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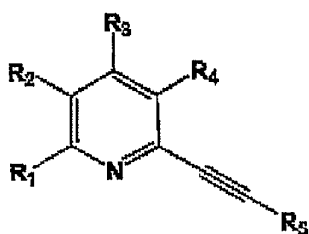
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(54) Title: NOVEL AMINOPYRIDINE DERIVATIVES AS mGluR5 ANTAGONISTS



(I)

(57) Abstract: The invention relates to novel aminopyridine derivatives of formula (I) wherein R₁ is methyl an R₄ and amino group NR₆R₇ and R₅ forms an arylalkynyl- or heteroarylalkynyl-group. The compounds are useful in the prevention or treatment of central nervous system disorders as well as other disorders modulated by mGluR5 receptors.

NOVEL AMINOPYRIDINE DERIVATIVES AS mGluR5 ANTAGONISTS

Extensive literature exists relating to pyridine compounds however there is very little data concerning 3-amino-2-arylalkynyl-, 3-amino-2-heteroarylalkynyl-pyridine derivatives which are agents of the invention.

The present invention relates to substituted 3-amino arylalkynyl-pyridines and 3-amino heteroarylalkynyl-pyridines.

US-patent N° 6,384,235B2 and Rodriguez et al. Angewandte Chemie, International Edition 2000, 39, 14, 2488-2490 describes 3-amino-(2-phenylethynyl)pyridine as synthetic intermediates. WO 99/40091 discloses certain 3-amino-(2-phenylethynyl) pyridines as synthetic intermediates which are subsequently ring closed.

WO 99/02497 describes certain 2-heteroalkynyl pyridines as modulating mGluRs and a very broad generic disclosure. However, none of the specifically disclosed compounds are 3-amino-2-aryl or heteroaryl ethynyl pyridines. WO 02/46166 describes various compounds having the structure phenyl-A-B as mGluR antagonists but it has no disclosure of phenyl ethynylpyridines.

The already known structure in the field of mGluR5 ligands like 2-methyl-6-(phenylethynyl)-pyridine (MPEP) suffer from poor bioavailability and selectivity (R. Kuhn et al. Amino Acids, 2002, 23, 207-211; N.D.P. Cosford et al. J. Med. Chem. 2003, 46, 204-206).

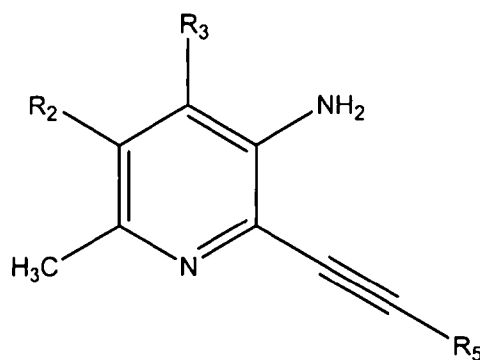
It has now surprisingly been found that amino pyridine compounds of the invention show potent activity and selectivity on mGluR5 receptor and demonstrate advantageous properties over compounds of the prior art. Improvements have been observed in one or more of the following characteristics of the compounds of the invention: the selectivity for the target, the solubility, the bioavailability, the brain penetration, the activity in behavioural models of psychiatric and neurological disorders. They can be used in the treatment or prevention of mGluR5 mediated disorders.

L-glutamate is the main excitatory neurotransmitter in the mammalian brain and acts through two heterogeneous families of receptors: ionotropic and metabotropic glutamate receptors (mGluR) (Nakanishi S et al. 1998, Brain Res Brain Res Rev., 26:230-235). To date eight subtypes of mGluR have been cloned and classified into three groups on the basis of sequence similarities and pharmacological properties. mGluR1 and mGluR5 belong to group I and initiate cellular responses through a G-protein mediated mechanism and are coupled to phospholipase C and stimulate phosphoinositide hydrolysis (Schoepp DD et al. 1999, Neuropharmacology, 38:1431-1476).

The mGluR5 receptor protein has been localized peripherally in structures involved in nociceptive transmission and recent findings suggest that mGluR5 antagonists can be used for the treatment of inflammatory and neuropathic pain, chronic and acute pain (B.A. Chizh in Amino Acids 2002, 23, 169-176).

mGluR5 receptors are also abundant in CNS throughout cortex, hippocampus, caudate-putamen and nucleus accumbens. As these brain areas are thought to be involved in emotional and motivational processes, the mGluR5 receptor has been considered a potential drug target for treatment of psychiatric and neurological disorders. Treatable diseases are psychosis, epilepsy, schizophrenia, Alzheimer's disease, cognitive disorders, memory deficits, Parkinson's disease, hypoxia, ischemia, dementia caused by AIDS, migraine, depression, mood disorders and anxiety disorders. Other treatable indications are nicotine, cocaine, amphetamine, benzodiazepine, opiate or alcohol abuse or addiction and substance tolerance or dependence, bulimia nervosa, anorexia nervosa, gambling dependence, smoking, sex dependence or obsessive compulsive disorders (Brauner-Osborne H *et al.*, 2000, *J Med Chem.* **43**: 2609-45; Bordi F and Ugolini A. 1999, *Prog Neurobiol.* **59**: 55-79; Spooren W *et al.* 2003, *Behav Pharmacol*: **14**: 257-77).

According to a first embodiment of the invention, there is provided a compound of the formula:



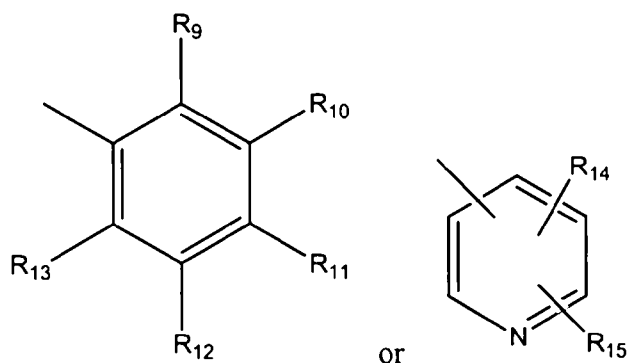
I-A

wherein

R₂ and R₃ are independently selected from hydrogen, C₁-C₆-alkyl;

R₅ represents a group of formula:

2a



wherein

- 5 R₉, R₁₀, R₁₁, R₁₂ and R₁₃ independently are hydrogen, halogen, cyano, nitro, C₁-C₆-alkyl, halo-C₁-C₆-alkyl, C₁-C₆-alkoxy, carboxy-C₁-C₆-alkyl or carboxyaryl;
 R₁₄ and R₁₅ independently are as defined for R₉ - R₁₃ above;

or pharmaceutical acceptable salts, hydrates or solvates of such compounds.

10 According to a second embodiment of the invention, there is provided a pharmaceutical composition comprising a therapeutically effective amount of a compound in accordance with the first embodiment of the present invention and a pharmaceutically acceptable carrier and/or excipient.

15 According to a third embodiment of the invention, there is provided a method of treating or preventing a condition in a mammal, including a human, the treatment or prevention of which is affected or facilitated by the neuromodulatory effect of mGluR5 antagonists, comprising administering to a mammal in need of such treatment or prevention, an effective amount of a compound in accordance with the first embodiment of the present invention or the composition in accordance with the second embodiment of the present invention.

20 According to a fourth embodiment of the invention, there is provided a method useful for treating or preventing central nervous system disorders selected from: tolerance or dependence, depression, bipolar disorder, psychiatric disease such as psychotic disorders, attention-deficit/hyperactivity disorder, Parkinson's disease, memory impairment, Alzheimer's disease, dementia, delirium tremens, neurodegeneration, neurotoxicity, ischemia comprising administering to a mammal in need of such treatment
 25 or prevention, an effective amount of a compound in accordance with the first

embodiment of the present invention or the composition in accordance with the second embodiment of the present invention.

According to a fifth embodiment of the invention, there is provided a method useful for treating or preventing inflammatory or neuropathic pain comprising administering to a mammal in need of such treatment or prevention, an effective amount of a compound in accordance with the first embodiment of the present invention which substantially does not penetrate the central nervous system.

According to a sixth embodiment of the invention, there is provided a method of treating or preventing substance tolerance or dependence, bulimia nervosa, anorexia nervosa, gambling dependence, smoking dependence, sex dependence, substance withdrawal or obsessive compulsive disorders comprising administering to a mammal in need of such treatment or prevention, an effective amount of a compound in accordance with the first embodiment of the present invention or the composition in accordance with the second embodiment of the present invention.

According to a seventh embodiment of the invention, there is provided a method useful for treating or preventing alcohol, nicotine, cocaine, amphetamine, benzodiazepine, opiate or alcohol abuse or addiction comprising administering to a mammal in need of such treatment or prevention, an effective amount of a compound in accordance with the first embodiment of the present invention or the composition in accordance with the second embodiment of the present invention.

According to an eighth embodiment of the invention, there is provided a method useful for treating or preventing anxiety, panic disorder, phobia, posttraumatic stress disorder, generalized anxiety disorder, acute stress disorder comprising administering to a mammal in need of such treatment or prevention, an effective amount of a compound in accordance with the first embodiment of the present invention or the composition in accordance with the second embodiment of the present invention.

According to a ninth embodiment of the invention, there is provided a method useful for treating or preventing migraine comprising administering to a mammal in need of such treatment or prevention, an effective amount of a compound in accordance with the first embodiment of the present invention or the composition in accordance with the second embodiment of the present invention.

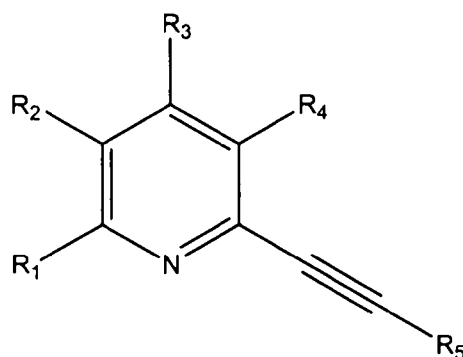
According to a tenth embodiment of the invention, there is provided the use of a compound of any one of formula I-A, I-B or I-C in accordance with the first embodiment of the present invention for the preparation of a medicament for treatment or prevention

2c

of a condition in a mammal, the treatment or prevention of which is affected or facilitated by the neuromodulatory effect of mGluR5 antagonists.

The present invention relates to a method of treating or preventing a condition in a mammal, including a human, the treatment or prevention of which is affected or facilitated by the neuromodulatory effect of mGluR5 antagonists.

The present invention is concerned with novel aminopyridine derivatives, and their uses, which conform to the general formula:

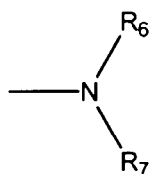


I

wherein

R₁ is methyl

R₂ and R₃ are independently selected from hydrogen, halogen, nitro, C₁-C₆-alkyl;

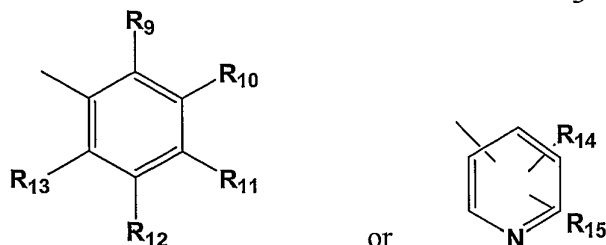


R₄ is

R₆ and R₇

which may be the same or different are hydrogen or a group of formula:
 —X—R₈ wherein X is =CH-N(R₈)₂ and R₈ is hydrogen, C₁-C₆-alkyl, halo-C₁-C₆-alkyl, aryl, aryl-C₁-C₆-alkyl, heteroaryl or heteroaryl-C₁-C₆-alkyl;

R₅ represents a group of formula:



wherein

R₉, R₁₀, R₁₁, R₁₂ and R₁₃ independently are hydrogen, halogen, cyano, nitro, C₁-C₆-alkyl, halo-C₁-C₆-alkyl, C₁-C₆-alkoxy, carboxy-C₁-C₆-alkyl or carboxyaryl;

R₁₄ and R₁₅ independently are as defined for R₉ – R₁₃ above;

or pharmaceutically acceptable salts, hydrates or solvates of such compounds for the prevention or treatment of central nervous system (CNS) disorders as well as other disorders modulated by mGluR5 receptors.

In the above definition, the term "C₁-C₆-alkyl" includes groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, tert-pentyl, hexyl or the like.

"Hydroxy-C₁-C₆-alkyl" includes groups such as hydroxymethyl, 2-hydroxyethyl, 3-hydroxypropyl, 4-hydroxybutyl, 5-hydroxypentyl, 6-hydroxyhexyl and the like.

"C₁-C₆-alkoxy" includes groups such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentyloxy, hexyloxy or the like.

"Halogen" includes atoms such as fluorine, chlorine and iodine.

"Halo-C₁-C₆-alkyl" includes groups such as chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, bromomethyl, 1-chloroethyl, 1,1-dichloroethyl, 2-chloroethyl, 2,2,2-trichloroethyl, 1-fluoroethyl, 1,1-difluoroethyl, 2-fluoroethyl, 2,2,2-trifluoroethyl, 2-bromoethyl, 3-chloropropyl, 3-fluoropropyl, 3-bromopropyl and the like.

"Halo-C₁-C₆-alkoxy" includes groups such as chloromethoxy, fluoromethoxy, difluoromethoxy, trifluoromethoxy, 2-fluoroethoxy, 2,2,2-trifluoroethoxy and the like.

"Carboxy-C₁-C₆-alkyl" includes groups such as carboxymethyl, 2-carboxyethyl, 3-carboxypropyl, 4-carboxybutyl, 5-carboxypentyl, 6-carboxyhexyl or the like.

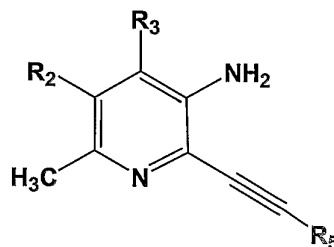
"Aryl" includes C₆-C₁₀ aryl groups such as phenyl, 1-naphtyl, 2-naphtyl and the like.

"Heteroaryl" includes 5-10 membered heterocyclic groups containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur to form a ring such as furyl (furan ring), benzofuranyl (benzofuran), thienyl (thiophene), benzothiophenyl (benzothiophene), pyrrolyl (pyrrole ring), imidazolyl (imidazole ring), pyrazolyl (pyrazole ring), thiazolyl (thiazole ring), isothiazolyl (isothiazole ring), triazolyl (triazole ring).

ring), tetrazolyl (tetrazole ring), pyridil (pyridine ring), pyrazynyl (pyrazine ring), pyrimidinyl (pyrimidine ring), pyridazinyl (pyridazine ring), indolyl (indole ring), isoindolyl (isoindole ring), benzoimidazolyl (benzimidazole ring), purinyl group (purine ring), quinolyl (quinoline ring), phtalazinyl (phtalazine ring), naphtyridinyl (naphtyridine ring), quinoxalinyl (quinoxaline ring), cinnolyl (cinnoline ring), pteridinyl (pteridine ring), oxazolyl (oxazole ring), isoxazolyl (isoxazole ring), benzoxazolyl (benzoxazole ring), furazanyl (furazan ring) and the like.

"Heteroaryl-C1-C6-alkyl" includes groups wherein examples of heteroaryl are the same as those illustrated in the above definition, such as 2-furylmethyl, 3-furylmethyl, 2-thienylmethyl, 3-thienylmethyl, 2-imidazolylmethyl, 2-thiazolylmethyl, 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, 2-quinolylmethyl and the like.

Preferred compounds of the present invention are compounds of formula **I-A** depicted below

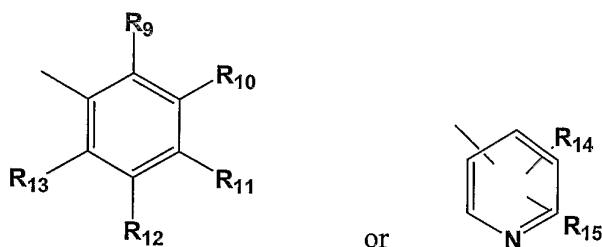


I-A

wherein

R_2 and R_3 are independently selected from hydrogen, C1-C6-alkyl;

R_5 represents a group of formula



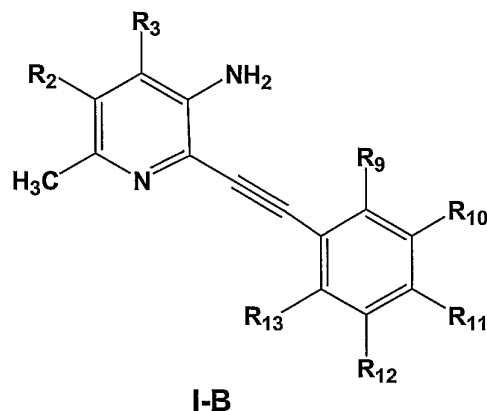
wherein

R_9 , R_{10} , R_{11} , R_{12} and R_{13} independently are hydrogen, halogen, cyano, nitro, C1-C6-alkyl, halo-C1-C6-alkyl, C1-C6-alkoxy, carboxy-C1-C6-alkyl or carboxyaryl;

R_{14} and R_{15} independently are as defined for $R_9 - R_{13}$ above;

or pharmaceutically acceptable salts, hydrates or solvates of such compounds.

More preferred compounds of the present invention are compounds of formula **I-B**



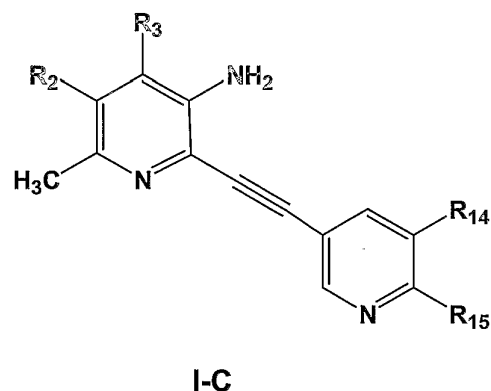
wherein

R_2 and R_3 are independently selected from hydrogen, C1-C6-alkyl;

R_9 , R_{10} , R_{11} , R_{12} and R_{13} independently are hydrogen, halogen, cyano, nitro, C1-C6-alkyl, halo-C1-C6-alkyl, C1-C6-alkoxy, carboxy-C1-C6-alkyl or carboxyaryl;

or pharmaceutically acceptable salts, hydrates or solvates of such compounds.

Particularly preferred compounds of the present invention are compounds of formula **I-C**



wherein

R_2 and R_3 are independently selected from hydrogen, C1-C6-alkyl;

R_{14} and R_{15} independently are hydrogen, halogen, cyano, nitro, C1-C6-alkyl, halo-C1-C6-alkyl, C1-C6-alkoxy, carboxy-C1-C6-alkyl or carboxyaryl;

or pharmaceutically acceptable salts, hydrates or solvates of such compounds.

Specifically preferred compounds are:

(6-Methyl-2-phenylethynyl-pyridin-3-yl)amine
N, N-Dimethyl-N'-(6-methyl-2-phenylethynyl-pyridin-3-yl)-formamidine
(2-(3-Fluoro-phenylethynyl)-6-methyl-pyridin-3-yl)amine
(2-(3-Methoxy-phenylethynyl)-6-methyl-pyridin-3-yl)amine
(6-Methyl-2-pyridin-3-ylethynyl-pyridin-3-yl)amine
(2-(4-Fluoro-phenylethynyl)-6-methyl-pyridin-3-yl)amine
(2-(3,5-Difluoro-phenylethynyl)-6-methyl-pyridin-3-yl)amine
(2-(5-Fluoro-pyridin-3-ylethynyl)-6-methyl-pyridin-3-yl)amine
3-(3-Amino-6-methyl-pyridin-2-ylethynyl)-benzonitrile
(2-(5-Chloro-pyridin-3-ylethynyl)-6-methyl-pyridin-3-yl)amine
(2-(3-Chloro-phenylethynyl)-6-methyl-pyridin-3-yl)amine
(2-(3-Fluoro-phenylethynyl)-4,6-dimethyl-pyridin-3-yl)amine
(2-(3-Chloro-phenylethynyl)-4,6-dimethyl-pyridin-3-yl)amine

The present invention relates to the pharmaceutically acceptable acid addition salts of compounds of the formula (I) or compositions comprising compounds of formula (I) together with pharmaceutically acceptable carriers or excipients.

The present invention relates to a method of treating or preventing a condition in a mammal, including a human, the treatment or prevention of which is affected or facilitated by the neuromodulatory effect of mGluR5 antagonists.

The present invention relates to a method useful for treating or preventing peripheral and central nervous system disorders selected from: substance tolerance or dependence, anxiety disorders, depression, mood disorders, psychiatric disease such as psychosis, inflammatory or neuropathic pain, memory deficits, Alzheimer's disease, Parkinson's disease, migraine, ischemia, drug abuse and addiction.

The present invention relates to pharmaceutical compositions which provide from about 0.01 to 1000 mg of the active ingredient per unit dose. The compositions may be administered by any suitable route. For example orally in the form of capsules, etc., parenterally in the form of solutions for injection, topically in the form of unguents or lotions, ocularly in the form of eye-drops, rectally in the form of suppositories, intranasally or transcutaneously in the form of delivery system like patches.

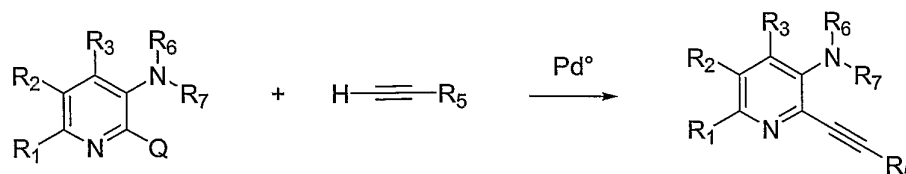
The pharmaceutical formulations of the invention may be prepared by conventional methods in the art; the nature of the pharmaceutical composition employed will depend on the desired route of administration. The total daily dose usually ranges from about 0.05 – 2000 mg.

The invention also provides for use of compounds or compositions as defined above in the manufacture of medicaments for treatment or prevention of the stated disorders.

The compounds of Formula I may be prepared by general routes of synthesis as disclosed in the following methods.

Scheme 1 illustrates the preparation of compounds of formula I by reacting an alkyne derivative, for example ethynylbenzene, with a substituted aminopyridine (or a precursor), for example 2-bromo-6-methyl-pyridin-3-ylamine. Thus in Scheme 1, R₁, R₂, R₃, R₅, R₆ and R₇ are as defined above and Q includes halides such as Cl, Br, I or trifluoromethanesulfonyl and paratoluenesulfonyl. This general route of synthesis has been described in M.H. Norman et al. J. Med. Chem. 2000, 43, 4288-4312.

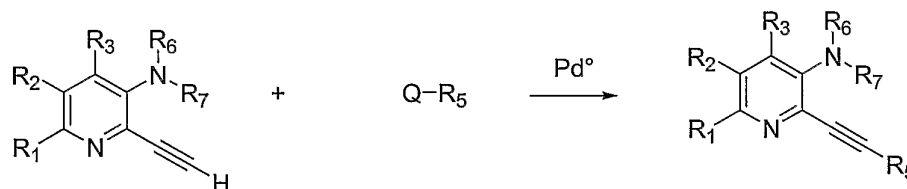
Scheme 1



This palladium catalyzed C-C coupling reaction requires a catalyst such as PdCl₂(PPh₃)₂, Pd(PPh₃)₄, Pd(OAc)₂ or Pd on carbon in a suitable solvent like DMF, acetonitrile or benzene. Typically a co-catalyst such as copper(I) iodide and a base (e.g., triethylamine, diisopropylamine, KOAc...) will also be present in the reaction mixture. The coupling reaction typically proceeds by allowing the reaction temperature to warm slowly from about 0° up to ambient temperature, or heated to a temperature anywhere between 30°C and 150°C. The reaction mixture is then maintained at a suitable temperature for a time in the range of about 1 up to 24 hours, with about 12 hours typically being sufficient. The product from the reaction can be isolated and purified employing standard techniques, such as solvent extraction, chromatography, crystallization, distillation, sublimation, and the like.

In another embodiment of the present invention, depicted in Scheme 2, an alkynyl-substituted aminopyridine (or a precursor) is reacted with a compound bearing a reactive functional group Q as defined above.

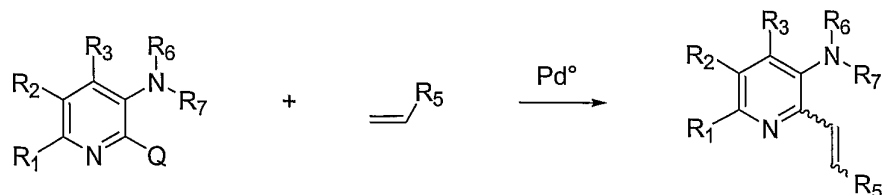
Scheme 2



Thus, in Scheme 2, R₁, R₂, R₃, R₅, R₆, R₇, Q, the catalysts and reaction conditions are as described for Scheme 1.

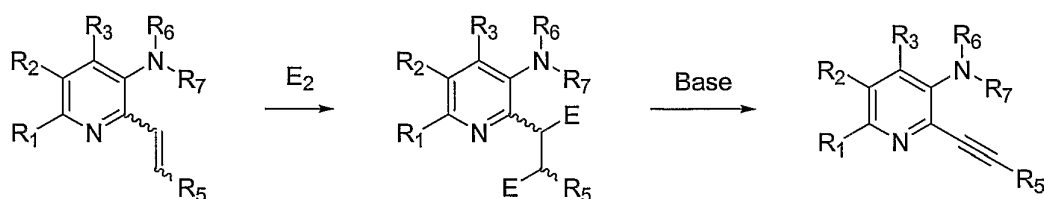
Another embodiment of the present invention is illustrated in Scheme 3. A substituted aminopyridine (or a precursor) is reacted with an alkene derivative, as described in C. Niu et al. Tetrahedron, 1998, 54, 6311-6318, in a manner similar to the procedure presented for Scheme 1.

8
Scheme 3



The alkene derivative product from Scheme 3 may be converted to an alkyne derivative using the approach outlined in Scheme 4.

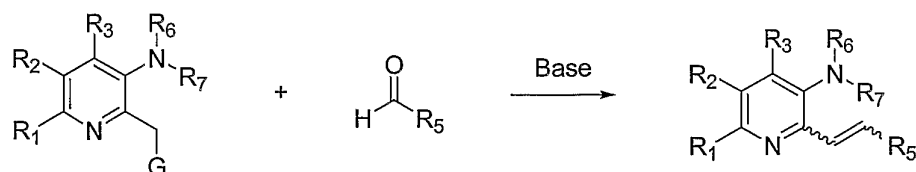
Scheme 4



This synthetic route refers to the methods described in G.R. Newkome et al. J. Org. Chem. 1980, 45, 4380-4385 or F. Gasparini et al. Bioorg. Med. Chem. Lett. 2002, 12, 407-410. The alkene derivatives may be treated with a halogenating agent such as chlorine or bromine in CHCl_3 or CCl_4 . The resulting halogenated derivatives are then treated with a suitable base such as NaOH, KOH or KO^tBu , which promotes a double elimination reaction to afford the alkyne. The reaction is carried out in a solvent like ethanol, *tert*-butanol, THF, etc. at an appropriate temperature, usually between 0°C and 150°C .

In another embodiment of the present invention, a substituted aminopyridine (or a precursor) is reacted with an aldehyde to provide a substituted alkene following the procedure developed in D. Guay et al. Bioorg. Med. Chem. Lett. 1998, 8, 453-458. (Scheme 5)

Scheme 5

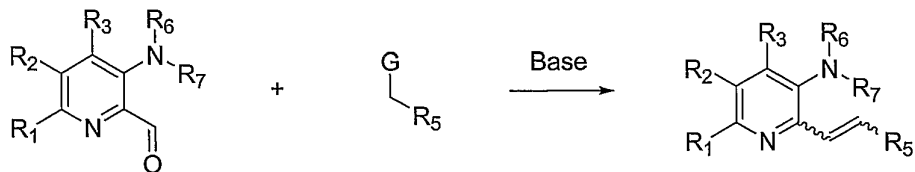


Thus, in Scheme 5, G is PR_3 or $\text{P}(\text{O})(\text{OR})_2$. The reaction is carried out with suitable catalysts including bases such as KH, NaH, *n*-butyllithium etc., in THF, acetonitrile, benzene, etc., at an appropriate temperature, usually between about 0°C and 150°C .

In yet another embodiment of the present invention, a substituted heterocyclic aldehyde is reacted with a compound containing an activated methylene to provide a

substituted alkene following the procedure developed in M. Cushman et al. J. Med. Chem. 1991, 34, 2579-2588. (Scheme 6)

Scheme 6



Thus, in Scheme 6, G, the catalysts and reaction conditions are as described for Scheme 5.

The alkene products from the reactions in Scheme 5 and Scheme 6 may be converted to an alkyne derivative using reagents and conditions as described for Scheme 4.

Substituted aminopyridines of formula I-A can be obtained from the corresponding nitropyridine compounds by a selective reduction of the nitro moiety with the method described in S. Glase et al. J. Med. Chem. 1996, 39, 3179-3187, using a mixture of Fe and aqueous HCl as the reducing agent.

The reactions described in scheme 1 to 6 can lead to free amino compounds when R₆ and R₇ are hydrogen. A subsequent functionalisation into amidine compounds of the invention can be performed according to standard methods familiar to those skilled in the art of converting free amino derivatives.

The compounds of Formula I which are basic in nature can form a wide variety of different pharmaceutically acceptable salts with various inorganic and organic acids. These salts are readily prepared by treating the base compounds with a substantially equivalent amount of the chosen mineral or organic acid in a suitable organic solvent such as methanol, ethanol or isopropanol.

Pharmacology

Some of the compounds of Formula I have been tested according to the following methods.

mGluR5 binding assay

Affinity of compounds of the invention was examined following a radioligand binding technique using whole rat brain and tritiated 2-methyl-6-(phenylethynyl)-pyridine ([³H]-MPEP) as a ligand following similar methods to those described in F. Gasparini et al. Bioorg. Med. Chem. Lett. 2002, 12, 407-409 and in J. F. Anderson et al. J. Pharmacol. Exp. Ther. 2002, 303, 3, 1044-1051.

- Membrane preparation:

Cortices were dissected out from brains of 200-300g Sprague-Dawley rats (Charles River Laboratories, L'Arbresle, France). Tissues were homogenized in 10 volumes

(vol/wt) of ice-cold 50 mM Hepes-NaOH (pH 7.4) using a Polytron disrupter (Kinematica AG, Luzern, Switzerland) and centrifuged for 30 min at 40,000 g. (4°C). The supernatant was discarded and the pellet washed twice by resuspension in 10 volumes 50 mM HEPES-NaOH. Membranes were then collected by centrifugation and washed before final resuspension in 10 volumes of 20 mM HEPES-NaOH, pH 7.4. Protein concentration was determined by the Bradford method (Bio-Rad protein assay, Reinach, Switzerland) with bovine serum albumin as standard.

- ³H]-MPEP binding experiments:

Membranes were thawed and resuspended in binding buffer containing 20 mM HEPES-NaOH, 3 mM MgCl₂, 100 mM NaCl, pH 7.4. Competition studies were carried out by incubating for 1h at 4°C: 3 nM [³H]-MPEP (46,85 Ci/mmol, Tocris, Cookson Ltd, Bristol, U.K.), 50 µg membrane and a concentration range of 0.03 nM-30 µM of compounds, for a total reaction volume of 300 µl. The non-specific binding was defined using 30 µM MPEP. Reaction was terminated by rapid filtration over glass-fiber filter plates (Unifilter 96-well GF/B filter plates, Perkin-Elmer, Schwerzenbach, Switzerland) using 4 x 400 µl ice cold buffer using cell harvester (Filtermate, Perkin-Elmer, Downers Grove, USA). Radioactivity was determined by liquid scintillation spectrometry using a 96-well plate reader (TopCount, Perkin-Elmer, Downers Grove, USA).

- Data analysis:

The inhibition curves were generated using the Prism GraphPad program (Graph Pad Software Inc, San Diego, USA). IC₅₀ determinations were made from data obtained from 8 point concentrations response curves using a nonlinear regression analysis.

The compounds of this application as measured in the assay described above have IC₅₀ values in the range of less than 10 µM. Preferred compounds include the examples n° 3, 7, 10, 12 and 13 which have IC₅₀ values of less than 30 nM.

In-vitro selectivity profile

Compounds of the invention show an improved selectivity on mGluR5 receptor. This indicates a greater specificity and a better safety profile.

In-vivo

Compounds of the invention are effective in models demonstrating the usefulness of the compounds for treating neuropathic inflammatory pain (B.A. Chizh, Amino Acids 2002, 23, 169-176), anxiety (W. P. J. M. Spooren et al. J. Pharmacol. Exp. Ther. 2000, 295, 3, 1267-1275; W.P.J.M. Spooren et al. Eur. J. Pharmacol. 2002, 435, 161-170), Parkinson disease (N. Breyse et al. J. Neurosci. 2003, 10, 23, 23, 8302-8309), migraine (P. De Vries et al. 1999, 375, 61-74), depression (I.A. Paul and P. Skolnick, Ann. N Y Acad. Sci. 2003, 1003, 250-72) and addictive disorders (N. E. Paterson et al. Psychopharmacology 2003, 167, 257-264; C. Chiamulera et al. Nature Neurosci. 2001, 4, 9, 873-874).

The compounds of the present invention present a high selectivity and affinity for mGluR5 receptor. As functional antagonists, they are useful for the production of

medications, especially for the treatment or prevention of central nervous system disorders as well as other disorders modulated by this receptor.

Reasonable variations are not to be regarded as a departure from the scope of the invention. It will be obvious that the thus described invention may be varied in many ways by those skilled in the art.

The following non-limiting examples are intending to illustrate the invention. The physical data given for the compounds exemplified are consistent with the assigned structure of those compounds.

EXAMPLES

Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification. Specifically, the following abbreviations may be used in the examples and throughout the specification.

¹ H (proton)	ml (milliliters)
CHCl ₃ (chloroform)	μl (microliters)
CuI (copper iodide)	μmol (micromoles)
DCM (dichloromethane)	mmol (millimoles)
dec. (decomposition)	M.p. (melting point)
DMSO[D ₆] (deuterated dimethylsulfoxide)	NH ₄ OH (ammonium hydroxide)
h (hour)	NaOH (sodium hydroxide)
LC-MS (Liquid Chromatography Mass Spectrometry)	Na ₂ SO ₄ (sodium sulphate)
M (molar)	NMR (Nuclear Magnetic Resonance)
MeOH (methanol)	PBr ₃ (Phosphorus tribromide)
mg (milligrams)	PdCl ₂ (PPh ₃) ₂ (Bis(triphenylphosphine) palladium (II) dichloride)
MHz (megahertz)	RT (Retention Time)

All reactions are conducted under an inert atmosphere at room temperature unless otherwise noted.

¹H NMR spectra were recorded either on a Bruker ARX400 or on a Bruker 500MHz. Chemical shifts are expressed in parts per million (ppm, δ units). Coupling constants are in units of hertz (Hz) Splitting patterns describe apparent multiplicities and are designated as s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet).

LC-MS spectra were recorded on a Waters Micromass ZQ 2996 system by the following conditions: Column 3.0*50mm stainless steel packed with 5μm XTerra RP C-18; flow rate 0.8ml/min; mobile phase: A phase = 0.07% formic acid in water, B phase = 0.07% formic acid in acetonitrile. 0-0.5min (A: 95%, B: 5%), 0.5-6.0min (A: 0%, B: 100%), 6.0-6.5min (A: 95%, B: 5%), 6.5-7min (A: 95%, B: 5%); UV detection Diode Array :200-400nm; Injection volume: 5 μl. All mass spectra were taken under electrospray ionisation (ESI) methods.

Melting point determination was performed on a Buchi B-540 apparatus.

The reactions were monitored by thin-layer chromatography on 0.20 mm silica gel plates (60F₂₅₄, Merck or G/UV₂₅₄ Macherey Nagel) and visualized with UV light. Flash column chromatography was performed on silica gel (220-440 mesh, Fluka).

Example 1

(6-Methyl-2-phenylethynyl-pyridin-3-yl)amine hydrochloride

To a solution of CuI (10 mg, 50 μ mol) in triethylamine (5 ml) were added (2-bromo-6-methyl-pyridin-3-yl)amine (200 mg, 1.07 mmol) and (PPh₃)₂PdCl₂ (36 mg, 50 μ mol). The reaction mixture was cooled to 0°C and phenylacetylene (176 μ l, 1.60 mmol) was added. The reaction mixture was allowed to warm to room temperature and then heated under reflux for 14 h. The solvent was evaporated and the crude residue was purified by flash chromatography (hexane/ethyl acetate 4:1) to yield 105 mg (0.50 mmol, 47%) of (6-methyl-2-phenylethynyl-pyridin-3-yl)amine as a yellow solid.

R_f: 0.09 (Hexane/ethyl acetate 4:1). M. p.: 154-155°C. ¹H NMR (CDCl₃, 400 MHz) δ : 2.47 (s, 3 H), 4.13-4.17 (br. s, 2 H), 6.93-7.01 (2 H), 7.34-7.39 (3 H), 7.57-7.63 (2 H).

(6-methyl-2-phenylethynyl-pyridin-3-yl)amine (105 mg, 0.50 mmol) was dissolved in CHCl₃ (2 ml) and treated with 1.56 ml (1.25 mmol) of 0.8 M hydrochloric acid solution in diethyl ether. After evaporation of the solvent and trituration of the residue with ethyl acetate, 107 mg (0.44 mmol, 87%) of the title hydrochloride were obtained as a yellowish solid.

R_f: 0.50 (Hexane/ethyl acetate 1:1). M. p.: 183°C. ¹H NMR (DMSO[d₆], 400 MHz) δ : 2.57 (s, 3 H), 3.20-4.00 (br. s, 3 H), 7.51-7.57 (4 H), 7.71 (d, J=8.8 Hz, 1 H), 7.80-7.84 (2 H). LC-MS (RT): 2.14 min.; MS (ES+) gave m/z: 209.1.

13
Example 3(2-(3-Fluoro-phenylethynyl)-6-methyl-pyridin-3-yl)amine hydrochloride

Following the same procedure as described in Example 1, (2-bromo-6-methyl-pyridin-3-yl)amine (200 mg, 1.07 mmol) reacted with $(PPh_3)_2PdCl_2$ (36 mg, 0.05 mmol), CuI (10 mg, 0.05 mmol) and 1-ethynyl-3-fluorobenzene (148 μ l, 1.28 mmol) in triethylamine (5 ml). The crude residue was purified by flash chromatography (hexane/ethyl acetate 4:1) to yield 145 mg (0.64 mmol, 60%) of (2-(3-fluoro-phenylethynyl)-6-methyl-pyridin-3-yl)amine as a pale yellow solid. The hydrochloride of (2-(3-fluoro-phenylethynyl)-6-methyl-pyridin-3-yl)amine was prepared as described in Example 1 to yield 148 mg (0.56 mmol, 88%) of the title hydrochloride as a yellow solid.

R_f: 0.52 (Hexane/ethyl acetate 1:1). M. p.: 199-200°C (dec.). ¹H NMR (DMSO-[D₆], 400 MHz) δ : 2.52 (s, 3 H), 6.20-7.24 (br. s, 2 H), 7.35-7.43 (m, 1 H), 7.48 (d, J=8.0 Hz, 1 H), 7.52-7.61 (2 H), 7.62-7.67 (m, 1 H), 7.68-7.72 (m, 1 H). LC-MS (RT): 2.26 min.; MS (ES+) gave m/z: 227.1. Anal. Calcd for C₁₄H₁₂ClFN₂: C, 64.01%; H, 4.60%; Cl, 13.50%; F, 7.23%; N, 10.66%. Found: C, 63.30%; H, 4.62%; Cl, 13.56%; F, 6.98%; N, 10.57%.

Example 4

(2-(3-Methoxy-phenylethynyl)-6-methyl-pyridin-3-yl)amine.

Following the same procedure as described in Example 1, (2-bromo-6-methyl-pyridin-3-yl)amine (200 mg, 1.07 mmol) reacted with $(PPh_3)_2PdCl_2$ (37 mg, 0.05 mmol), CuI (10 mg, 0.05 mmol) and 1-ethynyl-3-methoxy-benzene (204 μ l, 1.60 mmol) in triethylamine (5 ml) during 1.5 h. The crude residue was purified by flash chromatography (hexane/ethyl acetate 4:1) to yield 118 mg (0.50 mmol, 46%) of (2-(3-methoxy-phenylethynyl)-6-methyl-pyridin-3-yl)amine as a yellow brown solid.

R_f: 0.30 (Hexane/ethyl acetate 1:1). M. p.: 165-166°C. ¹H NMR (DMSO-[D₆], 400 MHz) δ : 2.60 (s, 3 H), 3.85 (s, 3 H), 7.11-7.16 (m, 1 H), 7.37-7.49 (3 H), 7.56 (d, J=8.4 Hz, 1 H), 7.77 (d, J=8.8 Hz, 1 H). LC-MS (RT): 2.31 min.; MS (ES+) gave m/z: 239.1.

Example 5

(6-Methyl-2-pyridin-3-ylethynyl-pyridin-3-yl)amine hydrochloride

Following the same procedure as described in Example 1, (2-bromo-6-methyl-pyridin-3-yl)amine (200 mg, 1.07 mmol) reacted with $(PPh_3)_2PdCl_2$ (37 mg, 0.05 mmol), CuI (10 mg, 0.05 mmol) and 3-ethynyl-pyridine (110 mg, 1.07 mmol) in triethylamine (1.6 ml). The crude residue was purified by flash chromatography (DCM-DCM/MeOH 97:3) to yield 100 mg (0.48 mmol, 49%) of (6-methyl-2-pyridin-3-ylethynyl-pyridin-3-yl)amine as a yellow powder. The hydrochloride of (6-methyl-2-pyridin-3-ylethynyl-pyridin-3-yl)amine was prepared as described in Example 1 to yield after trituration with pentane 145 mg (100%) of the title hydrochloride as a yellow solid.

M. p.: 156.4-158°C. ^1H NMR (DMSO- d_6 , 500 MHz) δ : 2.54 (s, 3 H), 7.52 (d, $J=9$ Hz, 1 H), 7.61-7.68 (m, 1 H), 7.69 (d, $J=9.0$, 1 H), 8.25 (d, $J=7.5$, 1 H), 8.68-8.86 (br. s, 1 H), 8.93-9.15 (br. s, 1 H). LC-MS (RT): 0.65 min.; MS (ES+) gave m/z : 210.1.

Example 6

(2-(4-Fluoro-phenylethynyl)-6-methyl-pyridin-3-yl)amine hydrochloride

Following the same procedure as described in Example 1, (2-bromo-6-methyl-pyridin-3-yl)amine (200 mg, 1.07 mmol) reacted with $(\text{PPh}_3)_2\text{PdCl}_2$ (36 mg, 0.05 mmol), CuI (10 mg, 0.05 mmol) and 1-ethynyl-4-fluorobenzene (184 μl , 1.07 mmol) in triethylamine (5 ml). The crude residue was purified by flash chromatography (hexane/ethyl acetate 7:3) to yield 164 mg (0.72 mmol, 68%) of (2-(4-fluoro-phenylethynyl)-6-methyl-pyridin-3-yl)amine as a yellow solid. The hydrochloride of (2-(4-fluoro-phenylethynyl)-6-methyl-pyridin-3-yl)amine was prepared as described in Example 1 to yield after trituration with ethyl acetate 154 mg (0.51 mmol, 71%) of the title hydrochloride as a yellow solid.

R_f : 0.43 (hexane/ethyl acetate 1:1). M. p.: 122°C (dec.). ^1H NMR (DMSO- d_6 , 400 MHz) δ : 2.53 (s, 3 H), 4.45-5.54 (br. s, 2 H), 7.36-7.43 (2 H), 7.52 (d, $J=8.8$ Hz, 1 H), 7.67 (d, $J=8.8$ Hz, 1 H), 7.82-7.89 (2 H). LC-MS (tr): 2.24 min.; MS (ES+) gave m/z : 227.1.

Example 7

(2-(3,5-Difluoro-phenylethynyl)-6-methyl-pyridin-3-yl)amine hydrochloride

Following the same procedure as described in Example 1, (2-bromo-6-methyl-pyridin-3-yl)amine (800 mg, 4.28 mmol) reacted with $(\text{PPh}_3)_2\text{PdCl}_2$ (150 mg, 0.21 mmol), CuI (41 mg, 0.21 mmol) and ethynyltrimethylsilane (840 mg, 8.55 mmol) in triethylamine (30 ml). The crude residue was purified by flash chromatography (hexane/ethyl acetate 8:2) to yield 330 mg (1.61 mmol, 38%) of (6-methyl-2-trimethylsilyl-ethynyl-pyridin-3-yl)amine as a beige solid.

(6-methyl-2-trimethylsilyl-ethynyl-pyridin-3-yl)amine (330 mg, 1.61 mmol) was dissolved in MeOH (3 ml) and cooled to 0°C, to the resulting solution was added 1 M solution of NaOH (1.6 ml). The ice bath was removed and the reaction mixture was stirred at room temperature for 4 h. 90 μl of acetic acid was added. The reaction mixture was partially concentrated and the residue was extracted with ethyl acetate. The organic layers were washed with water, brine, dried over Na_2SO_4 , filtered and concentrated to yield 160 mg (1.21 mmole, 75%) of (2-ethynyl-6-methyl-pyridin-3-yl)amine as a brown solid which was used in the next step without further purification.

To a solution of CuI (4.3 mg, 23 μmol) in triethylamine (5 ml) were added (2-ethynyl-6-methyl-pyridin-3-yl)amine (60 mg, 0.45 mmol), $(\text{PPh}_3)_2\text{PdCl}_2$ (16 mg, 23 μmol), and 1,3-difluoro-5-iodobenzene (109 mg, 0.45 mmol). The reaction mixture was stirred at room temperature for 20 h. The solvent was evaporated to afford a brown oil which was taken up in DCM and the solution was washed with water. The aqueous phase was extracted twice with DCM. The organic phases were dried over Na_2SO_4 , filtered and concentrated. The crude residue was purified by flash chromatography

15

(hexane/ethyl acetate 7:3) to yield 64 mg (0.26 mmol, 58%) of (2-(3,5-difluorophenylethynyl)-6-methyl-pyridin-3-yl)amine as a yellow solid.

The hydrochloride of (2-(3,5-difluorophenylethynyl)-6-methyl-pyridin-3-yl)amine was prepared as described in Example 1 to yield after trituration with diethyl ether 64 mg (0.20 mmol, 78%) of the title hydrochloride as a yellow powder.

R_f: 0.61 (hexane/ethyl acetate 1:1). M.p.: 212°C (dec.). ¹H NMR (DMSO-[D₆], 400 MHz) δ: 2.49 (s, 3 H), 6.12-7.08 (br. s, 2 H), 7.44-7.55 (2 H), 7.56-7.68 (3 H). LC-MS (RT): 2.39 min.; MS (ES+) gave m/z: 245.0.

Example 8

(2-(5-Fluoro-pyridin-3-ylethynyl)-6-methyl-pyridin-3-yl)amine hydrochloride

To a solution of CuI (11 mg, 0.06 mmol) in triethylamine (5 ml) were added (2-ethynyl-6-methyl-pyridin-3-yl)amine (40 mg, 0.30 mmol, described in Example 7), (PPh₃)₂PdCl₂ (21 mg, 0.06 mmol), and 3-fluoro-5-iodopyridine (111 mg, 0.45 mmol). The reaction mixture was stirred at room temperature for 14 h. The solvent was evaporated. The crude residue was purified by flash chromatography (cyclohexane/ethyl acetate 7:3) to yield 15 mg (66 μmol, 22%) of (2-(5-fluoro-pyridin-3-ylethynyl)-6-methyl-pyridin-3-yl)amine as a yellow solid.

The hydrochloride of (2-(5-fluoro-pyridin-3-ylethynyl)-6-methyl-pyridin-3-yl)amine was prepared as described in Example 1 to yield after trituration with ethyl acetate 6 mg (20 μmol, 30%) of the title hydrochloride as a brown semi-solid.

R_f: 0.31 (cyclohexane/ethyl acetate 7:3). LC-MS (RT): 1.71 min.; MS (ES+) gave m/z: 228.0.

Example 9

3-(3-Amino-6-methyl-pyridin-2-ylethynyl)-benzonitrile hydrochloride

To a solution of CuI (2.4 mg, 12 μmol) in triethylamine (4 ml) were added (2-ethynyl-6-methyl-pyridin-3-yl)amine (33 mg, 0.33 mmol, described in Example 7), (PPh₃)₂PdCl₂ (8.8 mg, 12 μmol), and 3-iodobenzonitrile (57 mg, 0.25 mmol). The reaction mixture was stirred at room temperature for 48 h. The solvent was evaporated and the crude residue was purified by flash chromatography (cyclohexane/ethyl acetate 1:1) to yield 16 mg (69 μmol, 21%) of 3-(3-amino-6-methyl-pyridin-2-ylethynyl)-benzonitrile as a pale yellow solid.

The hydrochloride of 3-(3-amino-6-methyl-pyridin-2-ylethynyl)-benzonitrile was prepared as described in Example 1 to yield after trituration with diethyl ether 10 mg (33 μmol, 47%) of the title hydrochloride as a yellow powder.

R_f: 0.36 (hexane/ethyl acetate 1:1). M. p.: 132.4-134°C. LC-MS (RT): 2.13 min.; MS (ES+) gave m/z: 234.1.

16
Example 10(2-(5-Chloro-pyridin-3-ylethynyl)-6-methyl-pyridin-3-yl)amine hydrochloride

Following the same procedure as described in Example 1, (2-bromo-6-methyl-pyridin-3-yl)amine (150 mg, 0.80 mmol) reacted with $(PPh_3)_2PdCl_2$ (28 mg, 40 μ mol), CuI (8 mg, 40 μ mol) and 3-chloro-5-ethynyl-pyridine (165 mg, 1.20 mmol) in triethylamine (5 ml). The crude residue was purified by flash chromatography (hexane/ethyl acetate 7:3) to yield 141 mg (0.58 mmol, 72%) of (2-(5-chloro-pyridin-3-ylethynyl)-6-methyl-pyridin-3-yl)amine as a yellow solid.

The hydrochloride of (2-(5-chloro-pyridin-3-ylethynyl)-6-methyl-pyridin-3-yl)amine was prepared as described in Example 1 to yield 152 mg (0.48 mmol, 83%) of the title hydrochloride as a yellow solid.

R_f: 0.12 (Hexane/ethyl acetate 1:1). M. p.: 193°C (dec.). ¹H NMR (DMSO-[D₆], 400 MHz) δ : 2.59 (s, 3 H), 5.81-7.41 (br. s, 2 H), 7.58 (d, J=8.8 Hz, 1 H), 7.73 (d, J=8.8 Hz, 1 H), 8.43-8.44 (m, 1 H), 8.79 (d, J=1.6 Hz, 1 H), 8.89 (d, J=2.0 Hz, 1 H). LC-MS (RT): 2.03 min.; MS (ES+) gave m/z: 244.0.

Example 11

(2-(3-Chloro-phenylethynyl)-6-methyl-pyridin-3-yl)amine hydrochloride

To a solution of CuI (5.0 mg, 28 μ mol) in triethylamine (5 ml) were added (2-ethynyl-6-methyl-pyridin-3-yl)amine (75 mg, 0.57 mmol described in Example 7), $(PPh_3)_2PdCl_2$ (20 mg, 28 μ mol), and 1-chloro-3-iodobenzene (135 mg, 0.57 mmol). The reaction mixture was stirred at room temperature for 4 h. The solvent was evaporated to afford a brown oil which was taken up in DCM and the solution was washed with water. The aqueous phase was extracted twice with DCM. The organic phases were dried over Na₂SO₄, filtered and concentrated. The crude residue was purified by flash chromatography (hexane/ethyl acetate 7:3) to yield 54 mg (0.22 mmol, 39%) of (2-(3-chloro-phenylethynyl)-6-methyl-pyridin-3-yl)amine as a yellow solid.

The hydrochloride of (2-(3-chloro-phenylethynyl)-6-methyl-pyridin-3-yl)amine was prepared as described in Example 1 to yield after trituration with diethyl ether 51 mg (0.16 mmol, 73%) of the title hydrochloride as a yellow powder.

R_f: 0.57 (hexane/ethyl acetate 1:1). M. p.: 195°C (dec.). ¹H NMR (DMSO-[D₆], 400 MHz) δ : 2.51 (s, 3 H), 6.43-7.11 (br. s, 2 H), 7.50 (d, J=8.4 Hz, 1 H), 7.52-7.58 (m, 1 H), 7.59-7.69 (2 H), 7.72 (d, J=8.0 Hz, 1 H), 7.97 (s, 1 H). LC-MS (RT): 2.54 min.; MS (ES+) gave m/z: 243.0. Anal. Calcd for C₁₄H₁₂Cl₂N₂+ 0.5 H₂O: C, 58.35%; H, 4.55%; Cl, 24.61%; N, 9.72%. Found: C, 58.15%; H, 4.49%; Cl, 24.60%; N, 9.48%.

Example 12

(2-(3-Fluoro-phenylethynyl)-4,6-dimethyl-pyridin-3-yl)amine hydrochloride.

To a solution of 1.80 g (11.0 mmol) of 2-chloro-4,6-dimethyl-pyridin-3-ylamine (prepared as described in J. M. Klunder et al. J. Med. Chem., 35, 1992, 1887-1897) in toluene (10 ml) was added PBr₃ (18 ml). The reaction mixture was stirred for 48 h under reflux. After cooling the reaction mixture, it was poured onto ice, basified with

NaOH 2 M solution (400 ml) and the aqueous phase was extracted twice with ethyl acetate. The combined organic phases were washed with brine, dried over Na₂SO₄, filtered and evaporated. The crude residue was purified by flash chromatography (cyclohexane/ethyl acetate 7:3) to yield 2.31 g (38%) of 2-bromo-4,6-dimethyl-pyridin-3-ylamine containing small amount of 2-chloro-4,6-dimethyl-pyridin-3-ylamine as a yellow oil.

To a solution of CuI (41 mg, 0.2 mmol) in triethylamine (12 ml) were added 2-bromo-4,6-dimethyl-pyridin-3-ylamine (870 mg, 4.33 mmol), (PPh₃)₂PdCl₂ (152 mg, 0.22 mmol), and 1-ethynyl-3-fluorobenzene (500 µl, 4.33 mmol). The reaction mixture was stirred for 30 min. at room temperature and for 3 h under reflux. The solvent was evaporated and the crude residue was purified by flash chromatography (cyclohexane/ethyl acetate 4:1) to yield 745 mg (3.10 mmol, 72%) of (2-(3-fluoro-phenylethynyl)-4,6-dimethyl-pyridin-3-yl)amine as a brown solid.

The hydrochloride of (2-(3-fluoro-phenylethynyl)-4,6-dimethyl-pyridin-3-yl)amine was prepared as described in Example 1 to yield after trituration with pentane 680 mg (2.46 mmol, 79%) of the title hydrochloride as a yellow powder.

R_f: 0.37 (cyclohexane/ethyl acetate 7:3). M. p.: 210°C. ¹H NMR (DMSO-[D₆], 500 MHz) δ: 2.33 (s, 3 H), 2.51 (s, 3 H), 6.31-6.72 (br. s, 3 H), 7.36-7.42 (m, 1 H), 7.47 (s, 1 H), 7.53-7.59 (m, 1 H), 7.60-7.63 (m, 1 H), 7.70-7.74 (m, 1 H). LC-MS (tr): 2.29 min.; MS (ES+) gave m/z: 241.1. Anal. Calcd for C₁₅H₁₄ClFN₂: C, 65.10%; H, 5.10%; Cl, 12.81%; F, 6.87%; N, 10.12%. Found: C, 64.73%; H, 4.97%; Cl, 12.78%; F, 6.71%; N 9.87%.

Example 13

(2-(3-Chloro-phenylethynyl)-4,6-dimethyl-pyridin-3-yl)amine hydrochloride.

To a solution of CuI (5.7 mg, 30 µmol) in triethylamine (1.6 ml) were added 2-bromo-4,6-dimethyl-pyridin-3-ylamine (120 mg, 0.60 mmol, described in Example 12), (PPh₃)₂PdCl₂ (21 mg, 30 µmol), and 1-ethynyl-3-chlorobenzene (98 mg, 0.72 mmol). The reaction mixture was stirred for 30 min. at room temperature and for 3 h under reflux. The solvent was evaporated and the crude residue was purified by flash chromatography (cyclohexane/ethyl acetate 4:1) to yield 39 mg (0.15 mmol, 25%) of (2-(3-chloro-phenylethynyl)-4,6-dimethyl-pyridin-3-yl)amine as a brown oil.

The hydrochloride of (2-(3-chloro-phenylethynyl)-4,6-dimethyl-pyridin-3-yl)amine was prepared as described in Example 1 to yield after trituration with pentane 25 mg (85 µmol, 57%) of the title hydrochloride as a yellow powder.

R_f: 0.37 (cyclohexane/ethyl acetate 7:3). M. p.: 204°C. LC-MS (tr): 2.56 min.; MS (ES+) gave m/z: 257.0.

Typical examples of recipes for the formulation of the invention are as follows:

1) Tablets

Compound of the example 3	5 to 50 mg
Di-calcium phosphate	20 mg
Lactose	30 mg
Talcum	10 mg

18

Magnesium stearate	5 mg
Potato starch	ad 200 mg

In this example, the compound of the example 3 can be replaced by the same amount of any of the described examples 1 to 13.

2) Suspension:

An aqueous suspension is prepared for oral administration so that each 1 milliliter contains 1 to 5 mg of one of the described example, 50 mg of sodium carboxymethyl cellulose, 1 mg of sodium benzoate, 500 mg of sorbitol and water ad 1 ml.

3) Injectable

A parenteral composition is prepared by stirring 1.5 % by weight of active ingredient of the invention in 10% by volume propylene glycol and water.

4) Ointment

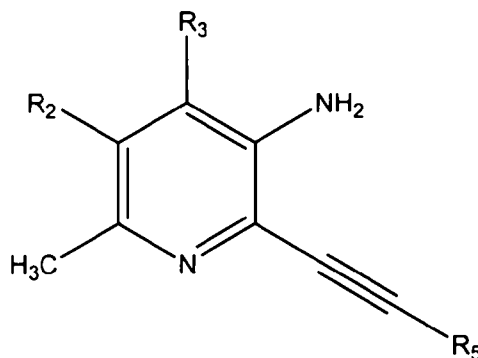
Compound of the example 3	5 to 1000 mg
Stearyl alcohol	3 g
Lanoline	5 g
White petroleum	15 g
Water	ad 100 g

In this example, the compound 3 can be replaced by the same amount of any of the described examples 1 to 13.

Reasonable variations are not to be regarded as a departure from the scope of the invention. It will be obvious that the thus described invention may be varied in many ways by those skilled in the art.

The claims defining the invention are as follows:

1. A compound of the formula:

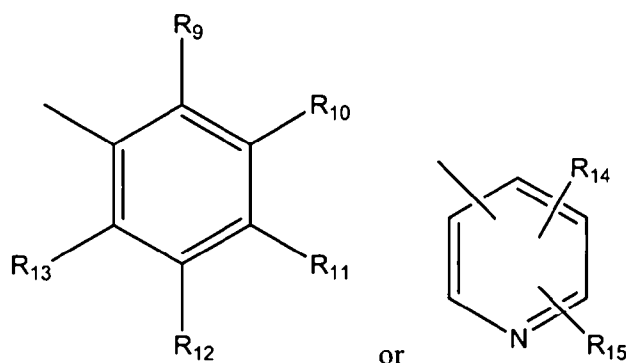


I-A

wherein

R₂ and R₃ are independently selected from hydrogen, C₁-C₆-alkyl;

R₅ represents a group of formula:



wherein

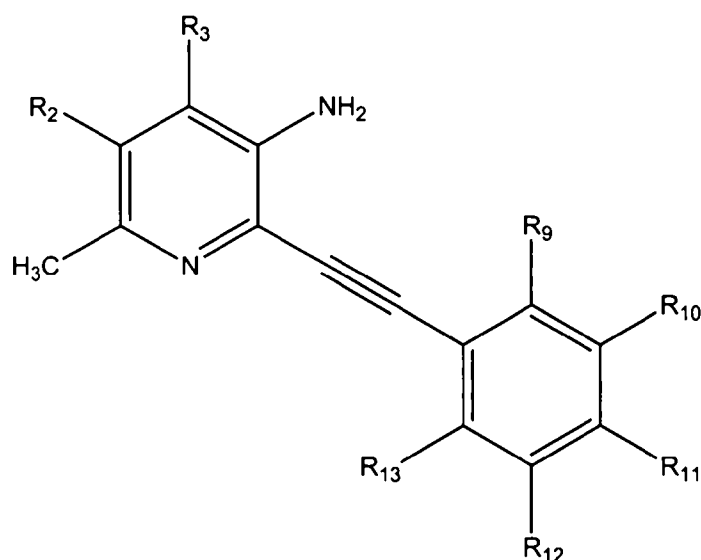
R₉, R₁₀, R₁₁, R₁₂ and R₁₃ independently are hydrogen, halogen, cyano, nitro, C₁-C₆-alkyl, halo-C₁-C₆-alkyl, C₁-C₆-alkoxy, carboxy-C₁-C₆-alkyl or carboxyaryl;

R₁₄ and R₁₅ independently are as defined for R₉ - R₁₃ above;

or pharmaceutical acceptable salts, hydrates or solvates of such compounds.

2. A compound according to claim 1 having the formula:

20



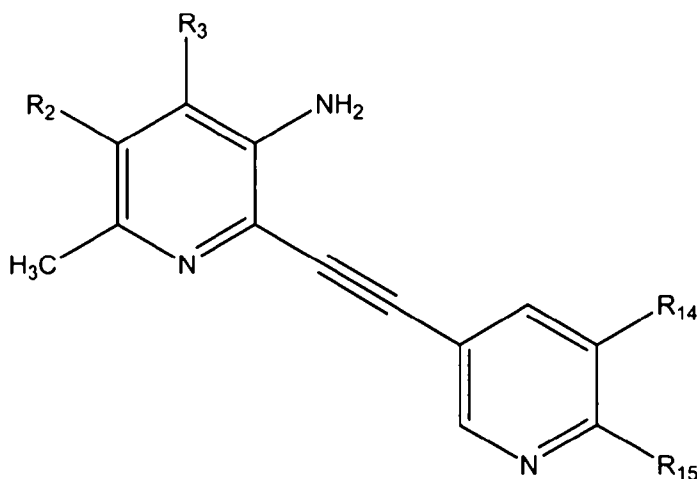
I-B

wherein

R_2 and R_3 are independently selected from hydrogen, C_1 - C_6 -alkyl;

- 5 R_9 , R_{10} , R_{11} , R_{12} and R_{13} independently are hydrogen, halogen, cyano, nitro, C_1 - C_6 -alkyl, halo- C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy, carboxy- C_1 - C_6 -alkyl or carboxyaryl; or pharmaceutical acceptable salts, hydrates or solvates of such compounds.

3. A compound according to claim 1 having the formula:



I-C

wherein

R_2 and R_3 are independently selected from hydrogen, C_1 - C_6 -alkyl;

R_{14} and R_{15} independently are hydrogen, halogen, cyano, nitro, C_1 - C_6 -alkyl, halo- C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy, carboxy- C_1 - C_6 -alkyl or carboxyaryl;

or pharmaceutical acceptable salts, hydrates or solvates of such compounds.

4. A compound according to claims 1 to 3, wherein said compound is selected from:

(6-Methyl-2-phenylethynyl-pyridin-3-yl)amine

(2-(3-Fluoro-phenylethynyl)-6-methyl-pyridin-3-yl)amine

5 (2-(3-Methoxy-phenylethynyl)-6-methyl-pyridin-3-yl)amine

(6-Methyl-2-pyridin-3-ylethynyl-pyridin-3-yl)amine

(2-(4-Fluoro-phenylethynyl)-6-methyl-pyridin-3-yl)amine

(2-(3,5-Difluoro-phenylethynyl)-6-methyl-pyridin-3-yl)amine

(2-(5-Fluoro-pyridin-3-ylethynyl)-6-methyl-pyridin-3-yl)amine

10 3-(3-Amino-6-methyl-pyridin-2-ylethynyl)-benzonitrile

(2-(5-Chloro-pyridin-3-ylethynyl)-6-methyl-pyridin-3-yl)amine

(2-(3-Chloro-phenylethynyl)-6-methyl-pyridin-3-yl)amine

(2-(3-Fluoro-phenylethynyl)-4,6-dimethyl-pyridin-3-yl)amine

(2-(3-Chloro-phenylethynyl)-4,6-dimethyl-pyridin-3-yl)amine

15 and pharmaceutically acceptable salts thereof.

5. A compound of Formula I-A, substantially as hereinbefore described with reference to any one of the examples

6. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to claims 1 to 5 and a pharmaceutically acceptable carrier
20 and/or excipient.

7. A method of treating or preventing a condition in a mammal, including a human, the treatment or prevention of which is affected or facilitated by the neuromodulatory effect of mGluR5 antagonists, comprising administering to a mammal in need of such treatment or prevention, an effective amount of a compound according to
25 claims 1 to 5 or the composition of claim 6.

8. A method useful for treating or preventing central nervous system disorders selected from: tolerance or dependence, depression, bipolar disorder, psychiatric disease such as psychotic disorders, attention-deficit/hyperactivity disorder, Parkinson's disease, memory impairment, Alzheimer's disease, dementia, delirium tremens, neurodegeneration, neurotoxicity, ischemia comprising administering to a mammal in
30 need of such treatment or prevention, an effective amount of a compound according to claims 1 to 5 or the composition of claim 6.

9. A method useful for treating or preventing inflammatory or neuropathic pain comprising administering to a mammal in need of such treatment or prevention, an

effective amount of a compound according to claims 1 to 5 which substantially does not penetrate the central nervous system.

10. A method of treating or preventing substance tolerance or dependence, bulimia nervosa, anorexia nervosa, gambling dependence, smoking dependence, sex
5 dependence, substance withdrawal or obsessive compulsive disorders comprising administering to a mammal in need of such treatment or prevention, an effective amount of a compound according to claims 1 to 5 or the composition of claim 6.

11. A method useful for treating or preventing alcohol, nicotine, cocaine, amphetamine, benzodiazepine, opiate or alcohol abuse or addiction comprising
10 administering to a mammal in need of such treatment or prevention, an effective amount of a compound according to claims 1 to 5 or the composition of claim 6.

12. A method useful for treating or preventing anxiety, panic disorder, phobia, posttraumatic stress disorder, generalized anxiety disorder, acute stress disorder
15 comprising administering to a mammal in need of such treatment or prevention, an effective amount of a compound according to claims 1 to 5 or the composition of claim 6.

13. A method useful for treating or preventing migraine comprising administering to a mammal in need of such treatment or prevention, an effective amount of a compound according to claims 1 to 5 or the composition of claim 6.

14. Use of a compound of any one of formula I-A, I-B or I-C according to claims
20 1 to 5 for the preparation of a medicament for treatment or prevention of a condition in a mammal, the treatment or prevention of which is affected or facilitated by the neuromodulatory effect of mGluR5 antagonists.

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