HETEROCYCLIC THIOESTERS AND KETONES

This application is a continuation-in-part of U.S. Patent Application No. 08/721,765, filed September 25, 1996, the entire content of which is herein incorporated by reference.

BACKGROUND OF THE INVENTION

1. Field of Invention

This invention relates to neurotrophic low molecular weight, small molecule heterocyclic thioesters and ketones 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.

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 FKBPs. 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.

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 drug and immunophilin. 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 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 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). 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 compounds with a high affinity for FKBPs 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 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, 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 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 neurotropin-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).

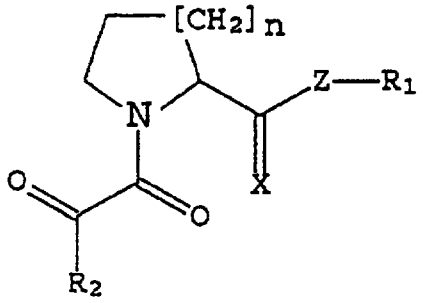
To prevent the side effects associated with use of the immunosuppressant compounds, the present invention provides non-immunosuppressive compounds containing small molecule FKBP rotamase inhibitors for enhancing neurite outgrowth, and promoting neuronal growth and regeneration in various neuropathological 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.

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



II

or a pharmaceutically acceptable salt thereof, wherein:

n is 1 or 2;

X is O or S;

Z is selected from the group consisting of S, CH_2, CHR_1 and $C(R_1)_2$;

R_1 is selected from the group consisting of C_1-C_5 straight or branched chain alkyl, C_2-C_5 straight or branched chain alkenyl, Ar_1 and mixtures thereof, wherein said R_1 is unsubstituted or substituted with halo, nitro, C_1-C_5 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, hydroxy, C_1-C_4 alkoxy, C_2-C_4

alkenyloxy, phenoxy, benzyloxy, amino, Ar_1 or a mixture thereof;

R_2 is selected from the group consisting of C_1-C_9 straight or branched chain alkyl, C_2-C_9 straight or branched chain alkenyl, C_3-C_8 cycloalkyl, C_5-C_7 cycloalkenyl and Ar_1; and

Ar_1 is phenyl, benzyl, pyridyl, fluorenyl, thioindolyl or naphthyl wherein said Ar_1 is unsubstituted or substituted with halo, hydroxy, nitro, C_1-C_6 straight or branched chain alkyl, C_2-C_5 straight or branched chain alkenyl, C_1-C_4 alkoxy, C_2-C_4 alkenyloxy, phenoxy, benzyloxy, amino or a mixture thereof.

The present invention also relates to a pharmaceutical composition comprising:

(i) an effective amount of the compound of claim 1 for effecting a neuronal activity; and

(ii) a pharmaceutically acceptable carrier.

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

administering to the animal an effective amount of the compound of formula II.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1(A) is a representative photomicrograph of untreated sensory neurons.

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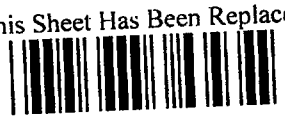


FIG. 1(B) is a representative photomicrograph of compound 1 (10 pM) promoting neurite outgrowth in sensory neurons.

FIG. 1(C) is a representative photomicrograph of compound 1 (1 nM) promoting neurite outgrowth in sensory neurons.

FIG. 1(D) is a representative photomicrograph of compound 1 (1 μM) promoting neurite outgrowth in sensory neurons.

FIG. 2(A) is a representative photomicrograph of untreated sensory neurons.

FIG. 2(B) is a representative photomicrograph of compound 9 (10 pM) promoting neurite outgrowth in sensory neurons.

FIG. 2(C) is a representative photomicrograph of compound 9 (1 nM) promoting neurite outgrowth in sensory neurons.

FIG. 2(D) is a representative photomicrograph of compound 9 (100 nM) promoting neurite outgrowth in sensory neurons.

FIG. 3(A) is a representative photomicrograph of untreated sensory neurons.

FIG. 3(B) is a representative photomicrograph of compound 10 (10 pM) promoting neurite outgrowth in sensory neurons.

FIG. 3(C) is a representative photomicrograph of compound 9 (1 nM) promoting neurite outgrowth in sensory neurons.

FIG. 3(D) is a representative photomicrograph of compound 9 (100 nM) promoting neurite outgrowth in sensory neurons.

FIG. 4 presents quantitation for the recovery of TH-positive dopaminergic neurons in the striatum of animals receiving compounds 1, 9 and 10.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

"Alkyl" refers to a branched or unbranched saturated hydrocarbon chain containing 1 to 6 carbon atoms, such as methyl, ethyl, propyl, iso-propyl, butyl, iso-butyl, tert-butyl, n-pentyl, n-hexyl and the like, unless otherwise indicated.

"Alkoxy" refers to the group -OR wherein R is alkyl as herein defined. Preferably, R is a branched or unbranched saturated hydrocarbon chain containing 1 to 3 carbon atoms.

"Halo" refers to fluoro, chloro, bromo or iodo, unless otherwise indicated.

"Isomers" are different compounds that have the same molecular formula. "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.

"Pharmaceutically acceptable salt" refers to a salt of the inventive compounds which possesses the desired pharmacological activity and which is neither biologically nor otherwise undesirable. The salt 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, glycerophosphate, hemisulfate heptanoate, hexanoate, hydrochloride hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, thiocyanate, tosylate and undecanoate. Examples of a base salt include ammonium salts, alkali metal salts such as sodium and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine

and lysine. Also, the basic nitrogen-containing groups can be quarternized with agents including: lower alkyl halides such as methyl, ethyl, propyl and butyl chlorides, bromides and iodides; dialkyl sulfates such as dimethyl, diethyl, dibutyl and diamyl sulfates; long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; and aralkyl halides such as benzyl and phenethyl bromides.

"Phenyl" refers to any possible isomeric phenyl radical, optionally monosubstituted or multisubstituted with substituents selected from the group consisting of alkyl, alkoxy, hydroxy, halo and haloalkyl.

"Treating" refers to:

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

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

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

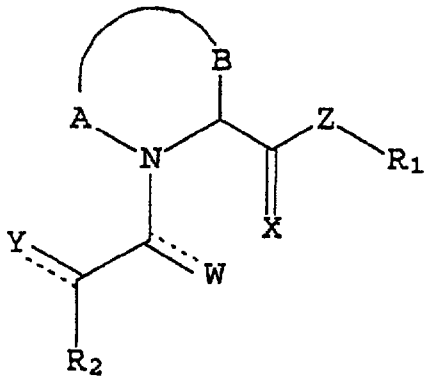
Compounds of the Invention

The neurotrophic low molecular weight, small 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-trans* isomerase activity, or rotamase, activity of the binding protein and unexpectedly stimulate neurite growth.

FORMULA I

In particular, this invention relates to a compound of formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

A and B, together with the nitrogen and carbon atoms to which they are respectfully attached, 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;

Z is either S, CH_2, CHR_1 or $C(R_1)_2$;

W and Y are independently O, S, CH_2 or H_2;

R_1 is C_1-C_6 straight or branched chain alkyl or alkenyl, which is substituted in one or more position(s) with $(Ar_1)_n$, $(Ar_1)_n$ connected by a C_1-C_6 straight or branched chain alkyl or alkenyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl connected by a C_1-C_6 straight or branched chain alkyl or alkenyl, Ar_2 or a combination thereof;

n is 1 or 2;

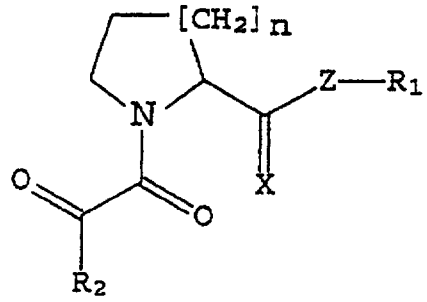
R_2 is either C_1-C_9 straight or branched chain alkyl or alkenyl, C_3-C_9 cycloalkyl, C_5-C_7 cycloalkenyl or Ar_1, wherein said alkyl, alkenyl, cycloalkyl or cycloalkenyl is either unsubstituted or substituted in one or more position(s) with C_1-C_4 straight or branched chain alkyl or alkenyl, hydroxyl or a combination thereof; and

Ar_1 and Ar_2 are independently a mono-, bi- or tricyclic, carbo- or heterocyclic ring, wherein the ring is either unsubstituted or substituted in one to three position(s) with halo, hydroxyl, nitro, trifluoromethyl, C_1-C_6 straight or branched chain alkyl or alkenyl, C_1-C_4 alkoxy, C_1-C_4 alkenyloxy, phenoxy, benzyloxy, amino or a combination thereof; wherein the individual ring sizes are 5-6 members; and wherein the heterocyclic ring contains 1-6 heteroatom(s) selected from the group consisting of O, N, S and a combination thereof.

Suitable mono- and bicyclic, carbo- and heterocyclic rings include, without limitation, naphthyl, indolyl, furyl, thiazolyl, thienyl, pyridyl, quinolinyl, isoquinolinyl, fluorenyl and phenyl.

FORMULA II

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



II

or a pharmaceutically acceptable salt thereof, wherein:

n is 1 or 2;

X is O or S;

Z is selected from the group consisting of S, CH_2, CHR_1 and $C(R_1)_2$;

R_1 is selected from the group consisting of C_1-C_5 straight or branched chain alkyl, C_2-C_5 straight or branched chain alkenyl, Ar_1 and mixtures thereof, wherein said R_1 is unsubstituted or substituted with halo, nitro, C_1-C_5 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, hydroxy, C_1-C_4 alkoxy, C_2-C_4

alkenyloxy, phenoxy, benzyloxy, amino, Ar_1 or a mixture thereof;

R_2 is selected from the group consisting of C_1-C_9 straight or branched chain alkyl, C_2-C_9 straight or branched chain alkenyl, C_3-C_8 cycloalkyl, C_5-C_7 cycloalkenyl and Ar_1; and

Ar_1 is phenyl, benzyl, pyridyl, fluorenyl, thioindolyl or naphthyl wherein said Ar_1 is unsubstituted or substituted with halo, hydroxy, nitro, C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, C_1-C_4 alkoxy, C_2-C_4 alkenyloxy, phenoxy, benzyloxy, amino or a mixture thereof.

Specific examples of these embodiments are presented in TABLE I.

TABLE I

No.	n	X	Z	R_1	R_2
1	1	O	CH_2	3-Phenylpropyl	3-3-Dimethylpentyl
2	1	O	CH_2	3-(3-Pyridyl)propyl	3-3-Dimethylpentyl
3	1	O	CH_2	3-Phenylpropyl	tert-Butyl
4	1	O	CH_2	3-(3-Pyridyl)propyl	tert-Butyl
5	1	O	CH_2	3-(3-Pyridyl)propyl	Cyclohexyl
6	1	O	CH_2	3-(3-Pyridyl)propyl	Cyclopentyl
7	1	O	CH_2	3-(3-Pyridyl)propyl	Cycloheptyl
8	1	O	CH_2	2-(9-Fluorenyl)ethyl	3,3-Dimethylpentyl
9	1	O	S	2-Phenethyl	3,3-Dimethylpentyl
10	2	O	S	2-Phenethyl	3,3-Dimethylpentyl

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	11	1	O	S	Methyl(2-thioindole)	3,3-Dimethylpentyl
	12	1	O	S	2-Phenethyl	Cyclohexyl
	13	2	O	S	2-Phenethyl	tert-Butyl
	14	2	O	S	2-Phenethyl	Phenyl
	15	1	O	CH_2	3-(4-Methoxyphenyl)propyl	3,3-Dimethylpentyl
	16	2	O	CH_2	4-(4-Methoxyphenyl)butyl	3,3-Dimethylpentyl
	17	2	O	CH_2	4-Phenylbutyl	3,3-Dimethylpentyl
	18	2	O	CH_2	4-Phenylbutyl	Phenyl
	19	2	O	CH_2	4-Phenylbutyl	Cyclohexyl
	20	1	S	CH_2	3-Phenylpropyl	3,3-Dimethylpentyl
	21	1	S	S	2-Phenethyl	3,3-Dimethylpentyl
	22	2	S	CH_2	3-Phenylpropyl	3,3-Dimethylpentyl
	23	2	S	S	2-Phenethyl	3,3-Dimethylpentyl
	24	2	O	CHR_1	3-Phenylpropyl	3,3-Dimethylpentyl
	25	2	O	CHR_1	3-Phenylpropyl	Cyclohexyl
	26	2	O	CHR_1	3-Phenylpropyl	Phenyl
	27	2	O	CHR_1	3-Phenylpropyl	3,4,5-Trimethoxyphenyl
	28	1	O	S	2-Phenethyl	Cyclopentyl
	29	2	O	S	3-Phenylpropyl	tert-Butyl
	30	1	O	S	3-Phenylpropyl	3,3-Dimethylpentyl
	31	1	O	S	3-(3-Pyridyl)propyl	3,3-Dimethylpentyl
	32	1	O	S	3-Phenylpropyl	Cyclohexyl
	33	1	O	S	4-Phenylbutyl	Cyclohexyl
	34	1	O	S	4-Phenylbutyl	3,3-Dimethylpentyl
	35	1	O	S	3-(3-Pyridyl)propyl	Cyclohexyl
	36	1	O	S	3,3-Diphenylpropyl	3,3-Dimethylpentyl
	37	1	O	S	3,3-Diphenylpropyl	Cyclohexyl
	38	1	O	S	3-(4-Methoxyphenyl) propyl	3,3-Dimethylpentyl
	39	2	O	S	4-Phenylbutyl	tert-Butyl

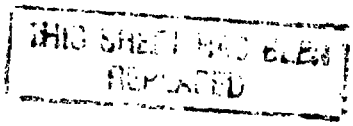
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40	2	O	S	1,5-Diphenylpentyl	3,3-Dimethylpentyl
41	2	O	S	1,5-Diphenylpentyl	Phenyl
42	2	O	S	3-(4-Methoxyphenyl) propyl	3,3-Dimethylpentyl
43	2	O	S	3-(4-Methoxyphenyl) propyl	Phenyl
44	2	O	S	3-(1-Naphthyl)propyl	3,3-Dimethylpentyl
45	1	O	S	3,3-Di(4-fluoro)phenyl-propyl	3,3-Dimethylpentyl
46	1	O	S	4,4-Di(4-fluoro)phenyl-butyl	3,3-Dimethylpentyl
47	1	O	S	3-(1-Naphthyl)propyl	3,3-Dimethylpentyl
48	1	O	S	2,2-Diphenylethyl	3,3-Dimethylpentyl
49	2	O	S	2,2-Diphenylethyl	3,3-Dimethylpentyl
50	2	O	S	3,3-Diphenylpropyl	3,3-Dimethylpentyl
51	1	O	S	3-(4-{Trifluoromethyl}-phenyl)propyl	3,3-Dimethylpentyl
52	1	O	S	3-(2-Naphthyl)propyl	3,3-Dimethylpentyl
53	2	O	S	3-(1-Naphthyl)propyl	3,3-Dimethylpentyl
54	1	O	S	3-(3-Chloro)phenylpropyl	3,3-Dimethylpentyl
55	1	O	S	3-(3-{Trifluoromethyl}-phenyl)propyl	3,3-Dimethylpentyl
56	1	O	S	3-(2-Biphenyl)propyl	3,3-Dimethylpentyl
57	1	O	S	3,3-Dimethylpentyl	
58	1	O	S	3-(3-Fluorophenyl)propyl	3,3-Dimethylpentyl
59	2	O	S	4-Phenylbutyl	3,3-Dimethylpentyl
60	2	O	S	3-Phenylpropyl	3,3-Dimethylpentyl
61	1	O	S	3-(2-Chloro)phenylpropyl	3,3-Dimethylpentyl
62	2	O	S	3-(3-Chloro)phenylpropyl	3,3-Dimethylpentyl
63	2	O	S	3-(2-Fluoro)phenylpropyl	3,3-Dimethylpentyl

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64	2	O	S	3-(3-Fluoro)phenylpropyl	3,3-Dimethylpentyl
65	1	O	S	3-(2,5-Dimethoxyphenyl)-propyl	3,3-Dimethylpentyl
66	1	O	CH_2	3-Phenylpropyl	Cyclohexyl
67	1	O	CH_2	3-Phenylethyl	tert-Butyl
68	2	O	CH_2	4-Phenylbutyl	Cyclohexyl
69	2	O	CHR_1	2-Phenylethyl	tert-Butyl
70	1	O	CH_2	3,3-Di(4-fluorophenyl)-propyl	3,3-Dimethylpentyl
71	2	O	CH_2	3-Phenylpropyl	3,3-Dimethylpentyl

The most preferred examples of TABLE I are named as follows:

1 (2*S*)-2-({1-Oxo-5-phenyl}-pentyl-1-(3,3-dimethyl-1,2-dioxopentyl)pyrrolidine

2 3,3-Dimethyl-1-[(2*S*)-2-(5-(3-pyridyl)pentanoyl)-1-pyrrolidine]-1,2-pentanedione

3 (2*S*)-2-({1-Oxo-4-phenyl}-butyl-1-(3,3-dimethyl-1,2-dioxobutyl)pyrrolidine

9 2-Phenyl-1-ethyl 1-(3,3-dimethyl-1,2-dioxopentyl)-2-piperidinecarbothioate

10 2-Phenyl-1-ethyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate

11 (3-Thioindolyl)methyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate

12 2-Phenyl-1-ethyl (2*S*)-1-(2-cyclohexyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate

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14 2-Phenyl-1-ethyl 1-(2-phenyl-1,2-dioxoethyl)-2-piperidinecarbothioate

28 2-Phenyl-1-ethyl (2*S*)-1-(1-cyclopentyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate

29 3-Phenyl-1-propyl 1-(3,3-dimethyl-1,2-dioxobutyl)-2-piperidinecarbothioate

30 3-Phenyl-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate

31 3-(3-Pyridyl)-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate

32 3-Phenyl-1-propyl (2*S*)-1-(2-cyclohexyl-1,2-dioxoethyl)-2-pyrrolidinecarbothioate

33 4-Phenyl-1-butyl (2*S*)-1-(2-cyclohexyl-1,2-dioxoethyl)-2-pyrrolidinecarbothioate

34 4-Phenyl-1-butyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate

35 3-(3-Pyridyl)-1-propyl (2*S*)-1-(2-cyclohexyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate

36 3,3-Diphenyl-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate

37 3,3-Diphenyl-1-propyl (2*S*)-1-(2-cyclohexyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate

38 3-(*para*-Methoxyphenyl)-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate

39 4-Phenyl-1-butyl 1-(1,2-dioxo-3,3-dimethylbutyl) -2-piperidinecarbothioate

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40 1,5-Diphenyl-3-pentyl 1-(3,3-dimethyl-1,2-dioxopentyl)-2-piperidinecarbothioate

41 1,5-Diphenyl-3-mercaptopentyl 1-(3-phenyl-1,2-dioxoethyl)-2-piperidinecarbothioate

42 3-(*para*-Methcxyphenyl)-1-propyl 1-(1,2-dioxo-3,3-dimethylpentyl)piperidine-2-carbothioate

43 3-(*para*-Methoxyphenyl)-1-propyl 1-(2-phenyl-1,2-dioxoethyl)piperidine-2-carbothioate

44 3-(1-Naphthyl)-1-propyl 1-(3,3-dimethyl-1,2-dioxopentyl)piperidine-2-carbothioate

45 3,3-Di(*para*-fluoro)phenyl-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate

46 4,4-Di(*para*-fluorophenyl)butyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-pyrrolidinecarbothioate

47 3-(1-Naphthyl)propyl (2*S*)-1-(3,3-dimethyl-2-oxopentanoyl)-2-pyrrolidinecarbothioate

48 2,2-Diphenylethyl (2*S*)-1-(3,3-dimethyl-2-oxopentanoyl)tetrahydro-1H-2-pyrrolecarbothioate

49 2,2-Diphenylethyl (2*S*)-1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarbothioate

50 3,3-Diphenylpropyll-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarbothioate

51 3-[4-(Trifluoromethyl)phenyl]propyl (2*S*)-1-(3,3-dimethyl-2-oxopentanoyl)-2-pyrrolidinecarbothioate

52 3-(2-Naphthyl)propyl (2*S*)-1-(3,3-dimethyl-2-oxopentanoyl)-2-pyrrolidinecarbothioate

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53 3-(2-Naphthyl)propyl (2*R,S*)-1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarbothioate

54 3-(3-Chlorophenyl)propyl (2*S*)-1-(3,3-dimethyl-2-oxopentanoyl)-2-pyrrolidinecarbothioate

55 3-[3-(Trifluoromethyl)phenyl)propyl (2*S*)-1-(3,3-dimethyl-2-oxopentanoyl)-2-pyrrolidinecarbothioate

56 3-(1-Biphenyl)propyl (2*S*)-1-(3,3-dimethyl-2-oxopentanoyl)-2-pyrrolidinecarbothioate

57 3-(2-Fluorophenyl)propyl (2*S*)-1-(3,3-dimethyl-2-oxopentanoyl)-2-pyrrolidinecarbothioate

58 3-(3-Fluorophenyl)propyl (2*S*)-1-(3,3-dimethyl-2-oxopentanoyl)-2-pyrrolidinecarbothioate

59 4-Phenylbutyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarbothioate

60 3-Phenylpropyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarbothioate

61 3-(2-Chlorophenyl)propyl (2*S*)-1-(3,3-dimethyl-2-oxopentanoyl)-2-pyrrolidinecarbothioate

62 3-(2-Chlorophenyl)propyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarbothioate

63 3-(2-Fluorophenyl)propyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarbothioate

64 3-(3-Fluorophenyl)propyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarbothioate

65 3-(3,4-Dimethoxyphenyl)propyl(2*S*)-1-(3,3-dimethyl-2-oxopentanoyl)-2-pyrrolidinecarbothioate

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66 (2*S*)-2-({1-Oxo-4-phenyl}-butyl-1-(2-Cyclohexyl-1,2-dioxoethyl)pyrrolidine

67 2-({1-Oxo-4-phenyl}-butyl-1-(3,3-dimethyl-1,2-dioxobutyl)pyrrolidine

68 2-({1-Oxo-6-phenyl}-hexyl-1-(3,3-dimethyl-1,2-dioxobutyl)piperidine

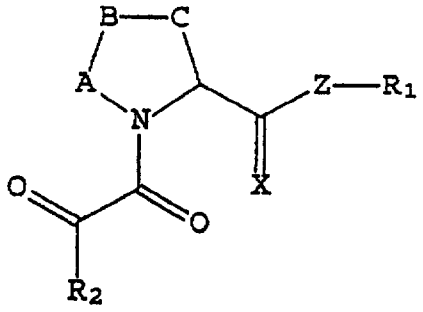
69 2-({1-Oxo-[2-{2'-phenyl}ethyl]-4-phenyl}-butyl-1-(3,3-dimethyl-1,2-dioxobutyl)piperidine

70 1-{(2*S*)-2-[5,5-di(4-Fluorophenyl)pentanoyl]-2-pyrrolidine}-3,3-dimethyl-1,2-pentanedione

71 3,3-Dimethyl-1-[2-(4-phenylpentanoyl)piperidino]-1,2-pentanedione

FORMULA III

Another preferred embodiment is a compound of formula III:



III

or a pharmaceutically acceptable salt thereof, wherein:

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A, B, C and D are independently CH_2, O, S, SO, SO_2, NH or NR_2;

X is O or S;

Z is S, CH_2, CHR_1 or $C(R_1)_2$;

R_1 is C_1-C_6 straight or branched chain alkyl or alkenyl, which is substituted in one or more position(s) with $(Ar_1)_n$, $(Ar_1)_n$ connected by a C_1-C_6 straight or branched chain alkyl or alkenyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl connected by a C_1-C_6 straight or branched chain alkyl or alkenyl, Ar_2 or a combination thereof;

n is 1 or 2;

R_2 is either C_1-C_9 straight or branched chain alkyl or alkenyl, C_3-C_8 cycloalkyl, C_5-C_7 cycloalkenyl or Ar_1, wherein said alkyl, alkenyl, cycloalkyl or cycloalkenyl is either unsubstituted or substituted in one or more position(s) with C_1-C_4 straight or branched chain alkyl or alkenyl, hydroxyl or a combination thereof; and

Ar_1 and Ar_2 are independently a mono-, bi- or tricyclic, carbo- or heterocyclic ring, wherein the ring is either unsubstituted or substituted in one to three position(s) with halo, hydroxyl, nitro, trifluoromethyl, C_1-C_5 straight or branched chain alkyl or alkenyl, C_1-C_4 alkoxy, C_1-C_4 alkenyloxy, phenoxy, benzyloxy, amino or a combination thereof; wherein the individual ring sizes are 5-6 members; and wherein the heterocyclic ring contains 1-6 heteroatom(s) selected from the group

consisting of O, N, S and a combination thereof.

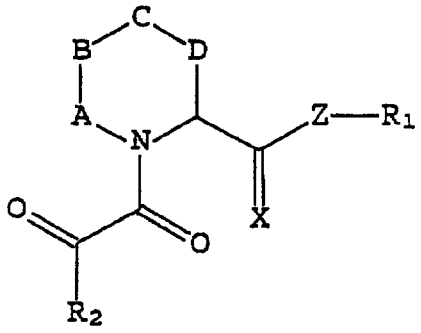
Particularly preferred compounds of formula III are presented in TABLE II.

TABLE II

No.	A	B	C	X	Z	R_1	R_2
72	CH_2	S	CH_2	O	S	2-phenethyl	3,3-dimethyl-pentyl
73	CH_2	S	CH_2	O	CH_2	3-phenylpropyl	3,3-dimethyl-pentyl
74	CH_2	CH_2	NH	O	S	2-phenethyl	3,3-dimethyl-pentyl
75	CH_2	S	CH_2	S	S	2-phenethyl	3,3-dimethyl-pentyl

FORMULA IV

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



IV

or a pharmaceutically acceptable salt thereof, wherein:

A, B, C and D are independently CH_2, O, S, SO, SO_2, NH or NR_2;

X is O or S;

Z is S, CH_2, CHR_1 or $C(R_1)_2$;

R_1 is C_1-C_6 straight or branched chain alkyl or alkenyl, which is substituted in one or more position(s) with $(Ar_2)_n$, $(Ar_1)_n$ connected by a C_1-C_6 straight or branched chain alkyl or alkenyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl connected by a C_1-C_6 straight or branched chain alkyl or alkenyl, Ar_2 or a combination thereof;

n is 1 or 2;

R_2 is either C_1-C_9 straight or branched chain alkyl or alkenyl, C_3-C_9 cycloalkyl, C_5-C_7 cycloalkenyl or Ar_1, wherein said alkyl, alkenyl, cycloalkyl or cycloalkenyl is either unsubstituted or substituted in one or more position(s) with C_1-C_4 straight or branched chain alkyl or alkenyl, hydroxyl or a combination thereof; and

Ar_1 and Ar_2 are independently a mono-, bi- or tricyclic, carbo- or heterocyclic ring, wherein the ring is either unsubstituted or substituted in one to three position(s) with halo, hydroxyl, nitro, trifluoromethyl, C_1-C_6 straight or branched chain alkyl or alkenyl, C_1-C_4 alkoxy, C_1-C_4 alkenyloxy, phenoxy, benzyloxy, amino or a combination thereof; wherein the individual ring sizes are 5-6 members; and wherein the heterocyclic ring

contains 1-6 heteroatom(s) selected from the group consisting of O, N, S and a combination thereof.

Particularly preferred compounds of formula IV are presented in TABLE III.

TABLE III

No.	A	B	C	D	X	Z	R_1	R_2
76	CH_2	CH_2	O	CH_2	O	CH_2	3-phenylpropyl	3,3-dimethylpentyl
77	CH_2	CH_2	O	CH_2	O	S	2-phenethyl	3,3-dimethylpentyl
78	CH_2	CH_2	S	CH_2	O	CH_2	3-phenylpropyl	3,3-dimethylpentyl
79	CH_2	CH_2	S	CH_2	O	S	2-phenethyl	3,3-dimethylpentyl

The compounds of this invention possess asymmetric centers and thus can be produced as mixtures of stereoisomers or as individual stereoisomers. 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 resolving 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 compounds of this invention possess at least one asymmetric center and thus can be produced as mixtures of stereoisomers or as

individual R- and S-stereoisomers. The individual enantiomers may be obtained by resolving a racemic or non-racemic mixture of an intermediate at some appropriate stage of the synthesis. It is understood that the individual R- and S- stereoisomers as well as mixtures of stereoisomers are encompassed by this invention. The S-stereoisomer is most preferred due to its greater activity.

Methods of Using the Compounds of the Invention

The compounds of the present invention have an affinity for the FK506 binding protein, particularly FKBP12, which is present in the brain. When the inventive compounds bind to FKBP in the brain, they exhibit excellent neurotrophic activity. 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 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 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 damaged neurons, promotion of neuronal regeneration, prevention of neurodegeneration and treatment of neurological disorder.

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 neuropathies such as those caused by lead, dapsone, ticks, porphyria or Guillain-Barré syndrome; Alzheimer's disease; and 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 disease state, traumatic injury 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, Parkinson's

Disease and amyotrophic lateral sclerosis.

For these purposes, the compounds may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, 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, intraperitoneally, intrathecally, intraventricularly, intrasternal and intracranial injection or infusion techniques.

To be effective therapeutically as central nervous system targets, the compounds 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.

The compounds 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 such as a synthetic mono- or di-glyceride may be employed. 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.

Additionally, the compounds may be administered orally in the form of capsules, tablets, aqueous suspensions or solutions. 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. The oral dosage forms may further contain sweetening and/or flavoring and/or coloring agents.

The compounds 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.

Furthermore, the compounds may 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 can be readily prepared for each of these areas.

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 a solution in isotonic, pH adjusted sterile saline, either with or without a preservative such as benzylalkonium chloride. Alternatively, the compounds may be formulated into ointments, such as petrolatum, for ophthalmic use.

For topical application to the skin, the compounds can be formulated into suitable ointments containing the compounds suspended or dissolved in, for example, mixtures with one or more of the following: mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, the compounds can be formulated into suitable lotions or creams 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 ester wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

Topical application to the lower intestinal tract can be effected in a rectal suppository formulations (see above) or in suitable enema formulations.

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 and diet of the patient; the time of administration; the rate of excretion; drug combination; the severity of the particular disease being treated; and the 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 neurotropin-3. The dosage level of other neurotrophic drugs will depend upon the factors previously stated and the neurotrophic effectiveness of the drug combination.

Pharmaceutical Compositions of the Invention

The present invention also relates to a pharmaceutical composition comprising:

(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 invention also applies to the pharmaceutical compositions of the present invention.

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 (2*S*)-2-({1-oxo-5-phenyl}-pentyl-1-(3,3-dimethyl-1,2-dioxopentyl)pyrrolidine (1)

(2*S*)-2-(1-oxo-4-phenyl)butyl-N-benzylpyrrolidine. 1-chloro-4-phenylbutane (1.78 g; 10.5 mmol) in 20 mL of THF was added to 0.24 g (10 mmol) of magnesium turnings in 50 mL of refluxing THF. After the addition was complete, the mixture was refluxed for an additional 5 hours, and then added slowly to a refluxing solution of N-benzyl-L-proline ethyl ester (2.30 g (10 mmol) in 100 mL of THF. After 2 hours of further reflux, the mixture was cooled and treated with 5 mL of 2 N HCl. The reaction mixture was diluted with ether (100 mL) and washed with saturated $NaHCO_3$, water and brine. The organic phase was dried, concentrated and chromatographed, eluting with 5:1 CH_2Cl_2:EtOAc to obtain 2.05 g (64%) of the ketone as an oil, ^1H NMR ($CDCl_3$; 300 MHz): 1.49-2.18 (m, 8H); 2.32-2.46 (m, 1H); 2.56-2.65 (m, 2H); 2.97-3.06 (m, 1H); 3.17-3.34 (m, 1H); 3.44-3.62 (m, 1H); 4.02-4.23 (m, 2H); 7.01-7.44 (m, 10H).

(2*S*)-2-(1-oxo-4-phenyl)butylpyrrolidine. The ketone compound (500 mg) and palladium hydroxide (20% on carbon, 50 mg) was hydrogenated at 40 psi in a Paar shaker overnight. The catalyst was removed by filtration and the solvent was removed in vacuo. The free amine was obtained as a yellow oil (230 mg; 100%), ^1H NMR ($CDCl_3$;

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300 MHz): 1.75-2.34 (m, 10H); 2.55 (m, 2H); 2.95 (dm, 1H); 3.45-3.95 (m, 1H); 4.05 (m, 1H); 7.37 (m, 5H).

(2*S*)-2-(1-oxo-4-phenyl)butyl-1-(1,2-dioxo-2-methoxyethyl)pyrrolidine. To a solution of (2*S*)-2-(1-oxo-4-phenyl)butylpyrrolidine (230 mg; 1.0 mmol) in CH_2Cl_2(20 mL) at 0°C was added dropwise methyloxalyl chloride (135 mg; 1.1 mmol). After stirring at 0°C for 3 hours, the reaction was quenched with saturated NH_4Cl and the organic phase was washed with water and brine and dried and concentrated. The crude residue was purified on a silica gel column, eluting with 20:1 CH_2Cl_2:EtOAc to obtain 300 mg of the oxamate as a clear oil (98%), ^1H NMR ($CDCl_3$; 300 MHz): 1.68 (m, 4H); 1.91-2.38 (m, 4H); 2.64 (t, 2H); 3.66-3.80 (m, 2H); 3.77, 3.85 (s, 3H total); 4.16 (m, 2H); 4.90 (m, 1H); 7.16 (m, 3H); 7.27 (m, 2H).

(2*S*)-2-({1-oxo-5-phenyl}-pentyl-1-(3,3-dimethyl-1,2-dioxopentyl)pyrrolidine (1). To a solution of the oxamate above (250 mg; 0.79 mmol) in anhydrous ether (15 mL), cooled to - 78°C, was added 1,1-dimethylpropyl-magnesium chloride (0.8 mL of a 1.0 M solution in ether; 0.8 mmol). After stirring the resulting mixture at -78°C for 2 hours, the reaction was quenched by the addition of 2 mL of saturated NH_4Cl, followed by 100 mL of EtOAc. The organic phase was washed with brine, dried, concentrated, and purified on a silica gel column, eluting with 50:1 CH_2Cl_2:EtOAc. Compound 1 was obtained

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as a clear oil, 120 mg, ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.87 (t, 3H, J=7.5); 1.22 (s, 3H); 1.25 (s, 3H); 1.67 (m, 4H); 1.70-2.33 (m, 6H); 2.61 (t, 2H, J=7.1); 3.52 (m, 2H); 4.17 (t, 2H, J=6.2); 4.52 (m, 1H); 7.16-7.49 (m, 5H). Anal. Calcd. for $C_{22}H_{31}NO_3$ - H_2O: C, 70.37; H, 8.86; N, 3.73. Found: 70.48; H, 8.35; N, 3.69.

EXAMPLE 2

Synthesis of 2-phenyl-1-ethyl 1-(3,3-dimethyl-1,2-dioxopentyl)-2-piperidinecarbothioate (9)

Methyl (2*S*)-1-(1,2-dioxo-2-methoxyethyl)-2-pyrrolidinecarboxylate. A solution of L-proline methyl ester hydrochloride (3.08 g; 18.60 mmol) in dry methylene chloride was cooled to 0°C and treated with triethylamine (3.92 g; 38.74 mmol; 2.1 eq). After stirring the formed slurry under a nitrogen atmosphere for 15 min, a solution of methyl oxalyl chloride (3.20 g; 26.12 mmol) in methylene chloride (45 mL) was added dropwise. The resulting mixture was stirred at 0°C for 1.5 hour. After filtering to remove solids, the organic phase was washed with water, dried over $MgSO_4$ and concentrated. The crude residue was purified on a silica gel column, eluting with 50% ethyl acetate in hexane, to obtain 3.52 g (88%) of the product as a reddish oil. Mixture of *cis-trans* amide rotamers; data for trans rotamer given. ^{1}H NMR ($CDCl_3$): δ 1.93 (dm, 2H); 2.17(m, 2H); 3.62(m, 2H); 3.71 (s, 3H);

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3.79, 3.84 (s, 3H total); 4.86 (dd, 1H, J=8.4, 3.3).

Methyl (2*S*)-1-(1,2-dioxo-3,3-dimethylpentyl)-2-pyrrolidinecarboxylate. A solution of methyl (2*S*)-1-(1,2-dioxo-2-methoxyethyl)-2-pyrrolidinecarboxylate (2.35 g; 10.90 mmol) in 30 mL of tetrahydrofuran (THF) was cooled to -78°C and treated with 14.2 mL of a 1.0 M solution of 1,1-dimethylpropylmagnesium chloride in THF. After stirring the resulting homogeneous mixture at -78°C for three hours, the mixture was poured into saturated ammonium chloride (100 mL) and extracted into ethyl acetate. The organic phase was washed with water, dried, and concentrated, and the crude material obtained upon removal of the solvent was purified on a silica gel column, eluting with 25% ethyl acetate in hexane, to obtain 2.10 g (75%) of the oxamate as a colorless oil, ^{1}H NMR ($CDCl_3$): δ 0.88 (t, 3H); 1.22, 1.26 (s, 3H each); 1.75(dm, 2H); 1.87-2.10 (m, 3H); 2.23 (m, 1H); 3.54 (m, 2H); 3.76 (s, 3H); 4.52 (dm, 1H, J=8.4, 3.4).

(2*S*)-1-(1,2-dioxo-3,3-dimethylpentyl)-2-pyrrolidine-carboxylic acid. A mixture of methyl (2*S*)-1-(1,2-dioxo-3,3-dimethylpentyl)-2-pyrrolidinecarboxylate (2.10 g; 8.23 mmol), 1 N LiOH (15 mL), and methanol (50 mL) was stirred at 0°C for 30 minutes and at room temperature overnight. The mixture was acidified to pH 1 with 1 N HCl, diluted with water, and extracted into 100 mL of methylene chloride. The organic extract was washed with

brine and concentrated to deliver 1.73 g (87%) of snow-white solid which did not require further purification, ^{1}H NMR ($CDCl_3$): δ 0.87 (t, 3H); 1.22, 1.25 (s, 3H each); 1.77 (dm, 2H); 2.02 (m, 2H); 2.17 (m, 1H); 2.25 (m, 1H); 3.53 (dd, 2H, J=10.4, 7.3); 4.55 (dd, 1H, J=8.6, 4.1).

2-phenyl-1-ethyl 1-(3,3-dimethyl-1,2-dioxopentyl)-2-piperidinecarbothioate (9). To a solution of (2*S*)-1-(1,2-dioxo-3,3-dimethylpentyl)-2-pyrrolidinecarboxylic acid (241 mg; 1.0 mmol) in CH_2Cl_2 (10 mL) was added dicyclohexylcarbodiimide (226 mg; 1.1 mmol). After stirring the resulting mixture for 5 minutes, the solution was cooled to 0°C and treated with a solution of phenyl mercaptan (138 mg; 1.0 mmol) and 4-dimethylaminopyridine (6 mg) in 5 ml of CH_2Cl_2. The mixture was allowed to warm to room temperature with stirring overnight. The solids were removed by filtration and the filtrate was concentrated in vacuo; the crude residue was purified by flash chromatography (10:1 hexane:EtOAc) to obtain 302 mg (84%) of 9 as an oil, ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.85 (t, 3H, J=7.5); 1.29 (s, 3H); 1.31 (s, 3H); 1.70-2.32 (m, 6H); 2.92 (t, 2H, J=7.4); 3.22(t, 2H, J=7.4); 3.58 (m, 2H); 4.72 (m, 1H); 7.23-7.34 (m, 5H). Anal. Calcd. for $C_{20}H_{27}NO_3S \cdot 0.4H_2O$: C, 65.15; H, 7.60; N, 3.80. Found: C, 65.41; H, 7.49; N, 3.72.

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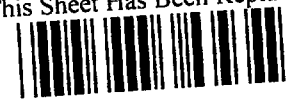
EXAMPLE 3

Synthesis of 2-phenyl-1-ethyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate (10)

Methyl 1-(1,2-dioxo-2-methoxyethyl)-2-piperidinecarboxylate. A solution of methyl pipecolate hydrochloride (8.50 g; 47.31 mmol) in dry methylene chloride (100 mL) was cooled to 0°C and treated with triethylamine (10.5 g; 103 mmol; 2.1 eq). After stirring the formed slurry under a nitrogen atmosphere for 15 minutes, a solution of methyl oxalyl chloride (8.50 g; 69.4 mmol) in methylene chloride (75 mL) was added dropwise. The resulting mixture was stirred at 0°C for 1.5 hours. After filtering to remove solids, the organic phase was washed with water, dried over $MgSO_4$ and concentrated. The crude residue was purified on a silica gel column, eluting with 50% ethyl acetate in hexane, to obtain 9.34 g (86%) of the product as a reddish oil. Mixture of *cis-trans* amide rotamers; data for *trans* rotamer given. ^1H NMR ($CDCl_3$): δ 1.22-1.45 (m, 2H); 1.67-1.78 (m, 3H); 2.29 (m, 1H); 3.33 (m, 1H); 3.55 (m, 1H); 3.76 (s, 3H); 3.85, 3.87 (s, 3H total); 4.52 (dd, 1H).

Methyl 1-(1,2-dioxo-3,3-dimethylpentyl)-2-piperidinecarboxylate. A solution of methyl 1-(1,2-dioxo-2-methoxyethyl)-2-piperidinecarboxylate (3.80 g; 16.57 mmol) in 75 mL of tetrahydrofuran (THF) was cooled to -

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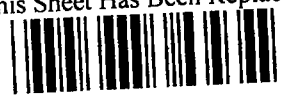
78°C and treated with 20.7 mL of a 1.0 M solution of 1,1-dimethyl-propylmagnesium chloride in THF. After stirring the resulting homogeneous mixture at -78°C for three hours, the mixture was poured into saturated ammonium chloride (100 mL) and extracted into ethyl acetate. The organic phase was washed with water, dried, and concentrated, and the crude material obtained upon removal of the solvent was purified on a silica gel column, eluting with 25% ethyl acetate in hexane, to obtain 3.32 g (74%) of the oxamate as a colorless oil, ^{1}H NMR ($CDCl_3$): δ 0.88 (t, 3H); 1.21, 1.25 (s, 3H each); 1.35-1.80 (m, 7H); 2.35 (m, 1H); 3.24 (m, 1H); 3.41 (m, 1H); 3.76 (s, 3H); 5.32 (d, 1H).

1-(1,2-dioxo-3,3-dimethylpentyl)-2-piperidine-carboxylic acid. A mixture of methyl 1-(1,2-dioxo-3,3-dimethylpentyl)-2-piperidinecarboxylate (3.30 g; 12.25 mmol), 1 N LiOH (15 mL), and methanol (60 mL) was stirred at 0°C for 30 minutes and at room temperature overnight. The mixture was acidified to pH 1 with 1 N HCl, diluted with water, and extracted into 100 mL of methylene chloride. The organic extract was washed with brine and concentrated to deliver 2.80 g (87%) of snow-white solid which did not require further purification, ^{1}H NMR ($CDCl_3$): δ 0.89 (t, 3H); 1.21, 1.24 (s, 3H each); 1.42-1.85 (m, 7H); 2.35 (m, 1H); 3.22 (d, 1H); 3.42(m, 1H); 5.31 (d, 1H).

2-phenyl-1-ethyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate (10). To a solution of 1-(1,2-dioxo-3,3-dimethylpentyl)-2-piperidine-carboxylic acid (255 mg; 1.0 mmol) in CH_2Cl_2 (10 mL) was added dicyclohexylcarbodiimide (226 mg; 1.1 mmol). After stirring the resulting mixture for 5 minutes, the solution was cooled to 0°C and treated with a solution of phenyl mercaptan (138 mg; 1.0 mmol) and 4-dimethylaminopyridine (6 mg) in 5 ml of CH_2Cl_2. The mixture was allowed to warm to room temperature with stirring overnight. The solids were removed by filtration and the filtrate was concentrated in vacuo; the crude residue was purified by flash chromatography (10:1 hexane:EtOAc) to obtain 300 mg (80%) of 10 as an oil, ^1H NMR ($CDCl_3$, 300 MHz): d 0.94 (t, 3H, J=7.5); 1.27 (s, 3H); 1.30 (s, 3H); 1.34-1.88 (m, 7H); 2.45 (m, 1H); 2.90 (t, 2H, J=7.7); 3.26 (t, 2H, J=7.7); 3.27 (m, 1H); 3.38 (m, 1H); 5.34 (m, 1H); 7.24-7.36 (m, 5H). Anal. Calcd. for $C_{21}H_{29}NO_3S$: C, 67.17; H, 7.78; N, 3.73. Found: C, 67.02; H, 7.83; N, 3.78.

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

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K_i Test Procedure

Inhibition of the peptidyl-prolyl isomerase (rotamase) activity of the inventive compounds 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 for representative compounds in Table IV. 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 mL of ice cold assay buffer (25 mM HEPES, pH 7.8, 100 mM NaCl), 10 mL of FKBP (2.5 mM in 10 mM Tris-Cl pH 7.5, 100 mM NaCl, 1 mM dithiothreitol), 25 mL of chymotrypsin (50 mg/ml in 1 mM HCl) and 10 mL of test compound at various concentrations in dimethyl sulfoxide. The reaction is initiated by the addition of 5 mL 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 Table IV under the column "Ki".

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

The neurotrophic effects of the FKBP inhibitor compounds were demonstrated by evaluating the ability of the compounds to promote neurite outgrowth in cultured chick sensory neurons from dorsal root ganglia. 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 serum, and also containing 10 μM cytosine ß-D arabinofuranoside (Ara C) at 37°C in an environment containing 5% CO_2. Twenty-four hours later, the DRGs were treated with various concentrations of

nerve growth factor, immunophilin ligands or combinations of NFG plus drugs. Forty-eight hours after drug treatment, the ganglia 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, 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.

Dose-response curves were generated from which ED_{50} values were obtained. The results of these experiments are presented in Table IV under the column "ED50". Representative photomicrographs of untreated (control) sensory neurons and of compounds 1 (10 pM, 1 nM, 1 μM), 9 (10 pM, 1 nM, 100 nM) and 10 (10 pM, 1 nM, 100 nM) promoting neurite outgrowth in sensory neurons are shown in FIG.'s 1(A-D), 2(A-D) and 3(A-D), respectively.

MPTP Model of Parkinson's Disease

The remarkable neurotrophic and neuroregenerative effects of the present inventive compounds were further demonstrated in an animal model of neurodegenerative disease. MPTP lesioning of dopaminergic neurons in mice was used as an animal model of Parkinson's Disease. Four

week old male CD1 white mice were dosed i.p. with 30 mg/kg of MPTP for 5 days. Test compounds (4 mg/kg), or vehicle, were 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 were sacrificed and the striata were dissected and homogenized. Immunostaining was performed on saggital 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 was observed as compared to non-lesioned animals. Lesioned animals receiving test compounds showed a significant recovery of TH-stained dopaminergic neurons.

The results of these experiments are presented in TABLE IV under the column "% TH recovery". Quantitation for the recovery of TH-positive dopaminergic neurons in the striatum of animals receiving compounds 1, 9 and 10, and for representative control and lesioned animals not receiving the test drugs, are presented in FIG. 4.

TABLE IV

In Vitro Test Results

Example #	Ki, nM	ED50, nM	% TH recovery
1	31	0.4	23
2	210	--	--
3	85	--	--
9	104	0.5	61
10	12	0.8	54
11	299	0.36	53
12	442	0.025	--
14	313	0.9	48
28	108	0.9	41
29	59	0.003	50
30	11	0.00025	65
31	8.7	--	31
32	362	--	52
33	1698	--	--
34	34	0.9	48
35	62	--	--
36	7	--	56
37	68	--	--
38	8.9	0.011	37.32

	39	347	--	--
	40	1226		
	41	366	--	--
	42	28	--	--
5	43	259	--	--
	44	188	--	25
	45	31	--	--
	46	757	--	--
	47	21	--	50
10	48	127	--	28
	49	1334	--	--
	50	55	--	62
	51	33	--	--
	52	6	--	--
15	53	261	--	--
	54	37	--	--
	55	30	--	--
	56	880	--	--
	57	57	--	--
20	58	79	--	--
	59	962	--	--
	60	90	--	--

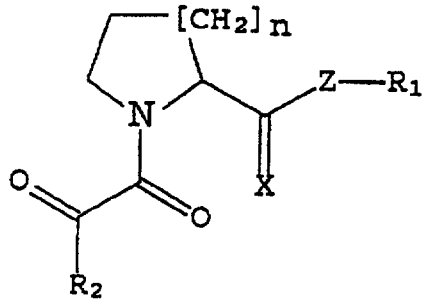
61	139	--	--
62	196	--	--
63	82	--	--
64	163	--	--
65	68	--	--
66	306	5	38
67	177	--	--
68	284	--	--
69	49	--	23
70	457	--	25
71	788	--	--

All publications and patents identified above are hereby incorporated by reference.

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 follcwing claims.

WE CLAIM:

1. A compound of formula II:



II

or a pharmaceutically acceptable salt thereof, wherein:

n is 1 or 2;

X is O or S;

Z is selected from the group consisting of S, CH_2, CHR_1 and $C(R_1)_2$;

R_1 is selected from the group consisting of C_1-C_5 straight or branched chain alkyl, C_2-C_5 straight or branched chain alkenyl, Ar_1 and mixtures thereof, wherein said R_1 is unsubstituted or substituted with halo, nitro, C_1-C_5 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, hydroxy, C_1-C_4 alkoxy, C_2-C_4 alkenyloxy, phenoxy, benzyloxy, amino, Ar_1 or a mixture thereof;

R_2 is selected from the group consisting of C_1-C_9 straight or branched chain alkyl, C_2-C_9 straight or branched chain alkenyl, C_3-C_8 cycloalkyl, C_5-C_7

cycloalkenyl and Ar_1; and

Ar_1 is phenyl, benzyl, pyridyl, fluorenyl, thioindolyl or naphthyl wherein said Ar_1 is unsubstituted or substituted with halo, hydroxy, nitro, C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, C_1-C_4 alkoxy, C_2-C_4 alkenyloxy, phenoxy, benzyloxy, amino or a mixture thereof.

2. The compound of claim 1, wherein:

n is 1; and

X is O.

3. The compound of claim 2, wherein Z is CH_2.

4. The compound of claim 3, which is selected from the group consisting of:

(2*S*)-2-({1-Oxo-5-phenyl}-pentyl-1-(3,3-dimethyl-1,2-dioxopentyl)pyrrolidine;

3,3-Dimethyl-1-[(2*S*)-2-(5-(3-pyridyl)pentanoyl)-1-pyrrolidine]-1,2-pentanedione;

(2*S*)-2-({1-Oxo-4-phenyl}-butyl-1-(3,3-dimethyl-1,2-dioxobutyl)pyrrolidine;

(2*S*)-2-({1-Oxo-4-phenyl}-butyl-1-(2-cyclohexyl-1,2-dioxoethyl)pyrrolidine;

2-({1-Oxo-4-phenyl}-butyl-1-(3,3-dimethyl-1,2-dioxobutyl)pyrrolidine; and

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* C L M S *

1-{(2*S*)-2-[5,5-di(4-Fluorophenyl)pentanoyl]-2-pyrrolidine}-3,3-dimethyl-1,2-pentanedione.

5. The compound of claim 2, wherein Z is S.

6. The compound of claim 5, which is selected from the group consisting of:

2-Phenyl-1-ethyl 1-(3,3-dimethyl-1,2-dioxopentyl)-2-piperidinecarbothioate;

(3-Thioindolyl)methyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate;

2-Phenyl-1-ethyl (2*S*)-1-(2-cyclohexyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate;

2-Phenyl-1-ethyl (2*S*)-1-(1-cyclopentyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate;

3-Phenyl-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate;

3-(3-Pyridyl)-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate;

3-Phenyl-1-propyl (2*S*)-1-(2-cyclohexyl-1,2-dioxoethyl)-2-pyrrolidinecarbothioate;

4-Phenyl-1-butyl (2*S*)-1-(2-cyclohexyl-1,2-dioxoethyl)-2-pyrrolidinecarbothioate;

4-Phenyl-1-butyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate;

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3-(3-Pyridyl)-1-propyl (2*S*)-1-(2-cyclohexyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate;

3,3-Diphenyl-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate;

3,3-Diphenyl-1-propyl (2*S*)-1-(2-Cyclohexyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate;

3-(*para*-Methoxyphenyl)-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate;

3,3-Di(*para*-Fluoro)phenyl-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate;

4,4-Di(*para*-fluorophenyl)butyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-pyrrolidinecarbothioate;

3-(1-Naphthyl)propyl (2*S*)-1-(3,3-dimethyl-2-oxopentanoyl)-2-pyrrolidinecarbothioate;

2,2-Diphenylethyl (2*S*)-1-(3,3-dimethyl-2-oxopentanoyl)tetrahydro-1H-2-pyrrolecarbothioate;

3-[4-(Trifluoromethyl)phenyl]propyl (2*S*)-1-(3,3-dimethyl-2-oxopentanoyl)-2-pyrrolidinecarbothioate;

3-(2-Naphthyl)propyl (2*S*)-1-(3,3-dimethyl-2-oxopentanoyl)-2-pyrrolidinecarbothioate;

3-(3-Chlorophenyl)propyl (2*S*)-1-(3,3-dimethyl-2-oxopentanoyl)-2-pyrrolidinecarbothioate;

3-[3-(Trifluoromethyl)phenyl)propyl (2*S*)-1-(3,3-dimethyl-2-oxopentanoyl)-2-pyrrolidinecarbothioate;

3-(1-Biphenyl)propyl (2*S*)-1-(3,3-dimethyl-2-oxopentanoyl)-2-pyrrolidinecarbothioate;

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3-(2-Fluorophenyl)propyl (2*S*)-1-(3,3-dimethyl-2-oxopentanoyl)-2-pyrrolidinecarbothioate;

3-(3-Fluorophenyl)propyl (2*S*)-1-(3,3-dimethyl-2-oxopentanoyl)-2-pyrrolidinecarbothioate;

3-(2-Chlorophenyl)propyl (2*S*)-1-(3,3-dimethyl-2-oxopentanoyl)-2-pyrrolidinecarbothioate; and

3-(3,4-Dimethoxyphenyl)propyl (2*S*)-1-(3,3-dimethyl-2-oxopentanoyl)-2-pyrrolidinecarbothioate.

7. The compound of claim 1, wherein:

n is 1; and

X is S.

8. The compound of claim 7, wherein Z is CH_2.

9. The compound of 7, wherein Z is S.

10. The compound of claim 1, wherein:

n is 2; and

X is O.

11. The compound of claim 10, wherein Z is CH_2.

12. The compound of claim 11, which is selected from the group consisting of:

2-({1-Oxo-6-phenyl}-hexyl-1-(3,3-dimethyl-1,2-dioxobutyl)piperidine; and

3,3-Dimethyl-1-[2-(4-phenylpentanoyl)piperidino]-1,2-pentanedione.

13. The compound of claim 10, wherein Z is S.

14. The compound of claim 13, which is selected from the group consisting of:

2-Phenyl-1-ethyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate;

2-Phenyl-1-ethyl 1-(2-phenyl-1,2-dioxoethyl)-2-piperidinecarbothioate;

3-Phenyl-1-propyl 1-(3,3-dimethyl-1,2-dioxobutyl)-2-piperidinecarbothioate;

4-Phenyl-1-butyl 1-(1,2-dioxo-3,3-dimethylbutyl)-2-piperidinecarbothioate;

1,5-Diphenyl-3-pentyl 1-(3,3-dimethyl-1,2-dioxopentyl)-2-piperidinecarbothioate;

1,5-Diphenyl-3-mercaptopentyl 1-(3-phenyl-1,2-dioxoethyl)-2-piperidinecarbothioate;

3-(*para*-Methoxyphenyl)-1-propyl 1-(1,2-dioxo-3,3-dimethylpentyl)piperidine-2-carbothioate;

3-(*para*-Methoxyphenyl)-1-propyl 1-(2-phenyl-1,2-dioxoethyl)piperidine-2-carbothioate;

3-(1-Naphthyl)-1-propyl 1-(3,3-dimethyl-1,2-dioxopentyl)piperidine-2-carbothioate;

2,2-Diphenylethyl (2*S*)-1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarbothioate;

3,3-Diphenylpropyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarbothioate;

3-(2-Naphthyl)propyl (2*R*,*S*)-1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarbothioate;

4-Phenylbutyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarbothioate;

3-Phenylpropyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarbothioate;

3-(2-Chlorophenyl)propyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarbothioate;

3-(2-Fluorophenyl)propyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarbothioate; and

3-(3-Fluorophenyl)propyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarbothioate.

15. The compound of claim 1, wherein:

n is 2; and

X is S.

16. The compound of claim 15, wherein Z is CH_2.

17. The compound of 15, wherein Z is S.

18. The compound of claim 15, wherein Z is CHR_1.

19. The compound of claim 18, which is 2-({1-Oxo-[2-{2'-phenyl}ethyl]-4-phenyl}-butyl-1-(3,3-dimethyl-1,2-dioxobutyl)piperidine.

20. A pharmaceutical composition comprising:

(i) an effective amount of the compound of claim 1 for effecting a neuronal activity; and

(ii) a pharmaceutically acceptable carrier.

21. The pharmaceutical composition of claim 20, wherein, in said compound:

n is 1; and

X is O.

22. The pharmaceutical composition of claim 21, wherein, in said compound, Z is CH_2.

23. The pharmaceutical composition of claim 22, wherein said compound is selected from the group consisting of:

(2*S*)-2-({1-Oxo-5-phenyl}-pentyl-1-(3,3-dimethyl-1,2-dioxopentyl)pyrrolidine;

3,3-Dimethyl-1-[(2*S*)-2-(5-(3-pyridyl)pentanoyl)-1-pyrrolidine]-1,2-pentanedione;

(2*S*)-2-({1-Oxo-4-phenyl}-butyl-1-(3,3-dimethyl-1,2-dioxobutyl)pyrrolidine;

(2*S*)-2-({1-Oxo-4-phenyl}-butyl-1-(2-cyclohexyl-1,2-dioxoethyl)pyrrolidine;

2-({1-Oxo-4-phenyl}-butyl-1-(3,3-dimethyl-1,2-dioxobutyl)pyrrolidine; and

1-{(2*S*)-2-[5,5-di(4-Fluorophenyl)pentanoyl]-2-pyrrolidine}-3,3-dimethyl-1,2-pentanedione.

24. The pharmaceutical composition of claim 21, wherein, in said compound, Z is S.

25. The pharmaceutical composition of claim 24, wherein said compound is selected from the group consisting of:

2-Phenyl-1-ethyl 1-(3,3-dimethyl-1,2-dioxopentyl)-2-piperidinecarbothioate;

(3-Thioindolyl)methyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate;

2-Phenyl-1-ethyl (2*S*)-1-(2-cyclohexyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate;

2-Phenyl-1-ethyl (2*S*)-1-(1-cyclopentyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate;

3-Phenyl-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate;

3-(3-Pyridyl)-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate;

3-Phenyl-1-propyl (2*S*)-1-(2-cyclohexyl-1,2-dioxoethyl)-2-pyrrolidinecarbothioate;

4-Phenyl-1-butyl (2*S*)-1-(2-cyclohexyl-1,2-dioxoethyl)-2-pyrrolidinecarbothioate;

4-Phenyl-1-butyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate;

3-(3-Pyridyl)-1-propyl (2*S*)-1-(2-cyclohexyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate;

3,3-Diphenyl-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate;

3,3-Diphenyl-1-propyl (2*S*)-1-(2-Cyclohexyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate;

3-(*para*-Methoxyphenyl)-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate;

3,3-Di(*para*-Fluoro)phenyl-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate;

4,4-Di(*para*-fluorophenyl)butyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-pyrrolidinecarbothioate;

3-(1-Naphthyl)propyl (2*S*)-1-(3,3-dimethyl-2-oxopentanoyl)-2-pyrrolidinecarbothioate;

2,2-Diphenylethyl (2*S*)-1-(3,3-dimethyl-2-oxopentanoyl)tetrahydro-1H-2-pyrrolecarbothioate;

3-[4-(Trifluoromethyl)phenyl]propyl (2*S*)-1-(3,3-dimethyl-2-oxopentanoyl)-2-pyrrolidinecarbothioate;

3-(2-Naphthyl)propyl (2*S*)-1-(3,3-dimethyl-2-oxopentanoyl)-2-pyrrolidinecarbothioate;

3-(3-Chlorophenyl)propyl (2*S*)-1-(3,3-dimethyl-2-oxopentanoyl)-2-pyrrolidinecarbothioate;

3-[3-(Trifluoromethyl)phenyl)propyl (2*S*)-1-(3,3-dimethyl-2-oxopentanoyl)-2-pyrrolidinecarbothioate;

3-(1-Biphenyl)propyl (2*S*)-1-(3,3-dimethyl-2-oxopentanoyl)-2-pyrrolidinecarbothioate;

3-(2-Fluorophenyl)propyl (2*S*)-1-(3,3-dimethyl-2-oxopentanoyl)-2-pyrrolidinecarbothioate;

3-(3-Fluorophenyl)propyl (2*S*)-1-(3,3-dimethyl-2-oxopentanoyl)-2-pyrrolidinecarbothioate;

3-(2-Chlorophenyl)propyl (2*S*)-1-(3,3-dimethyl-2-oxopentanoyl)-2-pyrrolidinecarbothioate; and

3-(3,4-Dimethoxyphenyl)propyl (2*S*)-1-(3,3-dimethyl-2-oxopentanoyl)-2-pyrrolidinecarbothioate.

26. The pharmaceutical composition of claim 20, wherein, in said compound:

n is 1; and

X is S.

27. The pharmaceutical composition of claim 26, wherein, in said compound, Z is CH_2.

28. The pharmaceutical composition of 26, wherein, in said compound, Z is S.

29. The pharmaceutical composition of claim 20, wherein, in said compound:

n is 2; and

X is O.

30. The pharmaceutical composition of claim 29, wherein, in said compound, Z is CH_2.

31. The pharmaceutical composition of claim 30, wherein said compound is selected from the group consisting of:

2-({1-Oxo-6-phenyl}-hexyl-1-(3,3-dimethyl-1,2-dioxobutyl)piperidine; and

3,3-Dimethyl-1-[2-(4-phenylpentanoyl)piperidino]-1,2-pentanedione.

32. The pharmaceutical composition of claim 29, wherein, in said compound, Z is S.

33. The pharmaceutical composition of claim 32, wherein said compound is selected from the group consisting of:

2-Phenyl-1-ethyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate;

2-Phenyl-1-ethyl 1-(2-phenyl-1,2-dioxoethyl)-2-piperidinecarbothioate;

3-Phenyl-1-propyl 1-(3,3-dimethyl-1,2-dioxobutyl)-2-piperidinecarbothioate;

4-Phenyl-1-butyl 1-(1,2-dioxo-3,3-dimethylbutyl) -2-piperidinecarbothioate;

1,5-Diphenyl-3-pentyl 1-(3,3-dimethyl-1,2-dioxopentyl)-2-piperidinecarbothioate;

1,5-Diphenyl-3-mercaptopentyl 1-(3-phenyl-1,2-dioxoethyl)-2-piperidinecarbothioate;

3-(*para*-Methoxyphenyl)-1-propyl 1-(1,2-dioxo-3,3-dimethylpentyl)piperidine-2-carbothioate;

3-(*para*-Methoxyphenyl)-1-propyl 1-(2-phenyl-1,2-dioxoethyl)piperidine-2-carbothioate;

3-(1-Naphthyl)-1-propyl 1-(3,3-dimethyl-1,2-dioxopentyl)piperidine-2-carbothioate;

2,2-Diphenylethyl (2*S*)-1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarbothioate;

3,3-Diphenylpropyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarbothioate;

3-(2-Naphthyl)propyl (2*R,S*)-1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarbothioate;

4-Phenylbutyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarbothioate;

3-Phenylpropyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarbothioate;

3-(2-Chlorophenyl)propyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarbothioate;

3-(2-Fluorophenyl)propyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarbothioate; and

3-(3-Fluorophenyl)propyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarbothioate.

34. The pharmaceutical composition of claim 20, wherein, in said compound:

n is 2; and

X is S.

35. The pharmaceutical composition of claim 34, wherein, in said compound, Z is CH_2.

36. The pharmaceutical composition of 34, wherein, in said compound, Z is S.

37. The pharmaceutical composition of claim 34, wherein, in said compound, Z is CHR_1.

38. The pharmaceutical composition of claim 37, wherein said compound is 2-({1-Oxo-[2-{2'-phenyl}ethyl]-4-phenyl}-butyl-1-(3,3-dimethyl-1,2-

dioxobutyl)piperidine.

39. A method for effecting a neuronal activity in an animal, comprising:

administering to the animal an effective amount of the compound of claim 1.

40. The method of claim 39, 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.

41. The method of claim 40, wherein the neurological disorder is selected from the group consisting of peripheral neuropathy caused by physical injury or disease state, traumatic injury to the brain, physical damage to the spinal cord, stroke associated with brain damage, and neurological disorder relating to neurodegeneration.

42. The method of claim 41, wherein the neurological disorder relating to neurodegeneration is selected from the group consisting of Alzheimer's Disease, Parkinson's Disease, and amyotrophic lateral sclerosis.

43. The method of claim 39, wherein, in said compound:

n is 1; and

X is O.

44. The method of claim 43, wherein, in said compound, Z is CH_2.

45. The method of claim 44, wherein said compound is selected from the group consisting of:

(2*S*)-2-({1-Oxo-5-phenyl}-pentyl-1-(3,3-dimethyl-1,2-dioxopentyl)pyrrolidine;

3,3-Dimethyl-1-[(2*S*)-2-(5-(3-pyridyl)pentanoyl)-1-pyrrolidine]-1,2-pentanedione;

(2*S*)-2-({1-Oxo-4-phenyl}-butyl-1-(3,3-dimethyl-1,2-dioxobutyl)pyrrolidine;

(2*S*)-2-({1-Oxo-4-phenyl}-butyl-1-(2-cyclohexyl-1,2-dioxoethyl)pyrrolidine;

2-({1-Oxo-4-phenyl}-butyl-1-(3,3-dimethyl-1,2-dioxobutyl)pyrrolidine; and

1-{(2*S*)-2-[5,5-di(4-Fluorophenyl)pentanoyl]-2-pyrrolidine}-3,3-dimethyl-1,2-pentanedione.

46. The method of claim 43, wherein, in said compound, Z is S.

47. The method of claim 46, wherein said compound is selected from the group consisting of:

2-Phenyl-1-ethyl 1-(3,3-dimethyl-1,2-dioxopentyl)-2-piperidinecarbothioate;

(3-Thioindolyl)methyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate;

2-Phenyl-1-ethyl (2*S*)-1-(2-cyclohexyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate;

2-Phenyl-1-ethyl (2*S*)-1-(1-cyclopentyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate;

3-Phenyl-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate;

3-(3-Pyridyl)-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate;

3-Phenyl-1-propyl (2*S*)-1-(2-cyclohexyl-1,2-dioxoethyl)-2-pyrrolidinecarbothioate;

4-Phenyl-1-butyl (2*S*)-1-(2-cyclohexyl-1,2-dioxoethyl)-2-pyrrolidinecarbothioate;

4-Phenyl-1-butyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate;

3-(3-Pyridyl)-1-propyl (2*S*)-1-(2-cyclohexyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate;

3,3-Diphenyl-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate;

3,3-Diphenyl-1-propyl (2*S*)-1-(2-Cyclohexyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate;



3-(*para*-Methoxyphenyl)-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate;

3,3-Di(*para*-Fluoro)phenyl-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate;

4,4-Di(*para*-fluorophenyl)butyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-pyrrolidinecarbothioate;

3-(1-Naphthyl)propyl (2*S*)-1-(3,3-dimethyl-2-oxopentanoyl)-2-pyrrolidinecarbothioate;

2,2-Diphenylethyl (2*S*)-1-(3,3-dimethyl-2-oxopentanoyl)tetrahydro-1H-2-pyrrolecarbothioate;

3-[4-(Trifluoromethyl)phenyl]propyl (2*S*)-1-(3,3-dimethyl-2-oxopentanoyl)-2-pyrrolidinecarbothioate;

3-(2-Naphthyl)propyl (2*S*)-1-(3,3-dimethyl-2-oxopentanoyl)-2-pyrrolidinecarbothioate;

3-(3-Chlorophenyl)propyl (2*S*)-1-(3,3-dimethyl-2-oxopentanoyl)-2-pyrrolidinecarbothioate;

3-[3-(Trifluoromethyl)phenyl)propyl (2*S*)-1-(3,3-dimethyl-2-oxopentanoyl)-2-pyrrolidinecarbothioate;

3-(1-Biphenyl)propyl (2*S*)-1-(3,3-dimethyl-2-oxopentanoyl)-2-pyrrolidinecarbothioate;

3-(2-Fluorophenyl)propyl (2*S*)-1-(3,3-dimethyl-2-oxopentanoyl)-2-pyrrolidinecarbothioate;

3-(3-Fluorophenyl)propyl (2*S*)-1-(3,3-dimethyl-2-oxopentanoyl)-2-pyrrolidinecarbothioate;

3-(2-Chlorophenyl)propyl (2*S*)-1-(3,3-dimethyl-2-oxopentanoyl)-2-pyrrolidinecarbothioate; and

3-(3,4-Dimethoxyphenyl)propyl (2*S*)-1-(3,3-dimethyl-2-oxopentanoyl)-2-pyrrolidinecarbothioate.

48. The method of claim 39, wherein, in said compound:

n is 1; and

X is S.

49. The method of claim 48, wherein, in said compound, Z is CH_2.

50. The method of claim 48, wherein, in said compound, Z is S.

51. The method of claim 39, wherein, in said compound:

n is 2; and

X is O.

52. The method of claim 51, wherein, in said compound, Z is CH_2.

53. The method of claim 52, wherein said compound is selected from the group consisting of:

2-({1-Oxo-6-phenyl}-hexyl-1-(3,3-dimethyl-1,2-dioxobutyl)piperidine; and

3,3-Dimethyl-1-[2-(4-phenylpentanoyl)piperidino]-1,2-pentanedione.

54. The method of claim 51, wherein, in said compound, Z is S.

55. The method of claim 54, wherein said compound is selected from the group consisting of:

2-Phenyl-1-ethyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate;

2-Phenyl-1-ethyl 1-(2-phenyl-1,2-dioxoethyl)-2-piperidinecarbothioate;

3-Phenyl-1-propyl 1-(3,3-dimethyl-1,2-dioxobutyl)-2-piperidinecarbothioate;

4-Phenyl-1-butyl 1-(1,2-dioxo-3,3-dimethylbutyl) -2-piperidinecarbothioate;

1,5-Diphenyl-3-pentyl 1-(3,3-dimethyl-1,2-dioxopentyl)-2-piperidinecarbothioate;

1,5-Diphenyl-3-mercaptopentyl 1-(3-phenyl-1,2-dioxoethyl)-2-piperidinecarbothioate;

3-(*para*-Methoxyphenyl)-1-propyl 1-(1,2-dioxo-3,3-dimethylpentyl)piperidine-2-carbothioate;

3-(*para*-Methoxyphenyl)-1-propyl 1-(2-phenyl-1,2-dioxoethyl)piperidine-2-carbothioate;

3-(1-Naphthyl)-1-propyl 1-(3,3-dimethyl-1,2-dioxopentyl)piperidine-2-carbothioate;

2,2-Diphenylethyl (2*S*)-1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarbothioate;

3,3-Diphenylpropyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarbothioate;

3-(2-Naphthyl)propyl (2*R*,*S*)-1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarbothioate;

4-Phenylbutyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarbothioate;

3-Phenylpropyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarbothioate;

3-(2-Chlorophenyl)propyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarbothioate;

3-(2-Fluorophenyl)propyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarbothioate; and

3-(3-Fluorophenyl)propyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarbothioate.

56. The method of claim 39, wherein, in said compound:

n is 2; and

X is S.

57. The method of claim 56, wherein, in said compound, Z is CH_2.

58. The method of 56, wherein, in said compound, Z is S.

59. The method of claim 56, wherein in said compound, Z is CHR_1.

60. The method of claim 59, wherein said compound is 2-({1-Oxo-[2-{2'-phenyl}ethyl]-4-phenyl}-butyl-1-(3,3-dimethyl-1,2-dioxobutyl)piperidine.

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