

N-LINKED SULFONAMIDES OF HETEROCYCLIC THIOESTERS

This is a continuation-in-part application of U.S. Patent Application Serial No. 08/775,584 filed December 31, 1996.

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BACKGROUND OF THE INVENTION1. Field of Invention

This invention relates to neurotrophic low molecular weight, small molecule N-linked sulfonamides of heterocyclic thioesters having an affinity for FKBP-type immunophilins and their use as inhibitors of the enzyme activity associated with immunophilin proteins, particularly peptidyl-prolyl isomerase, or rotamase, enzyme activity.

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2. Description of Related Art

The term immunophilin refers to a number of proteins that serve as receptors for the principal immunosuppressant drugs, Cyclosporin A (CsA), FK506, and rapamycin. Known classes of immunophilins are cyclophilins and FK506 binding proteins, or FKBP's. Cyclosporin A binds to cyclophilin A while FK506 and rapamycin bind to FKBP12. These immunophilin-drug complexes interface with various intracellular signal transduction systems, especially the immune and nervous systems.

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Immunophilins are known to have peptidyl-prolyl isomerase (PPIase), or rotamase, enzyme activity. It

has been determined that rotamase enzyme activity plays a role in the catalyzation of the interconversion of the cis and trans isomers of peptide and protein substrates for the immunophilin proteins.

Immunophilins were originally discovered and studied in the immune tissue. It was initially postulated by those skilled in the art that inhibition of the immunophilins' rotamase activity leads to inhibition of T-cell proliferation, thereby causing the immunosuppressive activity exhibited by immunosuppressant drugs, such as cyclosporin A, FK506 and rapamycin. Further study has shown that the inhibition of rotamase activity, in and of itself, does not result in immunosuppressive activity. Schreiber et al., *Science*, 1990, vol. 250, pp. 556-559. Instead, immunosuppression appears to stem from the formulation of a complex of immunosuppressant drugs and immunophilins. It has been shown that the immunophilin-drug complexes interact with ternary protein targets as their mode of action. Schreiber et al., *Cell*, 1991, vol. 66, pp. 807-815. In the case of FKBP-FK506 and cyclophilin-CsA, the immunophilin-drug complexes bind to the enzyme calcineurin and inhibit the T-cell receptor signalling which leads to T-cell proliferation. Similarly, the immunophilin-drug

complex of FKBP-rapamycin interacts with the RAFT1/FRAP protein and inhibits the IL-2 receptor signalling.

Immunophilins have been found to be present at
5 high concentrations in the central nervous system. Immunophilins are enriched 10-50 times more in the central nervous system than in the immune system. Within neural tissues, immunophilins appear to influence nitric oxide synthesis, neurotransmitter
10 release and neuronal process extension.

It has been found that picomolar concentrations of an immunosuppressant such as FK506 and rapamycin stimulate neurite outgrowth in PC12 cells and sensory neurons, namely dorsal root ganglion cells (DRGs).
15 Lyons et al., *Proc. of Natl. Acad. Sci.*, 1994, vol. 91, pp. 3191-3195. In whole animal experiments, FK506 has been shown to stimulate nerve regeneration following facial nerve injury.

Surprisingly, it has been found that certain
20 compounds with a high affinity for FKBP are potent rotamase inhibitors and exhibit excellent neurotrophic effects. Furthermore, these rotamase inhibitors are devoid of immunosuppressive activity. These findings suggest the use of rotamase inhibitors in treating
25 various peripheral neuropathies and enhancing neuronal regrowth in the central nervous system (CNS). Studies

have demonstrated that neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS) may occur due to the loss of, or decreased availability of, a neurotrophic substance specific for a particular population of neurons affected in the disorder.

Several neurotrophic factors affecting specific neuronal populations in the central nervous system have been identified. For example, it has been hypothesized that Alzheimer's disease results from a decrease or loss of nerve growth factor (NGF). It has thus been proposed to treat Senile Dementia Alzheimer's Type (SDAT) patients with exogenous nerve growth factor or other neurotrophic proteins, such as brain derived growth factor, glial derived growth factor, ciliary neurotrophic factor and neurotrophin-3, to increase the survival of degenerating neuronal populations.

Clinical application of these proteins in various neurological disease states is hampered by difficulties in the delivery and bioavailability of large proteins to nervous system targets. By contrast, immunosuppressant drugs with neurotrophic activity are relatively small and display excellent bioavailability and specificity. However, when administered chronically, immunosuppressant drugs

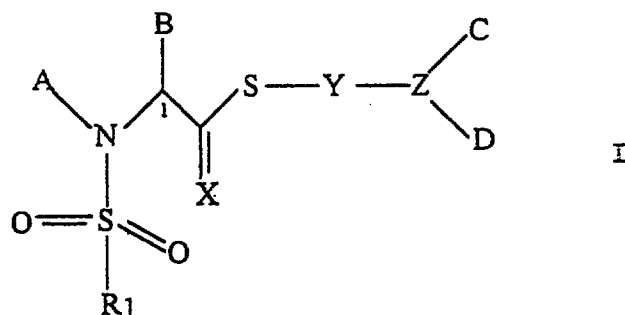
exhibit a number of potentially serious side effects including nephrotoxicity, such as impairment of glomerular filtration and irreversible interstitial fibrosis (Kopp et al., *J. Am. Soc. Nephrol.*, 1991, 1:162); neurological deficits, such as involuntary tremors, or non-specific cerebral angina, such as non-localized headaches (De Groen et al., *N. Engl. J. Med.*, 1987, 317:861); and vascular hypertension with complications resulting therefrom (Kahan et al., *N. Engl. J. Med.*, 1989, 321:1725).

In order to prevent the side effects associated with use of the immunosuppressant compounds, the present invention provides non-immunosuppressive compounds containing small molecule FKBP rotamase inhibitors for enhancing neurite outgrowth, and promoting neuronal growth and regeneration in various neuropathological situations where neuronal repair can be facilitated, including: peripheral nerve damage caused by physical injury or disease state such as diabetes; physical damage to the central nervous system (spinal cord and brain); brain damage associated with stroke; and neurological disorders relating to neurodegeneration, such as Parkinson's disease, SDAT (Alzheimer's disease), and amyotrophic lateral sclerosis.

SUMMARY OF THE INVENTION

The present invention relates to neurotrophic low molecular weight, small molecule compounds having an affinity for FKBP-type immunophilins. Once bound to these proteins, the neurotrophic compounds are potent inhibitors of the enzyme activity associated with immunophilin proteins, particularly peptidyl-prolyl isomerase, or rotamase, enzyme activity. A key feature of the compounds of the present invention is that they do not exert any significant immunosuppressive activity in addition to their neurotrophic activity. Another significant feature is the novel addition of a thioester linkage showing unexpected increase in bioavailability and potency.

Specifically, the present invention relates to a compound of formula I:



or a pharmaceutically acceptable salt, ester, or solvate thereof, wherein:

A and B are taken together, with the nitrogen and carbon atoms to which they are respectively attached, to form a 5-7 membered saturated or unsaturated

heterocyclic ring containing any combination of CH_2 , O, S, SO, SO_2 , NH or NR_2 ;

X is either O or S;

Y is a direct bond to Z, a $\text{C}_1\text{-C}_6$ straight or
5 branched chain alkyl, or a $\text{C}_2\text{-C}_6$ straight or branched
chain alkenyl, wherein any of the carbon atoms of said
alkyl or alkenyl are optionally substituted in one or
more positions with amino, halo, haloalkyl,
thiocarbonyl, ester, thioester, alkoxy, alkenoxy,
10 cyano, nitro, imino, alkylamino, aminoalkyl,
sulfhydryl, thioalkyl, sulfonyl, oxygen to form a
carbonyl, or wherein any of the carbon atoms of said
alkyl or alkenyl are optionally replaced with O, NH,
 NR_2 , S, SO, or SO_2 , wherein R_2 is selected from the
15 group consisting of hydrogen, $(\text{C}_1\text{-C}_6)$ -straight or
branched chain alkyl, $(\text{C}_3\text{-C}_6)$ -straight or branched
chain alkenyl or alkynyl, and $(\text{C}_1\text{-C}_4)$ bridging alkyl
wherein said bridging alkyl forms a heterocyclic ring
starting with the nitrogen of NR_1 and ending with one
20 of the carbon atoms of said alkyl or alkenyl chain,
and wherein said heterocyclic ring is optionally fused
to an Ar group;

Z is a direct bond, or a $\text{C}_1\text{-C}_6$ straight or
branched chain alkyl, or a $\text{C}_2\text{-C}_6$ straight or branched
25 chain alkenyl, wherein any of the carbon atoms of said
alkyl or alkenyl are optionally substituted in one or

more positions with amino, halo, haloalkyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, oxygen to form a carbonyl, or wherein any of the carbon atoms of said alkyl or alkenyl are optionally replaced with O, NH, NR₂, S, SO, or SO₂, wherein R₂ is selected from the group consisting of hydrogen, (C₁-C₆)-straight or branched chain alkyl, (C₃-C₆)-straight or branched chain alkenyl or alkynyl, and (C₁-C₄) bridging alkyl wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR₁ and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group;

C and D are independently:

hydrogen, Ar, C₁-C₆ straight or branched chain alkyl, or C₂-C₆ straight or branched chain alkenyl, wherein any of the carbon atoms of said alkyl or alkenyl are optionally substituted in one or more position(s) with C₃-C₆ cycloalkyl, C₅-C₇ cycloalkenyl, hydroxyl, carbonyl oxygen, or Ar, wherein said alkyl, alkenyl, cycloalkyl or cycloalkenyl groups are optionally substituted with C₁-C₆ alkyl, C₂-C₆ alkenyl, hydroxy, amino, halo, haloalkyl, thiocarbonyl, ester, thioester, alkoxy, -alkenoxo, cyano, nitro, imino,

alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, wherein any of the carbon atoms of said alkyl or alkenyl are optionally substituted in one or more positions with oxygen to form a carbonyl, or
5 wherein any of the carbon atoms of said alkyl or alkenyl are optionally replaced with O, NH, NR₂, S, SO, or SO₂, wherein R₂ is selected from the group consisting of hydrogen, (C₁-C₆)-straight or branched chain alkyl, (C₃-C₆)-straight or branched chain alkenyl
10 or alkynyl, and (C₁-C₄) bridging alkyl wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR₁ and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group;
15 wherein Ar is an aryl or heteroaryl moiety which is substituted or unsubstituted;
and

R₁ is selected from the group consisting of Ar, C₃-C₆ cycloalkyl, C₁-C₆ straight or branched chain
20 alkyl, C₂-C₆ straight or branched chain alkenyl, or C₁-C₆ straight or branched chain alkyl or C₂-C₆ straight or branched chain alkenyl which is substituted in one or more positions with Ar, amino, halo, haloalkyl, hydroxy, trifluoromethyl, C₁-C₆ straight or branched
25 chain alkyl, C₂-C₆ straight or branched chain alkenyl, carbonyl, thiocarbonyl, ester, thioester, alkoxy,

alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, substituted alkyl or alkenyl wherein any of the carbon atoms of the alkyl or alkenyl are optionally replaced with S, SO, SO₂, O, or NR₂ wherein R₂ is selected from the group consisting of hydrogen, (C₁-C₆)-straight or branched chain alkyl, (C₃-C₆)-straight or branched chain alkenyl or alkynyl, and (C₁-C₄) bridging alkyl wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR₁ and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group or C₃-C₆ cycloalkyl.

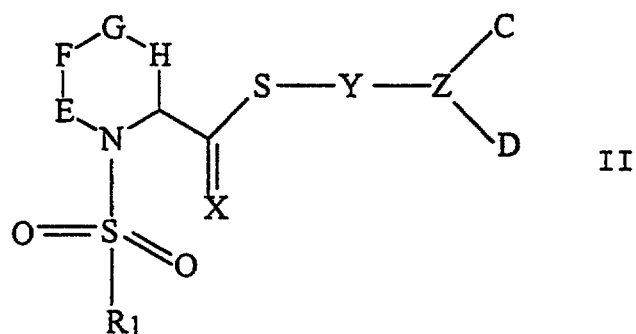
In preferred embodiments, Ar is a cyclic or fused cyclic ring and includes a mono-, bi- or tricyclic, carbo- or heterocyclic ring, wherein the ring is either unsubstituted or substituted in one to five position(s) with halo, haloalkyl, hydroxyl, nitro, trifluoromethyl, C₁-C₆ straight or branched chain alkyl, C₂-C₆ straight or branched chain alkenyl, C₁-C₆ alkoxy, C₂-C₆ alkenyloxy, phenoxy, benzyloxy, amino, thiocarbonyl, ester, thioester, cyano, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, and sulfonyl; wherein the individual ring sizes are 5-8 members; wherein the heterocyclic ring contains 1-4 heteroatom(s) selected from the group consisting of O,

N, or S; wherein aromatic or tertiary alkyl amines are optionally oxidized to a corresponding N-oxide.

Particularly preferred Ar groups include phenyl, benzyl, naphthyl, pyrrolyl, pyrrolidinyl, pyridinyl, pyrimidinyl, purinyl, quinolinyl, isoquinolinyl, 5 furyl, thiophenyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, and thienyl.

A preferred embodiment of this invention is a compound of formula II:

10



or a pharmaceutically acceptable salt, ester, or solvate thereof, wherein:

15 E, F, G and H are independently CH₂, O, S, SO, SO₂, NH or NR₂ wherein at least two of E, F, G, and H are CH₂;

X is either O or S;

Y is a direct bond to Z, a C₁-C₆ straight or 20 branched chain alkyl, or a C₂-C₆ straight or branched chain alkenyl, wherein any of the carbon atoms of said alkyl or alkenyl are optionally substituted in one or more positions with amino, halo, haloalkyl,

thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, oxygen to form a carbonyl, or wherein any of the carbon atoms of said alkyl or alkenyl are optionally replaced with O, NH, NR₂, S, SO, or SO₂, wherein R₂ is selected from the group consisting of hydrogen, (C₁-C₆)-straight or branched chain alkyl, (C₃-C₆)-straight or branched chain alkenyl or alkynyl, and (C₁-C₄) bridging alkyl wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR₁ and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group;

15 Z is a direct bond, or a C₁-C₆ straight or branched chain alkyl, or a C₂-C₆ straight or branched chain alkenyl, wherein any of the carbon atoms of said alkyl or alkenyl are optionally substituted in one or more positions with amino, halo, haloalkyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, oxygen to form a carbonyl, or wherein any of the carbon atoms of said alkyl or alkenyl are optionally replaced with O, NH, NR₂, S, SO, or SO₂, wherein R₂ is selected from the group consisting of hydrogen, (C₁-C₆)-straight or

branched chain alkyl, (C₃-C₆)-straight or branched chain alkenyl or alkyñyl, and (C₁-C₄) bridging alkyl wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR₁ and ending with one
5 of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group;

C and D are independently:

hydrogen, Ar, C₁-C₆ straight or branched chain
10 alkyl, or C₂-C₆ straight or branched chain alkenyl, wherein any of the carbon atoms of said alkyl or alkenyl are optionally substituted in one or more position(s) with C₃-C₆ cycloalkyl, C₅-C₇ cycloalkenyl, hydroxyl, carbonyl oxygen, or Ar, wherein said alkyl,
15 alkenyl, cycloalkyl or cycloalkenyl groups are optionally substituted with C₁-C₆ alkyl, C₂-C₆ alkenyl, hydroxy, amino, halo, haloalkyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl,
20 sulfonyl, wherein any of the carbon atoms of said alkyl or alkenyl are optionally substituted in one or more positions with oxygen to form a carbonyl, or wherein any of the carbon atoms of said alkyl or alkenyl are optionally replaced with O, NH, NR₂, S, SO,
25 or SO₂, wherein R₂ is selected from the group consisting of hydrogen, (C₁-C₆)-straight or branched

chain alkyl, (C₃-C₆)-straight or branched chain alkenyl
or alkynyl, and (C₁-C₄) bridging alkyl wherein said
bridging alkyl forms a heterocyclic ring starting with
the nitrogen of NR₁ and ending with one of the carbon
atoms of said alkyl or alkenyl chain, and wherein said
heterocyclic ring is optionally fused to an Ar group;

wherein Ar is an aryl or heteroaryl moiety which
is substituted or unsubstituted;

and

R₁ is selected from the group consisting of Ar,
C₃-C₆ cycloalkyl, C₁-C₆ straight or branched chain
alkyl, C₂-C₆ straight or branched chain alkenyl, or C₁-
C₆ straight or branched chain alkyl or C₂-C₆ straight
or branched chain alkenyl which is substituted in one
or more positions with Ar, amino, halo, haloalkyl,
hydroxy, trifluoromethyl, C₁-C₆ straight or branched
chain alkyl, C₂-C₆ straight or branched chain alkenyl,
carbonyl, thiocarbonyl, ester, thioester, alkoxy,
alkenoxo, cyano, nitro, imino, alkylamino, aminoalkyl,
sulfhydryl, thioalkyl, sulfonyl, substituted alkyl or
alkenyl wherein any of the carbon atoms of the alkyl
or alkenyl are optionally replaced with S, SO, SO₂, O,
or NR₂ wherein R₂ is selected from the group consisting
of hydrogen, (C₁-C₆)-straight or branched chain alkyl,
(C₂-C₆)-straight or branched chain alkenyl or alkynyl,
and (C₁-C₄) bridging alkyl wherein said bridging alkyl

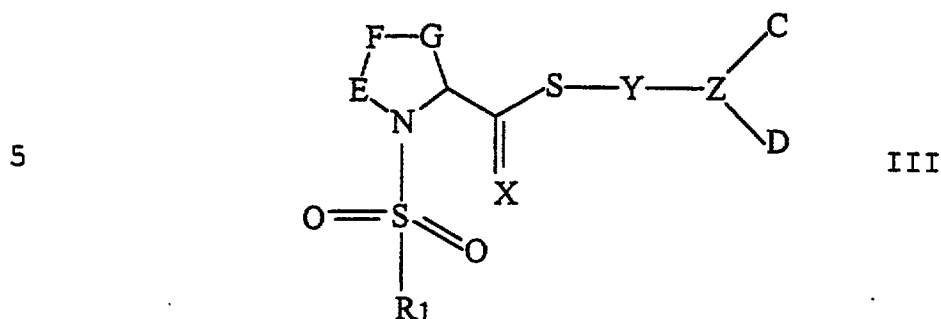
forms a heterocyclic ring starting with the nitrogen of NR₁ and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group or C₃-C₈ cycloalkyl.

In preferred embodiments, Ar is a cyclic or fused cyclic ring and includes a mono-, bi- or tricyclic, carbo- or heterocyclic ring, wherein the ring is either unsubstituted or substituted in one to five position(s) with halo, haloalkyl, hydroxyl, nitro, trifluoromethyl, C₁-C₆ straight or branched chain alkyl, C₂-C₆ straight or branched chain alkenyl, C₁-C₆ alkoxy, C₂-C₆ alkenyloxy, phenoxy, benzyloxy, amino, thiocarbonyl, ester, thioester, cyano, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, and sulfonyl; wherein the individual ring sizes are 5-8 members; wherein the heterocyclic ring contains 1-4 heteroatom(s) selected from the group consisting of O, N, or S; wherein aromatic or tertiary alkyl amines are optionally oxidized to a corresponding N-oxide.

Particularly preferred Ar groups include phenyl, benzyl, naphthyl, pyrrolyl, pyrrolidinyl, pyridinyl, pyrimidinyl, purinyl, quinolinyl, isoquinolinyl, furyl, thiophenyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, and thienyl.

Another preferred embodiment is a compound of

formula III:



or a pharmaceutically acceptable salt, ester, or solvate thereof, wherein:

E, F, and G are independently CH₂, O, S, SO, SO₂, NH or NR₂ wherein at least 2 of E, F, and G are CH₂;

X is either O or S;

Y is a direct bond to Z, a C₁-C₆ straight or branched chain alkyl, or a C₂-C₆ straight or branched chain alkenyl, wherein any of the carbon atoms of said alkyl or alkenyl are optionally substituted in one or more positions with amino, halo, haloalkyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, oxygen to form a carbonyl, or wherein any of the carbon atoms of said alkyl or alkenyl are optionally replaced with O, NH, NR₂, S, SO, or SO₂, wherein R₂ is selected from the group consisting of hydrogen, (C₁-C₆)-straight or branched chain alkyl, (C₃-C₆)-straight or branched

chain alkenyl or alkynyl, and (C₁-C₄) bridging alkyl wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR₁ and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group;

Z is a direct bond, or a C₁-C₆ straight or branched chain alkyl, or a C₂-C₆ straight or branched chain alkenyl, wherein any of the carbon atoms of said alkyl or alkenyl are optionally substituted in one or more positions with amino, halo, haloalkyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, oxygen to form a carbonyl, or wherein any of the carbon atoms of said alkyl or alkenyl are optionally replaced with O, NH, NR₂, S, SO, or SO₂, wherein R₂ is selected from the group consisting of hydrogen, (C₁-C₆)-straight or branched chain alkyl, (C₂-C₆)-straight or branched chain alkenyl or alkynyl, and (C₁-C₄) bridging alkyl wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR₁ and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group;

C and D are independently:

hydrogen, Ar, C₁-C₆ straight or branched chain alkyl, or C₂-C₆ straight or branched chain alkenyl, wherein any of the carbon atoms of said alkyl or alkenyl are optionally substituted in one or more position(s) with C₃-C₈ cycloalkyl, C₅-C₇ cycloalkenyl, hydroxyl, carbonyl oxygen, or Ar, wherein said alkyl, alkenyl, cycloalkyl or cycloalkenyl groups are optionally substituted with C₁-C₆ alkyl, C₂-C₆ alkenyl, hydroxy, amino, halo, haloalkyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, wherein any of the carbon atoms of said alkyl or alkenyl are optionally substituted in one or more positions with oxygen to form a carbonyl, or wherein any of the carbon atoms of said alkyl or alkenyl are optionally replaced with O, NH, NR₂, S, SO, or SO₂, wherein R₂ is selected from the group consisting of hydrogen, (C₁-C₆)-straight or branched chain alkyl, (C₃-C₆)-straight or branched chain alkenyl or alkynyl, and (C₁-C₄) bridging alkyl wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR₁ and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group;

wherein Ar is an aryl or heteroaryl moiety which is substituted or unsubstituted;

and

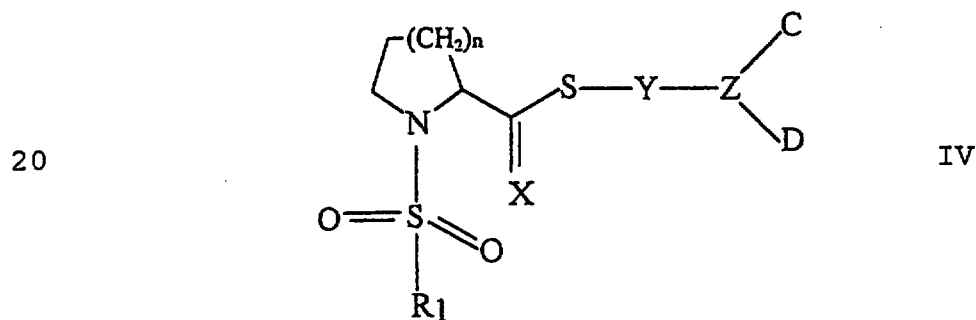
R_1 is selected from the group consisting of Ar, C_3-C_8 cycloalkyl, C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, or C_1-C_6 straight or branched chain alkyl or C_2-C_6 straight or branched chain alkenyl which is substituted in one or more positions with Ar, amino, halo, haloalkyl, hydroxy, trifluoromethyl, C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, carbonyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, substituted alkyl or alkenyl wherein any of the carbon atoms of the alkyl or alkenyl are optionally replaced with S, SO, SO_2 , O, or NR_2 wherein R_2 is selected from the group consisting of hydrogen, (C_1-C_6) -straight or branched chain alkyl, (C_3-C_6) -straight or branched chain alkenyl or alkynyl, and (C_1-C_4) bridging alkyl wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR_1 and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group or C_3-C_8 cycloalkyl.

In preferred embodiments, Ar is a cyclic or fused cyclic ring and includes a mono-, bi- or tricyclic, carbo- or heterocyclic ring, wherein the ring is

either unsubstituted or substituted in one to five position(s) with halo, haloalkyl, hydroxyl, nitro, trifluoromethyl, C₁-C₆ straight or branched chain alkyl, C₂-C₆ straight or branched chain alkenyl, C₁-C₆ alkoxy, C₂-C₆ alkenyloxy, phenoxy, benzyloxy, amino, thiocarbonyl, ester, thioester, cyano, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, and sulfonyl; wherein the individual ring sizes are 5-8 members; wherein the heterocyclic ring contains 1-4 heteroatom(s) selected from the group consisting of O, N, or S; wherein aromatic or tertiary alkyl amines are optionally oxidized to a corresponding N-oxide.

Particularly preferred Ar groups include phenyl, benzyl, naphthyl, pyrrolyl, pyrrolidinyl, pyridinyl, pyrimidinyl, purinyl, quinolinyl, isoquinolinyl, furyl, thiophenyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, and thienyl.

A further particularly preferred embodiment of this invention is a compound of formula IV:



or a pharmaceutically acceptable salt, ester, or solvate thereof, wherein:

n is 1, 2 or 3 forming a 5-7 member heterocyclic ring;

5 X is either O or S;

Y is a direct bond to Z, a C₁-C₆ straight or branched chain alkyl, or a C₂-C₆ straight or branched chain alkenyl, wherein any of the carbon atoms of said alkyl or alkenyl are optionally substituted in one or
10 more positions with amino, halo, haloalkyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, oxygen to form a carbonyl, or wherein any of the carbon atoms of said
15 alkyl or alkenyl are optionally replaced with O, NH, NR₂, S, SO, or SO₂, wherein R₂ is selected from the group consisting of hydrogen, (C₁-C₅)-straight or branched chain alkyl, (C₃-C₆)-straight or branched chain alkenyl or alkynyl, and (C₁-C₄) bridging alkyl
20 wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR₂ and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group;

25 Z is a direct bond, or a C₁-C₆ straight or branched chain alkyl, or a C₂-C₆ straight or branched

chain alkenyl, wherein any of the carbon atoms of said alkyl or alkenyl are optionally substituted in one or more positions with amino, halo, haloalkyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, oxygen to form a carbonyl, or wherein any of the carbon atoms of said alkyl or alkenyl are optionally replaced with O, NH, NR₂, S, SO, or SO₂, wherein R₂ is selected from the group consisting of hydrogen, (C₁-C₆)-straight or branched chain alkyl, (C₃-C₆)-straight or branched chain alkenyl or alkynyl, and (C₁-C₄) bridging alkyl wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR₁ and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group;

C and D are independently:

hydrogen, Ar, C₁-C₆ straight or branched chain alkyl, or C₂-C₆ straight or branched chain alkenyl, wherein any of the carbon atoms of said alkyl or alkenyl are optionally substituted in one or more position(s) with C₃-C₆ cycloalkyl, C₅-C₇ cycloalkenyl, hydroxyl, carbonyl oxygen, or Ar, wherein said alkyl, alkenyl, cycloalkyl or cycloalkenyl groups are optionally substituted with C₁-C₆ alkyl, C₂-C₆ alkenyl,

hydroxy, amino, halo, haloalkyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, wherein any of the carbon atoms of said alkyl or alkenyl are optionally substituted in one or more positions with oxygen to form a carbonyl, or wherein any of the carbon atoms of said alkyl or alkenyl are optionally replaced with O, NH, NR₂, S, SO, or SO₂, wherein R₂ is selected from the group consisting of hydrogen, (C₁-C₆)-straight or branched chain alkyl, (C₃-C₆)-straight or branched chain alkenyl or alkynyl, and (C₁-C₄) bridging alkyl wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR₁ and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group; wherein Ar is an aryl or heteroaryl moiety which is substituted or unsubstituted; and

R₁ is selected from the group consisting of Ar, C₃-C₈ cycloalkyl, C₁-C₆ straight or branched chain alkyl, C₂-C₆ straight or branched chain alkenyl, or C₁-C₆ straight or branched chain alkyl or C₂-C₆ straight or branched chain alkenyl which is substituted in one or more positions with Ar, amino, halo, haloalkyl, hydroxy, trifluoromethyl, C₁-C₆ straight or branched

chain alkyl, C₂-C₆ straight or branched chain alkenyl, carbonyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, substituted alkyl or
5 alkenyl wherein any of the carbon atoms of the alkyl or alkenyl are optionally replaced with S, SO, SO₂, O, or NR₂ wherein R₂ is selected from the group consisting of hydrogen, (C₁-C₆)-straight or branched chain alkyl, (C₃-C₆)-straight or branched chain alkenyl or alkynyl,
10 and (C₁-C₄) bridging alkyl wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR₁ and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group or C₃-C₈
15 cycloalkyl.

In preferred embodiments, Ar is a cyclic or fused cyclic ring and includes a mono-, bi- or tricyclic, carbo- or heterocyclic ring, wherein the ring is either unsubstituted or substituted in one to five
20 position(s) with halo, haloalkyl, hydroxyl, nitro, trifluoromethyl, C₁-C₆ straight or branched chain alkyl, C₂-C₆ straight or branched chain alkenyl, C₁-C₆ alkoxy, C₂-C₆ alkenyloxy, phenoxy, benzyloxy, amino, thiocarbonyl, ester, thioester, cyano, imino,
25 alkylamino, aminoalkyl, sulfhydryl, thioalkyl, and sulfonyl; wherein the individual ring sizes are 5-8

members; wherein the heterocyclic ring contains 1-4 heteroatom(s) selected from the group consisting of O, N, or S; wherein aromatic or tertiary alkyl amines are optionally oxidized to a corresponding N-oxide.

5 Particularly preferred Ar groups include phenyl, benzyl, naphthyl, pyrrolyl, pyrrolidinyl, pyridinyl, pyrimidinyl, purinyl, quinolinyl, isoquinolinyl, furyl, thiophenyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, and thienyl.

10 Particularly preferred compounds of the present invention are selected from the group consisting of:

3-(4-Methoxyphenyl)propyl (2S)-1-(phenylsulfonyl)-2-pyrrolidinecarbothioate (4);

15 3-(4-Methoxyphenyl)propyl (2S)-1-(benzylsulfonyl)-2-pyrrolidinecarbothioate (5);

3-(4-Methoxyphenyl)propyl (2S)-1-[(4-methylphenyl)sulfonyl]-2-pyrrolidinecarbothioate (6);

(2,2-methylphenyl)ethyl (2S)-1-[(4-ethylphenyl)sulfonyl]-2-pyrrolidinecarbothioate (21);

20 3-Phenylpropyl (2S)-1-(phenylsulfonyl)-2-pyrrolidinecarbothioate (22);

3-Phenylpropyl (2S)-1-(benzylsulfonyl)-2-pyrrolidinecarbothioate (23);

25 3-(1-Naphthyl)propyl (2S)-1-(benzylsulfonyl)-2-pyrrolidinecarbothioate (24);

3-Phenylpropyl (2S)-1-[(4-ethylphenyl)sulfonyl]-

2-pyrrolidinecarbothioate (25);

3-(4-Methoxyphenyl)propyl 1-[(4-methylphenyl)sulfonyl]-2-piperidinecarbothioate (26);

5 3-(4-Methoxyphenyl)propyl 1-(benzylsulfonyl)-2-piperidinecarbothioate (27);

3-(4-Methoxyphenyl)propyl 1-(phenylsulfonyl)-2-piperidinecarbothioate (28);

3-[4-(Trifluoromethyl)phenyl]propyl 1-[(4-methylphenyl)sulfonyl]-2-piperidinecarbothioate (29);

10 and a pharmaceutically acceptable salt, ester, or solvate, hydrate, or a mixture thereof (numbers in parentheses indicate compound numbers; See also Table I and Examples).

15 The present invention further relates to a method of effecting a neuronal activity in an animal, comprising:

administering to the animal a neurotrophically effective amount of the compound of formula I, II, III or IV.

20 The present invention further relates to the use of any of the compounds of Formula I, II, III, IV or in Table I below in the preparation of a medicament for the treatment of a disease such as peripheral neuropathy caused by physical injury or disease state,
25 physical damage to the brain, physical damage to the spinal cord, stroke associated with brain damage,

Alzheimer's Disease, Parkinson's Disease, and amyotrophic lateral sclerosis.

The present invention also contemplates processes for manufacturing the novel compounds, particularly
5 the processes delineated in Schemes A, B, C, and D.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

"Alkyl" means a branched or unbranched saturated
10 hydrocarbon chain comprising a designated number of carbon atoms. For example, C₁-C₆ straight or branched alkyl hydrocarbon chain contains 1 to 6 carbon atoms, and includes but is not limited to substituents such as methyl, ethyl, propyl, iso-propyl, butyl, iso-
15 butyl, tert-butyl, n-pentyl, n-hexyl, and the like, unless otherwise indicated.

"Alkenyl" means a branched or unbranched unsaturated hydrocarbon chain comprising a designated number of carbon atoms. For example, C₂-C₆ straight or
20 branched alkenyl hydrocarbon chain contains 2 to 6 carbon atoms having at least one double bond, and includes but is not limited to substituents such as ethenyl, propenyl, iso-propenyl, butenyl, iso-butenyl, tert-butenyl, n-pentenyl, n-hexenyl, and the like,
25 unless otherwise indicated.

"Alkoxy" means the group -OR wherein R is alkyl

as herein defined. Preferably, R is a branched or unbranched saturated hydrocarbon chain containing 1 to 6 carbon atoms.

"Ar" means an aryl or heteroaryl moiety which is substituted or unsubstituted, especially a cyclic or fused cyclic ring and includes a mono-, bi- or tricyclic, carbo- or heterocyclic ring, wherein the ring is either unsubstituted or substituted in one to five position(s) with halo, haloalkyl, hydroxyl, nitro, trifluoromethyl, C₁-C₆ straight or branched chain alkyl, C₂-C₆ straight or branched chain alkenyl, C₁-C₆ alkoxy, C₂-C₆ alkenyloxy, phenoxy, benzyloxy, amino, thiocarbonyl, ester, thioester, cyano, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, and sulfonyl; wherein the individual ring sizes are 5-8 members; wherein the heterocyclic ring contains 1-4 heteroatom(s) selected from the group consisting of O, N, or S; wherein aromatic or tertiary alkyl amines are optionally oxidized to a corresponding N-oxide. Particularly preferred aryl or heteroaryl moieties include but are not limited to phenyl, benzyl, naphthyl, pyrrolyl, pyrrolidinyl, pyridinyl, pyrimidinyl, purinyl, quinolinyl, isoquinolinyl, furyl, thiophenyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, and thienyl.

"Halo" means at least one fluoro, chloro, bromo,

or iodo moiety, unless otherwise indicated.

"Phenyl" includes all possible isomeric phenyl radicals, optionally monosubstituted or multi-substituted with substituents selected from the group consisting of amino, halo, haloalkyl, hydroxy, trifluoromethyl, C₁-C₆ straight or branched chain alkyl, C₂-C₆ straight or branched chain alkenyl, carbonyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, NR₂ wherein R₂ is selected from the group consisting of hydrogen, (C₁-C₆)-straight or branched chain alkyl, (C₃-C₆)-straight or branched chain alkenyl or alkynyl, and (C₁-C₄) bridging alkyl wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR₁ and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group.

The term "pharmaceutically acceptable salt, ester, or solvate" refers to salt, ester, or solvates of the subject compounds which possess the desired pharmacological activity and which are neither biologically nor otherwise undesirable. The salt, ester, or solvates can be formed with inorganic acids such as acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate,

citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, gluconate, glycerophosphate, hemisulfate, heptanoate, hexanoate, 5 hydrochloride hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, naphthylate, 2-naphthalenesulfonate, nicotinate, oxalate, sulfate, thiocyanate, tosylate and undecanoate. Base salt, ester, or solvates 10 include ammonium salts, alkali metal salts such as sodium and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salt with organic bases such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as 15 arginine, lysine, and so forth. Also, the basic nitrogen-containing groups can be quarternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, 20 dibutyl and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides and others. Water or oil-soluble or dispersible products are thereby obtained.

25 The compounds of this invention may possess at least one asymmetric center and thus can be produced

as mixtures of stereoisomers or as individual enantiomers or diastereomers. The individual stereoisomers may be obtained by using an optically active starting material, by resolving a racemic or non-racemic mixture of an intermediate at some appropriate stage of the synthesis, or by resolution of the compound of formula (I). It is understood that the individual stereoisomers as well as mixtures (racemic and non-racemic) of stereoisomers are encompassed by the scope of the present invention. The S-stereoisomer at atom 1 of formula I is most preferred due to its greater activity.

"Isomers" are different compounds that have the same molecular formula and includes cyclic isomers such as (iso)indole and other isomeric forms of cyclic moieties.

"Stereoisomers" are isomers that differ only in the way the atoms are arranged in space.

"Enantiomers" are a pair of stereoisomers that are non-superimposable mirror images of each other.

"Diastereoisomers" are stereoisomers which are not mirror images of each other.

"Racemic mixture" means a mixture containing equal parts of individual enantiomers. "Non-racemic mixture" is a mixture containing unequal parts of individual enantiomers or stereoisomers.

The term "preventing neurodegeneration" as used herein includes the ability to prevent neurodegeneration in patients newly diagnosed as having a neurodegenerative disease, or at risk of developing a new degenerative disease and for preventing further neurodegeneration in patients who are already suffering from or have symptoms of a neurodegenerative disease.

The term "treatment" as used herein covers any treatment of a disease and/or condition in an animal, particularly a human, and includes:

(i) preventing a disease and/or condition from occurring in a subject which may be predisposed to the disease and/or condition but has not yet been diagnosed as having it;

(ii) inhibiting the disease and/or condition, i.e., arresting its development; or

(iii) relieving the disease and/or condition, i.e., causing regression of the disease and/or condition.

The system used in naming the compounds of the present invention is shown below, using a compound of formula IV as an example.

A compound of the present invention, especially Formula IV, wherein n is 1, X is O, Y is $(CH_2)_2$, Z is CH, C is p-Methoxyphenyl, D is H and R_1 is Phenyl, is

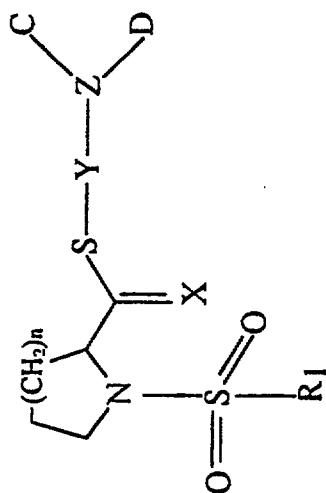
named 3-(4-Methoxyphenyl)propyl (2S)-1-(phenylsulfonyl)-2-pyrrolidinecarbothioate.

Compounds of the Invention

The neurotrophic low molecular weight, small
5 molecule FKBP inhibitor compounds of this invention
have an affinity for FKBP-type immunophilins, such as
FKBP12. When the neurotrophic compounds of this
invention are bound to an FKBP-type immunophilin, they
have been found to inhibit the prolyl-peptidyl cis-
10 trans isomerase activity, or rotamase, activity of the
binding protein and unexpectedly stimulate neurite
growth.

Specific exemplifications of these embodiments
are presented in TABLE I, below.

TABLE I



No.	n	X	Y	Z	C	D	R1
1	1	O	CH ₂	CH	Phenyl	H	Phenyl
2	1	O	CH ₂	CH	Phenyl	H	α-Methylphenyl
3	1	O	CH ₂	CH	Phenyl	H	4-Methylphenyl
4	1	O	(CH ₂) ₂	CH	p-Methoxyphenyl	H	Phenyl
5	1	O	(CH ₂) ₂	CH	p-Methoxyphenyl	H	α-Methylphenyl
6	1	O	(CH ₂) ₂	CH	p-Methoxyphenyl	H	4-Methylphenyl
7	1	O	(CH ₂) ₂	CH	Phenyl	Phenyl	Phenyl
8	1	O	(CH ₂) ₂	CH	Phenyl	Phenyl	α-Methylphenyl
9	1	O	(CH ₂) ₂	CH	Phenyl	Phenyl	4-Methylphenyl
10	2	O	(CH ₂) ₃	CH	Phenyl	H	Phenyl
11	2	O	(CH ₂) ₃	CH	Phenyl	H	α-Methylphenyl
12	2	O	(CH ₂) ₃	CH	Phenyl	H	4-Methylphenyl
13	2	O	(CH ₂) ₃	CH	Phenyl	H	Phenyl
14	2	O	(CH ₂) ₃	CH	Phenyl	H	α-Methylphenyl
15	2	O	(CH ₂) ₃	CH	Phenyl	H	4-Methylphenyl
16	2	O	Direct	CH	3-Phenylpropyl	3-Phenylpropyl	3, 4, 5-trimethoxyphenyl
17	2	O	Direct	CH	3-Phenylpropyl	3-Phenylpropyl	Cyclohexyl
18	2	O	Direct	CH	3-Phenylpropyl	3-Phenylpropyl	Phenyl
19	2	O	Direct	CH	3-Phenylethyl	3-Phenylethyl	α-Methylphenyl
20	2	O	Direct	CH	3-(4-Methoxyphenyl)propyl	3-Phenylpropyl	4-Methylphenyl
				CH	3-(2-Pyridyl)propyl	3-Phenylpropyl	4-Methylphenyl

21	1	0	CH ₃	CH	CH ₃	Phenyl	4-Ethylphenyl
22	1	0	(CH ₂) ₂	CH	Phenyl	Phenyl	
23	1	0	(CH ₂) ₂	CH	Phenyl	α-Methylphenyl	
24	1'	0	(CH ₂) ₂	CH	Naphthyl	α-Methylphenyl	
25	1	0	(CH ₂) ₂	CH	Phenyl	4-Ethylphenyl	
26	2	0	(CH ₂) ₂	CH	<i>p</i> -Methoxyphenyl	4-Methylphenyl	
27	2	0	(CH ₂) ₂	CH	<i>p</i> -Methoxyphenyl	α-Methylphenyl	
28	2	0	(CH ₂) ₂	CH	<i>p</i> -Methoxyphenyl	Phenyl	
29	2	0	(CH ₂) ₂	CH	3-(4-trifluoromethyl)- phenyl	4-Methylphenyl	

The compounds of the present invention may exist as stereoisomeric forms, either enantiomers or diastereoisomers. Included within the scope of the invention are the enantiomers, the racemic form, and
5 diastereoisomeric mixtures. Enantiomers and diastereoisomers can be separated by methods known to those skilled in the art.

Methods of Using the Compounds of the Invention

10 The compounds of the present invention have an affinity for the FK506 binding protein, particularly FKBP12, which is present in the neuronal tissue. When the inventive compounds bind to FKBP in neuronal tissue, they exhibit excellent neurotrophic activity.
15 This activity is useful in the stimulation of damaged neurons, the promotion of neuronal regeneration, the prevention of neurodegeneration, and the treatment of several neurological disorders known to be associated with neuronal degeneration and peripheral
20 neuropathies.

For the foregoing reasons, the present invention further relates to a method of effecting a neuronal activity in an animal, comprising:

administering to the animal a neurotrophically
25 effective amount of a compound of formula I, II, III or IV.

In a preferred embodiment, the neuronal activity is selected from the group consisting of stimulation of the growth of damaged neurons, promotion of neuronal regeneration, prevention of neurodegeneration and treatment of a neurological disorder.

The compounds of the present invention are particularly useful for preventing neurodegeneration in patients suffering from a neurodegenerative disease or who have symptoms of a neurodegenerative disease.

The compounds are also useful for preventing neurodegeneration in patients newly diagnosed as having a neurodegenerative disease or at risk for developing a neurodegenerative disease. These compounds are also useful for, but not limited to, preventing neurodegeneration in patients suffering from Parkinson's disease or having symptoms of Parkinson's disease. These treatment methods are exemplified in the MPTP model and data described herein.

The neurological disorders that may be treated include but are not limited to: trigeminal neuralgia; glossopharyngeal neuralgia; Bell's Palsy; myasthenia gravis; muscular dystrophy; amyotrophic lateral sclerosis; progressive muscular atrophy; progressive bulbar inherited muscular atrophy; herniated; ruptured or prolapsed invertebrate disk syndromes; cervical

spondylosis; plexus disorders; thoracic outlet
destruction syndromes; peripheral neuropathic such as
those caused by lead, dapson, ticks, porphyria, or
Guillain-Barré syndrome; Alzheimer's disease; and
5 Parkinson's disease.

The compounds of the present invention are
particularly useful for treating a neurological
disorder selected from the group consisting of:
peripheral neuropathy caused by physical injury or
10 disease state, physical damage to the brain, physical
damage to the spinal cord, stroke associated with
brain damage, and neurological disorder relating to
neurodegeneration. Examples of neurological disorders
relating to neurodegeneration are Alzheimer's Disease,
15 Parkinson's Disease, and amyotrophic lateral
sclerosis.

Pharmaceutical Compositions of the Invention

The present invention also relates to a pharmaceuti-
cal composition comprising:

- 20 (i) a neurotrophically effective amount of the
compound of formula I, II, III or IV, and
(ii) a pharmaceutically acceptable carrier.

The above discussion relating to the utility and
administration of the compounds of the present
25 invention also applies to the pharmaceutical
compositions of the present invention.

The term "pharmaceutically acceptable carrier" as used herein refers to any carrier, diluent, excipient, suspending agent, lubricating agent, adjuvant, vehicle, delivery system, emulsifier, disintegrant, 5 absorbant, preservative, surfactant, colorant, flavorant, or sweetener.

For these purposes the compounds of the present invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, 10 buccally, vaginally or via an implanted reservoir in dosage formulations containing conventional non-toxic pharmaceutically-acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous, intravenous, intramuscular, 15 intraperitoneally, intrathecally, intraventricularly, intrasternal and intracranial injection or infusion techniques.

For oral administration, the compounds of the present invention may be provided in any suitable 20 dosage form known in the art. For example, the compositions may be incorporated into tablets, powders, granules, beads, chewable lozenges, capsules, liquids, aqueous suspensions or solutions, or similar dosage forms, using conventional equipment and 25 techniques known in the art. Tablet dosage forms are preferred. Tablets may contain carriers such as

lactose and corn starch, and/or lubricating agents such as magnesium stearate. Capsules may contain diluents including lactose and dried corn starch. Aqueous suspensions may contain emulsifying and suspending agents combined with the active ingredient.

When preparing dosage form incorporating the compositions of the invention, the compounds may also be blended with conventional excipients such as binders, including gelatin, pregelatinized starch, and the like; lubricants, such as hydrogenated vegetable oil, stearic acid, and the like; diluents, such as lactose, mannose, and sucrose; disintegrants, such as carboxymethylcellulose and sodium starch glycolate; suspending agents, such as povidone, polyvinyl alcohol, and the like; absorbants, such as silicon dioxide; preservatives, such as methylparaben, propylparaben, and sodium benzoate; surfactants, such as sodium lauryl sulfate, polysorbate 80, and the like; colorants such as F.D. & C. dyes and lakes; flavorants; and sweeteners.

Compositions and methods of the invention also may utilize controlled release technology. Thus, for example, the inventive compounds may be incorporated into a hydrophobic polymer matrix for controlled release over a period of days. Such controlled release films are well known to the art. Particularly

preferred are transdermal delivery systems. Other examples of polymers commonly employed for this purpose that may be used in the present invention include nondegradable ethylene-vinyl acetate copolymer and degradable lactic acid-glycolic acid copolymers which may be used externally or internally. Certain hydrogels such as poly(hydroxyethylmethacrylate) or poly(vinylalcohol) also may be useful, but for shorter release cycles than the other polymer releases systems, such as those mentioned above.

To be effective therapeutically as central nervous system targets, the compounds of the present invention should readily penetrate the blood-brain barrier when peripherally administered. Compounds which cannot penetrate the blood-brain barrier can be effectively administered by an intraventricular route or other appropriate delivery system suitable for administration to the brain.

The compounds of the present invention may be administered in the form of sterile injectable preparations, for example, as sterile injectable aqueous or oleaginous suspensions. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparations may also be sterile injectable solutions

or suspensions in non-toxic parenterally-acceptable diluents or solvents, for example, as solutions in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as solvents or suspending mediums. For this purpose, any bland fixed oil may be employed including synthetic mono- or di-glycerides. Fatty acids such as oleic acid and its glyceride derivatives, including olive oil and castor oil, especially in their polyoxyethylated versions, are useful in the preparation of injectables. These oil solutions or suspensions may also contain long-chain alcohol diluents or dispersants.

The compounds of this invention may also be administered rectally in the form of suppositories. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at room temperature, but liquid at rectal temperature and, therefore, will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

The compounds of this invention may also be administered topically, especially when the conditions addressed for treatment involve areas or organs

readily accessible by topical application, including neurological disorders of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas.

5 For topical application to the eye, or ophthalmic use, the compounds can be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or, preferably, as solutions in isotonic, pH adjusted sterile saline, either with or without a preservative
10 such as benzylalkonium chloride. Alternatively for the ophthalmic uses the compounds may be formulated in an ointment such as petrolatum.

For topical application to the skin, the compounds can be formulated in a suitable ointment containing
15 the compound suspended or dissolved in, for example, a mixture with one or more of the following: mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, the
20 compounds can be formulated in a suitable lotion or cream containing the active compound suspended or dissolved in, for example, a mixture of one or more of the following: mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-
25 octyldodecanol, benzyl alcohol and water.

Topical application for the lower intestinal tract

an be effected in a rectal suppository formulation (see above) or in a suitable enema formulation.

Dosage levels on the order of about 0.1 mg to about 10,000 mg of the active ingredient compound are useful in the treatment of the above conditions, with preferred levels of about 0.1 mg to about 1,000 mg. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

It is understood, however, that a specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the severity of the particular disease being treated and form of administration.

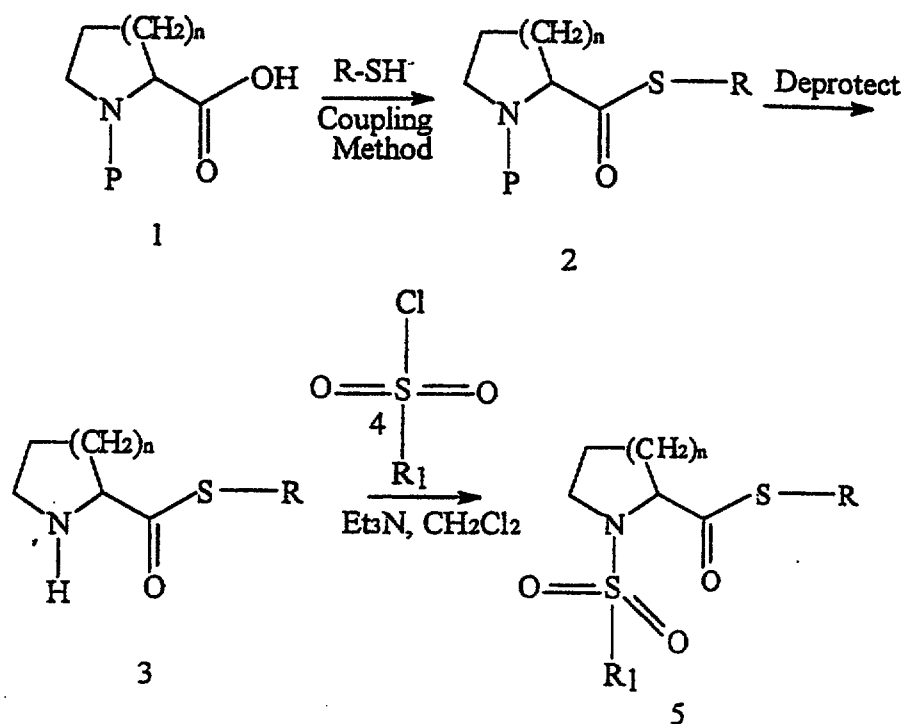
The compounds can be administered with other neurotrophic agents such as neurotrophic growth factor (NGF), glial derived growth factor, brain derived growth factor, ciliary neurotrophic factor, and neurotrophin-3. The dosage level of other neurotrophic drugs will depend upon the factors previously stated and the neurotrophic effectiveness of the drug combination.

The present invention relates to the use of any of the compounds seen in Table I in the preparation of a medicament for the treatment of a disease such as peripheral neuropathy caused by physical injury or disease state, physical damage to the brain, physical damage to the spinal cord, stroke associated with brain damage, Alzheimer's Disease, Parkinson's Disease, and amyotrophic lateral sclerosis.

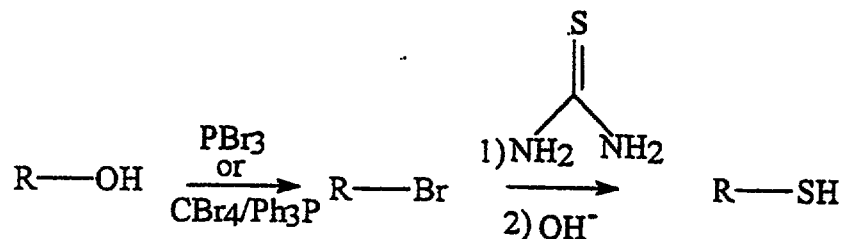
The present invention also contemplates processes for manufacturing the novel compounds, particularly the processes delineated in schemes A and B.

Methods of Making the Compounds of the Invention

The novel compounds of this invention may be readily prepared by standard techniques of organic chemistry, utilizing the general synthetic pathway depicted below. As described by Scheme A, cyclic amino acids 1 protected by suitable blocking groups P on the amino acid nitrogen may be reacted with thiols RSH to generate thioesters 2. After removal of the protecting group, the free amine 3 may be reacted with various sulfonyl chlorides 4 to provide final products 5 in good to excellent yield.



SCHEME A

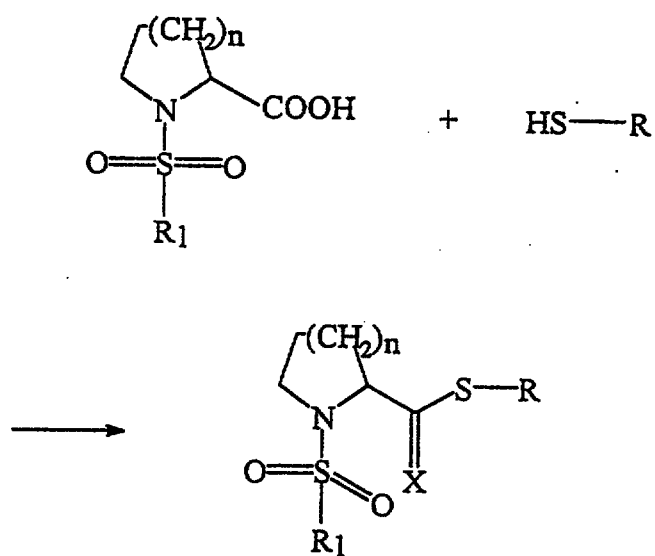


SCHEME B

Thiols R-SH may be conveniently prepared from the corresponding readily available alcohols or halides via a two step replacement of halogen by sulfur, as described in Scheme B. Halides may be reacted with thiourea, and the corresponding alkyl thiouronium salts hydrolyzed to provide thiols RSH. If alcohols are used as the starting materials, they may be first converted to the corresponding halides by standard methods. Additional protecting groups and minor variations are contemplated as within the scope of the present invention and would be known to a person of ordinary skill in the art.

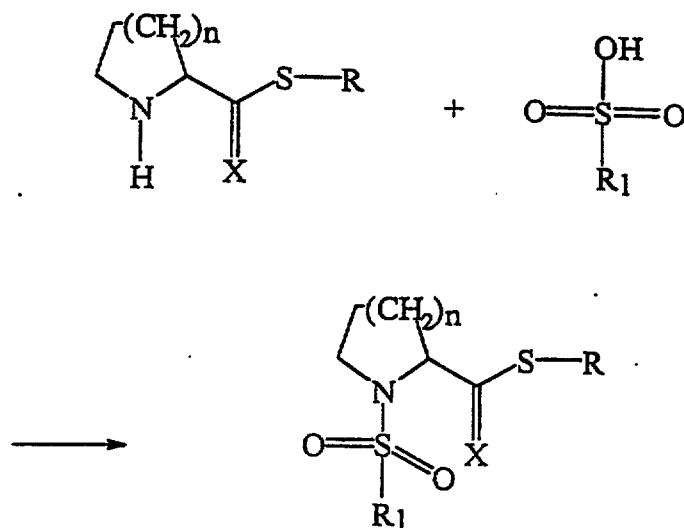
In addition to the methods of making the compounds above, generalized methods and processes for making the compounds of the present invention contemplated as

within the scope of the present invention are exemplified by the following Schemes C & D, wherein the compound of the left side of the equation may be contacted with the compound of the right side of the equation producing the novel inventive compounds of the present invention.



SCHEME C

Another generalized preferred Scheme for preparing the novel compounds of the present invention is exemplified by SCHEME D, below.

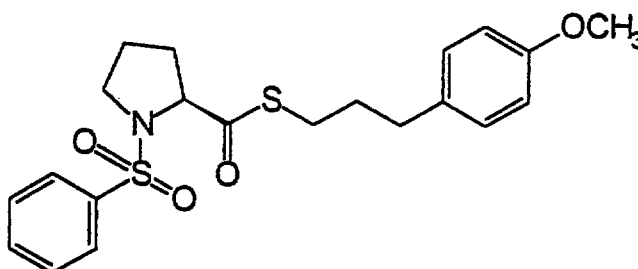


SCHEME D

Examples

The following examples are illustrative of the present invention and are not intended to be limitations thereon. Unless otherwise specified, all percentages are based on 100% by weight of the final compound.

Example 1



Synthesis of 3-(4-Methoxyphenyl)propyl (2S)-1-(phenylsulfonyl)-2-pyrrolidinecarbothioate(4)

3-(4-Methoxyphenyl)-1-propylbromide

To a solution of 3-(4-methoxyphenyl)-1-propanol (16.6 g; 0.1 mol) in 250 mL of toluene, cooled to 0°C, was added dropwise 26 mL of phosphorus tribromide (0.27 mol). Following completion of the addition the reaction was stirred at room temperature for 1 hour, then refluxed for an additional hour. The reaction was cooled and poured onto ice, the layers were separated, and the organic phase washed with saturated sodium bicarbonate (3x) and brine (3x). The crude material obtained upon drying and evaporation of the

solvent was chromatographed, eluting with 10% EtOAc/hexane, to obtain 14 g (61%) of 3-(4-methoxyphenyl)-1-propylbromide.

5 3-(4-Methoxyphenyl)-1-propylmercaptan

A mixture of 3-(4-methoxyphenyl)-1-propylbromide (14 g; 61 mmol) and thiourea (5.1 g; 67 mmol) in ethanol (150 mL) was refluxed for 48 hours. Evaporation of the solvent provided a clear glassy compound, which
10 was dissolved in 50 mL of water and treated with 100 mL of 40% aqueous sodium hydroxide. After stirring the resulting mixture for two hours, the product was extracted into ether (3x), and the combined organic extracts were washed with sodium bicarbonate and
15 brine, dried, and concentrated. Chromatographic purification of the crude thiol on a silica gel column eluting with 2% ether in hexane delivered 10.2 g of 3-(4-methoxyphenyl)-1-propylmercaptan as a clear liquid ¹H NMR (300 MHz, CDCl₃): δ 1.34 (t, 1H); 1.88-
20 1.92 (m, 2H); 2.49-2.53 (m, 2H); 2.64-2.69 (m, 2H); 3.77 (s, 3H); 6.80-6.84 (m, 2H); 7.06-7.24 (m, 2H).

25 3-(4-Methoxyphenyl) N-(tert-butyloxycarbonyl)-2-pyrrolidinecarbothioate

A mixture of N-(tert-butyloxycarbonyl)-(S)-proline (2.0g; 9.29 mmol); 3-(4-methoxyphenyl)-1-propylmercaptan (1.86 g; 10.22 mmol), 1-(3-

dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.96 g; 10.22 mmol) and 4-dimethylaminopyridine (catalytic) in dry methylene chloride (50 mL) was stirred overnight. The reaction mixture was diluted with methylene chloride (50 mL) and water 100 (mL), and the layers were separated. The organic phase was washed with water (3 x 100 mL), dried over magnesium sulfate, and concentrated to provide 3.05 g of the product as a thick oil, ¹H NMR (300 MHz, CDCl₃): δ 1.15 (s, 9H); 1.84-2.31 (m, 6H); 2.61 (m, 2H); 2.83 (m, 2H); 3.51 (m, 2H); 3.75 (s, 3H); 6.79 (d, 2H, J=8.04); 7.05 (m, 2H).

3-(4-Methoxyphenyl)-2-pyrrolidinecarbothioate

A solution of 3-(4-methoxyphenyl) N-(tert-butyloxycarbonyl)-2-pyrrolidinecarbothioate (3.0 g; 8.94 mmol) in methylene chloride (60 mL) and trifluoroacetic acid (6 mL) was stirred at room temperature for three hours. Saturated potassium carbonate was added until the pH was basic, and the reaction mixture was extracted with methylene chloride (3x). The combined organic extracts were dried and concentrated to yield 1.73 g (69%) of the free amine as a thick oil, ¹H NMR (300 MHz, CDCl₃): δ 1.80-2.23 (m, 6H); 2.62 (m, 2H); 2.81 (m, 2H); 3.01 (m, 2H); 3.75 (s, 3H); 3.89 (m, 1H); 6.81 (m, 2H); 7.06 (m, 2H).

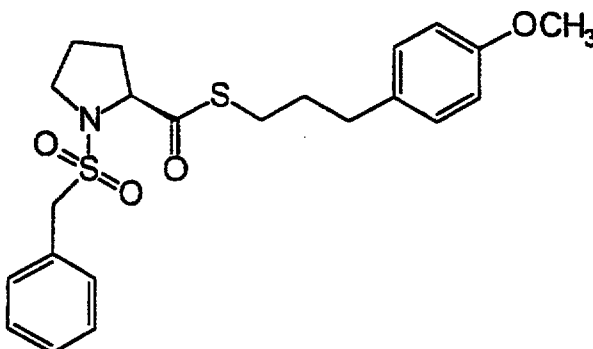
3-(4-Methoxyphenyl)propyl (2S)-1-(phenylsulfonyl)-2-pyrrolidinecarbothioate

A solution of 3-(4-methoxyphenyl)-2-pyrrolidinecarbothioate (567 mg; 2.03 mmol) and benzenesulfonyl chloride (358 mg; 2.03 mmol) in methylene chloride (5 mL) was treated with diisopropylethylamine (290 mg; 2.23 mmol) and stirred overnight at room temperature. The reaction mixture was filtered to remove solids and applied directly to a silica gel column, eluting with 25% ethyl acetate in hexane, to obtain 540 mg of compound 4 (Table I) as a clear oil, ¹H NMR (300 MHz, CDCl₃): δ 1.65-1.89 (m, 6H); 2.61 (t, 2H, J=7.3); 2.87 (t, 2H, J=7.6); 3.26 (m, 1H); 3.54 (m, 1H); 3.76 (s, 3H); 4.34 (dd, 1H, J=2.7, 8.6); 6.79 (d, 2H, J=8.7); 7.06 (d, 2H, J=8.6); 7.49-7.59 (m, 3H); 7.86 (dd, 2H, J = 1.5, 6.8). Thin Layer Chromatography yielded a result of R_f = 0.36 (25% EtOAc:Hexane).

20

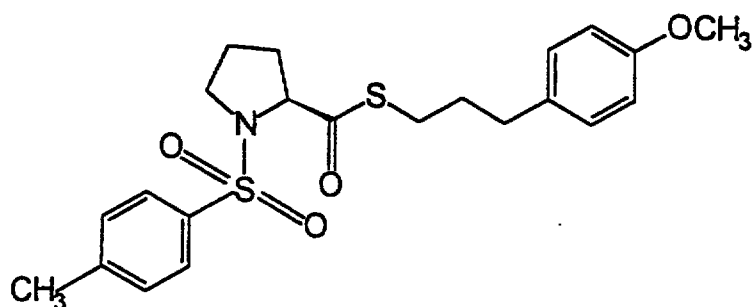
25

Example 2



Synthesis of 3-(4-Methoxyphenyl)propyl (2S)-1-(benzylsulfonyl)-2-pyrrolidinecarbothioate (5)

A solution of 3-(4-Methoxyphenyl)-2-pyrrolidinecarbothioate (645 mg; 2.30 mmol) and benzylsulfonyl chloride (440 mg; 2.30 mmol) in methylene chloride (5 mL) was treated with diisopropylethylamine (330 mg; 2.53 mmol) and stirred overnight at room temperature. Purification as described for Example 1 provided the compound of Example 2 (Compound 5, Table I) as a clear oil, ¹H NMR (300 MHz, CDCl₃): δ 1.98-2.06 (m, 6H); 2.77 (t, 2H, J=7.3); 3.02 (t, 2H, J=7.3); 3.42 (m, 1H); 3.45 (m, 2H); 3.91 (s, 3H); 4.42-4.76 (m, 3H); 6.95 (d, 2H, J=8.6); 7.21 (d, 2H, J=8.6); 7.51 (m, 3H); 7.61-7.64 (m, 2H). Thin Layer Chromatography yielded a result of R_f = 0.36 (25% EtOAc:Hexane).

Example 3

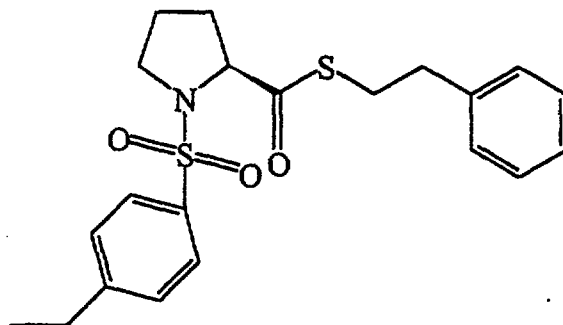
5 Synthesis of 3-(4-Methoxyphenyl)propyl (2S)-1-[(4-methylphenyl)sulfonyl]-2-pyrrolidinecarbothioate (6)

 A solution of 3-(4-Methoxyphenyl)-2-pyrrolidinecarbothioate (567 mg; 2.30 mmol) and (4-methylphenyl)sulfonyl chloride (425 mg; 2.23 mmol) in
10 methylene chloride (5 mL) was stirred overnight at room temperature. Purification as described for Example 1 provided the compound of Example 3 (Compound 6, Table I) as a clear oil, ¹H NMR (300 MHz, CDCl₃): δ
15 1.67-1.94 (m, 6H); 2.40 (s, 3H); 2.61 (t, 2H, J=7.3); 2.84 (m, 2H, J=7.2); 3.22 (m, 1H); 3.52 (m, 1H); 3.76 (s, 3H);
 4.32 (dd, 1H, J=2.9, 8.5); 6.79 (d, 2H, J=6.5); 7.07 (d, 2H, J=6.5); 7.29 (d, 2H, J=6.5); 7.74 (d, 2H, J=6.5). Thin Layer Chromatography yielded a result of R_f = 0.40
20 (25% EtOAc:Hexane).

 As discussed above, the compounds of the present invention have an affinity for the FK506 binding protein, particularly FKBP12. The inhibition of the
25 prolyl peptidyl *cis-trans* isomerase activity of FKBP

may be measured as an indicator of this affinity.

Example 4

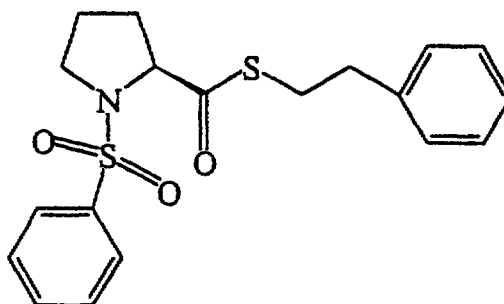


5 Synthesis of Phenethyl (2S)-1-[(4-ethylphenyl)sulfonyl]-2-pyrrolidinecarbothioate (21)

10 The compound was prepared in accordance with the procedures used in the above examples and yielded and optically pure compound as a clear oil of molecular weight 403.55, molecular formula of $C_{21}H_{25}NO_3S_2$, 1H NMR ($CDCl_3$, 300 MHz): δ 1.52-2.02 (m, 9H); 2.68 (t, 2H, $J=8.6$); 2.87 (t, 2H, $J=8.6$); 3.27 (m, 1H); 3.53 (m, 1H); 4.33 (m, 1H); 7.17 (m, 3H); 7.27 (m, 1H); 7.49-7.65 (m, 3H); 7.85 (d, 2H, $J=6.2$). Thin Layer Chromatography yielded a result of $R_f = 0.24$ (25 EtOAc:Hexane).

15

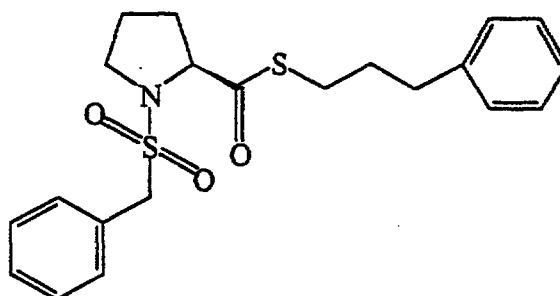
Example 5



5 Synthesis of Phenethyl (2S)-1-(phenylsulfonyl)-2-pyrrolidinecarbothioate (22)

The compound was prepared in accordance with the procedures used in the above examples and yielded an
10 optically pure compound as an oil with a molecular weight of 389.53, molecular formula of $C_{20}H_{23}NO_3S_2$, 1H NMR ($CDCl_3$, 300 MHz): δ 1.54-2.02 (m, 4H); 1.88 (q, 2H, $J=7.58$); 2.67 (t, 2H, $J=7.46$); 2.87 (t, 2H, $J=7.25$); 3.21-3.29 (m, 1H); 3.52-3.59 (m, 1H); 4.24
15 (d, 1H, $J=8.44$); 7.14-7.19 (m, 3H); 7.23-7.28 (m, 2H); 7.49-7.62 (m, 3H); 7.85 (d, 2H, $J=7.66$). Thin Layer Chromatography yielded a result of $R_f = 0.25$ (25% EtOAc:Hexane).

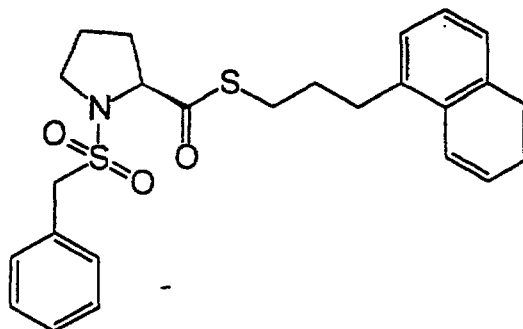
Example 6



5 Synthesis of 3-Phenylpropyl (2S)-1-(benzylsulfonyl)-2-pyrrolidinecarbothioate (23)

The compound was prepared in accordance with the procedures used in the above examples and yielded an
10 optically pure compound as a solid with a molecular weight of 403.56, molecular formula of $C_{21}H_{25}NO_3S_2$, melting point of 62-64°C, 1H NMR ($CDCl_3$, 300 MHz): δ 1.86-1.97 (m, 5H); 2.05 (m, 1H); 2.70 (t, 2H, $J=7.29$); 2.91 (t, 2H, $J=7.23$); 3.15 (m, 1H); 3.29 (m, 1H); 4.41
15 (m, 3H); 7.18 (m, 3H); 7.28 (m, 2H); 7.38 (m, 3H); 7.48 (m, 2H). Thin Layer Chromatography yielded a result of $R_f = 0.27$ (25% EtOAc/Hexane).

Example 7



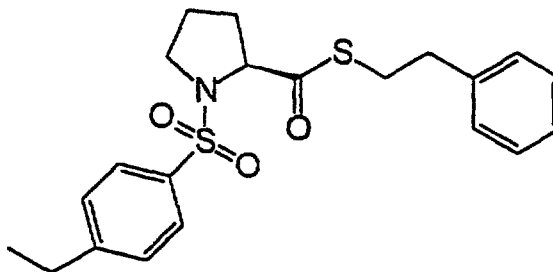
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Synthesis of 3-(1-Naphthyl)propyl (2S)-1-(benzylsulfonyl)-2-pyrrolidinecarbothioate (24)

The compound was made in accordance with the procedures followed in the above examples and yielded an optically active compound as a clear oil with a molecular weight of 453.62, molecular formula of $C_{25}H_{27}NO_3S_2$, 1H NMR ($CDCl_3$, 300 MHz): δ 1.81-2.06 (m, 6H); 2.98 (t, 2H, $J=7.2$); 3.15 (m, 3H); 3.29 (m, 1H); 4.30-4.44 (m, 3H); 7.29-7.51 (m, 9H); 7.71 (d, 1H, $J=8.1$); 7.82 (d, 1H, $J=8.1$); 8.00 (d, 1H, $J=8.1$). Thin Layer Chromatography yielded a result of $R_f = 0.26$ (25% EtOAc/Hexane).

15

Example 8



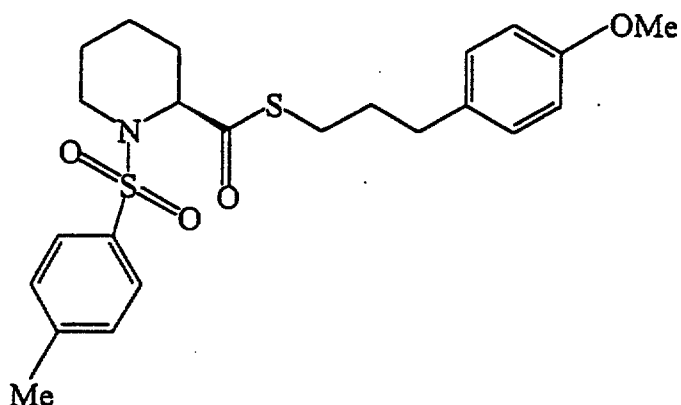
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Synthesis of 3-Phenylpropyl (2S)-1-[(4-ethylphenyl)sulfonyl]-2-pyrrolidinecarbothioate (25)

The compound was made in accordance with the procedures used in the above examples and yielded an optically pure compound as a clear oil with a molecular weight of 417.58, molecular formula of $C_{22}H_{27}NO_3S_2$, 1H NMR ($CDCl_3$, 300 MHz): δ 1.39-2.02 (m, 9H);

2.73 (m, 4H); 2.89 (t, 2H, J=7.5); 3.27 (m, 1H); 3.53 (m, 1H); 4.35 (d, 1H, J=8.2); 7.14-7.52 (m, 7H); 7.73 (d, 2H, J=7.2). Thin Layer Chromatography yielded a result of $R_f = 0.39$ (25% EtOAc/hexane).

5

Example 9

10

Synthesis of 3-(4-Methoxyphenyl)propyl 1-[(4-methylphenyl)sulfonyl]-2-piperidinecarbothioate (26)

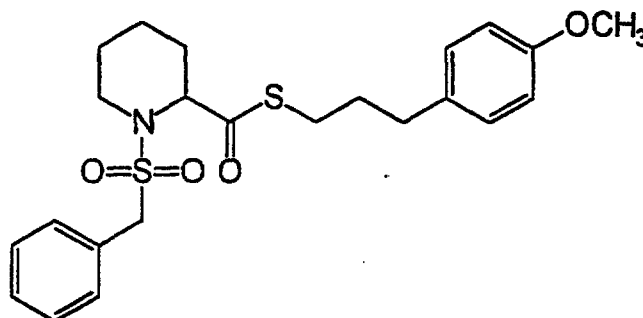
15

The compound was prepared in accordance with the procedures used in the above examples and yielded a racemic compound as a clear oil with a molecular weight of 447.55, molecular formula of $C_{23}H_{29}NO_4S_2$, 1H NMR ($CDCl_3$, 300 MHz): δ 1.25-1.32 (m, 2H); 1.45-1.52 (m, 4H); 1.78-1.85 (m, 2H); 2.19 (bd, 1H, J=4.59); 2.38 (s, 3H); 2.58 (t, 2H, J=6.88); 2.79 (t, 2H, J=6.73); 3.15-3.24 (m, 1H); 3.76 (s, 3H); 4.72-4.74 (m, 1H); 6.80 (d, 2H, J=8.39); 7.04 (d, 2H, J=8.61); 7.24 (d, 2H, J=10.53); 7.70 (d, 2H, J=8.53). Thin Layer Chromatography yielded a result of $R_f = 0.35$ (25%

20

EtOAc/hexane).

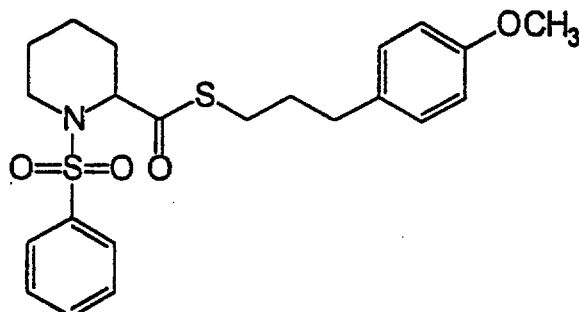
Example 10



5

Synthesis of 3-(4-Methoxyphenyl)propyl 1-(benzylsulfonyl)-2-piperidinecarbothioate (27)

The compound was prepared in accordance with the
10 procedures followed in the above examples and yielded
a racemic compound as a clear oil with a molecular
weight of 447.55, molecular formula of $C_{23}H_{29}NO_3S_2$, 1H
NMR ($CDCl_3$, 300 MHz): δ 1.28-1.64 (m, 5H); 1.82-1.92
(m, 2H); 2.20 (bd, 1H, $J=14.51$); 2.62 (t, 2H, $J=7.54$); 2.90
15 (t, 2H, $J=7.36$); 3.13 (dt, 1H, $J=2.56, 12.93$); 3.49
(bd, 1H, $J=12.84$); 3.76 (s, 3H); 4.27 (s, 2H); 4.55-4.56
(m, 1H); 6.80 (d, 2H, $J=8.54$); 7.06 (d, 2H, $J=8.39$); 7.32-
7.35 (m, 3H); 7.43-7.46 (m, 2H). Thin Layer
Chromatography yielded a result of $R_f = 0.32$ (25%
20 EtOAc/hexane).

Example 11

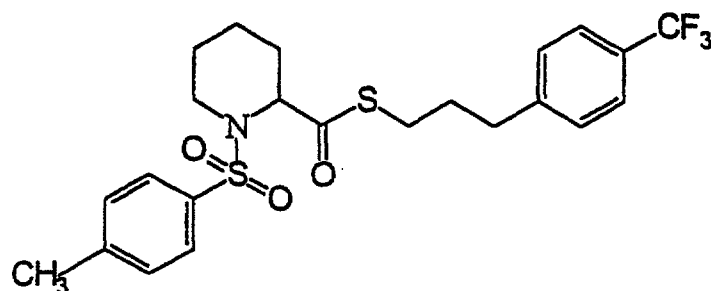
5

Synthesis of 3-(4-Methoxyphenyl)propyl 1-(phenylsulfonyl)-2-piperidinecarbothioate (28)

The compound was prepared in accordance with the procedures followed in the above examples and yielded a racemic compound as a clear oil with molecular weight of 433.55, molecular formula of $C_{22}H_{24}NS_2O_4$, 1H NMR ($CDCl_3$, 300 MHz): δ 1.31-1.47 (m, 1H); 1.51-1.56 (m, 4H); 1.80 (q, 2H, $J=7.45$, 14.95); 2.21 (bd, 1H, $J=13.36$); 2.58 (t, 2H, $J=7.49$); 2.79 (t, 2H, $J=7.19$); 3.18-3.26 (m, 1H); 3.77 (s, 3H); 3.83 (bd, 1H, $J=13.54$); 4.74-4.76 (m, 1H); 6.81 (d, 2H, $J=8.56$); 7.05 (d, 2H, $J=8.43$); 7.44-7.54 (m, 3H); 7.83 (d, 2H, $J=7.52$). Thin Layer Chromatography yielded a result of $R_f = 0.37$ (25% EtOAc/hexane).

20

Example 12



5 Synthesis of 3-[4-(Trifluoromethyl)phenyl]propyl 1-
 [(4-methylphenyl)sulfonyl]-2-piperidinecarbothioate
 (29)

 The compound was prepared in accordance with the
procedures in the above examples and yielded a racemic
10 compound with molecular weight of 485.46, molecular
 formula of $C_{23}H_{26}F_3NO_3S_2$, 1H NMR ($CDCl_3$, 300 MHz): δ 1.19-
1.34 (m, 3H); 1.46-1.53 (m, 2H); 1.87-2.03 (m, 2H); 2.13-
2.34 (m, 1H); 2.41 (s, 3H); 2.71 (t, 2H, $J=7.4$); 2.87
(t, 2H, $J=7.36$); 3.20-3.35 (m, 1H); 3.87 (bd, 1H, $J=7.91$);
15 4.80-4.83 (m, 1H); 7.31-7.40 (m, 4H); 7.50-7.58 (m, 2H);
7.80-7.87 (m, 2H). Thin Layer Chromatography yielded
a result of $R_f = 0.66$ (50% Hexane:EtOAc).

20

Ki Test Procedure

 The compounds of the invention are shown to inhibit
peptidyl-prolyl isomerase (rotamase) activity and can
be evaluated by known methods described in the
literature (Harding, et al., Nature, 1989, 341:758-

760; Holt et al. *J. Am. Chem. Soc.*, 115:9923-9938).

These values are obtained as apparent K_i 's and are presented in Tables II(a) and II(b). The *cis-trans* isomerization of an alanine-proline bond in a model substrate, N-succinyl-Ala-Ala-Pro-Phe-*p*-nitroanilide, is monitored spectrophotometrically in a chymotrypsin-coupled assay, which releases *para*-nitroanilide from the *trans* form of the substrate. The inhibition of this reaction caused by the addition of different concentrations of inhibitor is determined, and the data is analyzed as a change in first-order rate constant as a function of inhibitor concentration to yield the apparent K_i values.

In a plastic cuvette are added 950 μ L of ice cold assay buffer (25 mM HEPES, pH 7.8, 100 mM NaCl), 10 μ L of FKBP (2.5 mM in 10 mM Tris-Cl pH 7.5, 100 mM NaCl, 1 mM dithiothreitol), 25 μ L of chymotrypsin (50 mg/mL in 1 mM HCl) and 10 μ L of test compound at various concentrations in dimethyl sulfoxide. The reaction is initiated by the addition of 5 μ L of substrate (succinyl-Ala-Phe-Pro-Phe-*para*-nitroanilide, 5 mg/mL in 2.35 mM LiCl in trifluoroethanol).

The absorbance at 390 nm versus time is monitored for 90 seconds using a spectrophotometer and the rate constants are determined from the absorbance versus time data files.

The data for these experiments for representative compounds are presented in Tables II(a) and II(b) under the column "Ki".

5 The neurotrophic effects of the compounds of the present invention can be demonstrated in cellular biological experiments in vitro, as described below.

Chick Dorsal Root Ganglion

Cultures and Neurite Outgrowth

10 Dorsal root ganglia were dissected from chick embryos of ten day gestation. Whole ganglion explants were cultured on thin layer Matrigel-coated 12 well plates with Liebovitz L15 plus high glucose media supplemented with 2 mM glutamine and 10% fetal calf
15 serum, and also containing 10 μ M cytosine β -D arabinofuranoside (Ara C) at 37°C in an environment containing 5% CO₂. Twenty-four hours later, the DRGs were treated with various immunophilin ligands. Forty-eight hours after drug treatment, the ganglia
20 were visualized under phase contrast or Hoffman Modulation contrast with a Zeiss Axiovert inverted microscope. Photomicrographs of the explants were made, and neurite outgrowth was quantitated. Neurites longer than the DRG diameter were counted as positive,
25 with total number of neurites quantitated per each experimental condition. Three to four DRGs are

cultured per well, and each treatment was performed in duplicate.

The data for these experiments for representative compounds are presented in Table II(c) under the column "ED₅₀".

5

TABLE II(a)
In Vitro Test Results

	<u>Ex. No.</u>	<u>Ki, nM^r</u>
5	1	+++
	2	++
	3	++
	4	+
	5	+++
10	6	++
	7	++
	8	+++
	9	+++
	10	+++
15	11	++
	12	+++
	13	+++
	14	+++
	15	+++
20	16	++
	21	*
	22	*
	23	++
	24	*
25	25	*
	26	*
	27	*
	28	++
	29	++
30		

Table II(b)
Numerical In Vitro Test Results

	<u>Ex. No.</u>	<u>Ki, nM^r</u>
35	4	204
	5	22
	6	145
	21	780
	22	551
40	23	107
	24	671
	25	984
	26	659
	27	82
45	28	196
	29	69

TABLE II(c)
Chick DRG In Vitro Neurite Test Results

	<u>Ex. No.</u>	<u>ED50, nM</u>
5	1	++++
	2	+++
	3	+++
	4	++
	5	+++
10	6	++
	7	+++
	8	++++
	9	++++
	10	+++
15	11	+++
	12	+++
	13	++++
	14	+++
	15	++++
20	16	++

* Relative potencies of compounds are ranked according to the following scale: ++++ denotes Ki or ED50 < 1 nM; +++ denotes Ki or ED50 of 1-50 nM; ++ denotes Ki or ED 50 of 51-200 nM; + denotes Ki or ED50 of 201-500 nM; * denotes Ki or ED50 of > 500nM.

MPTP Model of Parkinson's Disease

The remarkable neurotrophic and neuroregenerative effects of the present inventive compounds can be further demonstrated in an animal model of neurodegenerative disease. MPTP lesioning of dopaminergic neurons in mice is used as an animal model of Parkinson's Disease. Four week old male CD1 white mice are dosed i.p. with 30 mg/kg of MPTP for 5 days. Test compounds (4 mg/kg), or vehicle,

are administered s.c. along with the MPTP for 5 days, as well as for an additional 5 days following cessation of MPTP treatment. At 18 days following MPTP treatment, the animals are sacrificed and the striata dissected and perfusion-fixed.

Immunostaining is performed on sagittal and coronal brain sections using anti-tyrosine hydroxylase 1 g to quantitate survival and recovery of dopaminergic neurons. In animals treated with MPTP and vehicle,

a substantial loss of functional dopaminergic terminals is observed as compared to non-lesioned animals. Lesioned animals receiving test compounds show a significant recovery of TH-stained

dopaminergic neurons. This model presents

quantitation for the recovery of TH-positive dopaminergic neurons in the striatum of animals receiving the compounds of the present invention.

Data for representative control and lesioned animals not receiving the test drugs is also presented

against the data from the animals receiving the compounds of the present invention in Table III.

Table IIIMPTP Model of Parkinson's Disease Test Results

<u>Comp. No.</u>	<u>% Recovery Tyrosine Hydroxylase</u>
4	42
5 6	37
23	80
24	40

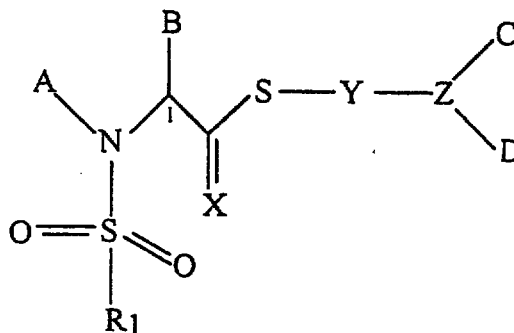
The phrase "preventing neurodegeneration" relates to the remarkable ability of the compounds of the present invention to significantly prevent nerve damage when the compounds are given concurrently with a lesioning agent, such as MPTP. This also provides a reasonable correlation between the scope of the claims and the ability to prevent neurodegeneration in patients newly diagnosed as having a neurodegenerative disease, or at risk of developing a neurodegenerative disease. The compounds also provide methods for preventing further neurodegeneration in patients who are already suffering from or have symptoms of a neurodegenerative disease.

The invention being thus described, it will be obvious that the same may be varied in many ways. Such variations are not to be regarded as a departure from the spirit and scope of the invention

and all such modifications are intended to be included within the scope of the following claims.

WHAT IS CLAIMED IS:

1. A compound of formula I:



I

or a pharmaceutically acceptable salt, ester, or solvate thereof, wherein:

A and B are taken together, with the nitrogen and carbon atoms to which they are respectively attached, to form a 5-7 membered saturated or unsaturated heterocyclic ring containing any combination of CH_2 , O, S, SO, SO_2 , NH or NR_2 in any chemically stable oxidation state;

X is either O or S;

Y is a direct bond to Z, a C_1 - C_6 straight or branched chain alkyl, or a C_2 - C_6 straight or branched chain alkenyl, wherein any of the carbon atoms of said alkyl or alkenyl are optionally substituted in one or more positions with amino, halo, haloalkyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl,



sulfhydryl, thioalkyl, sulfonyl, oxygen to form a carbonyl, or wherein any of the carbon atoms of said alkyl or alkenyl are optionally replaced with O, NH, NR₂, S, SO, or SO₂, wherein R₂ is selected from the group consisting of hydrogen, (C₁-C₆)-straight or branched chain alkyl, (C₃-C₆)-straight or branched chain alkenyl or alkynyl, and (C₁-C₄) bridging alkyl wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR₂ and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group;

Z is a direct bond, or a C₁-C₆ straight or branched chain alkyl, or a C₁-C₆ straight or branched chain alkenyl, wherein any of the carbon atoms of said alkyl or alkenyl are optionally substituted in one or more positions with amino, halo, haloalkyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, oxygen to form a carbonyl, or wherein any of the carbon atoms of said alkyl or alkenyl are optionally replaced with O, NH, NR₂, S, SO, or SO₂, wherein R₂ is selected from the group consisting of hydrogen, (C₁-C₆)-straight or branched chain alkyl, (C₃-C₆)-straight or branched chain alkenyl or alkynyl, and (C₃-C₄) bridging alkyl



wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR_1 and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is
5 optionally fused to an Ar group;

C and D are independently:

hydrogen, Ar, C_1-C_6 straight or branched chain alkyl, or C_2-C_6 straight or branched chain alkenyl, wherein any of the carbon atoms of said alkyl or
10 alkenyl are optionally substituted in one or more position(s) with C_3-C_6 cycloalkyl, C_5-C_6 cycloalkenyl, hydroxyl, carbonyl oxygen, or Ar, wherein said alkyl, alkenyl, cycloalkyl or cycloalkenyl groups are optionally substituted with C_1-C_6 alkyl, C_2-C_6
15 alkenyl, hydroxy, amino, halo, haloalkyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, wherein any of the carbon atoms of said alkyl or alkenyl are optionally
20 substituted in one or more positions with oxygen to form a carbonyl, or wherein any of the carbon atoms of said alkyl or alkenyl are optionally replaced with O, NH, NR_2 , S, SO, or SO_2 , wherein R_2 is selected from the group consisting of hydrogen, (C_1-C_6)-straight or branched chain alkyl, (C_2-C_6)-
25 straight or branched chain alkenyl or alkynyl, and



(C₁-C₄) bridging alkyl wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR₁ and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said
5 heterocyclic ring is optionally fused to an Ar group;

wherein Ar is an aryl or heteroaryl moiety which is substituted or unsubstituted;
and

10 R₁ is selected from the group consisting of Ar, C₁-C₆ cycloalkyl, C₁-C₆ straight or branched chain alkyl, C₂-C₆ straight or branched chain alkenyl, or C₁-C₆ straight or branched chain alkyl or C₂-C₆ straight or branched chain alkenyl which is
15 substituted in one or more positions with Ar, amino, halo, haloalkyl, hydroxy, trifluoromethyl, C₁-C₆ straight or branched chain alkyl, C₂-C₆ straight or branched chain alkenyl, carbonyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro,
20 imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, substituted alkyl or alkenyl wherein any of the carbon atoms of the alkyl or alkenyl are optionally replaced with S, SO, SO₂, O, or NR₂ wherein R₂ is selected from the group
25 consisting of hydrogen, (C₁-C₆)-straight or branched chain alkyl, (C₂-C₆)-straight or branched chain



alkenyl or alkynyl, and (C₁-C₄) bridging alkyl
wherein said bridging alkyl forms a heterocyclic
ring starting with the nitrogen of NR₁ and ending
with one of the carbon atoms of said alkyl or
5 alkenyl chain, and wherein said heterocyclic ring is
optionally fused to an Ar group or C₃-C₆ cycloalkyl.

2. The compound of claim 1, wherein Ar is a cyclic
or fused cyclic ring and includes a mono-, bi- or
10 tricyclic, carbo- or heterocyclic ring, wherein the
ring is either unsubstituted or substituted in one
to five position(s) with halo, haloalkyl, hydroxyl,
nitro, trifluoromethyl, C₁-C₆ straight or branched
chain alkyl, C₂-C₆ straight or branched chain
15 alkenyl, C₁-C₆ alkoxy, C₁-C₆ alkenyloxy, phenoxy,
benzyloxy, amino, thiocarbonyl, ester, thioester,
cyano, imino, alkylamino, aminoalkyl, sulfhydryl,
thioalkyl, and sulfonyl; wherein the individual ring
sizes are 5-8 members; wherein the heterocyclic ring
20 contains 1-4 heteroatom(s) selected from the group
consisting of O, N, or S; wherein aromatic or
tertiary alkyl amines are optionally oxidized to a
corresponding N-oxide.

25 3. The compound of claim 2, wherein the mono- or
bicyclic, carbo- or heterocyclic ring is selected



* C L N S *

from the group consisting of phenyl, benzyl,
naphthyl, pyrrolyl, pyrrolidinyl, pyridinyl,
pyrimidinyl, purinyl, quinolinyl, isoquinolinyl,
furyl, thiophenyl, imidazolyl, oxazolyl, thiazolyl,
5 pyrazolyl, and thienyl.

4. The compound of claim 1, wherein the compound
has an affinity for FKBP-type immunophilins.

10 5. The compound of claim 4, wherein the FKBP-type
immunophilins are FKBP12.

6. The compound of claim 1, wherein the compound
inhibits rotamase enzyme activity.

15

7. A compound selected from the group consisting
of:

3-(4-Methoxyphenyl)propyl (2S)-1-(phenylsulfonyl)-
2-pyrrolidinecarbothioate;

20 3-(4-Methoxyphenyl)propyl (2S)-1-(benzylsulfonyl)-
2-pyrrolidinecarbothioate;

3-(4-Methoxyphenyl)propyl (2S)-1-[(4-methyl
phenyl)sulfonyl]-2-pyrrolidinecarbothioate;

25 (2,2-Phenylmethyl)ethyl (2S)-1-[(4-ethylphenyl)
sulfonyl]-2-pyrrolidinecarbothioate;

3-Phenylpropyl (2S)-1-(phenylsulfonyl)-2-



pyrrolidinecarbothioate;

3-Phenylpropyl (2S)-1-(benzylsulfonyl)-2-
pyrrolidinecarbothioate;

3-(1-Naphthyl)propyl (2S)-1-(benzylsulfonyl)-2-
5 pyrrolidinecarbothioate;

3-Phenylpropyl (2S)-1-[(4-ethylphenyl)sulfonyl]-2-
pyrrolidinecarbothioate;

3-(4-Methoxyphenyl)propyl 1-[(4-methylphenyl)
sulfonyl]-2-piperidinecarbothioate;

10 3-(4-Methoxyphenyl)propyl 1-(benzylsulfonyl)-2-
piperidinecarbothioate;

3-(4-Methoxyphenyl)propyl 1-(phenylsulfonyl)-2-
piperidinecarbothioate;

15 3-[4-(Trifluoromethyl)phenyl]propyl 1-[(4-methyl
phenyl)sulfonyl]-2-piperidinecarbothioate;

and a pharmaceutically acceptable salt, ester, or
solvate thereof.

8. A pharmaceutical composition comprising a
20 neurotrophically effective amount of the compound of
claim 1 and a pharmaceutically acceptable carrier.

9. A method of effecting a neuronal activity in an
animal, comprising:

25 administering to the animal a neurotrophically
effective amount of the compound of claim 1.



* C L M S *

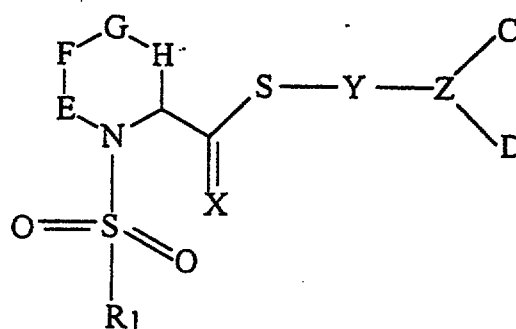
10. The method of claim 9, wherein the neuronal activity is selected from the group consisting of stimulation of damaged neurons, promotion of neuronal regeneration, prevention of
5 neurodegeneration and treatment of neurological disorder.

11. The method of claim 10, wherein the neurological disorder is selected from the group
10 consisting of peripheral neuropathy caused by physical injury or disease state, physical damage to the brain, physical damage to the spinal cord, stroke associated with brain damage, and neurological disorder relating to neurodegeneration.

15
12. The method of claim 11, wherein the neurological disorder relating to neurodegeneration is selected from the group consisting of Alzheimer's Disease, Parkinson's Disease, and amyotrophic
20 lateral sclerosis.

13. A compound of formula II:





II

5

or a pharmaceutically acceptable salt, ester, or solvate thereof, wherein:

E, F, G, and H are independently CH₂, O, S, SO, SO₂, NH or NR₂;

10

X is either O or S;

15

Y is a direct bond to Z, a C₁-C₂ straight or branched chain alkyl, or a C₂-C₃ straight or branched chain alkenyl, wherein any of the carbon atoms of said alkyl or alkenyl are optionally substituted in one or more positions with amino, halo, haloalkyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, oxygen to form a carbonyl, or wherein any of the carbon atoms of said alkyl or alkenyl are optionally replaced with O, NH, NR₂, S, SO, or SO₂, wherein R₂ is selected from the group consisting of hydrogen, (C₁-C₆)-straight or branched chain alkyl, (C₂-C₆)-straight or branched chain alkenyl or alkynyl, and (C₁-C₄) bridging alkyl

20



wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR_1 and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group;

Z is a direct bond, or a C_1-C_6 straight or branched chain alkyl, or a C_2-C_6 straight or branched chain alkenyl, wherein any of the carbon atoms of said alkyl or alkenyl are optionally substituted in one or more positions with amino, halo, haloalkyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, oxygen to form a carbonyl, or wherein any of the carbon atoms of said alkyl or alkenyl are optionally replaced with O, NH, NR_2 , S, SO, or SO_2 , wherein R_2 is selected from the group consisting of hydrogen, (C_1-C_3) -straight or branched chain alkyl, (C_1-C_3) -straight or branched chain alkenyl or alkynyl, and (C_1-C_4) bridging alkyl wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR_1 and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group;

C and D are independently:

hydrogen, Ar, C_1-C_6 -straight or branched chain



alkyl, or C₂-C₆ straight or branched chain alkenyl, wherein any of the carbon atoms of said alkyl or alkenyl are optionally substituted in one or more position(s) with C₃-C₈ cycloalkyl, C₅-C₇ cycloalkenyl, hydroxyl, carbonyl oxygen, or Ar, wherein said alkyl, alkenyl, cycloalkyl or cycloalkenyl groups are optionally substituted with C₁-C₂ alkyl, C₁-C₂ alkenyl, hydroxy, amino, halo, haloalkyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, wherein any of the carbon atoms of said alkyl or alkenyl are optionally substituted in one or more positions with oxygen to form a carbonyl, or wherein any of the carbon atoms of said alkyl or alkenyl are optionally replaced with O, NH, NR₁, S, SO, or SO₂, wherein R₁ is selected from the group consisting of hydrogen, (C₁-C₂)-straight or branched chain alkyl, (C₃-C₆)-straight or branched chain alkenyl or alkynyl, and (C₁-C₄) bridging alkyl wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR₁ and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group;

wherein Ar is an aryl or heteroaryl moiety which



is substituted or unsubstituted;

and

R_1 is selected from the group consisting of Ar, C_3 - C_8 cycloalkyl, C_1 - C_6 straight or branched chain alkyl, C_2 - C_6 straight or branched chain alkenyl, or C_1 - C_6 straight or branched chain alkyl or C_2 - C_6 straight or branched chain alkenyl which is substituted in one or more positions with Ar, amino, halo, haloalkyl, hydroxy, trifluoromethyl, C_1 - C_4 straight or branched chain alkyl, C_2 - C_6 straight or branched chain alkenyl, carbonyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, substituted alkyl or alkenyl wherein any of the carbon atoms of the alkyl or alkenyl are optionally replaced with S, SO, SO_2 , O, or NR_2 wherein R_2 is selected from the group consisting of hydrogen, (C_1-C_4) -straight or branched chain alkyl, (C_2-C_6) -straight or branched chain alkenyl or alkynyl, and (C_1-C_4) bridging alkyl wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR_2 and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group or C_1 - C_8 cycloalkyl.



14. The compound of claim 13, wherein Ar is a cyclic or fused cyclic ring and includes a mono-, bi- or tricyclic, carbo- or heterocyclic ring, wherein the ring is either unsubstituted or substituted in one to five position(s) with halo, haloalkyl, hydroxyl, nitro, trifluoromethyl, C₁-C₅ straight or branched chain alkyl, C₂-C₅ straight or branched chain alkenyl, C₁-C₅ alkoxy, C₂-C₅ alkenyloxy, phenoxy, benzyloxy, amino, thiocarbonyl, ester, thioester, cyano, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, and sulfonyl; wherein the individual ring sizes are 5-8 members; wherein the heterocyclic ring contains 1-4 heteroatom(s) selected from the group consisting of O, N, or S; wherein aromatic or tertiary alkyl amines are optionally oxidized to a corresponding N-oxide.

15. The compound of claim 14, wherein Ar is selected from the group consisting of phenyl, benzyl, naphthyl, pyrrolyl, pyrrolidinyl, pyridinyl, pyrimidinyl, purinyl, quinolinyl, isoquinolinyl, furyl, thiophenyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, and thienyl.

16. The compound of claim 13, wherein the compound



has an affinity for FKBP-type immunophilins.

17. The compound of claim 16, wherein the FKBP-type immunophilins are FKBP12.

5

18. The compound of claim 13, wherein the compound inhibits rotamase enzyme activity.

19. A pharmaceutical composition comprising a
10 neurotrophically effective amount of the compound of claim 13 and a pharmaceutically acceptable carrier.

20. A method of effecting a neuronal activity in an animal, comprising:

15 administering to the animal a neurotrophically effective amount of the compound of claim 13.

21. The method of claim 20, wherein the neuronal activity is selected from the group consisting of
20 stimulation of damaged neurons, promotion of neuronal regeneration, prevention of neurodegeneration and treatment of neurological disorder.

25 22. The method of claim 21, wherein the neurological disorder is selected from the group

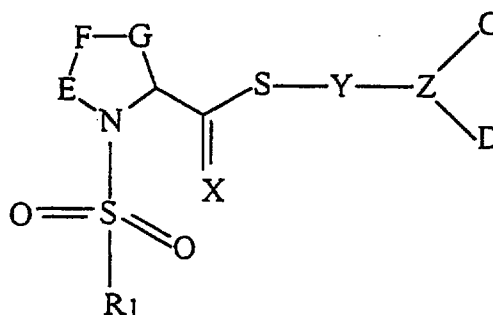


consisting of peripheral neuropathy caused by
physical injury or disease state, physical damage to
the brain, physical damage to the spinal cord,
stroke associated with brain damage, and
5 neurological disorder relating to neurodegeneration.

23. The method of claim 22, wherein the
neurological disorder relating to neurodegeneration
is selected from the group consisting of Alzheimer's
10 Disease, Parkinson's Disease, and amyotrophic
lateral sclerosis.

24. A compound of formula III:

15



III

or a pharmaceutically acceptable salt, ester, or
20 solvate thereof, wherein:

E, F, and G are independently CH₂, O, S, SO, SO₂,
NH or NR₂;

X is either O or S;

Y is a direct bond to Z, a C₁-C₆ straight or



branched chain alkyl, or a C_2-C_6 straight or branched chain alkenyl, wherein any of the carbon atoms of said alkyl or alkenyl are optionally substituted in one or more positions with amino, halo, haloalkyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, oxygen to form a carbonyl, or wherein any of the carbon atoms of said alkyl or alkenyl are optionally replaced with O, NH, NR_2 , S, SO, or SO_2 , wherein R_2 is selected from the group consisting of hydrogen, (C_1-C_6) -straight or branched chain alkyl, (C_3-C_6) -straight or branched chain alkenyl or alkynyl, and (C_1-C_4) bridging alkyl wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR_2 and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group;

Z is a direct bond, or a C_1-C_6 straight or branched chain alkyl, or a C_2-C_6 straight or branched chain alkenyl, wherein any of the carbon atoms of said alkyl or alkenyl are optionally substituted in one or more positions with amino, halo, haloalkyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, oxygen to form a



carbonyl, or wherein any of the carbon atoms of said alkyl or alkenyl are optionally replaced with O, NH, NR₂, S, SO, or SO₂, wherein R₂ is selected from the group consisting of hydrogen, (C₁-C₆)-straight or
5 branched chain alkyl, (C₃-C₆)-straight or branched chain alkenyl or alkynyl, and (C₁-C₄) bridging alkyl wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR₁ and ending with one of the carbon atoms of said alkyl or
10 alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group;

C and D are independently:

hydrogen, Ar, C₁-C₆ straight or branched chain alkyl, or C₃-C₆ straight or branched chain alkenyl,
15 wherein any of the carbon atoms of said alkyl or alkenyl are optionally substituted in one or more position(s) with C₁-C₆ cycloalkyl, C₃-C₆ cycloalkenyl, hydroxyl, carbonyl oxygen, or Ar, wherein said alkyl, alkenyl, cycloalkyl or cycloalkenyl groups
20 are optionally substituted with C₁-C₆ alkyl, C₁-C₆ alkenyl, hydroxy, amino, halo, haloalkyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, wherein any of the
25 carbon atoms of said alkyl or alkenyl are optionally substituted in one or more positions with oxygen to



form a carbonyl, or wherein any of the carbon atoms of said alkyl or alkenyl are optionally replaced with O, NH, NR₂, S, SO, or SO₂, wherein R₂ is selected from the group consisting of hydrogen, (C₁-C₆)-straight or branched chain alkyl, (C₃-C₆)-straight or branched chain alkenyl or alkynyl, and (C₁-C₄) bridging alkyl wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR₂ and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group;

wherein Ar is an aryl or heteroaryl moiety which is substituted or unsubstituted;

and

R₁ is selected from the group consisting of Ar, C₁-C₆ cycloalkyl, C₁-C₆ straight or branched chain alkyl, C₁-C₆ straight or branched chain alkenyl, or C₁-C₆ straight or branched chain alkyl or C₂-C₆ straight or branched chain alkenyl which is substituted in one or more positions with Ar, amino, halo, haloalkyl, hydroxy, trifluoromethyl, C₁-C₆ straight or branched chain alkyl, C₂-C₆ straight or branched chain alkenyl, carbonyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl,



thioalkyl, sulfonyl, substituted alkyl or alkenyl
wherein any of the carbon atoms of the alkyl or
alkenyl are optionally replaced with S, SO, SO₂, O,
or NR₂ wherein R₂ is selected from the group
5 consisting of hydrogen, (C₁-C₆)-straight or branched
chain alkyl, (C₃-C₆)-straight or branched chain
alkenyl or alkynyl, and (C₁-C₄) bridging alkyl
wherein said bridging alkyl forms a heterocyclic
ring starting with the nitrogen of NR₁ and ending
10 with one of the carbon atoms of said alkyl or
alkenyl chain, and wherein said heterocyclic ring is
optionally fused to an Ar group or C₃-C₆ cycloalkyl.

25. The compound of claim 24, wherein Ar is a
15 cyclic or fused cyclic ring and includes a mono-,
bi- or tricyclic, carbo- or heterocyclic ring,
wherein the ring is either unsubstituted or
substituted in one to five position(s) with halo,
haloalkyl, hydroxyl, nitro, trifluoromethyl, C₁-C₆
20 straight or branched chain alkyl, C₂-C₆ straight or
branched chain alkenyl, C₁-C₆ alkoxy, C₂-C₆
alkenyloxy, phenoxy, benzyloxy, amino, thiocarbonyl,
ester, thioester, cyano, imino, alkylamino,
aminoalkyl, sulfhydryl, thioalkyl, and sulfonyl;
25 wherein the individual ring sizes are 5-8 members;
wherein the heterocyclic ring contains 1-4



heteroatom(s) selected from the group consisting of O, N, or S; wherein aromatic or tertiary alkyl amines are optionally oxidized to a corresponding N-oxide.

5

26. The compound of claim 25, wherein Ar is selected from the group consisting of phenyl, benzyl, naphthyl, pyrrolyl, pyrrolidinyl, pyridinyl, pyrimidinyl, purinyl, quinolinyl, isoquinolinyl, 10 furyl, thiophenyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, and thienyl.

15

27. The compound of claim 24, wherein the compound has an affinity for FKBP-type immunophilins.

28. The compound of claim 27, wherein the FKBP-type immunophilins are FKBP12.

20

29. The compound of claim 24, wherein the compound inhibits rotamase enzyme activity.

25

30. A pharmaceutical composition comprising a neurotrophically effective amount of the compound of claim 24 and a pharmaceutically acceptable carrier.

31. A method of effecting a neuronal activity in an



animal, comprising:

administering to the animal a neurotrophically effective amount of the compound of claim 24.

5 32. The method of claim 31, wherein the neuronal activity is selected from the group consisting of stimulation of damaged neurons, promotion of neuronal regeneration, prevention of neurodegeneration and treatment of neurological
10 disorder.

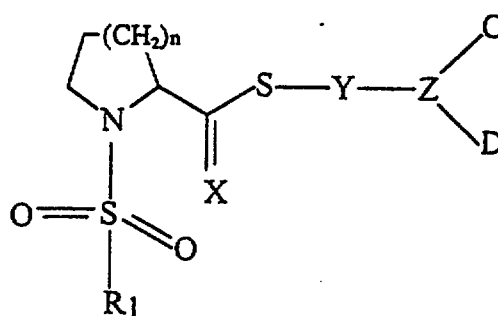
33. The method of claim 32, wherein the neurological disorder is selected from the group consisting of peripheral neuropathy caused by
15 physical injury or disease state, physical damage to the brain, physical damage to the spinal cord, stroke associated with brain damage, and neurological disorder relating to neurodegeneration.

20 34. The method of claim 33, wherein the neurological disorder relating to neurodegeneration is selected from the group consisting of Alzheimer's Disease, Parkinson's Disease, and amyotrophic lateral sclerosis.

25

35. A compound of formula IV:





IV

5 or a pharmaceutically acceptable salt, ester, or
solvate thereof, wherein:

n is 1, 2 or 3 forming a 5-7 member heterocyclic
ring;

X is either O or S;

10 Y is a direct bond to Z, a C₁-C₅ straight or
branched chain alkyl, or a C₂-C₅ straight or branched
chain alkenyl, wherein any of the carbon atoms of
said alkyl or alkenyl are optionally substituted in
one or more positions with amino, halo, haloalkyl,
15 thiocarbonyl, ester, thioester, alkoxy, alkenoxy,
cyano, nitro, imino, alkylamino, aminoalkyl,
sulfhydryl, thioalkyl, sulfonyl, oxygen to form a
carbonyl, or wherein any of the carbon atoms of said
alkyl or alkenyl are optionally replaced with O, NH,
20 NR₂, S, SO, or SO₂, wherein R₂ is selected from the
group consisting of hydrogen, (C₁-C₄)-straight or
branched chain alkyl, (C₃-C₄)-straight or branched
chain alkenyl or alkynyl, and (C₁-C₄) bridging alkyl
wherein said bridging alkyl forms a heterocyclic



ring starting with the nitrogen of NR_1 and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group;

5 Z is a direct bond, or a $\text{C}_1\text{-C}_6$ straight or branched chain alkyl, or a $\text{C}_2\text{-C}_6$ straight or branched chain alkenyl, wherein any of the carbon atoms of said alkyl or alkenyl are optionally substituted in one or more positions with amino, halo, haloalkyl, 10 thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, oxygen to form a carbonyl, or wherein any of the carbon atoms of said alkyl or alkenyl are optionally replaced with O, NH, 15 NR_2 , S, SO, or SO_2 , wherein R_2 is selected from the group consisting of hydrogen, $(\text{C}_1\text{-C}_4)$ -straight or branched chain alkyl, $(\text{C}_3\text{-C}_6)$ -straight or branched chain alkenyl or alkynyl, and $(\text{C}_1\text{-C}_4)$ bridging alkyl wherein said bridging alkyl forms a heterocyclic 20 ring starting with the nitrogen of NR_2 and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group;

C and D are independently:

25 hydrogen, Ar, $\text{C}_1\text{-C}_4$ straight or branched chain alkyl, or $\text{C}_1\text{-C}_4$ straight or branched chain alkenyl,



wherein any of the carbon atoms of said alkyl or alkenyl are optionally substituted in one or more position(s) with C_3 - C_8 cycloalkyl, C_5 - C_7 cycloalkenyl, hydroxyl, carbonyl oxygen, or Ar, wherein said

5 alkyl, alkenyl, cycloalkyl or cycloalkenyl groups are optionally substituted with C_1 - C_6 alkyl, C_2 - C_6 alkenyl, hydroxy, amino, halo, haloalkyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl,

10 sulfhydryl, thioalkyl, sulfonyl, wherein any of the carbon atoms of said alkyl or alkenyl are optionally substituted in one or more positions with oxygen to form a carbonyl, or wherein any of the carbon atoms of said alkyl or alkenyl are optionally replaced

15 with O, NH, NR_2 , S, SO, or SO_2 , wherein R_2 is selected from the group consisting of hydrogen, (C_1 - C_8)-straight or branched chain alkyl, (C_3 - C_6)-straight or branched chain alkenyl or alkynyl, and (C_1 - C_4) bridging alkyl wherein said bridging alkyl

20 forms a heterocyclic ring starting with the nitrogen of NR_1 and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group;

25 wherein Ar is an aryl or heteroaryl moiety which is substituted or unsubstituted;



and

R_1 is selected from the group consisting of Ar, C_3 - C_6 cycloalkyl, C_1 - C_6 straight or branched chain alkyl, C_2 - C_6 straight or branched chain alkenyl, or
5 C_1 - C_6 straight or branched chain alkyl or C_2 - C_6 straight or branched chain alkenyl which is substituted in one or more positions with Ar, amino, halo, haloalkyl, hydroxy, trifluoromethyl, C_1 - C_6 straight or branched chain alkyl, C_2 - C_6 straight or
10 branched chain alkenyl, carbonyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, substituted alkyl or alkenyl wherein any of the carbon atoms of the alkyl or
15 alkenyl are optionally replaced with S, SO, SO_2 , O, or NR_2 wherein R_2 is selected from the group consisting of hydrogen, (C_1-C_4) -straight or branched chain alkyl, (C_2-C_4) -straight or branched chain alkenyl or alkynyl, and (C_1-C_4) bridging alkyl
20 wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR_1 and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group or C_3 - C_6 cycloalkyl.

25

36. The compound of claim 35, wherein Ar is a



cyclic or fused cyclic ring and includes a mono-,
bi- or tricyclic, carbo- or heterocyclic ring,
wherein the ring is either unsubstituted or
substituted in one to five position(s) with halo,
5 haloalkyl, hydroxyl, nitro, trifluoromethyl, C₁-C₆
straight or branched chain alkyl, C₂-C₆ straight or
branched chain alkenyl, C₁-C₆ alkoxy, C₂-C₆
alkenyloxy, phenoxy, benzyloxy, amino, thiocarbonyl,
ester, thioester, cyano, imino, alkylamino,
10 aminoalkyl, sulfhydryl, thioalkyl, and sulfonyl;
wherein the individual ring sizes are 5-8 members;
wherein the heterocyclic ring contains 1-4
heteroatom(s) selected from the group consisting of
O, N, or S; wherein aromatic or tertiary alkyl
15 amines are optionally oxidized to a corresponding N-
oxide.

37. The compound of claim 36, wherein Ar is
selected from the group consisting of phenyl,
20 benzyl, naphthyl, pyrrolyl, pyrrolidinyl, pyridinyl,
pyrimidinyl, purinyl, quinolinyl, isoquinolinyl,
furyl, thiophenyl, imidazolyl, oxazolyl, thiazolyl,
pyrazolyl, and thienyl.

25 38. The compound of claim 35, wherein the compound
has an affinity for -FKBP-type immunophilins.



39. The compound of claim 38, wherein the FKBP-type immunophilins are FKBP12.

5 40. The compound of claim 35, wherein the compound inhibits rotamase enzyme activity.

41. A pharmaceutical composition comprising a neurotrophically effective amount of the compound of claim 35 and a pharmaceutically acceptable carrier.

10

42. A method of effecting a neuronal activity in an animal, comprising:

administering to the animal a neurotrophically effective amount of the compound of claim 35.

15

43. The method of claim 42, wherein the neuronal activity is selected from the group consisting of stimulation of damaged neurons, promotion of neuronal regeneration, prevention of neurodegeneration and treatment of neurological disorder.

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44. The method of claim 43, wherein the neurological disorder is selected from the group consisting of peripheral neuropathy caused by physical injury or disease state, physical damage to

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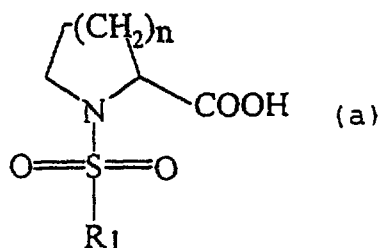
the brain, physical damage to the spinal cord, stroke associated with brain damage, and neurological disorder relating to neurodegeneration.

- 5 45. The method of claim 44, wherein the neurological disorder relating to neurodegeneration is selected from the group consisting of Alzheimer's Disease, Parkinson's Disease, and amyotrophic lateral sclerosis.

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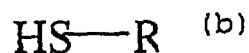
46. A process for preparing a compound of Formula I, II, III, or IV, which comprises:

contacting a compound of structure (a)



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with a compound of structure (b),



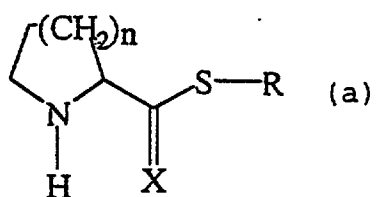
wherein said contacting results in a compound of Formula I, II, III, or IV.

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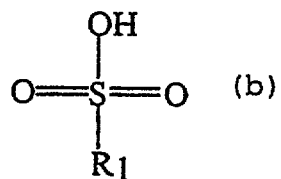
47. A process for preparing a compound of Formula I, II, III, or IV, which comprises:

contacting a compound of structure (a)





with a compound of structure (b),



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wherein said contacting results in a compound of
Formula I, II, III, or IV.

