Title: P38 and JNK MAPK INHIBITORS FOR THE TREATMENT AND PROPHYLAXIS OF DEGENERATIVE DISEASES OF THE NERVOUS SYSTEM

Abstract: The present invention provides new p38 and JNK mitogen activated protein (MAP) kinase allosteric inhibitors which are useful for the treatment and/or prophylaxis of degenerative diseases of the nervous system. The present invention thus provides compounds for use in a method for treatment and/or prophylaxis of said diseases as well as for use in therapy in general. The compounds bind to the region composed of amino acids at positions 170 - 199 of Mitogen-activated protein kinase 14 (Uniprot accession nr Q16539 or SEQ ID No 1) and/or Mitogen-activated protein kinase 11 (Uniprot accession nr Q15759 or SEQ ID No 2), SEQ ID NO.1 and SEQ ID NO.2 being the amino acid sequences of MAPK14 (p38α) and MAPK11 (p38β), respectively. The specific region composed of amino acids at positions 170 - 199 is herein disclosed as SEQ ID NO.4 for Mitogen-activated protein kinase 14 and SEQ ID NO.5 for Mitogen-activated protein kinase 11 and are believed to be new inhibitory binding sites.
p38 and JNK MAPK inhibitors for the treatment and prophylaxis of degenerative diseases of the nervous system

Field of the invention

The present invention provides new p38 and JNK mitogen activated protein kinase (MAPK) allosteric inhibitors which are useful for the treatment and prophylaxis of degenerative diseases of the nervous system. Examples of such diseases include Parkinson's disease, Alzheimer's disease, retinitis pigmentosa, age-related macular degeneration and dementia.

Background art

p38a MAP kinase (MAPK) is an intracellular serine/threonine kinase involved in the regulation of inflammatory cell signals and plays a central role in the regulation of pro-inflammatory cytokine production. Activation of p38a is produced by upstream kinases M KK6 and M KK3 . At molecular level, like other protein kinases, p38a is responsible for the transfer of the γ-phosphate form ATP to a range of substrate proteins including the transcription factors ATF2, Elk-1 and MEF2A and downstream kinases like MK2, MK3, PEAK, MNK1/2 and MSK1 , modulating their function (Stokoe et al., 1992, EMBO J. 11, 3985-3994).

p38α has been identified as a potential target for anti-inflammatory drugs, and different binding sites for these drugs have been identified (Akella et al., January 2008, Biochim Biophys Acta; 1784(1) : 48-55). Yong et al. review different p38 MAPK inhibitors which are under development as potential drugs for the treatment of inflammatory diseases and cancer (Yong et al., 2009, Expert Opin. Investig. Drugs; 18(12)) . The majority of the drug candidates have proved to be competitive with ATP, binding to the active site. A few inhibitors have also been found that bind to a site adjacent to the active site. Akella et al. discuss the
potential relevance of other binding sites such as the binding sites for D-motifs, FXFP and the Backside site.

Recently, evidences from both clinical studies and preclinical animal models have implicated overproduction of proinflammatory cytokines as a contributor to pathophysiology progression in chronic neurodegenerative disorders like Alzheimer's disease, Parkinson's disease and multiple sclerosis (e.g. A. D., Bachstetter et al., Ageing and Disease 2010, Vol. 1, No. 3, pp. 139-211). This indicates that p38 MAPK signalling pathways could be viable targets for modulating inflammatory responses in neurological diseases.

Other MAP kinase that is also an important pharmaceutical target in the treatment of degenerative diseases of nervous system is the JNK MAP kinase. JNK MAP kinase provides key signals in the brain for both neuronal apoptosis and amyloidigenic processing of APP, the two most important characteristics of Alzheimer's disease.

Despite several p38 MAPK inhibitors have been reported, they are currently no studies on use of p38 and JNK MAPK inhibitors for the treatment of degenerative diseases of nervous system or not even information available on whether any of such compounds are capable of passing through the blood-brain barrier.

Summary of the invention

Accordingly, the object underlying the present invention is to provide compounds, in particular, p38 and JNK MAPK inhibitors as well as compositions and formulations thereof that are useful for the treatment and/or prophylaxis of degenerative diseases of the nervous system. The term "degenerative diseases of the nervous system" as used herein refers to a group of disorders in which there is gradual, generally symmetric, relentlessly progressive wasting away of neurons. Typically, the degenerative diseases of the nervous system begin insidiously and run a gradually progressive course which may extend over many years. A common
feature of these diseases is a nearly selective involvement of anatomically or physiologically related systems of neurons.

A common way of classifying various degenerative diseases of nervous system is based on grouping them according to the clinical features that may be found in an actual case. Thus, one group of said diseases include syndromes in which progressive dementia is an outstanding feature in the absence of other prominent neurologic signs. This group of degenerative diseases comprises inter alia senile dementia and Alzheimer's disease which both involve diffuse cerebral atrophy. A further example of this group is the Pick's disease involving circumscribed cerebral atrophy.

A further important group of degenerative diseases of the nervous system are syndromes in which progressive dementia is combined with other neurologic signs. Examples of such disorders are, for instance, Huntington's chorea and cerebrocerebellar degenerations which occur principally in adults. A further subgroup of examples of said disorders occur both in children and adults and include inter alia amaurotic family idiocy (neuronal lipidoses), leukodystrophy, familial myoclonus epilepsy, Hallervorden–Spatz disease and Wilson's disease (hepatolenticular degeneration, Westphal-Strumpell pseudosclerosis).

A further important group of degenerative diseases of the nervous system are syndromes chiefly manifested by gradual development of abnormalities of posture of involuntary movements. This group of disorders includes paralysis agitans (Parkinson's disease), dystonia musculorum deformans (torsion dystonia), Hallervorden–Spatz disease and other restricted dyskinesias, familial tremor and spasmodic torticollis.

A further important group of degenerative diseases of the nervous system are syndromes chiefly manifested by slowly developing ataxia. These disorders include but are not limited to cerebellar degenerations and spinocerebellar degenerations (Friedrich's ataxia, Marie's hereditaxy ataxia) etc.
A further group of degenerative diseases of the nervous system includes syndromes with slowly developing muscular weakness and wasting. The corresponding disorders may proceed without sensory changes such as, for instance, amyotrophic lateral sclerosis (ALS), progressive muscular atrophy, cachexia, sarcopenia, progressive bulbar palsy, or primary lateral sclerosis in adults or disorders such as infantile muscular atrophy (Werdnig-Hoffmann disease), diverse forms of familial progressive muscular atrophy (including Wohlfart-Kugelberg-Welander syndrome) or hereditary spastic paraplegia in children or young adults. Said group of diseases further includes those with sensory changes such as progressive neural muscular atrophy, e.g. peroneal muscular atrophy (Charcot-Marie-Tooth) and hypertrophic interstitial neuropathy (Dejerine-Sottas) or miscellaneous forms of chronic progressive neuropathy.

Finally, a further group of degenerative diseases of the nervous system are syndromes chiefly manifested by progressive visual loss. These disorders include inter alia hereditary optic atrophy (Leber's disease), age-related macular degeneration and pigmentary degeneration of the retina (retinitis pigmentosa).

The present invention further provides compounds for use in a method for treatment and/or prophylaxis of degenerative diseases of the nervous system and associated diseases. Preferably, the compound of the present invention is capable of binding to the region composed of amino acids at positions 170 - 139 of Mitogen-activated protein kinase 14 (Uniprot accession nr Q16539 or SEQ ID No 1) and/or Mitogen-activated protein kinase 11 (Uniprot accession nr Q15759 or SEQ ID No 2), SEQ ID NO. 1 and SEQ ID NO. 2 being the amino acid sequences of MAPK14 (p38α) and MAPK11 (p38β), respectively. The specific region composed of amino acids at positions 170 - 199 is herein disclosed as SEQ ID NO. 4 for Mitogen-activated protein kinase 14 and SEQ ID NO. 5 for Mitogen-activated protein kinase 11 and are believed to be new inhibitory binding sites. Its three-dimensional structure is available from the Protein Data Bank (PDB entry 20ZA).
Importantly, the compounds of the present invention not only act as efficient p38 and JNK MAPK inhibitors but also possess excellent blood-brain barrier permeability. Accordingly, administration of compounds of the present invention to a patient leads to a considerable accumulation of said compounds in the brain and nervous system tissues of the patient. This enables interaction of said compounds with p38 and JNK MAPK in the corresponding tissues and allows an efficient treatment and/or prophylaxis of degenerative diseases of the nervous system.

In particular, the present invention provides compounds of the general Formula (I):

\[
\begin{align*}
\text{(I)} & \\
\end{align*}
\]

or a salt thereof, wherein

A is a polycyclic aromatic, heteroaromatic, alicyclic, heteroalicyclic substituent or is represented by the following structure:

\[
\begin{align*}
\end{align*}
\]

R\textsuperscript{1} is a hydrogen atom, a halogen atom or a C\textsubscript{1-6}-alkyl group optionally substituted with one or more halogen atoms,

R\textsuperscript{2} is a C\textsubscript{1-6}-aliphatic group optionally substituted with one or more halogen atoms,

X is represented by -O-, -S-, -S(0)-, -S(0)\textsubscript{2}-, -NH-, -C(0)-, or -CH\textsubscript{2}-,

Y\textsuperscript{1}, Z\textsuperscript{1}, Z\textsuperscript{2} and Z\textsuperscript{3} are independently represented by -CH- or -N-, and
Wis represented by -O-, -S-, -NH-, or -C(=O)-; and wherein the polycyclic aromatic, heteroaromatic, alicyclic, heteroalicyclic substituent can be optionally substituted by -W-R².

The present invention also provides methods of treatment and/or prophylaxis using the p38 and JNK MAPK inhibitors described herein for the treatment and/or prophylaxis of degenerative diseases of the nervous system.

In a further aspect, the present invention relates to a pharmaceutical composition comprising a therapeutically effective amount of the compound of the general Formula (I) or a salt thereof as active ingredient. The pharmaceutical composition of the present invention is preferably formulated as an oral dosage form to allow its convenient administration to the patient.

A further aspect of the present invention is the compound of the general Formula (I) for use in the treatment of a human or animal body, in particular for use in the treatment and/or prophylaxis of degenerative diseases of the nervous system. In other words, the present invention provides methods of treatment using the p38 and JNK MAPK inhibitors described herein for the treatment of a human or animal body, in particular a method for the treatment of degenerative diseases of nervous system.

Figures

Fig. 1; Alleviation of the pathology produced in rats by the acute intracerebrovesicular injection of an oligomeric Aβ2₅₋35 peptide preparation by the compound 1.

Fig. 2; Decrease of the Aβ1₋₄² level increase in rats as a consequence of administration of the compound 1.

Detailed description

The present invention provides compounds for use in therapy and/or prophylaxis of degenerative diseases of the nervous system, in
particular to p38 and JNK mediated neurodegenerative diseases. The compounds of the present invention are capable of passing the blood-brain barrier and bind to the region composed of amino acids at positions 170 - 199 of SEQ ID NO.1 and/or SEQ ID NO.2, SEQ ID NO.1 and SEQ ID NO.2 being the amino acid sequences of MAPK14 (p38α) and MAPK11 (p38β), respectively. The compounds of the present invention have preferably an inhibitory effect on the protein of SEQ ID NO.1 and/or SEQ ID NO.2, but not on the mutant R186A or R189A of the protein of SEQ ID NO.1 and/or SEQ ID NO.2.

One aspect of the present invention relates to the compound of general Formula (I)

\[ \text{R1 is a hydrogen atom, a halogen atom or a C}_{1-6}\text{-alkyl group optionally substituted with one or more halogen atoms} \]

\[ \text{R2 is a C}_{1-6}\text{-aliphatic group optionally substituted with one or more halogen atoms} \]

\[ \text{X is represented by } -\text{O}, -\text{S}, -\text{S}(\text{O})_2, -\text{NH}, -\text{C}(\text{O})_2, \text{ or } -\text{CH}_2^- \]
y, Z, Y, Z and Y are independently represented by -CH- or -N-, and
W is represented by -O-, -S-, -NH-, or -C(O)-; and
wherein the polycyclic aromatic, heteroaromatic, alicyclic, heteroalicyclic substituent can be optionally substituted by -W-R².

Preferably, polycyclic aromatic, heteroaromatic, alicyclic, heteroalicyclic substituents are fused bicyclic aromatic, heteroaromatic, alicyclic, heteroalicyclic substituents.

As used herein the term "polycyclic aromatic substituent" may refer to a group selected from naphthyl, anthracenyl, phenanthryl and tetrahydronaphthyl groups.

The term "polycyclic heteroaromatic substituent" may refer to a group selected from indanyl, indenyl, quinolyl, isoquinolyl, 1,2,3,4-tetrahydroquinolyl, 1,2,3,4-tetrahydroisoquinolyl, benzimidazolyl, benzofuryl, benzothienyl, dihydrobenzofuranyl, dihydrobenzothienyl and benzisoxazolyl.

According to the present invention, the term "polycyclic alicyclic substituent" may refer to a group such as norbornyl, 1-adamantyl, 2-adamantyl, isobornyl, or decahydroacenaphthyl.

Finally, the term "polycyclic heterocyclic substituent" may refer to decahydroquinolyl, decahydroisoquinolyl, octahydroquinolyl, octahydroisoquinolyl or quinuclidinyl groups.

In some preferred embodiment of the present invention, the substituent A is represented by one of the following structures:

![Substituent Structures]

In yet a further preferred embodiment, the compounds of the present invention are represented by the general Formula (II):

\[ \text{Formula (II)} \]
or a salt thereof, wherein
R₁ is a hydrogen atom, a halogen atom or a C₁₋₆-alkyl group
optionally substituted with one or more halogen atoms,
R² is a C₁₋₆-aliphatic group optionally substituted with one
or more halogen atoms,
X is represented by \(-\text{O} -, -\text{S} -, -\text{S}(\text{O})_2 -, -\text{S}(\text{O})_3 -, -\text{NH} -, -\text{C}(\text{O})_2 -, \)
or \(-\text{CH}_2 -\).
Y¹, Z¹, Y², Z² and Y³ are independently represented by \(-\text{CH} -\)
or \(-\text{N} -\), and
W is represented by \(-\text{O} -, -\text{S} -, -\text{NH} -, \) or \(-\text{C}(\text{O})_2 -\).

In the present application, the term "a halogen atom" may refer to
a fluorine atom, a chlorine atom, a bromine atom or an iodine
atom, a fluorine or a chlorine atom being particularly preferred.
In a particularly preferred embodiment the term "a halogen atom"
refers to a fluorine atom.

The term "aliphatic group" as used herein may refer to a straight
chain or branched alkyl group, a cycloalkyl group, an alkylcyclo-
alkyl group, a cycloalkylalkyl group, an alkenyl group, an alkynyl
group, an alkadienyl group or an alkynenyl group. The aliphatic
group may be saturated or contain one or several carbon-carbon
double and/or triple bonds. Accordingly, the term "C₁₋₆-aliphatic
group" encompasses \(\text{C}_n\)-alkyl groups, \(\text{C}_3₋₆\)-cycloalkyl groups,
\(\text{C}_4₋₆\)-alkylcycloalkyl groups, \(\text{C}_4₋₅\) cycloalkylalkyl groups,
\(\text{C}_2₋₆\)-alkenyl groups, \(\text{C}_2₋₆\)-alkynyl groups, \(\text{C}_4₋₆\)-alkadienyl groups
and \( \text{C}_4\text{-alkynenyl} \) groups. Preferably, the term "\( \text{C}_1\text{-g-aliphatic} \) group" refers to a \( \text{C}_1\text{-g-alkyl} \) group.

The term "alkyl group" refers to straight chain or branched alkyl group. Thus, the term "\( \text{C}_1\text{-g-alkyl} \) group" refers to straight chain or branched alkyl group having between 1 and 6 carbon atoms. Examples of \( \text{C}_1\text{-g-alkyl} \) groups include are not limited to methyl, ethyl, \( n\text{-propyl} \), \( i\text{-propyl} \), \( n\text{-butyl} \), \( i\text{-butyl} \), \text{tert.} \text{-butyl} \), \( n\text{-pentyl} \) and \( n\text{-hexyl} \) groups. In one preferred embodiment of the present invention, "\( \text{C}_1\text{-g-alkyl} \) group" is a straight chain or branched alkyl group having one to four carbon atoms. In a particularly preferred embodiment, the "\( \text{C}_1\text{-g-alkyl} \) group" is methyl, ethyl or \( n\text{-propyl} \).

The term "\( \text{C}_3\text{-g-cycloalkyl} \) group" may refer to cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. The term "\( \text{C}_4\text{-g-alkylcycloalkyl} \) group" may, for instance, refer to a cyclopropylmethyl, a \( 1\text{-cyclopropylethyl} \), a \( 2\text{-cyclopropylethyl} \) or to a cyclopentylmethylnethyl group. A "\( \text{C}_4\text{-g-eyeloalkylalkyl} \) group" in the general Formula (I) may be represented by inter alia methylcyclopropyl, methylcyclobutyl or methylcyclopentyl groups, which may be \( (E) \) - or \( (Z) \) - isomers.

The term "alkenyl group" refers to straight chain or branched aliphatic group comprising a carbon-carbon double bond. Thus, the term "\( \text{C}_2\text{-g-alkenyl} \) group" refers to straight chain or branched alkenyl group having between 2 and 6 carbon atoms. Examples of \( \text{C}_2\text{-g-alkenyl} \) groups include are not limited to vinyl, allyl, methallyl, \( 1\text{-propenyl} \) and \( 5\text{-hexenyl} \) groups. In one preferred embodiment of the present invention, "\( \text{C}_2\text{-g-alkenyl} \) group" is a vinyl or an allyl group.

The term "alkynyl group" refers to straight chain or branched aliphatic group comprising a carbon-carbon triple bond. Thus, the term "\( \text{C}_2\text{-g-alkynyl} \) group" refers to straight chain or branched alkynyl group having between 2 and 6 carbon atoms. Examples of
C\textsubscript{2}-g-alkynyl groups include are not limited to ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl and 1-hexynyl. In one preferred embodiment of the present invention, "C\textsubscript{2-6}-alkynyl group" is ethynyl, 1-propynyl or 2-propynyl group.

The term "alkadienyl group" refers to straight chain or branched aliphatic group comprising two carbon-carbon double bounds. Thus, the term "C\textsubscript{4-6}-alkadienyl group" refers to straight chain or branched alkadienyl group having between 4 and 6 carbon atoms. Examples of C\textsubscript{4-6}-alkadienyl groups include are not limited to 1,3-butadienyl, 1,3-pentadienyl or 2,4-pentadienyl.

The term "alkynenyl group" refers to straight chain or branched aliphatic group comprising two carbon-carbon double bounds. Thus, the term "C\textsubscript{4-6}-alkynenyl group" refers to straight chain or branched alkynenyl group having between 4 and 6 carbon atoms. Examples of C\textsubscript{4-6}-alkynenyl groups include are not limited to but-1-en-3-inyl, pent-1-en-3-inyl or hex-1-en-3-inyl.

The aliphatic group such as alkyl group, e.g. the C\textsubscript{1-6}-alkyl group may be optionally substituted with one or more halogen atoms. Thus, for instance, the corresponding substituent may be a perfluorated alkyl group such as, for instance, trifluoromethyl, pentafluoroethyl or n-heptafuoropropyl. In a particularly preferred embodiment of the present invention, the term "C\textsubscript{1-6}-aliphatic group optionally substituted with one or more halogen atoms" refers to a trifluoromethyl group.

In one preferred embodiment, the present invention provides the compound of general Formula (I) or a salt thereof wherein

\[ R^1 \text{ is a halogen atom, or a C\textsubscript{1-6}-alkyl group optionally substituted with one or more halogen atoms, } \]

\[ R^2 \text{ is a C\textsubscript{2-6}-alkyl group optionally substituted with one or more halogen atoms, } \]
\(Y^2, Z^1\) and \(Z^2\) are represented by \(-CH-\) and \(Y^2\) is represented by \(-N-\), and
\[W \text{ is represented by } -O-.\]

In a further preferred embodiment, the present invention provides the compound of general Formula (I) or a salt thereof, wherein
\[R^1 \text{ is a halogen atom, or a } C_{1-6}-\text{alkyl group optionally substituted with one or more halogen atoms,}\]
\[R^2 \text{ is a } C_{2-6}-\text{alkyl group optionally substituted with one or more halogen atoms,}\]
\(Y^2, Z^1\) and \(Y^2\) are represented by \(-CH-\) and \(Z^2\) is represented by \(-N-\), and
\[W \text{ is represented by } -O-.\]

In a further preferred embodiment, the compound of the present invention is represented by the general Formula (I) wherein
\[R^1 \text{ is a halogen atom, or a } C_{1-6}-\text{alkyl group optionally substituted with one or more halogen atoms,}\]
\[R^2 \text{ is a } C_{2-6}-\text{alkyl group optionally substituted with one or more halogen atoms,}\]
\[Y^1, Z^1, Y^2 \text{ and } Z^2\] are represented by \(-CH-\) and
\[W \text{ is represented by } -O-.\]

In yet a further preferred embodiment, the compound of the present invention is represented by the general Formula (I) wherein
\[R^1 \text{ is a chlorine atom, or a } C_{1-3}-\text{alkyl group optionally substituted with one or more halogen atoms,}\]
\[R^2 \text{ is a } C_{2-4}-\text{alkyl group optionally substituted with one or more halogen atoms,}\]
\[Y^3 \text{ is represented by } -CH-, \text{ and}\]
\[W \text{ is represented by } -O-.\]
In a particularly preferred embodiment, the compound of the present invention is represented by the general Formula (I) wherein

\[ R^1 \text{ is a fluorine atom, a chlorine atom, or a methyl group,} \]
\[ R^2 \text{ is an ethyl group or a } n\text{-propyl group,} \]
\[ X \text{ is represented by } -O-, -S-, \text{ or } -\text{NH}-, \]
\[ Y^1, Z^1, Y^2, Z^2 \text{ and } Y^3 \text{ are represented by } -\text{CH}-, \text{ and} \]
\[ W \text{ is represented by } -0-. \]

As will be appreciated by those skilled in the art, the structural moiety

![Structural Moiety](image)

in the general Formula (I) may have a 1,4-substitution pattern, a 1,3-substitution pattern or a 1,2-substitution pattern. In one embodiment of the present invention, said moiety has a 1,3-substitution pattern. Thus, the compound of the present invention is represented by the Formula (Ia):

![Formula (Ia)](image)

In yet another embodiment of the present invention, the corresponding structural moiety has a 1,4-substitution pattern. Thus, the compound of the present invention is represented by the Formula (Ib):

![Formula (Ib)](image)
In a particularly preferred embodiment of the present invention, the structural fragment

\[
\begin{array}{c}
\text{Formula (Ib)}
\end{array}
\]

in the general Formula (I) may be selected from the group comprising the following substituents;
Preferably, the structural moiety

\[
\begin{align*}
  & \text{Preferably, the structural moiety in the general Formula (1) is represented by a structure selected from the group comprising the following structural elements:} \\
  & \text{Examples of particularly preferred compounds of the present invention include but are not limited to the following compounds:}
\end{align*}
\]

(1) and (2)
A further aspect of the present invention relates to use of the compounds of Formula (I) for therapy and/or prophylaxis of degenerative diseases of nervous system. The corresponding degenerative diseases of nervous system may be selected from the group consisting of senile dementia, Alzheimer's disease, Pick's disease, Huntington's chorea, cerebrocerebellar degeneration, amaurotic family idiocy (neuronal lipidoses), leukodystrophy, familial myoclonus epilepsy, and Wilson's disease (hepatolenticular degeneration, Westphal-Strumpell pseudosclerosis),

In a further embodiment, the degenerative diseases of the nervous system may be selected from the group consisting of paralysis agitans (Parkinson's disease), dystonia musculorum deformans (torsion dystonia), Hallervorden-Spatz disease and other restricted dyskinesias, familial tremor and spasmodic torticollis,
cerebellar degenerations and spinocerebellar degenerations
(Friedreich's ataxia, Marie's hereditary ataxia), amyotrophic lateral sclerosis, progressive muscular atrophy, progressive bulbar palsy, primary lateral sclerosis, infantile muscular atrophy (Werdnig-Hofmann disease), other forms of familial progressive muscular atrophy (including Wohlfart-Kugelberg-Welander syndrome), cachexia and sarcopenia, hereditary spastic paraplegia, progressive neural muscular atrophy, peroneal muscular atrophy (Charcot-Marie-Tooth), hypertrophic interstitial neuropathy (Dejerine-Sottas), miscellaneous forms of chronic progressive neuropathy, hereditary optic atrophy (Leber's disease), age-related macular degeneration and pigmented degeneration of the retina (retinitis pigmentosa).

Yet, in a further embodiment the degenerative diseases of the nervous system are selected from the group consisting of depression and schizophrenia.

In a particularly preferred embodiment of the present invention, the compounds of the general Formula (I) are used in the treatment and/or prophylaxis of Alzheimer's disease.

The compounds of Formula (I) can be prepared essentially as described by Fernandez et al., 2002, Tetrahedron Letters 43, 4741-4745; Starchenkov et al., Chemistry of Heterocyclic Compounds 1997, 33(19), 1219-1233; and Khim. Geterotskil. Soedin., 1997, 1402-1416.

The compounds of the invention include pharmaceutically acceptable salts, amides, and prodrugs therof, including but not limited to carboxylate salts, amino acid addition salts, amides, and prodrugs of the compounds of the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of patients without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well
as the zwitterionic forms, where possible, of the compounds of the invention.

The term "salts" refers to the relatively non-toxic, inorganic and organic acid addition salts of compounds of the present invention. These salts can be prepared in situ during the final isolation and purification of the compounds or by separately reacting the purified compound in its free base form with a suitable organic or inorganic acid and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, nitrate, acetate, oxalate, valerate, olate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate mesylate, glucoheptonate, lactobsonate, and laurylsulphonate salts, and the like. These may include cations based on the alkali and alkaline earth metals, such as sodium, lithium, potassium, calcium, magnesium, and the like, as well as non-toxic ammonium, quaternary ammonium, and amine cations including, but not limited to ammonium, tetramethyl ammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like. (See, for example, Berge S.M, et al., "Pharmaceutical Salts," J. Pharm. Sci., 1977;66:1-19 which is incorporated herein by reference.)

A further aspect of the present invention includes pharmaceutical compositions comprising a therapeutically effective amount of one or more compounds of the invention disclosed above, associated with a pharmaceutically acceptable carrier. For administration, the compounds are ordinarily combined with one or more adjuvants appropriate for the indicated route of administration. The compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanolic acids, stearic acid, talc, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, acacia, gelatin, sodium alginate, polyvinyl pyrrolidone, and/or polyvinyl alcohol, and tableted or encapsulated for conventional administration. Alternatively, the compounds of this invention may be dissolved in saline, water,
polyethylene glycol, propylene glycol, carboxymethyl cellulose colloidal solutions, ethanol, corn oil, peanut oil, cottonseed oil, sesame oil, tragacanth gum, and/or various buffers. Other adjuvants and modes of administration are well known in the pharmaceutical art. The carrier or diluent may include time delay material, such as glyceryl monostearate or glyceryl distearate alone or with a wax, or other materials well known in the art.

Examples of pharmaceutically acceptable, non-toxic amides of the compounds of this invention include amides derived from secondary amines. Amides of the compounds of the invention may be prepared according to conventional methods.

The term "prodrug" refers to compounds that are rapidly transformed in vivo to yield the parent compound of the above formulae, for example, by hydrolysis in blood. A thorough discussion of prodrugs is provided in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are hereby incorporated, by reference.

The compounds of the present invention can be administered individually or in combination, usually in the form of a pharmaceutical composition. Such compositions are prepared in a manner well known in the pharmaceutical art and comprise at least one active compound.

Accordingly, a further aspect of the present invention includes pharmaceutical compositions comprising as one or more compounds of the invention disclosed above, associated with a pharmaceutically acceptable carrier. For administration, the compounds are ordinarily combined with one or more adjuvants appropriate for the indicated route of administration. The compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanolic
acids, stearic acid, talc, magnesium stearate, magnesium oxide, sodium alginate, polyvinylpyrrolidine, and/or polyvinyl alcohol, and tableted or encapsulated for conventional administration. Alternatively, the compounds of this invention may be dissolved in saline, water, polyethylene glycol, propylene glycol, carboxymethyl cellulose colloidal solutions, ethanol, corn oil, peanut oil, cottonseed oil, sesame oil, tragacanth gum, and/or various buffers. Other adjuvants and modes of administration are well known in the pharmaceutical art. The carrier or diluent may include time delay material, such as glyceryl monostearate or glyceryl distearate alone or with a wax, or other materials well known in the art.

Preferred embodiments of the present invention include the following (1) to (15):

(1) A compound of general Formula (II)

\[
\begin{align*}
\text{II} & \quad \text{or a salt thereof, whereby} \\
R^1 & \text{is a hydrogeon atom, a halogen atom or a C}_{1-6}\text{-alkyl group} \\
& \text{optionally substituted with one or more halogen atoms,} \\
R^2 & \text{is a C}_{1-6}\text{-aliphatic group optionally substituted with one} \\
& \text{or more halogen atoms,} \\
X & \text{is represented by } -O-, -S-, -S\{0\}_-, -S\{0\}_2-, \text{--NH--, } --\text{C}(0)-, \\
& \text{or } -\text{CH}_2-, \\
\end{align*}
\]
\( Y^1, Z^1, Y^2, Z^2 \) and \( Y^3 \) are independently represented by \(- \text{CH}\)- or \(- \text{N}\)-, and

\( W \) is represented by \(- \text{O}\)-, \(- \text{S}\)-, \(- \text{NH}\)-, or \(- \text{C}(\text{O})\)-.

(2) The compound of general Formula (II) according to (1) or a salt thereof, whereby

\( R^1 \) is a halogen atom, or a \( \text{C}^{\text{g}}\)-alkyl group optionally substituted with one or more halogen atoms,

\( R^2 \) is a \( \text{C}_{2-6}\)-alkyl group optionally substituted with one or more halogen atoms,

\( Y^2, Z^1 \) and \( Z^2 \) are represented by \(- \text{CH}\)- and \( Y^2 \) is represented by \(- \text{N}\)-, and

\( W \) is represented by \(- \text{O}\)-.

(3) The compound of general Formula (II) according to (1) or a salt thereof, whereby

\( R^1 \) is a halogen atom, or a \( \text{C}^{\text{1-6}}\)-alkyl group optionally substituted with one or more halogen atoms,

\( R^2 \) is a \( \text{C}_{2-6}\)-alkyl group optionally substituted with one or more halogen atoms,

\( Y^2, Z^1 \) and \( Y^2 \) are represented by \(- \text{CH}\)- and \( Z^2 \) is represented by \(- \text{N}\)-, and

\( W \) is represented by \(- \text{O}\)-.

(4) The compound of general Formula (II) according to (1) or a salt thereof, whereby

\( R^1 \) is a halogen atom, or a \( \text{C}^{\text{1-6}}\)-alkyl group optionally substituted with one or more halogen atoms,

\( R^2 \) is a \( \text{C}_{2-6}\)-alkyl group optionally substituted with one or more halogen atoms,

\( Y^1, Z^1, Y^2 \) are represented by \(- \text{CH}\)-, and

\( W \) is represented by \(- \text{O}\)-.
(5) The compound of general Formula (II) or a salt thereof according to any of (1) to (4), whereby

\[ R^1 \] is a chlorine atom, or a C\textsubscript{1-3}-alkyl group optionally substituted with one or more halogen atoms,

\[ R^2 \] is a C\textsubscript{2-4}-alkyl group optionally substituted with one or more halogen atoms,

\[ Y^3 \] is represented by \(-\text{CH}-\), and

\[ W \] is represented by \(-\text{O}-\).

(6) The compound of general Formula (II) or a salt thereof according to any of (1) to (5), whereby

the compound is represented by the Formula (IIa):

![Chemical Structure](image)

(IIa)

(7) The compound of general Formula (II) or a salt thereof according to any of (1) to (5), whereby the compound is represented by the Formula (lib):

![Chemical Structure](image)
(8) The compound of general Formula (II) or a salt thereof according to (6) or (7), whereby
\[ R^1 \] is a fluorine atom, a chlorine atom, or a methyl group,
\[ R^2 \] is an ethyl group or an \( n \)-propyl group,
\[ X \] is represented by \(-O-, -S-, \) or \(-CH_2-\),
\[ Y^1, Z^1, Y^2, Z^2 \] and \( Y^3 \) are represented by \(-CH-, \) and
\[ W \] is represented by \(-O-\).

(9) The compound of general Formula (II) according to any of (1)
to (8) or a salt thereof for use in the treatment of a human or
animal body.

(10) The compound of general Formula (II) according to any of (1)
to (8) or a salt thereof for use in the treatment or prophylaxis
of a degenerative disease of the nervous system.

(11) The compound of general Formula (II) according to any of (1)
to (8) or a salt thereof for use according to (10), whereby the
degenerative disease of the nervous system is selected from the
group consisting of senile dementia, Alzheimer's disease, Pick's
disease, Huntington's chorea, cerebrocerebel lar degeneration,
amaurotic family idiocy (neuronal lipidoses), leukodystrophy,
familial myoclonus epilepsy, and Wilson's disease.
(hepatolenticular degeneration, Westphal–Strumpell pseudosclerosis).

(12) The compound of general Formula (II) according to any of (1) to (8) or a salt thereof for use according to (10), whereby the degenerative disease of the nervous system is selected from the group consisting of paralysis agitans (Parkinson's disease), dystonia musculorum deformans (torsion dystonia), Hallervorden–Spatz disease and other restricted dyskinesias, familial tremor and spasmodic torticollis, cerebellar degenerations and spinocerebellar degenerations (Friedreich's ataxia, Marie's hereditary ataxia), amyotrophic lateral sclerosis, progressive muscular atrophy, cachexia and sarcopenia, progressive bulbar palsy, primary lateral sclerosis, infantile muscular atrophy (Werdnig–Hoffmann disease), other forms of familial progressive muscular atrophy (including Wohlfart-Kugelberg-Welander syndrome), hereditary spastic paraplegia, progressive neural muscular atrophy, peroneal muscular atrophy (Charcot–Marie-Tooth), hypertrophic interstitial neuropathy (Dejerine–Sottas), miscellaneous forms of chronic progressive neuropathy, hereditary optic atrophy (Leber's disease), age-related macular degeneration and pigmentary degeneration of the retina (retinitis pigmentosa),

(13) The compound of general Formula (II) according to any of (1) to (8) or a salt thereof for use according to (10), whereby the degenerative disease of the nervous system is selected from the group consisting of depression and schizophrenia.

(14) A pharmaceutical composition comprising a therapeutically effective amount of the compound of general Formula (II) according to any of (1) to (8) or of a salt thereof as active ingredient.

(15) The pharmaceutical composition according to (14), whereby said pharmaceutical composition is an oral dosage form.

The following examples are intended for the sole purpose of
Illustrating the present invention.

Examples

Example 1: Binding assay

1.1. Materials and Methods

p38

To examine the inhibition of the compounds 1 to 12, in vitro kinase assays were performed. Purified recombinant activated p38alpha (10 nM) (ProQinase) was preincubated 10 minutes at 30°C with the compound of interest at concentrations between 1 and 100 µM in duplicate in a final volume of 30 µl of kinase buffer (Hepes 60 mM pH 7.5, MgCl2 3 mM, MnCl2 3 mM, sodium orthovanadate 3 µM, DTT 1.2 mM). After preincubation, peptide substrate (SignalChem #PQ3-58) and ATP were added to a final concentration of 10 µM and 100 µM respectively, and then incubated 40 minutes at 30°C for the kinase reaction. Phosphorylation was analysed with ADP-Glo™ (Promega #V9101) and emitted luminescence was measured with BMG Fluostar microplate reader.

JNK

To examine the inhibition of the compounds 1 to 12, in vitro kinase assays were performed. Purified recombinant activated JNK (10 nM) (ProQinase) was preincubated 10 minutes at 30°C with the compound of interest at concentrations between 1 and 100 µM in duplicate in a final volume of 30 µl of kinase buffer (Hepes 60 mM pH 7.5, MgCl2 3 mM, MnCl2 3 mM, sodium orthovanadate 3 µM, DTT 1.2 mM). After preincubation, peptide substrate (SignalChem #P03-58) and ATP were added to a final concentration of 10 µM and 100 µM respectively, and then incubated 40 minutes at 30°C for the kinase reaction. Phosphorylation was analyzed with ADP-Glo™ (Promega #V9101) and emitted luminescence was measured with BMG Fluostar microplate reader.

Thpl - inhibition of TNF-α Secretion by a Human Monocytic Cell Line, THP-1
THP-1 cells, growing in log phase, were collected by centrifugation and resuspended in RPMI 1640 (Sigma Aldrich), to a final cell concentration of 2 x 10^6 cells/ml. Cells were plated into 24-well plates (BD Biosciences). Dilutions of compounds in dimethyl sulfoxide (DMSO) were added to the culture to a final concentration M. The final DMSO concentration was 0.5%. The cells ranging from 0.1 to 50 suspensions were preincubated with compounds for 1 h at 37°C in a 5% CO_2 humidified atmosphere before the addition of LPS (Sigma Aldrich, L2654) to a g/ml. After that, cells were incubated for 3 h followed final concentration of 2 °C by centrifugation to pellet cells. Cell supernatants were stored at 4 °C until human analysis for TNF-cy content. TNF-a levels were determined by ELISA (TNF Biotrak, GE Healthcare) following the manufacturer’s directions. The percentage inhibition was calculated for each compound concentration tested, and the IC_{50} was calculated for each compound.

p38/JHK INHIBITORS PROTECT FROM ACTIVATED THP-1 TOXIC SUPERNATANT IN SH-SY5Y CELLS

SH-SY5Y cell line was expanded and maintained in DMEM with 10% FBS, 2 mM glutamine and antibiotics. Cells were differentiated as previously published (Gimenez-Cassina et al. J. Neurosci. Res; 2006). Briefly, 7 x 10^3 cells/cm^2 were seeded onto Matrigel Basement-coated culture 24-well plates and allowed to attach overnight. Cell were then exposed to 10μM retinoic acid for 5 days. Subsequently, the cells were cultured in Neurobasal medium, with B27, 2 mM GlutamaxI, 2 mM dbAMPc, 20 mM KCl, 50 ng/ml hBDNF and antibiotics for an additional 5 days.

In parallel, human monocytic THP-1 cells were seeded in 24-well plates (2 x 10^6 cells/ml) in Neurobasal medium without serum and incubated for 24 h in the presence or absence of stimulants LPS (1 μg/ml) and IFNα (333 U/ml). After incubation, cultures were centrifuged and supernatants were transferred to differentiated SH-SY5Y cells. The cells were then incubated for an additional
72 h in the presence or absence of inhibitors. After treatment, viability of cells was evaluated by Cell Titer Glo kit (Promega) and luminiscence was measured with a BMG Fluostar microplate reader. Supernatant from nonstimulated THP-1 cells was used as high control.

1.2. Results
The assays were carried out at 10 µM and at 1 µM. The collected results are summarized in Tables 1 and 2 below.
<table>
<thead>
<tr>
<th></th>
<th>Comp 1</th>
<th>Comp 2</th>
<th>Comp 3</th>
<th>Comp 4</th>
<th>Comp 5</th>
<th>Comp 6</th>
<th>Comp 7</th>
<th>Comp 8</th>
<th>Comp 9</th>
<th>Comp 10</th>
<th>Comp 11</th>
<th>Comp 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>JNK</td>
<td>98%</td>
<td>91%</td>
<td>96%</td>
<td>74%</td>
<td>97%</td>
<td>91%</td>
<td>101%</td>
<td>55%</td>
<td>51%</td>
<td>50%</td>
<td>74%</td>
<td>90%</td>
</tr>
<tr>
<td>THP1</td>
<td>74%</td>
<td>69%</td>
<td>58%</td>
<td>41%</td>
<td>65%</td>
<td>39%</td>
<td>33%</td>
<td>37%</td>
<td>39%</td>
<td>31%</td>
<td>50%</td>
<td>51%</td>
</tr>
<tr>
<td>Neurons</td>
<td>51%</td>
<td>32%</td>
<td>42%</td>
<td>22%</td>
<td>55%</td>
<td>37%</td>
<td>38%</td>
<td>26%</td>
<td>43%</td>
<td>47%</td>
<td>42%</td>
<td>35%</td>
</tr>
</tbody>
</table>

Table 1. % of inhibition at 10 µM (for neurons is % of rescue)

<table>
<thead>
<tr>
<th></th>
<th>Comp 1</th>
<th>Comp 2</th>
<th>Comp 3</th>
<th>Comp 4</th>
<th>Comp 5</th>
<th>Comp 6</th>
<th>Comp 7</th>
<th>Comp 8</th>
<th>Comp 9</th>
<th>Comp 10</th>
<th>Comp 11</th>
<th>Comp 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>JNK</td>
<td>37%</td>
<td>41%</td>
<td>23%</td>
<td>25%</td>
<td>41%</td>
<td>32%</td>
<td>19%</td>
<td>16%</td>
<td>23%</td>
<td>25%</td>
<td>21%</td>
<td>15%</td>
</tr>
<tr>
<td>THP1</td>
<td>49%</td>
<td>36%</td>
<td>31%</td>
<td>31%</td>
<td>37%</td>
<td>35%</td>
<td>34%</td>
<td>32%</td>
<td>26%</td>
<td>30%</td>
<td>24%</td>
<td>24%</td>
</tr>
<tr>
<td>Neurons</td>
<td>51%</td>
<td>42%</td>
<td>37%</td>
<td>19%</td>
<td>44%</td>
<td>28%</td>
<td>21%</td>
<td>17%</td>
<td>27%</td>
<td>19%</td>
<td>30%</td>
<td>45%</td>
</tr>
<tr>
<td>Neurons</td>
<td>33%</td>
<td>25%</td>
<td>21%</td>
<td>11%</td>
<td>32%</td>
<td>22%</td>
<td>18%</td>
<td>12%</td>
<td>33%</td>
<td>33%</td>
<td>41%</td>
<td>36%</td>
</tr>
</tbody>
</table>

Table 2. % of inhibition at 1 µM (for neurons is % of rescue)
Thus, all tested compounds 1 to 12 acted as efficient inhibitors of p38 and JNK MAP kinases.

Example 2  Single dose intraperitoneal and intravenous blood brain barrier permeability study in male Sprague Dawley rat

The objective of these tests was to determine the plasma and brain concentration of the compound 1 in male Sprague Dawley rat after single intraperitoneal (i.p.) and intravenous (i.v.) administration.

2.1 Experimental Procedure

The design of the experiments is summarised in Table 3 below:

<table>
<thead>
<tr>
<th>Group</th>
<th>Test compound</th>
<th>Dose (mg/kg)</th>
<th>Dose Volume (mL/Kg)</th>
<th>Dose conc. (mg/mL)</th>
<th>Route</th>
<th>Number of animals</th>
<th>Sample collection time points (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>10</td>
<td>2</td>
<td>5</td>
<td>i.p.</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>10</td>
<td>2</td>
<td>5</td>
<td>i.v.</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 3. Design of the experiments

2.2. Test compound Administration

The compound 1 was administered intravenously (i.v.) through tail vein and intraperitoneally (i.p.) in abdominal cavity. After dosing of each animal, the time was documented. All animals were observed for any abnormal behavioural signs exhibited after drug administration throughout the study duration.

Formulation details
Weight of the compound 1: 30.14 mg
Formulation vehicle: 20 Vol.-% Cremophore, 10 Vol.-% ethanol, 70 Vol.-% normal saline
Volume of formulation vehicle: 6.028 ml
2.3. Bioanalysis Study Design

Bioanalysis was performed using fit-for-purpose LC-MS/MS method for the quantification of test compounds in plasma samples and brain homogenate. The method was validated for calibration curve consisted of nine non-zero calibration standards along with a double blank and zero standard samples. Study samples were analysed along with two sets of quality control samples (6 QC samples: low, medium and high QC sample).

2.4. Sample Collection Details—Blood

Anticoagulant: Lithium Heparin tubes
Collection Site: Blood: Cannulated Jugular vein
Sample Size: Approximately 0.25-0.30 ml blood
Sample Process: Blood samples were placed on ice prior to centrifugation and centrifuged within 15 min at 5000 rpm for 10 min at 4 °C
Sample Storage: CondPlasma samples promptly stored at -80±10 °C until bioanalysis

2.5. Sample Collection Details—Brain

Process of Sample Collection
Immediately after blood withdrawal, in situ brain perfusion was performed using chilled saline. The chest of the rat was exposed, the abdominal aorta was clamped and both jugular veins were cut. Intra-cardial perfusion was performed through an insertion in the left ventricle. Perfusion of each rat was followed by exanguination for brain collection. The skin over the cranium was incised and deflected. The head was flexed and a cut was made through the muscles and the spinal cord at the junction of the foreman magnum and atlas vertebra. A circumferential incision was carefully made in the cranium using a bone cutter. The roof of the cranium was lifted off to expose the meninges and brain. The meninges were removed carefully. Then holding the head with the nose pointing upward, the anterior part of the brain was lifted to
separate the brain. Separated brain was immediately weighed and frozen at -80 ± 10 °C until homogenization.

**Sample Storage Condition**

Brain samples were promptly stored at -80±10 °C until bioanalysis.

**Brain Homogenization**

Brain samples were thawed on ice. An appropriate volume of ice cold homogenizing media (Normal Saline) was added. Brain samples were homogenized on ice with the Polytron® homogenizer and volume was adjusted with homogenizing media to achieve 1 g of brain per 5 ml of homogenate. After homogenization, the brain homogenate were immediately frozen at -80 °C until analysis.

**2.6 Results**

The results of the analysis are summarised in Tables 4 and 5 below:

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>Mean</th>
<th>Std Dev</th>
<th>% CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma (ng/mL)</td>
<td>162.96</td>
<td>293.38</td>
<td>156.26</td>
<td>204.20</td>
<td>77.30</td>
<td>37.86</td>
</tr>
<tr>
<td>Brain Homogenate (ng/g)</td>
<td>322.70</td>
<td>394.80</td>
<td>439.45</td>
<td>385.65</td>
<td>58.91</td>
<td>15.28</td>
</tr>
</tbody>
</table>

Table 4. Concentration in rat plasma and brain homogenate i.v. at 2 h

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>Mean</th>
<th>Std Dev</th>
<th>% CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma (ng/mL)</td>
<td>123.03</td>
<td>63.64</td>
<td>87.75</td>
<td>91.47</td>
<td>29.87</td>
<td>32.65</td>
</tr>
<tr>
<td>Brain Homogenate (ng/g)</td>
<td>49.10</td>
<td>31.30</td>
<td>44.55</td>
<td>41.65</td>
<td>9.25</td>
<td>22.20</td>
</tr>
</tbody>
</table>

Table 5. Concentration in rat plasma and brain homogenate i.p. at 2 h

Thus, the above results illustrate that the compound 1 has an excellent blood-brain permeability. Accordingly, this compound as well as other structurally related compounds of the present invention are capable of reaching p38α and JNK MAP kinases located in the brain and in nervous tissues.
Example 3: Analysis of the protective properties of a test compound 1 against \( \alpha\beta_{25-35} \) amyloid peptide-induced toxicity in vivo in rats

The purpose of the study was to determine whether the test compound 1 can alleviate the pathology produced in rats by the acute intracerebroventricular (i.c.v) injection of an oligomeric \( \alpha \beta_{25-35} \) peptide preparation.

The compound efficacy was evaluated 7 days after the peptide administration, on:
- the attenuation of the \( \alpha\beta_{25-35} \)-induced learning deficits (recognition long-term memory: novel object recognition);
- the attenuation of the \( \alpha\beta_{25-35} \)-induced \( \alpha\beta_{1-42} \) accumulation in the rat hippocampus.

One administration procedure was examined: the compound 1 (10 mg/kg) administered intraveinously (i.v.) once a day during 9 days.

3.2 Protocols and Materials

Animals and treatment groups.
36 male Sprague Dawley RjHan:SD rats (230-260 g) were used, 3 animal groups with \( n = 12 \) per group were constituted in the following manner:

<table>
<thead>
<tr>
<th>Group Description</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Sc.\alpha\beta + vehicle (i.v.)</td>
<td>12</td>
</tr>
<tr>
<td>2. \alpha\beta_{25-35} + vehicle (i.v.)</td>
<td>12</td>
</tr>
<tr>
<td>3. \alpha\beta_{25-35} + compound 1 (10 mg/kg i.v.)</td>
<td>12</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>36</strong></td>
</tr>
</tbody>
</table>

On day 0, \( \alpha\beta_{25-35} \) (oligomeric, 9 nmol) or scrambled \( \alpha\beta_{25-35} \) peptide control (Sc.\alpha\beta, 9 nmol) was administered i.c.v, at 03:00 am.
Compound 1 or vehicle, was administered i.v. once-a-day between day 0 and day 9, at 09:30 am.

On day 8 and 9, the recognition long-term memory of the animals was assessed using the novel object recognition (NOR) procedure. Habituation (session without object) was performed on day 7.

On day 10, all animals were sacrificed, the frontal cortex and hippocampi dissected out. One hippocampus was used for the ELISA analyses of Aβ1-42 content.

Formulations
All solutions were freshly prepared before each administration. The vehicle was Ethanol 5% (Fiuka), Cremophor <ref C-5135, Batch 32H0925, Sigma-Aldrich) 20% in physiological saline and administered in 2.5 mg/ml. Treatment groups were prepared as follows:
Group 1, 2: vehicle solution (distilled water)
Group 3: compound 1 at 2.5 mg/ml.

Amyloid-β peptides
Aβ25-35
- Denomination: amyloid-β protein (25-35), human, mouse, rat
- CAS: 131602-53-4
- Supplier: Polypeptides (France)
- Reference: SC489
- Batch: AW13285A
- Molecular Weight: 1060.28
- Storage Temp: -20 °C
- Appearance: white powder

ScaAβ:
- Denomination: scrambled amyloid-β protein (25-35), human, mouse, rat
Peptides preparation and injection
Rats received a bilateral i.e.v. injection of Aβ25-35 peptide (2 x 5 nmol/side), or Sc Aβ peptide (2 x 5 nmol/side), using the stereotaxic method. Animals were anesthetized with an intramuscular injection of 0.2 ml of a mixture of ketamxne hydrochloride (80 mg/kg b.w.) and xylazine (10 mg/kg b.w.). They were then fixed on a stereotaxic frame (David KoPf), their skull exposed, cleaned with H₂O₂ and holes drilled at the stereotaxic coordinates AP: −1 mm and L: ±1.5 mm. They were then bilaterally injected (2 x 5 µl) into the lateral ventricles at V: −3.5 mm. The skin was then sutured and cleaned with betadine 10% solution (Asta Medica).

The homogeneous oligomeric preparation of the Aβ25-35 peptide was performed according to the AMYLGEN's owned procedure.

Administration of the test compound and/or the vehicle solution
- Route: i.v., into the tail vein
- Frequency: once daily at 10:00 am.
- Treatment length: 9 days, from day 0 (immediately after the peptide injection) to day 8 (2 h before the NOR session 2).

Animals
Male Sprague Dawley rats, weighing 230-260 g, from Janvier (Saint Berthevin, France), were kept for housing and experiments took place within the animal facility building of the University of Montpellier 2 (CECEMA, Office of Veterinary Services agreement #
Animals were housed in groups of 3 individuals with access to food and water ad libitum, except during behavioural experiments. They were kept in a temperature and humidity controlled animal facility on a 12 h/12 h light/dark cycle (lights off at 07:00 pm). Rats were numbered by marking their tails using permanent markers. All animal procedures were conducted in strict adherence to the EU Directive 86/609, modified by the decrees 87-848 and 2001-464.

Randomization of the treatments and animals
Animal treatments were randomized. All drug injections were performed once-a-day by a personnel not involved in the behavioural experiments.

Mortality
Acute or delayed mortality was checked every day. One animal deceased after the stereotaxic surgery. No animal deceased during the i.v. treatment period.

3.3 Behavioural and biochemical analyses

Novel object recognition
Session 1: on day 7 after peptide injection, rats were placed individually in a squared open-field (100 cm x 100 cm x 50 cm high) made in white plexiglas with a floor equipped with infrared light emitting diodes. Rats were habituated to the open-field during a 10-min duration session.

Session 2: on day 8 after peptide injection, two identical objects (50 ml plastic vials with caps) were placed at defined positions (at ¼ and ¾ of one diagonal of the open-field). Each rat was placed in the open-field and the exploratory activity recorded during a 10-min duration session. The activity was analyzed using the nosetrack™ protocol (Viewpoint), in terms of number of contact with objects and duration of contacts. The open-field and objects
were cleaned using a 50% ethanol solution between two experiments, Session 3: on day 9, the object in position #1 was replaced by a novel one (a soft plastic chair feet protection) differing in color shape and texture from the familiar object. Each rat was placed again in the open-field and the exploratory activity recorded during a 10-min duration session. The activity was analyzed similarly. The preferential exploration index was calculated as the ratio of the number (or duration) of contacts with the object in position #1 over the total number (or duration) of contacts with the two objects.

Animals showing no contact with one object or less than 10 contacts with one object during session 2 were considered as not satisfactorily exploring each identical object and discarded from the calculations. Five animals were discarded accordingly. Attrition was therefore 11.1%, which remains moderate in this procedure.

Sacrifice of the animals and brain sampling
At the end of the behaviour, all rats were sacrificed by decapitation and frontal cortex and both hippocampi were rapidly removed, weighed and kept in liquid nitrogen until assayed.

ELISA assays
Samples were prepared from one hippocampus tissues of each rat per group and homogenized in an extraction buffer specific to the commercial ELISA assay kits.

Kits used:
\( A\beta_{1-42} \): Supplier USCN, Ref. SEA946Ra, Batch number L140311213.

After thawing, the hippocampus were homogenized in 50 mM Tris-150 mM NaCl buffer, pH 7.5, and sonicated for 20 s. After centrifugation (16,100 g for 15 min, 4 °C), supernatants were used
for Aβ1-42 ELISA assay according to the manufacturer instructions. Absorbance was read at 450 nm and sample concentration was calculated using the standard curve. Results will be expressed in pg of Aβ1-42 per mg of tissue. All samples were assayed in duplicates.

Measure of protein concentration
Quantification of proteins was performed with the Pierce BCA (bicinchoninic acid) protein assay kit (Pierce, Ref #23227) to evaluate extraction performance and allow normalization. Standard solutions were prepared by dilution in series from a bovine serum albumin stock solution at 2 mg/ml in 0.9% NaCl with sodium azide (Ref. 23209, Pierce), as follows:
- Solution A: 2 mg/ml, 75 µl stock solution.
- Solution B: 1 mg/ml, 50 µl of solution A + 50 µl PBS
- Solution C: 0.5 mg/ml, 50 µl of solution B + 50 µl PBS
- Solution D: 0.25 mg/ml, 50 µl of solution C + 50 µl PBS
- Solution E: 0.125 mg/ml, 50 µl of solution D + 50 µl PBS
- Solution F: 0.05 mg/ml, 10 µl of solution E + 90 µl PBS
- Solution G: 0.025 mg/ml, 50 µl of solution F + 50 µl PBS
- Solution H: 100 µl PBS (0 mg/ml)

10 µl of standard and samples were added in duplicates on a 96 well plate (samples will be diluted 5x in PBS). Working reagent was added, 200 µl/well (Reagent A + Reagent B to ratio 50/1), then mixed 30 s and before incubating the plate at 37°C for 30 min. The absorbance was measured at 562 nm.

The total protein concentrations were then calculated from standard curve dilutions and served to normalize Elisa.

Statistical analyses
All values were expressed as mean ± S.E.M. Statistical analyses were performed on the different conditions using one-way ANOVA (F value), followed by the Dunnett's post-hoc multiple comparison test, p < 0.05 was considered as statistically significant.
Novel object data (contact preference with object #2 or novel object, calculated in terms of number or duration of contact) were expressed as mean ± S.E.M. and analysed using a one-way ANOVA and one-sample t-test vs the "no preference" level (50%) for each treatment group.

3.4 Results and Comments

Novel object recognition

This procedure is usually a high attrition procedure, since animals must interact with both objects during the two sessions with objects, to be included in the calculations. Animals showing an extreme place bias in exploration of the two identical objects in session 2 ($P_{of} > 90\%$ or $< 10\%$) are also discarded. In this study, 4 animals were discarded accordingly, which represent a 11% attrition. They distributed in two of the three experimental groups, suggesting no link with a particular treatment.

The collected experimental results are summarized in the diagrams shown in Figures 1a-d. These diagrams illustrate the effect of the compound 1 in rats submitted to the novel object recognition test, 8-9 days after $A\beta_{25-35}$ injection: place preference in term of time spent in the closed arm over time spent in the open arm in (a) and place preference in term of entries into the closed arm over entries into the open arm in (b).

* $p < 0.05$, *** $p < 0.001$ vs, no preference level (50%), one sample t-test; Alk3al2 stands for the group treated with the compound 1.

Object preference in session 2, calculated using contacts to objects (Fig. 1a) or duration of contacts (Fig. 1b) was around 50% for all groups, with the notable exception of the $A\beta_{25-35}$/compound 1-treated group that was significantly higher than 50%. Indeed, two animals showed very high (> 65%) preference for the object #2.
Novel object preference in session 3 showed that Sc, Aβ/Veh-treated animals expressed a significant preference for the novel object, both in terms of number of contacts (Fig. 1c) and duration of contact (Fig. 1d). The Aβ2 5-35/Veh-treated animals failed to show any preference for the novel object (Fig. 1c, d).

The compound 1 treatment alleviated the impairments, since both parameters appeared highly significantly different from the 50% level (Fig. 1c, 1d).

Measurement of Aβ1-42 levels by ELISA

The Aβ1-42 level in the hippocampus of control Sc, Aβ/Veh-treated rats was estimated about 1.2 pg/mg tissue. The Aβ2 5-35-induced toxicity induced a significant +158% increase in Aβ1-42 tissue content (Fig. 2).

Figure 2 shows Aβ1-42 contents in the rat hippocampus treated with the compound 1, 9 days after Aβ2 5-35 injection.

Veh: vehicle solution. ** p < 0.01 vs. Sc, Aβ/Veh, Dunnett’s test; Alk3al2 stands for the group treated with the compound 1.

The treatment of animals with the compound 1 decreased the Aβ1-42 level increase, since the data was not significantly different from the Sc, Aβ/Veh-treated group value (Fig. 2), a high intra-assay variation was noted leading to a marked dispersion of the data,
1. A compound of general Formula (I)

or a salt thereof, wherein

A is a polycyclic aromatic, heteroaromatic, alicyclic, heteroalicyclic substituent or is represented by the following structure:

R<sup>1</sup> is a hydrogen atom, a halogen atom or a C<sub>1-g</sub>-alkyl group optionally substituted with one or more halogen atoms,

R<sup>2</sup> is a C<sub>1-g</sub>-aliphatic group optionally substituted with one or more halogen atoms,

X is represented by -O-, -S-, -S(0)-, -S(0)<sub>2</sub>-, -NH-, -C(0)-, or -CH<sub>2</sub>-,

Y<sup>1</sup>, Z<sup>1</sup>, Y<sup>2</sup>, Z<sup>2</sup> and Y<sup>3</sup> are independently represented by -CH- or -N-, and

W is represented by -O-, -S-, -NH-, or -C(0)-; and

wherein the polycyclic aromatic, heteroaromatic, alicyclic, heteroalicyclic substituent can be optionally substituted by -W-R<sup>2</sup>.

2. The compound of general Formula (I) according to Claim 1, wherein the compound is represented by the Formula (II);
or a salt thereof, wherein

R is a hydrogen atom, a halogen atom or a C1-6-alkyl group
optionally substituted with one or more halogen atoms,

R2 is a C1-g-aliphatic group optionally substituted with one
or more halogen atoms,

X is represented by -O-, -S-, -S(O)−, -S(O)2−, -NH-, -C(O)−,
or -CE2−,

γ1, γ2, Z1, Z2 and Z3 are independently represented by -CH−
or -N−, and

W is represented by -O-, -S-, -NH-, or -C(O)−.

3. The compound of general Formula (I) according to Claim 1 or 2
or a salt thereof, wherein

R is a halogen atom, or a C1-6-alkyl group optionally
substituted with one or more halogen atoms,

R2 is a C2-g-alkyl group optionally substituted with one or
more halogen atoms,

γ2, Z1 and Z2 are represented by =CH− and γ2 is represented
by =N−, and

W is represented by -O−.

4. The compound of general Formula (I) according to Claim 1 or 2
or a salt thereof, wherein
R\(^1\) is a halogen atom, or a C\(_{1-6}\) -alkyl group optionally substituted with one or more halogen atoms,

R\(^2\) is a C\(_{2-6}\) -alkyl group optionally substituted with one or more halogen atoms,

Y\(^1\), Z\(^1\), Y\(^2\) and Z\(^2\) are represented by =CH-, and

W is represented by -O-.

5. The compound of general Formula (I) according to Claim 1 or 2 or a salt thereof, wherein

R\(^1\) is a halogen atom, or a ¼ -6-alkyl group optionally substituted with one or more halogen atoms,

R\(^2\) is a C\(_{2-6}\)-alkyl group optionally substituted with one or more halogen atoms,

Y\(^1\), Z\(^1\), Y\(^2\) and Z\(^2\) are represented by =CH-, and

W is represented by -O-.

6. The compound of general Formula (I) or a salt thereof according to any of Claims 1 to 5, wherein

R\(^1\) is a chlorine atom, or a Ci-3-alkyl group optionally substituted with one or more halogen atoms,

R\(^2\) is a C\(_{2-4}\)-alkyl group optionally substituted with one or more halogen atoms,

Y\(^3\) is represented by -CH-, and

W is represented by -O-.

7. The compound of general Formula (I) or a salt thereof according to any of Claims 1 to 6, wherein

the compound is represented by the Formula (IIa):
8. The compound of general Formula (I) or a salt thereof according to any of Claims 1 to 6, wherein the compound is represented by the Formula (lib):

9. The compound of general Formula (I) or a salt thereof according to Claim 7 or 8, wherein

- $R^1$ is a fluorine atom, a chlorine atom, or a methyl group,
- $R^2$ is an ethyl group or a $n$-propyl group,
- $X$ is represented by $-O-, -S-, \text{ or } -\text{CH}_2-$,
- $Y$, $Z$, $Y^2$, $Z^2$, and $Y^3$ are represented by $-\text{CH-}$, and
- $W$ is represented by $-O-$.
10. The compound of general Formula (I) according to any of Claims 1 to 9 or a salt thereof for use in the treatment of a human or animal body.

11. The compound of general Formula (I) according to any of Claims 1 to 9 or a salt thereof for use in the treatment or prophylaxis of a degenerative disease of the nervous system, wherein the degenerative disease of the nervous system is preferably selected from the group consisting of senile dementia, Alzheimer's disease, Pick's disease, Huntington's chorea, cerebrocerebellar degeneration, amaurotic family idiocy (neuronal lipidoses), leukodystrophy, familial myoclonus epilepsy, and Wilson's disease (hepatolenticular degeneration, Westphal-Strumpell pseudosclerosis).

12. The compound of general Formula (I) according to any of Claims 1 to 9 or a salt thereof for use according to Claim 11, wherein the degenerative disease of the nervous system is selected from the group consisting of paralysis agitans (Parkinson's disease), dystonia musculorum deformans (tortion dystonia), Hallervorden-Spatz disease and other restricted dyskinesias, familial tremor and spasmodic torticollis, cerebellar degenerations and spinocerebellar degenerations (Friedreich's ataxia, Marie's hereditary ataxia), amyotrophic lateral sclerosis, progressive muscular atrophy, cachexia and sarcopenia, progressive bulbar palsy, primary lateral sclerosis, infantile muscular atrophy (Werdnig-Hoffmann disease), other forms of familial progressive muscular atrophy (including Wohlfart-Kugelberg-Welander syndrome), hereditary spastic paraplegia, progressive neural muscular atrophy, peroneal muscular atrophy (Charcot-Marie-Tooth), hypertrophic interstitial neuropathy (Dejerine-Sottas), miscellaneous forms of chronic progressive neuropathy, hereditary optic atrophy (Leber's disease), age-related macular degeneration and pigmentary degeneration of the retina (retinitis pigmentosa).
13. The compound of general Formula (I) according to any of Claims 1 to 9 or a salt thereof for use according to Claim 11, wherein the degenerative disease of the nervous system is selected from the group consisting of depression and schizophrenia,

14. A pharmaceutical composition comprising a therapeutically effective amount of the compound of general Formula (I) according to any of Claims 1 to 9 or of a salt thereof as active ingredient,

15. The pharmaceutical composition according to Claim 14, wherein said pharmaceutical composition is an oral dosage form.
Figures

**Fig. 1/2**

(a) Object #2 preference (contacts, %)

(b) Object #2 preference (time, %)

(c) Novel object preference (contacts, %)

(d) Novel object preference (time, %)

Legend:
- Sc.Aβ
- Aβ25-35
- AIK3a12
- Veh

*Significant difference

**Significant difference**
Fig. 2/2

![Bar chart showing AS25-35 levels compared to Sc.AS and AS25-35 treated with Veh or ALK3a12.](image-url)
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D498/22 A61K31/4985
ADD.

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)
C07D A61K

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

Electronic database consulted during the international search (name of database and, where practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y,P</td>
<td>wo 2014/094816 AI (ALLINKY BIOPHARMA [ES])</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>26 June 2014 (2014-06-26) claims 9-12</td>
<td></td>
</tr>
<tr>
<td>X</td>
<td>DATABASE PubChem Compound [Online]</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2005, XP002742404, retrieved from NCBI</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Database access no. 2722100 compound 2722100</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-/-</td>
<td></td>
</tr>
</tbody>
</table>

[X] Further documents are listed in the continuation of Box C.  [X] See patent family 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 application or patent but published on or after the international filing date

'L' document which may throw doubts on priority claim(s) on 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

'Z' document member of the same patent family

Date of the actual completion of the international search
23 July 2015

Date of mailing of the international search report
10/08/2015

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016

Grassi, Dami an

Form PCT/ISA/210 (second sheet) (April 2005)
### DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>DATABASE PubChem Compound [Online] 2005, XP002742405, retrieved from NCBI Database access on no. 4210432 compound 4210432</td>
<td>1, 2</td>
</tr>
<tr>
<td>X</td>
<td>DATABASE PubChem Compound [Online] 2009, XP002742406, retrieved from NCBI Database access on no. 42291960 compound 42291960</td>
<td>1</td>
</tr>
<tr>
<td>X</td>
<td>DATABASE PubChem Compound [Online] 2009, XP002742407, retrieved from NCBI Database access on no. 42291961 compound 42291961</td>
<td>1</td>
</tr>
<tr>
<td>X</td>
<td>DATABASE PubChem Compound [Online] 2009, XP002742408, retrieved from NCBI Database access on no. 74229934 compound 74229934</td>
<td>1</td>
</tr>
<tr>
<td>Y, P</td>
<td>PI ERRE KOCH ET AL: &quot;Inhibitors of c-Jun N-Terminal Kinases: An Update&quot;, JOURNAL OF MEDICINAL CHEMISTRY, vol. 58, no. 1, January 8, 2015, pages 72-95, XP055202980, ISSN: 0022-2623, DOI: 10.1021/jm501212r, page 72, left-hand column; page 74, right-hand column; figures 3, 6, 7, 8, 10, 11, 16-19, 21, 22, 28</td>
<td>1</td>
</tr>
</tbody>
</table>

Form PCT/ISA/210 [continuation of second sheet] (April 2008)
<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patent document cited in search report</td>
<td>Publication date</td>
<td>Patent family member(s)</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>-----------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>WO 2014094816</td>
<td>26-06-2014</td>
<td>NONE</td>
</tr>
<tr>
<td>WO 2008028860</td>
<td>13-03-2008</td>
<td>AR 062666 AI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AT 543498 T</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU 2007293917 AI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BR PI0717035 A2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2662998 AI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CL 2007002572 AI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CN 101511359 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 2066319 AI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ES 2378577 T3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IL 197015 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 5325783 B2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2010502668 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>KR 20090040908 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PE 06592008 AI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TW 200819440 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2008103142 AI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WO 2008028860 AI</td>
</tr>
</tbody>
</table>