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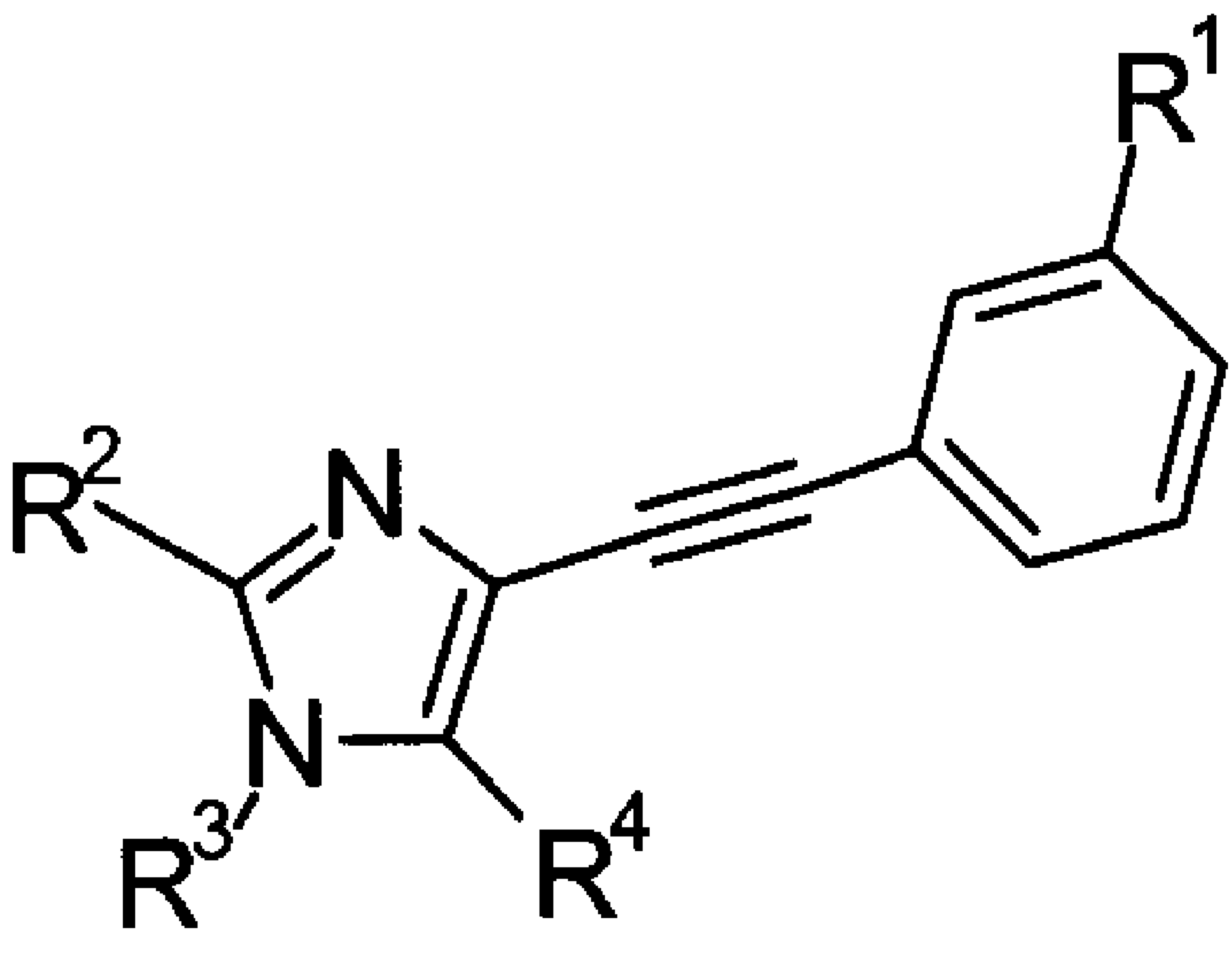
(54) Titre : DERIVES D'IMIDAZOLES SUBSTITUES PAR HETEROARYLE, UTILISES COMME ANTAGONISTES DU RECEPTEUR DE GLUTAMATE

(54) Title: HETEROARYL-SUBSTITUTED IMIDAZOLE DERIVATIVES AS GLUTAMATE RECEPTOR ANTAGONISTS



I

(57) Abrégé/Abstract:
The present invention relates to imidazole derivatives of the general formula (I) wherein R^1, R^2, R^3 and R^4 are as defined in the specification as well as to pharmaceutically acceptable salts thereof and to processes for the preparation thereof. The invention

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(57) **Abrégé(suite)/Abstract(continued):**
also relates to the use of said imidazole derivatives for the preparation of medicaments and to medicaments containing them for the prevention or the treatment of mGluR5 receptor mediated disorders, such as acute and/or chronic neurological disorders, in particular anxiety, or for the treatment of chronic and acute pain.

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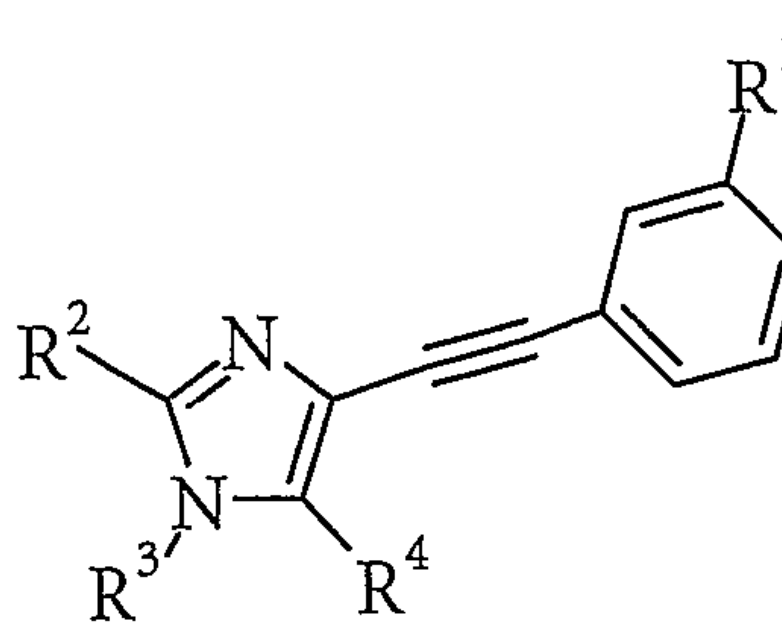
(54) Title: HETEROARYL-SUBSTITUTED IMDAZOLE DERIVATIVES AS GLUTAMATE RECEPTOR ANTAGONISTS

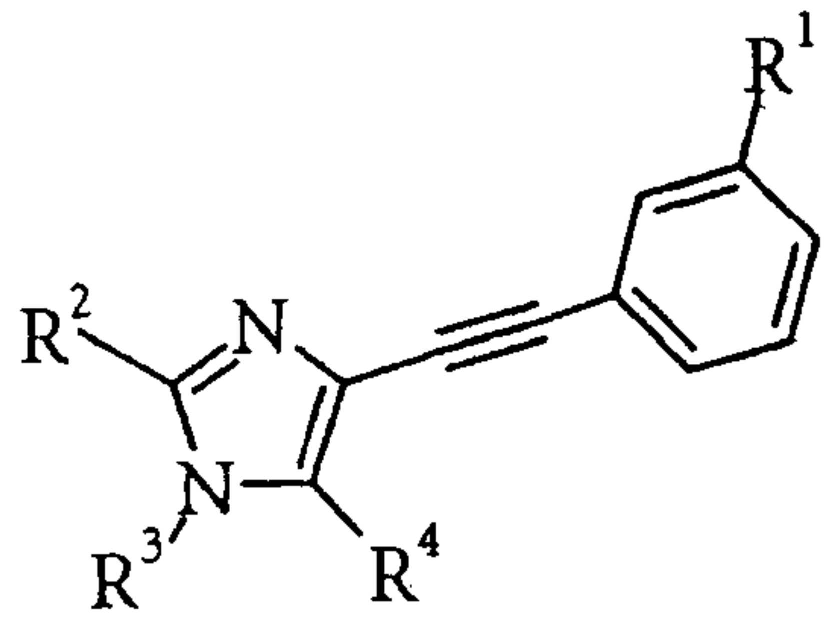


(I)

(57) Abstract: The present invention relates to imidazole derivatives of the general formula (I) wherein R^1, R^2, R^3 and R^4 are as defined in the specification as well as to pharmaceutically acceptable salts thereof and to processes for the preparation thereof. The invention also relates to the use of said imidazole derivatives for the preparation of medicaments and to medicaments containing them for the prevention or the treatment of mGluR5 receptor mediated disorders, such as acute and/or chronic neurological disorders, in particular anxiety, or for the treatment of chronic and acute pain.

HETEROARYL-SUBSTITUTED IMIDAZOLE DERIVATIVES AS GLUTAMATE RECEPTOR ANTAGONISTS

The present invention relates to imidazole derivatives of the general formula



I

wherein

R^1 signifies halogen, lower alkyl, lower alkoxy, CF_3, CF_2H, OCF_3, OCF_2H, or cyano;

R^2 signifies lower alkyl;

R^3 signifies heteroaryl, which is optionally substituted by one, two or three substituents, selected from the group consisting of halogen, lower alkyl, cycloalkyl, lower alkyl-halogen, cyano, lower alkoxy, NR'R" or by 1-morpholinyl, or by 1-pyrrolidinyl, optionally substituted by $(CH_2)_{0,1}OR$, or by piperidinyl, optionally substituted by $(CH_2)_{0,1}OR$, or by thiomorpholinyl, 1-oxo-thiomorpholinyl or 1,1-dioxo-thiomorpholinyl or by piperazinyl, optionally substituted by lower alkyl or $(CH_2)_{0,1}$-cycloalkyl;

R is hydrogen, lower alkyl or $(CH_2)_{0,1}$-cycloalkyl;

R', R" are independently from each other hydrogen, lower alkyl, $(CH_2)_{0,1}$-cycloalkyl or $(CH_2)_{1,2}$-OR;

R^4 is hydrogen, C(O)H, or CH_2R^5 wherein R^5 is hydrogen, OH, C_1-C_6-alkyl, C_3-C_{12}-cycloalkyl,

as well as to pharmaceutically acceptable salts thereof.

WO 02/46166 of which the Applicant is proprietor already discloses substituted imidazole derivatives as $mGluR_5$ antagonists.

Nevertheless the compounds of the instant invention surprisingly shown less side-effects than the compounds of the prior art.

It has now surprisingly been found that the compounds of general formula I are metabotropic glutamate receptor antagonists. Compounds of formula I are distinguished by having valuable therapeutic properties. They can be used in the treatment or prevention of mGluR5 receptor mediated disorders.

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

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

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

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

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

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

Disorders mediated full or in part by mGluR5 are for example acute, traumatic and chronic degenerative processes of the nervous system, such as Alzheimer's disease, senile dementia, Parkinson's disease, Huntington's chorea, amyotrophic lateral sclerosis and multiple sclerosis, psychiatric diseases such as schizophrenia and anxiety, depression, pain and drug dependency *(Expert Opin. Ther. Patents (2002), 12, (12)).*

Selective mGluR5 antagonists are especially useful for the treatment of anxiety and pain.

The invention relates to compounds of formula I and their pharmaceutically acceptable salts, to the above-mentioned compounds as pharmaceutically active substances and their production.

The invention also relates to a process for preparing a compound according to general formula I following the general procedures as outlined above for compounds of formula I.

Moreover the invention relates also to medicaments containing one or more compounds of the present invention and pharmaceutically acceptable excipients for the treatment and prevention of mGluR5 receptor mediated disorders, such as acute and/or chronic neurological disorders, in particular anxiety and chronic or acute pain.

The invention also relates to the use of a compound in accordance with the present invention as well as its pharmaceutically acceptable salt for the manufacture of medicaments for the treatment and prevention of mGluR5 receptor mediated disorders as outlined above.

The following definitions of general terms used in the present description apply irrespective of whether the terms in question appear alone or in combination. The term “lower alkyl" used in the present description denotes straight-chain or branched saturated hydrocarbon residues with 1 to 6 carbon atoms, preferably with 1 to 4 carbon atoms, such as methyl, ethyl, n-propyl, i-propyl, n-butyl, t-butyl and the like.

The term “lower alkoxy” denotes a group wherein the alkyl residues are as defined above and which is attached via an oxygen atom.

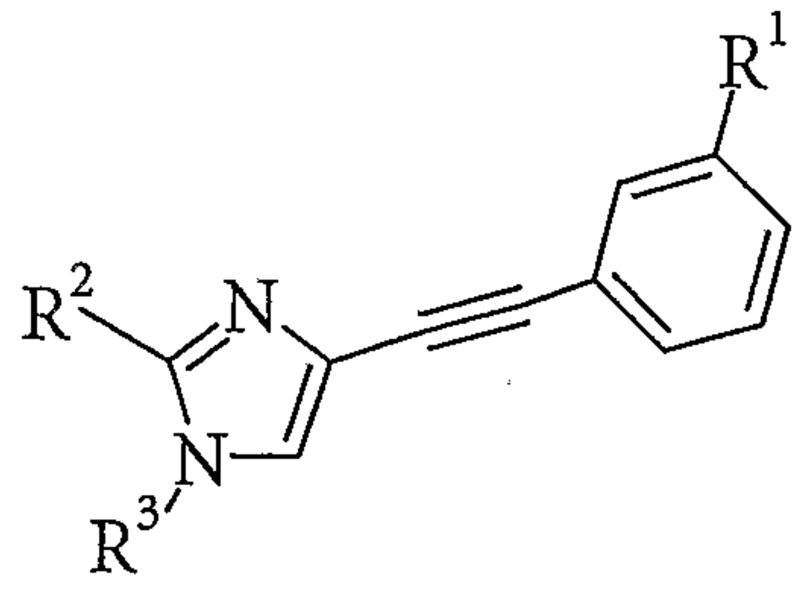
The term "halogen" denotes fluorine, chlorine, bromine and iodine.

The term "heteroaryl" refers to an aromatic 5- or 6-membered ring containing one or more heteroatoms selected from nitrogen, oxygen or sulphur. Preferred are those heteroaryl groups selected from nitrogen or oxygen. Especially preferred are the groups pyrazinyl, pyridinyl, pyrimidinyl, pyridazinyl or furanyl. Examples of such especially preferred heteroaryl groups are pyridin-2,3 or 4-yl, pyrimidin-2-yl, pyridazin-3 or 5-yl or furan-3-yl.

The term "cycloalkyl" denotes a saturated carbocyclic group, containing 3 – 12 carbon atoms, preferably, 3-6 carbon atoms.

The term "pharmaceutically acceptable salt" refers to any salt derived from an inorganic or organic acid or base.

Encompassed in formula I are also the compounds of general formula IA:



IA

wherein

R^1 signifies halogen, lower alkyl, lower alkoxy, CF_3 or cyano;

R^2 signifies lower alkyl;

R^3 signifies heteroaryl, which is optionally substituted by one, two or three substituents, selected from the group consisting of halogen, lower alkyl, lower alkyl-halogen, cyano, NR'R" or by
1-morpholinyl, or by
1-pyrrolidinyl, optionally substituted by $(CH_2)_{0,1}OR$, or by
piperidinyl, optionally substituted by $(CH_2)_{0,1}OR$, or by
1,1-dioxo-thiomorpholinyl or by
piperazinyl, optionally substituted by lower alkyl or $(CH_2)_{0,1}$-cycloalkyl;

R is hydrogen, lower alkyl or $(CH_2)_{0,1}$-cycloalkyl;

R', R" are independently from each other hydrogen, lower alkyl, $(CH_2)_{0,1}$-cycloalkyl or $(CH_2)_{1,2}OR$;

as well as pharmaceutically acceptable salts thereof.

Preferred compounds of formula I are those, in which R^1 is chloro or cyano.

Especially preferred are those compounds from this group, in which R^3 is unsubstituted or substituted pyrimidin-2yl, for example the following compounds:

2-[4-(3-chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-pyrimidine,
2-[4-(3-chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-4-trifluoromethyl-pyrimidine,
2-[4-(3-chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-4-methyl-pyrimidine,
2-[4-(3-chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-5-fluoro-pyrimidine or

3-[1-(4-Methoxy-pyrimidin-2-yl)-2-methyl-1H-imidazol-4-ylethynyl]-benzonitrile.

Especially preferred are further those compounds of this group, wherein R^3 is unsubstituted or substituted pyridin-2-yl, for example the following compounds:

3-[2-methyl-1-(6-methyl-pyridin-2-yl)-1H-imidazol-4-ylethynyl]-benzonitrile,
3-[2-methyl-1-(6-trifluoromethyl-pyridin-2-yl)-1H-imidazol-4-ylethynyl]-benzonitrile,
3-[2-methyl-1-(5-methyl-pyridin-2-yl)-1H-imidazol-4-ylethynyl]-benzonitrile,
3-[2-methyl-1-(4-methyl-pyridin-2-yl)-1H-imidazol-4-ylethynyl]-benzonitrile,
2-[4-(3-chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-6-methyl-pyridine,
2-[4-(3-chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-6-trifluoromethyl-pyridine,
2-[4-(3-chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-5-methyl-pyridine,
3-[4-(3-chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-5-fluoro-pyridine,
2-[4-(3-chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-5-methyl-pyridine,
2-[4-(3-chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-4-methyl-pyridine,
3-[4-(3-chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-5-fluoro-pyridine or
4-{6-[4-(3-chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-pyridin-2-yl}-thiomorpholine.

Further preferred are those compounds of this group, wherein R^3 is unsubstituted or substituted pyridin-3-yl, for example the following compounds:

2-chloro-5-[4-(3-chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-pyridine or
2-[4-(3-chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-4-methyl-pyridine.

Preferred are further those compounds of this group, wherein R^3 is pyridazinyl or pyrazinyl which may be substituted or unsubstituted, for example the following compounds:

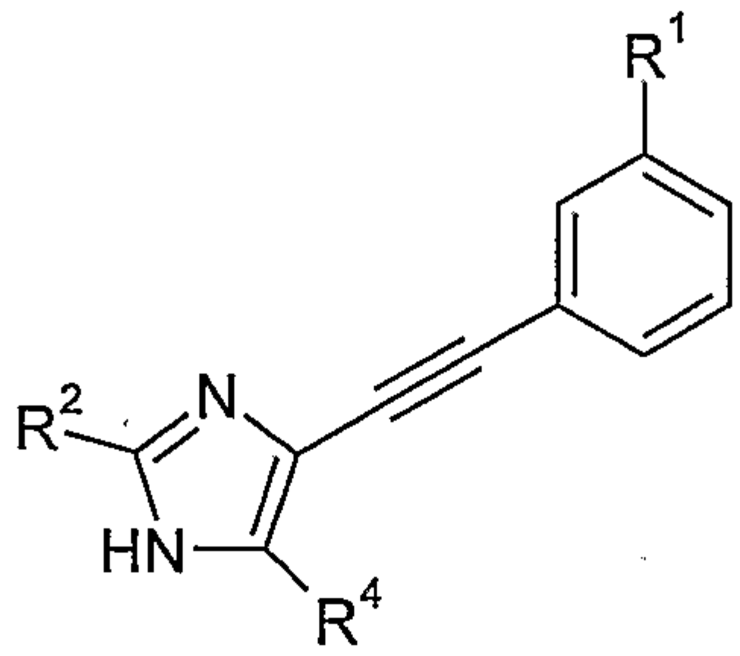
5-[4-(3-chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-3-methyl-pyridazine,
3-[4-(3-chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-6-methyl-pyridazine or
2-[4-(3-Chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-pyrazine

Further preferred are those compounds of this group, wherein R^3 is furan-3-yl, for example the following compound:

5-(3-chloro-phenylethynyl)-1-furan-3-yl-2-methyl-1H-imidazole.

The compounds of formula I or IA of the invention may be prepared according to a process which comprises:

(a) reacting a compound of formula II



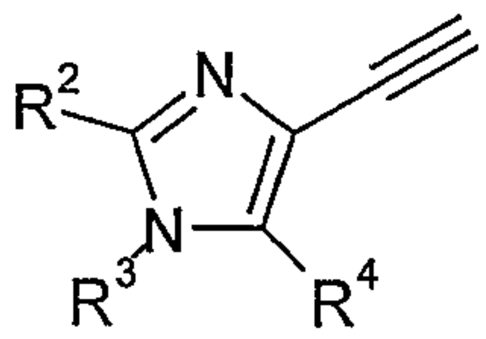
(II)

wherein R^1, R^2 and R^4 have the meanings as defined above,
with a compound of formula III

$$R^3\text{-}Z \qquad \text{(III)}$$

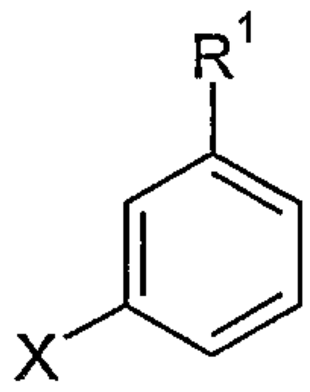
wherein R^3 has the meanings as defined above and Z is halogen or $B(OH)_2$; or

(b) reacting a compound of formula IV



(IV)

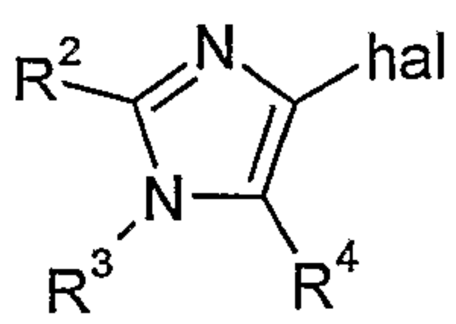
wherein R^2, R^3 and R^4 have the meanings as defined above,
with a compound of formula V



(V)

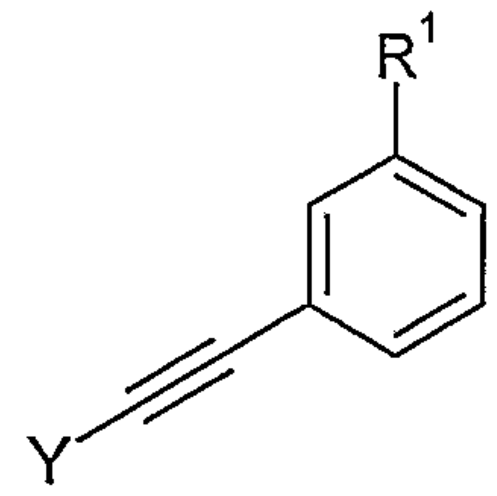
wherein R^1 has the meanings as defined above and X is halogen; or

(c) reacting a compound of formula VI



(VI)

wherein R^2, R^3 and R^4 have the meanings as defined above and hal is halogen,
with a compound of formula VII



(VII)

wherein R^1 has the meaning as defined above and Y is trimethylsilyl or hydrogen,

and if desired,

converting the compounds obtained into pharmaceutically acceptable acid addition salts.

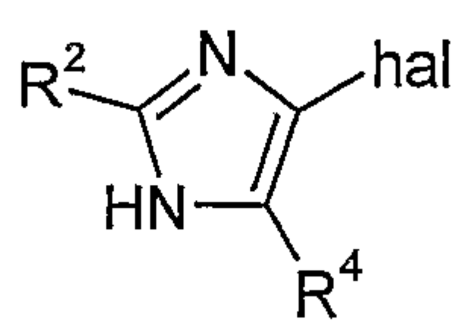
The reaction as described in (a) may be carried out in accordance with standard procedures, e.g. by arylation of a compound of formula II using an aromatic boronic acid and a copper catalyst in a solvent like dichloromethane or tetrahydrofurane [see e.g. Colmann et al., Org. Lett. 2:1233 (2000)] or by heating a compound of formula II and a compound of formula III wherein Z is halogen with a base like potassium carbonate or cesium carbonate in a solvent like dimethylformamide, or Pd catalyzed according to Buchwald conditions [see e.g. Example 8; Buchwald et al., Tetrahedron Lett. 40:2657 (1999)]. The reaction as described in (b) may be carried out by a Sonogashira coupling of a compound of formula IV and a compound of formula V in the presence of, e.g., CuI, $(Ph_3P)_2PdCl_2$, Et_3N in a solvent like tetrahydrofuran or dimethylformamide [Sonogashira et al., Synthesis 777 (1977)]. In one embodiment the meaning X in compounds of formula V is bromine or iodine. The reaction as described in (c) above may, e.g. be carried out in the presence of CuI, $(Ph_3P)_2PdCl_2$, Et_3N, n-Bu_4F in a solvent like tetrahydrofuran or dimethylformamide.

The salt forms are made by standard procedures known to the skilled artisan.

The compounds of formulae II, IV, VI und VII are novel and also an embodiment of the present invention.

The compounds of formulae III and V are commercially available or their preparation is known to the skilled artisan.

The compounds of formula II may be prepared by reacting a compound of formula VIII

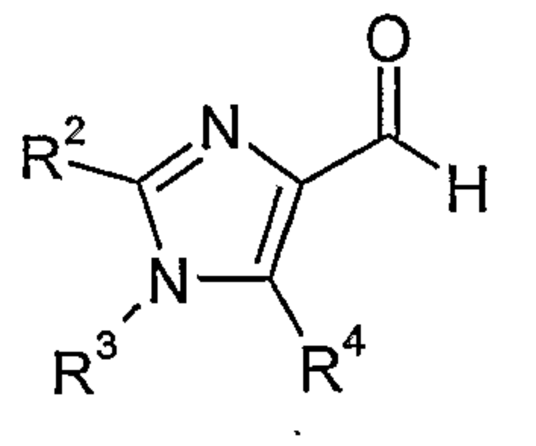


(VIII)

wherein R^2 and R^4 have the above meanings and hal is halogen,
with a compound of formula VII as above.

The compounds of formula VIII may be prepared as described e.g. in Cliff and Pyne [Synthesis 681-682 (1994)].

The compounds of formula IV may be prepared by reacting a compound of formula IX



(IX)

wherein R^2, R^3 and R^4 have the meanings as defined above,
with dimethyl (1-diazo-2-oxopropyl)phosphonate as described in Ohira [Synth.Comm. 19:561-564 (1989)].

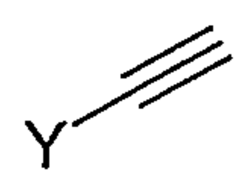
Compounds of formula VI may be prepared by reacting a compound of formula VIII as above with a compound of formula X

$$R^3\text{-B(OH)}_2 \qquad \text{(X)}$$

wherein R^3 has the meanings as defined above.

The reaction may take place by arylation of a compound of formula VIII using an aromatic boronic acid (compound of formula X) and a copper catalyst in a solvent like dichloromethane or tetrahydrofurane under an oxygen atmosphere [see e.g. Colmann et al., Org.Lett. 2:1233 (2000)].

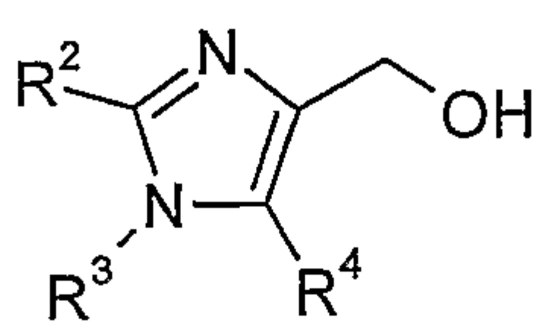
Compounds of formula VII may be prepared by reacting a compound of formula V as above with a compound of formula XI



(XI)

The reaction may take place by a Sonogashira coupling in the presence of eg. CuI, $(Ph_3P)_2PdCl_2$, Et_3N in a solvent like tetrahydrofuran or dimethylformamide [Sonogashira et al., Synthesis 777 (1977)].

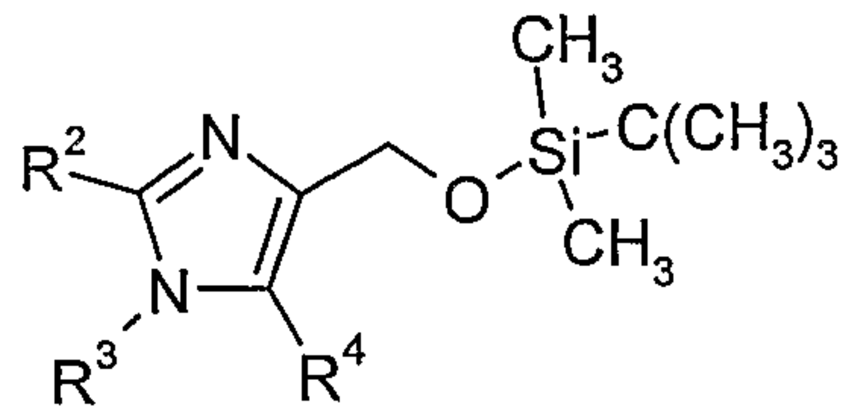
Compounds of formula IX may be prepared by oxidizing a compound of formula XII



(XII)

according to methods known to the skilled artisan.

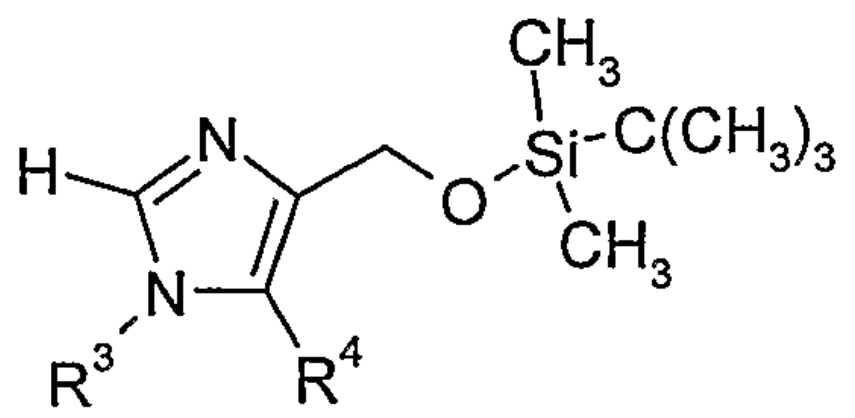
Compounds of formula XII may be prepared by deprotecting a compound of formula XIII



(XIII)

according to methods known to the skilled artisan.

Compounds of formula XIII may be prepared by alkylating a compound of formula XIV



(XIV)

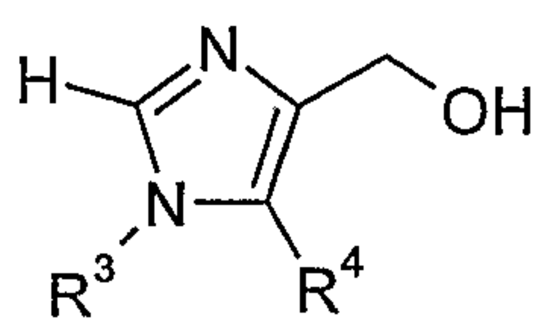
with an alkylating agent of formula XVa

R^2-hal (XVa)

according to methods known to the skilled artisan.

Starting compounds of formula XVa are commercially available.

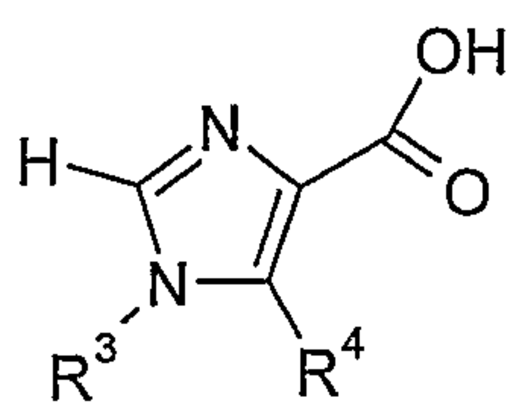
Compounds of formula XIV may be prepared by treating a compound of formula XV



(XV)

with tert.-butyl dimethyl silyl chloride according to methods known to the skilled artisan.

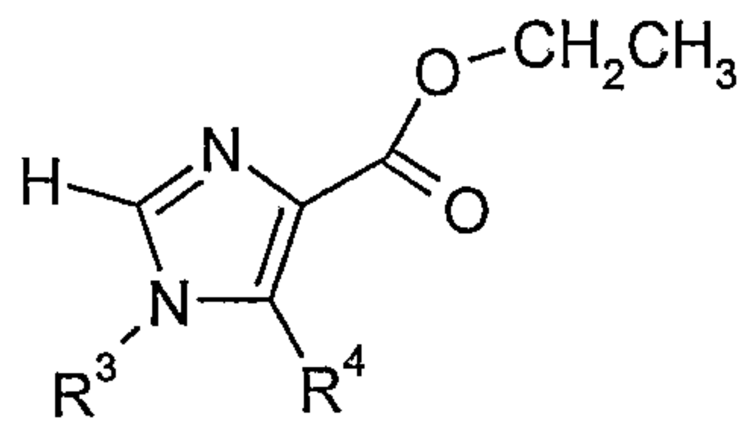
Compounds of formula XV may be prepared by treating a compound of formula XVI



(XVI)

with a reducing agent according to methods known to the skilled artisan.

Compounds of formula XVI may be prepared by hydrolysing a compound of formula XVII



(XVII)

according to methods known to the skilled artisan.

Compounds of formula XVII may be prepared by treating a compound of formula XVIII

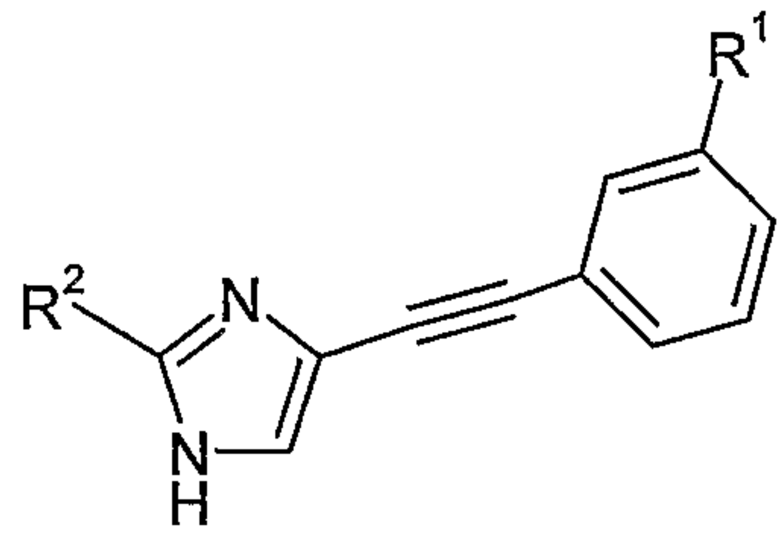
R^3-NH_2 (XVIII)

with e.g. triethyl orthoformate, ethylnitro acetate, glacial acetic acid and iron powder according to methods known to the skilled artisan.

Compounds of formula XVIII are commercially available.

The compounds of general formula I, IA and their pharmaceutically acceptable salts can also be manufactured by the general procedure, as shown below:

a) reacting a compound of formula



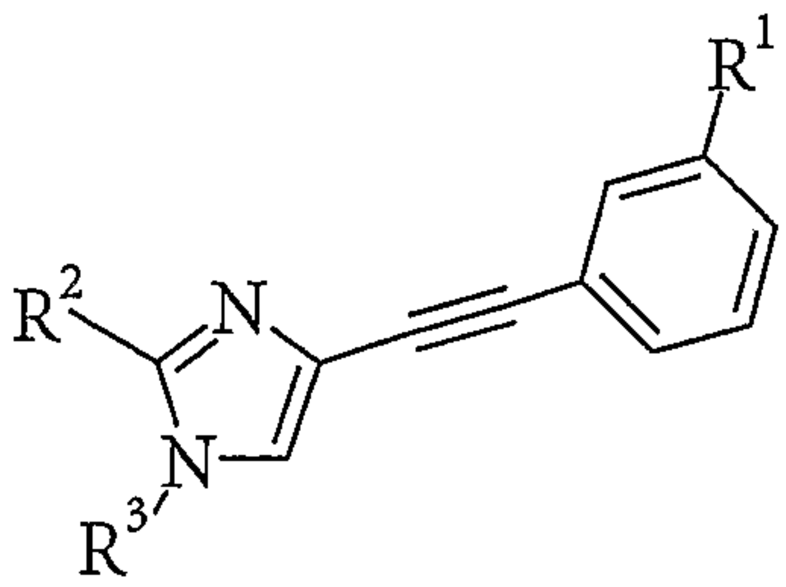
II

with a compound of formula

R^3-Z III

wherein R^3 has the meanings as defined above and Z is halogen or $B(OH)_2$,

to a compound of formula



IA

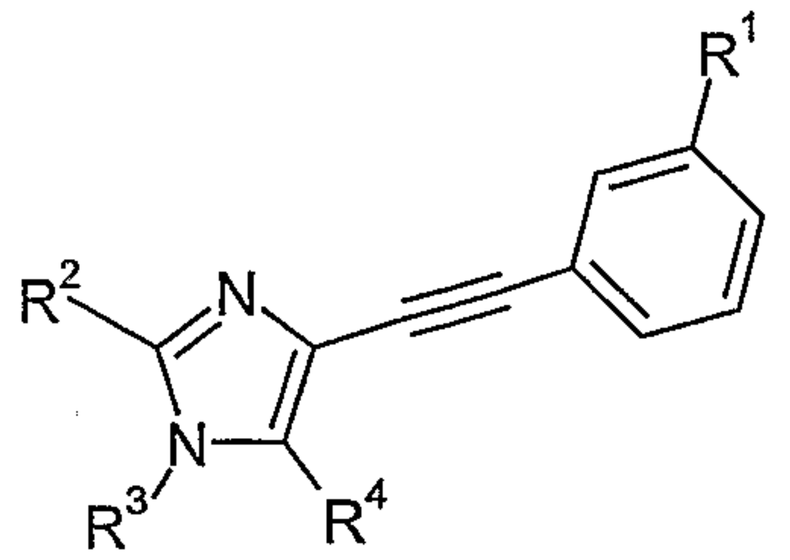
wherein R^1, R^2 and R^3 are as described above and Hal is preferably chloro or fluoro, and

if desired, when R^4 is other than hydrogen,

a) reacting the compound of formula IA with a compound of formula:

$$R^4Hal \quad VI$$

to a compound of formula



I

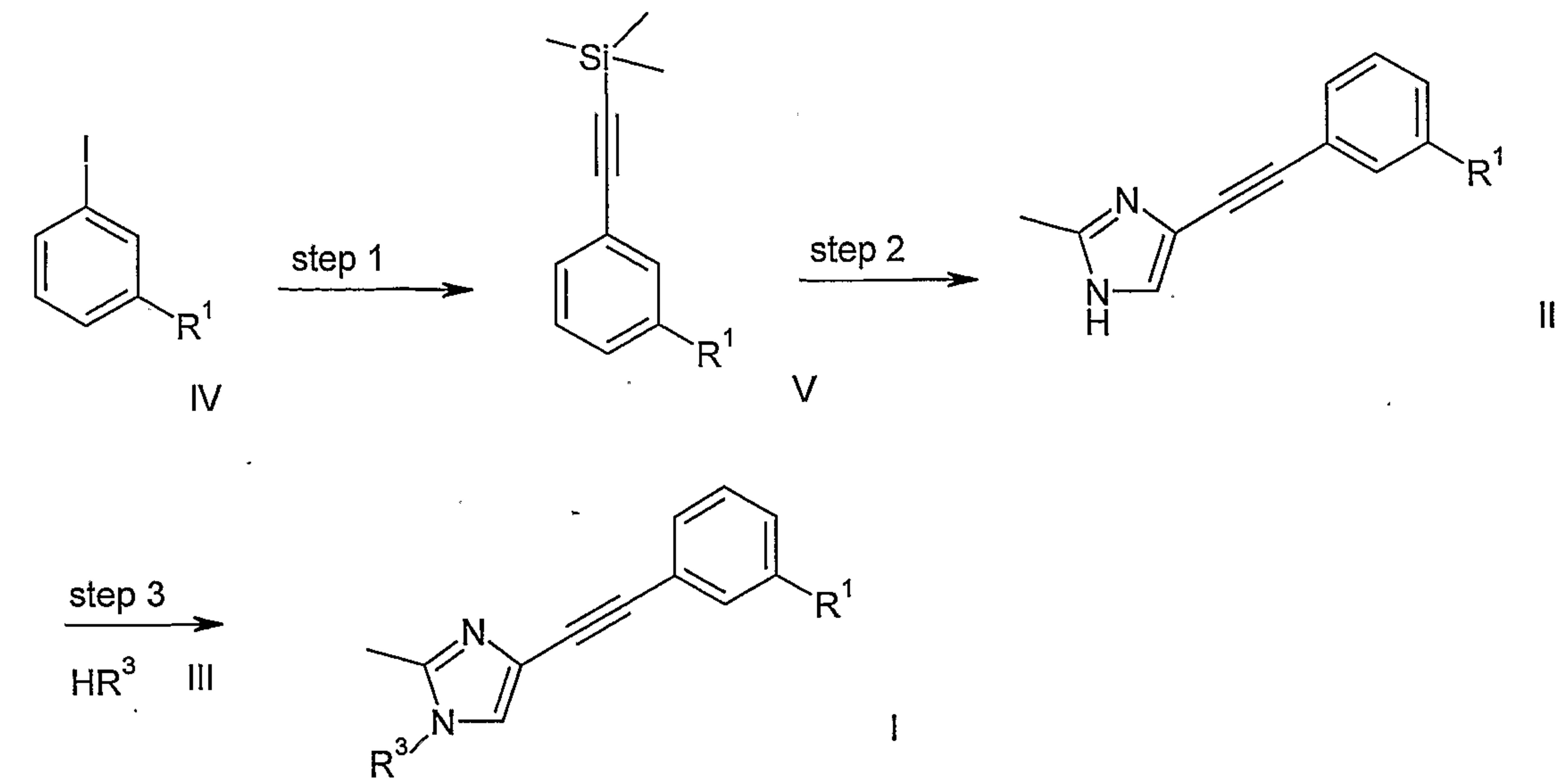
wherein R^1, R^2, R^3 and R^4 are as described above, and if desired,

converting the compounds obtained into pharmaceutically acceptable acid addition salts.

The procedure is summarized in scheme 1.

The starting materials are known compounds or may be prepared according to methods known in the art, for example as described in example C.

Scheme 1



Step 1

A compound of formula IV, for example 1-chloro-3-iodobenzene is dissolved in THF and triethyl amine. This mixture is evacuated and backfilled with argon to remove oxygen from the solution. Triphenylphosphine and bis(triphenylphosphine)palladium(II)chloride are added and the reaction mixture is stirred at room temperature for about 1 h. Copper(I)iodide and trimethylsilylacetylen are added. The reaction mixture is stirred at room temperature overnight. After purification the desired product of formula V is obtained.

Step 2

Solution 1: The obtained compound of formula V, for example (3-chloro-phenylethynyl)-trimethyl-silane and 5-iodo-2-methyl-1H-imidazole (synthesis: M.D. Cliff, S.G. Pyne, *Synthesis* 1994, 681-682) are dissolved in dry THF and dry DMF. This mixture is evacuated and backfilled with argon to remove oxygen from the solution. Solution 2: Triphenylphosphine, bis(triphenylphosphine)-palladium(II)chloride, copper(I)iodide and triethyl amine are dissolved in dry THF. This mixture was also evacuated and backfilled with argon to remove oxygen from the solution.

Solution 2 is heated to about 40 °C and solution 1 is added dropwise. The reaction mixture is heated to about 60 °C and tetrabutylammonium fluoride solution is added dropwise. The reaction is than stirred at room temperature overnight. After purification the desired product of formula II is obtained. This material which still contained tetrabutylammonium salts is used without any further purification for the next step.

Step 3

The compound of formula II, for example 4-(3-chloro-phenylethynyl)-2-methyl-1H-imidazole is dissolved in dimethyl formamide. Potassium carbonate and a compound of formula III, for example 2-chloro-pyrimidine are added and the reaction mixture is stirred at about 80 °C overnight. After work-up and purification the desired compound of formula I is obtained.

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, hydrobromic acid, sulphuric acid, nitric acid, phosphoric acid or citric acid, formic acid, fumaric acid, maleic acid, acetic acid, succinic acid, tartaric acid, methanesulphonic acid, p-toluenesulphonic 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, ethanol addiction, 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 billiay colic, menstruation, migraine and gout.

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

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 $CaCl_2$, 25 mM $MgCl_2$ binding buffer at pH 7.4 to a final assay concentration of 20 µg protein/ well.

Saturation isotherms were determined by addition of twelve [^{3}H]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 [^{3}H]MPEP (2nM) and IC_{50} 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.

For functional assays, [Ca^{2+}]i measurements were performed as described previously by Porter et al. [Br. J. Pharmacol. 128:13-20 (1999)] on recombinant human mGlu 5a receptors in HEK-293 cells. The cells were dye loaded using Fluo 4-AM (obtainable by FLUKA, 0.2µM final concentration). [Ca^{2+}]i measurements were performed using a fluorometric imaging plate reader (FLIPR, Molecular Devices Corporation, La Jolla, CA, USA). Antagonist evaluation was performed following a 5 min preincubation with the test compounds followed by the addition of a submaximal addition of agonist.

The inhibition (antagonists) curves were fitted with a four parameter logistic equation giving IC_{50}, and Hill coefficient using an iterative non linear curve fitting software (Xcel fit).

For binding experiments the Ki values of the compounds tested are given. The Ki value is defined by the following formula:

$$K_i = IC_{50} / [1 + L / K_d]$$

in which the IC50 values are those concentrations of the compounds tested which cause 50 % inhibition of the competing radioligand ([^{3}H]MPEP). L is the concentration of radioligand used in the binding experiment and the K_d value of the radioligand is empirically determined for each batch of membranes prepared.

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 $K_i < 160$ nM.

Example No.	Ki (nM)	Example No.	Ki (nM)	Example No.	Ki (nM)	Example No.	Ki (nM)
1	63	9	11	26	94	35	39
2	28	20	11	27	130	38	99
3	31	22	60	31	88	39	9
8	157	25	32	33	66	40	68

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 as 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 0.01-20 mg/kg/day, with a dosage of 0.1-10 mg/kg/day being preferred for all of the indications described. The daily dosage for an adult human being weighing 70 kg accordingly lies between 0.7-1400 mg per day, preferably between 7 and 700 mg per day.

The following examples are provided to further elucidate the invention:

Example 1

2-[4-(3-Chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-pyrimidine

4-(3-Chloro-phenylethynyl)-2-methyl-1H-imidazole (200 mg, 0.92 mmol) was dissolved in 5 mL dimethyl formamide. Potassium carbonate (255 mg, 1.85 mmol) and 2-chloro-pyrimidine (159 mg, 1.38 mmol) were added and the reaction mixture was stirred at

80°C overnight. The reaction mixture was poured into 70 mL water and extracted three times with ethyl acetate (100 mL each). The combined organic extracts were dried with sodium sulfate, filtered and evaporated. The crude product was recrystallized from diisopropyl ether and the desired compound was obtained as an off-white solid (212 mg, 78 %), MS:m/e = 295.1 (M+H$^+$).

Example 2

2-[4-(3-Chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-4-trifluoromethyl-pyrimidine

The title compound, MS: m/e = 363.1 (M+H$^+$), was prepared in accordance with the general method of example 1 from 4-(3-chloro-phenylethynyl)-2-methyl-1H-imidazole and 2-chloro-4-(trifluoromethyl)pyrimidine.

Example 3

3-[2-Methyl-1-(6-methyl-pyridin-2-yl)-1H-imidazol-4-ylethynyl]-benzonitrile

The title compound, MS: m/e = 299.2 (M+H$^+$), was prepared in accordance with the general method of example 1 from 3-(2-methyl-1H-imidazol-4-ylethynyl)-benzonitrile and 2-fluoro-6-methylpyridine.

Example 4

3-[2-Methyl-1-(6-trifluoromethyl-pyridin-2-yl)-1H-imidazol-4-ylethynyl]-benzonitrile

The title compound, MS: m/e = 353.1 (M+H$^+$), was prepared in accordance with the general method of example 1 from 3-(2-methyl-1H-imidazol-4-ylethynyl)-benzonitrile and 2-fluoro-6-trifluoromethylpyridine.

Example 5

3-[2-Methyl-1-(5-methyl-pyridin-2-yl)-1H-imidazol-4-ylethynyl]-benzonitrile

The title compound, MS: m/e = 299.2 (M+H$^+$), was prepared in accordance with the general method of example 1 from 3-(2-methyl-1H-imidazol-4-ylethynyl)-benzonitrile and 2-fluoro-5-methylpyridine.

Example 6

3-[2-Methyl-1-(4-methyl-pyridin-2-yl)-1H-imidazol-4-ylethynyl]-benzonitrile

The title compound, MS: m/e = 299.2 (M+H$^+$), was prepared in accordance with the general method of example 1 from 3-(2-methyl-1H-imidazol-4-ylethynyl)-benzonitrile and 2-fluoro-4-methylpyridine.

Example 7

2-Chloro-5-[4-(3-chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-pyridine

The title compound, MS: m/e = 328.1 (M$^+$), was prepared in accordance with the general method of example 1 from 4-(3-chloro-phenylethynyl)-2-methyl-1H-imidazole and 2-chloro-5-fluoropyridine.

Example 8

5-[4-(3-Chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-3-methyl-pyridazine

The title compound, MS: m/e = 309.2 ($M+H^+$), was prepared in accordance with the general method of example 1 from 4-(3-chloro-phenylethynyl)-2-methyl-1H-imidazole and 5-chloro-3-methyl-pyridazine.

Example 9

4-(3-Chloro-phenylethynyl)-1-furan-3-yl-2-methyl-1H-imidazole

4-(3-Chloro-phenylethynyl)-2-methyl-1H-imidazole (200 mg, 0.92 mmol) was dissolved in 10 mL dichloromethane. Powdered molecular sieves (3 A, 200 mg), 3-furane-boronic acid (207 mg, 1.85 mmol) and $[Cu(OH)TMEDA]_2Cl_2$ (43 mg, 0.093 mmol) were added. Oxygen was bubbled through the reaction mixture for 10 minutes and stirring was continued at room temperature overnight. The reaction mixture was filtered through a dicalite speed plus pad and washed with 50 mL dichloromethane. The filtrate was washed with 50 mL water, dried with magnesium sulfate, filtered and evaporated. The crude product was purified by flash chromatography on silica gel (dichloromethane / methanol 100:0 -> 90:10 gradient) and the desired compound was as a brown oil (21 mg, 8 %), MS: m/e = 283.1 ($M+H^+$).

Example 10

2-[4-(3-Chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-4-methyl-pyrimidine

The title compound, MS: m/e = 309.1 ($M+H^+$), was prepared in accordance with the general method of example 1 from 4-(3-chloro-phenylethynyl)-2-methyl-1H-imidazole and 2-chloro-4-methyl-pyrimidine (prepared according to Harden, D. B.; Makrosz, M. J.; Strekowski, L.; *J. Org. Chem.* 1988, *53*, 4137).

Example 11

2-[4-(3-Chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-5-fluoro-pyrimidine

The title compound, MS: m/e = 313.1 ($M+H^+$), was prepared in accordance with the general method of example 1 from 4-(3-chloro-phenylethynyl)-2-methyl-1H-imidazole and 2-chloro-5-fluoro-pyrimidine.

Example 12

3-[4-(3-Chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-6-methyl-pyridazine

The title compound, MS: m/e = 309.3 ($M+H^+$), was prepared in accordance with the general method of example 1 from 4-(3-chloro-phenylethynyl)-2-methyl-1H-imidazole and 3-chloro-6-methyl-pyridazine.

Example 13

2-[4-(3-Chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-6-methyl-pyridine

The title compound, MS: m/e = 308.2 ($M+H^+$), was prepared in accordance with the general method of example 1 from 4-(3-chloro-phenylethynyl)-2-methyl-1H-imidazole and 2-fluoro-6-methyl-pyridine.

Example 14

2-[4-(3-Chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-6-trifluoromethyl-pyridine

The title compound, MS: m/e = 362.2 ($M+H^+$), was prepared in accordance with the general method of example 1 from 4-(3-chloro-phenylethynyl)-2-methyl-1H-imidazole and 2-fluoro-6-trifluoromethyl-pyridine.

Example 15

2-[4-(3-Chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-5-methyl-pyridine

The title compound, MS: m/e = 308.2 ($M+H^+$), was prepared in accordance with the general method of example 1 from 4-(3-chloro-phenylethynyl)-2-methyl-1H-imidazole and 2-fluoro-5-methyl-pyridine.

Example 16

2-[4-(3-Chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-4-methyl-pyridine

The title compound, MS: m/e = 308.2 ($M+H^+$), was prepared in accordance with the general method of example 1 from 4-(3-chloro-phenylethynyl)-2-methyl-1H-imidazole and 2-fluoro-4-methyl-pyridine.

Example 17

3-[4-(3-Chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-5-fluoro-pyridine

The title compound, MS: m/e = 312.1 ($M+H^+$), was prepared in accordance with the general method of example 1 from 4-(3-chloro-phenylethynyl)-2-methyl-1H-imidazole and 3,5-difluoro-pyridine.

Example 18

2-[4-(3-Chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-4-methyl-pyrimidine

The title compound, MS: m/e = 309.1 ($M+H^+$), was prepared in accordance with the general method of example 1 from 4-(3-chloro-phenylethynyl)-2-methyl-1H-imidazole and 2-chloro-4-methylpyrimidine.

Example 19

3-[2-Methyl-1-(4-methyl-pyrimidin-2-yl)-1H-imidazol-4-ylethynyl]-benzonitrile

The title compound, MS: m/e = 300.4 ($M+H^+$), was prepared in accordance with the general method of example 1 from 3-(2-methyl-1H-imidazol-4-ylethynyl)-benzonitrile and 2-chloro-4-methylpyrimidine.

Example 20

3-[1-(4-Methoxy-pyrimidin-2-yl)-2-methyl-1H-imidazol-4-ylethynyl]-benzonitrile

The title compound, MS: m/e = 316.1 (M+H$^+$), was prepared in accordance with the general method of example 1 from 3-(2-methyl-1H-imidazol-4-ylethynyl)-benzonitrile and 2-chloro-4-methoxypyrimidine.

Example 21

2-[4-(3-Chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-pyrazine

The title compound, MS: m/e = 295.3 (M+H$^+$), was prepared in accordance with the general method of example 1 from 4-(3-chloro-phenylethynyl)-2-methyl-1H-imidazole and 2-chloropyrazine.

Example 22

3-(2-Methyl-1-pyrazin-2-yl-1H-imidazol-4-ylethynyl)-benzonitrile

The title compound, MS: m/e = 286.1 (M+H$^+$), was prepared in accordance with the general method of example 1 from 3-(2-methyl-1H-imidazol-4-ylethynyl)-benzonitrile and 2-chloropyrazine.

Example 23

4-[4-(3-Chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-pyrimidine

The title compound, MS: m/e = 294.1/296.1 (M+H$^+$), was prepared in accordance with the general method of example 1 from 4-(3-chloro-phenylethynyl)-2-methyl-1H-imidazole and 4-chloro-pyrimidine.

Example 24

3-[4-(3-Chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-6-methyl-pyridazine

The title compound, MS: m/e = 309.3 (M+H$^+$), was prepared in accordance with the general method of example 1 from 4-(3-chloro-phenylethynyl)-2-methyl-1H-imidazole and 3-chloro-6-methylpyrazine.

Example 25

3-Chloro-6-[4-(3-chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-pyridazine

The title compound, MS: m/e = 329.1 (M$^+$), was prepared in accordance with the general method of example 1 from 4-(3-chloro-phenylethynyl)-2-methyl-1H-imidazole and 3,6-dichloropyridazine.

Example 26

3-[4-(3-Chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-6-methoxy-pyridazine

3-Chloro-6-[4-(3-chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-pyridazine (100 mg, 0.30 mmol) was dissolved in 2 mL methanol and 1.5 mL sodium methanolate solution were added. The reaction mixture was refluxed for 3h. After cooling to room temperature the reaction mixture was treated with 30 mL water and extracted three times with ethyl acetate (50 mL each). The combined organic extracts were dried with magnesium sulfate, filtered and evaporated and the desired product was obtained as a white solid (53 mg, 53%), MS: m/e = 325.3 (M+H$^+$).

Example 27

{6-[4-(3-Chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-pyridazin-3-yl}-dimethyl-amine

3-Chloro-6-[4-(3-chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-pyridazine (100 mg, 0.30 mmol) was dissolved in 2 mL dimethylforamide and dimethylamine hydrochloride (124 mg, 1.5 mmol) and cesium carbonate (396 mg, 1.2 mmol) were added. The reaction mixture was heated in the microwave at 140°C for 60 min. After cooling to room temperature the reaction mixture was treated with 50 mL water and extracted three times with ethyl acetate (50 mL each). The combined organic extracts were dried with magnesium sulfate, filtered and evaporated. The crude material was purified by flash chromatography (methylene chloride/methanol 100:0 -> 90:10 gradient) and the desired product was obtained as a white solid (57 mg, 55%), MS: m/e = 338.1 (M+H$^+$).

Example 28

2-[4-(3-Chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-6-methyl-pyridine

The title compound, MS: m/e = 308.2 (M$^+$), was prepared in accordance with the general method of example 1 from 4-(3-chloro-phenylethynyl)-2-methyl-1H-imidazole and 2-fluoro-6-methylpyridine.

Example 29

2-[4-(3-Chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-6-trifluoromethyl-pyridine

The title compound, MS: m/e = 362.2 (M$^+$), was prepared in accordance with the general method of example 1 from 4-(3-chloro-phenylethynyl)-2-methyl-1H-imidazole and 2-fluoro-6-trifluoromethyl-pyridine.

Example 30

2-[4-(3-Chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-5-methyl-pyridine

The title compound, MS: m/e = 308.2 (M$^+$), was prepared in accordance with the general method of example 1 from 4-(3-chloro-phenylethynyl)-2-methyl-1H-imidazole and 2-fluoro-5-methylpyridine.

Example 31

5-Methyl-2-[2-methyl-4-(3-trifluoromethyl-phenylethynyl)-imidazol-1-yl]-pyridine

The title compound, MS: m/e = 342.1 (M$^+$), was prepared in accordance with the general method of example 1 from 2-methyl-4-(3-trifluoromethyl-phenylethynyl)-1H-imidazole and 2-fluoro-5-methylpyridine.

Example 32

2-[4-(3-Chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-4-methyl-pyridine

The title compound, MS: m/e = 308.2 (M^+), was prepared in accordance with the general method of example 1 from 4-(3-chloro-phenylethynyl)-2-methyl-1H-imidazole and 2-fluoro-4-methylpyridine.

Example 33

2-Chloro-5-[2-methyl-4-(3-trifluoromethyl-phenylethynyl)-imidazol-1-yl]-pyridine

The title compound, MS: m/e = 362.3 (M^+), was prepared in accordance with the general method of example 1 from 2-methyl-4-(3-trifluoromethyl-phenylethynyl)-1H-imidazole and 2-chloro-5-fluoropyridine.

Example 34

3-[4-(3-Chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-5-fluoro-pyridine

The title compound, MS: m/e = 312.1 (M^+), was prepared in accordance with the general method of example 1 from 4-(3-chloro-phenylethynyl)-2-methyl-1H-imidazole and 3,5-difluoropyridine.

Example 35

3-[1-(5-Fluoro-pyridin-3-yl)-2-methyl-1H-imidazol-4-ylethynyl]-benzonitrile

The title compound, MS: m/e = 303.5 (M^+), was prepared in accordance with the general method of example 1 from 3-(2-methyl-1H-imidazol-4-ylethynyl)-benzonitrile and 3,5-difluoropyridine.

Example 36

3-Fluoro-5-[2-methyl-4-(3-trifluoromethyl-phenylethynyl)-imidazol-1-yl]-pyridine

The title compound, MS: m/e = 346.3 (M^+), was prepared in accordance with the general method of example 1 from 2-methyl-4-(3-trifluoromethyl-phenylethynyl)-1H-imidazole and 3,5-difluoropyridine.

Example 37

{5-[4-(3-Chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-pyridin-3-yl}-dimethyl-amine

The title compound, MS: m/e = 337.3 (M^+), was prepared in accordance with the general method of example 27 from 3-[4-(3-chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-5-fluoro-pyridine and dimethylamine hydrochloride.

Example 38

3-[1-(5-Dimethylamino-pyridin-3-yl)-2-methyl-1H-imidazol-4-ylethynyl]-benzonitrile

The title compound, MS: m/e = 328.4 (M^+), was prepared in accordance with the general method of example 27 from 3-[1-(5-fluoro-pyridin-3-yl)-2-methyl-1H-imidazol-4-ylethynyl]-benzonitrile and dimethylamine hydrochloride.

Example 39

4-{6-[4-(3-Chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-pyridin-2-yl}-thiomorpholine

The title compound, MS: m/e = 395.1, 397.1 ($M+H^+$), was prepared in accordance with the general method of example 27 from 2-[4-(3-chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-6-fluoro-pyridine and thiomorpholine.

Example 40

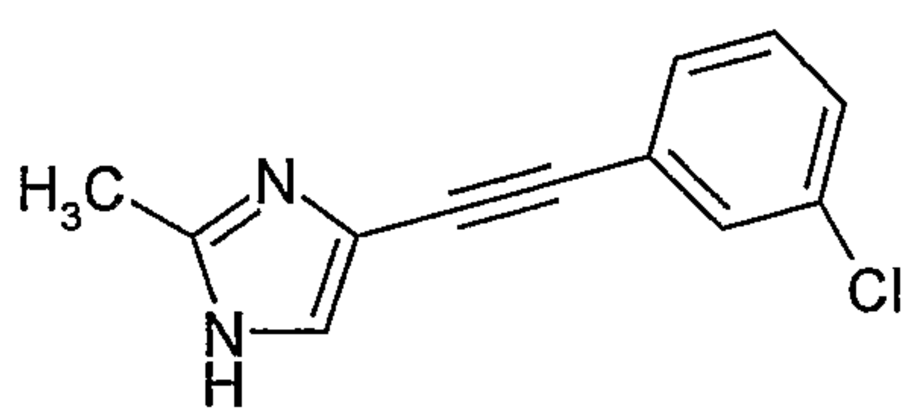
4-{6-[4-(3-Chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-pyridin-2-yl}-thiomorpholine-1,1-dioxide

4-{6-[4-(3-Chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-pyridin-2-yl}-thiomorpholine (250 mg, 0.63 mmol) was dissolved in 6 mL of methanol and Oxone monopersulfate triple salt (389 mg, 0.63 mmol) was added. The reaction mixture was stirred at room temperature for 4 days. Then additional Oxone monopersulfate triple salt (78 mg, 1.3 mmol) was added to drive the reaction to completion. The reaction mixture was treated with 50 mL water. The pH was adjusted to 9 by addition of sat. sodium bicarbonate solution, and the reaction mixture was extracted three times with methylene chloride (50 mL each). The combined organic extracts were dried with magnesium sulfate, filtered and evaporated. The crude material was purified by flash chromatography (heptane/ethyl acetate 1:4) and the desired product was obtained as a white solid (97 mg, 36%), MS: m/e = 427.4, 429.4 ($M+H^+$).

Synthesis of Intermediates:

Example A

4-(3-Chloro-phenylethynyl)-2-methyl-1H-imidazole



Step 1

(3-Chloro-phenylethynyl)-trimethyl-silane

1-Chloro-3-iodobenzene (10.0 g, 41.9 mmol) was dissolved in 100 mL dry THF and 17.5 mL triethyl amine. This mixture was evacuated and backfilled with argon several times to remove oxygen from the solution. Triphenylphosphine (329 mg, 1.25 mmol) and bis(triphenylphosphine)palladium(II)chloride (1.47 g, 2.09 mmol) were added and the reaction mixture was stirred at room temperature for 1 h. Copper(I)iodide (239 mg, 1.25 mmol) and trimethylsilylacetylen (6.28 g, 6.39 mmol) were added. The reaction mixture was stirred at room temperature overnight. The solvent was evaporated. The residue was taken up in 500 mL water and extracted three times with ethyl acetate (500 mL each). The combined organic extracts were dried with magnesium sulfate, filtered and evaporated. The crude product was purified by flash-chromatography on silica gel (heptane/ethyl acetate 100:0 -> 80:20 gradient). The desired product was obtained as a light yellow oil (7.38 g, purity ~70 %, yield ~59 %).

Step 2

4-(3-Chloro-phenylethynyl)-2-methyl-1H-imidazole

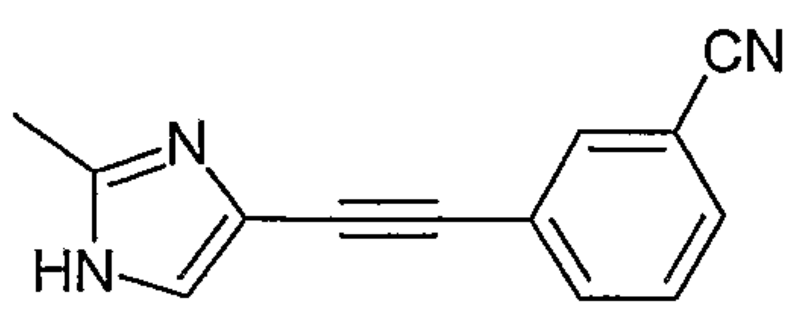
Solution 1: (3-Chloro-phenylethynyl)-trimethyl-silane (7.1 g, 70 %, 23.8 mmol) and 5-iodo-2-methyl-1H-imidazole (4.5 g, 21.6 mmol, synthesis: M.D. Cliff, S.G. Pyne, *Synthesis* 1994, 681-682) were dissolved in 50 mL dry THF and 5 mL dry DMF. This mixture was evacuated and backfilled with argon several times to remove oxygen from the solution.

Solution 2: Triphenylphosphine (113 mg, 0.43 mmol), bis(triphenylphosphine)-palladium(II)chloride (910 mg, 1.30 mmol), copper(I)iodide (41 mg, 0.22 mmol) and triethyl amine (4.52 mL, 32 mmol) were dissolved in 50 mL dry THF. This mixture was also evacuated and backfilled with argon several times to remove oxygen from the solution

Solution 2 was heated to 40 °C and solution 1 was added dropwise. The reaction mixture was heated to 60 °C and tetrabutylammonium fluoride solution (1M in THF, 28 mL, 28 mmol) was added dropwise during 45 min. The reaction was than stirred at room temperature overnight. The solvent was evaporated. The residue was taken up in 200 mL water and extracted three times with ethyl acetate (200 mL each). The combined organic extracts were dried with magnesium sulfate, filtered and evaporated. The crude product was purified by flash-chromatography on silica gel (methylene chloride/methanol 100:0 -> 95:5 gradient) and the desired product was obtained as a light brown solid (6.93 g, purity ~50 %, yield ~74 %). This material which still contained tetrabutylammonium salts was used without any further purification for the next step.

Example B

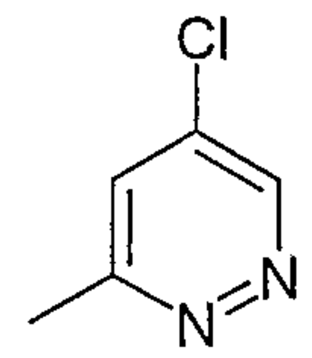
3-(2-methyl-1H-imidazol-4-ylethynyl)-benzonitrile



The title compound was prepared in accordance with the general method of example A (step 1 and 2) from 3-iodo-benzonitrile and 5-iodo-2-methyl-1H-imidazole.

Example C

5-Chloro-3-methyl-pyridazine



Step 1

3-Methyl-pyridazine-2-oxide

3-Methylpyridazine (10 g, 106 mmol) was dissolved in 62 mL acetic acid and hydrogen peroxide (30 % in water, 58 mL, 568 mmol) was added. The reaction mixture was heated at reflux for 6h and the solvents were evaporated. The residue was taken up in 200 mL water, neutralized with sodium carbonate and extracted three times with dichloromethane (150 mL each). The combined organic extracts were dried with magnesium sulfate, filtered and evaporated. The crude product was purified by three consecutive recrystallizations from toluene and the desired product was obtained as a white solid (800 mg, 6 %).

Step 2

6-Methyl-4-nitro-pyridazine-1-oxide

3-Methyl-pyridazine-1-oxide (450 mg, 4.09 mmol) was dissolved in 2 mL conc. sulfuric acid. Nitric acid (0.47 mL, 11.4 mmol) was added dropwise and the reaction mixture was heated at reflux for 4h. The reaction mixture was carefully poured into crushed ice and the mixture was extracted three times with dichloromethane (50 mL each). The combined organic extracts were dried with magnesium sulfate, filtered and evaporated. The crude product (270 mg, 42 %) was used without any further purification for the next step.

Step 3

4-Bromo-6-methyl-pyridazine-1-oxide

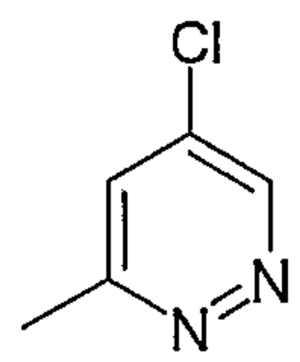
6-Methyl-4-nitro-pyridazine-1-oxide (270 mg, 1.74 mmol) was dissolved in 2 mL acetic acid, acetyl bromide (650 mL, 8.7 mmol) was added and the reaction mixture was heated at reflux for 1h. The reaction mixture was poured into crushed ice, the mixture was neutralized by addition of sodium hydroxide and extracted three times with dichloromethane (50 mL each). The combined organic extracts were dried with magnesium sulfate, filtered and evaporated. The crude product was purified by flash-chromatography on silica gel (heptane/ethyl acetate 80:20 -> 30:70 gradient) and the desired product was obtained as a light brown solid (150 mg, 45 %).

Step 4

5-Chloro-3-methyl-pyridazine

4-Bromo-6-methyl-pyridazine-1-oxide (150 mg, 0.79 mmol) was dissolved in 5 mL chloroform. Phosphorus trichloride (501 mg, 3.65 mmol, dissolved in 1 mL chloroform) was added at 0 °C. The reaction mixture was stirred at room temperature for 36h and then poured into crushed ice. The mixture was neutralized by addition of sodium carbonate and extracted three times with dichloromethane (50 mL each). The combined organic extracts were dried with magnesium sulfate, filtered and evaporated. The crude product was purified by flash-chromatography on silica gel (heptane/ethyl acetate 80:20 -> 30:70 gradient) and the desired product was obtained as a brown oil (70 mg, 69 %).

Example D
5-Chloro-3-methyl-pyridazine



Step 1: 3-Methyl-pyridazine-1-oxide

3-Methylpyridazine (10 g, 106 mmol) was dissolved in 62 mL acetic acid and hydrogen peroxide (30% in water, 58 mL, 568 mmol) was added. The reaction mixture was heated at reflux for 6h and the solvents were evaporated. The residue was taken up in 200 mL water, neutralized with sodium carbonate and extracted three times with dichloromethane (150 mL each). The combined organic extracts were dried with magnesium sulfate, filtered and evaporated. The crude product was purified by three consecutive recrystallizations from toluene and the desired product was obtained as a white solid (800 mg, 6%).

Step 2: 6-Methyl-4-nitro-pyridazine-1-oxide

3-Methyl-pyridazine-1-oxide (450 mg, 4.09 mmol) was dissolved in 2 mL conc. sulfuric acid. Nitric acid (0.47 mL, 11.4 mmol) was added dropwise and the reaction mixture was heated at reflux for 4h. The reaction mixture was carefully poured into crushed ice and the mixture was extracted three times with dichloromethane (50 mL each). The combined organic extracts were dried with magnesium sulfate, filtered and evaporated. The crude product (270 mg, 42%) was used without any further purification for the next step.

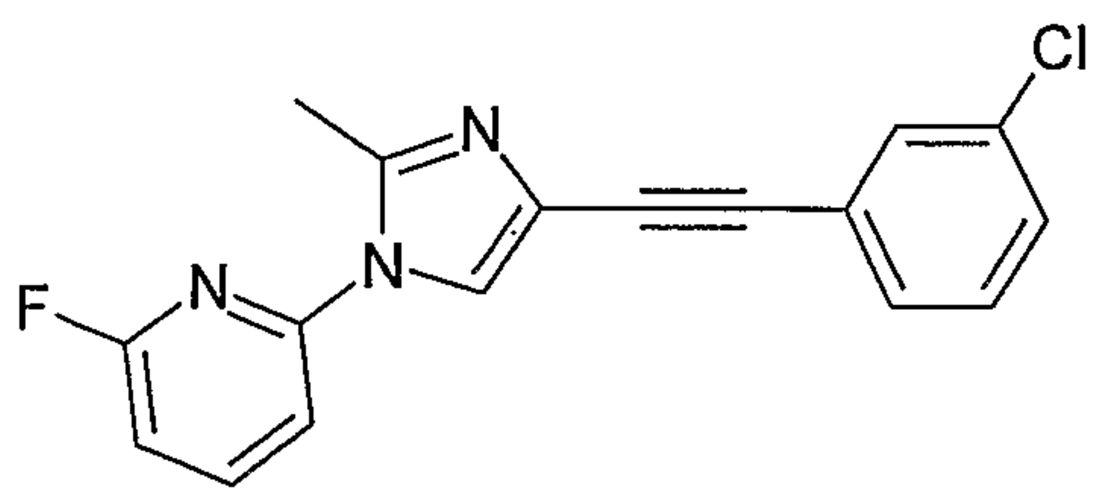
Step 3: 4-Bromo-6-methyl-pyridazine-1-oxide

6-Methyl-4-nitro-pyridazine-1-oxide (270 mg, 1.74 mmol) was dissolved in 2 mL acetic acid, acetyl bromide (650 mL, 8.7 mmol) was added and the reaction mixture was heated at reflux for 1h. The reaction mixture was poured into crushed ice, the mixture was neutralized by addition of sodium hydroxide and extracted three times with dichloromethane (50 mL each). The combined organic extracts were dried with magnesium sulfate, filtered and evaporated. The crude product was purified by flash-chromatography on silica gel (heptane/ethyl acetate 80:20 -> 30:70 gradient) and the desired product was obtained as a light brown solid (150 mg, 45%).

Step 4: 5-Chloro-3-methyl-pyridazine
4-Bromo-6-methyl-pyridazine-1-oxide (150 mg, 0.79 mmol) was dissolved in 5 mL chloroform. Phosphorus trichloride (501 mg, 3.65 mmol, dissolved in 1 mL chloroform) was added at 0°C. The reaction mixture was stirred at room temperature for 36h and then poured into crushed ice. The mixture was neutralized by addition of sodium carbonate and extracted three times with dichloromethane (50 mL each). The combined organic extracts were dried with magnesium sulfate, filtered and evaporated. The crude product was purified by flash-chromatography on silica gel (heptane/ethyl acetate 80:20 -> 30:70 gradient) and the desired product was obtained as a brown oil (70 mg, 69%).

Example E

2-[4-(3-Chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-6-fluoro-pyridine:



The title compound, MS: m/e = 312.0, 314.0 (M+H$^+$), was prepared in accordance with the general method of example 1 from 4-(3-chloro-phenylethynyl)-2-methyl-1H-imidazole and 2,6-difluoropyridine.
Preparation of the pharmaceutical compositions:

Example I

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

mg/Tablet	
Active ingredient	100
Powdered. lactose	95
White corn starch	35

Polyvinylpyrrolidone	8
Na carboxymethylstarch	10
Magnesium stearate	2
Tablet weight	250

Example II

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

mg/Tablet

Active ingredient	200
Powdered. lactose	100
White corn starch	64
Polyvinylpyrrolidone	12
Na carboxymethylstarch	20
Magnesium stearate	4
Tablet weight	400

Example III

Capsules of the following composition are produced:

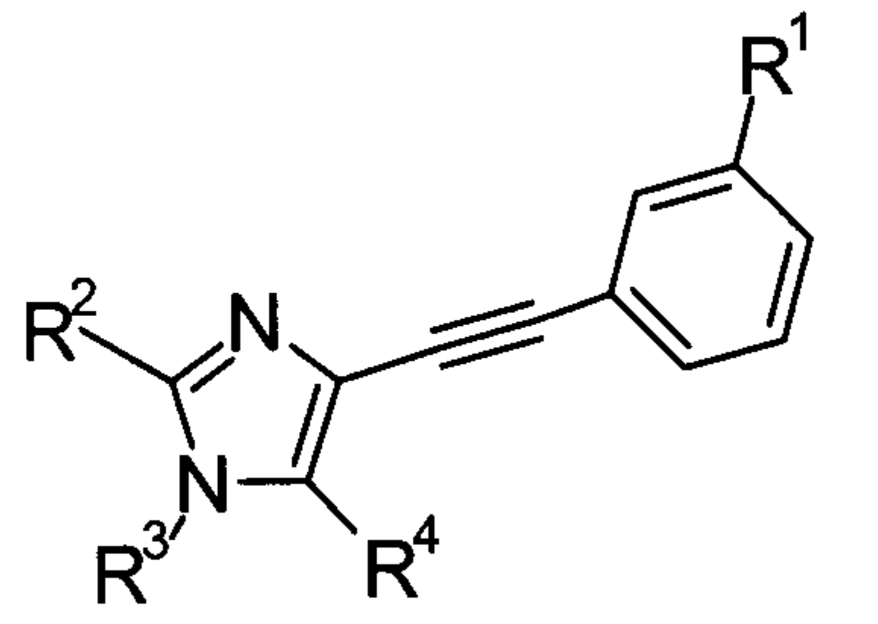
mg/Capsule

Active ingredient	50
Crystalline. lactose	60
Microcrystalline cellulose	34
Talc 5	
Magnesium stearate	1
Capsule fill weight	150

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.

CLAIMS:

1. A compound of the general formula



I

wherein

R^1 signifies halogen, C_1-C_6-alkyl, C_1-C_6-alkoxy, CF_3, CF_2H, OCF_3, OCF_2H, or cyano;

R^2 signifies C_1-C_6-alkyl;

R^3 signifies 5 or 6 membered heteroaryl, which is optionally substituted by one, two or three substituents, of halogen, C_1-C_6-alkyl, C_3-C_6-cycloalkyl, C_1-C_6-alkyl-halogen, cyano, C_1-C_6-alkoxy, or NR'R'', or by

1-morpholinyl, or by

1-pyrrolidinyl, optionally substituted by $(CH_2)_{0,1}OR$, or by

piperidinyl, optionally substituted by $(CH_2)_{0,1}OR$, or by

thiomorpholinyl, 1-oxo-thiomorpholinyl, or 1,1-dioxo-thiomorpholinyl, or by

piperazinyl, optionally substituted by C_1-C_6-alkyl or $(CH_2)_{0,1}$- C_3-C_6-cycloalkyl;

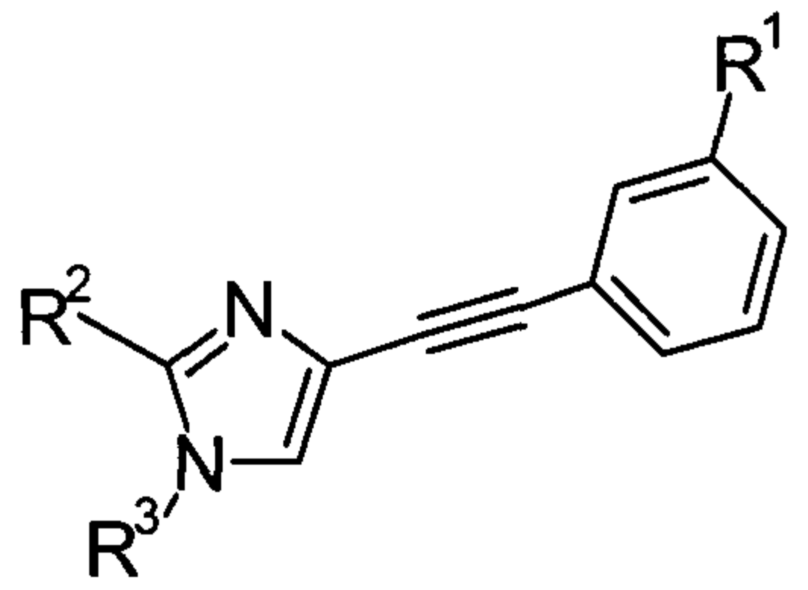
R is hydrogen, C_1-C_6-alkyl or $(CH_2)_{0,1}$- C_3-C_6-cycloalkyl;

R', R'' are independently from each other hydrogen, C_1-C_6-alkyl, $(CH_2)_{0,1}$- C_3-C_6-cycloalkyl or $(CH_2)_{1,2}$-OR;

R^4 is hydrogen, C(O)H, or CH_2R^5 wherein R^5 is hydrogen, OH, C_1-C_6-alkyl, or C_3-C_{12}-cycloalkyl,

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 of the general formula



IA

wherein

R^1 signifies halogen, C_1-C_6-alkyl, C_1-C_6-alkoxy, CF_3 or cyano;

R^2 signifies C_1-C_6-alkyl;

R^3 signifies 5 or 6 membered heteroaryl, which is optionally substituted by one, two or three substituents, of halogen, C_1-C_6-alkyl, C_1-C_6-alkyl-halogen, cyano, or NR'R'' or by

1-morpholinyl, or by

1-pyrrolidinyl, optionally substituted by $(CH_2)_{0,1}OR$, or by

piperidinyl, optionally substituted by $(CH_2)_{0,1}OR$, or by

1,1-dioxo-thiomorpholinyl or by

piperazinyl, optionally substituted by C_1-C_6-alkyl or $(CH_2)_{0,1}$- C_3-C_6-cycloalkyl;

R is hydrogen, C_1-C_6-alkyl or $(CH_2)_{0,1}$- C_3-C_6-cycloalkyl;

R', R'' are independently from each other hydrogen, C_1-C_6-alkyl, $(CH_2)_{0,1}$- C_3-C_6-cycloalkyl or $(CH_2)_{1,2}OR$;

or a pharmaceutically acceptable salt thereof.

3. A compound of formula I in accordance with claim 1, wherein R^1 is chloro or cyano.

4. A compound of formula I in accordance with claim 3, wherein R^3 is unsubstituted or substituted pyrimidin-2yl.

5. A compound of formula I in accordance with claim 4, wherein the compound is

2-[4-(3-chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-pyrimidine,
2-[4-(3-chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-4-trifluoromethyl-pyrimidine,
2-[4-(3-chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-4-methyl-pyrimidine,
2-[4-(3-chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-5-fluoro-pyrimidine or
3-[1-(4-methoxy-pyrimidin-2-yl)-2-methyl-1H-imidazol-4-ylethynyl]-benzonitrile.

6. A compound of formula I in accordance with claim 3, wherein R^3 is unsubstituted or substituted pyridin-2-yl.

7. A compound of formula I in accordance with claim 6, wherein the compounds are
3-[2-methyl-1-(6-methyl-pyridin-2-yl)-1H-imidazol-4-ylethynyl]-benzonitrile,
3-[2-methyl-1-(6-trifluoromethyl-pyridin-2-yl)-1H-imidazol-4-ylethynyl]-benzonitrile,
3-[2-methyl-1-(5-methyl-pyridin-2-yl)-1H-imidazol-4-ylethynyl]-benzonitrile,
3-[2-methyl-1-(4-methyl-pyridin-2-yl)-1H-imidazol-4-ylethynyl]-benzonitrile,
2-[4-(3-chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-6-methyl-pyridine,
2-[4-(3-chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-6-trifluoromethyl-pyridine,
2-[4-(3-chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-5-methyl-pyridine,
3-[4-(3-chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-5-fluoro-pyridine,
2-[4-(3-chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-5-methyl-pyridine,
2-[4-(3-chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-4-methyl-pyridine,
3-[4-(3-chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-5-fluoro-pyridine or
4-{6-[4-(3-chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-pyridin-2-yl}-thiomorpholine.

8. A compound of formula I in accordance with claim 3, wherein R^3 is unsubstituted or substituted pyridin-3-yl.

9. A compound of formula I in accordance with claim 8, wherein the compounds are
2-chloro-5-[4-(3-chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-pyridine or
2-[4-(3-chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-4-methyl-pyridine.

10. A compound of formula I in accordance with claim 3, wherein R^3 is pyridazinyl or pyrazinyl which may be substituted or unsubstituted.

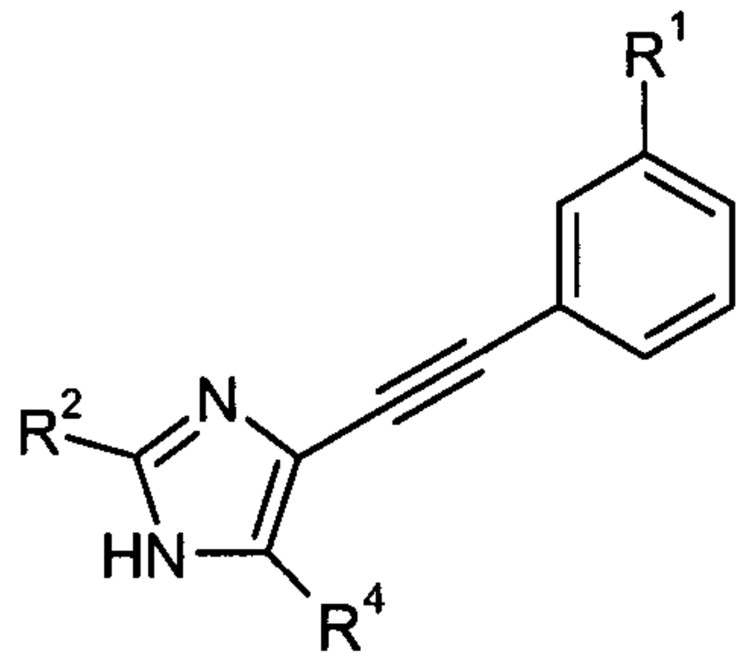
11. A compound of formula I in accordance with claim 10, wherein the compounds are
5-[4-(3-chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-3-methyl-pyridazine,
3-[4-(3-chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-6-methyl-pyridazine or
2-[4-(3-chloro-phenylethynyl)-2-methyl-imidazol-1-yl]-pyrazine.

12. A compound of formula I in accordance with claim 3, wherein R^3 is furan-3-yl.

13. A compound of formula I in accordance with claim 12, wherein the compound is 5-(3-chloro-phenylethynyl)-1-furan-3-yl-2-methyl-1H-imidazole.

14. A process for preparing a compound of formula I as defined in any one of claims 1 to 13, which process comprises:

(a) reacting a compound of formula II

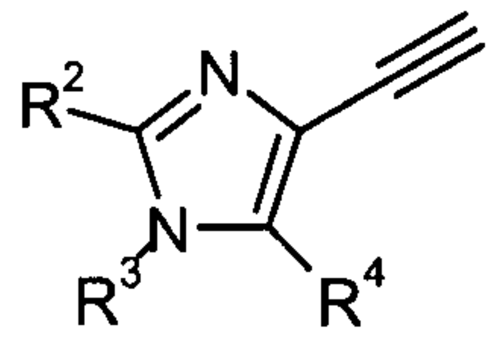


(II)

wherein R^1, R^2 and R^4 have the meanings as defined in claim 1,
with a compound of formula III

$$R^3\text{-}Z \qquad \text{(III)}$$

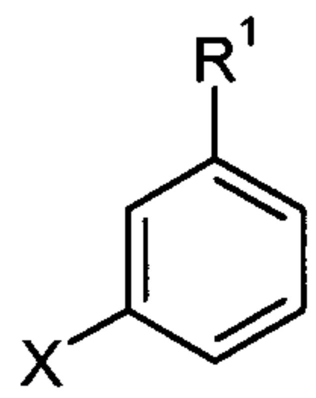
wherein R^3 has the meanings as defined in claim 1 and Z is halogen or $B(OH)_2$; or
(b) reacting a compound of formula IV



(IV)

wherein R^2, R^3 and R^4 have the meanings as defined in claim 1,

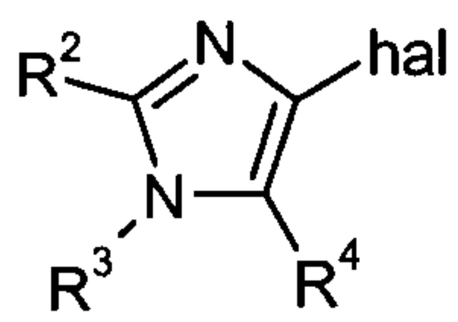
with a compound of formula V



(V)

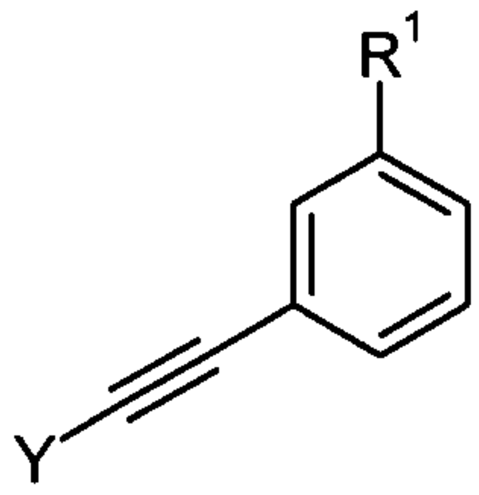
wherein R^1 has the meanings as defined in claim 1 and X is halogen; or

(c) reacting a compound of formula VI



(VI)

wherein R^2, R^3 and R^4 have the meanings as defined in claim 1 and hal is halogen, with a compound of formula VII



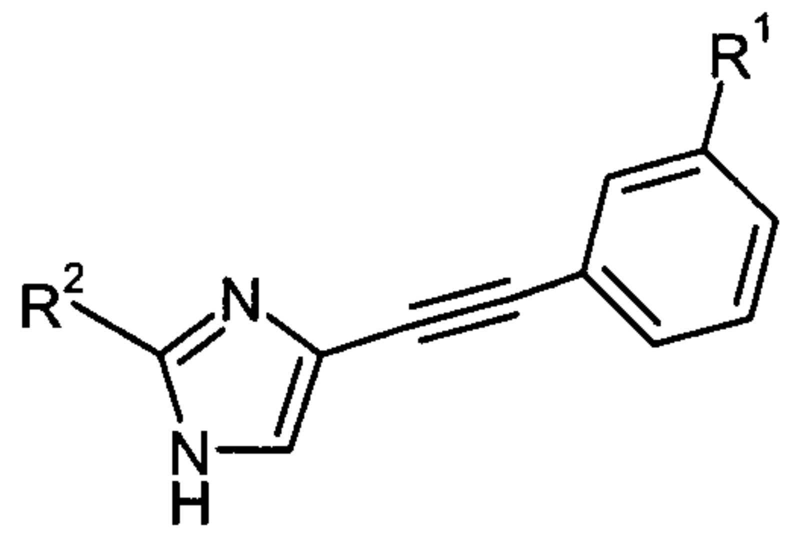
(VII)

wherein R^1 has the meaning as defined in claim 1 and Y is trimethylsilyl or hydrogen.

15. The process of claim 14, further comprising converting the compound obtained into a pharmaceutially acceptable addition salt.

16. A process for preparing a compound of formula I as defined in any one of claims 1 to 13, which process comprises:

(a) reacting a compound of formula

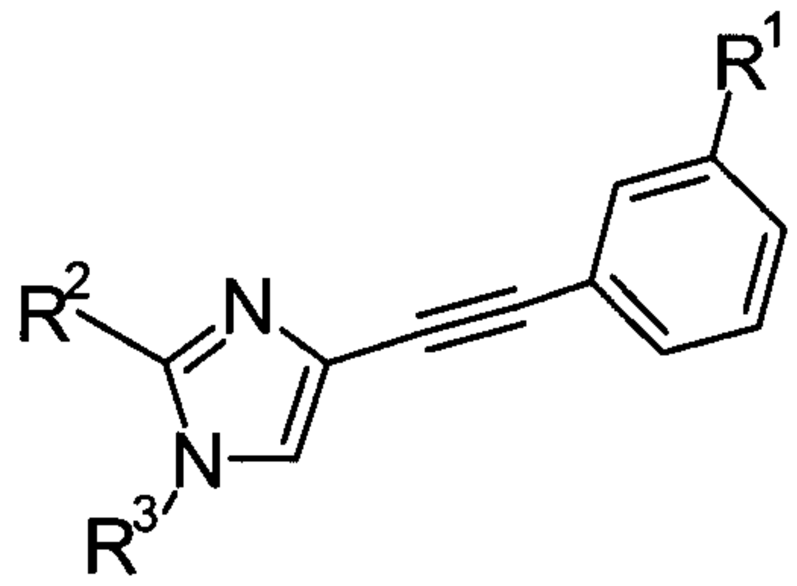


II

with a compound of formula

R^3-Z III

wherein R^3 has the meanings as defined in claim 1 and Z is halogen or $B(OH)_2$, to a compound of formula



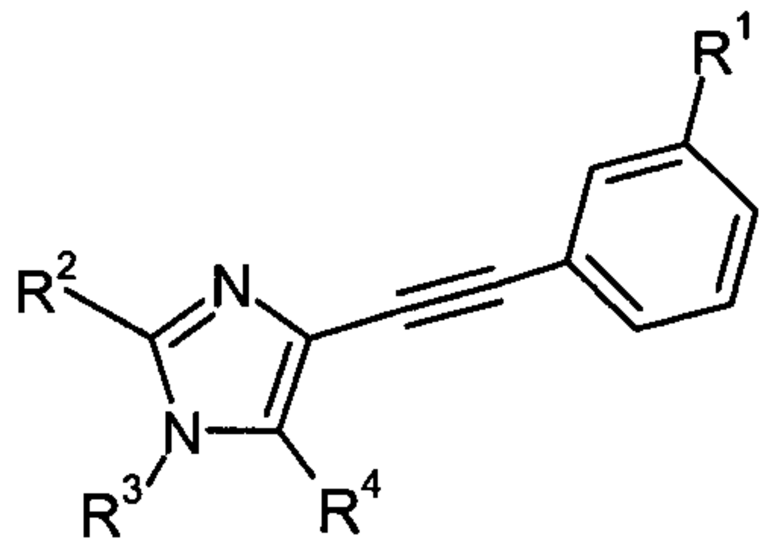
IA

wherein R^1, R^2 and R^3 are as defined in claim 1 and hal is chloro or fluoro, and if desired, when R^4 is other than hydrogen,

(b) reacting the compound of formula IA with a compound of formula:

R^4hal (VI)

to a compound of formula



I

wherein R^1, R^2, R^3 and R^4 are as defined in claim 1.

17. The process of claim 16, further comprising converting the compound obtained into a pharmaceutically acceptable acid addition salt.

18. A medicament containing one or more compounds as claimed in any one of claims 1 to 13 and pharmaceutically acceptable excipients for the treatment and prevention of mGluR5 receptor mediated disorders.

19. A medicament according to claim 18 for the treatment and prevention of an acute and/or chronic neurological disorder or for the treatment of chronic and acute pain or for the treatment of urinary incontinence.

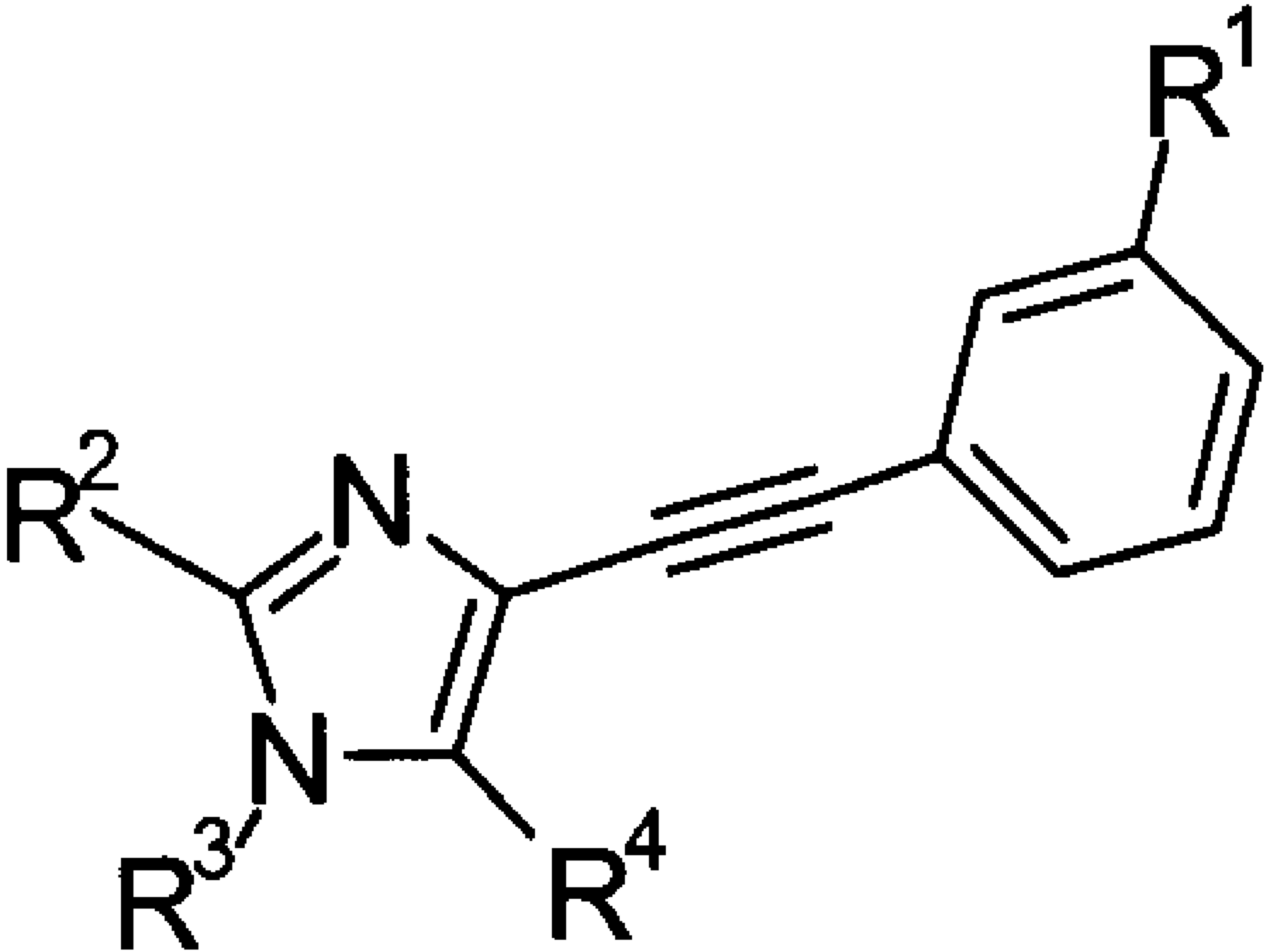
20. The medicament according to claim 19, wherein the neurological disorder is anxiety.

21. A compound in accordance with any one of claims 1 to 13 or its pharmaceutically acceptable salt for use in the treatment or prevention of an acute and/or chronic neurological disorder.

22. The use of a compound in accordance with any one of claims 1 to 13 or its pharmaceutically acceptable salt for the manufacture of medicaments for the treatment and prevention of mGluR5 receptor mediated disorders.

23. The use according to claim 22 for the manufacture of medicaments for the treatment and prevention of an acute and/or chronic neurological disorder or for the treatment of chronic and acute pain or for the treatment of urinary incontinence.

24. The use according to claim 23, wherein the neurological disorder is anxiety.



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