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(54) Title: NEW PEPTOID AGONISTS OF NERVE GROWTH FACTOR RECEPTOR AND THEIR USE AS MEDICAMENTS

(57) Abstract: Neutrophin binding to its specific receptors Trk A and p75 leads to the activation of multiple signalling cascades, culminating in neuroprotective and regenerative effects, including neuronal survival and neurite outgrowth. Neurotrophic factors have been used for the treatment of several neurodegenerative diseases. However, their use is limited by their inability to cross the blood-brain barrier, their short half life and their side effects. Small molecule neutrophin mimetics may be beneficial in treating a number of neurodegenerative disorders. The present invention shows the capacity of nerve growth factor agonist molecules of Formula I-IV, as defined in the specification, to induce differentiation in PC 12 cells, promote survival in RNI22 cells and activate Trk A, IRKs and SAPK/JNK phosphorylation to various extents in both cell lines. In addition these molecules were able to ameliorate acute experimental autoimmune encephalomyelitis (EAE), a multiple sclerosis (MS) animal model, inhibiting brain inflammation and reducing brain damage. We also observed suppression in the production of pro-inflammatory genes like the inducible nitric oxide synthase. These small molecules with NGF agonist activity may be beneficial for MS and other neurodegenerative diseases due to its neuroprotective and immunomodulatory properties.


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NEW PEPTOID AGONISTS OF NERVE GROWTH FACTOR RECEPTOR AND THEIR USE AS MEDICAMENTS

The present application claims priority to European Patent Application No. 09169045.3, filed August 31, 2009. The full disclosure of this application is herein incorporated by reference.

BACKGROUND OF THE INVENTION

Field of invention
This invention applies to the area of therapeutics for neurological, psychiatric disorders, and ageing. In particular, it relates to the neuroprotective effect of small molecule agonists of neurotrophin (Nerve Growth Factor –NGF-) receptor and the use of those agonists as medicaments.

Background art
Ageing, neurological and psychiatric disorders cause death and damage to nerve cells. Frequent and relevant damage to the nervous system can result from neuronal degeneration, ischemia, inflammation, immune responses, trauma, and cancer, among other things. As a consequence of these, nerve cells can die within minutes or hours or survive this initial damage in an impaired state that activates neurodegeneration, ending equally in cellular death.

Given the importance of the nervous system in enabling basic motor skills and sensing, there exists an interest in finding therapeutic weapons to protect the nervous system.

Neuroprotection is focused on the preservation, recovery, cure, or regeneration of the nervous system, its cells, structure, and function (Vajda et al., 2002). A goal of neuroprotection is to prevent or minimize the effects of an original damage to the nervous system, or to prevent or minimize the consequences of endogenous or
exogenous noxious processes causing damage to axons, neurons, synapses, and dendrites.

Treatment strategies in general are frequently based on the modulation of a single proposed injury factor. Although such treatments can be shown to be beneficial in highly constrained animal models, they are less likely to prove efficacious in the more complex human disorder that involves more variable degrees of injury severity in a genetically diverse population (Faden and Stoica, 2007). Importantly, since the presumed mechanisms of neuronal death are both complex and varied, such as oxidative stress, mitochondrial dysfunction, protein aggregation, apoptosis, and inflammation (Youdim et al., 2005), single compounds having multipotential effects on multiple injury mechanisms are desirable.

Several neuroprotective drugs are under investigation including the following classes: anti-inflammatory agents, N-methyl D-aspartate (NMDA) antagonists, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) antagonists, dexamabinol, sodium channel blockers, thyrotropin-releasing hormone (TRH), growth factors, glucocorticoids, caffeine, opioid antagonists, apoptosis inhibitors, free radical trappers/scavengers, erythropoietin, calcium channel blockers, magnesium sulfate, statins.

The ability of these pharmacological agents to limit secondary biochemical damage and cell death has been been disappointing (Faden and Stoica, 2007).

Neurotrophins are growth factors that regulate the development and maintenance of the peripheral and the central nervous systems (Lewin and Barde, 1996). Nerve growth factor (NGF) is a homodimeric protein from the neurotrophin family that plays a crucial role in neuronal survival, differentiation and growth (Levi-Montalcini, 1987) and binds two distinct cellular receptors: the tyrosine kinase receptor TrkA and the p75 receptor (Chao, 2003). NGF–TrkA binding activates the intrinsic tyrosine kinase of the receptor, causing tyrosine phosphorylation of TrkA and associated signalling partners and therefore activating promotion of cell survival or differentiation (Kaplan
and Miller, 2000). The p75 receptor is a member of the tumor necrosis factor receptor superfamily. Depending on the cellular environment and the type of ligand, p75 can act as transducer of pro-survival, pro-apoptotic, or pro-differentiation signals (Barker, 1998; Rabizadeh et al., 1999; Zaccaro et al., 2001; Saragovi and Zaccaro, 2002). Accordingly, depending on the metabolic route, binding to either TrkA or p75 receptors may trigger signals, depending on the cell type considered, linked to, indistinctly, differentiation and/or cell survival.

The potential of NGF as a therapeutic agent for several diseases has been indicated by several investigators. Such diseases include neurodegenerative disorders, nerve inflammation and certain types of cancers, multiple sclerosis, neuromyelitis optica, amyotrophic lateral sclerosis (ALS), Parkinson’s disease, Alzheimer’s disease, Friedreich’s ataxia, Huntington’s disease, Dementia with Lewy bodies, spinal muscular atrophy, major depressive disorder, schizophrenia, glaucoma or peripheral neuropathies (diabetic or AIDS neuropathy) (Longo et al, 2007; Schulte-Herbrüggen, 2007; Shi, 2007; Hellveg, 2008; Shoval, 2005; Apfel, 2002; Anand, 2004). NGF has significant immunoregulatory properties during CNS inflammation to contribute to the maintenance of the CNS privilege (Villoslada and Genain, 2004). During Experimental Autoimmune Encephalomyelitis (EAE) in marmoset, NGF was able to inhibit the development of the clinical symptoms when administered intracerebroventricul arly by continuous infusion apparently because of its ability to induce an immunosuppressive microenvironment in the CNS which leads to decreased CNS infiltration (Villoslada et al., 2000). The finding that NGF induces immunosuppression during autoimmune demyelination in addition to its neuroprotective properties in neurons and oligodendrocytes makes it a very good candidate for the treatment of CNS inflammatory diseases like MS. However, NGF is not the ideal drug candidate due to its inability to cross the blood-brain barrier (BBB) (Poduslo and Curran, 1996), its short half life and its side effects (Apfel, 2002). Much effort has been made in the search for small molecules with NGF agonist activity, with better pharmacokinetics and less side effects. To achieve this goal, different approaches have been attempted (Poduslo and Curran, 1996; Longo et al., 1997; Maliartchouk et al., 2000a; Maliartchouk et al., 2000b; Peleshok and Saragovi, 2006).
As such, there is an ongoing need for providing drugs, particularly NGF mimetics, with neuroprotective properties, which have preferably multipotential effects, but without the drawbacks of NGF. The present inventors have developed a family of compounds distinct from those disclosed in the art. The family of compounds of the invention are peptidomimetics of NGF, and agonists to Trk A and p75 specific receptors. Some of the compounds of the invention promote, as a way of example, cell survival to an extent even higher than NGF itself. The compounds of the invention are considered peptide-mimetics of neurotrophin and they all share a structure of N-alkylglycine trimers.

SUMMARY OF THE INVENTION

The present invention is related to the use of peptoid compounds of Formulae I-IV, below, and the pharmaceutically acceptable salts and prodrugs thereof, as agonists of nerve growth factor (NGF) receptors.

Compounds useful in the present invention have not been heretofore reported. Thus, one aspect of the present invention is directed to novel compounds of Formulae I-IV, as well as their pharmaceutically acceptable salts and prodrugs.

Another aspect of the invention is directed to the use of compounds of any of Formulae I-IV, and their pharmaceutically acceptable salts and prodrugs, as agonists of NGF receptors.

A further aspect of the invention is to provide a compound of any of Formulae I-IV, or a pharmaceutically acceptable salt or prodrug thereof, for use as a medicament. In one aspect of the invention, the medicament is for use in preventing or treating nerve cell death or damage. In one aspect of the invention, the medicament is for use in neuroprotection. In one aspect of the invention, the medicament is for use in regeneration of nerve cells. In one aspect of the invention, the medicament is for use in neuroenhancing. In one aspect, the medicament is for use in preventing or treating a neurological or a psychiatric disease. In one aspect of the invention, the medicament
is for use in preventing or treating a disease selected from the group consisting of a neurological disease, a preferentially neurodegenerative disorder (such as amyotrophic lateral sclerosis (ALS), Parkinson’s disease, Alzheimer’s disease, Friedreich’s ataxia, Huntington’s disease, Dementia with Lewy bodies, and spinal muscular atrophy), nerve inflammation (such as multiple sclerosis and neuromyelitis optica), major depressive disorder, schizophrenia, glaucoma, peripheral neuropathy (such as diabetic or AIDS neuropathy), and cancer (such as glioblastoma, astrocytoma, medulloblastoma, neurinoma, neuroblastoma, meningioma, colon cancer, pancreatic cancer, breast cancer, prostate cancer, leukemia, acute lymphocytic leukemia, osteosarcoma, hepatocellular carcinoma, ovarian carcinoma, lung adenocarcinoma, and esophageal carcinoma).

A further aspect of the invention is to provide a compound of any of Formulae I-IV (and specifically a compound of Formula II or III), or a pharmaceutically acceptable salt or prodrug thereof, for use as a medicament for treating multiple sclerosis.

A further aspect of the invention is to provide a compound of any of Formulae I-IV (and specifically a compound of Formula II), or a pharmaceutically acceptable salt or prodrug thereof, for use as a medicament, wherein the medicament is a neuroregenerative drug.

A further aspect of the invention is to provide a compound of any of Formulae I-IV (and specifically a compound of Formula II), or a pharmaceutically acceptable salt or prodrug thereof, for use as a medicament, wherein the medicament is an immunomodulator.

A further aspect of the invention is to provide a compound of any of Formulae I-IV (and specifically a compound of Formula II), or a pharmaceutically acceptable salt or prodrug thereof, for use as a medicament, wherein the medicament has a combination of neuroprotective and immunomodulatory effects.
A further aspect of the present invention is to provide a pharmaceutical composition, comprising a therapeutically effective amount of at least one compound of any of Formulae I-IV, or a pharmaceutically acceptable salt or prodrug thereof, and a pharmaceutically acceptable carrier.

A further aspect of the invention is to provide the use of a compound of any of Formulae I-IV, or a pharmaceutically acceptable salt or prodrug thereof, in the manufacture of a medicament for preventing or treating nerve cell death or damage.

A further aspect of the invention is to provide the use of a compound of any of Formulae I-IV, or a pharmaceutically acceptable salt or prodrug thereof, in the manufacture of a medicament for providing neuroprotection.

A further aspect of the invention is to provide the use of a compound of any of Formulae I-IV, or a pharmaceutically acceptable salt or prodrug thereof, in the manufacture of a medicament for the regeneration of nerve cells.

A further aspect of the invention is to provide the use of a compound of any of Formulae I-IV, or a pharmaceutically acceptable salt or prodrug thereof, in the manufacture of a medicament for preventing or treating a neurological disease or a psychiatric disease.

A further aspect of the invention is to provide the use of a compound of any of Formulae I-IV, or a pharmaceutically acceptable salt or prodrug thereof, in the manufacture of a medicament for preventing or treating a disease selected from the group consisting of a neurological disease, a preferentially neurodegenerative disorder (such as amyotrophic lateral sclerosis (ALS), Parkinson’s disease, Alzheimer’s disease, Friedrich’s ataxia, Huntington’s disease, Dementia with Lewy bodies, and spinal muscular atrophy), nerve inflammation (such as multiple sclerosis and neuromyelitis optica), major depressive disorder, schizophrenia, glaucoma, peripheral neuropathy (such as diabetic or AIDS neuropathy), and cancer (such as glioblastoma, astrocytoma, medulloblastoma, neurinoma, neuroblastoma, meningioma, colon cancer,

5 A further aspect of the invention is to provide the use of a compound of any of Formulae I-IV (and specifically a compound of Formula II or III), or a pharmaceutically acceptable salt or prodrug thereof, in the manufacture of a medicament for preventing or treating multiple sclerosis.

10 A further aspect of the invention is to provide the use of a compound of any of Formulae I-IV (and specifically a compound of Formula II), or a pharmaceutically acceptable salt or prodrug thereof, in the manufacture of a neuroregenerative drug.

A further aspect of the invention is to provide the use of a compound of any of Formulae I-IV (and specifically a compound of Formula II), or a pharmaceutically acceptable salt or prodrug thereof, in the manufacture of an immunomodulator.

A further aspect of the invention is to provide the use of a compound of any of Formulae I-IV (and specifically a compound of Formula II), or a pharmaceutically acceptable salt or prodrug thereof, in the manufacture of a medicament having a combination of neuroprotective and immunomodulatory effects.

A further aspect of the invention is to provide the use of a compound of any of Formulae I-IV, or a pharmaceutically acceptable salt or prodrug thereof, in the manufacture of a neuroenhancing drug.

A further aspect of the invention is to provide a method for preventing or treating nerve cell death or damage, comprising administering to a subject in need thereof an effective amount of a compound of any of Formulae I-IV, or a pharmaceutically acceptable salt or prodrug thereof, or an effective amount of a pharmaceutical composition comprising a compound of any of Formulae I-IV, or a pharmaceutically acceptable salt or prodrug thereof.
A further aspect of the invention is to provide a method for providing neuroprotection, comprising administering to a subject in need thereof an effective amount of a compound of any of Formulae I-IV, or a pharmaceutically acceptable salt or prodrug thereof, or an effective amount of a pharmaceutical composition comprising a compound of any of Formulae I-IV, or a pharmaceutically acceptable salt or prodrug thereof.

A further aspect of the invention is to provide a method for providing immunomodulation, comprising administering to a subject in need thereof an effective amount of a compound of any of Formulae I-IV (and specifically a compound of Formula II), or a pharmaceutically acceptable salt or prodrug thereof, or an effective amount of a pharmaceutical composition comprising a compound of any of Formulae I-IV (an specifically a compound of Formula II), or a pharmaceutically acceptable salt or prodrug thereof.

A further aspect of the invention is to provide a method for regenerating nerve cells, comprising administering to a subject in need thereof an effective amount of a compound of any of Formulae I-IV (and specifically a compound of Formula II), or a pharmaceutically acceptable salt or prodrug thereof, or an effective amount of a pharmaceutical composition comprising a compound of any of Formulae I-IV (and specifically a compound of Formula II), or a pharmaceutically acceptable salt or prodrug thereof.

A further aspect of the invention is to provide a method for preventing or treating a disease selected from the group consisting of a neurological disease, a preferentially neurodegenerative disorder (such as amyotrophic lateral sclerosis (ALS), Parkinson’s disease, Alzheimer’s disease, Friedreich’s ataxia, Huntington’s disease, Dementia with Lewy bodies, and spinal muscular atrophy), nerve inflammation (such as multiple sclerosis and neuromyelitis optica), major depressive disorder, schizophrenia, glaucoma, peripheral neuropathy (such as diabetic or AIDS neuropathy), and cancer (such as glioblastoma, astrocytoma, medulloblastoma, neurinoma, neuroblastoma,
meningioma, colon cancer, pancreatic cancer, breast cancer, prostate cancer, leukemia, acute lymphocytic leukemia, osteosarcoma, hepatocellular carcinoma, ovarian carcinoma, lung adenocarcinoma, and esophageal carcinoma), comprising administering to a subject in need thereof an effective amount of a compound of any of Formulae I-IV, or a pharmaceutically acceptable salt or prodrug thereof, or an effective amount of a pharmaceutical composition comprising a compound of any of Formulae I-IV, or a pharmaceutically acceptable salt or prodrug thereof.

A further aspect of the invention is to provide a method for preventing or treating multiple sclerosis, comprising administering to a subject in need thereof an effective amount of a compound of any of Formulae II or III, or a pharmaceutically acceptable salt or prodrug thereof, or an effective amount of a pharmaceutical composition comprising a compound of any of Formulae II or III, or a pharmaceutically acceptable salt or prodrug thereof.

A further aspect of the invention is to provide a method of treating a disease responsive to the stimulation of the activity of nerve growth factor, or a nerve growth factor receptor, in a mammal suffering from lack of stimulation thereof, comprising administering an effective amount a compound of any of Formulae I-IV, or a pharmaceutically acceptable salt or prodrug thereof.

A further aspect of the invention is to provide a compound of any of Formulae I-IV, or a pharmaceutically acceptable salt or prodrug thereof, for use in stimulating the activity of nerve growth factor, or a nerve growth factor receptor.

A further aspect of the present invention is to provide a method of stimulating nerve growth factor receptor activity in a subject in need thereof, comprising administering a compound of any of Formulae I-IV, or a pharmaceutically acceptable salt or prodrug thereof, to the subject. In one embodiment, the nerve growth factor receptor is TrkA receptor or p75 receptor.
A further aspect of the present invention is to provide a method of preparing a pharmaceutical composition, comprising admixing an effective amount of a compound of any of Formulae I-IV, or a pharmaceutically acceptable salt or prodrug thereof, with a pharmaceutically acceptable carrier.

Additional embodiments and advantages of the invention will be set forth in part in the description that follows, and will flow from the description, or may be learned by practice of the invention. The embodiments and advantages of the invention will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims.

It is to be understood that both the foregoing summary and the following detailed description are exemplary and explanatory only and not restrictive of the invention as claimed.

BRIEF DESCRIPTION OF THE DRAWINGS/FIGURES

FIG. 1 depicts induction of PC12 cells differentiation by NGF-like molecules. FIG. 1A: Representative images of PC12 cells differentiated for 3 days in the presence of N35-4-17C (20 ng/ml and 2 μg/ml) or NGF (100 ng/ml). Treatments were performed under reduced serum conditions (0.5% FBS and 1% HS). FIG. 1B: Differentiation levels induced after 3 days of treatment with N35-4-8C, N35-4-17C and N6-4-17C. Data are expressed as percentage of the differentiation (cells with neurite processes at least 2 times the diameter of the cell body) induced by NGF. Data are the mean ± SEM of at least three experiments, each in duplicate. *p < 0.05, **p < 0.01 (ANOVA) respect to control.

FIG. 2 shows effects of NGF-like molecules in promotion of RN22 cell survival. RN22 schwannoma cells in serum free medium were treated with copper sulphate (CuSO4) (150 μM) to generate stress and cell death. After that NGF (100 ng/ml) or NGF-like small Peptoids N35-4-8C, N35-4-17C and N6-4-17C were added at different concentrations. Cell viability was analyzed by MTT assay 24 h later.
Depicted are the means ± S.E. of three experiments, each in duplicate. *p < 0.05, **p < 0.01 (ANOVA) respect to stress control.

FIG. 3 depicts the time course of phosphorylation induced by N35-4-8C, N6-4-17C and N35-4-17C pretreatment. PC12 and RN22 cells were treated with NGF (100 ng/ml) or either one of the peptoids (100 ng/ml) for the time indicated. Cells were lysed and western blotting was done with anti-p-TrkA (Tyr 490) antibody (1:1000), anti-p-IkBα (Ser 32/36)(5A5) mouse antibody (1/1000) or anti-p-SAPK/JNK (Thr183/Tyr185) antibody (1:1000). The membrane were then stripped and re-probed with the anti TrkA antibody (1:1000), anti IκBα (L35A5) mouse antibody (1:1000), or anti-SAPK/JNK antibody (1/1000).

FIG. 4 depicts the results of N35-4-8C, N35-4-17C and N6-4-17C intraperitoneal administration in C57BL/6 EAE mice. FIG. 4A: N35-4-8C administration prevents EAE when administered at high dose (100 mg/kg). FIG. 4B: N35-4-17C administration prevents EAE when administered at low dose (25 mg/kg). FIG. 4C: N6-4-17C has no effects in EAE at any of the concentrations tested. The results are expressed as the mean plus standard deviation of the clinical score. Differences between groups were compared with the Mann-Whitney U test. * p < 0.05 respect to placebo group.

FIG. 5 depicts effects of N35-4-8C on brain and spinal cord tissues. FIG. 5A:- Brain and spinal cord from placebo and N35-4-8C treated animals were analyzed at the end of the experiments (day 26)- N35-4-8C-treated animals at the high concentration (100 mg/kg) had a significant lower histological scores at the brain and spinal cord level than placebo animals. Differences between groups were compared with the Mann-Whitney U test. * ( p < 0.05) respect to placebo group. FIG. 5B:- Luxol Fast Blue staining of brain and spinal cord tissues from placebo animals. FIG. 5C:- Luxol Fast Blue staining of brain and spinal cord tissues from animals treated with N35-4-8C.

FIG. 6 depicts effects of N35-4-8C on the peripheral immune response during EAE. FIG. 6A: N35-4-8C inhibits the proliferation of splenocytes isolated from naïve
C57BL/6 mice and stimulated with myelin oligodendrocyte glycoprotein (MOG; 10 μg/ml). Splenocytes were cultured for 2 hours with N35-4-8C before MOG addition. Data are means ± standard error. *p < 0.05 with respect to cells treated with MOG only. FIG. 6B: Gene expression profile of cytokines and inducible nitric oxide synthase (iNOS) assayed by quantitative reverse transcriptase –polymerase chain reaction (RT-PCR) in the spleen of placebo and treated animals at the end of the experiment. Data are expressed as fold change in gene expression levels in the treated groups compared with untreated controls. *p < 0.05. IFN = interferon; IL = interleukin; TNF = tumor necrosis factor.

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DETAILED DESCRIPTION OF THE INVENTION

One aspect of the invention is based on the use of compounds of Formulae I-IV, and the pharmaceutically acceptable salts and prodrugs thereof, as agonists of nerve growth factor (NGF) receptors. In view of this property, compounds of Formulae I-IV, and the pharmaceutically acceptable salts and prodrugs thereof, are useful for preventing or treating diseases responsive to the stimulation of nerve growth factor, or a nerve growth factor receptor.

The invention uses a chemical library (Masip et al., 2005) of oligomers of N-substituted glycines, also known as peptoids (5120 molecules distributed in 52 controlled mixtures). Peptoids are a family of non-natural molecules with a broad variety of biological activities. They exhibit enhanced stability, bioavailability toward proteolysis relative to natural peptides (Miller et al., 1994) and they have a modular scaffold that makes them amenable to structural optimisation approaches.

From the tested molecules the invention selected a family of compounds represented by those of Formula I which showed a good NGF like activity “in vitro” by inducing differentiation of PC12 cells and promoting cell survival of RN22 cells, therefore, having neuroprotective properties.

The compounds useful in this aspect of the invention are the peptoids represented by Formula I:
and pharmaceutically acceptable salts and prodrugs thereof,
wherein $R_1$ is phenyl substituted with halogen or trifluoromethyl, and further optionally substituted with one or two substituents selected from the group consisting of halogen, C$_{1-6}$ alkyl, (C$_{1-6}$)alkoxy, and halo(C$_{1-6}$)alkyl, or $R_1$ is pyrrolidin-1-yl, and $R_2$ is 2-oxo-pyrrolidin-1-ylmethyl or sulfamoylphenyl

In one embodiment, compounds useful in the present invention are compounds of Formula I, wherein $R_1$ is fluorophenyl or pyrrolidin-1-yl, and $R_2$ is 2-oxo-pyrrolidin-1-ylmethyl or sulfamoylphenyl as follows:

$R_1$: \[
\text{\includegraphics{fluorophenyl.png}}
\text{ or } \text{\includegraphics{pyrrolidin-1-yl.png}}
\]

$R_2$: \[
\text{\includegraphics{N-oxide.png}}
\text{ or } \text{\includegraphics{sulfamoylphenyl.png}}
\]

In one embodiment, compounds useful in the present invention are compounds of Formula I, wherein $R_1$ is fluorophenyl. In one embodiment, the fluorophenyl group is 2-fluorophenyl, 3-fluorophenyl or 4-fluorophenyl. Preferably, $R_1$ is 2-fluorophenyl.

In one embodiment, compounds useful in the present invention are compounds of Formula I, wherein $R_1$ is trifluoromethylphenyl. In one embodiment, the
trifluoromethylphenyl group is 2-trifluoromethylphenyl, 3-trifluoromethylphenyl or 4-trifluoromethylphenyl. Useful compounds include those where R₁ is 2-trifluoromethylphenyl.

In one embodiment, compounds useful in the present invention are compounds of Formula I, wherein R₁ is pyrrolidin-1-yl.

In one embodiment, compounds useful in the present invention are compounds of Formula I, wherein R₂ is 2-oxo-pyrrolidin-1-ylmethyl.

In one embodiment, compounds useful in the present invention are compounds of Formula I, wherein R₂ is sulfamoylphenyl. In one embodiment, the sulfamoylphenyl group is 2-sulfamoylphenyl, 3-sulfamoylphenyl, or 4-sulfamoylphenyl. Preferably, R₂ is 4-sulfamoylthethyl.

In one embodiment, compounds useful in the present invention are compounds having the Formula I:

\[
\begin{array}{c}
\text{R}_1 \\
\text{NH} \\
\text{CONH} \\
\text{CONH} \\
\text{NH} \\
\text{O} \\
\text{NH}_2 \\
\text{R}_2 \\
\end{array}
\]

and pharmaceutically acceptable salts and prodrugs thereof,

wherein R₁ is 2-fluorophenyl or pyrrolidin-1-yl, and R₂ is 2-oxo-pyrrolidin-1-ylmethyl or 4-sulfamoylphenyl as follows:
From the tested molecules the invention selected 3 peptoids which showed a good NGF like activity “in vitro” by inducing differentiation of PC12 cells, promotion of survival in RN22 cells (which express p75, but not TrkA) and phosphorylation of TrkA in PC12 cells, IkBα in both cell lines (PC12 and RN22) and SAPK/JNK in RN22 cell line. Moreover, these 3 molecules resulted effective in the multiple sclerosis animal model EAE, inhibiting brain inflammation and reducing brain damage.

Accordingly, preferred compounds according to present invention are the 3 members of the family of compounds of Formula I, represented by any of the following Formulae II-IV, and their pharmaceutically acceptable salts and prodrugs:

Formula II:

N-(2-(2’-Fluorophenyl)ethyl)glycyl]-[N-(3-methylbutyl)glycyl]-N-[3-(2’-oxopyrrolidinyl)propyl]glycinamide (N35-4-8C);
Formula III:

\[
\text{III} \quad \text{[N-(2-(2’-Fluorophenyl)ethyl)glycyl]-[N-(3-methylbutyl)glycyl]-N-[2-(4’-}
\text{sulfamoylphenyl)ethyl] glycaminamide (N35-4-17C); and}
\]

Formula IV:

\[
\text{IV} \quad \text{[N-(2-(1-Pyrrolidinyl)ethyl)glycyl]-[N-(3-methylbutyl)glycyl]-N-[2-(4’-}
\text{sulfamoylphenyl)ethyl] glycaminamide (N6-4-17C),}
\]

and pharmaceutically acceptable salts and/or prodrugs thereof.

In one embodiment, the compound of Formula I is the compound of Formula II, or a pharmaceutically acceptable salt or prodrug thereof.
In one embodiment, the compound of Formula I is the compound of Formula III, or a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, the compound of Formula I is the compound of Formula IV, or a pharmaceutically acceptable salt or prodrug thereof.

Useful alkyl groups are selected from straight-chained and branched C<sub>1-6</sub> alkyl groups, and more preferably straight chain C<sub>1-4</sub> alkyl groups and branched chain C<sub>1-4</sub> alkyl groups. Typical C<sub>1-6</sub> alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tert-butyl, iso-butyl, 3-pentyl, hexyl, among others.

Useful halo(C<sub>1-6</sub>)alkyl groups include any of the above-mentioned C<sub>1-6</sub> alkyl groups substituted by one or more fluorine, chlorine, bromine or iodine atoms (e.g., fluoromethyl, difluoromethyl, trifluoromethyl, pentafluoroethy, 1,1-difluoroethanyl and trichloromethyl groups). Preferably, the halo(C<sub>1-6</sub>)alkyl group is trifluoromethyl.

Useful C<sub>1-6</sub> alkoxy groups include oxygen substituted by one of the C<sub>1-6</sub> alkyl groups mentioned above (e.g., methoxy, ethoxy, propoxy, iso-propoxy, butoxy, tert-butoxy, iso-butoxy, sec-butoxy, and pentyloxy).

The term “prodrug”, as used herein, includes any compound derived from the compounds of any of Formulae I-IV, for example, the ester, amide, phosphate, etc., which, upon being administered to an individual, is capable of providing the compounds of any of Formulae I-IV or the pharmaceutically acceptable salt thereof, directly or indirectly, to said individual. Preferably, said derivative is a compound that increases the bioavailability of the compounds of any of Formulae I-IV when administered to an individual or that promotes the release of the compounds of any of Formulae I-IV in a biological compartment. The nature of said derivative is not critical, provided that it may be administered to an individual and that it provides the compounds of any of Formulae I-IV in an individual’s biological compartment. The preparation of said prodrug may be performed by conventional methods known by those skilled in the art. Conventional procedures for the selection and preparation of
suitable prodrug derivatives are described in, for example, *Design of Prodrugs*, H. Bundgaard ed., Elsevier (1985). An example of prodrug of the compounds of any of Formulae I-IV can be their encapsulation into liposomes. By this procedure, the peptoid is treated with the appropriate liposome precursor (combination of a phospholipid like lecithin, cholesterol and water) in order to be encapsulated. Depending upon the lipophilicity of the peptoid, the compound will be retained at the lipophilic part of the liposome or at the aqueous inner portion. Regarding the therapeutic polymer, the peptoid could be attached to the polymer by covalent bonds created after regioselective hydrolysis of the terminal carboxamide. This hydrolysis renders a free carboxylic acid that can be condensed with an amino or hydroxyl activated group of the polymer.

The term “pharmaceutically acceptable” means that a compound or combination of compounds is sufficiently compatible with the other ingredients of a formulation, and not deleterious to the patient up to those levels acceptable by the industry standards.

For therapeutic use, salts of the compounds of any of Formulae I-IV are those wherein the counter-ion is pharmaceutically acceptable.

The term "salt" as mentioned herein is meant to comprise any stable salts, which the compounds of any of Formulae I-IV are able to form. Preferred are the pharmaceutically acceptable salts. Salts that are not pharmaceutically acceptable are also embraced in the scope of the present invention, since they refer to intermediates that may be useful in the preparation of compounds with pharmacological activity.

The salts can conveniently be obtained by treating the base form of the compounds of any of Formulae I-IV with such appropriate acids as inorganic acids such as hydrochloric or hydrobromic acid, sulfuric, nitric, phosphoric and the like acids; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic (i.e. ethanedioic), malonic, succinic (i.e. butanedioic acid), maleic, fumaric, malic (i.e. hydroxybutanedioic acid), tartaric, citric, methanesulfonic, ethanesulfonic,
benzenesulfonic, p-toluenesulfonic, cyclamic, salicylic, p-aminosalicylic, pamoic and the like acids.

The pharmaceutically acceptable salts can be obtained by treating the base form of the compounds of any of Formulae I-IV with such appropriate pharmaceutically acceptable acids like inorganic acids, for example, including hydrochloric, hydrobromic and the like; sulfuric acid; nitric acid; phosphoric acid and the like; or organic acids, for example, acetic, propanoic, hydroxyacetic, 2-hydroxypropanoic, 2-oxopropanoic, oxalic, malonic, succinic, maleic, fumaric, malic, tartaric, 2-hydroxy-1,2,3-propane-tricarboxylic, methanesulfonic, ethanesulfonic, benzenesulfonic, 4-methylbenzene-sulfonic, cyclohexanesulfamic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids.

Conversely the salt form can be converted by treatment with alkali into the free base form.

The term "pharmaceutical composition" means for the purpose of the present invention any composition which comprises as an active compound, to which is attributed, fully or in part, the therapeutic (e.g. pharmaceutical) effect, at least one of the compounds of the invention or combinations thereof and that may optionally further comprise at least one pharmaceutically acceptable non-active ingredient, as an excipient, carrier or so.

The term “preventing” refers to keep from happening, existing, or alternatively delaying the onset or recurrence of a disease, disorder, or condition to which such term applies, or of one or more symptoms associated with a disease, disorder, or condition. The term “prevention” refers to the act of preventing, as “preventing” is defined immediately above.

The term “treating”, as used herein, refers to reversing, alleviating, or inhibiting the progress of the disorder or condition to which such term applies, or one or more
symptoms of such disorders or condition. The term “treatment” refers to the act of treating, as “treating” is defined immediately above.

The term “subject” means animals, in particular mammals such as dogs, cats, cows, horses, sheep, geese, and humans. Particularly preferred subjects are mammals, including humans of both sexes.

An “effective amount” of the compounds of any of Formulae I-IV and pharmaceutically acceptable salts or prodrugs thereof, may be in the range from 0.01 mg to 50 g per day, from 0.02 mg to 40 g per day, from 0.05 mg to 30 g per day, from 0.1 mg to 20 g per day, from 0.2 mg to 10 g per day, from 0.5 mg to 5 g per day, from 1 mg to 3 g per day, from 2 mg to 2 g per day, from 5 mg to 1.5 g per day, from 10 mg to 1 g per day, from 10 mg to 500 mg per day.

Nerve cells include those cells from any region of the brain, spinal cord, optic nerve, retina, and peripheral ganglia. Neurons include those in embryonic, fetal, or adult neural tissue, including tissue from the hippocampus, cerebellum, spinal cord, cortex (e.g., motor or somatosensory cortex), striatum, basal forebrain (cholinergic neurons), ventral mesencephalon (cells of the substantia nigra), and the locus ceruleus (neuroadrenaline cells of the central nervous system).

The invention also covers the use of the compounds of any of Formulae I-IV, and pharmaceutically acceptable salts and/or prodrugs thereof, as active ingredients in the manufacture of medicaments for the prevention or treatment of nerve cell death or damage. In other words, the present invention relates to the compounds of any of Formulae I-IV, and pharmaceutically acceptable salts and/or prodrugs thereof, for use in the prevention or treatment of nerve cell death or damage. Similarly, the present invention relates to a method of neuroprotection comprising administering to a subject in need thereof an effective amount of a compound of any of Formulae I-IV, or pharmaceutically acceptable salts and/or prodrugs thereof.
In one embodiment of the present invention, the compounds of any of Formulae I-IV, and pharmaceutically acceptable salts and/or prodrugs thereof, may be used for the prevention or treatment of one or more, preferably two or more, pathological or harmful conditions related to nerve cell death or damage selected from, but not being limited to, chemical substances such as oxidative stress conditions, toxic substances, infectious organisms, radiation, traumatic injury, hypoxia, ischemia, abnormal misfolded proteins, excitotoxins, free radicals, endoplasmic reticulum stressors, mitochondrial stressors including but not limited to inhibitors of the electron transport chain, Golgi apparatus antagonists, axonal damage or loss, demyelination, inflammation, pathological neuronal burst (seizures). Also preferably, the uses and methods of the present invention are directed to preventing or treating nerve cell death or damage, regardless of cause.

The terms “neuroprotection”, “neuroprotective”, or “neuroprotective effect” refer to the ability to prevent or reduce death or damage to nerve cells, including neurons and glia, or rescuing, resuscitating or reviving nerve cells, e.g., following in pathological or harmful conditions to the brain, central nervous system or peripheral nervous system. Thus, this neuroprotective effect comprises the conferred ability of neuronal cells to maintain or recover their neuronal functions. It stabilizes the cell membrane of a neuronal cell or helps in the normalization of neuronal cell functions. It prevents the loss of viability or functions of neuronal cells. It comprises the inhibition of progressive deterioration of neurons that leads to cell death. It refers to any detectable protection of neurons from stress. Neuroprotection includes the regeneration of nerve cells, i.e. the re-growth of a population of nerve cells after disease or trauma.

Currently the majority of the neurological and psychiatric diseases lacks specific treatments aimed to stop or ameliorate the course of the disease, which are called “disease modifying drugs”. This contrasts with the symptomatic therapies which are common for such diseases but do not change the course of the disease. A neuroprotective drug is a Disease Modifying Drug (DMD) for the treatment of brain diseases.
As such, in one embodiment, the present invention relates to the use of the compounds of any of Formulae I-IV, and pharmaceutically acceptable salts and/or prodrugs thereof, as active ingredients in the manufacture of a medicament for the regeneration of nerve cells. In other words, the present invention relates to the compounds of any of Formulae I-IV, and pharmaceutically acceptable salts and/or prodrugs thereof, for use for the regeneration of nerve cells. Similarly, the present invention relates to a method of regenerating nerve cells, comprising administering to a subject in need thereof an effective amount of a compound of any of Formulae I-IV, or a pharmaceutically acceptable salt and/or prodrug thereof.

Neuroprotection may be determined directly by, for example, measuring the delay or prevention of neuronal death, such as, for example, by a reduction in the number of apoptotic neurons in cerebrocortical cultures following a stress. Neuroprotection may also be determined directly by, for example, measuring the severity or extent of damage to, or functional loss by, a tissue or organ of the nervous system following such a stress, such as, for example, by measuring a decrease in the size of brain infarcts after occlusion of the middle cerebral artery (MCAO) or reperfusion injury. Also, neuroprotection can be identified by magnetic resonance imaging (measuring brain volume, tractography, levels of N-acetyl-aspartate by spectroscopy).

Alternatively, neuroprotection may be determined indirectly by detecting the activation of one or more biological mechanisms for protecting neurons, including, but not limited to, detecting activation of the Keap1/Nrf2 pathway or induction of one or more phase 2 enzymes, including but not limited to hemoxygenase-1 (HO-1). Methods of detecting and measuring neuronal protection are provided in the Examples below, and other such methods are known in the art.

The various uses and methods employing the compounds of any of Formulae I-IV, and pharmaceutically salts and/or prodrugs thereof, in the present invention comprise acute administration, i.e. occurring within several minutes to about several hours from injury, or chronic administration, suitable for chronic neurological or psychiatric diseases.
In one embodiment of the present invention, in the various uses and methods of neuroprotection or of prevention or treatment of nerve cell death or damage, the compounds of any of Formulae I-IV, and pharmaceutically acceptable salts and/or prodrugs thereof, are administered to a subject with a neurological or psychiatric disease.

Neurological diseases are those disorders of the central and peripheral nervous system, including disorders of the brain, spinal cord, cranial nerves, peripheral nerves, nerve roots, autonomic nervous system, neuromuscular junction, and muscle.

Diseases of the central and peripheral nervous system, which may be subject of prevention and/or treatment according to present invention include, without being limited to, as knowledge in clinical manifestations advances, Absence of the Septum Pellucidum, Acid Lipase Disease, Acid Maltase Deficiency, Acquired Epileptiform Aphasia, Acute Disseminated Encephalomyelitis, Adie’s Pupil, Adie’s Syndrome, Adrenoleukodystrophy, Agenesis of the Corpus Callosum, Agnosia, Aicardi Syndrome, Aicardi-Goutieres Syndrome Disorder, AIDS - Neurological Complications, Alexander Disease, Alpers' Disease, Alternating Hemiplegia, Alzheimer's Disease, Amyotrophic Lateral Sclerosis, Anencephaly, Aneurysm, Angelman Syndrome, Angiomatosis, Anoxia, Antiphospholipid Syndrome, Aphasia, Apraxia, Arachnoid Cysts, Arachnoiditis, Arnold-Chiari Malformation, Arteriovenous Malformation, Asperger Syndrome, Ataxia, Ataxia Telangiectasia, Ataxias and Cerebellar or Spinocerebellar Degeneration, Atrial Fibrillation and Stroke, Attention Deficit-Hyperactivity Disorder (ADHD), Autism, Autonomic Dysfunction, Back Pain, Barth Syndrome, Batten Disease, Becker's Myotonia, Behcet's Disease, Bell's Palsy, Benign Essential Blepharospasm, Benign Focal Amyotrophy, Benign Intracranial Hypertension, Bernhardt-Roth Syndrome, Binswanger's Disease, Blepharospasm, Bloch-Sulzberger Syndrome, Brachial Plexus Birth Injuries, Brachial Plexus Injuries, Bradbury-Eggleston Syndrome, Brain and Spinal Tumors, Brain Aneurysm, Brain infarction, Brain ischemia, Brain Injury, Brown-Squard Syndrome, Bulbospinal Muscular Atrophy, CADASIL, Canavan Disease, Carpal Tunnel Syndrome, Causalgia, Cavernomas, Cavernous Angioma, Cavernous Malformation, Central
Cervical Cord Syndrome, Central Cord Syndrome, Central Pain Syndrome, Central Pontine Myelinolysis, Cephalic Disorders, Ceramidase Deficiency, Cerebellar Degeneration, Cerebellar Hypoplasia, Cerebral Aneurysm, Cerebral Arteriosclerosis, Cerebral Atrophy, Cerebral Beriberi, Cerebral Cavernous Malformation, Cerebral Gigantism, Cerebral Hypoxia, Cerebral Palsy, Cerebro-Oculo-Facio-Skeletal Syndrome, Charcot-Marie-Tooth Disease, Chiari Malformation, Cholesterol Ester Storage Disease, Chorea, Choreoacanthocytosis, Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), Chronic Orthostatic Intolerance, Chronic Pain, Cockayne Syndrome Type II, Coffin Lowry Syndrome, COFS, Colpocephaly, Coma, Complex Regional Pain Syndrome, Congenital Facial Diplegia, Congenital Myasthenia, Congenital Myopathy, Congenital Vascular Cavernous Malformations, Corticobasal Degeneration, Cranial Arteritis, Craniosynostosis, Creutzfeldt-Jakob Disease, Cumulative Trauma Disorders, Cushing's Syndrome, Cytomegalic Inclusion Body Disease, Cytomegalovirus Infection, Dancing Eyes-Dancing Feet Syndrome, Dandy-Walker Syndrome, Dawson Disease, De Morier's Syndrome, Deep Brain Stimulation for Parkinson's Disease, Dejerine-Klumpke Palsy, Dementia, Dementia - Multi-Infarct, Dementia - Semantic, Dementia - Subcortical, Dementia With Lewy Bodies, Dentate Cerebellar Ataxia, Dentatorubral Atrophy, Dermatomyositis, Developmental Dyspraxia, Devic's Syndrome, Diabetic Neuropathy, Diffuse Sclerosis, Dravet Syndrome, Dysautonomia, Dysgraphia, Dyslexia, Dysphagia, Dyspraxia, Dyssynergia Cerebellaris Myoclonica, Dyssynergia Cerebellaris Progressiva, Dystonias, Early Infantile Epileptic Encephalopathy, Empty Sella Syndrome, Encephalitis, Encephalitis Lethargica, Encephaloceles, Encephalopathy, Encephalopathy, familial infantile, with intracranial calcification and chronic cerebrospinal fluid lymphocytosis; Cree encephalitis; Pseudo-Torch syndrome; Pseudotoxoplasmosis syndrome, Encephalotrigeminal Angiomatosis, Epilepsy, Epileptic Hemiplegia, Erb-Duchenne and Dejerine-Klumpke Palsies, Erb's Palsy, Essential Tremor, Extrapontine Myelinolysis, Fabry Disease, Fahr's Syndrome, Fainting, Familial Dysautonomia, Familial Hemangioma, Familial Idiopathic Basal Ganglia Calcification, Familial Periodic Paralyses, Familial Spastic Paralysis, Farber's Disease, Febrile Seizures, Fibromuscular Dysplasia, Fisher Syndrome, Floppy Infant Syndrome, Foot Drop, Friedreich's Ataxia, Frontotemporal Dementia, Gangliosidoses,
with Orthostatic Hypotension, Muscular Dystrophy, Myasthenia - Congenital, Myasthenia Gravis, Myelinoclastic Diffuse Sclerosis, Myoclonic Encephalopathy of Infants, Myoclonus, Myopathy, Myopathy - Congenital, Myopathy - Thyrotoxic, Myotonia, Myotonia Congenita, Narcolepsy, Neuroacanthocytosis, Neurodegeneration with Brain Iron Accumulation, Neurofibromatosis, Neuroleptic Malignant Syndrome, Neurological Complications of AIDS, Neurological Complications Of Lyme Disease, Neurological Consequences of Cytomegalovirus Infection, Neurological Manifestations of Pompe Disease, Neurological Sequelae Of Lupus, Neuromyelitis Optica, Neuromyotonia, Neuronal Ceroid Lipofuscinosis, Neuronal Migration Disorders, Neuropathy - Hereditary, Neurosarcoidosis, Neurotoxicity, Nevus Cavernosus, Niemann-Pick Disease, Normal Pressure Hydrocephalus, Occipital Neuralgia, Ohtahara Syndrome, Olivopontocerebellar Atrophy, Opsoclonus Myoclonus, Orthostatic Hypotension, O' Sullivan-McLeod Syndrome, Overuse Syndrome, Pain - Chronic, Pantothenate Kinase-Associated Neurodegeneration, Paraneoplastic Syndromes, Paresthesia, Parkinson's Disease, Paroxysmal Choreoathetosis, Paroxysmal Hemicrania, Parry-Romberg, Pelizaeus-Merzbacher Disease, Pena Shokeir II Syndrome, Perineural Cysts, Periodic Paralyses, Peripheral Neuropathy, Periventricular Leukomalacia, Persistent Vegetative State, Pervasive Developmental Disorders, Phytic Acid Storage Disease, Pick's Disease, Pinched Nerve, Piriformis Syndrome, Pituitary Tumors, Polymyositis, Pompe Disease, Porencephaly, Postherpetic Neuralgia, Postinfectious Encephalomyelitis, Post-Polio Syndrome, Postural Hypotension, Postural Orthostatic Tachycardia Syndrome, Postural Tachycardia Syndrome, Primary Dentatum Atrophy, Primary Lateral Sclerosis, Primary Progressive Aphasia, Prion Diseases, Progressive Hemifacial Atrophy, Progressive Locomotor Ataxia, Progressive Multifocal Leukoencephalopathy, Progressive Sclerosing Poliodystrophy, Progressive Supranuclear Palsy, Prosopagnosia, Pseudotumor Cerebri, Ramsay Hunt Syndrome I (formerly known as dyssynergia cerebellaris myoclonica, dyssynergia cerebellaris progressiva, dentatorubral degeneration, or Ramsey Hunt cerebellar syndrome), Ramsay Hunt Syndrome II (formerly known as herpes zoster oticus), Rasmussen's Encephalitis, Reflex Sympathetic Dystrophy Syndrome, Refsum Disease, Refsum Disease - Infantile, Repetitive Motion Disorders, Repetitive Stress Injuries, Restless

Psychiatric disorders, which may be the subject of prevention and/or treatment according to the present invention include those listed by the Diagnostic and
Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) published by the American Psychiatric Association, and covers all mental health disorders for both children and adults. In particular, psychiatric disorders include a disorder selected from Acute Stress Disorder; Adjustment Disorder Unspecified; Adjustment Disorder with Anxiety; Adjustment Disorder with Depressed Mood; Adjustment Disorder with Disturbance of Conduct; Adjustment Disorder with Mixed Anxiety and Depressed Mood; Adjustment Disorder with Mixed Disturbance of Emotions and Conduct; Agoraphobia without History of Panic Disorder; Anorexia Nervosa; Antisocial Personality Disorder; Anxiety Disorder Due to Medical Condition; Anxiety Disorder, NOS; Avoidant Personality Disorder; Bipolar Disorder NOS; Bipolar I Disorder, Most Recent Episode Depressed, In Full Remission; Bipolar I Disorder, Most Recent Episode Depressed, In Partial Remission; Bipolar I Disorder, Most Recent Episode Depressed, Mild; Bipolar I Disorder, Most Recent Episode Depressed, Moderate; Bipolar I Disorder, Most Recent Episode Depressed, Severe With Psychotic Features; Bipolar I Disorder, Most Recent Episode Depressed, Severe Without Psychotic Features; Bipolar I Disorder, Most Recent Episode Depressed, Unspecified; Bipolar I Disorder, Most Recent Episode Manic, In Full Remission; Bipolar I Disorder, Most Recent Episode Manic, In Partial Remission; Bipolar I Disorder, Most Recent Episode Manic, Mild; Bipolar I Disorder, Most Recent Episode Manic, Moderate; Bipolar I Disorder, Most Recent Episode Manic, Severe With Psychotic Features; Bipolar I Disorder, Most Recent Episode Manic, Severe Without Psychotic Features; Bipolar I Disorder, Most Recent Episode Mixed, In Full Remission; Bipolar I Disorder, Most Recent Episode Mixed, In Partial Remission; Bipolar I Disorder, Most Recent Episode Mixed, Mild; Bipolar I Disorder, Most Recent Episode Mixed, Moderate; Bipolar I Disorder, Most Recent Episode Mixed, Severe With Psychotic Features; Bipolar I Disorder, Most Recent Episode Mixed, Severe Without Psychotic Features; Bipolar I Disorder, Most Recent Episode Mixed, Unspecified; Bipolar I Disorder, Most Recent Episode Unspecified; Bipolar I Disorder, Most Recent Episode Hypomanic; Bipolar I Disorder, Single Manic Episode, In Full Remission; Bipolar I Disorder, Single Manic Episode, In Partial Remission; Bipolar I Disorder, Single Manic Episode, Mild; Bipolar I Disorder, Single Manic Episode, Moderate; Bipolar I Disorder, Single Manic Episode,
Severe With Psychotic Features; Bipolar I Disorder, Single Manic Episode, Severe Without Psychotic Features; Bipolar I Disorder, Single Manic Episode, Unspecified; Bipolar II Disorder; Body Dysmorphic Disorder; Borderline Personality Disorder; Breathing-Related Sleep Disorder; Brief Psychotic Disorder; Bulimia Nervosa; Circadian Rhythm Sleep Disorder; Conversion Disorder; Cyclothymic Disorder; Delusional Disorder; Dependent Personality Disorder; Depersonalization Disorder; Depressive Disorder NOS; Dissociative Amnesia; Dissociative Disorder NOS; Dissociative Fugue; Dissociative Identity Disorder; Dyspareunia; Dyssomnina NOS; Dyssomnia Related to Another Disorder; Dysthymic Disorder; Eating Disorder NOS; Exhibitionism; Female Dyspareunia Due to Medical Condition; Female Hypoactive Sexual Desire Disorder Due to Medical Condition; Female Orgasmic Disorder; Female Sexual Arousal Disorder; Fetishism; Frotteurism; Gender Identity Disorder in Adolescents or Adults; Gender Identity Disorder in Children; Gender Identity Disorder NOS; Generalized Anxiety Disorder; Histrionic Personality Disorder; Hypoactive Sexual Desire Disorder; Hypochondriasis; Impulse-Control Disorder NOS; Insomnia Related to Another Disorder; Intermittent Explosive Disorder; Kleptomania; Major Depressive Disorder, Recurrent, In Full Remission; Major Depressive Disorder, Recurrent, In Partial Remission; Major Depressive Disorder, Recurrent, Mild; Major Depressive Disorder, Recurrent, Moderate; Major Depressive Disorder, Recurrent, Severe With Psychotic Features; Major Depressive Disorder, Recurrent, Severe Without Psychotic Features; Major Depressive Disorder, Recurrent, Unspecified; Major Depressive Disorder, Single Episode, In Full Remission; Major Depressive Disorder, Single Episode, In Partial Remission; Major Depressive Disorder, Single Episode, Mild; Major Depressive Disorder, Single Episode, Moderate; Major Depressive Disorder, Single Episode, Severe With Psychotic Features; Major Depressive Disorder, Single Episode, Severe Without Psychotic Features; Major Depressive Disorder, Single Episode, Unspecified; Male Dyspareunia Due to Medical Condition; Male Erectile Disorder; Male Erectile Disorder Due to Medical Condition; Male Hypoactive Sexual Desire Disorder Due to Medical Condition; Male Orgasmic Disorder; Mood Disorder Due to Medical Condition; Narcissistic Personality Disorder; Narcolepsy; Nightmare Disorder; Obsessive Compulsive Disorder; Obsessive-Compulsive Personality Disorder; Other Female
Sexual Dysfunction Due to Medical Condition; Other Male Sexual Dysfunction Due to Medical Condition; Pain Disorder Associated with both Psychological Factors and Medical Conditions; Pain Disorder Associated with Psychological Features; Panic Disorder with Agoraphobia; Panic Disorder without Agoraphobia; Paranoid Personality Disorder; Paraphilia, NOS; Parasomnia NOS; Pathological Gambling; Pedophilia; Personality Disorder NOS; Posttraumatic Stress Disorder; Premature Ejaculation; Primary Hypersomnia; Primary Insomnia; Psychotic Disorder Due to Medical Condition, with Delusions; Psychotic Disorder Due to Medical Condition, with Hallucinations; Psychotic Disorder, NOS; Pyromania; Schizoaffective Disorder; Schizoid Personality Disorder; Schizophrenia, Catatonic Type; Schizophrenia, Disorganized Type; Schizophrenia, Paranoid Type; Schizophrenia, Residual Type; Schizophrenia, Undifferentiated Type; Schizophreniform Disorder; Schizotypal Personality Disorder; Sexual Aversion Disorder; Sexual Disorder NOS; Sexual Dysfunction NOS; Sexual Masochism; Sexual Sadism; Shared Psychotic Disorder; Sleep Disorder Due to A Medical Condition, Hypersomnia Type; Sleep Disorder Due to A Medical Condition, Insomnia Type; Sleep Disorder Due to A Medical Condition, Mixed Type; Sleep Disorder Due to A Medical Condition, Parasomnia Type; Sleep Terror Disorder; Sleepwalking Disorder; Social Phobia; Somatization Disorder; Somatoform Disorder NOS; Specific Phobia; Transvestic Fetishism; Trichotillomania; Undifferentiated Somatoform Disorder; Vaginismus; and Voyeurism.

Preferably, the compounds of any of Formulae I-IV, and pharmaceutically acceptable salts and/or prodrugs thereof, can be used in the treatment of diseases wherein NGF has been proven effective in the state of the art, either in vivo or in vitro, due to their improving effects on cell differentiation and cell survival, through either TrkA and/or p75 pathways. Therefore, the compounds covered in the present invention can be used in the treatment of neurological diseases selected among: neurodegenerative disorders, such as amyotrophic lateral sclerosis (ALS), Parkinson’s disease, Alzheimer’s disease, Friedreich’s ataxia, Huntington’s disease, Dementia with Lewy bodies, spinal muscular atrophy; nerve inflammation, such as multiple sclerosis and neuromyelitis optica, major depressive disorder, schizophrenia, glaucoma, or peripheral neuropathies, such as diabetic or AIDS neuropathy. Moreover, the
compounds of the invention can also be indicated for treatment of cancer, by modulating NGF cell differentiation activity and stopping cell proliferation. Among the cancer types in which NGF has been proven effective in the state of the art, either in vivo or in vitro, due to improving effects on cell differentiation and cell survival, through either TrkA and/or p75 pathways, the following may be cited: glioblastoma, astrocytoma, medulloblastoma, neurinoma, neuroblastoma, meningioma, colon cancer, pancreatic cancer, breast cancer, prostate cancer, leukemia, acute lymphocytic leukemia, osteosarcoma, hepatocellular carcinoma, ovarian carcinoma, lung adenocarcinoma or esophageic carcinoma.

In one embodiment of the present invention, in the various uses and methods of neuroprotection or of prevention or treatment of nerve cell death or damage, the compounds of any of Formulae I-IV, and pharmaceutically acceptable salts and/or prodrugs thereof, are administered to a healthy subject, preferably a healthy subject older than 18 years old, more preferably a healthy subject older than 45 years old, even more preferably a healthy subject older than 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 years old.

The term “healthy subject” is meant to comprise its plain meaning as well as those subjects that may suffer from one or more pathological conditions other than a neurological or psychiatric disease.

The neuroprotective properties of the compounds of any of Formulae I-IV, and pharmaceutically salts and/or prodrugs thereof, have as a consequence the partial or full prevention or treatment of the various disorders in the nervous system functions caused by the neuronal cell death or damage. Therefore, the present invention further relates to the use of the compounds of any of Formulae I-IV, its pharmaceutically acceptable salts and/or prodrugs thereof, as active ingredients in the manufacture of a medicament for the prevention or treatment of a neurological or psychiatric disease.

In other words, the present invention also relates to the compounds of any of Formulae I-IV, and pharmaceutically acceptable salts and/or prodrugs thereof, for use in the prevention or treatment of a neurological or psychiatric disease. Similarly, the
present invention also relates to a method of prevention or treatment of a neurological or psychiatric disease comprising administering to a subject in need thereof an effective amount of the compound of any of Formulae I-IV, or a pharmaceutically acceptable salt and/or prodrug thereof. The neurological or psychiatric disease may be any one from those listed above.

Preferably, the neurological or psychiatric disease is selected from neurodegenerative disorders, inflammation and certain types of cancers, multiple sclerosis, neuromyelitis optica, amyotrophic lateral sclerosis (ALS), Parkinson's disease, Alzheimer's disease, Friedreich's ataxia, Huntington's disease, Dementia with Lewy bodies, spinal muscular atrophy, major depressive disorder, schizophrenia, glaucoma or peripheral neuropathies (diabetic or AIDS neuropathy).

Another goal of present invention is the use of the compounds of any of Formulae I-IV, and pharmaceutically acceptable salts and/or prodrugs thereof, as neuroenhancing drugs or the use for manufacturing neuroenhancing drugs.

Neuroenhancing drugs include those that improve learning and memory, attention, mood, communicative skills and sexual performance. Examples of neuroenhancing drugs are those that target long-term synaptic potentiation (LTP) or long-term depression (LTD), modulation of calcium channels, or the cAMP response element-binding (CREB) protein. cAMP is the acronym for cyclic adenosine monophosphate. Particular examples of neuroenhancing drugs are phosphodiesterase inhibitors like rolipram; donepezil; agonists of the NMDA glutamate receptor like D-cycloserine; ampakines; modafinil; methylphenidate.

The compounds of any of Formulae I-IV, and pharmaceutically acceptable salts and/or prodrugs thereof, may be formulated into various pharmaceutical forms for administration purposes. As appropriate compositions there may be cited all compositions usually employed for systemically administering drugs, for example any solid (e.g. tablets, capsules, granules, etc.) or liquid composition (e.g. solutions, suspensions, emulsions, etc). To prepare the pharmaceutical compositions of the
compounds of any of Formulae I-IV, an effective amount of the compound of any of
Formulae I-IV, optionally in salt form or a prodrug, as the active ingredient is
combined in intimate admixture with a pharmaceutically acceptable carrier, which
carrier may take a wide variety of forms depending on the form of preparation desired
for administration. These pharmaceutical compositions are desirable in unitary
dosage form suitable, particularly, for administration orally, rectally, percutaneously,
intrathecal, intravenous or by parenteral injection. For example, in preparing the
compositions in oral dosage form, any of the usual pharmaceutical media may be
employed such as, for example, water, glycols, oils, alcohols and the like in the case
of oral liquid preparations such as suspensions, syrups, elixirs, emulsions and
solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders,
disintegrating agents and the like in the case of powders, pills, capsules, and tablets.
Because of their ease in administration, tablets and capsules represent the most
advantageous oral dosage unit forms, in which case solid pharmaceutical carriers are
obviously employed. For parenteral compositions, the carrier usually comprises
sterile water, at least in large part, though other ingredients, for example, to aid
solubility, may be included. Injectable solutions, for example, may be prepared in
which the carrier comprises saline solution, glucose solution or a mixture of saline and
glucose solution. Injectable suspensions may also be prepared in which case
appropriate liquid carriers, suspending agents and the like may be employed. Also
included are solid form preparations, which are intended to be converted, shortly
before use, to liquid form preparations. In the compositions suitable for percutaneous
administration, the carrier optionally comprises a penetration enhancing agent or a
suitable wetting agent, or both, optionally combined with suitable additives of any
nature in minor proportions, which additives do not introduce a significant deleterious
effect on the skin. A review of the different pharmaceutical forms for drug
administration and their preparation may be found in the book “Tratado de Farmacia

It is especially advantageous to formulate the aforementioned pharmaceutical
compositions in unit dosage form for ease of administration and uniformity of dosage.
Unit dosage form as used herein refers to physically discrete units suitable as unitary
dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such unit dosage forms are tablets (including scored or coated tablets), capsules, pills, suppositories, powder packets, wafers, injectable solutions or suspensions and the like, and segregated multiples thereof.

The compositions in accordance with this invention, including unit dosage forms, may contain the active ingredient in an amount that is in the range of about 0.1% to 70%, or about 0.5% to 50%, or about 1% to 25%, or about 5% to 20%, the remainder comprising the carrier, wherein the foregoing percentages are w/w versus the total weight of the composition or dosage form.

The dose of the compound of any of Formulae I-IV, its pharmaceutically acceptable salt and/or prodrug thereof, to be administered depends on the individual case and, as customary, is to be adapted to the conditions of the individual case for an optimum effect. Thus it depends, of course, on the frequency of administration and on the potency and duration of action of the compound employed in each case for therapy or prophylaxis, but also on the nature and severity of the disease and symptoms, and on the sex, age, weight co-medication and individual responsiveness of the subject to be treated and on whether the therapy is acute or prophylactic. Doses may be adapted in function of weight and for pediatric applications. Daily doses may be administered q.d. or in multiple quantities such as b.i.d., t.i.d. or q.i.d.

**Synthesis of Compounds**

The compounds of the present invention can be prepared using methods known to those skilled in the art in view of this disclosure. For example, compounds of the present invention can be prepared as described in Masip, et al., 2005.

**Testing of Compounds**

In addition to the tests described in the Examples, the compounds of the present invention can be tested in *in vitro* model for Parkinson's disease as follows: The human neuroblastoma cell line SH-SY5Y is used to study the neuroprotective effect of
the tested molecules in Parkinson disease. The cells are pre-treated for 3 hours with the tested molecules at different concentrations (20 ng/ml, 100 ng/ml, 2 μg/ml, 20 μg/ml and 50 μg/ml) with the tested molecules (100ng/ml). Then 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (100 μM) is added and incubated for 24 hrs. The number of surviving cells is determined the day after by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay.

The compounds of the present invention can also be tested in an Alzheimer disease in vitro model as follows: The human neuroblastoma cell line SH-SY5Y is used to study the neuroprotective effect of the tested compound in Alzheimer disease. The cells are pre-treated for 3 hours with the tested compound at different concentrations (20 ng/ml, 100 ng/ml, 2 μg/ml, 20 μg/ml and 50 μg/ml) with the tested compound (100 ng/ml). Then Amyloid beta fibrils (100 μM) is added and incubated for 24 hrs. The number of surviving cells is determined the day after by 3-(4,5-dimethylthiazol-2-yl)-2,5-
diphenyltetrazolium bromide (MTT) assay.

Further, the compounds of the present invention can be tested in a glaucoma model as follows: 12 Sprague Dawley rats (4 months of age) are anesthetized with isobutane and subjected to hypertonic saline solution injection into the episcleral vein of the right eye. Intraocular pressure is measured before the operation and is monitored one time a week using a TonoLab for 7 weeks. Treatment with the tested molecules begins one week after glaucoma induction by topical application at the conjunctive. The test molecule is dissolved into physiological solution and is used at two different concentration (200 μg/ml and 400 μg/ml). NGF is used as positive control (200 μg/ml) and the physiological solution, used to dissolve all the molecules, is subministered as placebo. The animals are divided into 4 groups (3 animals in each group): glaucoma-test molecule 200 μg/ml; glaucoma-test molecule 400 μg/ml; glaucoma-NGF; glaucoma-placebo. Three animals are used as control without glaucoma. Seven weeks after glaucoma induction, animals are sacrificed by overdose of anaesthetic and their eyes are taken and fixed in 4% of PFA. The eyes are included in paraffin and cut into 20 μm sections to be used for histological studies.
(hematoxilin-eosin staining). The cell count of the number of retinal ganglion cells (RGC) is performed randomly in ten different fields for each eye.

The following examples are illustrative, but not limiting, of the compounds, compositions and methods of the present invention. Suitable modifications and adaptations of the variety of conditions and parameters normally encountered in clinical therapy and which are obvious to those skilled in the art in view of this disclosure are within the spirit and scope of the invention.

Examples
EXAMPLE 1

Design of NGF agonists by combinatorial chemistry

General. Solvents, amines and other reagents were purchased from commercial suppliers and used without further purification. Reactions carried out under microwave irradiation were conducted in a 100 mL round bottomed flask equipped with a Dimroth condenser. The flask was introduced in the monomode cavity of a CEM Model Discover apparatus. The NMR spectra were recorded on a Varian Inova 500 apparatus (1H NMR, 500 MHz; 13C NMR, 125 MHz) and on a Unity 300 apparatus (1H NMR, 300 MHz; 13C NMR, 75 MHz). When appropriate, the assignment of 1H and 13C NMR peaks for compounds were confirmed by gDQCOSY and gHSQC experiments. The occurrence of different conformers led to highly complex spectra; the absorptions given below are referred to the major conformer present in the sample. The RP-HPLC analyses were performed with a Hewlett Packard Series 1100 (UV detector 1315A) modular system using a reverse-phase Kromasil 100 C8 (25 x 0.46 cm, 5 μm) column, with CH3CN-buffer ammonium formate (20 mM, pH=5.0) mixtures at 1 mL/min as mobile phase and monitoring at 220 nm. Semi-preparative RP-HPLC was performed with a Waters (Milford, MA, U.S.A.) system. High resolution mass spectra (HRMS-FAB) were carried out at the IQAC - Instituto de Química Avanzada de Cataluña - (Spain).

Synthesis of individual peptoids. The synthesis of individual peptoids N35-4-8C, N35-4-17C and N6-4-17C for the in vitro and in vivo assays was carried out
following the substructure procedure reported by the group of Zuckermann with some modifications (Zuckermann et al, 1992)

The synthesis was carried out on a 1% cross-linked polystyrene resin bearing the Fluorenylmethoxycarbonyl (Fmoc)-protected Rink amide linker AM RAM (0.79 mmol/g, Rapp Polymer; Germany). A suspension of 4 g of resin in 50 mL DMF was placed in a 100 mL round bottomed flask provided with a magnetic stirrer. The suspension was stirred for 5 min at 20 °C, the solvent was removed by filtration through a 60 mL polypropylene syringe provided with a polyethylene porous plaque. Then, resin was transferred again to the reaction flask.

1. *Fmoc deprotection*. A solution of 60 mL of 20% piperidine in DMF was added to the round bottomed flask containing the resin. The mixture was allowed to react under microwave activation for 5 min at 60 °C and 150 W. The resin was drained on the 60 mL syringe and washed with 40 mL DMF. The treatment was carried out in duplicate. Then, the resin was filtered and washed with DMF (3 × 40 mL), iPrOH (3 × 40 mL), and CH₂Cl₂ (3 × 40 mL). Finally, it was drained for 2 min and transferred to the reaction flask. The deprotection was monitored by using the TNBS test (red colour as positive).

2. *First acylation*. The resin was treated with a solution of 5 equivalents of bromoacetic acid (2.2 g, 15.8 mmol) and 5 equivalents of N,N-diisopropylcarbodiimide (2.5 mL, 15.8 mmol) in 50 mL of DMF. The acylation was conducted under microwave irradiation (5 min, 60 °C, 150 W). Then, the resin was filtered using the syringe, and washed with 40 mL of DMF. The reaction was carried out in duplicate. Afterwards, the resin was filtered and washed with DMF (3 × 40 mL), iPrOH (3 × 40 mL), and CH₂Cl₂ (4 × 10 mL). Next, it was drained for 2 min and the absence of primary amine was evaluated by TNBS test.

3. *First Amination coupling*. A suspension of the acylated resin in 50 mL DMF was treated with the suitable primary amine according to the final compound: 5 equivalents (2.2 mL, 15.8 mmol) of 2.2 mL 1-(3-aminopropyl)-2-pyrrolidinone, or 5 equivalents (3.2 g, 15.8 mmol) of 4-(2-aminoethyl)benzenesulfonamide. The reaction
was conducted under microwave irradiation (7 min, 80 °C, 150 W). The reaction was carried out in duplicate, washing and draining the resin through the syringe between the treatments. Finally, the resin was drained for 2 min and transferred to the flask. The incorporation of the amine was confirmed by the chloranil test (green colour for secondary amines).

4. Second and third acylation steps. They were carried out similarly to the first acylation step. In this case, two acylation treatments were enough to complete the reaction.

5. Second and third amination coupling steps. They were carried out similarly to the first amination step, but using the corresponding primary amines. Thus, 5 equivalents (1.8 ml, 15.8 mmol) of 3-methyl-1-butanimine were used for the second amination coupling. For the third amination, 5 equivalents (2.0 mL, 15.8 mmol) of 2-(2-fluorophenyl)ethanamine or 5 equivalents (2.0 mL, 15.8 mmol) of 2-(1-pyrrolidinyl)ethanamine were used as according to the composition of the corresponding peptoid.

6. Cleavage. After draining the resin, it was divided into 4 aliquots and each one was treated with 20 mL of the cleavage cocktail (60:40:2 (v/v/v) TFA/CH₂Cl₂/H₂O). The mixtures were stirred for 30 min at 20 °C and filtered through a 10 mL polypropylene syringes provided with a polyethylene porous plaque. The filtrates were collected in a 250 mL flask and solvents were removed under reduced pressure. Finally, the yellow oil residue that was obtained for the case of each peptoid was redissolved in H₂O/ACN mixture and lyophilized to give 1.25-1.80 g of the expected crude peptoid in purities higher than 85% by HPLC.

7. Purification and chemical characterization. Compounds were purified by semipreparative HPLC using a Waters PrePack®-C₁₈ (47 x 300 mm, 15-20 μm) column, eluting with CH₃CN/H₂O mixtures containing 0.1% TFA as mobile phases, and a flow rate of at 60 mL/min. a) Solvent gradient used for N35-4-8C: 10 min at 20% ACN, 60 min from 20% to 80%, 10 min from 80% to 100% and 10 min at 100% CAN; b) for N35-4-17C and N6-4-17C: 10 min at 10% ACN, 50 min
from 10% to 50%, 20 min from 50% to 80%, 10 min from 80% to 100% and 10 min at 100% ACN. Final compounds were obtained in purities higher to 98% by HPLC. Quantities obtained were: 830 mg of N35-4-8C (56% yield), 698 mg of N35-4-17C (40% yield), 863 mg of N6-4-17C (51% yield).

\[ \text{N-(2'(2'-Fluorophenyl)ethyl)glycyl-[N-(3-methylbutyl)glycyl]-N-[3-(2'-oxopyrrrolidinyl)propyl]glycinamide (N35-4-8C).} \]

$^1$H NMR (500 MHz, CD$_3$OD) $\delta$ 7.34 (1H, H$_A$), 7.32 (1H, H$_A$), 7.17 (1H, H$_A$), 7.12 (1H, H$_A$), 4.4-3.9 (6H, 3 x COCH$_3$N), 3.5-3.2 (10H, 4 x NCH$_2$CH$_2$ + 1 x HNCH$_2$CH$_2$), 3.10 (2H, HNCH$_2$CH$_2$), 2.36 (2H, COCH$_2$CH$_2$), 2.03 (2H, COCH$_2$CH$_2$), 1.9-1.7 (2H, NCH$_2$CH$_2$CH$_2$N), 1.60 (1H, (CH$_3$)$_2$CHCH$_2$CH$_2$N), 1.6-1.4 (2H, (CH$_3$)$_2$CHCH$_2$CH$_2$N), 0.94 (6H, (CH$_3$)$_2$CHCH$_2$CH$_2$N); 13C NMR (125 MHz, CD$_3$OD) $\delta$ 177.8 (CO), 170.9 (CO), 167.6 (CO), 166.7 (CO), 162.5 (C$_A$), 132.2 (CH$_A$), 130.6 (CH$_A$), 125.8 (C$_A$), 124.5 (C$_A$), 116.5 (CH$_A$), 50.8 (COCH$_3$N), 50.1 (COCH$_2$N), 49.9 (COCH$_2$N), 48.4 (HNCH$_2$CH$_2$), 48.2 (NCH$_2$CH$_2$), 46.9 (NCH$_2$CH$_2$), 46.4 (NCH$_2$CH$_2$), 41.2 (NCH$_2$CH$_2$), 37.1 ((CH$_3$)$_2$CHCH$_2$CH$_2$N), 32.0 (COCH$_2$CH$_2$), 27.1 ((CH$_3$)$_2$CHCH$_2$CH$_2$N), 27.0 (HNCH$_2$CH$_2$), 25.9 (NCH$_2$CH$_2$CH$_2$N), 22.8 (2 x (CH$_3$)$_2$CHCH$_2$CH$_2$N), 18.8 (COCH$_2$CH$_2$); HRMS calcd for C$_{26}$H$_{41}$FN$_5$O$_4$ 506.3143 (M + H)$^+$, found 506.3144.

\[ \text{N-(2'(2'-Fluorophenyl)ethyl)glycyl-[N-(3-methylbutyl)glycyl]-N-[2-(4'-sulfamoylphenyl)ethyl] glycinamide (N35-4-17C).} \]

$^1$H NMR (500 MHz, CD$_3$OD) $\delta$ 7.88 (d, $^3$J$_{HH}$=8 Hz, 2H, H$_A$), 7.46 (d, $^3$J$_{HH}$=8 Hz, 2H, H$_A$), 7.41 (1H, H$_A$), 7.38 (1H, H$_A$), 7.23 (1H, H$_A$), 7.16 (1H, H$_A$), 4.3-3.8 (6H, 3 x COCH$_3$N), 3.65 (2H, NCH$_2$CH$_2$C$_A$), 3.5-3.3 (4H, (CH$_3$)$_2$CHCH$_2$CH$_2$N + HNCH$_2$CH$_2$), 3.14 (2H, HNCH$_2$CH$_2$), 2.97 (t, $^3$J$_{HH}$=7.5 Hz, 2H, NCH$_2$CH$_2$C$_A$), 1.64 (1H, (CH$_3$)$_2$CHCH$_2$CH$_2$N), 1.6-1.3 (2H, (CH$_3$)$_2$CHCH$_2$CH$_2$N), 0.96 (6H, (CH$_3$)$_2$CHCH$_2$CH$_2$N); $^{13}$C NMR (125 MHz, CD$_3$OD) $\delta$ 170.7 (CO), 167.4 (CO), 166.7 (CO), 162.5 (C$_A$), 144.4 (C$_A$), 143.0 (C$_A$), 132.2 (CH$_A$), 130.8 (CH$_A$), 130.5 (2 x CH$_A$), 127.5 (2 x CH$_A$), 125.8 (CH$_A$), 124.4 (C$_A$), 116.6 (CH$_A$), 51.0 (COCH$_2$N), 50.3 (COCH$_2$N), 50.7 (NCH$_2$CH$_2$C$_A$), 49.9 (COCH$_2$N), 48.4 (HNCH$_2$CH$_2$), 47.5 (NCH$_2$CH$_2$), 37.0 ((CH$_3$)$_2$CHCH$_2$CH$_2$N), 34.4 (NCH$_2$CH$_2$C$_A$),
27.1 ((CH$_3$)$_2$CHCH$_2$CH$_2$N), 27.0 (HNCH$_2$CH$_2$), 22.8 (2 x (CH$_3$)$_2$CHCH$_2$CH$_2$N); HRMS calcd for C$_{27}$H$_{39}$FN$_5$O$_5$S 564.2656 (M + H$^+$), found 564.2640.

[N-(2-(1-Pyrrolidinyl)ethyl)glycyl]-[N-(3-methylbutyl)glycyl]-N-[2-(4'-sulfamoylphenyl)ethyl] glycinamide (N6-4-17C). $^1$H NMR (500 MHz, CD$_3$OD) $\delta$ 7.9-7.8 (2H, H$_{Ar}$), 7.5-7.4 (2H, H$_{Ar}$), 4.3-3.8 (6H, 3 x COCH$_2$N), 3.8-3.2 (12H, 4 x NCH$_2$CH$_2$ + HNCH$_2$CH$_2$), 3.1-2.9 (2H, NCH$_2$CH$_2$C$_{Ar}$), 2.12 (4H, NcycleCH$_2$CH$_2$CH$_2$CH$_2$), 1.60 (1H, (CH$_3$)$_2$CHCH$_2$CH$_2$N), 1.6-1.2 (2H, (CH$_3$)$_2$CHCH$_2$CH$_2$N), 0.92 (6H, (CH$_3$)$_2$CHCH$_2$CH$_2$N); $^{13}$C NMR (125 MHz, CD$_3$OD) $\delta$ 170.1 (CO), 167.3 (CO), 166.6 (CO), 144.6 (C$_{Ar}$), 143.1 (C$_{Ar}$), 130.5 (2 x CH$_{Ar}$), 127.6 (2 x CH$_{Ar}$), 55.7 (2 x NcycleCH$_2$CH$_2$), 51.3 (COCH$_2$N), 51.0 (COCH$_2$N), 50.9 (HNCH$_2$CH$_2$), 50.6 (COCH$_2$N), 50.3 (NCH$_2$CH$_2$C$_{Ar}$), 47.5 (NCH$_2$CH$_2$), 44.3 (HNCH$_2$CH$_2$), 37.1 ((CH$_3$)$_2$CHCH$_2$CH$_2$N), 34.3 (NCH$_2$CH$_2$C$_{Ar}$), 27.1 ((CH$_3$)$_2$CHCH$_2$CH$_2$N), 24.0 (NcycleCH$_2$CH$_2$CH$_2$CH$_2$), 22.8 (2 x (CH$_3$)$_2$CHCH$_2$CH$_2$N);

HRMS calcd for C$_{25}$H$_{43}$N$_6$O$_5$S 539.3016 (M + H$^+$), found 539.3022.

EXAMPLE 2

PC12 cell differentiation

N35-4-8C, N6-4-17C and N35-4-17C NGF-mimetic peptoids induce neuronal differentiation.

PC 12 cell differentiation was measured by plating cells onto collagen-coated 24-wells plates. NGF (100ng/ml) or the small chemicals at different concentrations were added and the percentage of cells with neurite processes greater than two cell bodies in length were counted after relevant treatment. For each experiment at least 300 cells were randomly measured (Burstein and Greene, 1978).

Cell culture. PC12 cells were maintained at 37°C in DMEM supplemented with 2.5% FBS, 15% of Horse serum (HS) and penicillin/streptomycin in a humidified 5% CO$_2$ incubator. The cells were grown on 60-and 100-mm tissue culture dishes (Becton Dickinson).
PC 12 cells were cultured for 3 days in the presence of the peptoids (from 2 ng/ml to 50 µg/ml) under reduced serum conditions (0.5% FBS and 1% HS). The peptoids N35-4-8C, N6-4-17C and N35-4-17C (FIG. 1) were found to induce the differentiation of PC12 cells at different concentrations to an extent substantially comparable with that induce by NGF (Foehr et al., 2000). Representative images of the activity of N35-4-17C on PC12 cells differentiation are shown in FIG. 1A. Similar activity was displayed by the peptoids N35-4-8C and N6-4-17C (FIG. 1B) showing a dose-response activity.

EXAMPLE 3

Survival assays

N35-4-8C, N6-4-17C and N35-4-17C NGF-mimetic peptoids promote myelin cells survival.

The library was also tested to assess their capacity to promote cell survival of myelin producing cells. To delineate p75 signalling independent of TrkA, we used a rat schwannoma cell line (RN22) expressing p75, but not TrkA, (Gentry et al., 2000).

Cell culture. The rat schwannoma cell line RN22 was cultured in 5% CO₂ at 37°C in Dulbecco’s modified Eagle’s medium (DMEM) with 10% fetal bovine serum (FBS) and penicillin/streptomycin.

RN22 cells were plated at 20,000 cells/well on a 24-well plate in DMEM alone and after allowing the cells to adhere for 3 days, cupper sulphate (CuSO4) (150 µM) was added with or without NGF (100 ng/ml) or the peptoids N35-4-8C, N6-4-17C and N35-4-17C at different concentrations (1 ng/ml – 10 µg/ml) to generate stress and cell death. After 24 h cell viability was studied by determining the amount of yellow MTT (Sigma) that was reduced to insoluble purple formazan. After removing the medium, the water-insoluble formazan was solubilised with DMSO (Sigma), and the dissolved material was measured spectrophotometrically at a wavelength of 570 nm, subtracting the background at 650 nm (Frade, 2005).
After 24 h, cell viability was tested and the peptoids N35-4-8C, N6-4-17C and N35-4-17C were found to promote survival of RN22 cells at different concentrations, the majority of them to an extent even higher than the NGF capacity (Foehr et al., 2000; Gentry et al., 2000)(FIG. 2).

EXAMPLE 4

Induction of TrkA, IκBa and SAPK/JNK phosphorylation

Activation of TrkA is the first event in the signalling cascade leading to differentiation and survival of NGF responsive neurons and PC12 cells (Greene and Tischler, 1976; Chao, 2003; Huang and Reichardt, 2003). To evaluate whether the neurotrophic activity of NGF-like peptoids was mediated by the interaction with TrkA receptor, we analyzed their capacity to induce TrkA phosphorylation in PC12 cells. The activity of peptoids was tested in the range of concentrations that were effective on PC12 cells differentiation.

*Western blot analysis.* Subconfluent cells were grown overnight in medium containing 2% FBS and 1% HS and stimulated with 100 ng/ml NGF or the NGF-like small chemicals for the indicated time points. Cells were then washed with cold phosphate-buffered saline (PBS) and briefly sonicated in SDS sample buffer (containing β-mercaptoethanol and 2 mM PMSF). Lysates (200 μg of total proteins) were separated on SDS-PAGE, and transferred to nitrocellulose (Whatman, Dassel, Germany). After blocking with 5% nonfat milk in TBST buffer (10mM Tris pH 7.5; 150 mM NaCl/0.2% Tween 20), blots were probed overnight at 4°C with anti-p-TrkA (Tyr 490) antibody (1:1000), anti TrkA antibody (1:1000), anti-p-IκBa (Ser 32/36)(5A5) mouse antibody (1/1000), anti IκBa (L35A5) mouse antibody (1:1000), anti-p-SAPK/JNK (Thr183/Tyr185) antibody (1:1000) or anti-SAPK/JNK antibody (1/1000)(all of them from Cell Signaling), followed by incubation with HRP-conjugated IgG (Jackson ImmunoResearch) for 1 h at room temperature (RT). Detection of phosphorylated species was performed by using the enhanced chemiluminescence (ECL) system (GE Healthcare Bio-Sciences, Piscataway, NJ).
Data in FIG. 3 show that the 3 peptoids induced significant TrkA phosphorylation although while NGF-stimulated TrkA phosphorylation had the maximum at 30 minutes and remained consistently high over a 2 hours time course, maximal values of the peptoids were shorter (5 or 15 minutes) and phosphorylation decreased at 30 minutes.

To investigate whether our NGF-like small chemicals activate p75 we analyzed the activation of the NF-κB pathway (Bonizzi G, Karin M. 2004) and the SAPK/JNK pathway (cell death) in PC12 and RN22 cell lines. Important for our studies, RN22 cells express high levels of the p75 receptor message and protein, whereas TrkA expression is undetectable (Gentry et al., 2000). NF-κB is functionally active as a transcriptional regulator in a dimeric form consisting of homo- or heterodimers, the prototypic NF-κB dimer consisting of the p65 and p50 subunits. The activation of NF-κB occurs primarily through the degradation of the IκB proteins, a family of inhibitory proteins bound to NF-κB dimers. In response to activating stimuli, the inhibitory proteins are phosphorylated, which targets them for ubiquitination and subsequent degradation. One member of the inhibitory family, IκBα, is degraded in response to the majority of the NF-κB activators (Ghosh et al., 1998). To examine NF-κB activation in response to NGF and the different selected peptoids, western blots of total cell extracts from RN22 and PC12 cells treated with NGF and the peptoids for varying times were probed with an antibody anti-phospho-IκBα (FIG. 4). Within 5 minutes after NGF addition p-IκBα levels were significantly increased prior to degradation. Phosphorylation of IκBα was also increased when the 3 peptoids were used but starting later (15 minutes after adding the compound) showing an activation of the pathway in PC12 and in RN22.

In several neuronal systems, JNK activation has been causally linked with the induction of programmed cell death (Bhakar et al., 2003). In culture, NGF signalling through p75 led to activation of both NF-Kb and JNK, resulting ultimately in programmed cell death (Yoon et al., 1998). To examine the activity of JNK in RN22 cells western blots were done with antibody anti-phospho-SAPK/JNK to assess
activation of the pathway. Activation of the JNK pathway was not seen with none of the peptoids (FIG. 4), although phosphorylation of SAP/JNK is obvious with NGF.

EXAMPLE 5

Effect of NGF-mimetic peptoids in encephalomyelitis autoimmune experimental, the animal model of Multiple Sclerosis

Animals, Experimental Autoimmune Encephalomyelitis Induction, and Treatment.

Trials were approved by the Parc Científic de Barcelona Committee on Animal Care. Female C57BL/6 mice from Harlan (8-12 weeks old) were immunized subcutaneously in both hind pads with 300 µg of myelin oligodendrocyte glycoprotein (MOG) peptide 35-55 (Spikem, Firenze) emulsified with 50 µg of Mycobacterium tuberculosis (H37Ra strain; Difco, Detroit, MI) in incomplete Freund’s adjuvant (IFA) as previously described (Adams et al. 2007). Mice were intraperitoneally injected with Pertussis toxin (Sigma)(500 ng) at the time of immunization and 2 days later. Animals were weighted and inspected for clinical signs of disease on a daily basis by a blinded observer. Disease severity of EAE was assessed according to the following scale: 0 = normal; 0.5 = mild limp tail; 1 = limp tail; 2 = mild paraparesis of the hind limbs, unsteady gait; 3 = moderate paraparesis, voluntary movements still possible; 4 = paraplegia or tetraparesis; 5 = moribund state. Data shown for the clinical studies are representative of two independent experiments performed with the indicated number of animals (Moreno et al., 2006).

The agonist molecules selected for the animal studies, N35-4-8C, N6-4-17C and N35-4-17C, were prepared in water with 5% DMSO. Animals were treated with the agonist molecule (25, 50 and 100 mg/kg) or placebo (water + 5% DMSO) through daily intraperitoneal injection starting after immunization. At the end of the study, mice were anesthetized and perfused intracardially with 4% of paraformaldehyde in 0.1M phosphate buffer (pH 7.6). Brains, spinal cords and spleens were dissected and either fixed or frozen until use. Serum was obtained from all animals included in the study, and transaminases levels were measured.
In order to evaluate the effects of the NGF-like peptoids “in vivo”, we studied the effect of the NGF-mimetic peptoids in the animal model of MS. C57BL/6 mice immunized with MOG35–55 peptide were treated daily with N35-4-8C, N6-4-17C and N35-4-17C intraperitoneally from day 0 to day 25 at a different concentrations of the compound. N35-4-8C was tested at 3 different concentrations selected in base to previous experiments using agonist molecules in animal models: 25 mg/kg, 50 mg/kg and 100 mg/kg. N35-4-8C administration was able to prevent EAE clinical severity significantly. By day 15, placebo animals developed a relapse of moderate severity with limb tails and a decrease in weight; by contrast, animals treated with the high N35-4-8C concentration (100 mg/kg) had almost a complete prevention of EAE (FIG. 4A). 50 mg/kg concentration had also an effect but more moderate and the lower concentration had no effect in disease clinical severity. N35-4-17C was also tested at the same concentrations. The lower concentration (25 mg/kg) prevents significantly the development of clinical symptoms in EAE in comparison with the placebo animals. The higher concentrations appear to have a toxic effect worsening the development of the clinical symptoms (FIG. 4B), confirmed by elevated transaminase levels in serum of these animals. N6-4-17C was not effective in reducing the clinical severity of EAE and arresting disease progression throughout the observation period that lasted for 26 days. Moreover, the treatment had higher clinical scores with a clear worsening in the progression of the disease (FIG. 4C). This agonist like molecule was also toxic for the animals with elevated transaminases levels in serum.

EXAMPLE 6

Effect of N35-4-8C NGF-mimetic peptoid in CNS and peripheral inflammation.

Real-time Quantitative Polymerase Chain Reaction. Brains and spinal cords from mice obtained at the time of death were homogenized in RNA lysis buffer. Total RNA was extracted using the RNeasy Mini Kit (Qiagen, Chatworth, CA) isolation system, including DNase treatment using the RNase-Free DNase Set (Qiagen). Total RNA (35 μg) was reverse transcribed using the Reverse Transcription System (High Capacity cDNA Archive Kit; Applied Biosystems, Foster City, CA). The real time
reaction was conducted at 25°C for 10 minutes, followed by 37°C for 2 hours, and
finally stored at 4°C. Primers and target-specific fluorescence-labeled TaqMan probes
were purchased from Applied Biosystems (TaqMan Gene Expression assays). We
used the TaqMan Universal Master Mix (Applied biosystems). Amplification of
complementary DNA was performed on a DNA Engine Opticon 2 Real-Time System
(MJ Research, Watertown, MA) using 0.9 μM for each primer and 0.25 μM for the
probe and 20ng complementary DNA. The reaction conditions were an initial 2
minutes at 50 °C, followed by 10 minutes at 95°C and 40 cycles of 15 seconds at 95°C
and 1 minute at 60°C. Each sample was run in triplicate, and in each plate the target
and the endogenous control were amplified in different wells. The expression of the
gene tested was quantified relative to the level of the housekeeping gene 18rRNA
(Palacios et al., 2008).

**Immunohistochemistry.** Histological evaluation was done on paraformaldehyde-fixed,
paraffin-embedded sections of brain and spinal cord. Sections 10 μm thick) were
stained with hematoxylin and Luxol Fast Blue to assess inflammation and
demyelination. Semiquantitative histological evaluation for inflammation and
demyelination was conducted and scored blindly using the following scale: 0 =
normal; 1 = 1 to 3/section perivascular cuffs with minimal demyelination; 2 = 3 to 10
perivascular cuffs/ section accompanied by moderate demyelination; 3 = wide-spread
perivascular cuffing, extensive demyelination with large confluent lesions (Villoslada
et al., 2001).

Immunohistochemical procedures were performed on 10 μm paraffin-embedded
sections of brain and spinal cord as described previously (Villoslada et al., 2001).
Primary antibodies were added at concentrations of 1/1000 for MCA500 (rat anti-
mouse CD3 from Serotec) and 1/500 for MCA1107 (rat anti-mouse CD4 from
Serotec). Specificity of the immunoreaction was determined by incubating sections
without the primary antibodies or using the corresponding isotype controls which
yielded no immunoreactivity.
**Proliferation assay.** Splenocytes from naïve, non immunized C57BL/6 mice were obtained for in vitro assessment of the effect of N35-4-8C in cell proliferation. Splenocyte proliferation assay was performed as described previously (Martinez-Forero et al., 2008).

Histological evaluation in the CNS showed that N35-4-8C treated animals have less inflammatory infiltrates in the brain and the spinal cord (p < 0.05; see FIG. 5A) when using the higher concentration (100 mg/kg). This concentration is the one able to prevent EAE in mice when administered from the same day of the immunization. Demyelination areas were also decreased in the N35-4-8C treated animals (100 mg/kg) comparing with the placebo group when spinal cord were stained and analysed with Luxol fast blue (FIG. 5B and FIG. 5C).

To assess which was the effect of this compound in the peripheral immune response, the proliferative response against the immunizing antigen (MOG) in splenocytes of naïve animals and the cytokine profile in spleen cells from placebo and treated animals were evaluated. MOG specific proliferative response was significantly lower in N35-4-8C treated splenocytes (p < 0.05; FIG. 6A). Gene expression of interleukin2 (IL2), Interferon γ (IFNγ), tumor necrosis factor α (TNFα), inducible nitric oxide synthase (iNOS) and interleukin 10 (IL10) was investigated by quantitative reverse transcriptase PCR at the end of the experiment in splenocytes from placebo and treated animals. We found a significant decrease of TNFα, IL2 and iNOS in the N35-4-8C treated animals in comparison with the placebo group (FIG. 6B). All these results suggest an immunomodulatory effect of N35-4-8C in EAE added to the neuroprotective effect due to p75 and Trk A activation.

**Statistical analysis.** Statistical analyses were performed with the two-tailed Mann-Whitney U test for comparing EAE scores, chi 2 test for comparing disease incidence and Kaplan–Meier curves for differences in day of onset of EAE. p values less than 0.05 were considered to indicate a significant difference. The statistical evaluation was conducted using the SPSS 16.0 statistical program (SPSS, Chicago, IL).
Having now fully described this invention, it will be understood by those of ordinary skill in the art that the same can be performed within a wide and equivalent range of conditions, formulations and other parameters without affecting the scope of the invention or any embodiment thereof.

Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

All patents and publications cited herein are fully incorporated by reference herein in their entirety.

References


CLAIMS

1. A compound or any pharmaceutically acceptable salt and/or prodrug thereof represented by Formula I:

\[
\begin{align*}
R_1 & \quad \text{NH} \quad \text{N} \quad \text{O} \quad \text{NH}_2 \\
\text{R}_1 & \quad \text{N} \quad \text{O} \\
\text{R}_2 & \quad \text{N} \quad \text{O} \\
\end{align*}
\]

wherein

\[
\begin{align*}
R_1: \quad & \text{F} \quad \text{or} \quad \text{N} \\
R_2: \quad & \text{N} \quad \text{O} \quad \text{or} \quad \text{SO}_2\text{NH}_2
\end{align*}
\]

2. A compound according to claim 1 selected among
Formula II:

\[
\text{Structure Image}
\]

Formula III:

\[
\text{Structure Image}
\]
Formula IV:

or any pharmaceutically acceptable salt and/or prodrug thereof.

3. The compound of claim 1 or 2, or any pharmaceutically acceptable salt and/or prodrug thereof, for use as medicaments.

4. The compound according to claim 3 for use as medicaments useful in the prevention or treatment of nerve cell death or damage.

5. The compound according to claim 3, wherein the medicament is a neuroprotective drug.

6. The compound according to claim 3, wherein the medicament is useful in the regeneration of nerve cells.

7. The compound according to claim 3, wherein the medicament is a neuroenhancing drug.

8. The compound according to claim 3, wherein the medicament is useful in the prevention or treatment of a neurological or psychiatric disease.
9. The compound according to claim 3, wherein the medicament is useful in the prevention or treatment of a disease selected from: neurological diseases, preferentially neurodegenerative disorders, such as amyotrophic lateral sclerosis (ALS), Parkinson’s disease, Alzheimer’s disease, Friedreich’s ataxia, Huntington’s disease, Dementia with Lewy bodies, spinal muscular atrophy; nerve inflammation, such as multiple sclerosis and neuromyelitis optica, major depressive disorder, schizophrenia, glaucoma; peripheral neuropathies, such as diabetic or AIDS neuropathy; and cancer, such as glioblastoma, astrocytoma, medulloblastoma, neurinoma, neuroblastoma, menigioma, colon cancer, pancreatic cancer, breast cancer, prostate cancer, leukemia, acute lymphocytic leukemia, osteosarcoma, hepatocellular carcinoma, ovarian carcinoma, lung adenocarcinoma, and esophageal carcinoma.

10. The compound of Formula II or III or any pharmaceutically acceptable salt and/or prodrug thereof, according to claim 3, wherein the medicament is useful in the treatment of multiple sclerosis.

11. The compound of Formula II or any pharmaceutically acceptable salt and/or prodrug thereof, according to claim 3, wherein the medicament is a neuroregenerative drug.

12. The compound of Formula II or any pharmaceutically acceptable salt and/or prodrug thereof, according to claim 3, wherein the medicament is an immunomodulator.

13. The compound of Formula II or any pharmaceutically acceptable salt and/or prodrug thereof, according to claim 3, wherein the medicament has a combination of neuroprotective and immunomodulatory effects.

14. A pharmaceutical composition, comprising a therapeutically effective amount of at least one compound of claim 1 or 2, or combinations thereof and, optionally, further
comprising, at least one pharmaceutically acceptable non-active ingredient, preferably at least one excipient and/or carrier.

15. Use of the compound of claim 1 or 2 as an active ingredient in the manufacture of a medicament for the prevention or treatment of nerve cell death or damage.

16. Use of the compound of claim 1 or 2 as an active ingredient in the manufacture of a neuroprotective medicament.

17. Use of the compound of claim 1 or 2 as an active ingredient in the manufacture of a medicament for the regeneration of nerve cells.

18. Use of the compound of claim 1 or 2 as an active ingredient in the manufacture of a medicament for the prevention or treatment of a neurological or psychiatric disease.

19. Use, according to claim 18, of the compound of claim 1 or 2 as an active ingredient in the manufacture of a medicament for the prevention or treatment of a disease selected from: neurological diseases, preferentially neurodegenerative disorders, such as amyotrophic lateral sclerosis (ALS), Parkinson's disease, Alzheimer's disease, Friedreich's ataxia, Huntington's disease, Dementia with Lewy bodies, spinal muscular atrophy; nerve inflammation, such as multiple sclerosis and neuromyelitis optica, major depressive disorder, schizophrenia, glaucoma; peripheral neuropathies, such as diabetic or AIDS neuropathy; and cancer, such as glioblastoma, astrocytoma, medulloblastoma, neurinoma, neuroblastoma, meningioma, colon cancer, pancreatic cancer, breast cancer, prostate cancer, leukemia, acute lymphocytic leukemia, osteosarcoma, hepatocellular carcinoma, ovarian carcinoma, lung adenocarcinoma, and esophageal carcinoma.

20. Use, according to claim 19, of the compound of Formula II or III, or any pharmaceutically acceptable salt and/or prodrug thereof, as active ingredient in the manufacture of a medicament for the prevention or treatment of multiple sclerosis.
21. Use of the compound of Formula II according to claim 2, or any pharmaceutically acceptable salt and/or prodrug thereof, as active ingredient in the manufacture of a neuroregenerative drug.

22. Use of the compound of Formula II according to claim 2, or any pharmaceutically acceptable salt and/or prodrug thereof, as active ingredient in the manufacture of an immunomodulator.

23. Use of the compound of Formula II according to claim 2, or any pharmaceutically acceptable salt and/or prodrug thereof, as active ingredient in the manufacture of a medicament which has a combination of neuroprotective and immunomodulatory effects.

24. Use of the compound of claim 1 or 2, or any pharmaceutically acceptable salt and/or prodrug thereof, as active ingredient in the manufacture of a neuroenhancing drug.

25. A method of prevention or treatment of nerve cell death or damage comprising administering to a subject in need thereof an effective amount of the compound of claim 1 or 2; or of the pharmaceutical composition of claim 13.

26. A method of neuroprotection, comprising administering to a subject in need thereof an effective amount of the compound of claim 1 or 2; or of the pharmaceutical composition of claim 13.

27. A method of neuroprotection, according to claim 26, further comprising immunomodulation, comprising administering to a subject in need thereof an effective amount of the compound of Formula II or any pharmaceutically acceptable salt and/or prodrug thereof; or of the pharmaceutical compositions of claim 13 containing the same.
28. A method of regenerating nerve cells, comprising administering to a subject in need thereof an effective amount of the compound of claim 1 or 2; or of the pharmaceutical composition of claim 13.

29. A method of regenerating nerve cells, according to claim 28, comprising administering to a subject in need thereof an effective amount of the compound of Formula II or any pharmaceutically acceptable salt and/or prodrug thereof; or of the pharmaceutical composition of claim 13 containing the same.

30. A method of prevention or treatment of a disease, comprising administering to a subject in need thereof an effective amount of the compound of claim 1 or 2; or of the pharmaceutical composition of claim 13, wherein the disease is selected from: neurological diseases, preferentially neurodegenerative disorders, such as amyotrophic lateral sclerosis (ALS), Parkinson’s disease, Alzheimer’s disease, Friedreich’s ataxia, Huntington’s disease, Dementia with Lewy bodies, spinal muscular atrophy; nerve inflammation, such as multiple sclerosis and neuromyelitis optica, major depressive disorder, schizophrenia, glaucoma; peripheral neuropathies, such as diabetic or AIDS neuropathy; and cancer, such as glioblastoma, astrocytoma, medulloblastoma, neurinoma, neuroblastoma, meningioma, colon cancer, pancreatic cancer, breast cancer, prostate cancer, leukemia, acute lymphocytic leukemia, osteosarcoma, hepatocellular carcinoma, ovarian carcinoma, lung adenocarcinoma, and esophageal carcinoma.

31. A method of prevention or treatment of multiple sclerosis, comprising administering to a subject in need thereof an effective amount of the compound of Formula II or III according to claim 2, or any pharmaceutically acceptable salt and/or prodrug thereof; or of the pharmaceutical composition of claim 13 containing the same.

32. A method of treating a disease responsive to the stimulation of the activity of nerve growth factor, or a nerve growth factor receptor, in a mammal suffering from
lack of stimulation thereof, comprising administering an effective amount a compound of claim 1 or claim 2, or a pharmaceutically acceptable salt or prodrug thereof.

33. A compound of claim 1 or 2, or a pharmaceutically acceptable salt or prodrug thereof, for use in stimulating the activity of nerve growth factor, or a nerve growth factor receptor.

34. A method of stimulating nerve growth factor receptor activity in a subject in need thereof, comprising administering a compound of claim 1 or 2, or a pharmaceutically acceptable salt or prodrug thereof.

35. The method of claim 34, wherein the nerve growth factor receptor is TrkA receptor or p75 receptor.

36. A method of preparing a pharmaceutical composition, comprising admixing an effective amount of a compound of claim 1 or 2, or a pharmaceutically acceptable salt or prodrug thereof, with a pharmaceutically acceptable carrier.

37. A compound having the Formula I:

![Formula I](image)

or a pharmaceutically acceptable salt or prodrug thereof,

wherein \( R_1 \) is phenyl substituted with halogen or trifluoromethyl, and further optionally substituted with one or two substituents selected from the group consisting
of halogen, C_{1-6} alkyl, \( (C_{1-6})\)alkoxy, and halo\( (C_{1-6})\)alkyl, or \( R_1 \) is pyrrolidin-1-yl, and \( R_2 \) is 2-oxo-pyrrolidin-1-ylmethyl or sulfamoylphenyl.
FIG. 2

Cell viability (MTT assay) values expressed as % relative to untreated cells.
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**FIG. 3**
FIG. 5
FIG. 6