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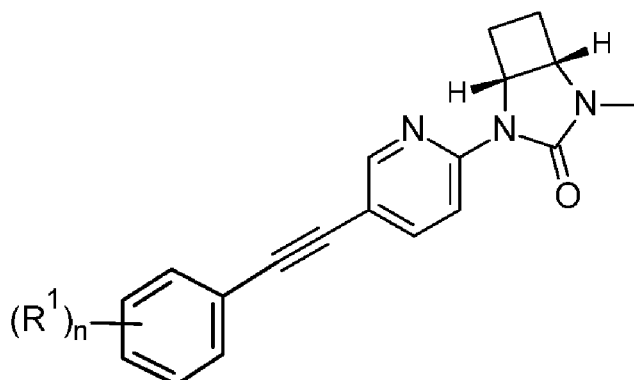
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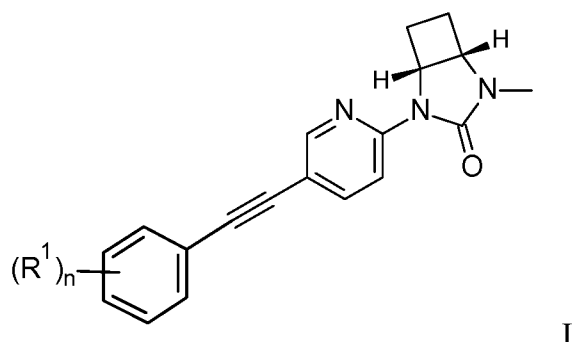


I

(57) Abstract: The present invention relates to ethynyl derivatives of formula (I) wherein R¹ is hydrogen or F; n is 1 or 2 or to a pharmaceutically acceptable acid addition salt thereof. It has now surprisingly been found that the compounds of general formula I are metabotropic glutamate receptor antagonists (negative allosteric modulators) for use in the treatment of anxiety and pain, depression, Fragile-X syndrom, autism spectrum disorders, Parkinson's disease, and gastroesophageal reflux disease (GERD).

ETHYNYL DERIVATIVES

The present invention relates to ethynyl derivatives of formula I



wherein

R^1 is hydrogen or F;

5 n is 1 or 2

or to a pharmaceutically acceptable acid addition salt thereof.

Preferred compounds are those, wherein $(R^1)_n$ is hydrogen, 3-fluoro, 4-fluoro or 2,5-difluoro.

It has now surprisingly been found that the compounds of general formula I are
10 metabotropic glutamate receptor antagonists (NAM = negative allosteric modulators).

Compounds with a similar main core have been generically described as positive allosteric modulators of the mGluR5 receptor. Surprisingly, it has been found that highly potent mGluR5 antagonists were obtained instead of mGluR5 positive allosteric modulators, which have a completely opposite pharmacology if compared with positive allosteric modulators.

15 A mGluR5 positive allosteric modulator (PAM) leads to increased receptor activity (Ca^{2+} mobilization) in presence of a fixed concentration of glutamate, whereas an allosteric antagonist (negative allosteric modulator, NAM) leads to a reduction of receptor activation.

Compounds of formula I are distinguished by having valuable therapeutic properties. They can be used in the treatment of anxiety and pain, depression, Fragile-X syndrom, autism spectrum
20 disorders, Parkinson's disease, and gastroesophageal reflux disease (GERD).

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 neuro-receptor.

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.

Negative allosteric modulators 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 Parkinson's disease, Fragile-X syndrome, autistic disorders, cognitive disorders and memory deficits, as well as chronic and acute pain and gastro-esophageal reflux disease (GERD).

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)).

Selective mGluR5 antagonists are especially useful for the treatment of disorders where reduction of mGluR5 receptor activation is desired, such as anxiety and pain, depression,

Fragile-X syndrome, autism spectrum disorders, Parkinson's disease, and gastro esophageal reflux disease (GERD)

Objects of the present invention are compounds of formula I and their pharmaceutically acceptable salts, the above-mentioned compounds as pharmaceutically active substances and their production. Further objects of the invention are medicaments based on a compound in accordance with the invention and their manufacture as well as the use of the compounds in the control or prevention of mGluR5 receptor (NAM) mediated disorders, which are anxiety and pain, depression, Fragile-X syndrome, autism spectrum disorders, Parkinson's disease, and gastro-esophageal reflux disease (GERD, and, respectively, for the production of corresponding medicaments.

Compounds of the present invention have been generically described in reference 1 (WO2011128279) as positive allosteric modulators of the mGluR5 receptor. Most similar exemplified compounds are linked to a 5- or 6-membered ring. Surprisingly it has been found that compounds having a smaller ring size, a 4-membered ring, and with the absolute stereochemistry of the bicyclic ring (1R,5S), are highly potent mGluR5 antagonists, which have a completely opposite pharmacology to that described in WO2011128279 for positive allosteric modulators.

One embodiment of the present invention are compounds of formula I, for example the following:

(1S,5R)-2-methyl-4-(5-(phenylethynyl)pyridin-2-yl)-2,4-diazabicyclo[3.2.0]heptan-3-one
(1R,5S)-2-(5-((4-fluorophenyl)ethynyl)pyridin-2-yl)-4-methyl-2,4-diazabicyclo[3.2.0] heptan-3-one
(1R,5S)-2-(5-((3-fluorophenyl)ethynyl)pyridin-2-yl)-4-methyl-2,4-diazabicyclo[3.2.0] heptan-3-one or
(1R,5S)-2-(5-((2,5-difluorophenyl)ethynyl)pyridin-2-yl)-4-methyl-2,4-diazabicyclo[3.2.0] heptan-3-one.

The main difference between positive- and negative allosteric modulators can be seen in figure 1. An mGluR5 positive allosteric modulator (PAM) leads to increased receptor activity (Ca^{2+} mobilisation) in presence of a fixed concentration of glutamate whereas an allosteric antagonist (negative allosteric modulator, NAM) leads to a reduction of receptor activation. The affinity for the receptor in Figure 1 is ca. 10^{-7} M for the PAM and between 10^{-7} M and 10^{-8} M for the NAM. These values can also be measured using a binding assay to displace a radioligand (= MPEP) see assay description.

Figure 1: Comparison of an mGluR5 positive allosteric modulator (PAM) and an mGluR5 antagonist (negative allosteric modulator = NAM)

The indications which can be addressed by the compounds are not the same. mGluR5-NAMs are beneficial for indications where a reduction of excessive receptor activity is desired, such as anxiety, pain, Fragile-X, autism spectrum disorders, and gastroesophageal reflux disease. mGluR5 PAMs on the other hand are useful in indications where a normalisation of decreased receptor activity is desired such as in psychosis, epilepsy, schizophrenia, Alzheimer's disease and associated cognitive disorders, as well as tuberous sclerosis.

This difference can be practically shown for example in an anxiety animal model such as the rat Vogel conflict drinking test where the compound of Example 1 shows anxiolytic activity at a minimal effective dose of 0.1 mg/Kg whereas mGluR-PAMs are not expected to show activity in this animal model (see figure 2).

Figure 2: Activity of compound "Example 2" in the rat Vogel conflict drinking test.

Biological Assays 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, 5×10^4 cells/well were seeded in poly-D-lysine coated, black/clear-bottomed 96-well plates. The cells were loaded with 2.5 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 EC₂₀ 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

5 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

10 EC₅₀, 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 EC₅₀ (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.

15 Positive signals obtained during the pre-incubation with the PAM test compounds (i.e. before application of an EC₂₀ 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 EC₂₀ concentration of L-glutamate was indicative of an inhibitory activity of the test compound.

20 In the list of examples below are shown the corresponding results for compounds which all have EC₅₀ values less or equal 100 nM.

WO2011128279 = Ref. 1

Example	mGlu5 PAM EC₅₀ [nM]	Efficacy [%]
Ref.1; Ex.106	30	42
Ref.1; Ex.109	18	37
Ex.1	inactive	
Ex.2	inactive	
Ex.3	inactive	
Ex. 4	inactive	

MPEP binding assay:

For binding experiments, cDNA encoding human mGlu 5a receptor was transiently transfected into EBNA cells using a procedure described by Schlaeger and Christensen [Cytotechnology 15:1-13 (1998)]. Cell membrane homogenates were stored at -80°C until the day of assay where upon they were thawed and resuspended and polytronised in 15 mM Tris-HCl, 120 mM NaCl, 100 mM KCl, 25 mM CaCl₂, 25 mM MgCl₂ binding buffer at pH 7.4 to a final assay concentration of 20 µg protein/ well.

Saturation isotherms were determined by addition of twelve [³H]MPEP concentrations (0.04-100 nM) to these membranes (in a total volume of 200 µl) for 1 h at 4°C. Competition experiments were performed with a fixed concentration of [³H]MPEP (2nM) and IC₅₀ values of test compounds evaluated using 11 concentrations (0.3-10,000nM). Incubations were performed for 1 h at 4° C.

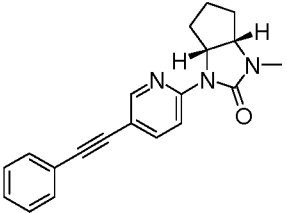
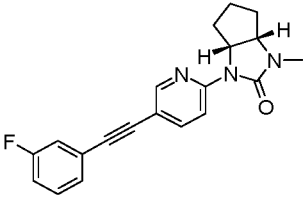
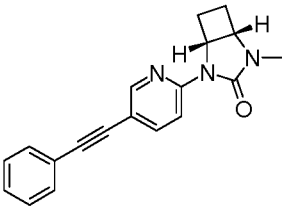
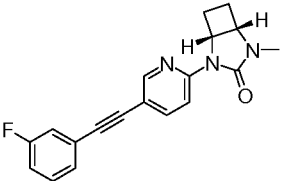
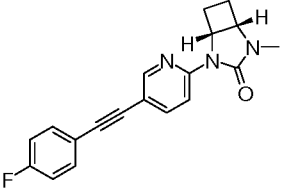
At the end of the incubation, membranes were filtered onto unifilter (96-well white microplate with bonded GF/C filter preincubated 1 h in 0.1% PEI in wash buffer, Packard BioScience, Meriden, CT) with a Filtermate 96 harvester (Packard BioScience) and washed 3 times with cold 50 mM Tris-HCl, pH 7.4 buffer. Nonspecific binding was measured in the presence of 10 µM MPEP. The radioactivity on the filter was counted (3 min) on a Packard Top-count microplate scintillation counter with quenching correction after addition of 45 µl of microscint 40 (Canberra Packard S.A., Zürich, Switzerland) and shaking for 20 min.

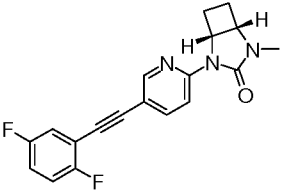
In the list of examples below are shown the corresponding results for compounds which all have EC₅₀ values less or equal to 20 nM.

Example	mGlu5-MPEP binding EC₅₀ (nM)
Ref.1; Ex.106	8
Ref.1; Ex.109	12
1	9
2	5
3	4
4	3

Comparison of the compounds of the invention versus the most similar compounds described in WO2011128279, examples 106 and 109:

As can be seen in the table below, the compounds of the invention show a clearly different profile compared to structurally similar compounds of prior art which is an advantage when
5 compounds showing NAM activity are desired.

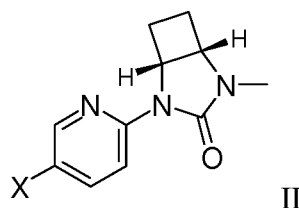
Ex.	Structure	EC ₅₀ (nM) mGlu5 PAM assay	Ki (nM) MPEP binding	Activity profile
Ref.1 Ex.106		30	8	PAM
Ref.1 Ex. 109		18	37	PAM
1		inactive	9	NAM
2		inactive	5	NAM
3		inactive	4	NAM

4		inactive	3	NAM
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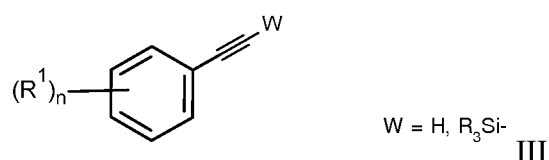
The compounds of formula I can be manufactured by the methods given below, by the methods given in the examples or by analogous methods. Appropriate reaction conditions for the individual reaction steps are known to a person skilled in the art. The reaction sequence is not limited to the one displayed in the schemes, however, depending on the starting materials and their respective reactivity the sequence of reaction steps can be freely altered. Starting materials are either commercially available or can be prepared by methods analogous to the methods given below, by methods described in references cited in the description or in the examples, or by methods known in the art.

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

reacting a compound of formula II

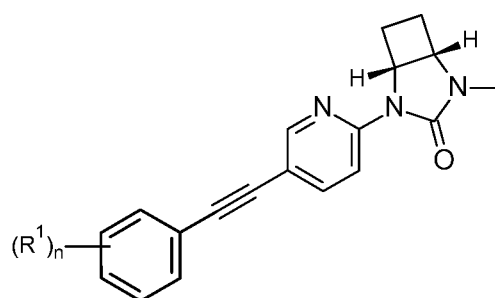


wherein X is a halogen atom selected from bromine or iodine
with a suitable aryl-acetylene of formula III



to form a compound of formula I

-9-



I

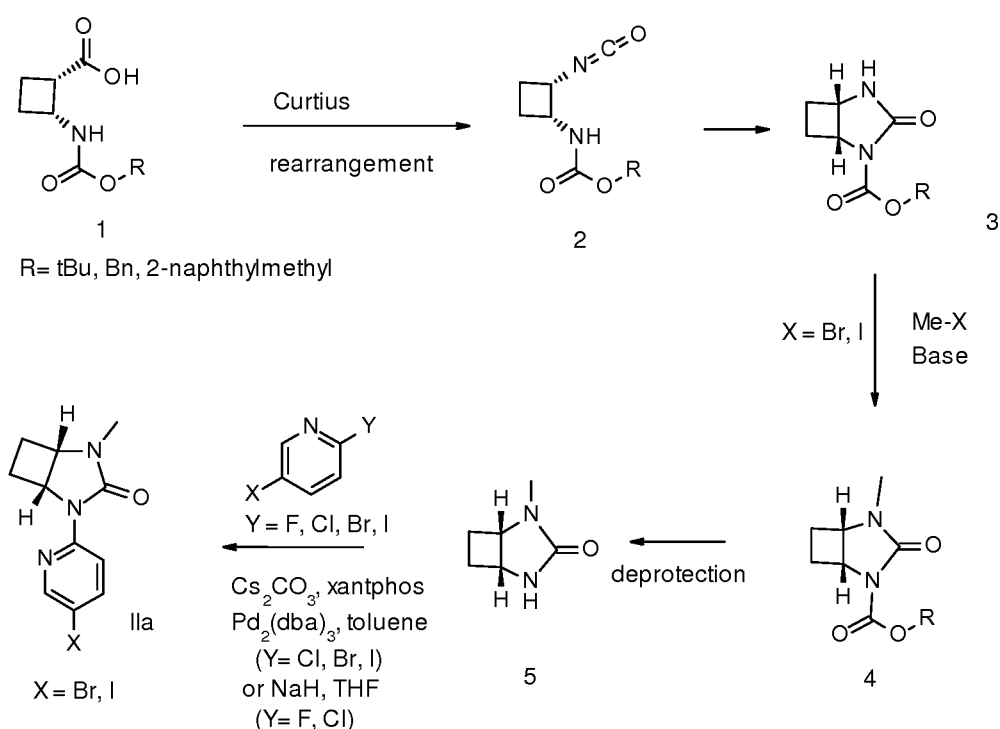
wherein the substituent R^1 is described above, in enantiomerically pure form with the absolute stereochemistry as drawn in formula I or by using II in racemic form followed by chiral separation of I to yield the optically pure enantiomer; and

- 5 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 3 and in examples 1 – 4.

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Scheme 1

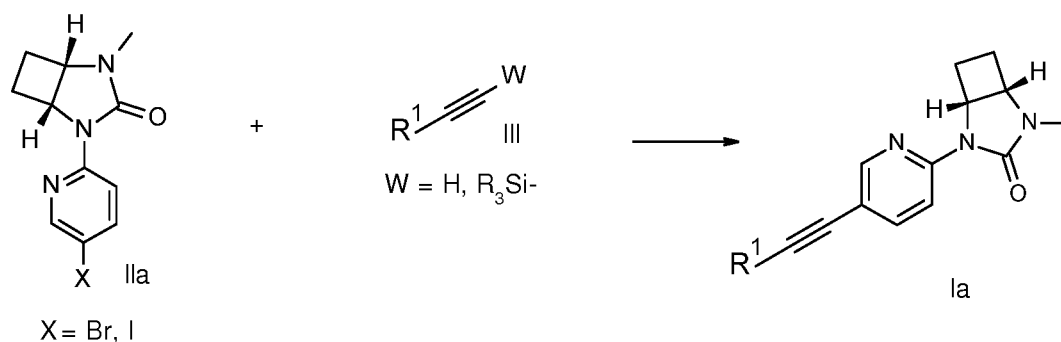


The synthesis of compounds of formula IIa is described in scheme 1. A halo-pyridine compound of formula IIa can be obtained by a Palladium catalyzed reaction of an appropriate dihalogenated pyridine such as 2-bromo-5-iodo-pyridine with an appropriately substituted cyclic urea of formula 5 (scheme 1). Reaction of a 2-chloro- or 2-fluoro-pyridine having a bromine or

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iodine in position 5 with a bicyclic urea of formula **5** can also form a compound of formula **IIa** by an aromatic nucleophilic substitution reaction using basic conditions such as for example NaH/THF or Cesium carbonate/DMF. The compound of formula **5** can be obtained starting from an appropriately protected 2-amino-1-carboxylic acid of formula **1** which can be obtained using procedures similar to those described by Gorrea & al., Tetrahedron asymmetry, 21, 339(2010). The acid function of **1** is transformed via an acylazide intermediate into the corresponding isocyanate **2** (Curtius rearrangement) which then cyclizes to form the bicyclic urea compound **3**. The free NH group of **3** can be methylated according to standard procedures to form compound **4** which is then deprotected to yield the cyclic urea **5**. It is also possible to obtain optically pure intermediates **2** to **5** starting from an optically pure protected acid of formula **1** or by separation of the racemic mixture at any stage of the synthesis using procedures known to persons skilled in the art.

Scheme 2



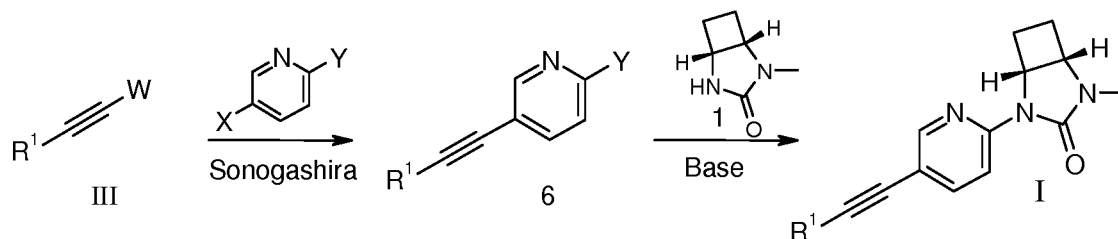
Wherein R¹ in this scheme means phenyl substituted by (R¹)_n.

The compound of formula IIa (X = Br, I) may react with a suitable aryl-acetylene of formula III (where W is either hydrogen or an in-situ cleavable protecting group such as a trialkylsilyl- or arylalkylsilyl-group, preferably hydrogen or trimethylsilyl) under Palladium catalyzed coupling conditions (Sonogashira reaction) to form a compound of formula Ia, wherein the substituent R¹ is described above. Another possibility consists of reacting IIa with trimethylsilyl acetylene to yield a compound of formula Ia where R¹ is trimethylsilyl and then do a second Sonogashira reaction with an appropriate aryl bromide or aryl iodide to yield a compound of formula I (scheme not shown).

In the case where the amino acid derivative 1 is in racemic form, the enantiomers can be separated at any given stage during the synthesis of compounds of formula I using procedures known to persons skilled in the art.

It is also possible to invert the sequence of reactions leading to compounds of formula I (scheme 3). In this case, the Sonogashira reaction between the arylacetylene derivative III and the dihalo-pyridine is performed first to yield an arylacetylene-pyridine compound of formula 6 which is then condensed with the bicyclic urea 1 to yield compounds of formula I.

Scheme 3



Wherein R¹ in this scheme means phenyl substituted by (R¹)_n.

Pharmaceutically acceptable salts of compounds of formula I can be manufactured readily according to methods known per se and taking into consideration the nature of the compound to be converted into a salt. Inorganic or organic acids such as, for example, hydrochloric acid, hydro-bromic acid, sulphuric acid, nitric acid, phosphoric acid or citric acid, formic acid, fumaric acid, maleic acid, acetic acid, succinic acid, tartaric acid, methane sulphonic acid, p-toluene sulphonic acid and the like are suitable for the formation of pharmaceutically acceptable salts of basic compounds of formula I. Compounds which contain the alkali metals or alkaline earth metals, for example sodium, potassium, calcium, magnesium or the like, basic amines or basic amino acids are suitable for the formation of pharmaceutically acceptable salts of acidic compounds.

The compounds of formula I and their pharmaceutically acceptable salts are, as already mentioned above, metabotropic glutamate receptor antagonists and can be used for the treatment or prevention of mGluR5 receptor mediated disorders, such as acute and/or chronic neurological disorders, cognitive disorders and memory deficits, as well as acute and chronic pain. Treatable neurological disorders are for instance epilepsy, schizophrenia, anxiety, acute, traumatic or chronic degenerative processes of the nervous system, such as Alzheimer's disease, senile dementia, Huntington's chorea, ALS, multiple sclerosis, dementia caused by AIDS, eye injuries, retinopathy, idiopathic parkinsonism or parkinsonism caused by medicaments as well as

conditions which lead to glutamate-deficient functions, such as e.g. muscle spasms, convulsions, migraine, urinary incontinence, nicotine addiction, psychoses, opiate addiction, anxiety, vomiting, dyskinesia and depression. Other treatable indications 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.

The compounds of formula I and their pharmaceutically acceptable salts are especially useful as analgesics. Treatable kinds of pain include inflammatory pain such as arthritis and rheumatoid disease, vasculitis, neuropathic pain such as trigeminal or herpetic neuralgia, diabetic neuropathy pain, causalgia, hyperalgesia, severe chronic pain, post-operative pain and pain associated with various conditions like cancer, angina, renal or biliary colic, menstruation, migraine and gout.

The pharmacological activity of the compounds was tested using the following method:

cDNA encoding rat mGlu 5a receptor was transiently transfected into EBNA cells using a procedure described by E.-J. Schlaeger and K. Christensen (*Cytotechnology* 1998, 15, 1-13). [Ca²⁺]_i measurements were performed on mGlu 5a transfected EBNA cells after incubation of the cells with Fluo 3-AM (obtainable by FLUKA, 0.5 μM final concentration) for 1 hour at 37°C followed by 4 washes with assay buffer (DMEM supplemented with Hank's salt and 20 mM HEPES). [Ca²⁺]_i measurements were done using a fluorometric imaging plate reader (FLIPR, Molecular Devices Corporation, La Jolla, CA, USA). When compounds were evaluated as antagonists they were tested against 10 μM glutamate as agonist.

The inhibition (antagonists) curves were fitted with a four parameter logistic equation giving IC₅₀, and Hill coefficient using the iterative non-linear curve fitting software Origin (Microcal Software Inc., Northampton, MA, USA).

The K_i values of the compounds tested are given. The K_i value is defined by the following formula:

$$K_i = \frac{IC_{50}}{1 + \frac{[L]}{EC_{50}}}$$

in which the IC₅₀ values are those concentrations of the compounds tested in μM by which 50 % of the effect of compounds are antagonized. [L] is the concentration and the EC₅₀ value is the concentration of the compounds in μM which brings about 50 % stimulation.

The compounds of the present invention are mGluR 5a receptor antagonists. The activities of compounds of formula I as measured in the assay described above are in the range of $K_i < 100 \mu\text{M}$.

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.

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 0.01-10 mg/kg/day, with a dosage of 0.1-5 mg/kg/day being preferred

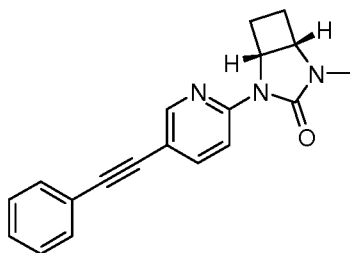
for all of the indications described. The daily dosage for an adult human being weighing 70 kg accordingly lies between 0.7-700 mg per day, preferably between 7 and 350 mg per day.

The following examples are provided to further elucidate the invention:

5

Example 1

(-)-(1S,5R)-2-methyl-4-(5-(phenylethynyl)pyridin-2-yl)-2,4-diazabicyclo[3.2.0]heptan-3-one



Step 1: (rac)-(1SR,2RS)-2-(Naphthalen-2-ylmethoxycarbonylamino)cyclobutanecarboxylic acid methyl ester:

- 10 To a well stirred solution of (rac)-(cis)-(1RS,2SR)-cyclobutane-1,2-dicarboxylic acid monomethyl ester (CAS: 31420-52-7) (10.8 g, 68.3 mmol), and N-methylmorpholine (7.6 g, 8.26 ml, 75.1 mmol) in 160 ml of 1,2-dichloroethane was added dropwise diphenylphosphoryl azide (20.7 g, 16.2 ml, 75.1 mmol). After stirring for 10 min at room temperature, the reaction was warmed to 60°C. 2-Naphthylmethyl alcohol (10.8 g, 68.3 mmol) and copper(I)chloride (68 mg,
- 15 0.68 mmol) were added and the reaction was stirred for another 16 h at 60°C. The reaction was concentrated in vacuo, the light brown oily residue (51 g) was diluted with 15 ml of dichloromethane and purified by flash chromatography on silicagel (SiO₂ (650g), Ethyl acetate/heptane 20:80) to yield 16.8 g of impure material containing unreacted naphthylmethanol. The material was repurified (Aminophase, 0% to 35% ethylacetate in
- 20 heptane gradient) to yield 11.1 g (52%) of the title compound as a white crystalline solid, MS: m/e = 314.2 (M+H⁺).

Step 2: (rac)-(1SR,2RS)-2-(Naphthalen-2-ylmethoxycarbonylamino)cyclobutanecarboxylic acid

- To a well stirred solution of (rac)-(1SR,2RS)-2-(naphthalen-2-ylmethoxycarbonylamino) cyclobutanecarboxylic acid methyl ester (*Example 1, step 1*) (4.2 g, 13.4 mmol), in 20 ml of dioxane was added water (70 ml). The solution was cooled to 5°C and 53.6 ml (26.8 mmol) of 0.5M sodium hydroxide solution were added dropwise over a period of 5 min. After stirring for 1h at 5°C, the reaction was allowed to warm up to room temperature with vigorous stirring. The clear solution was then cooled to 5°C and the pH was adjusted to 2.5 by addition of ca. 13 ml 2N
- 25

hydrochloric acid solution. The reaction was worked up with ethyl acetate. After drying, filtration and concentration in vacuo, 3.87 g (97%) of the title compound was obtained as a crystalline white solid, MS: $m/e = 300.2$ ($M+H^+$).

Step 3: (rac)-(1RS,5SR)-3-Oxo-2,4-diaza-bicyclo[3.2.0]heptane-2-carboxylic acid

5 naphthalen-2-ylmethyl ester

A solution of (rac)-(1SR,2RS)-2-(naphthalen-2-ylmethoxycarbonylamino)cyclobutane-carboxylic acid (*Example 1, step 2*) (2.34 g, 7.82 mmol) and N-methylmorpholine (0.79 g, 0.86 ml, 7.82 mmol) in 34 ml of dichloroethane was stirred at r.t. for 10 min. Then diphenylphosphoric acid azide (2.15 g, 1.69 ml, 7.82 mmol) was added dropwise at room temperature and the colorless solution was stirred for 1 h at room temperature during which the solution turned light yellow. The solution was then warmed to 50°C, stirred for 6 h and allowed to cool. After workup with dichloromethane/water, the combined organic phases were evaporated to dryness to yield a yellow solid which was recrystallized from ethyl acetate/heptane. The title compound (1.86 g, 80%) was obtained as a white crystalline solid, MS: $m/e = 297.3$ ($M+H^+$).

Step 4: (rac)-(1RS,5SR)-4-Methyl-3-oxo-2,4-diaza-bicyclo[3.2.0]heptane-2-carboxylic acid naphthalen-2-ylmethyl ester

To a solution of (rac)-(1RS,5SR)-3-Oxo-2,4-diaza-bicyclo[3.2.0]heptane-2-carboxylic acid naphthalen-2-ylmethyl ester (*Example 1, step 3*) (1.13 g, 3.81 mmol) in 11 ml of DMF was added a 60% suspension of sodium hydride in mineral oil (0.198 g, 4.96 mmol). The suspension was stirred for 35 minutes at room temperature (gas evolution), then iodomethane (0.81 g, 0.36 ml, 5.72 mmol) was added and the mixture was stirred at room temperature overnight. After quenching by addition of 3 ml sat. ammonium chloride solution and concentration in vacuo, the residue was worked up with ethyl acetate/water. The combined organic phases were dried and concentrated in vacuo. The residue was purified by flash chromatography on silicagel (50 g) eluting with a 20–100% ethyl acetate in heptane gradient to yield 0.98 g (82%) of a colorless oil, MS: $m/e = 311.2$ ($M+H^+$).

Step 5: (rac)-(1SR,5RS)-2-Methyl-2,4-diaza-bicyclo[3.2.0]heptan-3-one

A solution of (rac)-(1RS,5SR)-4-Methyl-3-oxo-2,4-diaza-bicyclo[3.2.0]heptane-2-carboxylic acid naphthalen-2-ylmethyl ester (*Example 1, step 4*) (0.97 g, 3.13 mmol) in 15 ml of methanol was hydrogenated for 48 h over 10% Pd/C (0.333 g, 0.313 mmol). The solution was purged with argon, the catalyst was filtered off and washed with ethyl acetate. The filtrate was concentrated in vacuo. The residue was purified by flash chromatography on silicagel (20 g) eluting with a

50–100% ethyl acetate in heptane gradient to yield 0.375 g (95%) of the title compound as a crystalline white solid, which was directly used in the next step without further characterisation.

Step 6: (rac)-(1RS,5SR)-2-(5-Iodo-pyridin-2-yl)-4-methyl-2,4-diaza-

5 bicyclo[3.2.0]heptan-3-one

To a solution of (rac)-(1SR,5RS)-2-methyl-2,4-diaza-bicyclo[3.2.0]heptan-3-one (*Example 1, step 5*) (375 mg, 2.97 mmol) and 2-fluoro-5-iodopyridine (683 mg, 3.06 mmol) in DMF (10 ml) was added a 60% suspension of sodium hydride in mineral oil (155 mg, 3.86 mmol). The reaction was stirred at room temperature overnight. After quenching by addition of 3 ml sat.

10 ammonium chloride solution and concentration in vacuo to eliminate the DMF, the residue was worked up with ethyl acetate/water. After drying and concentration in vacuo, the residue was purified by flash chromatography (SiO₂, 20g) using a 0% to 65% ethyl acetate in heptane gradient. One obtains the title compound, (549 mg, 56%), as a crystalline white solid, MS: m/e = 330.1 (M+H⁺).

15 Step 7: (rac)-(+/-)-(1SR,5RS)-2-Methyl-4-(5-(phenylethynyl)pyridin-2-yl)-2,4-diazabicyclo[3.2.0]heptan-3-one

In a 5 ml microwave tube were dissolved 110mg (0.33 mmol) of (rac)-(1RS,5SR)-2-(5-iodo-pyridin-2-yl)-4-methyl-2,4-diaza-bicyclo[3.2.0]heptan-3-one (*Example 1, step 6*) in 1.5 ml DMF. Argon was bubbled through the solution. Ethynylbenzene (73 µl, 68 mg, 0.67 mmol),
20 Bis(triphenylphosphine)palladium(II) chloride (14 mg, 20 µmol), copper (I) iodide (1.9 mg, 10.0 µmol), Triphenylphosphine (1.8 mg, 7.7 µmol) and 107 µl of Triethylamine (101 mg, 140 µl, 1.0 mmol) were added. The dark brown solution was stirred 3h at 60°C. The reaction was worked up with ethyl acetate/water, dried and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, 20g, 0% to 50% EtOAc in heptane gradient) to yield 95 mg (94%) of
25 the title compound as a light brown crystalline solid, MS: m/e = 304.2 (M+H⁺).

Step 8: (-)-(1S,5R)-2-Methyl-4-(5-(phenylethynyl)pyridin-2-yl)-2,4-diazabicyclo[3.2.0]heptan-3-one and (+)-(1R,5S)-2-methyl-4-(5-(phenylethynyl)pyridin-2-yl)-2,4-diazabicyclo[3.2.0]heptan-3-one

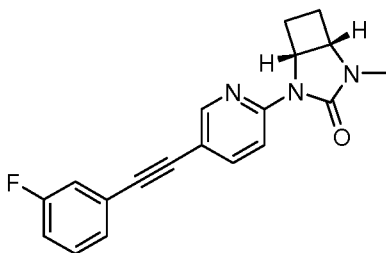
30 The racemic mixture of (rac)-(+/-)-(1SR,5RS)-2-methyl-4-(5-(phenylethynyl)pyridin-2-yl)-2,4-diazabicyclo[3.2.0]heptan-3-one (*Example 1, step 7*) (95mg) was separated by chiral HPLC: (Chiralpak AD® - 5 cm x 50 cm, 20 mM; 40% isopropanol/heptane, 35 ml/min, 18 Bar). Peak detection was realized using a UV-detector as well as an optical rotation detector (ORD) where one peak has a negative signal (the (-)-enantiomer), and the other peak has a positive signal (the

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(+)-enantiomer). The (-)-enantiomer, (-)-(1S,5R)-2-methyl-4-(5-(phenylethynyl)pyridin-2-yl)-2,4-diazabicyclo[3.2.0]heptan-3-one (39 mg) was obtained as a crystalline light yellow solid, MS: $m/e = 304.1$ ($M+H^+$). The (+)-enantiomer, (-)-(1R,5S)-2-methyl-4-(5-(phenylethynyl)pyridin-2-yl)-2,4-diazabicyclo [3.2.0]heptan-3-one (40 mg) was obtained as a light yellow solid, MS: $m/e = 304.1$ ($M+H^+$).

Example 2

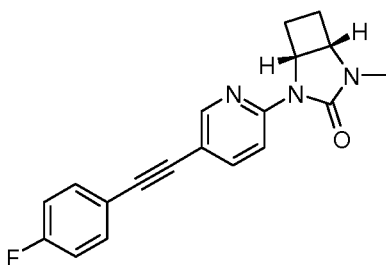
(-)-(1R,5S)-2-[5-(3-Fluoro-phenylethynyl)-pyridin-2-yl]-4-methyl-2,4-diazabicyclo [3.2.0]heptan-3-one



The title compound was prepared in accordance with the general method of Example 1, step 7 starting from (rac)-(1RS,5SR)-2-(5-iodo-pyridin-2-yl)-4-methyl-2,4-diazabicyclo[3.2.0]heptan-3-one (*Example 1, step 6*) (110 mg) and 1-ethynyl-3-fluorobenzene to yield 107 mg (96%) of racemic material ((+/-)-(1R,5S)-2-[5-(3-fluoro-phenylethynyl)-pyridin-2-yl]-4-methyl-2,4-diazabicyclo [3.2.0]heptan-3-one as a light yellow crystalline solid; MS: $m/e = 322.3$ ($M+H^+$) which was then separated by chiral HPLC using similar separation conditions as described in example 1, step 8 to yield the enantiomerically pure enantiomers (-)-(1R,5S)-2-[5-(3-fluoro-phenylethynyl)-pyridin-2-yl]-4-methyl-2,4-diazabicyclo[3.2.0] heptan-3-one as a light yellow solid, MS: $m/e = 322.3$ ($M+H^+$); and its enantiomer (+)-(1S,5R)-2-[5-(3-fluoro-phenylethynyl)-pyridin-2-yl]-4-methyl-2,4-diazabicyclo[3.2.0] heptan-3-one as a light yellow solid; MS: $m/e = 322.3$ ($M+H^+$).

Example 3

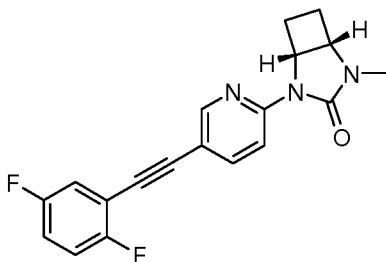
(-)-(1R,5S)-2-[5-(4-Fluoro-phenylethynyl)-pyridin-2-yl]-4-methyl-2,4-diazabicyclo[3.2.0] heptan-3-one



The title compound was prepared in accordance with the general method of Example 1, step 7 starting from (rac)-(1R,5SR)-2-(5-iodo-pyridin-2-yl)-4-methyl-2,4-diazabicyclo[3.2.0]heptan-3-one (*Example 1, step 6*) (110 mg) and 1-ethynyl-4-fluorobenzene to yield 104 mg (97%) of racemic material ((+/-)-(rac)-(1SR,5RS)-2-[5-(4-fluoro-phenylethynyl)-pyridin-2-yl]-4-methyl-2,4-diazabicyclo[3.2.0] heptan-3-one as a light yellow crystalline solid; MS: m/e = 322.3 (M+H⁺) which was then separated by chiral HPLC using similar separation conditions as described in example 1, step 8 to yield the enantiomerically pure enantiomers (-)-(1R,5S)-2-[5-(4-fluoro-phenylethynyl)-pyridin-2-yl]-4-methyl-2,4-diazabicyclo[3.2.0]heptan-3-one as a light yellow solid, MS: m/e = 322.3 (M+H⁺); and its enantiomer (+)-(1S,5R)-2-[5-(4-fluoro-phenylethynyl)-pyridin-2-yl]-4-methyl-2,4-diazabicyclo[3.2.0]heptan-3-one as a light yellow solid; MS: m/e = 322.3 (M+H⁺).

Example 4

(-)-(1R,5S)-2-[5-(2,5-Difluoro-phenylethynyl)-pyridin-2-yl]-4-methyl-2,4-diazabicyclo[3.2.0]heptan-3-one



15

The title compound was prepared in accordance with the general method of Example 1, step 7 starting from (rac)-(1R,5SR)-2-(5-iodo-pyridin-2-yl)-4-methyl-2,4-diazabicyclo[3.2.0]heptan-3-one (*Example 1, step 6*) (110 mg) and 2-ethynyl-1,4-difluorobenzene to yield 110 mg (97%) of racemic material ((+/-)-(rac)-(1SR,5RS)-2-[5-(2,5-difluoro-phenylethynyl)-pyridin-2-yl]-4-methyl-2,4-diazabicyclo[3.2.0] heptan-3-one as a light yellow crystalline solid; MS: m/e = 340.1 (M+H⁺) which was then separated by chiral HPLC using similar separation conditions as described in example 1, step 8 to yield the enantiomerically pure enantiomers (-)-(1R,5S)-2-[5-(2,5-difluoro-phenyl-ethynyl)-pyridin-2-yl]-4-methyl-2,4-diazabicyclo[3.2.0]heptan-3-one as a light yellow solid, MS: m/e = 340.1 (M+H⁺); and its enantiomer (+)-(1S,5R)-2-[5-(2,5-difluoro-phenyl-ethynyl)-pyridin-2-yl]-4-methyl-2,4-diazabicyclo[3.2.0]heptan-3-one as a light yellow solid; MS: m/e = 340.1 (M+H⁺).

25

Preparation of the pharmaceutical compositions:**Example I**

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

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

Example II

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

15		<u>mg/Tablet</u>
	Active ingredient	200
	Powdered. lactose	100
	White corn starch	64
	Polyvinylpyrrolidone	12
20	Na carboxymethylstarch	20
	Magnesium stearate	4
	Tablet weight	<u>400</u>

Example III

Capsules of the following composition are produced:

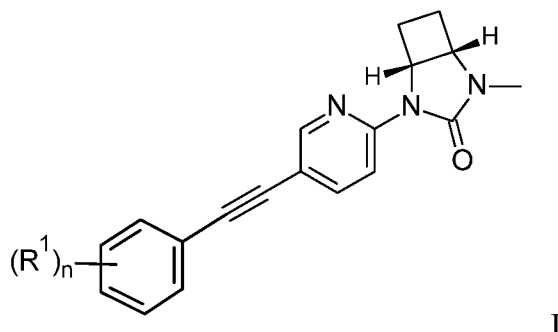
25		<u>mg/Capsule</u>
	Active ingredient	50
	Crystalline. lactose	60
	Microcrystalline cellulose	34
	Talc	5
30	Magnesium stearate	1
	Capsule fill weight	<u>150</u>

The active ingredient having a suitable particle size, the crystalline lactose and the microcrystalline cellulose are homogeneously mixed with one another, sieved and thereafter talc and magnesium stearate are admixed. The final mixture is filled into hard gelatine capsules of suitable size.

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Claims

1. A compound of formula I



wherein

5 R^1 is hydrogen or F;

n is 1 or 2

or a pharmaceutically acceptable acid addition salt thereof.

2. A compound of formula I according to claim 1, which compounds

10 are

(1S,5R)-2-methyl-4-(5-(phenylethynyl)pyridin-2-yl)-2,4-diazabicyclo[3.2.0]heptan-3-one

(1R,5S)-2-(5-((4-fluorophenyl)ethynyl)pyridin-2-yl)-4-methyl-2,4-diazabicyclo[3.2.0]
heptan-3-one

(1R,5S)-2-(5-((3-fluorophenyl)ethynyl)pyridin-2-yl)-4-methyl-2,4-diazabicyclo[3.2.0]

15 heptan-3-one or

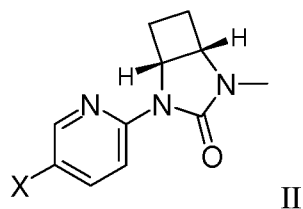
(1R,5S)-2-(5-((2,5-difluorophenyl)ethynyl)pyridin-2-yl)-4-methyl-2,4-diazabicyclo[3.2.0]
heptan-3-one.

3. A compound according to any one of claims 1 or 2 for use as therapeutically active
20 substance.

4. A process for preparation of a compound of formula I according to any one of claims
1 or 2, comprising the variant

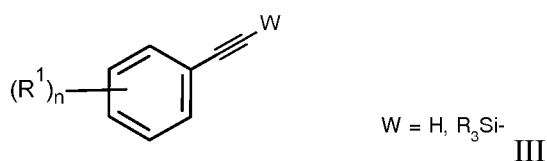
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reacting a compound of formula II

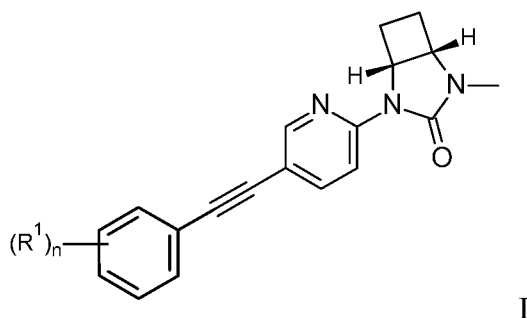


wherein X is a halogen atom selected from bromine or iodine

5 with a suitable aryl-acetylene of formula III



to form a compound of formula I



wherein the substituent R¹ is described above, in enantiomerically pure form with the absolute
 10 stereochemistry as drawn in formula I or by using II in racemic form followed by chiral
 separation of I to yield the optically pure enantiomer; and
 if desired, converting the compounds obtained into pharmaceutically acceptable acid addition
 salts.

15 5. A pharmaceutical composition comprising a compound in accordance with any one of
 claims 1 or 2 and a therapeutically active carrier.

6. The use of a compound according to any one of claims 1 or 2 for the treatment of anxiety
 and pain, depression, Fragile-X syndrome, autism spectrum disorders, Parkinson's disease, and
 20 gastro-esophageal reflux disease (GERD).

7. The use of a compound as claimed in any one of claims 1 or 2 for the manufacture of a medicament for the treatment of anxiety and pain, depression, Fragile-X syndrome, autism spectrum disorders, Parkinson's disease, and gastro-esophageal reflux disease (GERD).

5 8. A compound according to any one of claims 1 or 2 for use in the treatment of anxiety and pain, depression, Fragile-X syndrome, autism spectrum disorders, Parkinson's disease, and gastro-esophageal reflux disease (GERD).

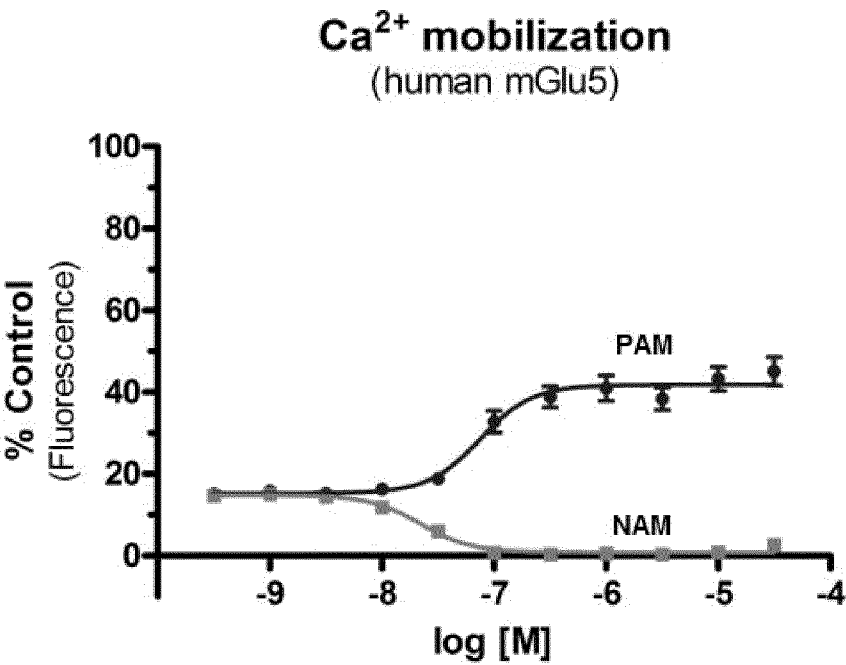
9. A method for the treatment of anxiety and pain, depression, Fragile-X syndrome, autism
10 spectrum disorders, Parkinson's disease, and gastro-esophageal reflux disease (GERD), which method comprises administering an effective amount of a compound as defined in any one of claims 1 or 2.

10. The invention as herein before described.

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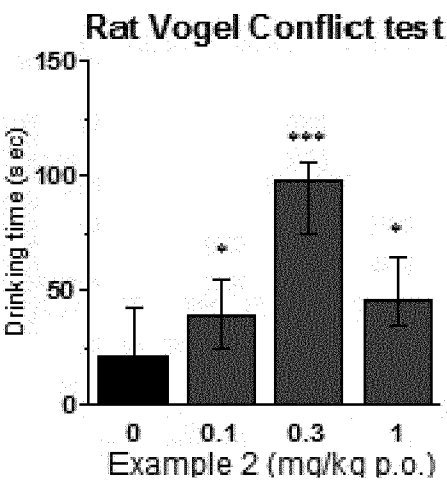
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Figure 1



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Figure 2



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/062202

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D401/04 A61K31/4439 A61P25/00 A61P1/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2011/128279 A1 (HOFFMANN LA ROCHE [CH]; GREEN LUKE [CH]; GUBA WOLFGANG [DE]; JAESCHKE) 20 October 2011 (2011-10-20) cited in the application abstract pages 18-24 pages 9-11 page 25, lines 4-16 examples 1-174 claims 1-30 ----- -/--	1-10



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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Date of the actual completion of the international search

17 August 2016

Date of mailing of the international search report

26/08/2016

Name and mailing address of the ISA/

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Authorized officer

Dunet, Guillaume

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2016/062202

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	WO 2007/035823 A2 (MOLECULAR NEUROIMAGING LLC [US]; TAMAGNAN GILLES D [US]; ALAGILLE DAVI) 29 March 2007 (2007-03-29) abstract pages 4-5 examples 1-7 figure 1 claims 1-13 -----	1-10
A	DAVID ALAGILLE ET AL: "Potent mGluR5 antagonists: Pyridyl and thiazolyl-ethynyl-3,5-disubstituted-phenyl series", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, AMSTERDAM, NL, vol. 21, no. 11, 12 April 2011 (2011-04-12), pages 3243-3247, XP028211456, ISSN: 0960-894X, DOI: 10.1016/J.BMCL.2011.04.047 [retrieved on 2011-04-20] abstract page 3243; figure 1 * Scheme 1 *; page 3244 * Scheme 2 *; page 3245 page 3245; table 1 -----	1-10
A	BACH P ET AL: "Metabotropic glutamate receptor 5 modulators and their potential therapeutic applications", EXPERT OPINION ON THERAPEUTIC PATENTS, INFORMA HEALTHCARE, GB, vol. 17, no. 4, April 2007 (2007-04), pages 371-384, XP002549979, ISSN: 1354-3776, DOI: 10.1517/13543776.17.4.371 abstract page 372; compounds 1-4 page 374; compounds 13-18 page 378; compounds 48, 49 page 379; compounds 50-52, 54 page 380; compounds 60, 61 ----- -/--	1-10

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/062202

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2014/026880 A1 (HOFFMANN LA ROCHE [CH]; HOFFMANN LA ROCHE [US]) 20 February 2014 (2014-02-20) abstract examples 1-11 claims 1-12 -----	1-10
A	WO 2014/060384 A1 (HOFFMANN LA ROCHE [CH]; HOFFMANN LA ROCHE [US]) 24 April 2014 (2014-04-24) abstract examples 1-4 claims 1-13 -----	1-10

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2016/062202

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