$ is C(O)O-benzyl or C(O)O-lower alkyl) $R^2$ is COOH




I ($R^2$ is H)

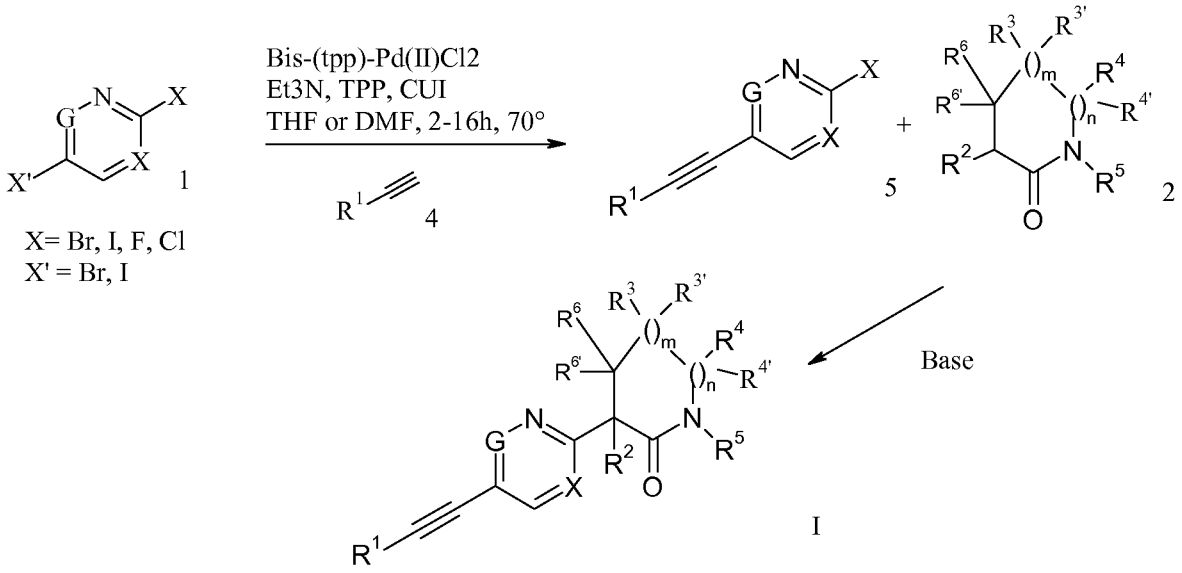
An acetylenic compound of formula **I** can be obtained for example when $R^2$ = COO-benzyl or COO-lower alkyl by hydrolysis of the ester group using for example, aqueous sodium of potassium hydroxide in a solvent such as methanol or ethanol followed by decarboxylation of the acid formed to yield a compound of general formula **I** where $R^2$ is hydrogen (scheme 2).

Scheme 3




The latter procedure can also be used to modify a compound of formula **3** where $R^2$ is an ester to form a compound of formula **3** where $R^2$ is hydrogen. Sonogashira coupling of the lactams **3** with appropriately substituted arylacetylenes **4** yield the desired ethynyl compounds of general formula **I** where $R^2$ is hydrogen (scheme 3).

Scheme 4




formula I can also be modified in certain cases, for example by first running the Sonogashira coupling to form an appropriately substituted aryl- or heteroaryl-ethynyl derivative **5** followed by reaction with a lactam of formula **2** using procedures similar to those described in schemes 1 to 3 (scheme 4).

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 µg/ml hygromycin and 15 µg/ml blasticidin (all cell culture reagents and antibiotics from Invitrogen, Basel, Switzerland).

About 24 hrs before an experiment, $5x10^4$ cells/well were seeded in poly-D-lysine coated, black/clear-bottomed 96-well plates. The cells were loaded with 2.5 µM 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-

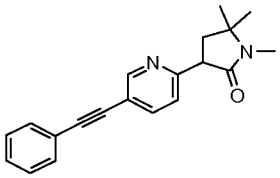
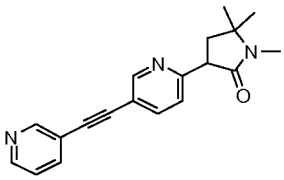
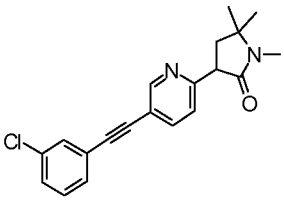
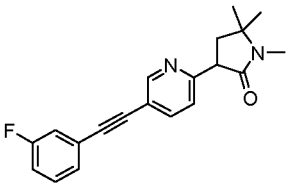
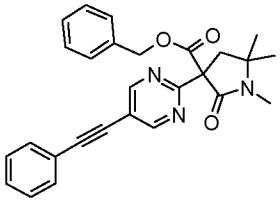
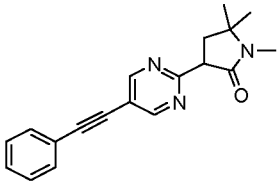
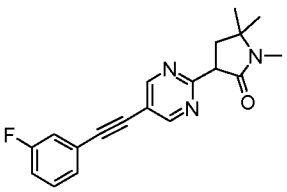
incubation step, the agonist L-glutamate was added to the cells at a concentration corresponding to $EC_{20}$ (typically around 80 μM) with on-line recording of fluorescence; in order to account for day-to-day variations in the responsiveness of cells, the $EC_{20}$ of glutamate was determined immediately ahead of each experiment by recording of a full dose-response curve of glutamate.

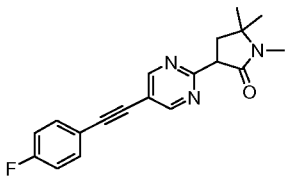
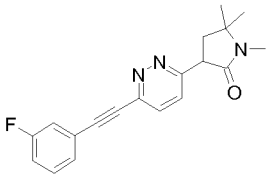
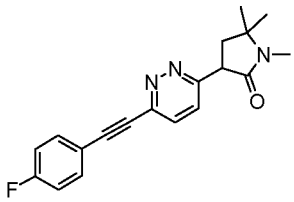
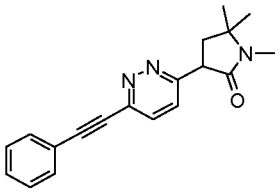
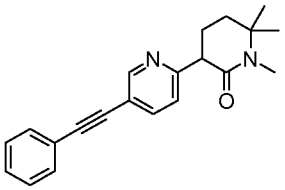
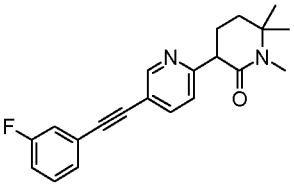
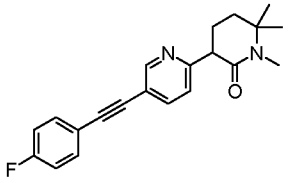
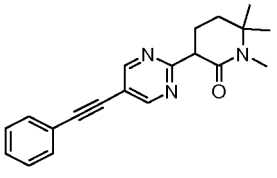
Responses were measured as peak increase in fluorescence minus basal (i.e. fluorescence without addition of L-glutamate), normalized to the maximal stimulatory effect obtained with saturating concentrations of L-glutamate. Graphs were plotted with the % maximal stimulatory using XLfit, a curve fitting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

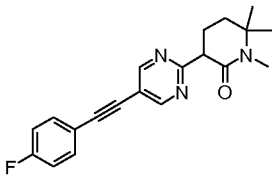
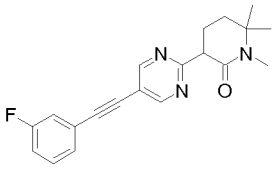
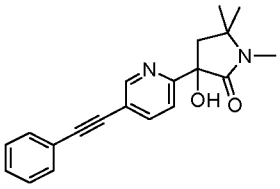
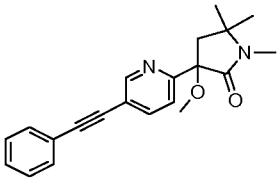
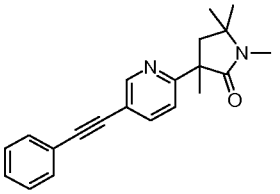
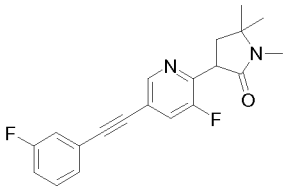
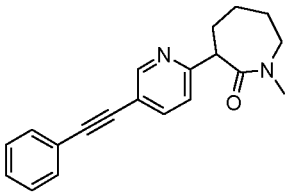
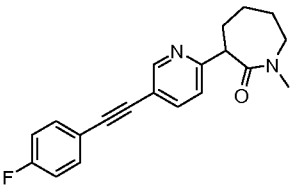
Positive signals obtained during the pre-incubation with the PAM test compounds (i.e. before application of an $EC_{20}$ concentration of L-glutamate) were indicative of an agonistic activity, the absence of such signals were demonstrating the lack of agonistic activities. A depression of the signal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

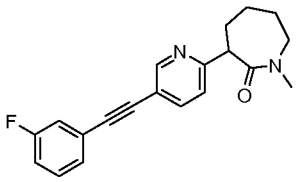
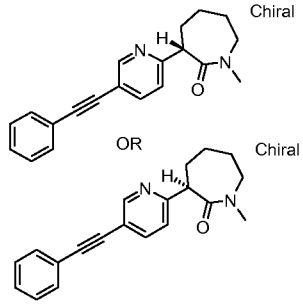
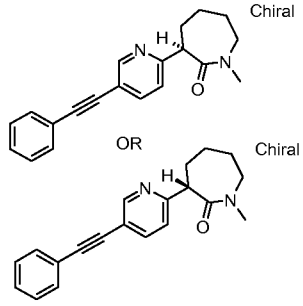
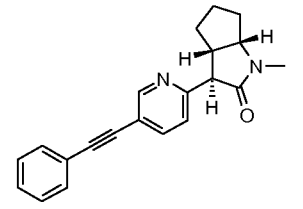
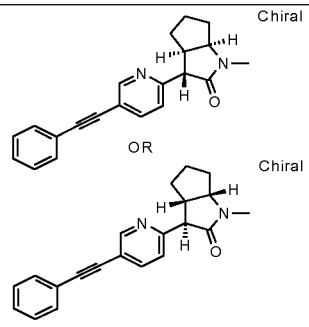
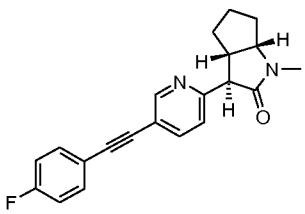
In the table below are shown the prepared compounds 1 – 46 with corresponding results ($EC_{50}$ in nM).

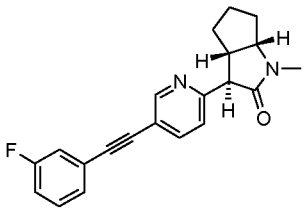
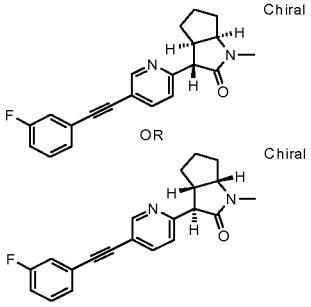
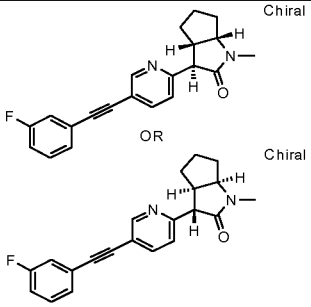
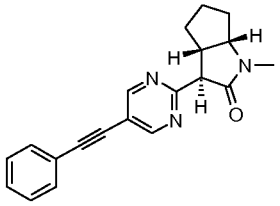
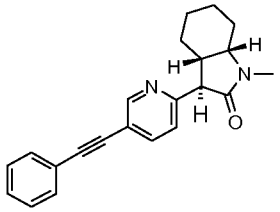
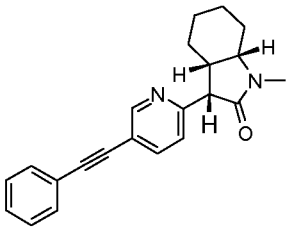
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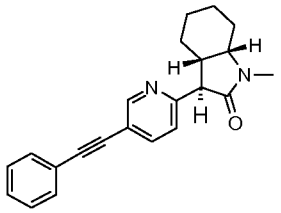
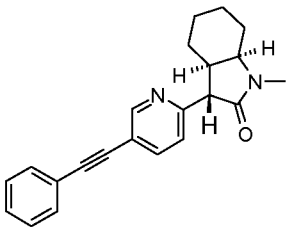
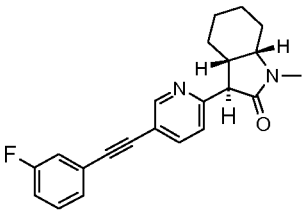
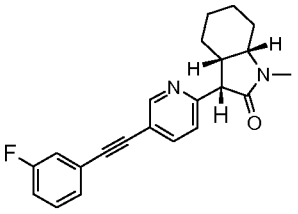
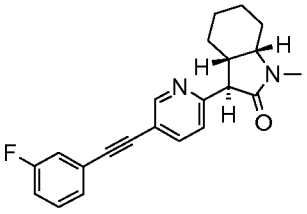
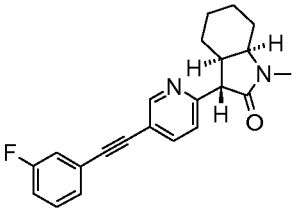
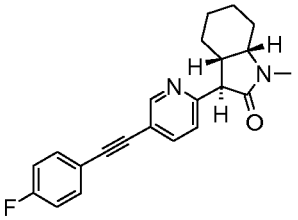
| Ex. | Structure | Name | $EC_{50}$ (nM) mGlu5 PAM | Eff. (%) |
|---|---|---|---|---|
| 1 |  | (RS)-1,5,5-trimethyl-3-(5-(phenylethynyl)pyridin-2-yl)pyrrolidin-2-one | 60 | 111 |
| 2 |  | (RS)-1,5,5-trimethyl-3-(5-(pyridin-3-ylethynyl)pyridin-2-yl)pyrrolidin-2-one | 981 | 107 |
| 3 |  | (RS)-3-(5-((3-chlorophenyl)ethynyl)pyridin-2-yl)-1,5,5-trimethylpyrrolidin-2-one | 38 | 81 |
| 4 |  | (RS)-3-(5-((3-fluorophenyl)ethynyl)pyridin-2-yl)-1,5,5-trimethylpyrrolidin-2-one | 61 | 103 |
| 5 |  | (RS)-benzyl 1,5,5-trimethyl-2-oxo-3-(5-(phenylethynyl)pyrimidin-2-yl)pyrrolidine-3-carboxylate | 528 | 48 |
| 6 |  | (RS)-1,5,5-trimethyl-3-(5-(phenylethynyl)pyrimidin-2-yl)pyrrolidin-2-one | 130 | 90 |
| 7 |  | (RS)-3-(5-((3-fluorophenyl)ethynyl)pyrimidin-2-yl)-1,5,5-trimethylpyrrolidin-2-one | 137 | 85 |

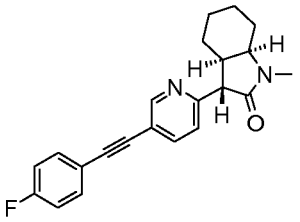
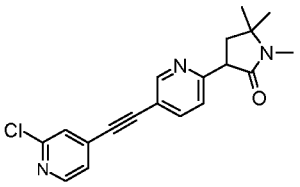
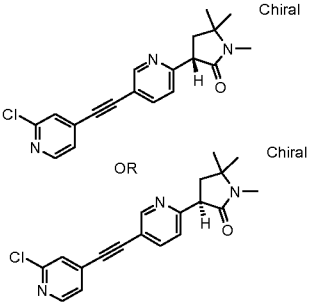
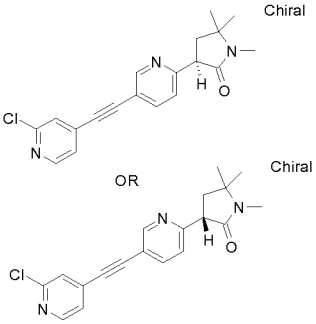
| | | | | |
|---|---|---|---|---|
| 8 |  | 3-(5-((4-fluorophenyl)ethynyl)pyrimidin-2-yl)-1,5,5-trimethylpyrrolidin-2-one | 390 | 105 |
| 9 |  | 3-(6-((3-fluorophenyl)ethynyl)pyridazin-3-yl)-1,5,5-trimethylpyrrolidin-2-one | 34 | 88 |
| 10 |  | 3-(6-((4-fluorophenyl)ethynyl)pyridazin-3-yl)-1,5,5-trimethylpyrrolidin-2-one | 247 | 99 |
| 11 |  | (RS)-1,5,5-trimethyl-3-(6-(phenylethynyl)pyridazin-3-yl)pyrrolidin-2-one | 58 | 115 |
| 12 |  | (RS)-1,6,6-trimethyl-3-(5-(phenylethynyl)pyridin-2-yl)piperidin-2-one | 113 | 103 |
| 13 |  | (RS)-3-(5-((3-fluorophenyl)ethynyl)pyridin-2-yl)-1,6,6-trimethylpiperidin-2-one | 98 | 90 |
| 14 |  | (RS)-3-(5-((4-fluorophenyl)ethynyl)pyridin-2-yl)-1,6,6-trimethylpiperidin-2-one | 212 | 96 |
| 15 |  | (RS)-1,6,6-trimethyl-3-(5-(phenylethynyl)pyrimidin-2-yl)piperidin-2-one | 179 | 91 |

| | | | | |
|---|---|---|---|---|
| 16 |  | (RS)-3-(5-((4-fluorophenyl)ethynyl)pyrimidin-2-yl)-1,6,6-trimethylpiperidin-2-one | 573 | 96 |
| 17 |  | (RS)-3-(5-((3-fluorophenyl)ethynyl)pyrimidin-2-yl)-1,6,6-trimethylpiperidin-2-one | 132 | 80 |
| 18 |  | (RS)-3-hydroxy-1,5,5-trimethyl-3-(5-(phenylethynyl)pyridin-2-yl)pyrrolidin-2-one | 414 | 126 |
| 19 |  | (RS)-3-methoxy-1,5,5-trimethyl-3-(5-(phenylethynyl)pyridin-2-yl)pyrrolidin-2-one | 96 | 108 |
| 20 |  | (RS)-1,3,5,5-tetramethyl-3-(5-(phenylethynyl)pyridin-2-yl)pyrrolidin-2-one | 90 | 109 |
| 21 |  | (RS)-3-(3-fluoro-5-((3-fluorophenyl)ethynyl)pyridin-2-yl)-1,5,5-trimethylpyrrolidin-2-one | 188 | 91 |
| 22 |  | (RS)-1-Methyl-3-(5-phenylethynyl-pyridin-2-yl)-azepan-2-one | 59 | 59 |
| 23 |  | (RS)-3-[5-(4-Fluoro-phenylethynyl)-pyridin-2-yl]-1-methyl-azepan-2-one | 90 | 61 |

| | | | | |
|---|---|---|---|---|
| 24 |  | (RS)-3-[5-(3-Fluoro-phenylethynyl)-pyridin-2-yl]-1-methyl-azepan-2-one | 39 | 69 |
| 25 |  | (S or R)-1-Methyl-3-(5-phenylethynyl-pyridin-2-yl)-azepan-2-one | 35 | 70 |
| 26 |  | (R or S)-1-Methyl-3-(5-phenylethynyl-pyridin-2-yl)-azepan-2-one | 265 | 69 |
| 27 |  | (3RS,3aSR,6aSR)-1-Methyl-3-(5-phenylethynyl-pyridin-2-yl)-hexahydro-cyclopenta[b]pyrrol-2-one | 47 | 53 |
| 28 |  | (3S,3aR,6aR) or (3R,3aS,6aS)-1-Methyl-3-(5-phenylethynyl-pyridin-2-yl)-hexahydro-cyclopenta[b]pyrrol-2-one | 24 | 58 |
| 29 |  | (3RS,3aSR,6aSR)-3-[5-(4-Fluoro-phenylethynyl)-pyridin-2-yl]-1-methyl-hexahydro-cyclopenta[b]pyrrol-2-one | 78 | 53 |

| | | | | |
|---|---|---|---|---|
| 30 |  | (3RS,3aSR,6aSR)-3-[5-(3-Fluoro-phenylethynyl)-pyridin-2-yl]-1-methyl-hexahydro-cyclopenta[b]pyrrol-2-one | 33 | 57 |
| 31 |  | (3R,3aS,6aS) or (3S,3aR,6aR)-3-[5-(3-Fluoro-phenylethynyl)-pyridin-2-yl]-1-methyl-hexahydro-cyclopenta[b]pyrrol-2-one | 25 | 51 |
| 32 |  | (3S,3aR,6aR) or (3R,3aS,6aS)-3-[5-(3-Fluoro-phenylethynyl)-pyridin-2-yl]-1-methyl-hexahydro-cyclopenta[b]pyrrol-2-one | 48 | 68 |
| 33 |  | (3RS,3aSR,6aSR)-1-Methyl-3-(5-phenylethynyl-pyrimidin-2-yl)-hexahydro-cyclopenta[b]pyrrol-2-one | 52 | 52 |
| 34 |  | (3RS,6SR,7SR)-1-Methyl-3-(5-phenylethynyl-pyridin-2-yl)-octahydro-indol-2-one | 185 | 82 |
| 35 |  | (3SR,6SR,7SR)-1-Methyl-3-(5-phenylethynyl-pyridin-2-yl) octahydro-indol-2-one | 101 | 60 |

| | | | | |
|---|---|---|---|---|
| 36 |  | (3R,6S,7S)-1-Methyl-3-(5-phenylethynyl-pyridin-2-yl)-octahydro-indol-2-one | 84 | 92 |
| 37 |  | (3S,6R,7R)-1-Methyl-3-(5-phenylethynyl-pyridin-2-yl)-octahydro-indol-2-one | 84 | 49 |
| 38 |  | (3RS,6SR,7SR)-3-[5-(3-Fluoro-phenylethynyl)-pyridin-2-yl]-1-methyl-octahydro-indol-2-one | 69 | 60 |
| 39 |  | (3SR,6SR,7SR)-3-[5-(3-Fluoro-phenylethynyl)-pyridin-2-yl]-1-methyl-octahydro-indol-2-one | 141 | 61 |
| 40 |  | (3R,6S,7S)-3-[5-(3-Fluoro-phenylethynyl)-pyridin-2-yl]-1-methyl-octahydro-indol-2-one | 89 | 68 |
| 41 |  | (3S,6R,7R)-3-[5-(3-Fluoro-phenylethynyl)-pyridin-2-yl]-1-methyl-octahydro-indol-2-one | 68 | 56 |
| 42 |  | (3R,6S,7S)-3-[5-(4-Fluoro-phenylethynyl)-pyridin-2-yl]-1-methyl-octahydro-indol-2-one | 57 | 63 |

| | | | | |
|---|---|---|---|---|
| 43 |  | (3S,6R,7R)-3-[5-(4-Fluoro-phenylethynyl)-pyridin-2-yl]-1-methyl-octahydro-indol-2-one | 146 | 53 |
| 44 |  | (RS)-3-[5-(2-Chloro-pyridin-4-ylethynyl)-pyridin-2-yl]-1,5,5-trimethyl-pyrrolidin-2-one | 88 | 32 |
| 45 |  | (S) or (R)-3-[5-(2-Chloro-pyridin-4-ylethynyl)-pyridin-2-yl]-1,5,5-trimethyl-pyrrolidin-2-one | 65 | 36 |
| 46 |  | (R) or (S)-3-[5-(2-Chloro-pyridin-4-ylethynyl)-pyridin-2-yl]-1,5,5-trimethyl-pyrrolidin-2-one | 103 | 40 |

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 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 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 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 weighing 70 kg accordingly lies between 0.7-1400 mg per day, preferably between 7 and 700 mg per day.

**Preparation of pharmaceutical compositions comprising compounds of the invention:**

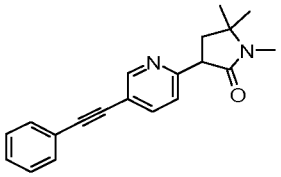
**Example A**

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

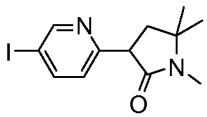
| | mg/Tablet |
|---|---|
| Active ingredient | 100 |
| Powdered. lactose | 95 |
| White corn starch | 35 |
| Polyvinylpyrrolidone | 8 |
| Na carboxymethylstarch | 10 |
| Magnesium stearate | 2 |
| Tablet weight | 250 |

**Example 1**

**(RS)-1,5,5-Trimethyl-3-(5-(phenylethynyl)pyridin-2-yl)pyrrolidin-2-one**



Step 1: (RS)-3-(5-Iodo-pyridin-2-yl)-1,5,5-trimethyl-pyrrolidin-2-one



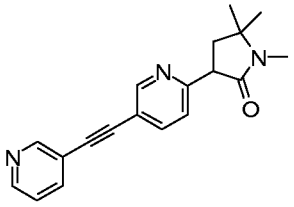
A solution of 2-fluoro-5-iodopyridine (260 mg, 1.17 mmol) and 1,5,5-trimethyl-pyrrolidin-2-one (148 mg, 1.17 mmol) in 6 ml of dry toluene was purged with Argon and cooled to -4°C. A 1M solution of sodium hexamethyldisilylamide (NaHMDS) in toluene (2.33 ml, 2.33 mmol) was added dropwise maintaining the temperature below 0°C. The red solution was stirred for 2h at 0°C, quenched by addition of 5 ml of saturated ammonium chloride solution. After extraction with ethyl acetate/water, drying over sodium sulfate and concentration; the residue (400 mg) was taken up in ethyl acetate, adsorbed onto 5 g of silicagel which was loaded onto a 20 g prepacked flash chromato-graphy column. After elution with a 0% to 75% ethyl acetate in heptane gradient, the fractions containing the desired product were collected to yield 145 mg (38%) of the title compound as a yellow viscous oil, MS: m/e = 331.0 ($M+H^+$).

Step 2: (RS)-1,5,5-Trimethyl-3-(5-(phenylethynyl)pyridin-2-yl)pyrrolidin-2-one

A solution of (RS)-3-(5-iodopyridin-2-yl)-1,5,5-trimethylpyrrolidin-2-one (140mg, 0.42 mmol), ethynylbenzene (65.0 mg, 69.9 µl, 0.64 mmol), triethylamine (129 mg, 177 µl, 1.27 mmol), bis(triphenylphosphine)palladium (II) chloride (17.9 mg, 25.4 µmol) and triphenylphosphine (3.34 mg, 12.7 µmol) in 4 ml of THF was purged with argon. Then copper (I) iodide (2.42 mg, 12.7 µmol) was added and the reaction was heated for 3h at 60°C. After extraction with ethyl acetate/water, drying over sodium sulfate and concentration; the residue was taken up in ethyl acetate, adsorbed onto 3 g of silicagel which was loaded onto a 20 g prepacked flash chromatography column. After elution with a 0% to 65% ethyl acetate in heptane gradient, the fractions containing the desired product were collected to yield 103 mg (72%) of the title compound as an amorphous yellow solid, MS: m/e = 305.2 ($M+H^+$).

**Example 2**

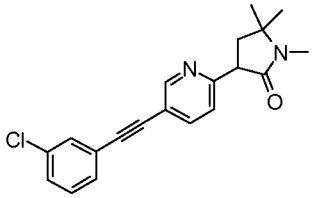
**(RS)-1,5,5-Trimethyl-3-(5-(pyridin-3-ylethynyl)pyridin-2-yl)pyrrolidin-2-one**



The title compound was obtained as an amorphous yellow solid, MS: m/e = 306.2 ($M+H^+$), using chemistry similar to that described in Example 1, step 2 from (RS)-3-(5-iodopyridin-2-yl)-1,5,5-trimethylpyrrolidin-2-one *(Example 1, step 1)* and 3-ethynyl-pyridine.

**Example 3**

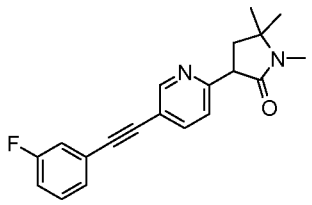
**(RS)-3-(5-((3-Chlorophenyl)ethynyl)pyridin-2-yl)-1,5,5-trimethylpyrrolidin-2-one**



The title compound was obtained as a yellow viscous oil, MS: m/e = 339.1, 341.1 ($M+H^+$), using chemistry similar to that described in Example 1, step 2 from (RS)-3-(5-iodopyridin-2-yl)-1,5,5-trimethylpyrrolidin-2-one *(Example 1, step 1)* and 3- ethynyl-3-chlorobenzene.

**Example 4**

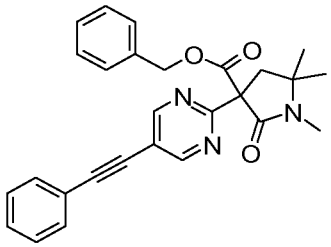
**(RS)-3-(5-((3-Fluorophenyl)ethynyl)pyridin-2-yl)-1,5,5-trimethylpyrrolidin-2-one**



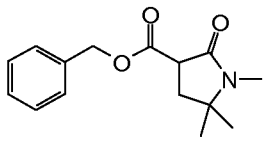
The title compound was obtained as a yellow viscous oil, MS: m/e = 323.3 ($M+H^+$), using chemistry similar to that described in Example 1, step 2 from (RS)-3-(5-iodopyridin-2-yl)-1,5,5-trimethylpyrrolidin-2-one *(Example 1, step 1)* and 1-ethynyl-3-fluoro-benzene.

**Example 5**

**(RS)-Benzyl 1,5,5-trimethyl-2-oxo-3-(5-(phenylethynyl)pyrimidin-2-yl)pyrrolidine-3-carboxylate**



Step 1: (RS)-1,5,5-Trimethyl-2-oxo-pyrrolidine-3-carboxylic acid benzyl ester



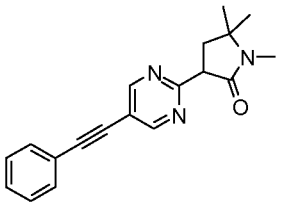
In a flame-dried 50 ml three necked flask under argon atmosphere were dissolved 1.27 g (10.0 mmol) of 5,5-dimethylpyrrolidin-2-one in 10 ml of dry THF. After cooling to -75°C, a 2 M solution of lithium diisopropylamide in THF (10.5 ml, 10.5 mmol) was added dropwise maintaining the temperature below -73°C. The solution was stirrred for 1h at -75°C Then a solution of dibenzyl carbonate (2.72 g, 11.0 mmol) in 5 ml of THF was added dropwise at -75°C, allowed to warm up to r.t. and stirred for 1h. The reaction was quenched by addition of 5 ml of saturated ammonium chloride solution. After extraction with ethyl acetate/water, drying over sodium sulfate and concentration; the residue was loaded onto a 50 g prepacked flash chromatography column. After elution with a 10% to 70% ethyl acetate in heptane gradient, the fractions containing the desired product were collected to yield 1.07 g (41%) of the title compound as a light yellow oil, MS: m/e = 262.2 ($M+H^+$).

Step 2: (RS)-Benzyl 1,5,5-trimethyl-2-oxo-3-(5-(phenylethynyl)pyrimidin-2yl)-pyrrolidine-3-carboxylate

A solution of (RS)-benzyl 1,5,5-trimethyl-2-oxopyrrolidine-3-carboxylate (206 mg, 787 µmol) in 4 ml of dry DMF was purged with argon and cooled to 0°C. Then a 60% suspension of sodium hydride (31.5 mg, 0.79 mmol) was added and the mixture was stirred for 40 min at room temperature whereby a white suspension was formed. Then 2-chloro-5-(phenylethynyl)pyrimidine (CAS: [1051388-40-9]) (130 mg, 606 µmol) was added, the mixture was stirred for 30 min at 80°C, and then quenched by addition of 1 ml of saturated ammonium chloride solution. After extraction with ethyl acetate/water, drying over sodium sulfate and concentration; the residue (440 mg, yellow oil) was taken up in ethyl acetate, adsorbed onto 3 g of silicagel and loaded onto a 20 g prepacked flash chromatography column. After elution with a 10% to 60% ethyl acetate in heptane gradient, the fractions containing the desired product were collected to yield 212 mg (80%) of the title compound as a light yellow waxy solid, MS: m/e = 440.3 ($M+H^+$).

**Example 6**

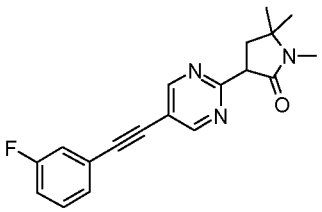
**(RS)-1,5,5-Trimethyl-3-(5-(phenylethynyl)pyrimidin-2-yl)pyrrolidin-2-one**



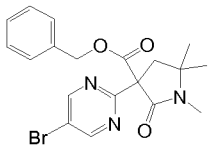
To a solution of (RS)-benzyl 1,5,5-trimethyl-2-oxo-3-(5-(phenylethynyl)pyrimidin-2-yl)pyrrolidine-3-carboxylate *(Example 5, step 2)* (205mg, 0.47 µmol) in 3 ml of ethanol was added 1N sodium hydroxide solution (933 µl, 0.94 mmol). After stirring for 1.5h at room temperature, the pH was neutralized by addition of 1N HCl, and the solvent was evaporated in vaccuo. The residue (165 mg, yellow oil) was loaded onto a 20 g prepacked flash chromatography column. After elution with a 15% to 100% ethyl acetate in heptane gradient, the fractions containing the desired product were collected to yield 94 mg (66%) of the title compound as a light yellow crystalline solid, MS: m/e = 306.2 ($M+H^+$).

**Example 7**

**(RS)-3-(5-((3-Fluorophenyl)ethynyl)pyrimidin-2-yl)-1,5,5-trimethylpyrrolidin-2-one**

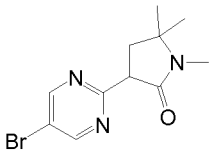


Step 1: (RS)-3-(5-Bromo-pyrimidin-2-yl)-1,5,5-trimethyl-2-oxo-pyrrolidine-3-carboxylic acid benzyl ester



The title compound was obtained as a colorless viscous oil, MS: m/e = 420.1, 418.2 ($M+H^+$), using chemistry similar to that described in Example 5, step 2 from (RS)-benzyl 1,5,5-trimethyl-2-oxopyrrolidine-3-carboxylate *(Example 5, step 1)* and 5-bromo-2-chloropyrimidine.

Step 2: (RS)-3-(5-Bromo-pyrimidin-2-yl)-1,5,5-trimethyl-pyrrolidin-2-one



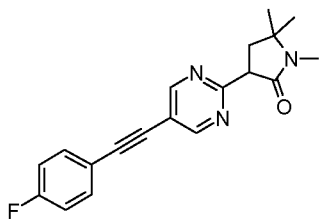
The title compound was obtained as a crystalline white solid, MS: m/e = 284.0, 286.0 ($M+H^+$), using chemistry similar to that described in Example 6 from (RS)-3-(5-bromo-pyrimidin-2-yl)-1,5,5-trimethyl-2-oxo-pyrrolidine-3-carboxylic acid benzyl ester.

Step 3: (RS)-3-(5-((3-Fluorophenyl)ethynyl)pyrimidin-2-yl)-1,5,5-trimethylpyrrolidin-2-one

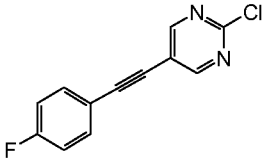
The title compound was obtained as a crystalline white solid, MS: m/e = 324.2 ($M+H^+$), using chemistry similar to that described in Example 1, step 2 from (RS)-3-(5-iodopyridin-2-yl)-1,5,5-trimethylpyrrolidin-2-one and 1-ethynyl-3-fluoro-benzene.

## Example 8

## (RS)-3-(5-((4-Fluorophenyl)ethynyl)pyrimidin-2-yl)-1,5,5-trimethylpyrrolidin-2-one

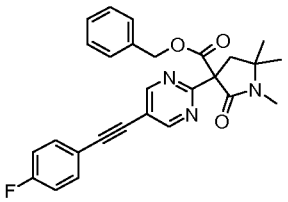


Step 1: 2-Chloro-5-(4-fluoro-phenylethynyl)-pyrimidine



A solution of 2-chloro-5-iodopyrimidine (600 mg, 2.5 mmol), 1-ethynyl-4-fluorobenzene (330 mg, 2.75 mmol), triethylamine (556 mg, 761 µl, 5.49 mmol), and bis(triphenyl-phosphine)palladium (II) chloride (175 mg, 250 µmol) in 7 ml of THF was purged with argon. Then copper (I) iodide (23.8 mg, 125 µmol) was added and the reaction was heated for 2h at room temperature. The dark solution was filtered and the solids were washed with THF. The residue was taken up in ethyl acetate, adsorbed onto 3 g of silicagel which was loaded onto a 50 g prepacked flash chromatography column. After elution with a 0% to 20% ethyl acetate in heptane gradient, the fractions containing the desired product were collected to yield 505 mg (87%) of the title compound as an crystalline light yellow solid, MS: m/e = 233.1, 235.1 ($M+H^+$).

Step 2: 3-[5-(4-Fluoro-phenylethynyl)-pyrimidin-2-yl]-1,5,5-trimethyl-2-oxo-pyrrolidine-3-carboxylic acid benzyl ester



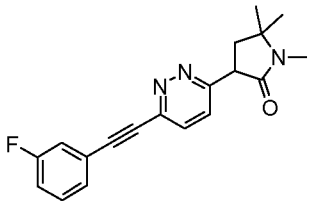
The title compound was obtained as a light yellow viscous oil, MS: m/e = 458.3 ($M+H^+$), using chemistry similar to that described in Example 5, step 2 from (RS)-1,5,5-trimethyl-2-oxo-pyrrolidine-3-carboxylic acid benzyl ester *(Example 5, step 1)* and 2-chloro-5-(4-fluoro-phenylethynyl)-pyrimidine.

Step 3: (RS)-3-(5-((4-Fluorophenyl)ethynyl)pyrimidin-2-yl)-1,5,5-trimethylpyrrolidin-2-one

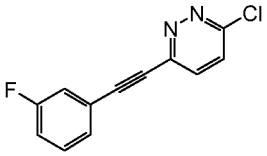
The title compound was obtained as a white waxy solid, MS: m/e = 324.2 ($M+H^+$), using chemistry similar to that described in Example 6 from 3-[5-(4-fluoro-phenylethynyl)-pyrimidin-2-yl]-1,5,5-trimethyl-2-oxo-pyrrolidine-3-carboxylic acid benzyl ester.

## Example 9

## (RS)-3-(6-((3-Fluorophenyl)ethynyl)pyridazin-3-yl)-1,5,5-trimethylpyrrolidin-2-one

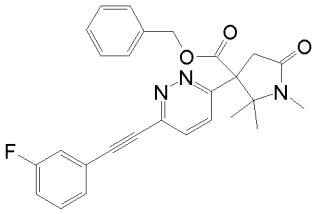


Step 1: 3-Chloro-6-(3-fluoro-phenylethynyl)-pyridazine



The title compound was obtained as a crystalline light yellow solid, MS: m/e = 233.1, 235.0 ($M+H^+$), using chemistry similar to that described in Example 8, step 1 from 3-chloro-6-iodopyridazine and 1-ethynyl-3-fluorobenzene.

Step 2: (RS)-3-[6-(3-Fluoro-phenylethynyl)-pyridazin-3-yl]-1,5,5-trimethyl-2-oxo-pyrrolidine-3-carboxylic acid benzyl ester



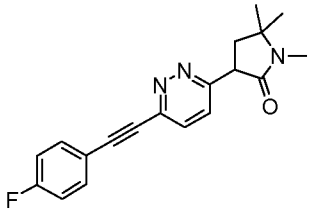
The title compound was obtained as a yellow gum, MS: m/e = 458.3 ($M+H^+$), using chemistry similar to that described in Example 5, step 2 from (RS)-1,5,5-trimethyl-2-oxo-pyrrolidine-3-carboxylic acid benzyl ester *(Example 5, step 1)* and 3-chloro-6-(3-fluoro-phenylethynyl)-pyridazine.

Step 3: (RS)-3-(6-((3-fluorophenyl)ethynyl)pyridazin-3-yl)-1,5,5-trimethylpyrrolidin-2-one

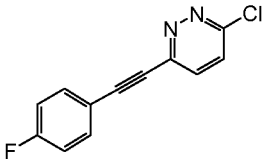
The title compound was obtained as a colorless viscous oil, MS: m/e = 324.2 ($M+H^+$), using chemistry similar to that described in Example 6 from (RS)-3-[6-(3-fluoro-phenyl-ethynyl)-pyridazin-3-yl]-1,5,5-trimethyl-2-oxo-pyrrolidine-3-carboxylic acid benzyl ester.

## Example 10

## (RS)-3-(6-((4-Fluorophenyl)ethynyl)pyridazin-3-yl)-1,5,5-trimethylpyrrolidin-2-one

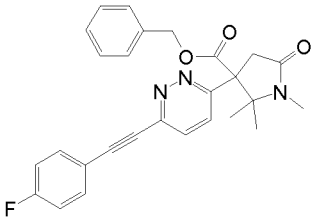


Step 1: 3-Chloro-6-(4-fluoro-phenylethynyl)-pyridazine



The title compound was obtained as a crystalline light yellow solid, MS: m/e = 233.1, 235.1 ($M+H^+$), using chemistry similar to that described in Example 8, step 1 from 3-chloro-6-iodopyridazine and 1-ethynyl-4-fluorobenzene.

Step 2: (RS)-3-[6-(3-Fluoro-phenylethynyl)-pyridazin-3-yl]-1,5,5-trimethyl-2-oxo-pyrrolidine-3-carboxylic acid benzyl ester



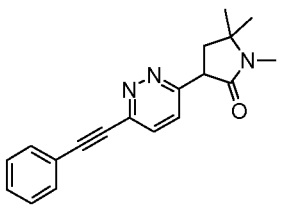
The title compound was obtained as a yellow viscous oil, MS: m/e = 458.3 ($M+H^+$), using chemistry similar to that described in Example 5, step 2 from (RS)-1,5,5-trimethyl-2-oxo-pyrrolidine-3-carboxylic acid benzyl ester *(example 5, step 1)* and 3-chloro-6-(4-fluoro-phenylethynyl)-pyridazine.

Step 3: (RS)-3-(6-((3-Fluorophenyl)ethynyl)pyridazin-3-yl)-1,5,5-trimethylpyrrolidin-2-one

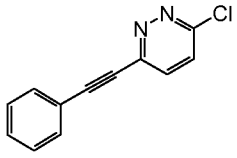
The title compound was obtained as a colorless viscous oil, MS: m/e = 324.2 ($M+H^+$), using chemistry similar to that described in Example 6 from (RS)-3-[6-(4-fluoro-phenyl-ethynyl)-pyridazin-3-yl]-1,5,5-trimethyl-2-oxo-pyrrolidine-3-carboxylic acid benzyl ester.

## Example 11

## (RS)-3-(6-(Phenylethynyl)pyridazin-3-yl)-1,5,5-trimethylpyrrolidin-2-one

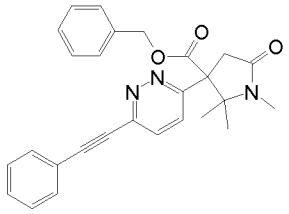


Step 1: 3-Chloro-6-(phenylethynyl)-pyridazine



The title compound was obtained as a crystalline light yellow solid, MS: m/e = 215.2, 217.2 ($M+H^+$), using chemistry similar to that described in Example 8, step 1 from 3-chloro-6-iodopyridazine and 1-ethynyl-benzene.

Step 2: (RS)-3-[6-(Phenylethynyl)-pyridazin-3-yl]-1,5,5-trimethyl-2-oxo-pyrrolidine-3-carboxylic acid benzyl ester



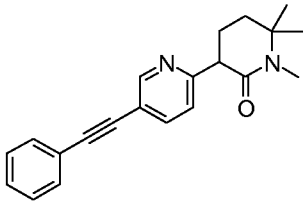
The title compound was obtained as a light yellow oil, MS: m/e = 440.2 ($M+H^+$), using chemistry similar to that described in Example 5, step 2 from (RS)-1,5,5-trimethyl-2-oxo-pyrrolidine-3-carboxylic acid benzyl ester *(Example 5, step 1)* and 3-chloro-6-(phenylethynyl)-pyridazine.

Step 3: (RS)-3-(6-(Phenylethynyl)pyridazin-3-yl)-1,5,5-trimethylpyrrolidin-2-one

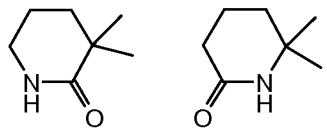
The title compound was obtained as a yellow waxy solid, MS: m/e = 306.3 ($M+H^+$), using chemistry similar to that described in Example 6 from (RS)-3-[6-(phenylethynyl)-pyridazin-3-yl]-1,5,5-trimethyl-2-oxo-pyrrolidine-3-carboxylic acid benzyl ester.

## Example 12

## (RS)-1,6,6-Trimethyl-3-(5-(phenylethynyl)pyridin-2-yl)piperidin-2-one

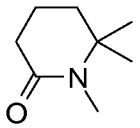


Step 1: 3 to 1 Mixture of 6,6-dimethyl-piperidin-2-one and 3,3-dimethyl-piperidin-2-one:



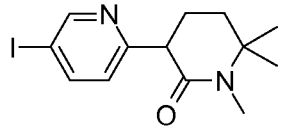
To 9.97 g (88.9 mmol) of 2,2,-dimethylcyclopentanone were added 70 ml of 98% formic acid with stirring. To this clear solution was added 15.1 g (133 mmol) of hydroxylamine-O-sulfonic acid in portions, maintaining the temeprature between 15-20°C using an ice-bath. After stirring for 5 min the white suspension became a clear solution. The mixture was then refluxed for 4h (100°C) and allowed to cool overnight. The resulting yellow solution was concentrated in vaccuo. The light orange resinous residue was taken up in 30 ml of water, 40 ml of 1N sodium hydroxide solution and 100 ml of chloroform and vigourously stirred until dissolution was complete. The pH of the aqueous phase was adjusted to 8 by addition of 25% NaOH solution. The organic phase was separated. The aqueous phase was extracted five times with 30 ml of chloroform. The combined organic phases were washed with 10 ml of water. The combined organic phases were concentrated in vaccuo to yield 9.9 g of a light orange semi-solid which was purified by chromatography over silicagel (ethyl acetate/methanol 9:1). Fractions containing the two isomers were collected to yield 4.72 g (41.8%) of a white solid which was directly used in the next step.

Step 2: 1,6,6-Trimethyl-piperidin-2-one



To a solution of a 3 to 1 mixture of 3,3-dimethylpiperidin-2-one and 6,6-dimethylpiperidin-2-one (4.72 g, 37.1 mmol) in 60ml of THF was added 60% sodium hydride suspension (1.93g, 48.2 mmol). The grey reaction mixture was stirred at room temperature for 30 minutes. Then methyl iodide (3.02 ml, 48.2 mmol) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was quenched with water, and worked up with ethyl acetate/water. The orange oil was chromatographed over a prepacked 70g silica column After elution with a 50% to 100% ethyl acetate in heptane gradient, the fractions containing the desired product were collected to yield 2.46 g (47%) of the title compound as a light yellow solid; and 0.91 g (17%) of isomeric 1,3,3-trimethyl-piperidin-2-one as a yellow oil.

Step 2: (RS)-5-Iodo-1',6',6'-trimethyl-3',4',5',6'-tetrahydro-1'H-[2,3']bipyridinyl-2'-one



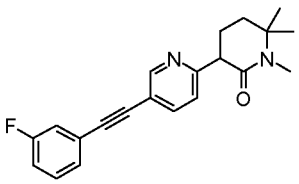
The title compound was obtained as a colorless viscous oil, MS: m/e = 345.1 ($M+H^+$), using chemistry similar to that described in Example 1, step 1 from 1,6,6-trimethyl-piperidin-2-one and 2-fluoro-5-iodopyridine.

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

The title compound was obtained as a light yellow viscous oil, MS: m/e = 319.2 ($M+H^+$), using chemistry similar to that described in Example 1, step 2 from (RS)-5-iodo-1',6',6'-trimethyl-3',4',5',6'-tetrahydro-1'H-[2,3']bipyridinyl-2'-one and 3-ethynyl-pyridine.

**Example 13**

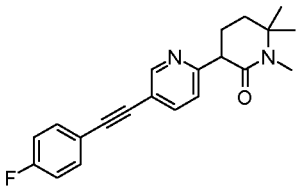
**(RS)-3-(5-((3-Fluorophenyl)ethynyl)pyridin-2-yl)-1,6,6-trimethylpiperidin-2-one**



The title compound was obtained as a light yellow viscous oil, MS: m/e = 337.2 ($M+H^+$), using chemistry similar to that described in Example 1, step 2 from (RS)-5-iodo-1',6',6'-trimethyl-3',4',5',6'-tetrahydro-1'H-[2,3']bipyridinyl-2'-one and 1-ethynyl-3-fluoro-benzene.

**Example 14**

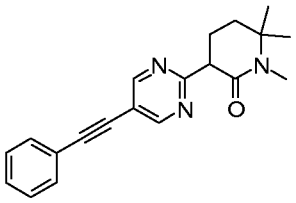
**(RS)-3-(5-((4-Fluorophenyl)ethynyl)pyridin-2-yl)-1,6,6-trimethylpiperidin-2-one**



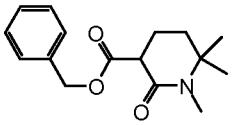
The title compound was obtained as a light yellow waxy solid, MS: m/e = 337.2 ($M+H^+$), using chemistry similar to that described in Example 1, step 2 from (RS)-5-iodo-1',6',6'-trimethyl-3',4',5',6'-tetrahydro-1'H-[2,3']bipyridinyl-2'-one and 1-ethynyl-4-fluoro-benzene.

**Example 15**

**(RS)-1,6,6-Trimethyl-3-(5-(phenylethynyl)pyrimidin-2-yl)piperidin-2-one**

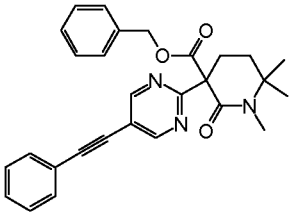


Step 1: (RS)-1,6,6-Trimethyl-2-oxo-piperidine-3-carboxylic acid benzyl ester



The title compound was obtained as a light yellow oil, using chemistry similar to that described in Example 5, step 1 from 1,6,6-trimethyl-piperidin-2-one and dibenzyl carbonate.

Step 2: (RS)-1,6,6-Trimethyl-2-oxo-3-(5-phenylethynyl-pyrimidin-2-yl)-piperidine-3-carboxylic acid benzyl ester



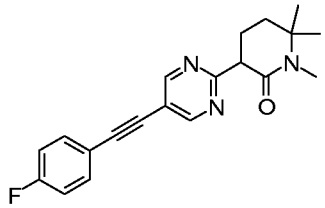
The title compound was obtained as a yellow oil, using chemistry similar to that described in Example 5, step 2 from (RS)-1,6,6-trimethyl-2-oxo-piperidine-3-carboxylic acid benzyl ester and 2-chloro-5-(phenylethynyl)pyrimidine (CAS: [1051388-40-9]).

Step 3: (RS)-1,6,6-Trimethyl-3-(5-(phenylethynyl)pyrimidin-2-yl)piperidin-2-one

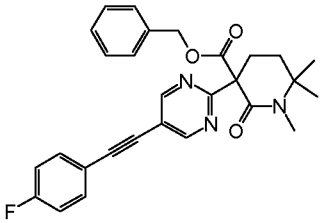
The title compound was obtained as a light yellow solid, MS: m/e = 320.2 ($M+H^+$), using chemistry similar to that described in Example 6 from (RS)-1,6,6-trimethyl-2-oxo-3-(5-phenylethynyl-pyrimidin-2-yl)-piperidine-3-carboxylic acid benzyl ester.

## Example 16

**(RS)-3-(5-((4-Fluorophenyl)ethynyl)pyrimidin-2-yl)-1,6,6-trimethylpiperidin-2-one**



Step 1: (RS)-1,6,6-Trimethyl-2-oxo-3-(5-((4-fluorophenyl)ethynyl)-pyrimidin-2-yl)-piperidine-3-carboxylic acid benzyl ester



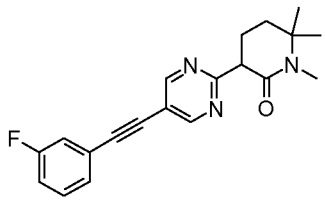
The title compound was obtained as an orange oil, using chemistry similar to that described in Example 5, step 2 from (RS)-1,6,6-trimethyl-2-oxo-piperidine-3-carboxylic acid benzyl ester and 2-chloro-5-(4-fluoro-phenylethynyl)-pyrimidine *(Example 8, step 1)*.

Step 2: (RS)-3-(5-((4-Fluorophenyl)ethynyl)pyrimidin-2-yl)-1,6,6-trimethylpiperidin-2-one

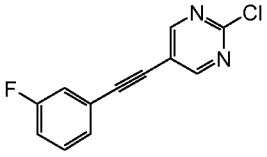
The title compound was obtained as an off-white solid, MS: m/e = 338.2 ($M+H^+$), using chemistry similar to that described in Example 6 from (RS)-1,6,6-trimethyl-2-oxo-3-(5-((4-fluorophenyl)ethynyl)-pyrimidin-2-yl)-piperidine-3-carboxylic acid benzyl ester.

## Example 17

## (RS)-3-(5-((3-Fluorophenyl)ethynyl)pyrimidin-2-yl)-1,6,6-trimethylpiperidin-2-one

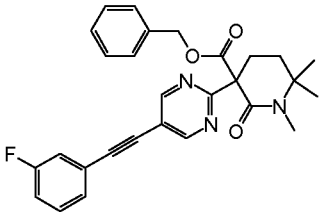


Step 1: 2-Chloro-5-(3-fluoro-phenylethynyl)-pyrimidine



The title compound was obtained as a yellow solid, MS: m/e = 233.0, 234.9 ($M+H^+$), using chemistry similar to that described in Example 8, step 1 from 2-chloro-5-iodopyrimidine and 1-ethynyl-3-fluorobenzene.

Step 2: (RS)-1,6,6-Trimethyl-2-oxo-3-(5-((3-fluorophenyl)ethynyl)-pyrimidin-2-yl)-piperidine-3-carboxylic acid benzyl ester



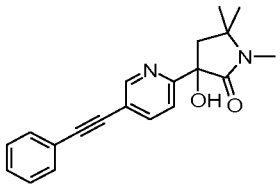
The title compound was obtained as a yellow oil, using chemistry similar to that described in example 5, step 2 from (RS)-1,6,6-trimethyl-2-oxo-piperidine-3-carboxylic acid benzyl ester and 2-chloro-5-(3-fluoro-phenylethynyl)-pyrimidine *(Example 8, step 1)*.

Step 3: (RS)-3-(5-((4-Fluorophenyl)ethynyl)pyrimidin-2-yl)-1,6,6-trimethylpiperidin-2-one

The title compound was obtained as a light brown solid, MS: m/e = 338.2 ($M+H^+$), using chemistry similar to that described in Example 6 from (RS)-1,6,6-trimethyl-2-oxo-3-(5-((3-fluorophenyl)ethynyl)-pyrimidin-2-yl)-piperidine-3-carboxylic acid benzyl ester.

**Example 18**

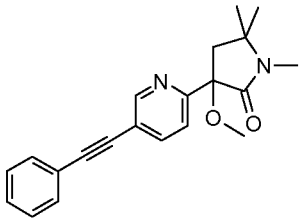
**(RS)-3-Hydroxy-1,5,5-trimethyl-3-(5-(phenylethynyl)pyridin-2-yl)pyrrolidin-2-one**



The title compound was obtained as byproduct in the synthesis of Example 1 as a light brown oil, MS: m/e = 321.2 ($M+H^+$).

**Example 19**

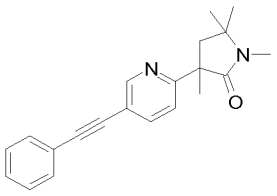
**(RS)-3-Methoxy-1,5,5-trimethyl-3-(5-(phenylethynyl)pyridin-2-yl)pyrrolidin-2-one**



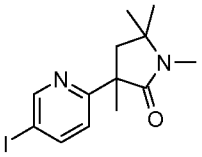
The title compound was obtained as a light yellow oil, MS: m/e = 335.2 ($M+H^+$), using chemistry similar to that described in Example 12, step 2 from (RS)-3-hydroxy-1,5,5-trimethyl-3-(5-(phenylethynyl)pyridin-2-yl)pyrrolidin-2-one *(Example 18)* and iodomethane.

**Example 20**

**(RS)-1,3,5,5-Tetramethyl-3-(5-(phenylethynyl)pyridin-2-yl)pyrrolidin-2-one**

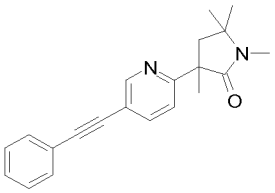


Step 1: (RS)-3-(5-Iodo-pyridin-2-yl)-1,3,5,5-tetramethyl-pyrrolidin-2-one



The title compound was obtained as a white solid, MS: m/e = 345.0 ($M+H^+$), using chemistry similar to that described in Example 12, step 2 from (RS)-3-(5-iodo-pyridin-2-yl)-1,5,5-trimethyl-pyrrolidin-2-one *(Example 1, step 1)* and iodomethane.

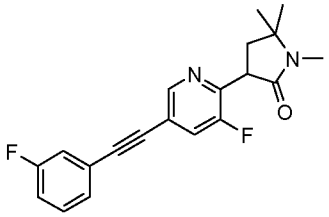
Step 2: (RS)-1,3,5,5-Tetramethyl-3-(5-(phenylethynyl)pyridin-2-yl)pyrrolidin-2-one



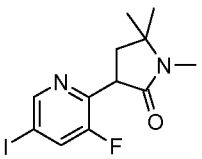
The title compound was obtained as a light brown oil, MS: m/e = 319.1 ($M+H^+$), using chemistry similar to that described in Example 1, step 2 from (RS)-3-(5-iodo-pyridin-2-yl)-1,3,5,5-tetramethyl-pyrrolidin-2-one *(Example 20, step 1)* and phenylacetylene.

## Example 21

**(RS)-3-(3-fluoro-5-((3-fluorophenyl)ethynyl)pyridin-2-yl)-1,5,5-trimethylpyrrolidin-2-one**

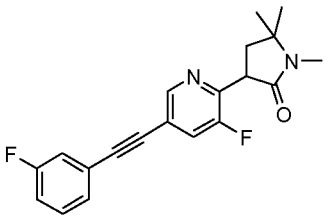


Step 1: (RS)-3-(3-Fluoro-5-iodo-pyridin-2-yl)-1,5,5-trimethyl-pyrrolidin-2-one



The title compound was obtained as a light brown solid, MS: m/e = 349.0 ($M+H^+$), using chemistry similar to that described in Example 1, step 1 from 2,3-difluoro-5-iodopyridine and 1,5,5-trimethyl-pyrrolidin-2-one.

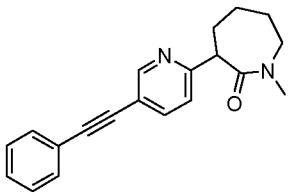
Step 2: (RS)-3-(3-fluoro-5-((3-fluorophenyl)ethynyl)pyridin-2-yl)-1,5,5-trimethylpyrrolidin-2-one



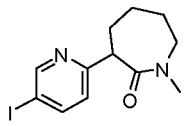
The title compound was obtained as a light brown oil, MS: m/e = 319.1 ($M+H^+$), using chemistry similar to that described in example 1, step 2 from (RS)-3-(3-fluoro-5-iodo-pyridin-2-yl)-1,5,5-trimethyl-pyrrolidin-2-one *(Example 21, step 1)* and 1-ethynyl-3-fluorobenzene.

## Example 22

## (RS)-1-Methyl-3-(5-phenylethynyl-pyridin-2-yl)-azepan-2-one

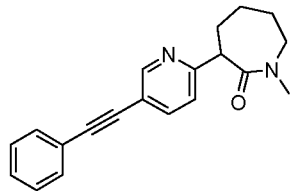


Step 1: (RS)-3-(5-Iodo-pyridin-2-yl)-1-methyl-azepan-2-one



The title compound was obtained as a light yellow solid, MS: m/e = 331.0 ($M+H^+$), using chemistry similar to that described in Example 1, step 1 from 2-fluoro-5-iodopyridine and 1-methyl-azepan-2-one.

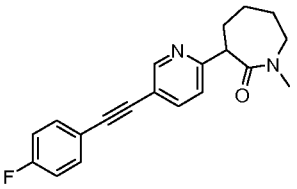
Step 2: (RS)-1-Methyl-3-(5-phenylethynyl-pyridin-2-yl)-azepan-2-one



The title compound was obtained as an orange solid, MS: m/e = 305.1 ($M+H^+$), using chemistry similar to that described in example 1, step 2 from (RS)-3-(5-iodo-pyridin-2-yl)-1-methyl-azepan-2-one *(Example 22, step 1)* and phenylacetylene.

**Example 23**

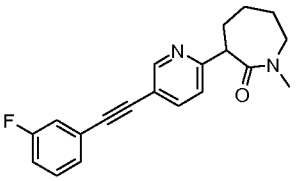
**(RS)-3-[5-(4-Fluoro-phenylethynyl)-pyridin-2-yl]-1-methyl-azepan-2-one**



The title compound was obtained as a light yellow solid, MS: m/e = 323.1 ($M+H^+$), using chemistry similar to that described in example 1, step 2 from (RS)-3-(5-iodo-pyridin-2-yl)-1-methyl-azepan-2-one *(Example 22, step 1)* and 1-ethynyl-4-fluoro-benzene.

**Example 24**

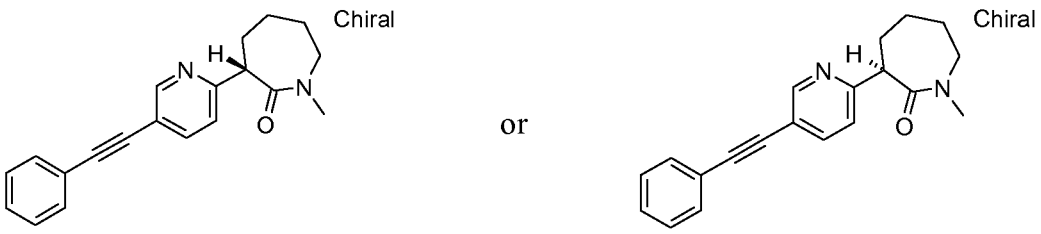
**(RS)-3-[5-(3-Fluoro-phenylethynyl)-pyridin-2-yl]-1-methyl-azepan-2-one**



The title compound was obtained as a light brown solid, MS: m/e = 323.1 ($M+H^+$), using chemistry similar to that described in example 1, step 2 from (RS)-3-(5-iodo-pyridin-2-yl)-1-methyl-azepan-2-one *(Example 22, step 1)* and 1-ethynyl-3-fluoro-benzene.

**Example 25**

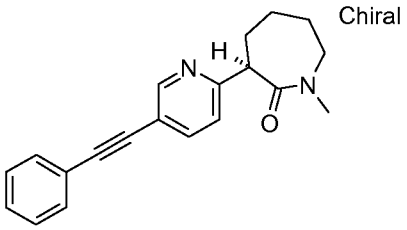
**(S or R)-1-Methyl-3-(5-phenylethynyl-pyridin-2-yl)-azepan-2-one**



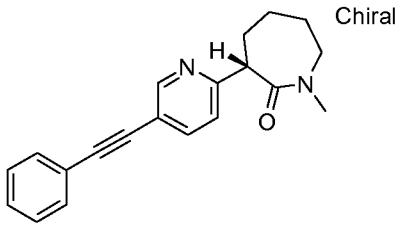
The title compound, a light yellow oil, MS: m/e = 305.1 ($M+H^+$), was prepared by separation of (RS)-1-methyl-3-(5-phenylethynyl-pyridin-2-yl)-azepan-2-one *(Example 22)* using a chiral column (Reprosil Chiral NR with heptane:ethanol 60:40 as solvent).

**Example 26**

**(R or S)-1-Methyl-3-(5-phenylethynyl-pyridin-2-yl)-azepan-2-one**



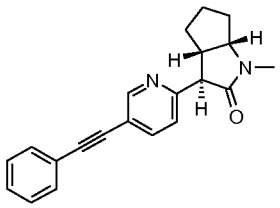

or



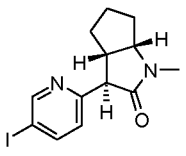

The title compound, a light yellow oil, MS: m/e = 305.1 ($M+H^+$), was prepared by separation of (RS)-1-methyl-3-(5-phenylethynyl-pyridin-2-yl)-azepan-2-one *(Example 22)* using a chiral column (Reprosil Chiral NR with heptane:ethanol 60:40 as solvent).

**Example 27**

**(3RS,3aSR,6aSR)-1-Methyl-3-(5-phenylethynyl-pyridin-2-yl)-hexahydro-cyclopenta[b]pyrrol-2-one**

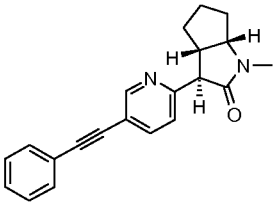



Step 1: (3RS,3aSR,6aSR)-3-(5-Iodo-pyridin-2-yl)-1-methyl-hexahydro-cyclopenta[b]pyrrol-2-one




The title compound was obtained as a yellow oil, MS: m/e = 342.9 ($M+H^+$), using chemistry similar to that described in Example 1, step 1 from 2-fluoro-5-iodopyridine and cis-1-methyl-hexahydro-cyclopenta[b]pyrrol-2-one *(CAS 169688-72-6)*.

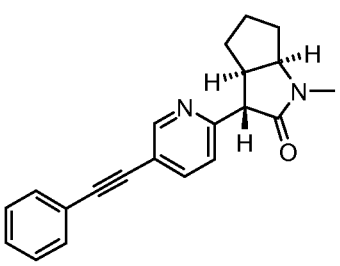
Step 2: (3RS,3aSR,6aSR)-1-Methyl-3-(5-phenylethynyl-pyridin-2-yl)-hexahydro-cyclopenta[b]pyrrol-2-one



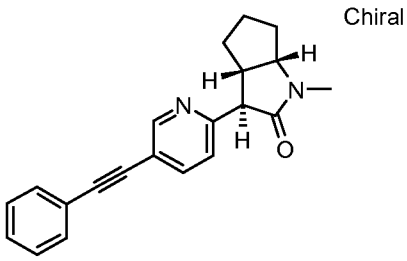
The title compound was obtained as a brown oil, MS: m/e = 317.1 ($M+H^+$), using chemistry similar to that described in example 1, step 2 from (3RS,3aSR,6aSR)-3-(5-iodo-pyridin-2-yl)-1-methyl-hexahydro-cyclopenta[b]pyrrol-2-one *(Example 27, step 1)* and phenylacetylene.

**Example 28**

**(3R,3aS,6aS) or (3S,3aR,6aR)-1-Methyl-3-(5-phenylethynyl-pyridin-2-yl)-hexahydro-cyclopenta[b]pyrrol-2-one**



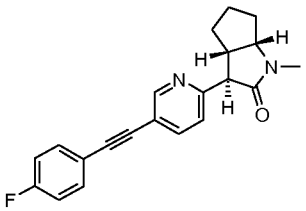

or




The title compound, a light yellow oil, MS: m/e = 317.1 ($M+H^+$), was prepared by separation of (3RS,3aSR,6aSR)-1-methyl-3-(5-phenylethynyl-pyridin-2-yl)-hexahydro-cyclopenta[b]pyrrol-2-one (*Example 27)* using a chiral column (Chiralpak AD with heptane:isopropanol 60:40 as solvent).

**Example 29**

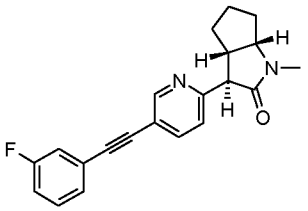
**(3RS,3aSR,6aSR)-3-[5-(4-Fluoro-phenylethynyl)-pyridin-2-yl]-1-methyl-hexahydro-cyclopenta[b]pyrrol-2-one**



The title compound was obtained as a light brown oil, MS: m/e = 335.1 ($M+H^+$), using chemistry similar to that described in example 1, step 2 from (3RS,3aSR,6aSR)-3-(5-iodo-pyridin-2-yl)-1-methyl-hexahydro-cyclopenta[b]pyrrol-2-one *(Example 27, step 1)* and 1-ethynyl-4-fluoro-benzene.

**Example 30**

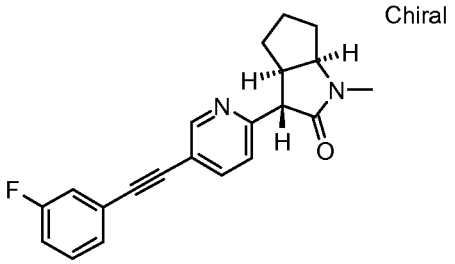
**(3RS,3aSR,6aSR)-3-[5-(3-Fluoro-phenylethynyl)-pyridin-2-yl]-1-methyl-hexahydro-cyclopenta[b]pyrrol-2-one**



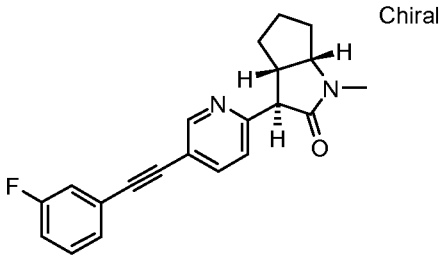
The title compound was obtained as a light brown oil, MS: m/e = 335.1 ($M+H^+$), using chemistry similar to that described in example 1, step 2 from (3RS,3aSR,6aSR)-3-(5-iodo-pyridin-2-yl)-1-methyl-hexahydro-cyclopenta[b]pyrrol-2-one *(Example 27, step 1)* and 1-ethynyl-3-fluoro-benzene.

**Example 31**

**(3R,3aS,6aS) or (3S,3aR,6aR)-3-[5-(3-Fluoro-phenylethynyl)-pyridin-2-yl]-1-methyl-hexahydro-cyclopenta[b]pyrrol-2-one**



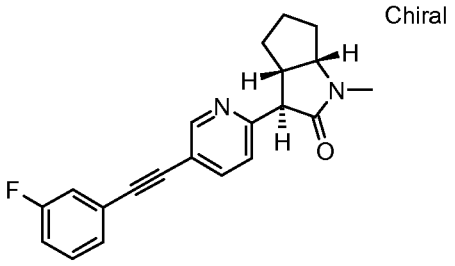

or



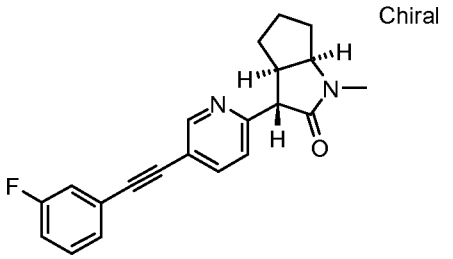

The title compound, a light yellow oil, MS: m/e = 335.1 ($M+H^+$), was prepared by separation of (3RS,3aSR,6aSR)-3-[5-(3-fluoro-phenylethynyl)-pyridin-2-yl]-1-methyl-hexahydro-cyclopenta[b]pyrrol-2-one (*Example 30)* using a chiral column (Reprosil Chiral NR with heptane:ethanol 60:40 as solvent).

**Example 32**

**(3S,3aR,6aR) or (3R,3aS,6aS)-3-[5-(3-Fluoro-phenylethynyl)-pyridin-2-yl]-1-methyl-hexahydro-cyclopenta[b]pyrrol-2-one**



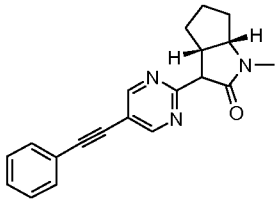

or




The title compound, a light yellow oil, MS: m/e = 335.1 ($M+H^+$), was prepared by separation of (3RS,3aSR,6aSR)-3-[5-(3-fluoro-phenylethynyl)-pyridin-2-yl]-1-methyl-hexahydro-cyclopenta[b]pyrrol-2-one (*Example 30)* using a chiral column (Reprosil Chiral NR with heptane:ethanol 60:40 as solvent).

**Example 33**

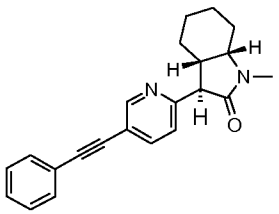
**(3RS,3aSR,6aSR)-1-Methyl-3-(5-phenylethynyl-pyrimidin-2-yl)-hexahydro-cyclopenta[b]pyrrol-2-one**

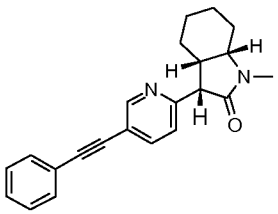



The title compound was obtained as a white solid, MS: m/e = 318.1 ($M+H^+$), using chemistry similar to that described in example 5 and example 6 starting from cis-1-methyl-hexahydro-cyclopenta[b]pyrrol-2-one *(CAS 169688-72-6)* instead of 5,5-dimethylpyrrolidin-2-one.

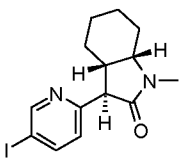
**Examples 34 and 35**

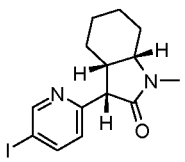
**(3RS,6SR,7SR)-1-Methyl-3-(5-phenylethynyl-pyridin-2-yl)-octahydro-indol-2-one and (3SR,6SR,7SR)-1-Methyl-3-(5-phenylethynyl-pyridin-2-yl)-octahydro-indol-2-one**




Step 1: 7:1-mixture of (3RS,5SR,6SR)-3-(5-Iodo-pyridin-2-yl)-1-methyl-octahydro-indol-2-one and (3SR,5SR,6SR)-3-(5-Iodo-pyridin-2-yl)-1-methyl-octahydro-indol-2-one



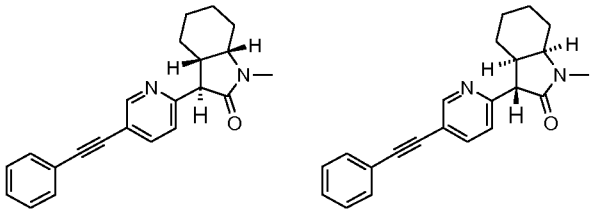
The title compound mixture was obtained as a yellow solid, MS: m/e = 357.1 ($M+H^+$), using chemistry similar to that described in Example 1, step 1 from 2-fluoro-5-iodopyridine and racemic cis-octahydro-1-methyl-2H-indol-2-one (CAS 116725-60-1).

Step 2: (3RS,6SR,7SR)-1-Methyl-3-(5-phenylethynyl-pyridin-2-yl)-octahydro-indol-2-one and (3SR,6SR,7SR)-1-Methyl-3-(5-phenylethynyl-pyridin-2-yl)-octahydro-indol-2-one

The title compound (3RS,6SR,7SR)-1-methyl-3-(5-phenylethynyl-pyridin-2-yl)-octahydro-indol-2-one (147 mg, major isomer, exo-adduct) was obtained as a light brown solid, MS: m/e = 331.2 ($M+H^+$), and the minor isomer (3SR,6SR,7SR)-1-methyl-3-(5-phenylethynyl-pyridin-2-yl)-octahydro-indol-2-one (22 mg) was obtained as a brown gum, MS: m/e = 331.2 ($M+H^+$), using chemistry similar to that described in example 1, step 2 from a 7:1-mixture of (3RS,6SR,7SR)-3-(5-iodo-pyridin-2-yl)-1-methyl-octahydro-indol-2-one and (3SR,6SR,7SR)-3-(5-iodo-pyridin-2-yl)-1-methyl-octahydro-indol-2one *(Example 34, step 1)* and phenylacetylene.

## Example 36 and 37

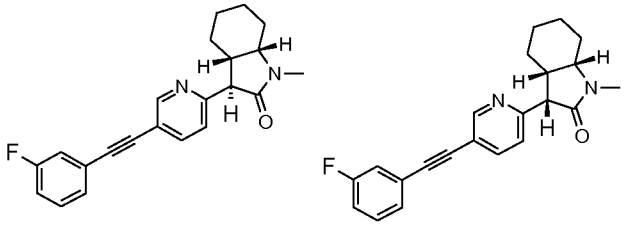
## (3R,6S,7S)-1-Methyl-3-(5-phenylethynyl-pyridin-2-yl)-octahydro-indol-2-one and (3S,6R,7R)-1-Methyl-3-(5-phenylethynyl-pyridin-2-yl)-octahydro-indol-2-one



(3R,6S,7S)-1-Methyl-3-(5-phenylethynyl-pyridin-2-yl)-octahydro-indol-2-one (56 mg, colorless gum), MS: m/e = 331.2 ($M+H^+$), and (3S,6R,7R)-1-methyl-3-(5-phenylethynyl-pyridin-2-yl)-octahydro-indol-2-one, (62 mg, light yellow gum), MS: m/e = 331.2 ($M+H^+$), were prepared by separation of racemic (3RS,3aSR,7aSR)-1-methyl-3-(5-phenylethynyl-pyridin-2-yl)-octahydro-indol-2-one (*Example 34)* using a chiral column (Reprosil Chiral NR with heptane:ethanol 80:20 as solvent).

## Examples 38 and 39

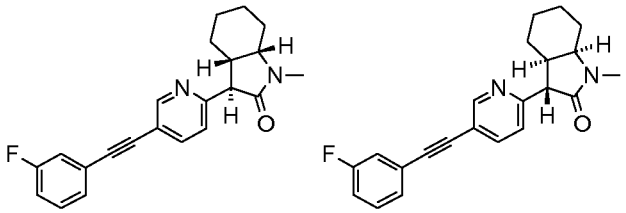
## (3RS,6SR,7SR)-3-[5-(3-Fluoro-phenylethynyl)-pyridin-2-yl]-1-methyl-octahydro-indol-2-one and (3SR,6SR,7SR)-3-[5-(3-Fluoro-phenylethynyl)-pyridin-2-yl]-1-methyl-octahydro-indol-2-one



The title compound (3RS,6SR,7SR)-3-[5-(3-fluoro-phenylethynyl)-pyridin-2-yl]-1-methyl-octahydro-indol-2-one (187 mg, major isomer, exo-adduct) was obtained as a yellow oil, MS: m/e = 349.3 ($M+H^+$), and the minor isomer (3SR,6SR,7SR)-3-[5-(3-fluoro-phenylethynyl)-pyridin-2-yl]-1-methyl-octahydro-indol-2-one (25 mg) was obtained as a light brown gum, MS: m/e = 349.3 ($M+H^+$), using chemistry similar to that described in example 34 and 35, step 2 from a 7:1-mixture of (3RS,3aSR,7aSR)-3-(5-iodo-pyridin-2-yl)-1-methyl-octahydro-indol-2-one and (3SR,3aSR,7aSR)-3-(5-iodo-pyridin-2-yl)-1-methyl-octahydro-indol-2one *(Example 34, step 1)* and 3-fluorophenylacetylene.

**Example 40 and 41**

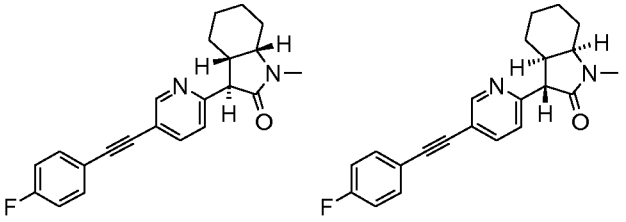
**(3R,6S,7S)-3-[5-(3-Fluoro-phenylethynyl)-pyridin-2-yl]-1-methyl-octahydro-indol-2-one and (3S,6R,7R)-3-[5-(3-Fluoro-phenylethynyl)-pyridin-2-yl]-1-methyl-octahydro-indol-2-one**



(3R,6S,7S)-3-[5-(3-fluoro-phenylethynyl)-pyridin-2-yl]-1-methyl-octahydro-indol-2-one (66 mg, colorless gum), MS: m/e = 349.3 ($M+H^+$), (3S,6R,7R)-3-[5-(3-fluoro-phenylethynyl)-pyridin-2-yl]-1-methyl-octahydro-indol-2-one (63 mg, colorless gum), MS: m/e = 349.3 ($M+H^+$), were prepared by separation of racemic (3RS,6SR,7SR)-3-[5-(3-fluoro-phenylethynyl)-pyridin-2-yl]-1-methyl-octahydro-indol-2-one (*Example 38)* using a chiral column (Reprosil Chiral NR with heptane:ethanol 60:40 as solvent).

**Example 42 and 43**

**(3R,6S,7S)-3-[5-(4-Fluoro-phenylethynyl)-pyridin-2-yl]-1-methyl-octahydro-indol-2-one and (3S,6R,7R)-3-[5-(4-Fluoro-phenylethynyl)-pyridin-2-yl]-1-methyl-octahydro-indol-2-one**



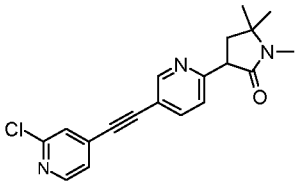
Step 1: (3RS,6SR,7SR)-3-[5-(4-Fluoro-phenylethynyl)-pyridin-2-yl]-1-methyl-octahydro-indol-2-one§

The title compound, racemic (3RS,6SR,7SR)-3-[5-(4-fluoro-phenylethynyl)-pyridin-2-yl]-1-methyl-octahydro-indol-2-one (189 mg, major isomer, exo-adduct) was obtained as a light brown oil, MS: m/e = 349.3 ($M+H^+$), using chemistry similar to that described in example 34, step 2 from a 7:1-mixture of (3RS,3aSR,7aSR)-3-(5-iodo-pyridin-2-yl)-1-methyl-octahydro-indol-2-one and (3SR,3aSR,7aSR)-3-(5-iodo-pyridin-2-yl)-1-methyl-octahydro-indol-2one *(Example 34, step 1)* and 4-fluorophenylacetylene. The minor isomer was not isolated.

(3R,6S,7S)-3-[5-(4-Fluoro-phenylethynyl)-pyridin-2-yl]-1-methyl-octahydro-indol-2-one (78 mg, light yellow gum), MS: m/e = 349.3 ($M+H^+$), (3S,6R,7R)-3-[5-(4-fluoro-phenylethynyl)-pyridin-2-yl]-1-methyl-octahydro-indol-2-one (75 mg, light yellow gum), MS: m/e = 349.3 ($M+H^+$), were prepared by separation of racemic (3RS,6SR,7SR)-3-[5-(4-fluoro-phenylethynyl)-pyridin-2-yl]-1-methyl-octahydro-indol-2-one (*Example 42)* using a chiral column (Reprosil Chiral NR with heptane:ethanol 60:40 as solvent).

## Example 44

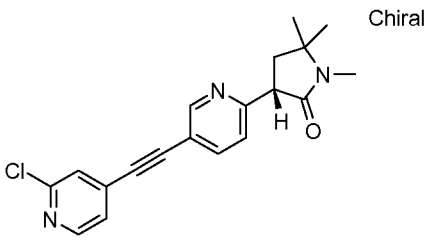
## (RS)-3-[5-(2-Chloro-pyridin-4-ylethynyl)-pyridin-2-yl]-1,5,5-trimethyl-pyrrolidin-2-one



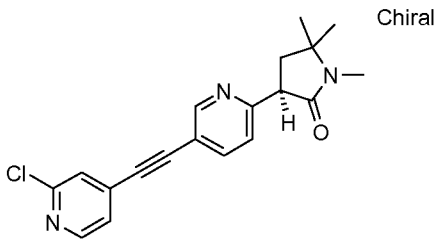
The title compound was obtained as a light yellow oil, MS: m/e = 340.3/342.4 ($M+H^+$), using chemistry similar to that described in Example 1, step 2 from (RS)-3-(5-iodopyridin-2-yl)-1,5,5-trimethylpyrrolidin-2-one *(Example 1, step 1)* and 2-chloro-4-ethynyl-pyridine *(CAS 945717-09-9)*.

## Example 45

## (S) or (R)-3-[5-(2-Chloro-pyridin-4-ylethynyl)-pyridin-2-yl]-1,5,5-trimethyl-pyrrolidin-2-one



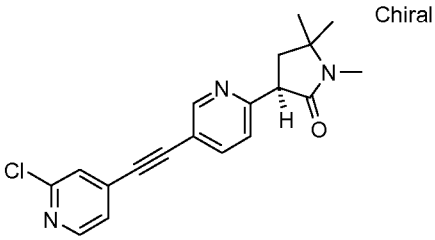

or



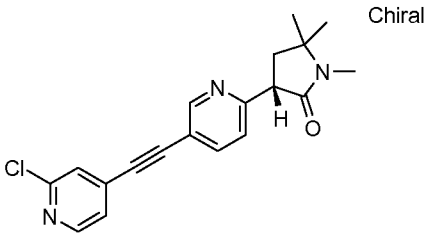

The title compound, a yellow solid, MS: m/e = 340.4/342.4 ($M+H^+$), was prepared by separation of (RS)-3-[5-(2-chloro-pyridin-4-ylethynyl)-pyridin-2-yl]-1,5,5-trimethyl-pyrrolidin-2-one (*Example 44)* using a chiral column (Chiralpak AD with heptane:isopropanol 60:40 as solvent).

**Example 46**

**(R) or (S)-3-[5-(2-Chloro-pyridin-4-ylethynyl)-pyridin-2-yl]-1,5,5-trimethyl-pyrrolidin-2-one**



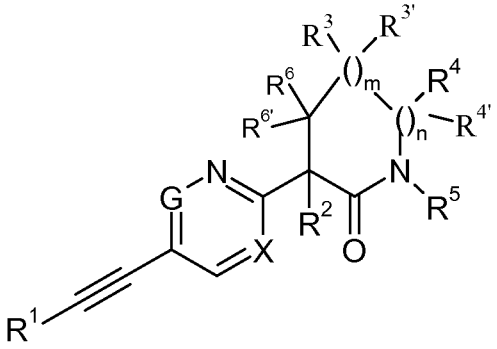

**or**




The title compound, a light yellow solid, MS: m/e = 340.4/342.4 ($M+H^+$), was prepared by separation of (RS)-3-[5-(2-chloro-pyridin-4-ylethynyl)-pyridin-2-yl]-1,5,5-trimethyl-pyrrolidin-2-one (*Example 44)* using a chiral column (Chiralpak AD with heptane:isopropanol 60:40 as solvent).

## Claims

1. A compound of formula



I

wherein

X is N or C-R, wherein R is hydrogen or halogen;

G is N or CH;

with the proviso that maximum one of G or X can be nitrogen;

$R^1$ is phenyl or pyridinyl, which are optionally substituted by halogen;

$R^2$ is hydrogen, lower alkyl, hydroxy, lower alkoxy or C(O)O-benzyl;

$R^3$,$R^{3'}$, $R^4$, $R^{4'}$, $R^6$, $R^{6'}$ are independently from each other hydrogen or lower alkyl;

or $R^6$ and $R^4$ may form together with the carbon atom to which they are attached a $C_{4-6}$-cycloalkyl ring, if m is 0 and n is 1 or 2;

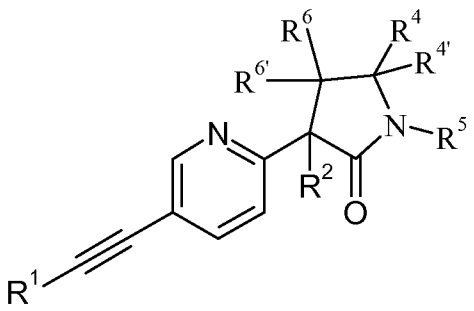
$R^5$ is hydrogen or lower alkyl;

n is 0, 1 or 2;

m is 0 or 1; with the proviso that n and m are not simultaneously 0;

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

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



IA

wherein

$R^1$ is phenyl or pyridinyl, which are optionally substituted by halogen;

$R^2$ is hydrogen, lower alkyl, hydroxy, lower alkoxy or C(O)O-benzyl;

$R^4$, $R^{4'}$, $R^6$, $R^{6'}$ are independently from each other hydrogen or lower alkyl;

or $R^6$ and $R^4$ may form together with the carbon atom to which they are attached a $C_{4-6}$-cycloalkyl ring;

$R^5$ is 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.

3. A compound of formula IA according to any one of claims 1 or 2, which compounds are

(RS)-1,5,5-trimethyl-3-(5-(phenylethynyl)pyridin-2-yl)pyrrolidin-2-one

(RS)-1,5,5-trimethyl-3-(5-(pyridin-3-ylethynyl)pyridin-2-yl)pyrrolidin-2-one

(RS)-3-(5-((3-chlorophenyl)ethynyl)pyridin-2-yl)-1,5,5-trimethylpyrrolidin-2-one

(RS)-3-(5-((3-fluorophenyl)ethynyl)pyridin-2-yl)-1,5,5-trimethylpyrrolidin-2-one

(RS)-3-hydroxy-1,5,5-trimethyl-3-(5-(phenylethynyl)pyridin-2-yl)pyrrolidin-2-one

(RS)-3-methoxy-1,5,5-trimethyl-3-(5-(phenylethynyl)pyridin-2-yl)pyrrolidin-2-one

(RS)-1,3,5,5-tetramethyl-3-(5-(phenylethynyl)pyridin-2-yl)pyrrolidin-2-one

(3RS,3aSR,6aSR)-1-methyl-3-(5-phenylethynyl-pyridin-2-yl)-hexahydro-cyclopenta[b]pyrrol-2-one

(3R,3aS,6aS) or (3S,3aR,6aR)-1-methyl-3-(5-phenylethynyl-pyridin-2-yl)-hexahydro-cyclopenta[b]pyrrol-2-one

(3RS,3aSR,6aSR)-3-[5-(4-fluoro-phenylethynyl)-pyridin-2-yl]-1-methyl-hexahydro-cyclopenta[b]pyrrol-2-one

(3RS,3aSR,6aSR)-3-[5-(3-fluoro-phenylethynyl)-pyridin-2-yl]-1-methyl-hexahydro-cyclopenta[b]pyrrol-2-one

(3R,3aS,6aS) or (3S,3aR,6aR)-3-[5-(3-fluoro-phenylethynyl)-pyridin-2-yl]-1-methyl-hexahydro-cyclopenta[b]pyrrol-2-one

(3S,3aR,6aR) or (3R,3aS,6aS)-3-[5-(3-fluoro-phenylethynyl)-pyridin-2-yl]-1-methyl-hexahydro-cyclopenta[b]pyrrol-2-one

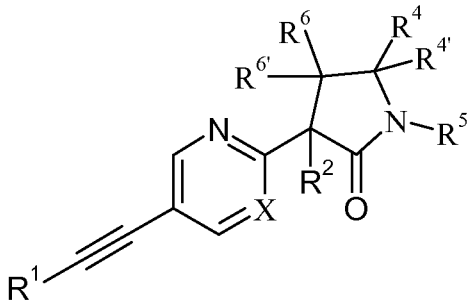
(3RS,6SR,7SR)-1-methyl-3-(5-phenylethynyl-pyridin-2-yl)-octahydro-indol-2-one

(3SR,6SR,7SR)-1-methyl-3-(5-phenylethynyl-pyridin-2-yl)-octahydro-indol-2-one

(3R,6S,7S)-1-methyl-3-(5-phenylethynyl-pyridin-2-yl)-octahydro-indol-2-one and (3S,6R,7R)-1-Methyl-3-(5-phenylethynyl-pyridin-2-yl)-octahydro-indol-2-one

(3RS,6SR,7SR)-3-[5-(3-fluoro-phenylethynyl)-pyridin-2-yl]-1-methyl-octahydro-indol-2-one
(3SR,6SR,7SR)-3-[5-(3-fluoro-phenylethynyl)-pyridin-2-yl]-1-methyl-octahydro-indol-2-one
(3R,6S,7S)-3-[5-(3-fluoro-phenylethynyl)-pyridin-2-yl]-1-methyl-octahydro-indol-2-one
(3S,6R,7R)-3-[5-(3-fluoro-phenylethynyl)-pyridin-2-yl]-1-methyl-octahydro-indol-2-one
(3R,6S,7S)-3-[5-(4-fluoro-phenylethynyl)-pyridin-2-yl]-1-methyl-octahydro-indol-2-one
(3S,6R,7R)-3-[5-(4-fluoro-phenylethynyl)-pyridin-2-yl]-1-methyl-octahydro-indol-2-one
(RS)-3-[5-(2-chloro-pyridin-4-ylethynyl)-pyridin-2-yl]-1,5,5-trimethyl-pyrrolidin-2-one
(S) or (R)-3-[5-(2-chloro-pyridin-4-ylethynyl)-pyridin-2-yl]-1,5,5-trimethyl-pyrrolidin-2-one or
(R) or (S)-3-[5-(2-chloro-pyridin-4-ylethynyl)-pyridin-2-yl]-1,5,5-trimethyl-pyrrolidin-2-one.

4. A compound of formula IB according to claim 1



IB

wherein

X is N or C-R, wherein R is halogen;

$R^1$ is phenyl or pyridinyl, which are optionally substituted by halogen;

$R^2$ is hydrogen, lower alkyl, hydroxy, lower alkoxy or C(O)O-benzyl;

$R^4$, $R^{4'}$, $R^6$, $R^{6'}$ are independently from each other hydrogen or lower alkyl;

or $R^6$ and $R^4$ may form together with the carbon atom to which they are attached a $C_{4-6}$-cycloalkyl ring,;

$R^5$ is hydrogen or lower alkyl;

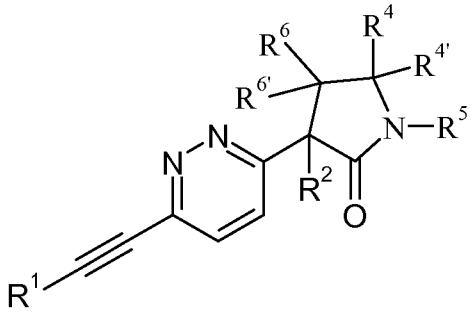
or a pharmaceutically acceptable acid addition salt, a racemic mixture, or its corresponding enantiomer and/or optical isomer and/or stereoisomer thereof.

5. A compound of formula IB according to any one of claims 1 or 4, which compounds are

(RS)-benzyl 1,5,5-trimethyl-2-oxo-3-(5-(phenylethynyl)pyrimidin-2-yl)pyrrolidine-3-carboxylate
(RS)-1,5,5-trimethyl-3-(5-(phenylethynyl)pyrimidin-2-yl)pyrrolidin-2-one
(RS)-3-(5-((3-fluorophenyl)ethynyl)pyrimidin-2-yl)-1,5,5-trimethylpyrrolidin-2-one

(RS)-3-(5-((4-fluorophenyl)ethynyl)pyrimidin-2-yl)-1,5,5-trimethylpyrrolidin-2-one or (3RS,3aSR,6aSR)-1-methyl-3-(5-phenylethynyl-pyrimidin-2-yl)-hexahydro-cyclopenta[b]pyrrol-2-one.

6. A compound of formula IC according to claim 1



IC

wherein

$R^1$ is phenyl or pyridinyl, which are optionally substituted by halogen;

$R^2$ is hydrogen, lower alkyl, hydroxy, lower alkoxy or C(O)O-benzyl;

$R^4$, $R^{4'}$, $R^6$, $R^{6'}$ are independently from each other hydrogen or lower alkyl;

or $R^6$ and $R^4$ may form together with the carbon atom to which they are attached a $C_{4-6}$-cycloalkyl ring;

$R^5$ is 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.

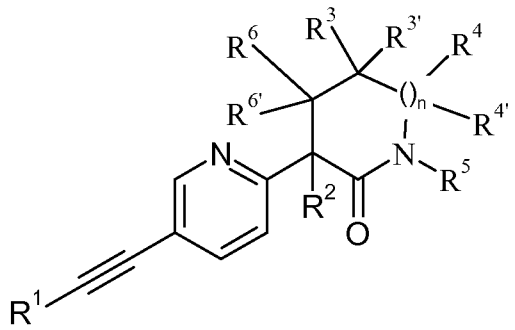
7. A compound of formula IC according to any one of claims 1 or 6, wherein the compounds are

(RS)-3-(6-((3-fluorophenyl)ethynyl)pyridazin-3-yl)-1,5,5-trimethylpyrrolidin-2-one

(RS)-3-(6-((4-fluorophenyl)ethynyl)pyridazin-3-yl)-1,5,5-trimethylpyrrolidin-2-one or

(RS)-3-(6-(phenylethynyl)pyridazin-3-yl)-1,5,5-trimethylpyrrolidin-2-one.

8. A compound of formula ID according to claim 1



ID

wherein

$R^1$ is phenyl or pyridinyl, which are optionally substituted by halogen;

$R^2$ is hydrogen, lower alkyl, hydroxy, lower alkoxy or C(O)O-benzyl;

$R^3$,$R^{3'}$, $R^4$, $R^{4'}$, $R^6$, $R^{6'}$ are independently from each other hydrogen or lower alkyl;

$R^5$ is hydrogen or lower alkyl;

n is 1 or 2;

or a pharmaceutically acceptable 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 any one of claims 1 or 8, wherein the compounds are

(RS)-1,6,6-trimethyl-3-(5-(phenylethynyl)pyridin-2-yl)piperidin-2-one

(RS)-3-(5-((3-fluorophenyl)ethynyl)pyridin-2-yl)-1,6,6-trimethylpiperidin-2-one

(RS)-3-(5-((4-fluorophenyl)ethynyl)pyridin-2-yl)-1,6,6-trimethylpiperidin-2-one

(RS)-1-methyl-3-(5-phenylethynyl-pyridin-2-yl)-azepan-2-one

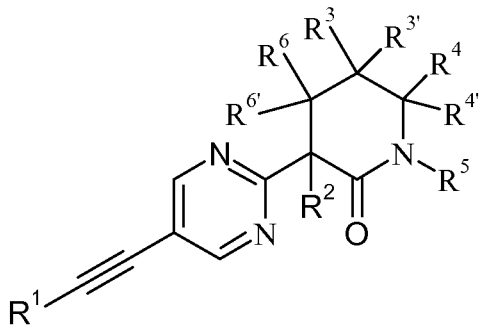
(RS)-3-[5-(4-fluoro-phenylethynyl)-pyridin-2-yl]-1-methyl-azepan-2-one

(RS)-3-[5-(3-fluoro-phenylethynyl)-pyridin-2-yl]-1-methyl-azepan-2-one

(S or R)-1-methyl-3-(5-phenylethynyl-pyridin-2-yl)-azepan-2-one or

(R or S)-1-methyl-3-(5-phenylethynyl-pyridin-2-yl)-azepan-2-one.

10. A compound of formula IE according to claim 1



IE

wherein

$R^1$ is phenyl or pyridinyl, which are optionally substituted by halogen;

$R^2$ is hydrogen, lower alkyl, hydroxy, lower alkoxy or C(O)O-benzyl;

$R^3$,$R^{3'}$, $R^4$, $R^{4'}$, $R^6$, $R^{6'}$ are independently from each other hydrogen or lower alkyl;

$R^5$ is 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.

11. A compound of formula IE according to any one of claims 1 or 10, which compounds are

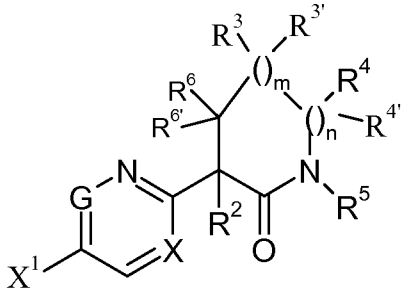
(RS)-1,6,6-trimethyl-3-(5-(phenylethynyl)pyrimidin-2-yl)piperidin-2-one

(RS)-3-(5-((4-fluorophenyl)ethynyl)pyrimidin-2-yl)-1,6,6-trimethylpiperidin-2-one or

(RS)-3-(5-((3-fluorophenyl)ethynyl)pyrimidin-2-yl)-1,6,6-trimethylpiperidin-2-one.

12. A process for preparation of a compound of formula I as described in any one of claims 1 - 11, comprising the variants

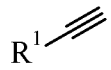
a) reacting a compound of formula



3

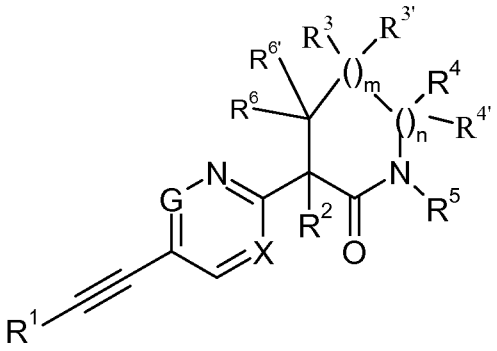
wherein $X^1$ is halogen

with a compound of formula



4

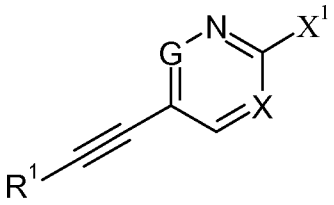
to a compound of formula



I

wherein the definitions are as described in claim 1 or

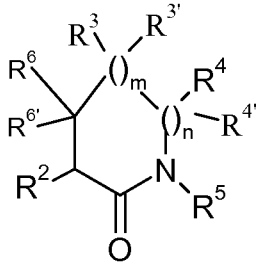
b) reacting a compound of formula



5

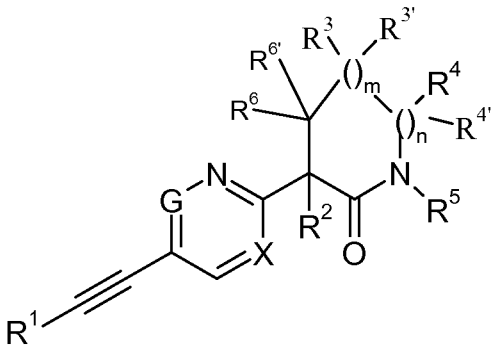
wherein $X^1$ is halogen

with a compound of formula



2

to form a compound of formula



I

wherein the definitions are as described in claim 1, or, if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts.

13. A compound according to any one of claim 1 -11, whenever prepared by a process as claimed in claim 12.

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

15. A pharmaceutical composition comprising a compound in accordance with any one of claims 1 –11 and a therapeutically active carrier.

16. The use of a compound according to any one of claims 1 –11 for the treatment of schizophrenia or cognitive diseases.

17. The use of a compound as claimed in any one of claims 1-11 for the manufacture of a medicament for the treatment of schizophrenia or cognitive diseases.

18. A compound according to any one of claims 1 –11 for the treatment of schizophrenia or cognitive diseases.

19. A method for the treatment of schizophrenia or cognitive diseases, which method comprises administering an effective amount of a compound as defined in any one of claims 1 –11.

20. The invention as herein before described.