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(54) Title: MONOAMINE NEUROTRANSMITTER RE-UPTAKE INHIBITOR FOR THE INHIBITION OF BETA-AMYLOID (Aß40 AND Aß42) -GENERATION

(57) Abstract: The invention relates to the use of a monoamine neurotransmitter re-uptake inhibitor comprising a 2,3-disubstituted tropane moiety for the preparation of a medicament for inhibiting β -amyloid generation.

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Monoamine Neurotransmitter Re-uptake Inhibitor for the inhibition of Beta-Amyloid ($A\beta_{40}$ and $A\beta_{42}$) -generation

The invention relates to the use of a monoamine neurotransmitter re-uptake inhibitor comprising a 2,3-disubstituted tropane moiety optionally in the form of its physiologically acceptable acid addition salts for the preparation of a medicament for inhibiting β-amyloid generation.

Background of the invention

Amyloid β-peptides (Aβ) are strongly aggregating peptides with approximate molecular masses of 4 kDa. The predominant forms, $A\beta_{40}$ and $A\beta_{42}$, are 40 and 42 amino acid residues in length, and are the major proteinaceous constituents of brain amyloid deposits in a variety of diseases. $A\beta_{42}$ is an early and central component of amyloid in diffuse and senile plaques, while $A\beta_{40}$ is the major peptide form in amyloid deposits in the cerebral microvasculature. $A\beta_{40}$ and $A\beta_{42}$ are derived by endoproteolysis of the larger amyloid precursor protein (APP) by the sequential activities of β-secretase at the amino-terminus, and a γ-secretase that cleaves at the C-terminus, respectively, of the Aβ domain. Alternative amino-terminal cleavage by α-secretase within the Aβ domain results in the generation of non-amyloidogenic fragments. Because Aβ peptides readily aggregate into insoluble amyloid plaques, lowering their generation is a major objective for the design of therapeutic and preventive strategies for the treatment of a variety of diseases.

Brief description of the invention

Surprisingly it has been found, that a monoamine neurotransmitter re-uptake inhibitor comprising a 2,3-disubstituted tropane moiety optionally in the form of its physiologically acceptable acid addition salts dose-dependently decreases the levels of $A\beta_{42}$ and $A\beta_{40}$ that are secreted into the supernatant by an APP transfected U373 astrocytoma cell line. Furthermore, it has been found that Aβ levels are significantly decreased in APP tg mice that have been treated with a monoamine neurotransmitter re-uptake inhibitor comprising a

2,3-disubstituted tropane moiety. Accordingly, one embodiment of the current invention relates to the use of a monoamine neurotransmitter re-uptake inhibitor comprising a 2,3-disubstituted tropane moiety optionally in the form of its physiologically acceptable acid addition salts for the preparation of a medicament for the treatment or prevention of a disease or condition associated with an increased level of one or more isoforms of amyloid β peptides (Aβ) and/or with a changed ratio of levels of Aβ isoforms and/or with the formation of plaques containing one or more amyloid β peptide isoforms in a mammal.

In a preferred embodiment the invention relates to the use of a monoamine neurotransmitter re-uptake inhibitor comprising a 2,3-disubstituted tropane moiety optionally in the form of its physiologically acceptable acid addition salts for the preparation of a medicament for the treatment or prophylaxis of diseases associated with the formation of diffuse and senile plaques. Furthermore, the invention relates to the use of a monoamine neurotransmitter re-uptake inhibitor comprising a 2,3-disubstituted tropane moiety optionally in the form of its physiologically acceptable acid addition salts for the preparation of a medicament for the treatment or prophylaxis of diseases associated with the formation of $A\beta_{40}$- and $A\beta_{42}$-containing plaques, preferably of $A\beta_{42}$-containing plaques.

Moreover the invention relates to the use of a monoamine neurotransmitter re-uptake inhibitor comprising a 2,3-disubstituted tropane moiety optionally in the form of its physiologically acceptable acid addition salts for the preparation of a medicament for the treatment or prophylaxis of amyloidosis associated with the formation of $A\beta_{40}$ and $A\beta_{42}$. Preferably the invention relates to the use of monoamine neurotransmitter re-uptake inhibitor comprising a 2,3-disubstituted tropane moiety optionally in the form of its physiologically acceptable acid addition salts for the preparation of a medicament for the treatment or prophylaxis of amyloidosis associated with the formation of $A\beta_{42}$.

In particular the invention relates to the use of a monoamine neurotransmitter re-uptake inhibitor comprising a 2,3-disubstituted tropane moiety optionally in the form of its

physiologically acceptable acid addition salts for the preparation of a medicament for the treatment or prophylaxis of brain amyloidosis.

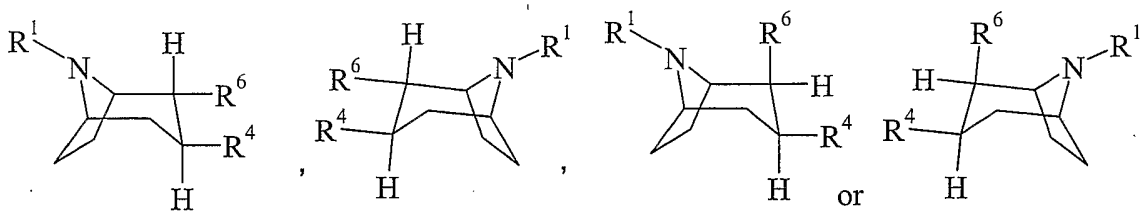
Moreover, the invention relates to the use of a monoamine neurotransmitter re-uptake inhibitor comprising a 2,3-disubstituted tropane moiety optionally in the form of its physiologically acceptable acid addition salts for the preparation of a medicament for the non-symptomatic or disease modifying treatment of patients suffering from Alzheimer's disease (AD).

Furthermore the invention relates to the use of a monoamine neurotransmitter re-uptake inhibitor comprising a 2,3-disubstituted tropane moiety optionally in the form of its physiologically acceptable acid addition salts for the preparation of a medicament for helping to prevent or delay the onset of AD, for treating patients with mild cognitive impairment (MCI), and preventing or delaying the onset of AD in those patients who would otherwise be expected to progress from MCI to AD, for treating Down's syndrome, for treating Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch Type, for treating cerebral beta-amyloid angiopathy and preventing its potential consequences such as single and recurrent lobar hemorrhages, for treating other degenerative dementias, including dementias of mixed vascular and degenerative origin, for treating dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, and diffuse Lewy body type AD.

Detailed description of the invention

As a rule the monoamine neurotransmitter re-uptake inhibitor comprising a 2,3-disubstituted tropane moiety are those which are disclosed by International patent applications WO 93/09814 and WO 97/30997.

Preferably the monoamine neurotransmitter re-uptake inhibitor comprising a 2,3-disubstituted tropane moiety are compounds of the general formula (I)



(I)

or a pharmaceutical acceptable addition salt thereof or the N-oxide thereof, wherein

R^1 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl or 2-hydroxyethyl;

R^6 is CH_2-X-R^3,

wherein X is O, S, or NR'; wherein

R' is hydrogen or alkyl; and

R^3 is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, or-CO-alkyl;

heteroaryl which may be substituted one or more times with

alkyl, cycloalkyl, or cycloalkylalkyl;

phenyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF_3, CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl;

phenylphenyl;

pyridyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF_3, CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl;

thienyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF_3, CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl ; or

benzyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF_3, CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl; or

$(CH_2)_nCO_2R^7$, COR^7, or CH_2R^8, wherein

R^7 is alkyl, cycloalkyl, or cycloalkylalkyl; phenyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF_3, CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl ; phenylphenyl ; pyridyl which may be substituted one or more times with substituents selected from

pyridyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF_3, CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl; o thienyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF_3, CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl; or benzyl;

n is 0 or 1; and

R^8 is O-phenyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF_3, CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl; or

O-CO-phenyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF_3, CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl; or

$CH=NOR^3$; wherein R^3 is o hydrogen; o alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl or aryl; all of which may be substituted with -COOH; -COO-alkyl; -COO-cycloalkyl; or phenyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF_3, CN, alkyl, cycloalkyl, alkoxy, cycloalkoxy, alkenyl, alkynyl, amino, and nitro;

R^4 is phenyl, 3,4-methylenedioxyphenyl, benzyl, naphthyl, or heteroaryl all of which may be substituted one or more times with substituents selected from the group consisting of halogen, CF_3, CN, alkoxy, cycloalkoxy, alkyl, cycloalkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl.

In a special embodiment of the compound of general formula I, R^6 is 1,2,4-oxadiazol-3-yl which may be substituted in the 5 position with alkyl, cycloalkyl, or cycloalkylalkyl; phenyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF_3, CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl; phenylphenyl; or benzyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF_3, CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl; or 1,2,4-oxadiazol-5-yl which may by substituted in the 3 position with alkyl, cycloalkyl, or cycloalkylalkyl; phenyl which may be substituted

one or more times with substituents selected from the group consisting of halogen, CF_3, CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl; phenylphenyl; benzyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF_3, CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl; pyridyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF_3, CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro and heteroaryl; or thienyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF_3, CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro and heteroaryl.

In a further special embodiment of the compound of general formula (I), R^6 is CH_2-X-R^3, wherein X is O, S, or NR'; wherein R' is hydrogen or alkyl ; and R^3 is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, or-CO-alkyl.

In a still further embodiment of the compound of general formula (I), R^6 is CH=NOR^3; wherein R^3 is hydrogen; alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl or aryl; all of which may be substituted with -COOH; -COO-alkyl; -COO-cycloalkyl; or phenyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF_3, CN, alkyl, cycloalkyl, alkoxy, cycloalkoxy, alkenyl, alkynyl, amino, and nitro.

In a further special embodiment of the compound of general formula (I), R^4 is phenyl, which is substituted once or twice with substituents selected from the group consisting of halogen, CF_3, CN, alkoxy, cycloalkoxy, alkyl, cycloalkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl.

In a more special embodiment, R^4 is phenyl substituted once or twice with chlorine.

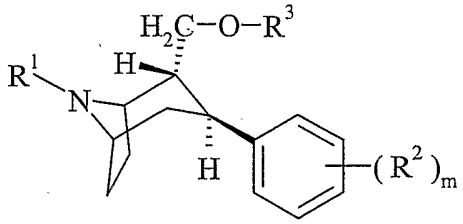
In a further special embodiment, the tropane derivative having dopamine reuptake inhibitor activity is a (1 R, 2R, 3S) -2, 3-disubstituted tropane derivative of formula I.

In a still further embodiment, the tropane derivative having dopamine reuptake inhibitory activity is a compound of general formula I wherein R^6 is-CH_2-X-R^3, wherein X is O or S, and R^3 is methyl, ethyl, propyl, or cyclopropylmethyl; -CH=NOR^3; wherein R^3 is hydrogen or alkyl, or 1,2,4-oxadiazol-5-yl which may by substituted in the 3 position with alkyl.

In a still further embodiment, the tropane derivative having dopamine reuptake inhibitory activity is a compound of general formula I wherein R^1 is hydrogen, methyl, ethyl or propyl.

In a still further embodiment, the tropane derivative having dopamine reuptake inhibitory activity is a compound of general formula I whereinR^4 is 3,4-dichlorophenyl.

More preferably those monoamine neurotransmitter re-uptake inhibitor comprising a 2,3-disubstituted tropane moiety are compounds of formula (I1)



(I 1)

wherein

R^1 represents a hydrogen atom or a C_{1-6} alkyl group, preferably a hydrogen atom, a methyl or an ethyl group;

R^2 each independently represents a halogen atom or a CF_3 or cyano group, preferably a fluorine, chlorine or bromine atom;

R^3 represents a hydrogen atom or a C_{1-6} alkyl or C_{3-6}-cycloalkyl-C_{1-3}-alkyl group, preferably a methyl, ethyl or n-propyl group; and

m is 0 or an integer from 1 to 3, preferably 1 or 2;

or a tautomer, a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof.

As used herein, the expression "C_{1-6} alkyl" includes methyl and ethyl groups, and straight-chained and branched propyl, butyl, pentyl and hexyl groups. Particular alkyl groups are methyl, ethyl, n-propyl, isopropyl and t-butyl.

The expression "C_{3-6} cycloalkyl" as used herein includes cyclic propyl, butyl, pentyl and hexyl groups such as cyclopropyl and cyclohexyl.

The term "halogen" as used herein includes fluorine, chlorine, bromine and iodine, of which fluorine and chlorine are preferred.

The term "physiologically functional derivative" as used herein includes derivatives obtained from the compound of formula (I) under physiological conditions, these are for example N-oxides, which are formed under oxidative conditions.

The term "pharmaceutically acceptable acid addition salt" as used herein includes those salts which are selected from among the acid addition salts formed with hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, acetic acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid and maleic acid, the salts obtained from hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid and acetic acid being particularly preferred. The salts of citric acid are of particular significance.

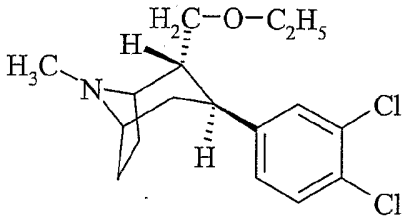
In a special embodiment, the tropane derivative having dopamine reuptake inhibitor activity is a compound of the general formula (I) selected from:
(1R,2R,3S)-2-(3-Cyclopropyl-1 2, 4-oxadiazol-5-yl)-3- (4-fluorophenyl) tropane;
(1R,2R,3S)-2-(3-Phenyl-1,2,4-oxadiazol-5-yl)-3-(4-fluorophenyi) tropane;
(1R,2R,3S)-2-(3-Phenyl-1,2,4-oxadiazol-5-yl)-3-(4-methylphenyl)-tropane;
(1R,2R,3S)-2-(3-Benyl-1,2, 4-oxadiazol-5-yl)-3-(4-fluorophenyl) tropane;
(1R,2R,3S)-2- (3-(4-Phenyl-phenyl)-1,2, 4-oxadiazol-5-yl)-3-(4-fluorophenyl) tropane;
(1R,2R,3S)-2-(3-Phenyl-1,2, 4-oxadiazol-5-yl)-3-(2-naphthyl) tropane;
(1R,2R,3S)-3-(3,4-Dichlorophenyl) tropane-2-aldoxime;

(1R,2R,3S)-3- (3,4-Dichlorophenyl)-tropane-2-O-methyl-aldoxime;
(1R,2R,3S)-3-(3,4-Dichlorophenyl)tropane-2-O-benzyl-aldoxime;
(1R,2R,3S)-3-(3,4-Dichlorophenyl) tropane-2-O-ethoxycarbonylmethyl-aldoxime;
(1R,2R,3S)-3-(3,4-Dichlorophenyl) tropane-2-O-methoxycarbonylmethyl-aldoxime;
(1R,2R,3S)-3-(3,4-Dichlorophenyl)tropane-2-O-(1-ethoxycarbonyl-1,1-dimethyl-methyl)-aldoxime;
(1R,2R,3S)-3-(3,4-Dichlorophenyl) tropane-2-O-carboxymethyl-2-aldoxime;
(1R,2R,3S)-N-Normethyl-3-(3,4-dichlorophenyl) tropane-2-O-methyl-aldoxime;
(1R,2R,3S)-N-Normethyl-3-(3,4-dichlorophenyl) tropane-2-O-benzyl-aldoxime;
(1R,2R,3S)-3-(4-Methylphenyl) tropane-2-O-methyl-aldoxime;
(1R,2R,3S)-3-(3,4-Dichlorophenyl)tropane-2-O-(1,1-dimethylethyl)-aldoxime;
(1R,2R,3S)-3-(4-Chlorophenyl) tropane-2-O-aldoxime;
(1R,2R,3S)-3-(4-Chlorophenyl) tropane-2-O-methylaldoxime hydrochloride;
(1R,2R,3S)-3-(4-Chlorophenyl)tropane-2-O-methoxycarbonylmethyl-aldoxime;
(1R,2R,3S)-3-(3,4-Dichlorophenyl) tropane-2-O- (2-propynyl)-aldoxime;
(1R,2R,3S)-3-(3,4-Dichlorophenyl)tropane-2-O-(2-methylpropyl)-aldoxime;
(1R,2R,3S)-3-(3,4-Dichlorophenyl)tropane-2-O-cyclopropylmethyl-aldoxime;
(1R,2R,3S)-3-(3,4-Dichlorophenyl) tropane-2-O-ethyl-aldoxime;
(1R,2R,3S)-2-Methoxymethyl-3-(3,4-dichlorophenyl)-tropane;
(1R,2R,3S)-2-Isopropoxymethyl-3-(3,4-dichlorophenyl)-tropane;
(1R,2R,3S)-2-Ethoxymethyl-3-(3,4-dichlorophenyl)-tropane;
(1R,2R,3S)-2-Ethoxymethyl-3-(3,4-dichlorophenyl)-nortropane;
(1R,2R, S)-2-Cyclopropylmethyloxymethyl-3-(3,4-dichlorophenyl)-tropane;
(1R,2R,3S)-2-Methoxymethyl-3-(4-chlorophenyl)-tropane;
(1R,2R,3S)-N-Normethyl-2-methoxymethyl-3-(4-chlorophenyl)-tropane;
(1R,2R,3S)-2-Ethoxymethyl-3-(4-chlorophenyl)-tropane;
(1R,2R,3S)-N-Normethyl-2-methoxymethyl-3-(3,4-dichlorophenyl)-tropane;
(1R,2R,3S)-N-Normethyl-2-ethoxymethyl-3-(3,4-dichlorophenyl)-tropane;
(1R,2R,3S)-N-Normethyl-2-ethoxymethyl-3-(4-chlorophenyl)-tropane;
(1R,2R,3S)-N-Normethyl-2-cyclopropylmethyloxymethyl-3-(4-chlorophenyl)-tropane;
(1R,2R,3S)-2-Cyclopropylmethyloxymethyl-3-(4-chlorophenyl)-tropane;

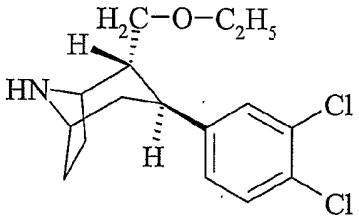
(1R,2R,3S)-2-Ethylthiomethyl-3-(3,4-dichlorophenyl)-tropane;
(1R,2R,3S)-2-Hydroxymethyl-3-(4-fluorophenyl) tropane;
(1R,2R,3S)-2-Hydroxymethyl-3-(3,4-dichlorophenyl) tropane;
(1R,2R,3S)-N-Normethyl-N-(tert-butoxycarbonyl)-2-hydroxymethyl-3-(3,4-dichlorophenyl) tropane;
(1R,2R,3S)-2-Hydroxymethyl-3-(4-chlorophenyl) tropane;
(1R,2R,3S)-2- (3- (2-Furanyl)-1,2,4-oxadiazol-5-yl)-3-(3, 4-dichlorophenyl)-tropane;
(1R,2R,3S)-2-(3-(3-Pyridyl)-1,2,4-oxadiazol-5-yl)-3-(3, 4-dichlorophenyl)-tropane;
(1R,2R,3S)-N-Normethyl-N-allyl-2-(3-(4-pyridyl)-1,2,4-oxadiazol-5-yl)-3-(3, 4-dichlorophenyl)-tropane;
(1R,2R,3S)-N-Normethyl-N-ethyl-2-(3-(4-pyridyl)-1,2,4-oxadiazol-5-yl)-3-(3, 4-dichlorophenyl)-tropane;
(1R,2R,3S)-N-Normethyl-N-(2-hydroxyethyl)-2-(3-(4-pyridyl)-1,2, 4-oxadiazol-5-yl)-3-(3,4-dichlorophenyl)-tropane;
(1R,2R,3S)-N-Normethyl-2-(3-(4-pyridyl)-1,2, 4-oxadiazol-5-yl)-3-(3, 4-dichlorophenyl)-tropane;
(1R,2R,3S)-N-Normethyl-N-allyl-2-(3-(3-pyridyl)-1,2,4-oxadiazol-5-yl)-3-(3, 4-dichlorophenyl)-tropane;
(1R,2R,3S)-N-Normethyl-N-allyl-2-(3-(2-pyridyl)-1,2, 4-oxadiazol-5-yl)-3-(3, 4-dichlorophenyl)-tropane;
(1R,2R,3S)-2-(3-(2-Thienyl)-1,2,4-oxadiazol-5-yl)-3-(4-chlorophenyl)-tropane;
(1R,2R,3S)-2-(3-(2-Thienyl)-1,2,4-oxadiazol-5-yl)-3-(3,4-dichlorophenyl)-tropane;
(1R,2R,3S)-2-(3-(4-Pyridyl)-1,2,4-oxadiazol-5-yl)-3-(3,4-dichlorophenyl)-tropane;
(1R,2R,3S)-2-(3-(2-Pyridyl)-1,2,4-oxadiazol-5-yl)-3-(3,4-dichlorophenyl)-tropane;
(1R,2R,3S)-2-(3-(4-Pyridyl)-1,2,4-oxadiazol-5-yl)-3-(4-chlorophenyl)-tropane;
(1R,2R,3S)-2-(3-(3-Pyridyl)-1,2,4-oxadiazol-5-yl)-3-(4-chlorophenyl)-tropane;
(1R,2R,3S)-2-(3-2-Pyridyl)-1,2,4-oxadiazol-5-yl)-3-(4-chlorophenyl)-tropane;
(1R,2R,3S)-2- (3-Phenyl-1,2,4-oxadiazol-5-yl)-3-(4-fluorophenyl)-tropane;
(1R,2R,3S)-2-(3-Phenyl-1,2,4-oxadiazol-5-yl)-3- (4-methylphenyl)-tropane;
(1R,2R,3S)-2-(3-Benzyl-1,2, 4-oxadiazol-5-yl)-3-(4-fluorophenyl)-tropane;
(1R,2R,3S)-2-(3-(4-Phenylphenyl)-1,2, 4-oxadiazol-5-yl)-3-(4-fluorophenyl)-tropane;

(1R,2R,3S)-2-(3-Phenyl-1,2,4-oxadiazol-5-yl)-3-(2-naphthyl)-tropane;
(1R,2R,3S)-2-(4-Chlorophenoxy-methyl)-3-(4-fluorophenyl)-tropane;
(1R,2R,3S)-2-(4-Chlorophenoxy-methyl)-3-(4-fluorophenyl)-tropane;
(1R,2R,3S)-2-(4-Chlorophenoxy-methyl)-3-(3,4-dichlorophenyl)-tropane;
(1R,2R,3S)-2-(4-Chlorophenoxy-methyl)-3-(4-methylphenyl)-tropane;
(1R,2R,3S)-2-(4-Benzoyloxy-methyl)-3-(4-fluorophenyl)-tropane;
(1R,2R,3S)-2-Carbomethoxy-3-(2-naphthyl)-tropane;
(1R,2R,3S)-2-Carbomethoxy-3-(3,4-dichlorophenyl)-tropane;
(1R,2R,3S)-2-Carbomethoxy-3-benzyl-tropane;
(1R,2R,3S)-2-Carbomethoxy-3-(4-chlorophenyl)-tropane;
(1R,2R,3S)-2-Carbomethoxy-3-(4-methylphenyl)-tropane;
(1R,2R,3S)-2-Carbomethoxy-3-(1-naphthyl)-tropane;
(1R,2R,3S)-2-Carbomethoxy-3-(4-phenylphenyl)-tropane;
(1R,2R,3S)-2-Carbomethoxy-3-(4-t-butyl-phenyl)-tropane;
(1R,2R,3S)-2-(4-Fluoro-benzoyl)-3-(4-fluorophenyl)-tropane; or a pharmaceutically acceptable addition salt thereof.

Most preferred are the compounds of formulae (IA) and (IB)



(IA)



(IB)

or pharmaceutically acceptable salts thereof, in particular the citrates thereof.

Accordingly, one embodiment of the current invention relates to the use of a monoamine neurotransmitter re-uptake inhibitor comprising a 2,3-disubstituted tropane moiety optionally in the form of its physiologically acceptable acid addition salts for the preparation of a medicament for the treatment or prevention of a disease or condition associated with an increased level of one or more isoforms of amyloid β peptides (Aβ)

and/or with a changed ratio of levels of Aβ isoforms and/or with the formation of plaques containing one or more amyloid β peptide isoforms in a mammal. Preferably the invention relates to the use of compound of formula IA for the preparation of a medicament for lowering the level of $A\beta_{42}$.

In a preferred embodiment of the invention relates to the use of formula IA for the preparation of a medicament for the treatment or prophylaxis of diseases associated with the formation of diffuse and senile plaques.

Furthermore, the invention relates to the use of the compound of formula IA for the preparation of a medicament for the treatment or prophylaxis of diseases associated with the formation of $A\beta_{40}$- and $A\beta_{42}$-containing plaques. Preferably, the invention relates to the use of the compound of formula IA for the preparation of a medicament for the treatment or prophylaxis of diseases associated with the formation of $A\beta_{42}$-containing plaques.

Moreover the invention relates to the use of the compound of formula IA for the preparation of a medicament for the treatment or prophylaxis of amyloidosis associated with the formation of $A\beta_{40}$, and $A\beta_{42}$. Preferably the invention relates to the use of the compound of formula IA for the preparation of a medicament for the treatment or prophylaxis of amyloidosis associated with the formation of $A\beta_{42}$.

In particular the invention relates to the use of the compound of formula IA for the preparation of a medicament for the treatment or prophylaxis of brain amyloidosis.

Furthermore the invention relates to the use of the compound of formula IA for the preparation of a medicament for the treatment or prophylaxis of vascular amyloidosis and age related amyloidosis.

Moreover, the invention relates to the use of the compound of formula IA for the preparation of a medicament for the treatment of patients suffering from mild to moderate

dementia of the Alzheimer type (DAT). Furthermore the invention relates to the use of the compound of formula IA for the preparation of a medicament for the prophylactic treatment of patients identified to have a high risk for developing dementia of the Alzheimer type.

Moreover, the invention relates to the use of the compound of formula IA for the preparation of a medicament for the treatment of patients suffering from mild cognitive impairment (MCI) or age associated memory impairment (AAMI).

Furthermore the invention relates to the use of the compound of formula IA for the preparation of a medicament for the prophylactic treatment of mild cognitive impairment (MCI) or age associated memory impairment (AAMI).

Methods:

Preferably the assay is carried out as follows:

Cell culture and drug treatment: U373 astrocytoma cells expressing human wtAPP695 were used to test the compound of formula IA for Aβ lowering potential. Cells were cultured in 96 well plates in DMEM medium, additionally supplemented with 10% FCS and 1% glutamine, until they have grown to a confluent cell layer. The cells were then incubated for 17 hours in the presence of the compound of formula IA in DMEM medium. Afterwards, 100 µl of the supernatant had been removed and measured with the ELISA as described below to determine the $A\beta_{42}$ peptide concentrations. The cells were washed, incubated again for 4 hours with the compound, before measuring the $A\beta_{40}$ levels. AlamarBlue assays (Serotec, Oxford, UK) were conducted to determine cytotoxicity.

Sandwich ELISA for Aβ:

Monoclonal 6E10 against $A\beta_{1-17}$ (Signet Laboratories, Inc., Dedham, MA, USA) was used to capture $A\beta_{40}$; SGY 3160 against $A\beta_{1-16}$ (Mayo Medical Ventures, Rochester, Minnesota,

USA) to capture $A\beta_{42}$. Both antibodies were diluted in PBS at a concentration of 8 µg/ml to coat a 96 well plate. Blocking was completed with 1% Block ACE (blocking reagent) (Dainippon Seiyaku, Asaka, Japan) in PBS for 2 hrs. The plates were then washed with PBST and the cell supernatants, diluted 1:1.5 in EC buffer (0.1 M NaH2PO4, 0.1 M Na2HPO4, 2 mM EDTA, 0.4 M NaCl, 0.2% BSA, 0.05% CHAPS, 0.4% Block ACE, 0.05% NaN3 pH 7.0) have been added into the wells, before the plates were stored at 4° C over night. Detector antibodies (alkaline phosphatase-coupled $RO\beta_{40}$ and $RO\beta_{42}$ against $A\beta_{40}$ and $A\beta_{42}$, respectively), were loaded onto the wells at 0.1 µg/ml in ACE Block for 2 hrs. The reporter system used was the Tropix ELISA-Light chemiluminescent detection system (Applied Biosystems (Tropix), Bedford, MA, USA).

Animal studies:

APPtg mice at 3 to 4 months of age were used. A compound of formula (IA) was prepared and administered in a suspension of 0.5% Tylose solution. The Acetylcholinesterase inhibitor Donepezil has been ordered from APIN chemicals (Code 32039d).

The compound of formula (IA) and Donepezil were administered per os, using an Acrofirm needle (model 1464LL). Controls were treated with Tylose only. Each group consisted of 12 or 13 mice with equal numbers of each sex. In the short term study, the animals were treated for the time period of 2.5 days. Twice a day a dose of 3 mg/kg was applied with interruption times of 11.5-12.5 hours. On the last day (day of sacrifice), one dose of 3 mg/kg was administered and the mice were sacrificed 5.5 hours later. In a 2 weeks study 3 mg/kg of compound of formula IA and 3,3 mg/kg of Donepezil were administered once a day. In a second long term 4 weeks study 3 mg/kg/day of compound of formula IA were administered, subdivided into two subdoses with an interruption time of 10-12 hours during the day. Each version of the *in vivo* experiments has been performed once.

The murine brains were rapidly removed from the skull and divided along the medial fissure. The cerebellum was removed before each half was quickly frozen down on a metal plate that had been cooled down on dry ice. Brains were placed in Eppendorf tubes, frozen

in liquid nitrogen and stored at -80° C until needed for Aβ extractions or compound measurements.

Aβ extraction:

Brains were thawed on ice. Mouse hemibrains were extracted in a homogenisation buffer consisting of 20 mM Tris (pH 8.5), 0.2% Triton X-100 and complete proteinase inhibitor with EDTA (Roche Diagnostics GmbH, Mannheim, Germany). The brains were homogenized in a volume (ml) 5 times the weight of the brain (mg) using a 2 ml Douncer Homogenator (B. Braun, Melsungen, Germany). This was carried out 12 times with a Stempel L, followed by a Stempel S. The homogenates were then ultracentrifuged in Ultracentrifuge tubes (Beckman, CA, USA) at 200.000 g (UZ Sorvall RC 120 GX, KENDRO Laboratories Products GmbH, Hanau, Germany) at 4° C for 1 hour. The post nuclear supernatants containing the soluble Aβ were collected and measured in a Sandwich ELISA (s.a.).

Statistical Analyses. Statistical analyses of data was done by one-sided t tests for differences between treatment and control group to determine the p values.

Results:

The compound of formula IA has been tested in an Aβ secretion assay. In this particular *in vitro* assay, the astrocytoma cell line U373 that stably overexpresses wild-type human amyloid precursor protein (APP), has been exposed to this compound. APP is proteolytically cleaved by 2 enzymes, BACE and γ secretase, to generate the Aβ peptides. Because of a flexible APP cleavage site of γ secretase, several Aβ isoforms are generated, majorly $A\beta_{40}$ and $A\beta_{42}$. The rate of Aβ generation/secretion into the medium in the presence or absence of the compound of formula IA in different concentrations has been measured by ELISA (Table 1). The % inhibition (-) or stimulation (+) has been determined in 2 independent experiments. The dose-response curves are shown in Figures 1 and 2.

Table 1:

Formula IA [μM]	$A\beta_{42}$ [%]	$A\beta_{40}$ [%]
1.56	-3.5, +4.5	-3.2, +16
3.12	-6.5, +16.1	-6.1, +8.0
6.25	-4.1, -12.1	-20.9, -2.8
12.5	-17.8, -23.2	-33.9, -24.8
25	-24.5, -48.9	-50.1, -50.3
50	-26.6, -62.3	-81.3, -88.5

The generation/secretion of both Aβ-isoforms are inhibited by the compound of formula 1A. Inhibition of $A\beta_{40}$ by this compound is more pronounced, compared to the $A\beta_{42}$ isoform (see Fig. 1, 2). In both cases, Aβ inhibition has been found to be dose-dependent.

In the short term *in vivo* experiment, the compound of formula IA revealed a statistically significant reduction of the $A\beta_{40}$ levels by 12.4% (p=0.0003) (see Fig. 3 and Table 2. Note, in Fig. 3 "ß" stands for "β"). $A\beta_{42}$ levels were slightly increased by 5.1% (p=0.9136). After a 2 weeks treatment, compound of formula IA revealed a significant reduction of the cerebral $A\beta_{40}$ levels by 18.6% (p=0.024) and $A\beta_{42}$ levels by 16,3% (p=0.0096) (see Table 2). Donepezil slightly increased $A\beta_{40}$ levels by 9.6 % (p=0.022) and $A\beta_{42}$ levels were decreases by 7.6% (p=0.402). The administration of compound of formula IA in the 4 weeks study revealed a significant reduction of $A\beta_{40}$ by 17,2% and 27.4% reduction for $A\beta_{42}$. Due to the testing strategy (dose response), the reduction of $A\beta_{40}$ in this experiment could not be shown to be significant.

Table 2: Reduction (-) and Stimulation (+) of cerebral Aβ levels

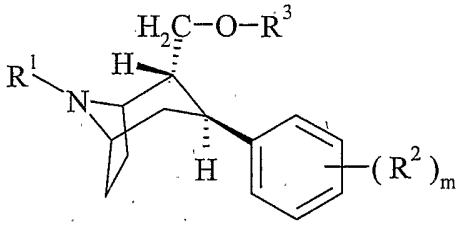
Compound	Experimental Design	Aβ40 [%]	Aβ42 [%]
Formula IA	2.5 days 2x 3.0 mg/kg day 1,2 1x 3.0 mg/kg day 3	-12.4 ± 1.9**	+5.1 ± 3.0
Formula IA	2 weeks 1x 3.0 mg/kg/day	-18.6 ± 7.1*	-16.3 ± 3.7**
Donepezil	2 weeks 3.3 mg/kg/day	+9.6 ± 3.1*	-7.6 ± 7.1
Formula IA	4 weeks 2x 1.5 mg/kg/day	-17.2 ± 8.7°	-27.4 ± 27.2°

Data expressed as mean ± SEM except for °(two-sided confidence interval) ** $p < 0.01$
* $p < 0.05$

Claims

1. A method of lowering the levels of $A\beta_{40}$ and $A\beta_{42}$ peptides in a mammal comprising administering to said mammal in need of treatment an effective amount of a monoamine neurotransmitter re-uptake inhibitor comprising a 2,3-disubstituted tropane moiety optionally in the form of its physiologically acceptable acid addition salts.

2. A method according to claim 1, wherein said monoamine neurotransmitter re-uptake inhibitor is is a compound of formula (I1)



(I1)

wherein

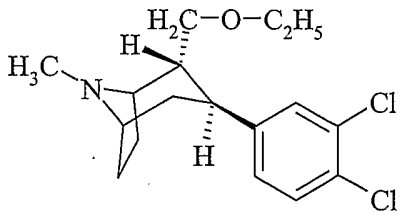
R^1 represents a hydrogen atom or a C_{1-6} alkyl group;

R^2 represents a halogen atom or a CF_3 or cyano group;

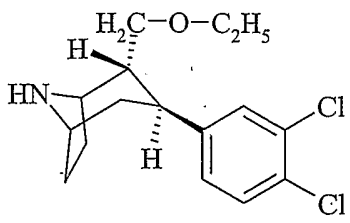
R^3 represents a hydrogen atom or a C_{1-6} alkyl or C_{3-6}-cycloalkyl-C_{1-3}-alkyl group; and

m is 0 or an integer from 1 to 3.

3. A method according to claim 1 or 2, wherein said monoamine neurotransmitter re-uptake inhibitor is the compound of formula (IA) or (IB)



(IA)



(IB)

4. A method according to any one of the preceding claims for the treatment or prophylaxis of diseases associated with the formation of diffuse and senile plaques.

5. A method according to any one of the preceding claims for the treatment or prophylaxis of diseases associated with the formation of $A\beta_{40}$- and $A\beta_{42}$- containing plaques.

6. A method according to any one of the preceding claims for the treatment or prophylaxis of amyloidosis associated with the formation of $A\beta_{40}$ and $A\beta_{42}$.

7. A method according to any one of the preceding claims for the treatment or prophylaxis of brain amyloidosis.

8. A method according to any one of the preceding claims for the treatment or prophylaxis of vascular amyloidosis and age related amyloidosis.

9. A method according to any one of the preceding claims for the prevention of the progression of Alzheimer disease in a patient suffering from said disease.

10. Use of a monoamine neurotransmitter re-uptake inhibitor comprising a 2,3-disubstituted tropane moiety or a physiologically acceptable acid addition salt thereof for the preparation of a medicament for the treatment or prevention of a disease or condition associated with an increased level of one or more isoforms of amyloid β peptides (Aβ) and/or with a changed ratio of levels of Aβ isoforms and/or with the formation of plaques containing one or more amyloid β peptide isoforms in a mammal.

DRAWINGS

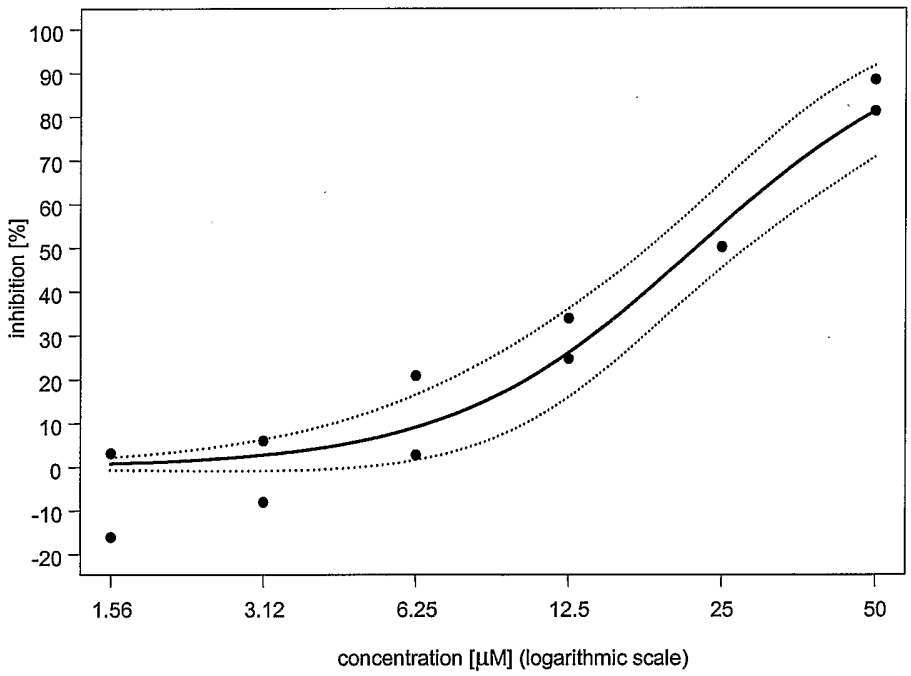


Fig. 1

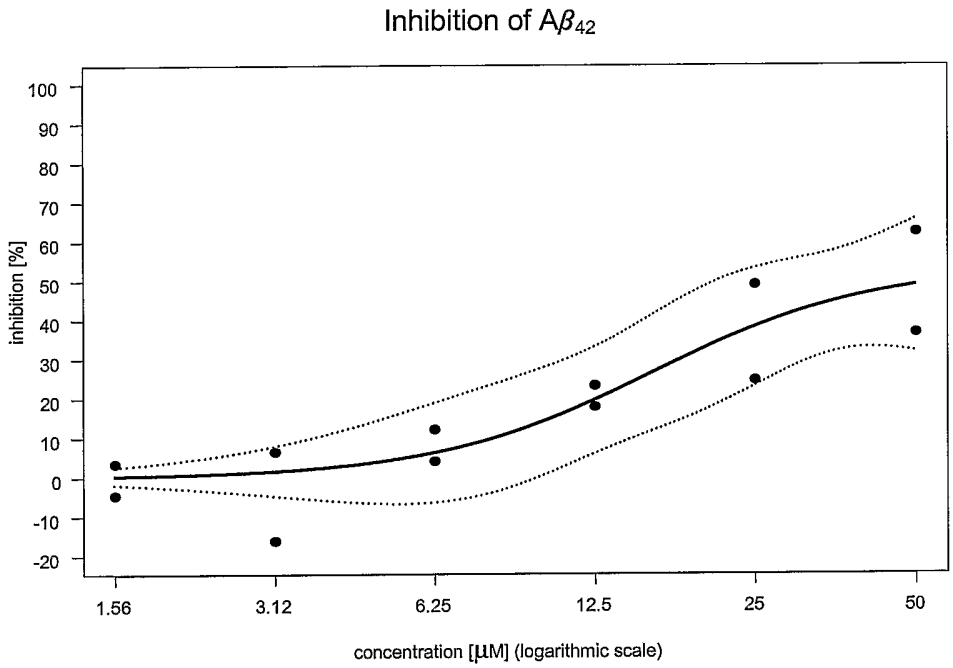

Inhibition of Aβ42
inhibition [%]
100
90
80
70
60
50
40
30
20
10
0
-10
-20
1.56
3.12
6.25
12.5
25
50
concentration [µM] (logarithmic scale)

Fig. 2

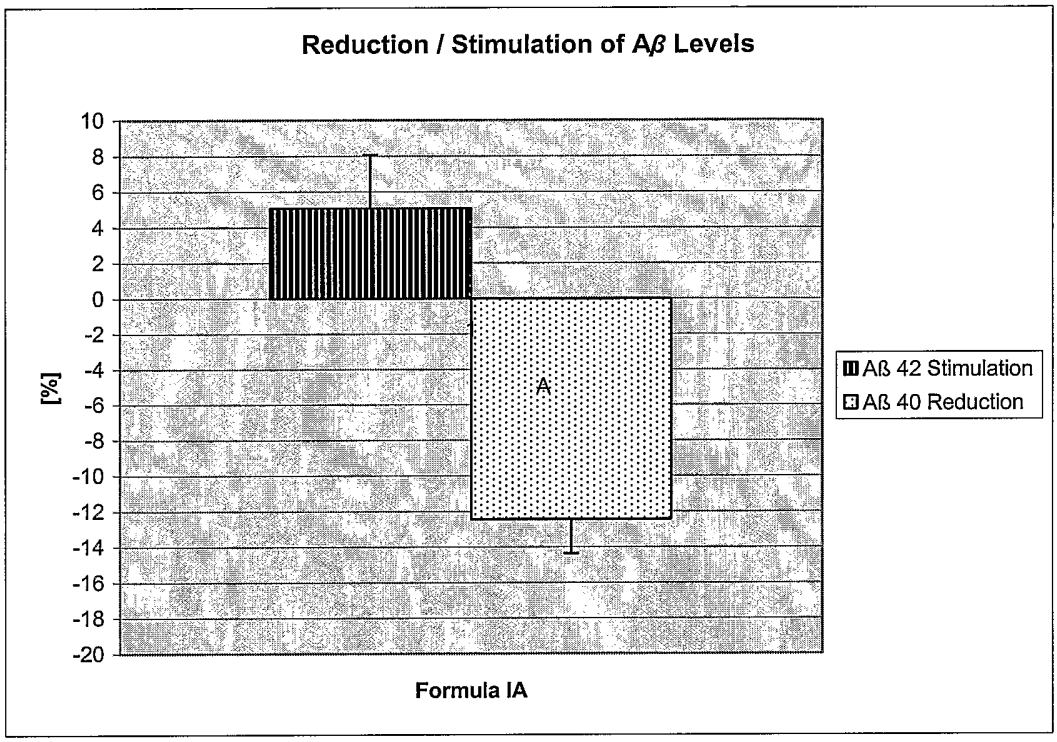

Reduction / Stimulation of Aβ Levels
10
8
6
4
2
0
-2
-4
-6
-8
-10
-12
-14
-16
-18
-20
[%]
A
Aß 42 Stimulation
Aß 40 Reduction
Formula IA

Fig. 3

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2005/005748

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/46 A61P25/00 A61P25/28

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, BIOSIS, EMBASE, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 2005/070429 A (BOEHRINGER INGELHEIM INTERNATIONAL GMBH; BOEHRINGER INGELHEIM PHARMA G) 4 August 2005 (2005-08-04) abstract page 2, line 16 - line 23 page 7, line 12 - page 11, line 20 page 15, line 1 - line 10; claims	1-10
E	WO 2005/070428 A (BOEHRINGER INGELHEIM INTERNATIONAL GMBH; BOEHRINGER INGELHEIM PHARMA G) 4 August 2005 (2005-08-04) abstract page 7, line 12 - page 11, line 20 page 15, line 17 - line 25; claims	1-10

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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

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

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

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 October 2005	02/11/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Hoff, P

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2005/005748

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2005/039580 A (BOEHRINGER INGELHEIM INTERNATIONAL GMBH; BOEHRINGER INGELHEIM PHARMA G) 6 May 2005 (2005-05-06) abstract page 2, line 21 - line 27 page 7, line 21 - page 12, line 3 page 15, line 12 - line 20; claims	1-10
P,X	WO 2004/072075 A (NIELSEN ELSEBET OESTERGAARD ; NEUROSEARCH AS (DK); OLSEN GUNNAR M (DK)) 26 August 2004 (2004-08-26) abstract page 10, line 5 - line 15; claims; examples	1,4-10
X	EP 1 130 020 A (NEUROSEARCH AS) 5 September 2001 (2001-09-05) abstract page 2, line 46 - line 52 claims 1-11; examples	1-10
X	WO 02/102801 A (GOULIAEV ALEX HAAHR ; DAHL BJARNE H (DK); NEUROSEARCH AS (DK); PETERS) 27 December 2002 (2002-12-27) abstract page 1, line 26 - page 2, line 9 page 9, line 33 - page 10, line 9; claims; examples	1-10
A	"THE MERCK MANUAL" 1999, MERCK RESEARCH LABORATORIES , XP002301210 page 1395, right-hand column, last paragraph - page 1398, right-hand column, last paragraph	1-10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2005/005748

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-9 are directed to a method of treatment of the human/animal body (Article 52(4) EPC), the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2005/005748

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005070429 A	04-08-2005	US 2005182089 A1	18-08-2005
WO 2005070428 A	04-08-2005	US 2005182090 A1	18-08-2005
WO 2005039580 A	06-05-2005	US 2005154009 A1	14-07-2005
WO 2004072075 A	26-08-2004	AU 2004212165 A1	26-08-2004
EP 1130020 A	05-09-2001	SI 885220 T1	31-12-2001
WO 02102801 A	27-12-2002	EP 1397358 A1	17-03-2004
		JP 2005508872 T	07-04-2005
		US 2004106643 A1	03-06-2004