This invention relates to a compound and the use of the compound of the formula...

wherein R₁, R₂, R₃, R₁ and R₂ are as defined in the description, A signifies —CH=CH— or —C=CC—; and B signifies...

wherein R⁰ to R²⁰, X and Y are as defined in the specification or a pharmaceutically acceptable salt thereof, for use in pharmaceutical compositions for the treatment or prevention of mGluR5 receptor mediated disorders.
PHENYLETHYNYL AND STYRYL DERIVATIVES OF IMIDAZOLE AND FUSED RING HETEROCYCLES

PRIORITY TO RELATED APPLICATIONS

[0001] This application is a Division of Ser. No. 10/396, 172, filed Mar. 25, 2003, now pending, which is a Division of Ser. No. 09/996,641, filed Nov. 28, 2001, now U.S. Pat. No. 6,706,707 issued Mar. 16, 2004.

CROSS-REFERENCE TO RELATED APPLICATION


BACKGROUND OF THE INVENTION

[0003] 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.

[0004] 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.

[0005] 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:

[0006] mGluR1 and mGluR5 belong to group I, mGluR2 and mGluR3 belong to group II and mGluR4, mGluR6, mGluR7 and mGluR8 belong to group III.

[0007] 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.

[0008] 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 medications 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.

[0009] 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.

SUMMARY OF THE INVENTION

[0010] The present invention is a method of treatment of mGluR5 receptor mediated disorders by administering a therapeutically effective amount phenylethynyl and phenylethynyl derivatives of the compound formula

![Chemical Structure]

[0011] wherein

[0012] R¹, R², R³, R⁴ and R⁵ are independently selected from the group consisting of hydrogen, lower alkyl, —(CH₂)n-halogen, lower alkoxy, —(CH₂)n—NRR¹, —(CH₂)n—N(R)—C(O)—lower alkyl, aryl or heteroaryl which is unsubstituted or substituted by one or more lower alkyl residues;

[0013] R, R¹ and R² are independently selected from the group consisting of hydrogen and lower alkyl;

[0014] A is selected from the group consisting of —CH=CH— or —C=C--; and

[0015] B is selected from the group consisting of

![Chemical Structures]
wherein

R is selected from the group consisting of hydrogen, lower alkyl, \(-\text{CH}_2\text{-OR}\); and halogen;

R' is selected from the group consisting of hydrogen, lower alkyl, \(-\text{CH}_2\text{-OR}\); halogen, nitro, unsubstituted heteroaryl and heteroaryl substituted by lower alkyl or cycloalkyl;

R is selected from the group consisting of hydrogen, lower alkyl, \(-\text{CH}_2\text{-OH}, -\text{CH}_2\text{-OR}\), and \(-\text{C(O)OR}^*\) and aryl;

R' is lower alkyl;

R' is selected from the group consisting of hydrogen, lower alkyl and halogen;

R is selected from the group consisting of hydrogen and alkyl;

R' is \(-\text{CH}_2\text{-N(R)-C(O)-lower alkyl}\);

R' is selected from the group consisting of hydrogen and lower alkyl;

R', R', R and R' are independently selected from the group consisting of hydrogen, lower alkyl, \(-\text{CH}_2\text{-halogen and lower alkoxy}\);

R' and R' are independently selected from the group consisting of hydrogen, lower alkyl, \(-\text{CH}_2\text{-halogen and lower alkoxy}\);

R' is hydrogen or lower alkyl;

R' is selected from the group consisting of hydrogen, lower alkyl and lower alkyl with at least one substituent selected from the group consisting of hydroxy or halogen;
[0042] R, R' and R" are selected from the group consisting hydrogen and lower alkyl;

[0043] B is selected from the group consisting of

[0044] wherein

[0045] R is selected from the group consisting of hydrogen, lower alkyl, -(CH)n-C(O)OR and halogen;

[0046] R' is selected from the group consisting of hydrogen, lower alkyl, -(CH)n-C(O)OR', halogen, nitro, unsubstituted heteroaryl and heteroaryl substituted by lower alkyl or cycloalkyl;

[0047] R is selected from the group consisting of hydrogen, lower alkyl, -(CH)n-OH, -(CH)n-C(O)OR' and ary1;

[0048] R is lower alkyl;

[0049] R is selected from the group consisting of hydrogen, lower alkyl and halogen;

[0050] R is hydrogen or alkyl;

[0051] R is -(CH)n-N(R)-C(O)-lower alkyl;

[0052] R is hydrogen or lower alkyl;

[0053] R, R, R and R are independently selected from the group consisting of hydrogen, lower alkyl, -(CH)n-halogen and lower alkoxy;

[0054] R, R and R are independently selected from the group consisting of hydrogen, lower alkyl, -(CH)n-halogen or lower alkoxy;

[0055] R signifies hydrogen or lower alkyl;

[0056] R signifies hydrogen, lower alkyl or lower alkyl carrying at least one substituent selected from hydroxy and halogen;

[0057] R is selected from the group consisting of hydrogen, lower alkyl, lower alkanoyl and nitro;

[0058] R, R and R are independently selected from the group consisting of hydrogen and lower alkyl;

[0059] n is 0, 1, 2, 3, 4, 5 or 6;

[0060] X is -CH-, -O- or -S-; and

[0061] Y is -CH= or N-;

[0062] and a pharmaceutically acceptable salt thereof; with the exception of

[0063] 1-methyl-2-phenylethynyl-1H-imidazole,

[0064] 1-methyl-2-(4-methoxy-phenylethynyl)-1H-imidazole,

[0065] 1-methyl-5-phenylethynyl-1H-imidazole, and

[0066] 1-methyl-4-phenylethynyl-1H-imidazole.

[0067] Furthermore, the present invention is a compound of the formula

[0068] wherein

[0069] R, R, R and R' are independently selected from the group consisting of hydrogen, lower alkyl, -(CH)n-halogen, lower alkoxy, -(CH)n-NRR', -(CH)n-N(R)-C(O)-lower alkyl, ary1, unsubstituted heteroaryl and heteroaryl substituted by at least one lower alky1 residue;

[0070] R, R' and R are hydrogen or lower alkyl;
[0071] \( R^8 \) is selected from the group consisting of hydrogen, lower alkyl, \( -(CH_2)_n-C(O)OR \) and halogen;

[0072] \( R^7 \) is selected from the group consisting of hydrogen, lower alkyl, \( -(CH_2)_n-C(O)OR \), halogen, nitro, unsubstituted heteroaryl and heteroaryl substituted by lower alkyl or cycloalkyl; and

[0073] \( R^8 \) signifies hydrogen, lower alkyl, \( -(CH_2)_n-OH \), \( -(CH_2)_n-C(O)OR \) or aryl;

[0074] or a pharmaceutically acceptable salt thereof.

[0075] The present invention also is a compound of formula

[0076] wherein

[0077] \( R^1, R^2, R^3, R^4 \) and \( R^8 \) are independently selected from the group consisting of hydrogen, lower alkyl, \( -(CH_2)_n-halogen \), lower alkoxy, \( -(CH_2)_n-NRR' \), \( -(CH_2)_n-N(R)-C(O)-lower alkyl \), aryl, unsubstituted heteroaryl and heteroaryl substituted by at least one lower alkyl;

[0078] \( R \) and \( R' \) are independently selected from the group consisting of hydrogen and lower alkyl;

[0079] \( R^8 \) is lower alkyl;

[0080] \( R^{10} \) is halogen; and

[0081] \( R^{11} \) is selected from the group hydrogen or alkyl;

[0082] or a pharmaceutically acceptable salt thereof.

**DETAILED DESCRIPTION OF THE INVENTION**

[0083] 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.

[0084] The term "cycloalkyl" denotes a saturated carbocyclic group containing from 3 to 7 carbon atoms, preferably cyclopropyl, cyclopentyl or cyclohexyl.

[0085] The term "halogen" denotes fluorine, chlorine, bromine and iodine.

[0086] The term "lower alkoxy" denotes a lower alkyl group as defined hereinbefore, which is bound via an oxygen atom, e.g. methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy and the like.

[0087] Preferred lower alkanoyl groups are formyl, ethanoyl or propanoyl.

[0088] Preferred aryl groups are phenyl or naphthyl.

[0089] Heteroaryl groups are selected from furyl, pyrrolyl, thiienyl, 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, 1,2,4oxadiazolyl, 1,2,3-oxadiazolyl, 1H-tetrazolyl, 2H-tetrazolyl, 1,2,3,4oxadiazolyl, [1,2,3,5]oxatriazolyl, 1,3-thiazolyl, 1,2-thiazolyl, 1H-pentazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolyl, quinolyl and their dihydro derivatives. When the heteroaryl group is substituted, it is preferably substituted by lower alkyl or cycloalkyl. Preferred heteroaryl groups are pyrrolyl and [1,2,4]oxadiazolyl, either substituted or unsubstituted.

[0090] 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.

[0091] Especially preferred are compounds of formula I for the above mentioned method of treatment, in which \( A \) signifies \(-C=O-\) and \( B \) signifies \( B1 \).

[0092] The following are examples of such compounds:

[0093] 3,5-dimethyl-2-phenylethynyl-3H-imidazole-4-carboxylic acid ethyl ester,

[0094] 5-methyl-2-phenylethynyl-3H-imidazole-4-carboxylic acid ethyl ester,

[0095] 2-(3-methoxy-phenylethynyl)-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester,

[0096] 1-methyl-2-phenylethynyl-1H-imidazole,

[0097] 2-(5-nitro-2-phenylethynyl-imidazol-1-yl)-ethanol,

[0098] 2-phenylethynyl-1H-imidazole,

[0099] 2(2,6-dichloro-phenylethynyl)-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester,

[0100] 5-methyl-1-phenyl-2-phenylethynyl-1H-imidazole-4-carboxylic acid ethyl ester,

[0101] 3,5-dimethyl-2-m-tolylethynyl-3H-imidazole-4-carboxylic acid ethyl ester,

[0102] 2-(3-acetylamino-phenylethynyl)-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester,

[0103] 2-[3-(2,5-dimethyl-pyrrol-1-yl)-phenylethynyl]-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester,

[0104] 5-(3,5-dimethyl-2-phenylethynyl-3H-imidazole-4-yl)-3-methyl-[1,2,4]oxadiazole,

[0105] 3-cyclopropyl-5-(3,5-dimethyl-2-phenylethynyl-3H-imidazole-4-yl)-[1,2,4]oxadiazole,

[0106] 2-(4-chloro-phenylethynyl)-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester,

[0107] 2-(4-fluoro-phenylethynyl)-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester,
[0108] 2-biphenyl-4-yloxy-3,5-dimethyl-3Himidazole-4-carboxylic acid ethyl ester,
[0109] 2-[(2-fluoro-phenylethynyl)-3,5-dimethyl-3Himidazole-4-carboxylic acid ethyl ester,
[0110] 2-(2-fluoro-phenylethynyl)-1-methyl-1H-imidazole,
[0111] 2-(4-amino-phenylethynyl)-3,5-dimethyl-3Himidazole-4-carboxylic acid ethyl ester,
[0112] 2-(2-chloro-phenylethynyl)-1-methyl-1H-imidazole and
[0113] (4,5-dichloro-2-phenylethynyl-imidazol-1-yl)-acetic acid ethyl ester.

[0114] Further preferred are compounds of formula I for the above mentioned method of treatment, in which A signifies —C═C— and B signifies B2.

[0115] An example for such a compound is 1-methyl-5-phenylethynyl-1H-imidazole.

[0116] Also preferred for the above mentioned method of treatment are compounds of formula I, in which A signifies —C═C— and B signifies B3.

[0117] An example for such a compound is N-[2-(4-methoxy-2-phenylethynyl-1H-indol-3-yl)-ethyl]-acetamide.

[0118] Preferred compounds of formula I for the above mentioned method of treatment are also those, in which A signifies —C═C— and B signifies B4.

[0119] The following are examples of such compounds:

[0120] 3-phenylethynyl-4H-5-thia-2,6,9b-triaza-cyclopenta[a]triphthalene or

[0122] Further preferred are compounds of formula I for the above mentioned method of treatment, in which A signifies —C═C— and B signifies B5.

[0123] Examples of such compounds are:

[0124] 1-chloro-3-(2-methyl-5-nitro-4-phenylethynyl-imidazolyl-1-yl)-propan-2-ol,
[0125] 3-methyl-5-phenylethynyl-1H-imidazole-4-carboxaldehyde,
[0126] 4-phenylethynyl-1H-imidazole,
[0127] 1-methyl-4-phenylethynyl-1H-imidazole and
[0128] 1,2-dimethyl-5-nitro-4-phenylethynyl-1H-imidazole.

[0129] Also preferred are compounds of formula I for the above mentioned method of treatment in which A signifies —C═C— and B signifies B6.

[0130] An example for such a compound is 1,3-dimethyl-5-phenylethynyl-1H-pyrazole.

[0131] Further preferred are compounds of formula I for the above mentioned method of treatment, in which A signifies —C═C—.

[0132] Especially preferred are those compounds of formula I for the above mentioned method of treatment, in which A signifies —C═C— and B signifies B1.

[0133] The following are examples of such compounds:

[0134] 4,5-diisopropyl-1-methyl-2-styryl-1H-imidazole,
[0135] 2-{2-(4-fluoro-phenyl)-vinyl}-4,5-diisopropyl-1-methyl-1H-imidazole,
[0136] 2-{2-(4-chloro-phenyl)-vinyl}-4,5-diisopropyl-1-methyl-1H-imidazole,
[0137] 2-{2-(4-butoxy-phenyl)-vinyl}-4,5-diisopropyl-1-methyl-1H-imidazole,
[0138] 4,5-diisopropyl-2-{2-(4-methoxy-phenyl)-vinyl}-1-methyl-1H-imidazole,
[0139] 4,5-diisopropyl-2-{2-(4-methoxy-phenyl)-vinyl}-1-methyl-1H-imidazole,
[0140] 2-{2-(4-chloro-3-fluoro-phenyl)-vinyl}-4,5-diisopropyl-1-methyl-1H-imidazole,
[0141] 2-{2-(4-ethoxy-phenyl)-vinyl}-4,5-diisopropyl-1-methyl-1H-imidazole,
[0142] 4,5-diisopropyl-1-methyl-2-[2-(2,3,4-tri-methoxy-phenyl)-vinyl]-1H-imidazole,
[0143] 2-{2-(2,4-dichloro-phenyl)-vinyl}-4,5-diisopropyl-1-methyl-1H-imidazole and
[0144] 4,5-diisopropyl-1-methyl-2-(2-p-tolyl-vinyl)-1H-imidazole.

[0145] Also preferred are compounds of formula I for the above mentioned method of treatment, in which A signifies —C═C— and B signifies B2.

[0146] Examples of such compounds are the following:

[0147] 4-bromo-1-methyl-5-styryl-1H-imidazole and
[0148] 1-methyl-5-styryl-1H-imidazole.

[0149] 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.

[0150] The following are examples of such compounds:

[0151] 2-(5-nitro-2-phenylethynyl-imidazol-1-yl)-ethanol,
[0152] 2-phenylethynyl-1H-imidazole,
[0153] 2-(2-fluoro-phenylethynyl)-1-methyl-1H-imidazole,
[0154] 2-(2-chloro-phenylethynyl)-1-methyl-1H-imidazole and
[0155] (4,5-dichloro-2-phenylethynyl-imidazol-1-yl)-acetic acid ethyl ester.

[0156] More preferred are compounds of formula I-A, in which B signifies B 1 and R' is selected from the group consisting of (CH₂)n—C(O)OR', unsubstituted heteroaryl and heteroaryl substituted by lower alkyl or cycloalkyl.

[0157] Especially preferred are those, in which R' signifies (CH₂)n—C(O)OR', wherein n is 0 and R is lower alkyl.

[0158] Examples of such compounds are the following:

[0159] 3,5-dimethyl-2-phenylethynyl-3H-imidazole-4-carboxylic acid ethyl ester,
Also preferred is a compound of formula

\[
\begin{align*}
R^1 & \quad R^2 & \quad R^3 & \quad R^4 & \quad R^5 \\
\text{I-B} & \quad & & & \\
\end{align*}
\]

wherein $R^1$, $R^2$, $R^3$, $R^4$ and $R^5$ are independently selected from the group consisting of each other, hydrogen, lower alkyl, $-(\text{CH}_2)_n$-halogen, lower alkoxy, $-(\text{CH}_2)_n$-NRR', $-(\text{CH}_2)_n$-N(R)—C(O)—lower alkyl, aryl, unsubstituted heteroaryl and heteroaryl substituted by at least one lower alkyl; and in which B signifies B1 and $R^7$ signifies lower alkyl or $-(\text{CH}_2)_n$—C(O)OR.

Especially preferred are those in which $R^7$ is lower alkyl.

Examples of such compounds are the following:

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

Further preferred compounds of formula I-B are those, in which B signifies B2 and $R^{10}$ is 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...
[0202] with a compound of formula

$$R^1 - R^2 - R^3$$

[0203] wherein $X$ signifies halogen or trifluoromethanesulfonyl and

[0204] $R^1$ to $R^5$ have the significances as defined before,

[0205] to obtain a compound of formula I-A in the case if A signifies $C\equiv C\equiv C$ and B has the significances as defined before;

[0206] or to obtain a compound of formula I-B in the case if A signifies $HC\equiv CH$ and B is

$$\begin{array}{c}
\text{B1)} \\
\text{B2)}
\end{array}$$

[0207] wherein

[0208] $R^6$ is selected from the group consisting of hydrogen, lower alkyl, $-(CH_2)_n-C(=O)OR$ and halogen;

[0209] $R^7$ is selected from the group consisting of hydrogen, lower alkyl, $-(CH_2)_n-C(O)OR^1$, halogen, nitro, or unsubstituted heteroaryl and heteroaryl substituted by lower alkyl or cycloalkyl;

[0210] $R^8$ is selected from the group consisting of hydrogen, lower alkyl,

[0211] $-(CH_2)_n-OH$,

[0212] $-(CH_2)_n-C(O)OR^1$ and aryl;

[0213] $R^9$ is lower alkyl;

[0214] $R^{10}$ is halogen; and

[0215] $R^{11}$ is selected from the group hydrogen and alkyl;

[0216] and if desired, converting a compound of formulas I-A or I-B into a

[0217] pharmaceutically

[0218] acceptable salt.

[0219] This process is catalyzed by palladium(II) salts.

[0220] In accordance with the invention, compounds of formula I, wherein $A$ signifies $C\equiv C\equiv C$, 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 $C\equiv C$-coupling reaction requires the presence of bis(triethylphosphine)-palladium(II)-chloride, cuprous iodide and triethylamine and is carried out in a polar solvent like dimethylformamide or acetone tri 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(triethylphosphine)-palladium(II)-chloride and triphenylphosphine and an excess of triethylamine at a temperature of 55°C within 16 hours.

[0221] The phenylethynyl derivatives of formula II are commercially available or can be easily prepared by methods well known in the art.

[0222] The compounds of formula III are also commercially available or can be prepared by appropriate methods depending on the heterocyclic system B.


[0224] 2-Trifluoromethanesulfonyl-1H-imidazoles of formula III 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 U.S. Pat. No. 3,303,199. The reaction with trifluoromethanesulfonic anhydride and triethylamine is carried out in dichloromethane at room temperature (Scheme 1, Tf\textsuperscript{=}=trifluoromethanesulfonyl).

[0225] 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 with $N$-hydroxy-carboxamidines of formula VIII in the presence of 1,1'-carbonyldimidazole and dimethyl-formamide 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

![Scheme 2](image)

[0226] 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.

[0227] 3-Iodo-4H-5-thia-2,6,9b-triaza-cyclopenta[a]naphtalenes and 3-i


[0230] Phenylethenyl derivatives of formula I can be prepared analogously by reacting a compound of formula III with a phenylethenyl of formula II.

[0231] 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

[0232] wherein X' is halogen,

[0233] with a compound of the formula

[0234] to obtain a compound of formula

[0235] wherein R1 to R4 are as described above and B is

[0236] wherein

[0237] R6 is selected from the group consisting of hydrogen, lower alkyl, —(CH2)n—C(O)OR and halogen;

[0238] R7 is selected from the group consisting of hydrogen, lower alkyl, —(CH2)n—C(O)OR, halogen, nitro, unsubstituted heteroaryl unsubstituted and heteroaryl substituted by lower alkyl or cycloalkyl;
R^6 is selected from the group consisting of hydrogen, lower alkyl, -(CH2)n-OH, -(CH2)n-C(O)OR" and aryl;

R^6 is lower alkyl;

R^10 is halogen; and

R^11 is selected from the group consisting of hydrogen or alkyl;

and 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 appropriate 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 triphenylphosphines (PPh3) and the appropriate benzyl halides X (Scheme 3).

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-1H-imidazole-4-carbaldehyde is obtained in accordance with a method as described in Chem. Pharm. Bull. 1994, 42, 1784-1790.

The pharmacoologically acceptable salts of compounds of formula I-A and I-B can be manufactured readily according to methods known to those skilled in the art 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 analogues. 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, postoperative pain and pain associated with various conditions like cancer, angina, renal or biliary colic, menstruation, migraine and gout.

The pharmacological activity of all of the example 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. Chris- tensen (Transient gene expression in mammalian cells grown in serum-free suspension culture; Cyto-technology, 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, Calif., 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 equations giving IC_{50}, and Hill coefficient using the iterative non linear curve fitting software Origin (Microcal Software Inc., Northampton, Mass., 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 preferably of 0.02 μM or less.

In the Table 1 below are shown specific activity data of the compounds of the present invention derived according to the procedure described above:
TABLE I Example No. Compound name IC<sub>50</sub> (µM)

<table>
<thead>
<tr>
<th>Example No.</th>
<th>Compound name</th>
<th>IC&lt;sub&gt;50&lt;/sub&gt; (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3,5-dimethyl-2-phenylethynyl-3H-imidazole-4-carboxylic acid ethyl ester</td>
<td>0.25</td>
</tr>
<tr>
<td>2</td>
<td>5-methyl-2-phenylethynyl-3H-imidazole-4-carboxylic acid ethyl ester</td>
<td>2.40</td>
</tr>
<tr>
<td>3</td>
<td>2-(3-methoxy-phenylethynyl)-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester</td>
<td>0.35</td>
</tr>
<tr>
<td>4</td>
<td>1-methyl-2-phenylethynyl-3H-imidazole</td>
<td>0.72</td>
</tr>
<tr>
<td>5</td>
<td>2-(5-nitro-2-phenylethynyl-imidazol-1-yl)-ethanol</td>
<td>2.11</td>
</tr>
<tr>
<td>6</td>
<td>2-phenylethynyl-3H-imidazole</td>
<td>0.20</td>
</tr>
<tr>
<td>7</td>
<td>2-(2,6-dichloro-phenylethynyl)-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester</td>
<td>0.10</td>
</tr>
<tr>
<td>8</td>
<td>5-methyl-1-phenyl-2-phenylethynyl-1H-imidazole-4-carboxylic acid ethyl ester</td>
<td>0.13</td>
</tr>
<tr>
<td>9</td>
<td>3,5-dimethyl-2-2-(3,4-methoxy-phenylethynyl)-3H-imidazole-4-carboxylic acid ethyl ester</td>
<td>2.12</td>
</tr>
<tr>
<td>10</td>
<td>2-(3-acetylaminophenylethynyl)-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester</td>
<td>0.18</td>
</tr>
<tr>
<td>11</td>
<td>(2-[3-(5-dimethyl-2-phenylethynyl-3H-imidazol-4-yl)-3-methyl-[1,2,3]triazole</td>
<td>0.011</td>
</tr>
<tr>
<td>12</td>
<td>(2-[4-chloro-phenylethynyl]-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester</td>
<td>0.010</td>
</tr>
<tr>
<td>13</td>
<td>2-(4-fluoro-phenylethynyl)-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester</td>
<td>0.25</td>
</tr>
<tr>
<td>14</td>
<td>2-biphenyl-4-ethyl-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester</td>
<td>0.21</td>
</tr>
<tr>
<td>15</td>
<td>2-(2-fluoro-phenylethynyl)-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester</td>
<td>0.09</td>
</tr>
<tr>
<td>16</td>
<td>2-(2-fluoro-phenylethynyl)-1-methyl-1H-imidazole</td>
<td>0.07</td>
</tr>
<tr>
<td>17</td>
<td>2-(4-amino-phenylethynyl)-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester</td>
<td>1.53</td>
</tr>
<tr>
<td>18</td>
<td>2-(2-chloro-phenylethynyl)-1-methyl-1H-imidazole</td>
<td>1.10</td>
</tr>
<tr>
<td>19</td>
<td>(4,5-dichloro-2-phenylethynyl-imidazol-1-yl)-acetic acid ethyl ester</td>
<td>0.52</td>
</tr>
<tr>
<td>20</td>
<td>1-methyl-5-phenylethynyl-1H-imidazole</td>
<td>0.22</td>
</tr>
<tr>
<td>21</td>
<td>N-[5-(5-methoxy-2-phenylethynyl-1H-imidazol-4-yl)-ethyl]-acetamide</td>
<td>0.58</td>
</tr>
<tr>
<td>22</td>
<td>3-phenylethynyl-4H-5-thio-2,6,9-triaza-cyclopestax[4]tosphathalene</td>
<td>0.15</td>
</tr>
<tr>
<td>23</td>
<td>3-phenylethynyl-4H-5-oxa-2,9H-diaza-cyclopestax[4]tosphathalene</td>
<td>0.07</td>
</tr>
<tr>
<td>24</td>
<td>1-chloro-3-[2-methyl-5-nitro-4-phenylethynyl-imidazol-1-yl]-propan-2-ol</td>
<td>0.23</td>
</tr>
<tr>
<td>25</td>
<td>3-methyl-5-phenylethynyl-4H-imidazole-4-carboxylic acid</td>
<td>1.79</td>
</tr>
<tr>
<td>26</td>
<td>4-phenethyl-3H-imidazole</td>
<td>3.36</td>
</tr>
<tr>
<td>27</td>
<td>1-methyl-4-phenethyl-1H-imidazole</td>
<td>0.50</td>
</tr>
<tr>
<td>28</td>
<td>1,2-dimethyl-5-nitro-4-phenethyl-1H-imidazole</td>
<td>0.02</td>
</tr>
<tr>
<td>29</td>
<td>1,3-dimethyl-5-phenylethynyl-1H-pyrazole</td>
<td>5-10</td>
</tr>
<tr>
<td>30</td>
<td>4,5-dimisopropyl-1-methyl-2-styryl-1H-imidazole</td>
<td>1.82</td>
</tr>
<tr>
<td>31</td>
<td>2-[4-(4-fluoro-phenyl)-vinyl]-4,5-dimisopropyl-1-methyl-1H-imidazole</td>
<td>5-10</td>
</tr>
<tr>
<td>32</td>
<td>4-[4-(chloro-phenyl)-vinyl]-4,5-dimisopropyl-1-methyl-1H-imidazole</td>
<td>5-10</td>
</tr>
<tr>
<td>33</td>
<td>2-[4-(butoxy-phenyl)-vinyl]-4,5-dimisopropyl-1-methyl-1H-imidazole</td>
<td>5-10</td>
</tr>
<tr>
<td>34</td>
<td>4,5-dimisopropyl-2-[4-(4-methoxy-3,6-trimethyl-phenyl)-vinyl]-1-methyl-1H-imidazole</td>
<td>5-10</td>
</tr>
<tr>
<td>35</td>
<td>4,5-dimisopropyl-2-[4-(4-methoxy-phenyl)-vinyl]-1-methyl-1H-imidazole</td>
<td>5-10</td>
</tr>
<tr>
<td>36</td>
<td>4-[4-(chloro-3-fluoro-phenyl)-vinyl]-4,5-dimisopropyl-1-methyl-1H-imidazole</td>
<td>10</td>
</tr>
<tr>
<td>37</td>
<td>2-[4-(3,4-ethoxy-phenyl)-vinyl]-4,5-dimisopropyl-1-methyl-1H-imidazole</td>
<td>10</td>
</tr>
<tr>
<td>38</td>
<td>4,5-dimisopropyl-2-[4-(3,4-ethoxy-phenyl)-vinyl]-1-methyl-1H-imidazole</td>
<td>10</td>
</tr>
<tr>
<td>39</td>
<td>2-[4-(2,4-dichloro-phenyl)-vinyl]-4,5-dimisopropyl-1-methyl-1H-imidazole</td>
<td>10</td>
</tr>
</tbody>
</table>

TABLE I-continued Example No. Compound name IC<sub>50</sub> (µM)

<table>
<thead>
<tr>
<th>Example No.</th>
<th>Compound name</th>
<th>IC&lt;sub&gt;50&lt;/sub&gt; (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>42</td>
<td>4,5-dimisopropyl-1-methyl-2-[2-(p-tolyl-vinyl)]-1H-imidazole</td>
<td>3.25</td>
</tr>
<tr>
<td>43</td>
<td>4-bromo-1-methyl-5-styryl-1H-imidazole</td>
<td>3.06</td>
</tr>
<tr>
<td>44</td>
<td>1-methyl-5-styryl-1H-imidazole</td>
<td>8.0</td>
</tr>
</tbody>
</table>

The compounds of formula I and pharmaceutically acceptable salts thereof can be used as pharmaceutical compositions, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, e.g. in the form of tablets, coated tablets, dragees, 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 compositions. 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, dragees 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, inverted sugar, glycerol 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 they 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 compositions 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, pharmaceutical compositions containing a therapeutically effective amount of 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 pharmaceutical compositions 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 adapted 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 pharmaceutical compositions, especially 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 U.S. Pat. No. 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, 60.5 mg (0.6 mmol) triethylamine, 32.4 mg (0.3 mmol) ethynylbenzene and 61.8 mg (0.25 mmol) 2-bromo-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester are dissolved in 1 ml 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 50x20 mm, solvent gradient 10-95% CH₂CN in 0.1% TFA(aq) over 60 min, λ=230 nm, flow rate 40 ml/min).

1H-NMR (400 MHz, CDCl₃, 25°C C): δ (ppm)= 1.39 (3H, t, J=7.22 Hz), 2.51 (3H, s), 3.99 (3H, s), 4.35 (2H, q, J=7.22 Hz), 7.54-7.40 (3H, m), 7.56-7.59 (2H, m).

13C-NMR (100 MHz, CDCl₃, 25°C C): δ (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 U.S. Pat. No. 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-ethyl-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-iodox-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

was obtained in accordance with the method as described in U.S. Pat. No. 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-ethylbenzoyl 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 U.S. Pat. No. 3,303,199.
[0285] b) 5-Methyl-1-phenyl-2-phenylethynyl-1H-imidazole-4-carboxylic Acid Ethyl Ester

[0286] 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) trilluoromethanesulfonic anhydride, 303 mg (3 mmol) triethylamine, and 10 ml dichloromethane was stirred for 1 h 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, 303 mg (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 dried over MgSO₄. 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).

[0287] 1H-NMR (400 MHz, CDCl₃, 25 °C): δ (ppm)= 1.44 (3H, t, J=7 Hz), 2.47 (3H, s), 4.42 (2H, q, J=7 Hz), 7.20-7.42 (5H, m), 7.34-7.38 (2H, m), 7.53-7.60 (3H, m).

[0288] 13C-NMR (100 MHz, CDCl₃, 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

[0289] The title compound, MS: m/e=283.6 (M+H⁺), was prepared in accordance with the general method of example 1b from 1-ethyl-3-methyl-benzene and 2-bromo-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester.

**EXAMPLE 10**

2-(3-Acetylamino-phenethyl)-3,5-dimethyl-3H-imidazole-4-carboxylic Acid Ethyl Ester

[0290] The title compound, MS: m/e=326.8 (M+H⁺), was prepared in accordance with the general method of example 1b from N-(3-ethyl-phenyl)-acetamide and 2-bromo-3,5-dimethyl-3H-imidazole-4-carboxylic acid ethyl ester.

**EXAMPLE 11**

(2-[3-(2,5-Dimethyl-pyrryl-yl)-phenethyl]-yl)-3,5-dimethyl-3H-imidazole-4-carboxylic Acid Ethyl Ester

[0291] 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-ethylphenyl)-2,5-dimethyl-1H-pyrryl.

**EXAMPLE 12**

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

[0292] a) 5-(3,5-Dimethyl-3H-imidazole-4-yl)-3-methyl-[1,2,4]oxadiazole

[0293] 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. NaHCO₃ solution (50 ml) and extracted with dichloromethane (7x30 ml). The combined organic layers were washed with brine (70 ml), dried (MgSO₄) 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+).

[0294] b) 5-(2-Bromo-3,5-dimethyl-3H-imidazol-4-yl)-3-methyl-[1,2,4]oxadiazole

[0295] To a stirred solution of 5-(3,5-dimethyl-3H-imidazol-4-yl)-3-methyl-[1,2,4]oxadiazole (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. NaHCO₃ solution (40 ml) and extracted with dichloromethane (2x30 ml). The combined organic layers were washed with brine (40 ml), dried (MgSO₄) and evaporated to give the crude product as yellow oil (0.84 g). Purification by column chromatography on silica gel (ethyl acetate/McOH 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+).

[0296] c) 5-(3,5-Dimethyl-2-phenylethynyl-3H-imidazol-4-yl)-3-methyl-[1,2,4]oxadiazole

[0297] 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(triphenylphosphin)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 16 h. The reaction mixture was poured into water (50 ml) and extracted with ethyl acetate (2x50 ml). The combined organic layers were washed with brine (40 ml), dried (MgSO₄) 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

[0298] a) 3-Cyclopropyl-5-(3,5-dimethyl-3H-imidazol-4-yl)-[1,2,4]oxadiazole

[0299] The title compound, off-white solid, m.p. 88°C and MS: m/e=204.3 (M+), was prepared from 3,5-dimethyl-3H-imidazol-4-carboxylic acid and N-hydroxy-cyclopropane-carboxamidine in accordance with the general procedure of example 12a.

[0300] b) 5-(2-Bromo-3,5-dimethyl-3H-imidazol-4-yl)-3-cyclopropyl-[1,2,4]oxadiazole

[0301] 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.

**EXAMPLE 14**

2-(4-Chloro-phenylethynyl)-3,5-dimethyl-3H-imidazole-4-carboxylic Acid Ethyl Ester

**EXAMPLE 15**

2-(4-Fluoro-phenylethynyl)-3,5-dimethyl-3H-imidazole-4-carboxylic Acid Ethyl Ester

**EXAMPLE 16**

2-Biphenyl-4-ylethynyl-3,5-dimethyl-3H-imidazole-4-carboxylic Acid Ethyl Ester

**EXAMPLE 17**

2-(2-Fluoro-phenylethynyl)-3,5-dimethyl-3H-imidazole-4-carboxylic Acid Ethyl Ester

**EXAMPLE 18**

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

**EXAMPLE 19**

2-(4-Amino-phenylethynyl)-3,5-dimethyl-3H-imidazole-4-carboxylic Acid Ethyl Ester

**EXAMPLE 13**

The title compound, MS: m/e=308.2 (M+H') was prepared in accordance with the general method of example 1b 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 1c.

**EXAMPLE 20**

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

**EXAMPLE 21**

(4,5-Dichloro-2-phenylethynyl-imidazol-1-yl)-acetic Acid Ethyl Ester

**EXAMPLE 22**

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

**EXAMPLE 23**

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

**EXAMPLE 24**

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

**EXAMPLE 25**

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

**EXAMPLE 26**

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

**EXAMPLE 27**

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

**EXAMPLE 28**

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

[0321] a) 3-Iodo-4H-5-oxa-2,9b-diaza-cyclopenta[a]naphthalene

[0322] 3-Iodo-4H-5-oxa-2,9b-diaza-cyclopenta[a]naphthalene was obtained in analogy to the method as described in EP 0 059 390.

[0323] b) 3-Phenylethynyl-4H-5-oxa-2,9b-diaza-cyclopenta[a]naphthalene

[0324] 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-1H-imidazol-1-yl)-propan-2-ol

[0325] a) Chloro-3-(4-iodo-2-methyl-5-nitro-imidazol-1-yl)-propan-2-ol

[0326] 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.

[0327] b) 1-Chloro-3-(2-methyl-5-nitro-4-phenylethynyl-imidazol-1-yl)-propan-2-ol

[0328] 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-1H-imidazole-4-carbaldehyde

[0329] a) 5-Bromo-3-methyl-1H-imidazole-4-carbaldehyde

[0330] 5-Bromo-3-methyl-1H-imidazole-4-carbaldehyde was obtained in accordance with the method as described in Chem. Pharm. Bull. 1994, 42, 1784-1790.

[0331] b) 3-Methyl-5-phenylethynyl-1H-imidazole-4-carbaldehyde

[0332] 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-1H-imidazole-4-carbaldehyde.

EXAMPLE 28
4-Phenylethynyl-1H-imidazole

[0333] The title compound, MS: m/e=169.2 (M+H⁺) was prepared in accordance with the general method of example 1b from 4-bromocarbazole and ethynylbenzene.

EXAMPLE 29
1-Methyl-4-phenylethynyl-1H-imidazole

[0334] 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

[0335] a) 1,2-Dimethyl-4-iodo-5-nitroimidazole

[0336] 1,2-Dimethyl-4-iodo-5-nitroimidazole was obtained according to the method as described in Aust. J. Chem. 1987, 40(8), 1399-1413.

[0337] b) 1,2-Dimethyl-5-nitro-4-phenylethynyl-1H-imidazole

[0338] 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

[0339] a) 5-Iodo-1,3-dimethyl-1H-pyrazole


[0341] b) 1,3-Dimethyl-5-phenylethynyl-1H-pyrazole

[0342] 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

[0343] a) 4,5-Diisopropyl-1-methyl-1H-imidazole-2-carbaldehyde

[0344] 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.

[0345] b) 4,5-Diisopropyl-1-methyl-2-styryl-1H-imidazole

[0346] 194 mg (0.5 mmol) benzyltri phenylphosphonium chloride 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 0.2 ml 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 50x20 mm, solvent gradient 10-95% CH3CN in 0.1% TFA(aq) over 6.0 min, X=230 nm, flow rate 40 ml/min).

EXAMPLE 33
2-{[2-(4-Fluoro-phenyl)-vinyl]-4,5-diisopropyl-1-methyl-1H-imidazole

[0347] 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-methoxybenzyltriphenylphosphonium chloride
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-methoxybenzyltriphenylphosphonium 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
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
b) 4,5-Diisopropyl-1-methyl-2-[2-(2,4-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-phenyl)-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-carboxaldehyde
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-carboxaldehyde.

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

[0371] Tablets of the following composition can be produced in a conventional manner:

<table>
<thead>
<tr>
<th>mg/Tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active ingredient: 100</td>
</tr>
<tr>
<td>Powdered. lactose: 95</td>
</tr>
<tr>
<td>White corn starch: 35</td>
</tr>
<tr>
<td>Polyvinylpyrrolidone: 8</td>
</tr>
<tr>
<td>Na carboxymethylstarch: 10</td>
</tr>
<tr>
<td>Magnesium stearate: 2</td>
</tr>
</tbody>
</table>

Tablet weight: 250 mg

EXAMPLE B

[0372] Tablets of the following composition can be produced in a conventional manner:

<table>
<thead>
<tr>
<th>mg/Tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active ingredient: 200</td>
</tr>
<tr>
<td>Powdered. lactose: 100</td>
</tr>
<tr>
<td>White corn starch: 64</td>
</tr>
<tr>
<td>Polyvinylpyrrolidone: 12</td>
</tr>
<tr>
<td>Na carboxymethylstarch: 20</td>
</tr>
<tr>
<td>Magnesium stearate: 4</td>
</tr>
</tbody>
</table>

Tablet weight: 400 mg

EXAMPLE C

[0373] Capsules of the following composition can be produced:

<table>
<thead>
<tr>
<th>mg/Capsule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active ingredient: 50</td>
</tr>
<tr>
<td>Crystalline. lactose: 60</td>
</tr>
<tr>
<td>Microcrystalline cellulose: 34</td>
</tr>
<tr>
<td>Talc: 5</td>
</tr>
<tr>
<td>Magnesium stearate: 1</td>
</tr>
</tbody>
</table>

Capsule fill weight: 150 mg

[0374] The active ingredient would be prepared having a suitable particle size, then the crystalline lactose and the microcrystalline cellulose can be homogeneously mixed with one another, sieved and thereafter talc and magnesium stearate admixed. The final mixture can be filled into hard gelatine capsules of suitable size.

1. A compound of formula

\[
\begin{align*}
\text{I-A} &
\end{align*}
\]

wherein

- \( R^1, R^2, R^3, R^4 \) and \( R^5 \) are independently selected from the group consisting of hydrogen, lower alkyl, \(-(CH_2)_n-\) halogen, lower alkoxy, \(-(CH_2)_n-NRR', -(CH_2)_n-N(R)-C(O)-lower alkyl, aryl, unsubstituted heteroaryl and heteroaryl substituted by one or more lower alkyl;
- \( R, R' \) and \( R'' \) are independently selected from the group consisting of hydrogen and lower alkyl;
- \( B \) is selected from the group consisting of...

\[
\begin{align*}
\text{I-A} &
\end{align*}
\]
R is selected from the group consisting of hydrogen, lower alkyl, -(CH2)n-OH, -(CH2)n-C(O)OR and aryl;
R2 is lower alkyl;
R10 is selected from the group consisting of hydrogen, lower alkyl and halogen;
R11 is selected from the group consisting of hydrogen and alkyl;
R12 is -(CH2)n-N(R)-C(O)-lower alkyl;
R13 is selected from the group consisting of hydrogen and lower alkyl;
R14, R15, R16 and R17 are independently selected from the group consisting of hydrogen, lower alkyl, -(CH2)n-halogen or lower alkoxy;
R18, R19 and R25 are independently selected from the group consisting of hydrogen, lower alkyl, -(CH2)n-halogen and lower alkoxy;
R22 is selected from the group consisting of hydrogen and lower alkyl;
R23 is selected from the group consisting of hydrogen, lower alkyl and lower alkyl substituted by at least one substituent selected from hydroxy or halogen;
R25 is selected from the group consisting of hydrogen, lower alkyl, lower alkanoyl and nitro;
R24, R25 and R26 are independently selected from the group consisting of hydrogen or lower alkyl;
n is 0, 1, 2, 3, 4, 5 or 6;
X is selected from the group consisting of -CH=, -O- and -S-; and
Y is selected from the group consisting of + and -N=; or a pharmaceutically acceptable salt thereof;
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.
2. A compound of claim 1 wherein B is B1.
3. A compound of claim 1 wherein B is B2.
4. A compound of claim 1 wherein B is B3.
5. A compound of claim 1 wherein B is B4.
6. A compound of claim 1 wherein B is B5.
7. A compound of claim 1 wherein B is B6.
8. A composition comprising a therapeutically effective amount of a compound of claim 1 and a pharmaceutically acceptable carrier.
9. A method of treating a disease selected from the group consisting of Alzheimer’s disease, Parkinson’s disease, Huntington’s disease, depression, anxiety, pain, epilepsy, amyotrophic lateral sclerosis (ALS) comprising administering a therapeutically effective amount of a compound of claim 1.

10. A compound of formula

wherein
R1, R2, R3, R4 and R5 are independently selected from the group consisting of hydrogen, lower alkyl, -(CH2)n-halogen, lower alkoxy, -(CH2)n-NRR’, -(CH2)n-N(R)-C(O)-lower alkyl, aryl or unsaturated heteroaryl, heteroaryl substituted by at least one lower alkyl;
R6 and R7 are independently selected from the group consisting of hydrogen and lower alkyl;
R7 is selected from the group consisting of hydrogen, lower alkyl, -(CH2)n-C(O)OR and halogen;
R8 is selected from the group consisting of hydrogen, lower alkyl, -(CH2)n-C(O)OR, halogen, nitro, unsubstituted heteroaryl and heteroaryl substituted by lower alkyl or cycloalkyl; and
R9 is selected from the group consisting of hydrogen, lower alkyl, -(CH2)n-OH, -(CH2)n-C(O)OR or aryl; or a pharmaceutically acceptable salt thereof.
11. A composition comprising a therapeutically effective amount of a compound of claim 10 and a pharmaceutically acceptable carrier.
12. A method of treating a disease selected from the group consisting of Alzheimer’s disease, Parkinson’s disease, Huntington’s disease, depression, anxiety, pain, epilepsy, amyotrophic lateral sclerosis (ALS) comprising administering a therapeutically effective amount of a compound of claim 10.
13. A compound of formula

wherein
R1, R2, R3, R4 and R5 are independently selected from the group consisting of hydrogen, lower alkyl, -(CH2)n-halogen, lower alkoxy, -(CH2)n-NRR’, -(CH2)n-N(R)-C(O)-lower alkyl, aryl, unsaturated heteroaryl and heteroaryl substituted by at least one lower alkyl;
R and R' are independently selected from the group consisting of hydrogen and lower alkyl;

R\(^9\) is lower alkyl;

R\(^{10}\) is halogen; and

R\(^{11}\) is selected from the group consisting of hydrogen and alkyl;

or a pharmaceutically acceptable salt thereof.


15. A method of treating a disease selected from the group consisting of Alzheimer's disease, Parkinson's disease, Huntington's disease, depression, anxiety, pain, epilepsy, amyotrophic lateral sclerosis (ALS) comprising administering a therapeutically effective amount of a compound of claim 13.

* * * * *