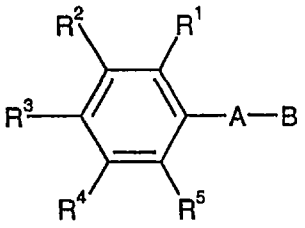
# PHENYLETHENYL OR PHENYLETHINYL DERIVATIVES AS GLUTAMATE RECEPTOR ANTAGONISTS

The present invention is concerned with the use of phenylethenyl and phenylethinyl derivatives of the general formula



I

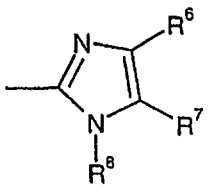
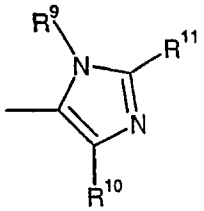
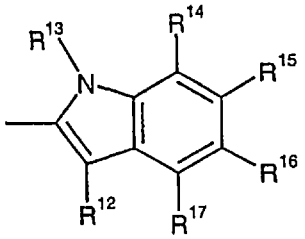
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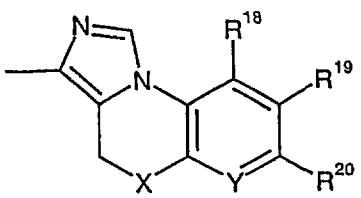
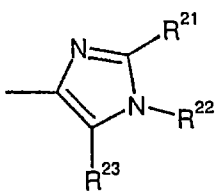
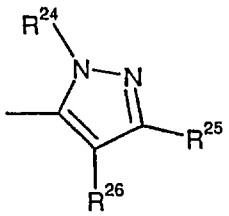
$R^1$, $R^2$, $R^3$, $R^4$ and $R^5$ signify, independently from each other, hydrogen, lower alkyl, $-(CH_2)_n$-halogen, lower alkoxy, $-(CH_2)_n$-NRR', $-(CH_2)_n$-N(R)-C(O)-lower alkyl, aryl or heteroaryl which is unsubstituted or substituted by one or more lower alkyl residues;

R, R' and R" signify, independently from each other, hydrogen or lower alkyl;

A signifies -CH=CH- or -C≡C-; and

B signifies

B1)  ; B2)  ; B3)  ;

B4)  ; B5)  or B6) 

wherein

$R^6$ signifies hydrogen, lower alkyl, -$(CH_2)_n$-C(O)OR or halogen;

$R^7$ signifies hydrogen, lower alkyl, -$(CH_2)_n$-C(O)OR', halogen, nitro or heteroaryl which is unsubstituted or substituted by lower alkyl or cycloalkyl;

$R^8$ signifies hydrogen, lower alkyl, -$(CH_2)_n$-OH, -$(CH_2)_n$-C(O)OR" or aryl;

$R^9$ signifies lower alkyl;

$R^{10}$ signifies hydrogen, lower alkyl or halogen;

$R^{11}$ signifies hydrogen or alkyl;

$R^{12}$ signifies -$(CH_2)_n$-N(R)-C(O)-lower alkyl;

$R^{13}$ signifies hydrogen or lower alkyl;

$R^{14}$, $R^{15}$, $R^{16}$ and $R^{17}$ signify, independently from each other, hydrogen, lower alkyl, -$(CH_2)_n$-halogen or lower alkoxy;

$R^{18}$, $R^{19}$ and $R^{20}$ signify, independently from each other, hydrogen, lower alkyl, -$(CH_2)_n$-halogen or lower alkoxy;

$R^{21}$ signifies hydrogen or lower alkyl;

$R^{22}$ signifies hydrogen, lower alkyl or lower alkyl carrying one or more substituents selected from hydroxy or halogen;

$R^{23}$ signifies hydrogen, lower alkyl, lower alkanoyl or nitro;

$R^{24}$, $R^{25}$ and $R^{26}$ signify, independently from each other, hydrogen or lower alkyl;

n is 0, 1, 2, 3, 4, 5 or 6;

X is -$CH_2$-, -O- or -S-; and

Y is –CH= or –N=;

and their pharmaceutically acceptable salts.

Some compounds of the present formula I are known compounds and have been described in the literature. For example the synthesis of 1-methyl-2-phenylethynyl-1H-imidazole, 1-methyl-5-phenylethynyl-1H-imidazole and 1-methyl-4-phenylethynyl-1H-

imidazole as well as the synthesis of the corresponding phenylethenyl derivatives is described in *Chem. Pharm. Bull.* 1987, 35(2), 823-828. The compounds have been prepared by palladium catalyzed reaction of corresponding halogen-1,3-azoles with phenylacetylene or styrene. 1-Methyl-2-(4-methoxyphenylethynyl)-1H-imidazole can be synthesized as nonlinear optical chromophore according to *Chem Mater.* 1994, 6(7), 1023-1032. The preparation of 2-alkyl-5-phenylethynyl-1H-imidazole-4-carboxaldehydes as intermediates for the manufacture of substituted imidazoles for use as angiotensin II blockers has been described in WO 91/00277. 1-Methyl-5-(2-phenylethenyl)-1H-imidazole has also been prepared as intermediate for the synthesis of heterocyclic food mutagens according to *Environ. Health Perspect.* 1986, 67, 41-45.

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 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.

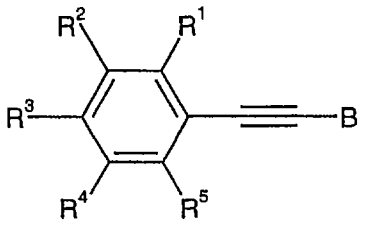
Other treatable indications in this connection are restricted brain function caused by bypass operations or transplants, poor blood supply to the brain, spinal cord injuries, head

injuries, hypoxia caused by pregnancy, cardiac arrest and hypoglycaemia. Further treatable indications are 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 and pain. Selective mGluR5 antagonists are especially useful for the treatment of anxiety and pain.

Objects of the present invention are the use of compounds of formula I and their pharmaceutically acceptable salts for the manufacture of medicaments for the treatment or prevention of mGluR5 receptor mediated disorders, novel compounds of formula I-A or formula 1-B per se, their manufacture, medicaments based on a compound in accordance with the invention and their production as well as the use of compounds of formula I-A or formula 1-B for the treatment or prevention of mGluR5 receptor mediated disorders, such as Alzheimer's disease, senile dementia, Parkinson's disease, Huntington's chorea, cognitive disorders and memory deficits, cerebral ischemia, amyotrophic lateral sclerosis (ALS) and multiple sclerosis, restricted brain functions 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, psychiatric diseases such as psychosis, epilepsy, schizophrenia and anxiety, depression as well as chronic and acute pain.

The present invention relates inter alia also to novel compounds of the general formula



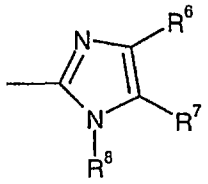
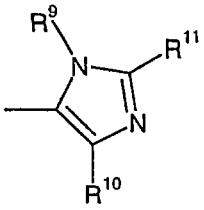
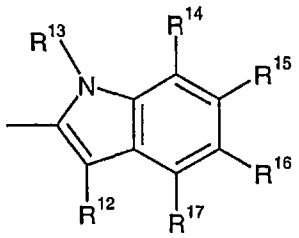

**I-A**

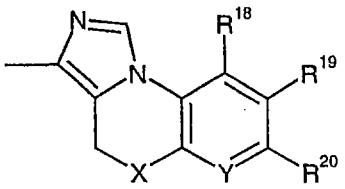
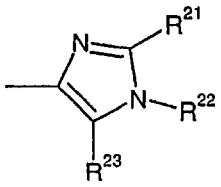
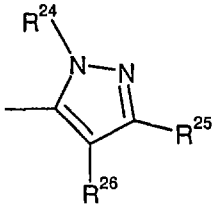
wherein

$R^1$, $R^2$, $R^3$, $R^4$ and $R^5$ signify, independently from each other, hydrogen, lower alkyl, $-(CH_2)_n$-halogen, lower alkoxy, $-(CH_2)_n$-NRR', $-(CH_2)_n$-N(R)-C(O)-lower alkyl, aryl or heteroaryl which is unsubstituted or substituted by one or more lower alkyl residues;

R, R' and R" signify, independently from each other, hydrogen or lower alkyl;

B signifies

B1)  ; B2)  ; B3)  ;

B4)  ; B5)  or B6)  ;

wherein

$R^6$ signifies hydrogen, lower alkyl, $-(CH_2)_n$-C(O)OR or halogen;

$R^7$ signifies hydrogen, lower alkyl, $-(CH_2)_n$-C(O)OR', halogen, nitro or heteroaryl which is unsubstituted or substituted by lower alkyl or cycloalkyl;

$R^8$ signifies hydrogen, lower alkyl, $-(CH_2)_n$-OH, $-(CH_2)_n$-C(O)OR" or aryl;

$R^9$ signifies lower alkyl;

$R^{10}$ signifies hydrogen, lower alkyl or halogen;

$R^{11}$ signifies hydrogen or alkyl;

$R^{12}$ signifies $-(CH_2)_n$-N(R)-C(O)-lower alkyl;

$R^{13}$ signifies hydrogen or lower alkyl;

$R^{14}$, $R^{15}$, $R^{16}$ and $R^{17}$ signify, independently from each other, hydrogen, lower alkyl, $-(CH_2)_n$-halogen or lower alkoxy;

$R^{18}$, $R^{19}$ and $R^{20}$ signify, independently from each other, hydrogen, lower alkyl, $-(CH_2)_n$-halogen or lower alkoxy;

$R^{21}$ signifies hydrogen or lower alkyl;

$R^{22}$ signifies hydrogen, lower alkyl or lower alkyl carrying one or more substituents selected from hydroxy or halogen;

$R^{23}$ signifies hydrogen, lower alkyl, lower alkanoyl or nitro;

$R^{24}$, $R^{25}$ and $R^{26}$ signify, independently from each other, hydrogen or lower alkyl;

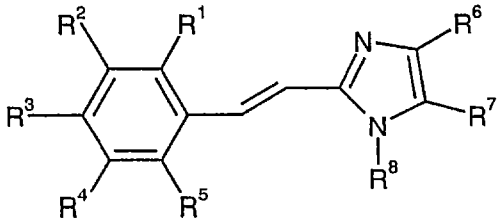
n is 0, 1, 2, 3, 4, 5 or 6;

X is $-CH_2-$, -O- or -S-; and

Y is –CH= or –N=;

and their pharmaceutically acceptable salts; with the exception of
1-methyl-2-phenylethynyl-1H-imidazole,
1-methyl-2-(4-methoxy-phenylethynyl)-1H-imidazole,
1-methyl-5-phenylethynyl-1H-imidazole, and
1-methyl-4-phenylethynyl-1H-imidazole.

Furthermore, the present invention relates to novel compounds of the general formula



**I-B-1**

wherein

$R^1$, $R^2$, $R^3$, $R^4$ and $R^5$signify, independently from each other, hydrogen, lower alkyl, $-(CH_2)_n$-halogen, lower alkoxy, $-(CH_2)_n$-NRR', $-(CH_2)_n$-N(R)-C(O)-lower alkyl, aryl or heteroaryl which is unsubstituted or substituted by one or more lower alkyl residues;

R, R' and R" signify, independently from each other, hydrogen or lower alkyl;

$R^6$ signifies hydrogen, lower alkyl, $-(CH_2)_n$-C(O)OR or halogen;

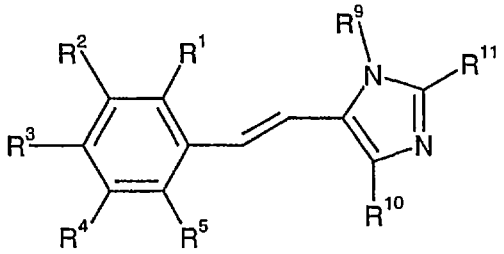
$R^7$ signifies hydrogen, lower alkyl, $-(CH_2)_n$-C(O)OR', halogen, nitro or heteroaryl

which is unsubstituted or substituted by lower alkyl or cycloalkyl; and

$R^8$ signifies hydrogen, lower alkyl, $-(CH_2)_n$-OH, $-(CH_2)_n$-C(O)OR" or aryl;

and their pharmaceutically acceptable salts.

The present invention also relates to compounds of formula



**I-B-2**

wherein

$R^1$, $R^2$, $R^3$, $R^4$ and $R^5$signify, independently from each other, hydrogen, lower alkyl, $-(CH_2)_n$-halogen, lower alkoxy, $-(CH_2)_n$-NRR', $-(CH_2)_n$-N(R)-C(O)-lower alkyl, aryl or heteroaryl which is unsubstituted or substituted by one or more lower alkyl residues;

R and R' signify, independently from each other, hydrogen or lower alkyl;

$R^9$ signifies lower alkyl;

$R^{10}$ signifies halogen; and

$R^{11}$ signifies hydrogen or alkyl;

and their pharmaceutically acceptable salts.

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 "cycloalkyl" denotes a saturated carbocyclic group containing from 3 to 7 carbon atoms, preferred are cyclopropyl, cyclopentyl or cyclohexyl.

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

The term "lower alkoxy" denotes a lower alkyl group as defined hereinbefore, which is bound via an oxygene atom, e.g. methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy and the like.

Preferred lower alkanoyl groups are formyl, ethanoyl or propanoyl.

Preferred aryl groups are phenyl or naphthyl.

Heteroaryl groups are selected from furyl, pyrrolyl, thienyl, 1H-imidazolyl, 2H-imidazolyl, 4H-imidazolyl, 1H-pyrazolyl, 3H-pyrazolyl, 4H-pyrazolyl, 1,2-oxazolyl, 1,3-oxazolyl, 1H-[1,2,4]triazolyl, 4H-[1,2,4]triazolyl, 1H-[1,2,3]triazolyl, 2H-[1,2,3]triazolyl, 4H-[1,2,3]triazolyl, [1,2,4]oxadiazolyl, [1,3,4]oxadiazolyl, [1,2,3]oxadiazolyl, 1H-tetrazolyl, 2H-tetrazolyl, [1,2,3,4]oxatriazolyl, [1,2,3,5]oxatriazolyl, 1,3-thiazolyl, 1,2-thiazolyl, 1H-pentazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolyl, quinolinyl and their dihydro derivatives. The heteroaryl group is optionally substituted by lower alkyl. Preferred heteroaryl groups are pyrrolyl and [1,2,4]oxadiazolyl.

The term "pharmaceutically acceptable salt" refers to any salt derived from an inorganic or organic acid or base which possesses the desired pharmacological activity of the parent compound.

Especially preferred are compounds of formula I for the above mentioned use, in which A signifies –C≡C- and B signifies B1.

The following are examples of such compounds:

3,5-dimethyl-2-phenylethynyl-3H-imidazole-4-carboxylic acid ethyl ester,
5-methyl-2-phenylethynyl-3H-imidazole-4-carboxylic acid ethyl ester,
2-(3-methoxy-phenylethynyl)-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester,
1-methyl-2-phenylethynyl-1H-imidazole,
2-(5-nitro-2-phenylethynyl-imidazol-1-yl)-ethanol,
2-phenylethynyl-1H-imidazole,
2-(2,6-dichloro-phenylethynyl)-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester,
5-methyl-1-phenyl-2-phenylethynyl-1H-imidazole-4-carboxylic acid ethyl ester,
3,5-dimethyl-2-*m*-tolylethynyl-3H-imidazole-4-carboxylic acid ethyl ester,
2-(3-acetylamino-phenylethynyl)-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester,
2-[3-(2,5-dimethyl-pyrrol-1-yl)-phenylethynyl]-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester,
5-(3,5-dimethyl-2-phenylethynyl-3H-imidazol-4-yl)-3-methyl-[1,2,4]oxadiazole,
3-cyclopropyl-5-(3,5-dimethyl-2-phenylethynyl-3H-imidazol-4-yl)-[1,2,4]oxadiazole,
2-(4-chloro-phenylethynyl)-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester,
2-(4-fluoro-phenylethynyl)-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester,
2-biphenyl-4-ylethynyl-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester,
2-(2-fluoro-phenylethynyl)-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester,
2-(2-fluoro-phenylethynyl)-1-methyl-1H-imidazole,

2-(4-amino-phenylethynyl)-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester,
2-(2-chloro-phenylethynyl)-1-methyl-1H-imidazole or
(4,5-dichloro-2-phenylethynyl-imidazol-1-yl)-acetic acid ethyl ester.

Further preferred are compounds of formula I for the above mentioned use, in which A signifies –C≡C- and B signifies B2.

An example for such a compound is 1-methyl-5-phenylethynyl-1H-imidazole.

Also preferred for the above mentioned use are compounds of formula I, in which A signifies –C≡C- and B signifies B3.

An example for such a compound is N-[2-(5-methoxy-2-phenylethynyl-1H-indol-3-yl)-ethyl]-acetamide.

Preferred compounds of formula I for the above mentioned use are also those, in which A signifies –C≡C- and B signifies B4.

The following are examples of such compounds:
3-phenylethynyl-4H-5-thia-2,6,9b-triaza-cyclopenta[a]naphthalene or
3-phenylethynyl-4H-5-oxa-2,9b-diaza-cyclopenta[a]naphthalene.

Further preferred are compounds of formula I for the above mentioned use, in which A signifies –C≡C- and B signifies B5.

Examples of such compounds are:

1-chloro-3-(2-methyl-5-nitro-4-phenylethynyl-imidazol-1-yl)-propan-2-ol,
3-methyl-5-phenylethynyl-3H-imidazole-4-carbaldehyde,
4-phenylethynyl-1H-imidazole,
1-methyl-4-phenylethynyl-1H-imidazole or
1,2-dimethyl-5-nitro-4-phenylethynyl-1H-imidazole.

Also preferred are compounds of formula I for the above mentioned use, in which A signifies –C≡C- and B signifies B6.

An example for such a compound is 1,3-dimethyl-5-phenylethynyl-1H-pyrazole.

Further preferred are compounds of formula I for the above mentioned use, in which A signifies –C=C-.

Especially preferred are those compounds of formula I for the above mentioned use, in which A signifies –C=C- and B signifies B1.

The following are examples of such compounds:
4,5-diisopropyl-1-methyl-2-styryl-1H-imidazole,
2-[2-(4-fluoro-phenyl)-vinyl]-4,5-diisopropyl-1-methyl-1H-imidazole,
2-[2-(4-chloro-phenyl)-vinyl]-4,5-diisopropyl-1-methyl-1H-imidazole,
2-[2-(4-butoxy-phenyl)-vinyl]-4,5-diisopropyl-1-methyl-1H-imidazole,
4,5-diisopropyl-2-[2-(4-methoxy-2,3,6-trimethyl-phenyl)-vinyl]-1-methyl-1H-imidazole,
4,5-diisopropyl-2-[2-(4-methoxy-phenyl)-vinyl]-1-methyl-1H-imidazole,
2-[2-(4-chloro-3-fluoro-phenyl)-vinyl]-4,5-diisopropyl-1-methyl-1H-imidazole,
2-[2-(4-ethoxy-phenyl)-vinyl]-4,5-diisopropyl-1-methyl-1H-imidazole,
4,5-diisopropyl-1-methyl-2-[2-(2,3,4-trimethoxy-phenyl)-vinyl]-1H-imidazole,
2-[2-(2,4-dichloro-phenyl)-vinyl]-4,5-diisopropyl-1-methyl-1H-imidazole or
4,5-diisopropyl-1-methyl-2-(2-p-tolyl-vinyl)-1H-imidazole.

Also preferred are compounds of formula I for the above mentioned use, in which A signifies –C=C- and B signifies B2.

Examples of such compounds are the following:
4-bromo-1-methyl-5-styryl-1H-imidazole or
1-methyl-5-styryl-1H-imidazole.

Further preferred objects of the present invention are compounds of formula I-A, in which B signifies B1 with the exception of 1-methyl-2-phenylethynyl-1H-imidazole and 1-methyl-2-(4-methoxy-phenylethynyl)-1H-imidazole.

The following are examples of such compounds:
2-(5-nitro-2-phenylethynyl-imidazol-1-yl)-ethanol,
2-phenylethynyl-1H-imidazole,
2-(2-fluoro-phenylethynyl)-1-methyl-1H-imidazole,
2-(2-chloro-phenylethynyl)-1-methyl-1H-imidazole or
(4,5-dichloro-2-phenylethynyl-imidazol-1-yl)-acetic acid ethyl ester.

More preferred are compounds of formula I-A, in which B signifies B1 and $R^7$ signifies $(CH_2)_n$-C(O)OR' or heteroaryl which is unsubstituted or substituted by lower alkyl or cycloalkyl. Especially preferred are those, in which $R^7$ signifies $(CH_2)_n$-C(O)OR', wherein N is 0 and R is lower alkyl.

Examples of such compounds are the following:
3,5-dimethyl-2-phenylethynyl-3H-imidazole-4-carboxylic acid ethyl ester,
5-methyl-2-phenylethynyl-3H-imidazole-4-carboxylic acid ethyl ester,
2-(3-methoxy-phenylethynyl)-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester,
2-(2,6-dichloro-phenylethynyl)-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester,

5-methyl-1-phenyl-2-phenylethynyl-1H-imidazole-4-carboxylic acid ethyl ester,
3,5-dimethyl-2-*m*-tolylethynyl-3H-imidazole-4-carboxylic acid ethyl ester,
2-(3-acetylamino-phenylethynyl)-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester,
2-[3-(2,5-dimethyl-pyrrol-1-yl)-phenylethynyl]-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester,
5-(3,5-dimethyl-2-phenylethynyl-3H-imidazol-4-yl)-3-methyl-[1,2,4]oxadiazole,
3-cyclopropyl-5-(3,5-dimethyl-2-phenylethynyl-3H-imidazol-4-yl)-[1,2,4]oxadiazole,
2-(4-chloro-phenylethynyl)-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester,
2-(4-fluoro-phenylethynyl)-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester,
2-biphenyl-4-ylethynyl-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester,
2-(2-fluoro-phenylethynyl)-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester, or
2-(4-amino-phenylethynyl)-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester.

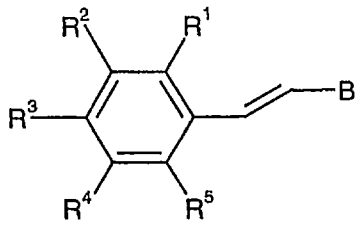
Also preferred are compounds of formula I-A, in which B signifies B4.

The following are examples of such compounds:
3-phenylethynyl-4H-5-thia-2,6,9b-triaza-cyclopenta[a]naphthalene or
3-phenylethynyl-4H-5-oxa-2,9b-diaza-cyclopenta[a]naphthalene.

Preferred compounds of formula I-A are also those, in which B signifies B5 with the exception of 1-methyl-4-phenylethynyl-1H-imidazole.

Examples of such compounds are the following:
1-chloro-3-(2-methyl-5-nitro-4-phenylethynyl-imidazol-1-yl)-propan-2-ol,
3-methyl-5-phenylethynyl-3H-imidazole-4-carbaldehyde,
4-phenylethynyl-1H-imidazole or
1,2-dimethyl-5-nitro-4-phenylethynyl-1H-imidazole.

Also preferred are compounds of formula




**I-B**

wherein $R^1$, $R^2$, $R^3$, $R^4$ and $R^5$ signify, independently from each other, hydrogen, lower alkyl, -$(CH_2)_n$-halogen, lower alkoxy, -$(CH_2)_n$-NRR', -$(CH_2)_n$-N(R)-C(O)-lower alkyl, aryl or heteroaryl which is unsubstituted or substituted by one or more lower alkyl residues;

and in which B signifies B1 and $R^7$ signifies lower alkyl or $-(CH_2)_n-C(O)OR'$. Especially preferred are those in which $R^7$ signifies lower alkyl.

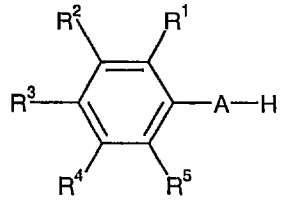
Examples of such compounds are the following:
4,5-diisopropyl-1-methyl-2-styryl-1H-imidazole,
2-[2-(4-fluoro-phenyl)-vinyl]-4,5-diisopropyl-1-methyl-1H-imidazole,
2-[2-(4-chloro-phenyl)-vinyl]-4,5-diisopropyl-1-methyl-1H-imidazole,
2-[2-(4-butoxy-phenyl)-vinyl]-4,5-diisopropyl-1-methyl-1H-imidazole,
4,5-diisopropyl-2-[2-(4-methoxy-2,3,6-trimethyl-phenyl)-vinyl]-1-methyl-1H-imidazole,
4,5-diisopropyl-2-[2-(4-methoxy-phenyl)-vinyl]-1-methyl-1H-imidazole,
2-[2-(4-chloro-3-fluoro-phenyl)-vinyl]-4,5-diisopropyl-1-methyl-1H-imidazole,
2-[2-(4-ethoxy-phenyl)-vinyl]-4,5-diisopropyl-1-methyl-1H-imidazole,
4,5-diisopropyl-1-methyl-2-[2-(2,3,4-trimethoxy-phenyl)-vinyl]-1H-imidazole,
2-[2-(2,4-dichloro-phenyl)-vinyl]-4,5-diisopropyl-1-methyl-1H-imidazole or
4,5-diisopropyl-1-methyl-2-(2-p-tolyl-vinyl)-1H-imidazole.

Further preferred compounds of formula I-B are those, in which B signifies B2 and $R^{10}$ signifies halogen.

An example of such a compound is 4-bromo-1-methyl-5-styryl-1H-imidazole.

The present compounds of formula I-A and I-B and their pharmaceutically acceptable salts can be prepared by methods known in the art, for example, by processes described below, which process comprises

reacting a compound of the formula




II

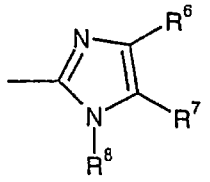
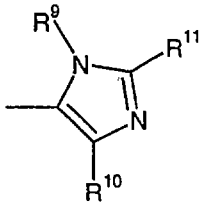
with a compound of formula

B—X III

wherein X signifies halogen or trifluoromethanesulfonyl and
$R^1$ to $R^5$ have the significances as defined before,

to obtain a compound of formula I-A in the case if A signifies -C≡C- and B has the significances as defined before;

or to obtain a compound of formula I-B in the case if A signifies –HC=CH- and B is

B1)  or B2) 

wherein

$R^6$ signifies hydrogen, lower alkyl, $-(CH_2)_n-C(O)OR$ or halogen;

$R^7$ signifies hydrogen, lower alkyl, $-(CH_2)_n-C(O)OR'$, halogen, nitro or heteroaryl which is unsubstituted or substituted by lower alkyl or cycloalkyl;

$R^8$ signifies hydrogen, lower alkyl, $-(CH_2)_n-OH$, $-(CH_2)_n-C(O)OR''$ or aryl;

$R^9$ signifies lower alkyl;

$R^{10}$ signifies halogen; and

$R^{11}$ signifies hydrogen or alkyl;

and if desired,

converting a compounds of formulas I-A or I-B into a pharmaceutically acceptable salt.

This reaction is catalyzed by palladium(II) salts.

In accordance with the invention, compounds of formula I, wherein A signifies -C≡C-, are prepared by reacting an acetylene derivative of formula II, for example ethynylbenzene, with a suitable compound of formula III, for example 2-bromo-3,5-dimethyl-3H-imidazole-4-carboxylic acid ester. According to the method as described in *Chem. Pharm. Bull.* 1987, 35(2), 823-828 this palladium catalyzed C-C-coupling reaction requires the presence of bis(triphenylphosphine)-palladium(II)-chloride, cuprous iodide and triethylamine and is carried out in a polar solvent like dimethylformamide or acetonitrile at a temperature of 90 °C to 100 °C within 1.5 to 3 hours. The reaction can also be carried out in the presence equimolar amounts of bis(triphenylphosphine)-palladium(II)-chloride and triphenylphosphine and an excess of triethylamine at a temperature of 55 °C within 16 hours.

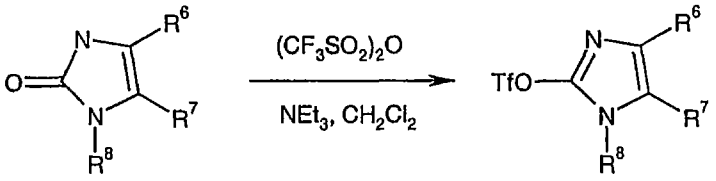
The phenylethynyl derivatives of formula II are commercially available or can be easily prepared by methods well known in the art.

The compounds of formula III are also commercially available or can be prepared by appropiate methods depending on the heterocyclic system B.

2-Halogeno-1H-imidazoles of formula III (B = B1) are prepared according to methods as described in US Patent No. (USP) 4,711,962, USP 3,341,548 and *Synth. Commun.* 1989, 19, 2551-2566.

2-Trifluoromethanesulfonyl-1H-imidazoles of formula IIIa can be prepared from a 2-oxo-2,3-dihydro-1H-imidazole of formula VI, for example from 5-methyl-2-oxo-1-phenyl-2,3-dihydro-1H-imidazole-4-carboxylic acid ethyl ester which is obtained according to the method as described in USP 3,303,199. The reaction with trifluoromethanesulfonic anhydride and triethylamine is carried out in dichloromethane at room temperature (Scheme 1, Tf = trifluoromethanesulfonyl).

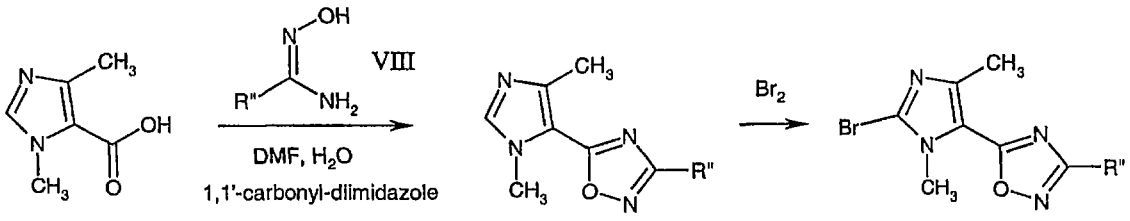
Scheme 1




VI IIIa

5-(2-Bromo-3,5-dimethyl-3H-imidazol-4-yl)-[1,2,4]oxadiazoles of formula IIIb are obtained by reacting 3,5-dimethyl-3H-imidazole-4-carboxylic acid VIIwith N-hydroxy-carboxamidines of formula VIII in the presence of 1,1'-carbonyldiimidazole and dimethylformamide as solvent to give imidazolyl-[1,2,4]oxadiazoles of formula IX which are then brominated at room temperature (Scheme 2, R" is lower alkyl or cycloalkyl).

Scheme 2




VII IX IIIb

A suitable indole derivative of formula III (B = B3), for example N-[2-(2-iodo-5-methoxy-1H-indol-3-yl)-ethyl]-acetamide, can be obtained in accordance with the method as described in *J. Labelled Compd. Radiopharm.* 1997, 39, 677-684.

3-Iodo-4H-5-thia-2,6,9b-triaza-cyclopenta[a]naphtalenes and 3-iodo-4H-5-oxa-2,9b-diaza-cyclopenta[a]naphthalenes of formula III (B = B4) are prepared in analogy to the method as described in EP 0 059 390.

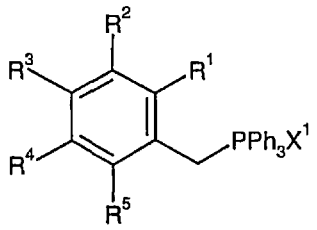
4-Halogeno-1H-imidazoles of formula III (B = B5) can be obtained according to methods as described for example in *J. Med. Chem.* 1974, 17(9), 1019-1020, *Chem. Pharm. Bull.* 1994, 42, 1784-1790 or *Aust. J. Chem.* 1987, 40(8), 1399-1413.

Compounds of formula III, in which B signifies B6, can be prepared for example in analogy to a method described in *Bull. Acad. Sci. USSR Div. Chem. Sci. (Engl. Transl.)* 1983, 626-628 and in *Izv. Akad. Nauk SSSR Ser. Khim.* 1983, 688-690.

Phenylethenyl derivatives of formula I can be prepared analogously by reacting a compound of formula III with a phenylethene of formula II.

Furthermore, compounds of formula I, in which A signifies -C=C-, and their pharmaceutically acceptable salts can also be obtained by

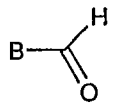
reacting a compound of the formula



IV

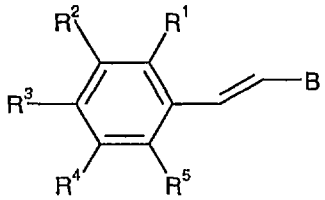
wherein $X^1$ signifies halogen,

with a compound of the formula



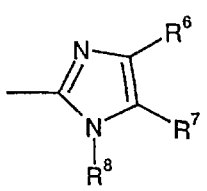
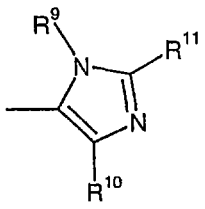
V

to obtain a compound of formula



I-B

wherein $R^1$ to $R^5$ have the significances as claimed in claim 1 and B is

B1)  or B2) 

wherein

$R^6$ signifies hydrogen, lower alkyl, $-(CH_2)_n-C(O)OR$ or halogen;

$R^7$ signifies hydrogen, lower alkyl, $-(CH_2)_n-C(O)OR'$, halogen, nitro or heteroaryl which is unsubstituted or substituted by lower alkyl or cycloalkyl;

$R^8$ signifies hydrogen, lower alkyl, $-(CH_2)_n-OH$, $-(CH_2)_n-C(O)OR''$ or aryl;

$R^9$ signifies lower alkyl;

$R^{10}$ signifies halogen; and

$R^{11}$ signifies hydrogen or alkyl;

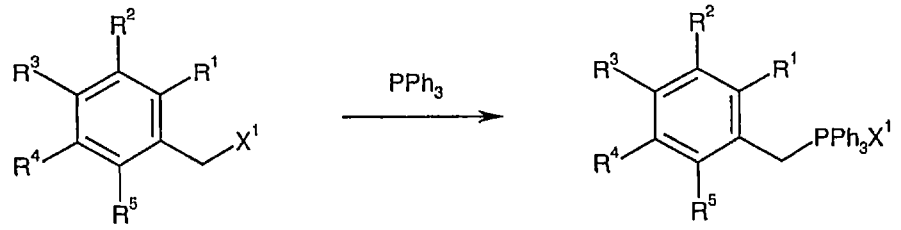
and if desired,

converting a compound of formula I-B into a pharmaceutically acceptable salt.

Thus, compounds of formula I-B are obtained in a Wittig reaction by treating an appropiate aldehyde of formula V, for example 4,5-diisopropyl-1-methyl-1H-imidazole-2-carbaldehyde, with a suitable benzyltriphenylphosphonium halide of formula IV, for example benzyltriphenylphosphoniumchloride in the presence of a strong base like a sodium alkoxide, sodium amide or sodium hydride.

Triphenylphosphonium salts of formula IV are prepared from triphenylphosphine ($PPh_3$) and the appropiate benzyl halides X (Scheme 3).

Scheme 3




X IV

Aldehydes of formula V can be obtained by methods known in the art. For example, 4,5-diisopropyl-1-methyl-1H-imidazole-2-carbaldehyde is prepared in analogy with a method as described in *Inorg. Chim. Acta* 1999, 296 (1), 208-221, and 5-bromo-3-methyl-3H-imidazole-4-carbaldehyde is obtained in accordance to a method as described in *Chem. Pharm. Bull.* 1994, 42, 1784-1790.

The pharmaceutically acceptable salts of coumpounds of formula I-A and I-B 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, 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 auch 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:

cDNA encoding rat mGlu 5a receptor was transiently transfected into EBNA cells using a procedure described by E.-J. Schlaeger and K. Christensen (Transient gene expression in mammalian cells grown in serum-free suspension culture; Cytotechnology, 30: 71-83,1999). $[Ca^{2+}]i$ measurements were performed on mGlu 5a transfected EBNA cells after incubation of the cells with Fluo 3-AM (obtainable by FLUKA, 0.5 μM final concentration) for 1 hour at 37 °C followed by 4 washes with assay buffer (DMEM supplemented with Hank's salt and 20 mM HEPES. $[Ca^{2+}]i$ measurements were done using a fluorometric imaging plate reader (FLIPR, Molecular Devices Corporation, La Jolla, CA, USA). When compounds were evaluated as antagonists they were tested against 10 μM glutamate as agonist.

The inhibition (antagonists) curves were fitted with a four parameter logistic equation giving $IC_{50}$, and Hill coefficient using the iterative non linear curve fitting software Origin (Microcal Software Inc., Northampton, MA, USA).

The compounds of the present invention are mGluR 5a receptor antagonists. The compounds show activities, as measured in the assay described above, of 10 μM or less, typically 2 μM or less, and ideally of 0.02 μM or less.

In the table below are shown specific activity data of the compounds of the present invention:

| Example No. | Compound name | $IC_{50}$ (μM) |
|---|---|---|
| 1 | 3,5-dimethyl-2-phenylethynyl-3H-imidazole-4-carboxylic acid ethyl ester | 0.25 |
| 2 | 5-methyl-2-phenylethynyl-3H-imidazole-4-carboxylic acid ethyl ester | 2.40 |
| 3 | 2-(3-methoxy-phenylethynyl)-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester | 0.35 |
| 4 | 1-methyl-2-phenylethynyl-1H-imidazole | 0.72 |
| 5 | 2-(5-nitro-2-phenylethynyl-imidazol-1-yl)-ethanol | 2.11 |
| 6 | 2-phenylethynyl-1H-imidazole | 0.20 |
| 7 | 2-(2,6-dichloro-phenylethynyl)-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester | 10 |
| 8 | 5-methyl-1-phenyl-2-phenylethynyl-1H-imidazole-4-carboxylic acid ethyl ester | < 10 |
| 9 | 3,5-dimethyl-2-m-tolylethynyl-3H-imidazole-4-carboxylic acid ethyl ester | 0.13 |
| 10 | 2-(3-acetylamino-phenylethynyl)-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester | 2.12 |
| 11 | (2-[3-(2,5-dimethyl-pyrrol-1-yl)-phenylethynyl]-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester | 0.18 |
| 12 | 5-(3,5-dimethyl-2-phenylethynyl-3H-imidazol-4-yl)-3-methyl-[1,2,4]oxadiazole | 0.011 |
| 14 | 2-(4-chloro-phenylethynyl)-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester | < 10 |
| 15 | 2-(4-fluoro-phenylethynyl)-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester | 0.25 |
| 16 | 2-biphenyl-4-ylethynyl-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester | 0.21 |
| 17 | 2-(2-fluoro-phenylethynyl)-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester | 0.09 |
| 18 | 2-(2-fluoro-phenylethynyl)-1-methyl-1H-imidazole | 0.07 |
| 19 | 2-(4-amino-phenylethynyl)-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester | 1.53 |

| Example No. | Compound name | $IC_{50}$ (μM) |
|---|---|---|
| 20 | 2-(2-chloro-phenylethynyl)-1-methyl-1H-imidazole | 1.10 |
| 21 | (4,5-dichloro-2-phenylethynyl-imidazol-1-yl)-acetic acid ethyl ester | 0.52 |
| 22 | 1-methyl-5-phenylethynyl-1H-imidazole | 0.22 |
| 23 | N-[2-(5-methoxy-2-phenylethynyl-1H-indol-3-yl)-ethyl]-acetamide | 0.58 |
| 24 | 3-phenylethynyl-4H-5-thia-2,6,9b-triaza-cyclopenta[a]naphthalene | 0.15 |
| 25 | 3-phenylethynyl-4H-5-oxa-2,9b-diaza-cyclopenta[a]naphthalene | 0.07 |
| 26 | 1-chloro-3-(2-methyl-5-nitro-4-phenylethynyl-imidazol-1-yl)-propan-2-ol | 0.23 |
| 27 | 3-methyl-5-phenylethynyl-3H-imidazole-4-carbaldehyde | 1.79 |
| 28 | 4-phenylethynyl-1H-imidazole | 3.36 |
| 29 | 1-methyl-4-phenylethynyl-1H-imidazole | 0.50 |
| 30 | 1,2-dimethyl-5-nitro-4-phenylethynyl-1H-imidazole | 0.02 |
| 31 | 1,3-dimethyl-5-phenylethynyl-1H-pyrazole | 5-10 |
| 32 | 4,5-diisopropyl-1-methyl-2-styryl-1H-imidazole | 1.82 |
| 33 | 2-[2-(4-fluoro-phenyl)-vinyl]-4,5-diisopropyl-1-methyl-1H-imidazole | 5-10 |
| 34 | 2-[2-(4-chloro-phenyl)-vinyl]-4,5-diisopropyl-1-methyl-1H-imidazole | 5-10 |
| 35 | 2-[2-(4-butoxy-phenyl)-vinyl]-4,5-diisopropyl-1-methyl-1H-imidazole | 5-10 |
| 36 | 4,5-diisopropyl-2-[2-(4-methoxy-2,3,6-trimethyl-phenyl)-vinyl]-1-methyl-1H-imidazole | 5-10 |
| 37 | 4,5-diisopropyl-2-[2-(4-methoxy-phenyl)-vinyl]-1-methyl-1H-imidazole | 5-10 |
| 38 | 2-[2-(4-chloro-3-fluoro-phenyl)-vinyl]-4,5-diisopropyl-1-methyl-1H-imidazole | 10 |
| 39 | 2-[2-(4-ethoxy-phenyl)-vinyl]-4,5-diisopropyl-1-methyl-1H-imidazole | 10 |
| 40 | 4,5-diisopropyl-1-methyl-2-[2-(2,3,4-trimethoxy-phenyl)-vinyl]-1H-imidazole | 10 |
| 41 | 2-[2-(2,4-dichloro-phenyl)-vinyl]-4,5-diisopropyl-1-methyl-1H-imidazole | 10 |
| 42 | 4,5-diisopropyl-1-methyl-2-(2-p-tolyl-vinyl)-1H-imidazole | 3.25 |
| 43 | 4-bromo-1-methyl-5-styryl-1H-imidazole | 3.06 |
| 44 | 1-methyl-5-styryl-1H-imidazole | 8.0 |

The compounds of formula I and pharmaceutically acceptable salts thereof can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical

preparations can be administered orally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. However, the administration can also be effected rectally, e.g. in the form of suppositories, or parenterally, e.g. in the form of injection solutions.

The compounds of formula I and pharmaceutically acceptable salts thereof can be processed with pharmaceutically inert, inorganic or organic carriers for the production of pharmaceutical preparations. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts and the like can be used, for example, as such carriers for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carriers for soft gelatine capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like; depending on the nature of the active substance no carriers are, however, usually required in the case of soft gelatine capsules. Suitable carriers for the production of solutions and syrups are, for example, water, polyols, sucrose, invert sugar, glucose and the like. Adjuvants, such as alcohols, polyols, glycerol, vegetable oils and the like, can be used for aqueous injection solutions of water-soluble salts of compounds of formula I, but as a rule are not necessary. Suitable carriers for suppositories are, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like.

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

As mentioned earlier, medicaments containing a compound of formula IA or IB 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 IA or IB 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.

Finally, as mentioned earlier, the use of compounds of formula I and of pharmaceutically acceptable salts thereof for the production of medicaments, especially for the for the treatment or prevention of mGluR5 receptor mediated disorders of the aforementioned kind, is also an object of the invention.

The following examples are provided for illustration of the invention. They should not be considered as limiting the scope of the invention, but merely as being representative thereof.

## Example 1

3,5-Dimethyl-2-phenylethynyl-3H-imidazole-4-carboxylic acid ethyl ester

a) 2-Bromo-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester

The title compound was prepared according to the method as described in USP 4,711,962.

b) 3,5-Dimethyl-2-phenylethynyl-3H-imidazole-4-carboxylic acid ethyl ester

In analogy to the method as described in *Chem. Pharm. Bull.* 1987, *35(2)*, 823-828, 17.5 mg (0.025 mmol) bis-(triphenylphosphine)-palladium-II-chloride, 2.9 mg (0.015 mmol) cuprous iodide, 60.5mg (0.6 mmol) triethylamine, 32.4 mg (0.3 mmol) ethynylbenzene and 61.8 mg (0.25mmol) 2-bromo-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester are dissolved in 1ml DMF and shaken for 3 h at 90 °C. The title compound (19.3 mg, 29%, MS: m/e = 269.3, $[M+H^+]$) was isolated from the reaction mixture by HPLC chromatography (YMC CombiPrep C18 column 50x20mm, solvent gradient 10-95% $CH_3CN$ in 0.1% TFA(aq) over 6.0min, $\lambda$ = 230nm, flow rate 40ml/min).

$^1$H-NMR (400MHz, $CDCl_3$, 25 °C): $\delta$ (ppm) = 1.39 (3H; t, J = 7.22Hz), 2.51 (3H, s), 3.99 (3H, s), 4.35 (2H, q, J = 7.22Hz), 7.34 – 7.40 (3H, m), 7.56 – 7.59 (2H, m).

$^{13}$C-NMR (100MHz, $CDCl_3$, 25 °C): $\delta$ (ppm) = 14.26, 15.78, 34.31, 60.44, 77.83, 94.86, 119.77, 121.14, 128.46, 129.48, 131.82, 134.55, 147.76, 160.58.

## Example 2

5-Methyl-2-phenylethynyl-3H-imidazole-4-carboxylic acid ethyl ester

a) 2-Bromo-5-methyl-3H-imidazole-4-carboxylic acid ethyl ester

The compound was prepared according to the method described in USP 4,711,962.

b) 5-Methyl-2-phenylethynyl-3H-imidazole-4-carboxylic acid ethyl ester

The title compound, MS: m/e = 255.2 ($M+H^+$) was prepared in accordance with the general method of example 1b from 2-bromo-5-methyl-3H-imidazole-4-carboxylic acid ethyl ester.

Example 3

2-(3-Methoxy-phenylethynyl)-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester

The title compound, MS: m/e = 299.3 ($M+H^+$) was prepared in accordance with the general method of example 1b from 2-bromo-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester and 1-ethynyl-3-methoxy-benzene.

Example 4

1-Methyl-2-phenylethynyl-1H-imidazole

The title compound, MS: m/e = 183.0 ($M+H^+$) was prepared in accordance with the general method of example 1b from 2-iodo-1-methyl-1H-imidazole.

Example 5

2-(5-Nitro-2-phenylethynyl-imidazol-1-yl)-ethanol

a) 2-(2-Iodo-5-nitro-imidazol-1-yl)-ethanol

2-(2-Iodo-5-nitro-imidazol-1-yl)-ethanol was obtained in accordance with the method as described in USP 3,341,548.

b) 2-(5-Nitro-2-phenylethynyl-imidazol-1-yl)-ethanol

The title compound, MS: m/e = 258.0 ($M+H^+$) was prepared in accordance with the general method of example 1b from 2-(2-iodo-5-nitro-imidazol-1-yl)-ethanol.

Example 6

2-Phenylethynyl-1H-imidazole

a) 2-Iodoimidazole

2-Iodoimidazole was prepared in accordance with the method as described in *Synth. Commun.* 1989, *19*, 2551-2566.

b) 2-Phenylethynyl-1H-imidazole

The title compound, MS: m/e = 169.4 ($M+H^+$) was prepared in accordance with the general method of example 1b from 2-iodoimidazole.

Example 7

2-(2,6-Dichloro-phenylethynyl)-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester

The title compound, MS: m/e = 197.4 ($M+H^+$) was prepared in accordance with the general method of example 1b from 1,3-dichloro-2-ethynyl-benzene and 2-bromo-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester.

Example 8

5-Methyl-1-phenyl-2-phenylethynyl-1H-imidazole-4-carboxylic acid ethyl ester

a) 5-Methyl-2-oxo-1-phenyl-2,3-dihydro-1H-imidazole-4-carboxylic acid ethyl ester

The title compound was obtained by the method as described in USP 3,303,199.

b) 5-Methyl-1-phenyl-2-phenylethynyl-1H-imidazole-4-carboxylic acid ethyl ester

A mixture of 492 mg (2 mmol) 5-methyl-2-oxo-1-phenyl-2,3-dihydro-1H-imidazole-4-carboxylic acid ethyl ester, 846 mg (3 mmol) trifluoromethanesulfonic anhydride, 303 mg (3 mmol) triethylamine and 10 ml dichloromethane was stirred for 1h at room temperature. The volatile components were evaporated under reduced pressure and the obtained residue was filtered over silica gel (ethyl acetate / hexane = 1:4 as eluent). After evaporation of the solvent under reduced pressure, a yellow oil (463 mg) was obtained. 378 mg of this oil, 122 mg (1.2 mmol) Phenylacetylene, 70 mg (0.1 mmol) bis-(triphenylphosphine)-palladium-II-chloride, 303mg (3 mmol) triethylamine, and 10 mg (0.05 mmol) of cuprous iodide were dissolved in 5 ml DMF and stirred for 1.5 h at 100 °C. The reaction mixture was cooled to room temperature, diluted with 30 ml ether, washed

with water and brine and dried over $MgSO_4$. Evaporation of the solvent gave an oil from which the title compound (277 mg, 51 %) was isolated by column chromatography (silica gel, Ethyl acetate / Hexane = 2:3 as eluant).

$^1$H-NMR (400 MHz, $CDCl_3$, 25 °C): δ (ppm) = 1.44 (3H, t, J = 7Hz), 2.47 (3H, s), 4.42 (2H, q, J = 7Hz), 7.20 – 7.42 (5H, m), 7.34 – 7.38 (2H, m), 7.53 – 7.60 (3H, m).

$^{13}$C-NMR (100 MHz, $CDCl_3$, 25°C): δ (ppm) = 11.53, 14.94, 60.90, 79.34, 92.92, 121.91, 127.79, 128.73, 129.47, 129.86, 130.00, 130.15, 131.90, 132.08, 135,42, 137.91, 163.75.

## Example 9

3,5-Dimethyl-2-m-tolylethynyl-3H-imidazole-4-carboxylic acid ethyl ester

The title compound, MS: m/e = 283.6 ($M+H^+$), was prepared in accordance with the general method of example 1b from 1-ethynyl-3-methyl-benzene and 2-bromo-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester.

## Example 10

2-(3-Acetylamino-phenylethynyl)-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester

The title compound, MS: m/e = 326.8 ($M+H^+$), was prepared in accordance with the general method of example 1b from N-(3-ethynyl-phenyl)-acetamide and 2-bromo-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester.

## Example 11

(2-[3-(2,5-Dimethyl-pyrrol-1-yl)-phenylethynyl]-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester

The title compound, MS: m/e = 362.8 ($M+H^+$), was prepared in accordance with the general method of example 1b from 2-bromo-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester and 1-(3-ethynyl-phenyl)-2,5-dimethyl-1H-pyrrole.

Example 12

5-(3,5-Dimethyl-2-phenylethynyl-3H-imidazol-4-yl)-3-methyl-[1,2,4]oxadiazole

a) 5-(3,5-Dimethyl-3H-imidazol-4-yl)-3-methyl-[1,2,4]oxadiazole

A solution of 3,5-dimethyl-3H-imidazole-4-carboxylic acid (1.0 g, 7.14 mmol) and 1,1'-carbonyldiimidazole (1.74 g, 10.7 mmol) in DMF (35 ml) was stirred at RT for 3 h. N-hydroxy-acetamidine (0.68 g, 9.18 mmol) was added, the reaction mixture was stirred at 16 h at 80 °C, evaporated and dissolved in acetic acid (30 ml). The solution was stirred at 100 °C for 2 h, evaporated, poured into sat. $NaHCO_3$ solution (50 ml) and extracted with dichloromethane (7 x 30 ml). The combined organic layers were washed with brine (70 ml), dried ($MgSO_4$) and evaporated to give the title compound (0.78 g, 61%) as a white solid, m.p. 95 °C and MS: m/e = 178.2 ($M^+$).

b) 5-(2-Bromo-3,5-dimethyl-3H-imidazol-4-yl)-3-methyl-[1,2,4]oxadiazole

To a stirred solution of 5-(3,5-dimethyl-3H-imidazol-4-yl)-3-methyl-[1,2,4]oxadiazol (0.7 g, 3.93 mmol) in chloroform (7 ml) was added dropwise at RT a solution of bromine (0.94 g, 0.30 ml, 5.89 mmol) in chloroform (7 ml). The reaction mixture was stirred at RT for 26 h, evaporated, poured into sat. $NaHCO_3$ solution (40 ml) and extracted with dichloromethane (2 x 30 ml). The combined organic layers were washed with brine (40 ml), dried ($MgSO_4$) and evaporated to give the crude product as yellow oil (0.84 g). Purification by column chromatography on silica gel (ethyl acetate/MeOH 98 : 2) gave the title compound (0.52 g, 51%) as a white solid, m.p. 89 °C and MS: m/e = 256, 258 ($M^+$).

c) 5-(3,5-Dimethyl-2-phenylethynyl-3H-imidazol-4-yl)-3-methyl-[1,2,4]oxadiazole

To a stirred solution of 5-(2-bromo-3,5-dimethyl-3H-imidazol-4-yl)-3-methyl-[1,2,4]oxadiazole (0.52 g, 2.02 mmol) in THF (10 ml) was added at RT bis(triphenyl-phosphin)palladium(II)chloride (71 mg, 0.1 mmol), phenylacetylene (0.31 g, 3.03 mmol), triphenylphosphine (27 mg, 0.1 mmol) and triethylamine (0.61 g, 6.07 mmol). Through the reaction mixture was bubbled argon for 10 min and stirring was continued at 55 °C for 16h. The reaction mixture was poured into water (50 ml) and extracted with ethyl acetate (2 x 50 ml). The combined organic layers were washed with brine (40 ml), dried ($MgSO_4$) and evaporated to give the crude product as yellow oil (0.81 g). Purification by column chromatography on silica gel (ethyl acetate/toluene 5 : 1) gave the title compound (0.31 g, 55%) as a light yellow solid, m.p. 137 °C and MS: m/e = 278.1 ($M^+$).

## Example 13

3-Cyclopropyl-5-(3,5-dimethyl-2-phenylethynyl-3H-imidazol-4-yl)-[1,2,4]oxadiazole

a) 3-Cyclopropyl-5-(3,5-dimethyl-3H-imidazol-4-yl)-[1,2,4]oxadiazole

The title compound, off-white solid, m.p. 88 °C and MS: m/e = 204.3 ($M^+$), was prepared from 3,5-dimethyl-3H-imidazole-4-carboxylic acid and N-hydroxy-cyclopropane-carboxamidine in accordance with the general procedure of example 12a.

b) 5-(2-Bromo-3,5-dimethyl-3H-imidazol-4-yl)-3-cyclopropyl-[1,2,4]oxadiazole

The title compound, white solid, m.p. 81 °C and MS: m/e = 282, 284 ($M^+$), was prepared by bromination of 3-cyclopropyl-5-(3,5-dimethyl-3H-imidazol-4-yl)-[1,2,4]oxadiazole in accordance with the general method of example 12b.

c) 3-Cyclopropyl-5-(3,5-dimethyl-2-phenylethynyl-3H-imidazol-4-yl)-[1,2,4]oxadiazole

The title compound, white solid, m.p. 120 °C and MS: m/e = 305.2 ($M+H^+$), was prepared from 5-(2-bromo-3,5-dimethyl-3H-imidazol-4-yl)-3-cyclopropyl-[1,2,4]oxadiazole and phenylacetylene in accordance with the general procedure of example 12c.

## Example 14

2-(4-Chloro-phenylethynyl)-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester

The title compound, MS: m/e = 303.0 ($M+H^+$) was prepared in accordance with the general method of example 1b from 2-bromo-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester and 1-chloro-4-ethynylbenzene.

## Example 15

2-(4-Fluoro-phenylethynyl)-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester

The title compound, MS: m/e = 286.8 ($M+H^+$) was prepared in accordance with the general method of example 1b from 2-bromo-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester and 1-ethynyl-4-fluorobenzene.

Example 16

2-Biphenyl-4-ylethynyl-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester

The title compound, MS: m/e = 345.4 ($M+H^+$) was prepared in accordance with the general method of example 1b from 2-bromo-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester and 4-ethynylbiphenyl.

Example 17

2-(2-Fluoro-phenylethynyl)-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester

The title compound, MS: m/e = 287.4 ($M+H^+$) was prepared in accordance with the general method of example 1b from 2-bromo-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester and 1-ethynyl-2-fluorobenzene.

Example 18

2-(2-Fluoro-phenylethynyl)-1-methyl-1H-imidazole

The title compound, MS: m/e = 201.2 ($M+H^+$) was prepared in accordance with the general method of example 1b from 2-iodo-1-methyl-1H-imidazole and 1-ethynyl-2-fluorobenzene.

Example 19

2-(4-Amino-phenylethynyl)-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester

The title compound, MS: m/e = 284.4 ($M+H^+$) was prepared in accordance with the general method of example 1b from 2-bromo-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester and 4-ethynylaniline.

Example 20

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

The title compound, MS: m/e = 217.6 ($M+H^+$) was obtained in accordance with the general method of example 1b from 2-iodo-1-methyl-1H-imidazole and 1-chloro-2-ethynylbenzene.

Example 21

(4,5-Dichloro-2-phenylethynyl-imidazol-1-yl)-acetic acid ethyl ester

The title compound, MS: m/e = 323.0 ($M+H^+$) was prepared in accordance with the general method of example 1b from ethyl (2-bromo-4,5-dichloroimidazole-1-yl) acetate and ethynylbenzene.

Example 22

1-Methyl-5-phenylethynyl-1H-imidazole

The title compound, MS: m/e = 183.4($M+H^+$) was prepared in accordance with the general method of example 1b from 5-iodo-1-methyl-1H-imidazole.

Example 23

N-[2-(5-Methoxy-2-phenylethynyl-1H-indol-3-yl)-ethyl]-acetamide

a) N-[2-(2-iodo-5-methoxy-1H-indol-3-yl)-ethyl]-acetamide

The title compound is obtained from N-[2-(5-methoxy-indol-3-yl)-ethyl]-acetamide according to the method as described in *J. Labelled Compd. Radiopharm.* 1997, *39*, 677-684.

b) N-[2-(5-Methoxy-2-phenylethynyl-1H-indol-3-yl)-ethyl]-acetamide

The title compound, MS: m/e = 333.3 ($M+H^+$) was prepared in accordance with the general method of example 1b from N-[2-(2-iodo-5-methoxy-1H-indol-3-yl)-ethyl]-acetamide.

Example 24

3-Phenylethynyl-4H-5-thia-2,6,9b-triaza-cyclopenta[a]naphthalene

a) 3-Iodo-4H-5-thia-2,6,9b-triaza-cyclopenta[a]naphthalene

In analogy to the method as described in EP 0 059 390 the title compound was obtained.

b) 3-Phenylethynyl-4H-5-thia-2,6,9b-triaza-cyclopenta[a]naphthalene

The title compound, MS: m/e = 290.3 ($M+H^+$) was prepared in accordance with the general method of example 1b from 3-iodo-4H-5-thia-2,6,9b-triaza-cyclopenta[a]naphthalene.

Example 25

3-Phenylethynyl-4H-5-oxa-2,9b-diaza-cyclopenta[a]naphthalene

a) 3-Iodo-4H-5-oxa-2,9b-diaza-cyclopenta[a]naphthalene

3-Iodo-4H-5-oxa-2,9b-diaza-cyclopenta[a]naphthalene was obtained in analogy to the method as described EP 0 059 390.

b) 3-Phenylethynyl-4H-5-oxa-2,9b-diaza-cyclopenta[a]naphthalene

The title compound, MS: m/e = 273.2 ($M+H^+$), 545.1 ($2M+H^+$), was prepared in accordance with the general method of example 1b from 3-iodo-4H-5-oxa-2,9b-diaza-cyclopenta[a]naphthalene.

Example 26

1-Chloro-3-(2-methyl-5-nitro-4-phenylethynyl-imidazol-1-yl)-propan-2-ol

a) 1-Chloro-3-(4-iodo-2-methyl-5-nitro-imidazol-1-yl)-propan-2-ol

1-Chloro-3-(4-iodo-2-methyl-5-nitro-imidazol-1-yl)-propan-2-ol was obtained by the method as described in *J. Med. Chem.* 1974, 17(9), 1019-20.

b) 1-Chloro-3-(2-methyl-5-nitro-4-phenylethynyl-imidazol-1-yl)-propan-2-ol

The title compound, MS: m/e = 319.7, 321.9 ($M+H^+$) was prepared in accordance with the general method of example 1b from 1-chloro-3-(4-iodo-2-methyl-5-nitro-imidazol-1-yl)-propan-2-ol.

Example 27

3-Methyl-5-phenylethynyl-3H-imidazole-4-carbaldehyde

a) 5-Bromo-3-methyl-3H-imidazole-4-carbaldehyde

5-Bromo-3-methyl-3H-imidazole-4-carbaldehyde was obtained in accordance with the method as described in *Chem. Pharm. Bull.* 1994, *42*, 1784-1790.

b) 3-Methyl-5-phenylethynyl-3H-imidazole-4-carbaldehyde

The title compound, MS: m/e = 210.6 ($M+H^+$) was prepared in accordance with the general method of example 1b from 5-bromo-3-methyl-3H-imidazole-4-carbaldehyde.

Example 28

4-Phenylethynyl-1H-imidazole

The title compound, MS: m/e = 169.2 ($M+H^+$) was prepared in accordance with the general method of example 1b from 4-bromoimidazole and ethynylbenzene.

Example 29

1-Methyl-4-phenylethynyl-1H-imidazole

The title compound, MS: m/e = 183.2 ($M+H^+$) was prepared in accordance with the general method of example 1b from 4-iodo-1-methyl-1H-imidazole.

Example 30

1,2-Dimethyl-5-nitro-4-phenylethynyl-1H-imidazole

a) 1,2-Dimethyl-4-iodo-5-nitroimidazole

1,2-Dimethyl-4-iodo-5-nitroimidazole was obtained according to the method as described in *Aust. J. Chem.* **1987**, *40(8)*, 1399-413

b) 1,2-Dimethyl-5-nitro-4-phenylethynyl-1H-imidazole

The title compound, MS: m/e = 242.4 ($M+H^+$) was prepared in accordance with the general method of example 1b from 1,2-dimethyl-4-iodo-5-nitroimidazole.

Example 31

1,3-Dimethyl-5-phenylethynyl-1H-pyrazole

a) 5-Iodo-1,3-dimethyl-1H-pyrazole

The title compound was obtained according to the method as described in *Bull.Acad.Sci.USSR Div.Chem.Sci.(Engl.Transl.)* **1983**; 626-628 and in *Izv.Akad.Nauk SSSR Ser.Khim.* **1983**; 688-690.

b) 1,3-Dimethyl-5-phenylethynyl-1H-pyrazole

The title compound, MS: m/e = 196.8 ($M+H^+$) was prepared in accordance with the general method of example 1b from 5-iodo-1,3-dimethyl-1H-pyrazole.

Example 32

4,5-Diisopropyl-1-methyl-2-styryl-1H-imidazole

a) 4,5-Diisopropyl-1-methyl-1H-imidazole-2-carbaldehyde

4,5-Diisopropyl-1-methyl-1H-imidazole-2-carbaldehyde was obtained analogously to the method as described in *Inorg. Chim. Acta* 1999, 296(1), 208-221.

b) 4,5-Diisopropyl-1-methyl-2-styryl-1H-imidazole

194 mg (0.5 mmol) benzyltriphenylphosphoniumchloride and 97 mg (0.5 mmol) 4,5-diisopropyl-1-methyl-1H-imidazole-2-carbaldehyde were added to 1.3 ml of a 0.5 M solution of MeONa in MeOH. The mixture was shaken at 60 °C for 3 days, then cooled to room temperature. After addition of 0.2ml formic acid, the title compound (59 mg, 44%, MS: m/e = 269.4 [M+H$^+$]) was isolated from the reaction mixture by HPLC chromatography (YMC CombiPrep C18 column 50x20mm, solvent gradient 10-95% $CH_3CN$ in 0.1% TFA(aq) over 6.0 min, $\lambda$ = 230 nm, flow rate 40 ml/min).

Example 33

2-[2-(4-Fluoro-phenyl)-vinyl]-4,5-diisopropyl-1-methyl-1H-imidazole

The title compound, MS: m/e = 286.8 (M+H$^+$), was prepared in accordance with the general method of example 32b from 4-fluorobenzyl triphenylphosphonium chloride.

Example 34

2-[2-(4-Chloro-phenyl)-vinyl]-4,5-diisopropyl-1-methyl-1H-imidazole

The title compound, MS: m/e = 302.9 (M+H$^+$), was prepared in accordance with the general method of example 32b from 4-chlorobenzyl triphenylphosphonium chloride.

Example 35

2-[2-(4-Butoxy-phenyl)-vinyl]-4,5-diisopropyl-1-methyl-1H-imidazole

The title compound, MS: m/e = 340.9 (M+H$^+$), was prepared in accordance with the general method of example 32b from (4-butoxybenzyl)triphenylphosphonium bromide.

Example 36

4,5-Diisopropyl-2-[2-(4-methoxy-2,3,6-trimethyl-phenyl)-vinyl]-1-methyl-1H-imidazole

a) 2,3,6-Trimethyl-4-methoxybenzyltriphenyl-phosphonium chloride

2,3,6-Trimethyl-4-methoxybenzyltriphenyl-phosphonium chloride was obtained in accordance with the method as described in *Liebigs Ann. Chem.* 1984, *10*, 1740-5.

b) 4,5-Diisopropyl-2-[2-(4-methoxy-2,3,6-trimethyl-phenyl)-vinyl]-1-methyl-1H-imidazole

The title compound, MS: m/e = 340.9 ($M+H^+$), was prepared in accordance with the general method of example 32b from 2,3,6-trimethyl-4-methoxybenzyltriphenyl-phosphonium chloride.

Example 37

4,5-Diisopropyl-2-[2-(4-methoxy-phenyl)-vinyl]-1-methyl-1H-imidazole

The title compound, MS: m/e = 298.9 ($M+H^+$), was prepared in accordance with the general method of example 32b from (4-methoxybenzyl)triphenylphosphonium bromide.

Example 38

2-[2-(4-Chloro-3-fluoro-phenyl)-vinyl]-4,5-diisopropyl-1-methyl-1H-imidazole

a) 4-Chloro-3-fluorobenzyl triphenylphosphonium bromide

4-Chloro-3-fluorobenzyl triphenylphosphonium bromide was obtained according to the method as described in EP 0 692 485.

b) 2-[2-(4-Chloro-3-fluoro-phenyl)-vinyl]-4,5-diisopropyl-1-methyl-1H-imidazole

The title compound, MS: m/e = 320.8 ($M+H^+$), was prepared in accordance with the general method of example 32b from 4-chloro-3-fluorobenzyl triphenylphosphonium bromide.

Example 39

2-[2-(4-Ethoxy-phenyl)-vinyl]-4,5-diisopropyl-1-methyl-1H-imidazole

The title compound, MS: m/e = 312.9 ($M+H^+$), was prepared in accordance with the general method of example 32b from (4-ethoxybenzyl)triphenylphosphonium bromide.

Example 40

4,5-Diisopropyl-1-methyl-2-[2-(2,3,4-trimethoxy-phenyl)-vinyl]-1H-imidazole

a) Triphenyl-(2,3,4-trimethoxy-benzyl)-phosphonium bromide

Triphenyl-(2,3,4-trimethoxy-benzyl)-phosphonium bromide was obtained according to the method as described in DE 43 07 049.

b) 4,5-Diisopropyl-1-methyl-2-[2-(2,3,4-trimethoxy-phenyl)-vinyl]-1H-imidazole

The title compound, MS: m/e = 359.0 ($M+H^+$), was prepared in accordance with the general method of example 32b from triphenyl-(2,3,4-trimethoxy-benzyl)-phosphonium bromide.

Example 41

2-[2-(2,4-Dichloro-phenyl)-vinyl]-4,5-diisopropyl-1-methyl-1H-imidazole

The title compound, MS: m/e = 336.8 ($M+H^+$), was prepared in accordance with the general method of example 32b from 2,4-dichlorobenzyltriphenylphosphonium chloride.

Example 42

4,5-Diisopropyl-1-methyl-2-(2-p-tolyl-vinyl)-1H-imidazole

The title compound, MS: m/e = 282.9 ($M+H^+$), was prepared in accordance with the general method of example 32b from 4-methylbenzyltriphenylphosphonium bromide.

Example 43

4-Bromo-1-methyl-5-styryl-1H-imidazole

a) 5-Bromo-3-methyl-3H-imidazole-4-carbaldehyde

5-Bromo-3-methyl-3H-imidazole-4-carbaldehyde was obtained by the method as described in *Chem. Pharm. Bull.* 1994, 42, 1784-1790.

b) 4-Bromo-1-methyl-5-styryl-1H-imidazole

The title compound, MS: m/e = 263.0 ($M+H^+$), was prepared in accordance with the general method of example 21b from 5-bromo-3-methyl-3H-imidazole-4-carbaldehyde.

## Example 44

1-Methyl-5-styryl-1H-imidazole

The title compound was obtained according to the method as described in *Chem. Pharm. Bull.* 1987; *35*, 823-828.

Example A

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

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

Example B

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 C

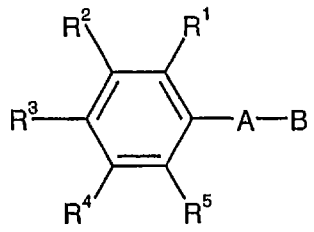
Capsules of the following composition are produced:

| | 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. The use of a compound of the general formula



I

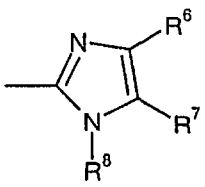
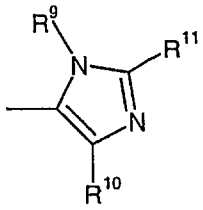
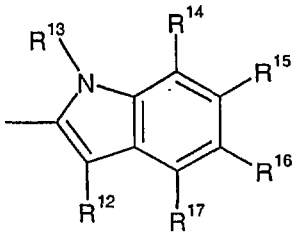
wherein

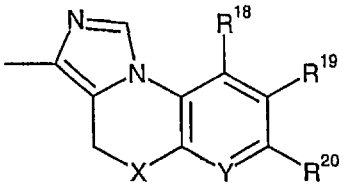
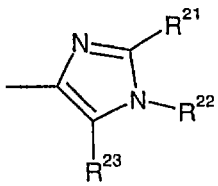
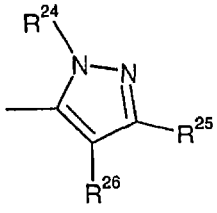
$R^1$, $R^2$, $R^3$, $R^4$ and $R^5$ signify, independently from each other, hydrogen, lower alkyl, $-(CH_2)_n$-halogen, lower alkoxy, $-(CH_2)_n$-NRR', $-(CH_2)_n$-N(R)-C(O)-lower alkyl, aryl or heteroaryl which is unsubstituted or substituted by one or more lower alkyl residues;

R, R' and R" signify, independently from each other, hydrogen or lower alkyl;

A signifies -CH=CH- or -C≡C-; and

B signifies

B1)  ; B2)  ; B3)  ;

B4)  ; B5)  or B6)  ;

wherein

$R^6$ signifies hydrogen, lower alkyl, $-(CH_2)_n$-C(O)OR or halogen;

$R^7$ signifies hydrogen, lower alkyl, $-(CH_2)_n$-C(O)OR', halogen, nitro or heteroaryl which is unsubstituted or substituted by lower alkyl or cycloalkyl;

$R^8$ signifies hydrogen, lower alkyl, $-(CH_2)_n$-OH, $-(CH_2)_n$-C(O)OR" or aryl;

$R^9$ signifies lower alkyl;

$R^{10}$ signifies hydrogen, lower alkyl or halogen;

$R^{11}$ signifies hydrogen or alkyl;

$R^{12}$ signifies $-(CH_2)_n$-N(R)-C(O)-lower alkyl;

$R^{13}$ signifies hydrogen or lower alkyl;

$R^{14}$, $R^{15}$, $R^{16}$ and $R^{17}$ signify, independently from each other, hydrogen, lower alkyl, $-(CH_2)_n$-halogen or lower alkoxy;

$R^{18}$, $R^{19}$ and $R^{20}$ signify, independently from each other, hydrogen, lower alkyl, $-(CH_2)_n$-halogen or lower alkoxy;

$R^{21}$ signifies hydrogen or lower alkyl;

$R^{22}$ signifies hydrogen, lower alkyl or lower alkyl carrying one or more substituents selected from hydroxy or halogen;

$R^{23}$ signifies hydrogen, lower alkyl, lower alkanoyl or nitro;

$R^{24}$, $R^{25}$ and $R^{26}$ signify, independently from each other, hydrogen or lower alkyl;

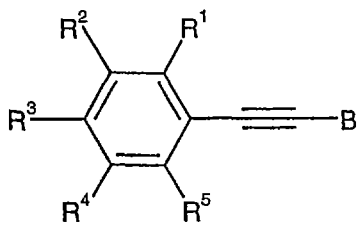
n is 0, 1, 2, 3, 4, 5 or 6;

X is $-CH_2-$, -O- or -S-; and

Y is –CH= or –N=;

and their pharmaceutically acceptable salts for the manufacture of medicaments for the treatment or prevention of mGluR5 receptor mediated disorders.

2. The use of a compound according to claim 1 having the formula




I-A

wherein $R^1$ to $R^5$ and B have the significances as defined in claim1.

3. The use of a compound according to claim 2, wherein B signifies B1 as defined in claim 1.

4. The use of a compound according to claim 3, which compound is selected from the group consisting of
3,5-dimethyl-2-phenylethynyl-3H-imidazole-4-carboxylic acid ethyl ester,
5-methyl-2-phenylethynyl-3H-imidazole-4-carboxylic acid ethyl ester,
2-(3-methoxy-phenylethynyl)-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester,
1-methyl-2-phenylethynyl-1H-imidazole,
2-(5-nitro-2-phenylethynyl-imidazol-1-yl)-ethanol,
2-phenylethynyl-1H-imidazole,
2-(2,6-dichloro-phenylethynyl)-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester,
5-methyl-1-phenyl-2-phenylethynyl-1H-imidazole-4-carboxylic acid ethyl ester,
3,5-dimethyl-2-*m*-tolylethynyl-3H-imidazole-4-carboxylic acid ethyl ester,
2-(3-acetylamino-phenylethynyl)-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester,
2-[3-(2,5-dimethyl-pyrrol-1-yl)-phenylethynyl]-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester,
5-(3,5-dimethyl-2-phenylethynyl-3H-imidazol-4-yl)-3-methyl-[1,2,4]oxadiazole,
3-cyclopropyl-5-(3,5-dimethyl-2-phenylethynyl-3H-imidazol-4-yl)-[1,2,4]oxadiazole,
2-(4-chloro-phenylethynyl)-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester,
2-(4-fluoro-phenylethynyl)-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester,
2-biphenyl-4-ylethynyl-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester,
2-(2-fluoro-phenylethynyl)-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester,
2-(2-fluoro-phenylethynyl)-1-methyl-1H-imidazole,
2-(4-amino-phenylethynyl)-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester,
2-(2-chloro-phenylethynyl)-1-methyl-1H-imidazole or
(4,5-dichloro-2-phenylethynyl-imidazol-1-yl)-acetic acid ethyl ester.

5. The use of compounds according to claim 2, wherein B signifies B2 as defined in claim 1.

6. The use of a compound according to claim 5, which compound is 1-methyl-5-phenylethynyl-1H-imidazole.

7. The use of compounds according to claim 2, wherein B signifies B3 as defined in claim 1.

8. The use of a compound according to claim 7, which compound is N-[2-(5-methoxy-2-phenylethynyl-1H-indol-3-yl)-ethyl]-acetamide.

9. The use of a compound according to claim 2, wherein B signifies B4 as defined in claim 1.

10. The use of a compound according to claim 9, which compound is selected from the group consisting of
3-phenylethynyl-4H-5-thia-2,6,9b-triaza-cyclopenta[a]naphthalene or
3-phenylethynyl-4H-5-oxa-2,9b-diaza-cyclopenta[a]naphthalene.

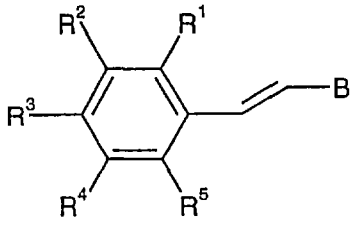
11. The use of a compound according to claim 2, wherein B signifies B5 as defined in claim 1.

12. The use of a compound according to claim 11, which compound is selected from the group consisting of
1-chloro-3-(2-methyl-5-nitro-4-phenylethynyl-imidazol-1-yl)-propan-2-ol,
3-methyl-5-phenylethynyl-3H-imidazole-4-carbaldehyde,
4-phenylethynyl-1H-imidazole,
1-methyl-4-phenylethynyl-1H-imidazole or
1,2-dimethyl-5-nitro-4-phenylethynyl-1H-imidazole.

13. The use of a compound according to claim 2, wherein B signifies B6 as defined in claim 1.

14. The use of a compound according to claim 13, which compound is 1,3-dimethyl-5-phenylethynyl-1H-pyrazole.

15. The use of a compound according to claim 1 having the formula




**I-B**

wherein $R^1$ to $R^5$ and B have the significances as defined in claim 1.

16. The use of a compound according to claim 15, wherein B signifies B1 as defined in claim 1.

17. The use of a compound according to claim 16, which compound is selected from the group consisting of
4,5-diisopropyl-1-methyl-2-styryl-1H-imidazole,

2-[2-(4-fluoro-phenyl)-vinyl]-4,5-diisopropyl-1-methyl-1H-imidazole,
2-[2-(4-chloro-phenyl)-vinyl]-4,5-diisopropyl-1-methyl-1H-imidazole,
2-[2-(4-butoxy-phenyl)-vinyl]-4,5-diisopropyl-1-methyl-1H-imidazole,
4,5-diisopropyl-2-[2-(4-methoxy-2,3,6-trimethyl-phenyl)-vinyl]-1-methyl-1H-imidazole,
4,5-diisopropyl-2-[2-(4-methoxy-phenyl)-vinyl]-1-methyl-1H-imidazole,
2-[2-(4-chloro-3-fluoro-phenyl)-vinyl]-4,5-diisopropyl-1-methyl-1H-imidazole,
2-[2-(4-ethoxy-phenyl)-vinyl]-4,5-diisopropyl-1-methyl-1H-imidazole,
4,5-diisopropyl-1-methyl-2-[2-(2,3,4-trimethoxy-phenyl)-vinyl]-1H-imidazole,
2-[2-(2,4-dichloro-phenyl)-vinyl]-4,5-diisopropyl-1-methyl-1H-imidazole or
4,5-diisopropyl-1-methyl-2-(2-p-tolyl-vinyl)-1H-imidazole.

18. The use of a compound according to claim 15, wherein B signifies B2 as defined in claim 1.

19. The use of a compound according to claim 18, which compound is selected from the group consisting of
4-bromo-1-methyl-5-styryl-1H-imidazole or
1-methyl-5-styryl-1H-imidazole.

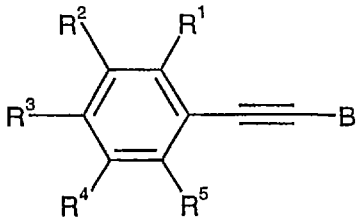
20. The use of a compound according to claim 15, wherein B signifies B3 as defined in claim 1.

21. The use of a compound according to claim 15, wherein B signifies B4 as defined in claim 1.

22. The use of a compound according to claim 15, wherein B signifies B5 as defined in claim 1.

23. The use of a compound according to claim 15, wherein B signifies B6 as defined in claim 1.

24. Compounds of formula



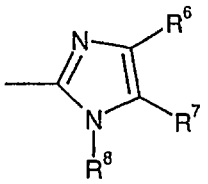
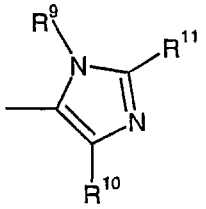
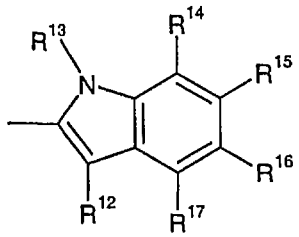

I-A

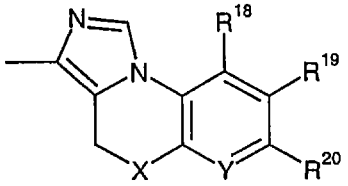
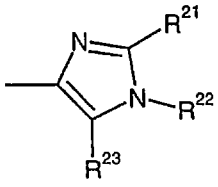
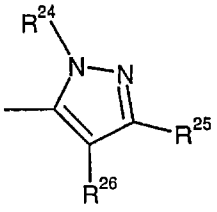
wherein

$R^1$, $R^2$, $R^3$, $R^4$ and $R^5$ signify, independently from each other, hydrogen, lower alkyl, $-(CH_2)_n$-halogen, lower alkoxy, $-(CH_2)_n$-NRR', $-(CH_2)_n$-N(R)-C(O)-lower alkyl, aryl or heteroaryl which is unsubstituted or substituted by one or more lower alkyl residues;

R, R' and R" signify, independently from each other, hydrogen or lower alkyl;

B signifies

B1)  ; B2)  ; B3)  ;

B4)  ; B5)  or B6)  ;

wherein

$R^6$ signifies hydrogen, lower alkyl, $-(CH_2)_n$-C(O)OR or halogen;

$R^7$ signifies hydrogen, lower alkyl, $-(CH_2)_n$-C(O)OR', halogen, nitro or heteroaryl which is unsubstituted or substituted by lower alkyl or cycloalkyl;

$R^8$ signifies hydrogen, lower alkyl, $-(CH_2)_n$-OH, $-(CH_2)_n$-C(O)OR" or aryl;

$R^9$ signifies lower alkyl;

$R^{10}$ signifies hydrogen, lower alkyl or halogen;

$R^{11}$ signifies hydrogen or alkyl;

$R^{12}$ signifies $-(CH_2)_n$-N(R)-C(O)-lower alkyl;

$R^{13}$ signifies hydrogen or lower alkyl;

$R^{14}$, $R^{15}$, $R^{16}$ and $R^{17}$ signify, independently from each other, hydrogen, lower alkyl, $-(CH_2)_n$-halogen or lower alkoxy;

$R^{18}$, $R^{19}$ and $R^{20}$ signify, independently from each other, hydrogen, lower alkyl, $-(CH_2)_n$-halogen or lower alkoxy;

$R^{21}$ signifies hydrogen or lower alkyl;

$R^{22}$ signifies hydrogen, lower alkyl or lower alkyl carrying one or more substituents selected from hydroxy or halogen;

$R^{23}$ signifies hydrogen, lower alkyl, lower alkanoyl or nitro;

$R^{24}$, $R^{25}$ and $R^{26}$ signify, independently from each other, hydrogen or lower alkyl;

n is 0, 1, 2, 3, 4, 5 or 6;

X is $-CH_2-$, -O- or -S-; and

Y is –CH= or –N=;

and their pharmaceutically acceptable salts;

with the exception of
1-methyl-2-phenylethynyl-1H-imidazole,
1-methyl-2-(4-methoxy-phenylethynyl)-1H-imidazole,
1-methyl-5-phenylethynyl-1H-imidazole, and
1-methyl-4-phenylethynyl-1H-imidazole.

25. A compound according to claim 24, wherein B signifies B1 as defined in claim 24.

26. A compound according to claim 25, wherein $R^7$ signifies $-(CH_2)_n$-C(O)OR' or heteroaryl which is unsubstituted or substituted by lower alkyl or cycloalkyl.

27. A compound according to claim 27, which compound is selected from the group consisting of
3,5-dimethyl-2-phenylethynyl-3H-imidazole-4-carboxylic acid ethyl ester,
5-methyl-2-phenylethynyl-3H-imidazole-4-carboxylic acid ethyl ester,
2-(3-methoxy-phenylethynyl)-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester,
2-(2,6-dichloro-phenylethynyl)-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester,
5-methyl-1-phenyl-2-phenylethynyl-1H-imidazole-4-carboxylic acid ethyl ester,
3,5-dimethyl-2-*m*-tolylethynyl-3H-imidazole-4-carboxylic acid ethyl ester,
2-(3-acetylamino-phenylethynyl)-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester,
2-[3-(2,5-dimethyl-pyrrol-1-yl)-phenylethynyl]-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester,
5-(3,5-dimethyl-2-phenylethynyl-3H-imidazol-4-yl)-3-methyl-[1,2,4]oxadiazole,

3-cyclopropyl-5-(3,5-dimethyl-2-phenylethynyl-3H-imidazol-4-yl)-[1,2,4]oxadiazole,
2-(4-chloro-phenylethynyl)-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester,
2-(4-fluoro-phenylethynyl)-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester,
2-biphenyl-4-ylethynyl-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester,
2-(2-fluoro-phenylethynyl)-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester, or
2-(4-amino-phenylethynyl)-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester.

28. A compound according to claim 25, which compound is selected from the group consisting of
2-(5-nitro-2-phenylethynyl-imidazol-1-yl)-ethanol,
2-phenylethynyl-1H-imidazole,
2-(2-fluoro-phenylethynyl)-1-methyl-1H-imidazole,
2-(2-chloro-phenylethynyl)-1-methyl-1H-imidazole or
(4,5-dichloro-2-phenylethynyl-imidazol-1-yl)-acetic acid ethyl ester.

29. A compound according to claim 24, wherein B signifies B2 as defined in claim 24.

30. A compound according to claim 24, wherein B signifies B3 as defined in claim 24.

31. A compound according to claim 30, which compound is
N-[2-(5-methoxy-2-phenylethynyl-1H-indol-3-yl)-ethyl]-acetamide.

32. A compound according to claim 24, wherein B signifies B4 as defined in claim 24.

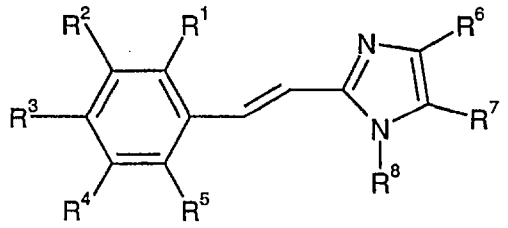
33. A compound according to claim 32, which compound is selected from the group consisting of
3-phenylethynyl-4H-5-thia-2,6,9b-triaza-cyclopenta[a]naphthalene or
3-phenylethynyl-4H-5-oxa-2,9b-diaza-cyclopenta[a]naphthalene.

34. A compound according to claim 24, wherein B signifies B5 as defined in claim 24.

35. A compound according to claim 34, which compound is selected from the group consisting of
1-chloro-3-(2-methyl-5-nitro-4-phenylethynyl-imidazol-1-yl)-propan-2-ol,
3-methyl-5-phenylethynyl-3H-imidazole-4-carbaldehyde,
4-phenylethynyl-1H-imidazole or
1,2-dimethyl-5-nitro-4-phenylethynyl-1H-imidazole.

36. A compound according to claim 24, wherein B signifies B6 as defined in claim 24.

37. Compounds of formula



**I-B-1**

wherein

$R^1$, $R^2$, $R^3$, $R^4$ and $R^5$ signify, independently from each other, hydrogen, lower alkyl, $-(CH_2)_n$-halogen, lower alkoxy, $-(CH_2)_n$-NRR', $-(CH_2)_n$-N(R)-C(O)-lower alkyl, aryl or heteroaryl which is unsubstituted or substituted by one or more lower alkyl residues;

R, R' and R" signify, independently from each other, hydrogen or lower alkyl;

$R^6$ signifies hydrogen, lower alkyl, $-(CH_2)_n$-C(O)OR or halogen;

$R^7$ signifies hydrogen, lower alkyl, $-(CH_2)_n$-C(O)OR', halogen, nitro or heteroaryl which is unsubstituted or substituted by lower alkyl or cycloalkyl; and

$R^8$ signifies hydrogen, lower alkyl, $-(CH_2)_n$-OH, $-(CH_2)_n$-C(O)OR" or aryl;

and their pharmaceutically acceptable salts.

38. A compound according to claim 37, wherein $R^7$ signifies lower alkyl or $-(CH_2)_n$-C(O)OR'.

39. A compound according to claim 38, which compound is selected from the group consisting of

4,5-diisopropyl-1-methyl-2-styryl-1H-imidazole,

2-[2-(4-fluoro-phenyl)-vinyl]-4,5-diisopropyl-1-methyl-1H-imidazole,

2-[2-(4-chloro-phenyl)-vinyl]-4,5-diisopropyl-1-methyl-1H-imidazole,

2-[2-(4-butoxy-phenyl)-vinyl]-4,5-diisopropyl-1-methyl-1H-imidazole,

4,5-diisopropyl-2-[2-(4-methoxy-2,3,6-trimethyl-phenyl)-vinyl]-1-methyl-1H-imidazole,

4,5-diisopropyl-2-[2-(4-methoxy-phenyl)-vinyl]-1-methyl-1H-imidazole,

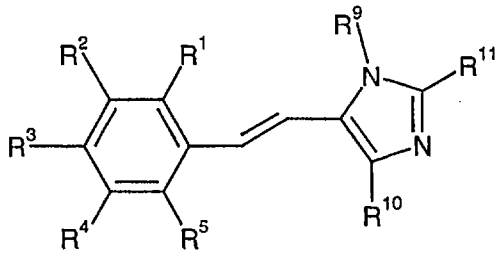
2-[2-(4-chloro-3-fluoro-phenyl)-vinyl]-4,5-diisopropyl-1-methyl-1H-imidazole,

2-[2-(4-ethoxy-phenyl)-vinyl]-4,5-diisopropyl-1-methyl-1H-imidazole,

4,5-diisopropyl-1-methyl-2-[2-(2,3,4-trimethoxy-phenyl)-vinyl]-1H-imidazole,

2-[2-(2,4-dichloro-phenyl)-vinyl]-4,5-diisopropyl-1-methyl-1H-imidazole or 4,5-diisopropyl-1-methyl-2-(2-p-tolyl-vinyl)-1H-imidazole.

40. Compounds of formula



**I-B-2**

wherein

$R^1$, $R^2$, $R^3$, $R^4$ and $R^5$ signify, independently from each other, hydrogen, lower alkyl, $-(CH_2)_n$-halogen, lower alkoxy, $-(CH_2)_n$-NRR', $-(CH_2)_n$-N(R)-C(O)-lower alkyl, aryl or heteroaryl which is unsubstituted or substituted by one or more lower alkyl residues;

R and R' signify, independently from each other, hydrogen or lower alkyl;

$R^9$ signifies lower alkyl;

$R^{10}$ signifies halogen; and

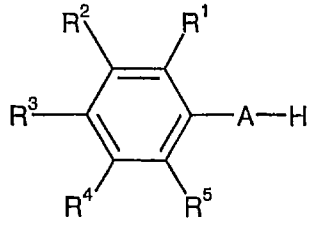
$R^{11}$ signifies hydrogen or alkyl;

and their pharmaceutically acceptable salts.

41. A compound according to claim 40, which compound is 4-bromo-1-methyl-5-styryl-1H-imidazole.

42. A process for the manufacture of compounds of formulas I-A and I-B as defined in claims 24-41 as well as their pharmaceutically acceptable salts, which process comprises

a) reacting a compound of the formula



II

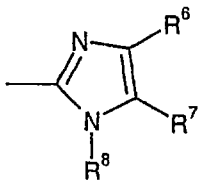
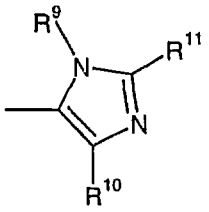
with a compound of formula

B—X III

wherein X signifies halogen or trifluoromethanesulfonyl,
$R^1$ to $R^5$ have the significances as claimed in claim 1,

to obtain a compound of formula I-A in the case if A signifies -C≡C- and B has the significances as defined in claim 24;

or to obtain a compound of formula I-B in the case if A signifies –HC=CH- and B is

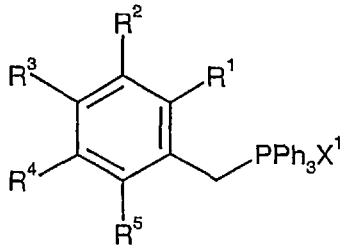
B1)  or B2) 

wherein

$R^6$ signifies hydrogen, lower alkyl, $-(CH_2)_n-C(O)OR$ or halogen;
$R^7$ signifies hydrogen, lower alkyl, $-(CH_2)_n-C(O)OR'$, halogen, nitro or heteroaryl which is unsubstituted or substituted by lower alkyl or cycloalkyl;
$R^8$ signifies hydrogen, lower alkyl, $-(CH_2)_n-OH$, $-(CH_2)_n-C(O)OR''$ or aryl;
$R^9$ signifies lower alkyl;
$R^{10}$ signifies halogen; and
$R^{11}$ signifies hydrogen or alkyl;
and if desired,
converting compounds of formulas I-A or I-B into pharmaceutically acceptable salts;

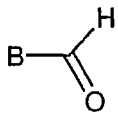
or

b) reacting a compound of the formula

 IV

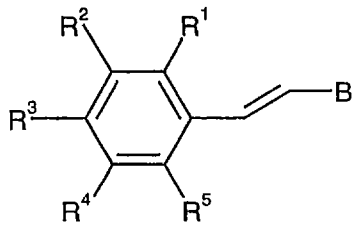
wherein $X^1$ signifies halogen,

with a compound of the formula



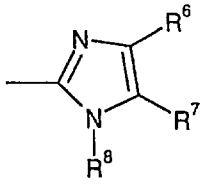
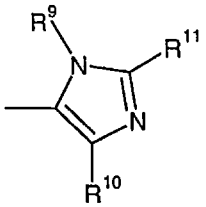
V

to obtain a compound of formula



I-B

wherein $R^1$ to $R^5$ have the significances as claimed in claim 1 and B is

B1)  or B2) 

wherein

$R^6$ signifies hydrogen, lower alkyl, $-(CH_2)_n-C(O)OR$ or halogen;

$R^7$ signifies hydrogen, lower alkyl, $-(CH_2)_n-C(O)OR'$, halogen, nitro or heteroaryl which is unsubstituted or substituted by lower alkyl or cycloalkyl;

$R^8$ signifies hydrogen, lower alkyl, $-(CH_2)_n-OH$, $-(CH_2)_n-C(O)OR''$ or aryl;

$R^9$ signifies lower alkyl;

$R^{10}$ signifies halogen; and

$R^{11}$ signifies hydrogen or alkyl;

and if desired,

converting a compound of formula I-B into a pharmaceutically acceptable salt.

43. A compound according to any one of claims 24 to 41, when manufactured by a process in accordance with claim 42.

44. A medicament containing one or more compounds as claimed in any one of the claims 24 to 41 and pharmaceutically acceptable excipients for the treatment or prevention of mGluR5 receptor mediated disorders.

45. A compound in accordance with claims 24 to 41 as well as its pharmaceutically acceptable salt for use in the treatment or prevention of diseases.

46. The use of a compound in accordance with claims 24 to 41 as well as its pharmaceutically acceptable salt for the manufacture of medicaments for the treatment or prevention of mGluR5 receptor mediated disorders.

47. The invention as hereinbefore described.

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