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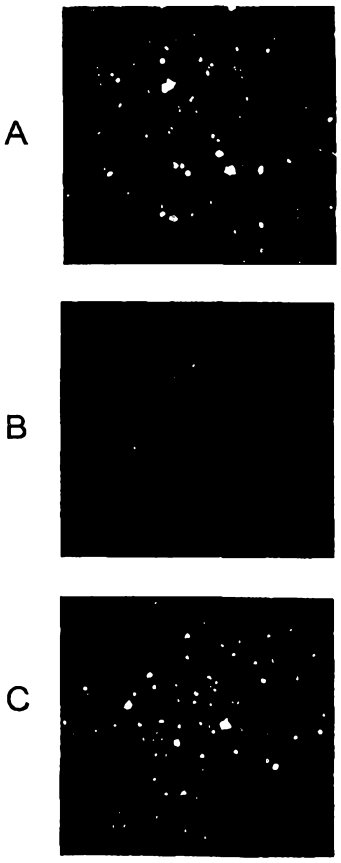
(54) Title: COMPOSITIONS AND USES FOR VISION AND MEMORY DISORDERS

(57) Abstract

This invention relates to novel compositions and uses of non-immunosuppressive FKBP neuroimmunophilin ligands for treating a vision disorder, improving vision, treating memory impairment or enhancing memory performance in an animal.



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COMPOSITIONS AND USES FOR VISION AND MEMORY DISORDERS

BACKGROUND OF THE INVENTION

1. Field of Invention

This invention relates to pharmaceutical compositions and methods for treating vision loss, preventing vision degeneration, and promoting vision regeneration ("neopsis") using low molecular weight, small molecule derivatives.

2. Description of Related Art

The visual system is composed of the eyes, ocular adnexa and the visual pathways. Dysfunction of the visual system may lead to permanent or temporary visual impairment, i.e. a deviation from normal in one or more functions of the eye. Visual impairment manifests itself in various ways and includes a broad range of visual dysfunctions and disturbances. Without limitation, these dysfunctions and disturbances include partial or total loss of vision, the need for correction of visual acuity for objects near and far, loss of visual field, impaired ocular motility without diplopia (double vision), impaired or skewed color perception, limited adaptation to light and dark, diminished accommodation, metamorphopsic distortion, impaired binocular vision, paresis of accommodation, iridoplegia, entropion, ectropion, epiphora, lagophthalmos, and scarring. *See Physicians' Desk Reference (PDR) for Ophthalmology*, 16th Edition, 6:47 (1988). The visual system may be adversely affected by various ophthalmologic disorders, diseases, injuries, and complications, including, without limitation, genetic disorders; [non-genetic disorders;] disorders associated with aging or degenerative diseases; disorders correlating to physical injury to the eye, head, or other

parts of the body resulting from external forces; disorders resulting from environmental factors; disorders resulting from a broad range of diseases; and combinations of any of the above.

The visual system is a complex system composed of numerous components. Visual impairment can involve the entire visual system, any one component, or any combination of components, depending upon the precise nature of the circumstances. The eye is composed of a lens, which is suspended in the zonules of Zinn and is focused by the ciliary body. The ciliary body also secretes aqueous humor, which fills the posterior chamber, passes through the pupil into the anterior chamber, then drains primarily via the canal of Schlemm. The iris regulates the quantity of light entering the eye by adjusting the size of its central opening, the pupil. A visual image is focused onto the retina, the fovea centralis being the retinal area of sharpest visual acuity. The conjunctiva is the mucus membrane which lines the eyelids and the eyeball, and ends abruptly at the limbus conjunctivae, the edge of the conjunctiva overlapping the cornea. The cornea is the clear, transparent anterior portion of the fibrous coat of the eye; it is important in light refraction and is covered with an epithelium that differs in many respects from the conjunctival epithelium.

The retina is the innermost, light sensitive portion of the eye, containing two types of photoreceptors, cones, which are responsible for color vision in brighter light, and rods, which are essential for vision in dim light but do not perceive colors. After light passes through the cornea, lens system, and the vitreous humor, it enters the retina from the inside; that is, it passes through the ganglion cells and nerve fibers, the inner and outer plexiform layers, the inner and outer nuclear layers, and the internal and external limiting membranes before it finally reaches the layer of

photoreceptors located near the outside of the retina, just inside the outermost pigment epithelium layer. The cells of the pigment epithelium layer act as an anatomical barrier to liquids and substances located outside of the eye, forming the "blood-retina" barrier, and provide nourishment, oxygen, a source of functionally useful substances like vitamin A, and phagocytosis of decomposition products to photoreceptor cells. There is no anatomical connection between the pigment epithelium and the photoreceptor layer, permitting separation of the layers in some pathological situations.

When rods or cones are excited by light, signals are transmitted through successive neurons in the retina itself, into the optic nerve fibers, and ultimately to the cerebral cortex. Both rods and cones contain molecules that decompose on exposure to light and, in the process, excite the nerve fibers leading from the eye. The molecule in rods is rhodopsin. The three light-sensitive molecules in cones, collectively called iodopsin, have compositions only slightly different from that of rhodopsin and are maximally excited by red, blue, or green light, respectively.

Neither rods nor cones generate action potentials. Rather, the light-induced membrane hyperpolarization generated in the outer, photosensitive segment of a rod or cone cell is transmitted from the outer segment through the inner segment to the synaptic body by direct conduction of the electrical voltage itself, a process called electrotonic conduction. At the synaptic body, the membrane potential controls the release of an unknown transmitter molecule. In low light, rod and cone cell membranes are depolarized and the rate of transmitter release is greatest. Light-induced hyperpolarization causes a marked decrease in the release of transmitter molecules.

The transmitters released by rod and cone cells induce signals in the bipolar neurons and horizontal cells. The signals in both these cells are also transmitted by

electrotonic conduction and not by action potential.

The rod bipolar neurons connect with as many as 50 rod cells, while the dwarf and diffuse bipolar cells connect with one or several cone cells. A depolarizing bipolar cell is stimulated when its connecting rods or cones are exposed to light. The release of transmitter molecules inhibits the depolarizing bipolar cell. Therefore, in the dark, when the rods and cones are secreting large quantities of transmitter molecules, the depolarizing bipolar cells are inhibited. In the light, the decrease in release of transmitter molecules from the rods and cones reduces the inhibition of the bipolar cell, allowing it to become excited. In this manner, both positive and negative signals can be transmitted through different bipolar cells from the rods and cones to the amacrine and ganglion cells.

As their name suggests, horizontal cells project horizontally in the retina, where they may synapse with rods, cones, other horizontal cells, or a combination of cells types. The function of horizontal cells is unclear, although some mechanism in the convergence of photoreceptor signaling has been postulated.

All types of bipolar cells connect with ganglion cells, which are of two primary types. A-type ganglion cells predominately connect with rod bipolar cells, while B-type ganglion cells predominately connect with dwarf and diffuse bipolar cells. It appears that A-type ganglion cells are sensitive to contrast, light intensity, and perception of movement, while B-type ganglion cells appear more concerned with color vision and visual acuity.

Like horizontal cells, the Amacrine cells horizontally synapse with several to many other cells, in this case bipolar cells, ganglion cells, and other Amacrine cells. The function of Amacrine cells is also unclear.

The axons of ganglion cells carry signals into the nerve fiber layer of the eye, where the axons converge into fibers

which further converge at the optic disc, where they exit the eye as the optic nerve. The ganglion cells transmit their signals through the optic nerve fibers to the brain in the form of action potentials. These cells, even when unstimulated, transmit continuous nerve impulses at an average, baseline rate of about 5 per second. The visual signal is superimposed onto this baseline level of ganglion cell stimulation. It can be either an excitatory signal, with the number of impulses increasing above the baseline rate, or an inhibitory signal, with the number of nerve impulses decreasing below the baseline rate.

As part of the central nervous system, the eye is in some ways an extension of the brain; as such, it has a limited capacity for regeneration. This limited regeneration capacity further complicates the challenging task of improving vision, resolving dysfunction of the visual system, and/or treating or preventing ophthalmologic disorders. Many disorders of the eye, such as retinal photic injury, retinal ischemia-induced eye injury, age-related macular degeneration, free radical-induced eye diseases, as well as numerous other disorders, are considered to be entirely untreatable. Other ophthalmologic disorders, e.g., disorders causing permanent visual impairment, are corrected only by the use of ophthalmic devices and/or surgery, with varying degrees of success.

The immunosuppressant drugs FK506, rapamycin, and cyclosporin are well known as potent T-cell specific immunosuppressants, and are effective against autoimmunity, transplant or graft rejection, inflammation, allergic responses, other autoimmune or immune-mediated diseases, and infectious diseases. It has been disclosed that application of Cyclosporin, FK-506, Rapamycin, Buspirone, Spiperone, and/or their derivatives are effective in treating some ophthalmologic disorders of these types. Several ophthalmologic disorders or vision problems are known to be

associated with autoimmune and immunologically-mediated activities; hence, immunomodulatory compounds are expected to demonstrate efficacy for treating those types of ophthalmologic disorders or vision problems.

The effects of FK506, Rapamycin, and related agents in the treatment of ophthalmologic diseases are disclosed in several U.S. patents (Goulet et al., U.S. Patent No. 5,532,248; Mochizuki et al., U.S. Patent No. 5,514,686; Luly et al., U.S. Patent No. 5,457,111; Russo et al., U.S. Patent No. 5,441,937; Kulkarni, U.S. Patent No. 5,387,589; Asakura et al., U.S. Patent No. 5,368,865; Goulet et al., U.S. Patent No. 5,258,389; Armistead et al., U.S. Patent No. 5,192,773; Goulet et al., U.S. Patent No. 5,189,042; and Fehr, U.S. Patent No. 5,011,844). These patents claim FK506 or Rapamycin related compounds and disclose the known use of FK506 or Rapamycin related compounds in the treatment of ophthalmologic disorders in association with the known immunosuppressive effects of FK506 and Rapamycin. The compounds disclosed in these patents are relatively large. Further, the cited patents relate to immunomodulatory compounds limited to treating autoimmunity or related diseases, or immunologically-mediated diseases, for which the efficacy of FK506 and Rapamycin is well known.

Other U.S. patents disclose the use of cyclosporin, Spiperone, Buspirone, their derivatives, and other immunosuppressive compounds for use in the treatment of ophthalmologic diseases (Sharpe et al., U.S. Patent No. 5,703,088; Sharpe et al., U.S. Patent No. 5,693,645; Sullivan, U.S. Patent No. 5,688,765; Sullivan, U.S. Patent No. 5,620,921; Sharpe et al., U.S. Patent No. 5,574,041; Eberle, U.S. Patent No. 5,284,826; Sharpe et al., U.S. Patent No. 5,244,902; Chiou et al., U.S. Patent Nos. 5,198,454 and 5,194,434; and Kaswan, U.S. Patent No. 4,839,342). These patents also relate to compounds useful for treating autoimmune diseases and cite the known use of cyclosporin,

Spiperone, Buspirone, their derivatives, and other immunosuppressive compounds in treating ocular inflammation and other immunologically-mediated ophthalmologic diseases.

The immunosuppressive compounds disclosed in the prior art suppress the immune system, by definition, and also exhibit other toxic side effects. Accordingly, there is a need for non-immunosuppressant, small molecule compounds, and compositions and methods for use of such compounds, that are useful in improving vision; preventing, treating, and/or repairing visual impairment or dysfunction of the visual system; and preventing, treating, and/or resolving ophthalmologic disorders.

There are also a number of patents on non-immunosuppressive compounds disclosing methods of use for permitting or promoting wound healing (whether from injury or surgery); controlling intraocular pressure (often resulting from glaucoma); controlling neurodegenerative eye disorders, including damage or injury to retinal neurons, damage or injury to retinal ganglion cells, and macular degeneration; stimulating neurite outgrowth; preventing or reducing oxidative damage caused by free radicals; and treating impaired oxygen and nutrient supply, as well as impaired waste product removal, resulting from low blood flow. These non-immunosuppressive substances fall into one of two general categories: naturally occurring molecules, such as proteins, glycoproteins, peptides, hormones, and growth factors; and synthetic molecules.

Within the group of naturally occurring non-immunosuppressive molecules, several hormones, growth factors, and signaling molecules have been patented for use as supplements to naturally occurring quantities of such molecules, as well as for targeting of specific cells where the particular molecule does not naturally occur in a mature individual. These patents generally claim methods of use for reducing or preventing the symptoms of ocular disease, or

arresting or reversing vision loss.

Specifically, Louis et al., U.S. Patent Nos. 5,736,516 and 5,641,749, disclose the use of a glial cell line derived neurotrophic factor (GDNF) to stop or reverse the degeneration of retinal neurons (i.e. photoreceptors) and retinal ganglion cells caused by glaucoma, or other degenerative or traumatic retinal diseases or injuries. O'Brien, et al., U.S. Patent Nos. 5,714,459 and 5,700,909, disclose the use of a glycoprotein, Saposin, and its derivatives for stimulating neurite outgrowth and increasing myelination. To stop or reverse degeneration of retinal neurons, LaVail et al., U.S. Patent No. 5,667,968, discloses the use of a variety of neurotrophic proteins, including brain-derived neurotrophic factor, ciliary neurotrophic factor, neurotrophin-3 or neurotrophin-4, acidic or basic fibroblast growth factors, interleukin, tumor necrosis factor-α, insulin-like growth factor-2 and other growth factors. Wong et al., U.S. Patent No. 5,632,984, discloses the use of interferons, especially interferon α-2a, for treating the symptoms of macular degeneration by reducing hemorrhage and limiting neovascularization. Finally, Wallace et al., U.S. Patent No. 5,441,937, discloses the use of a lung-derived neurotrophic factor (NTF) to maintain the functionality of ciliary ganglion and parasympathetic neuron cells.

A key characteristic of factors derived from specific cell lines is their localization to specific cell lines or tissues; systemic treatment with these molecules would run a substantial risk of unintended, and potentially dangerous, effects in cell lines where the genes encoding these molecules are inactive. Similarly, hormones and growth factors often activate a large number of genes in many cell lines; again, non-localized application of these molecules would run a substantial risk of provoking an inappropriate, and potentially dangerous, response.

Within the category of synthetic molecules, most of the patented compounds are immunosuppressive and disclose uses in treating inflammatory, autoimmune, and allergic responses, as discussed above. A few others are non-immunosuppressive and claim the ability to treat cellular degeneration, and in some cases promote cellular regeneration, most often in the context of their antioxidant properties.

Specifically, Tso et al., U.S. Patent No. 5,527,533, discloses the use of astaxanthin, a carotenoid antioxidant, for preventing or reducing photoreceptor damage resulting from the presence of free radicals. Similarly, Babcock et al., U.S. Patent No. 5,252,319, discloses the use of antioxidant aminosteroids for treating eye disease and injury, by increasing resistance to oxidative damage. Freeman, U.S. Patent No. 5,468,752, discloses the use of the antiviral phosphonylmethoxyalkylcytosines to reduce abnormally increased intraocular pressure.

Hamilton and Steiner disclose in U.S. Patent No. 5,614,547 novel pyrrolidine carboxylate compounds which bind to the immunophilin FKBP12 and stimulate nerve growth, but which lack immunosuppressive effects. Unexpectedly, it has been discovered that these non-immunosuppressant compounds promote improvements in vision and resolve ophthalmologic disorders. Yet their novel small molecule structure and non-immunosuppressive properties differentiate them from FK506 and related immunosuppressive compounds found in the prior art.

Further, these compounds may be differentiated from the non-immunosuppressive compounds used to treat vision disorders by their novel small molecule structure and their lack of general, systemic effects. Naturally occurring hormones, growth factors, cytokines, and signaling molecules are generally multifunctional and activate many genes in diverse cell lines. The present compounds do not, thus avoiding the unexpected, and potentially dangerous, side

effects of systemic use. Similarly, the present compounds also avoid the potential unexpected side effects of introducing cell line-specific molecules into other cell lines were they do not naturally occur.

SUMMARY OF THE INVENTION

The present invention relates to the surprising discovery that non-immunosuppressive immunophilin ligands, i.e. inhibitors or binding agents, may be useful for treating a vision disorder, improving vision, treating memory impairment or enhancing memory performance in an animal. Accordingly, novel compositions and methods of using non-immunosuppressive immunophilin ligands are provided. A preferred feature of the compounds of the present invention is that they do not exert any significant immunosuppressive activity.

Preferred embodiments of this invention also include methods and compositions wherein the non-immunosuppressive immunophilin ligand has an affinity for FKBP-type immunophilins, and in particular FKBP-12.

Preferred FKBP-type non-immunosuppressive immunophilin ligands include without limitation small molecule heterocyclic ring compounds having a first and second substituent group attached thereto wherein the first substituent group comprises i) an acidic moiety or ii) an alkyl, alkenyl, alkylaryl, alkenylaryl or group otherwise exemplified herein which is linked to the heterocyclic ring by an ester, thioester, amide, amine, ketone linkage, or a variation as disclosed herein, and wherein the second substituent group comprises an alkyl, alkenyl, alkylaryl, alkenylaryl, or group otherwise exemplified herein which is linked to the heterocyclic ring by a diketo, thiocarbonyl, carbamate, urea, sulfonyl, or a linkage as exemplified herein.

Preferred embodiments of the invention include methods

and compositions using a compound selected from formulas (I)-(XXIX).

Brief Description of the Drawings

Figure 1 A, B and C show that GPI 1046 protects retinal ganglion cells against degeneration following retinal ischemia.

Figure 2 shows that GPI 1046 prevents degeneration of optic nerve axons and myelin following retinal ischemia.

Figure 3 shows that GPI 1046 provides moderate protection against retinal ganglion cell death after optic nerve transection.

Figure 4 shows that GPI 1046 treatment duration significantly affects the process of optic nerve axonal degeneration after transection.

Figure 5 shows that GPI 1046 treatment produces a greater effect on optic nerve axons than ganglion cell bodies.

Figure 6 shows that GPI 1046 treatment for 28 days after optic nerve transection prevents myelin degeneration in the proximal stump.

Figure 7 shows that FKBP-12 immunohistochemistry labels oligodendroglia (large dark cells with fibrous processes), the cells which produce myelin, located between the fascicles of optic nerve fibers, and also some optic nerve axons.

Figure 8 shows GPI 1046 treatment for 28 days after optic nerve transection prevents myelin degeneration in the distal stump.

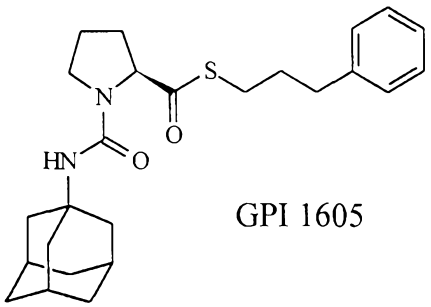
Figure 9 shows that 28 day treatment with GPI 1046 treatment beginning 8 weeks after onset of streptozotocin induced diabetes decreases the extent of neovascularization in the inner and outer retina and protects neurons in the inner nuclear layer (INL) and ganglion cell layer (GCL) from degeneration.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

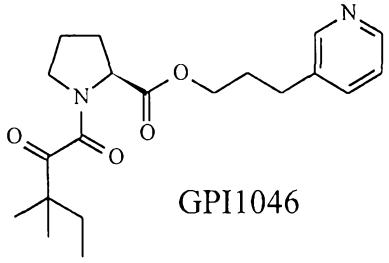
"Eye" refers to the anatomical structure responsible for vision in humans and other animals, and encompasses the following anatomical structures, without limitation: lens, vitreous body, ciliary body, posterior chamber, anterior chamber, pupil, cornea, iris, canal of Schlemm, zonules of Zinn, limbus, conjunctiva, choroid, retina, central vessels of the retina, optic nerve, fovea centralis, macula lutea, and sclera.

"GPI 1605" refers to a compound of formula



GPI 1605

"GPI 1046" refers to 3-(3-pyridyl)-1-propyl (2s)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate, a compound of formula



GPI1046

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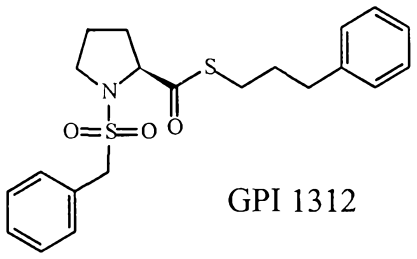

GPI 1312

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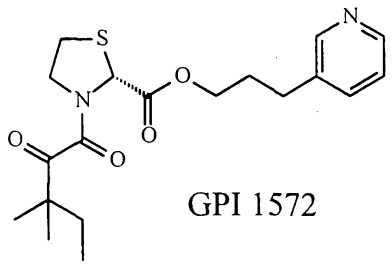

GPI 1572

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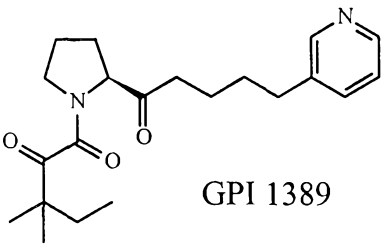

GPI 1389

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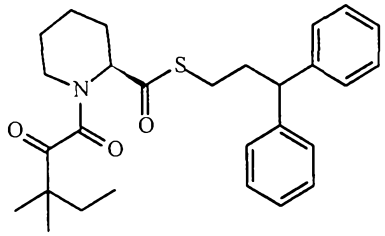

GPI 1511

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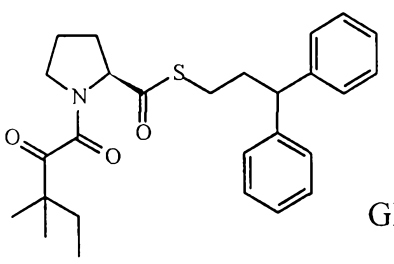


GPI 1234

"Isomers" refer to 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.

"Enhancing memory performance" refers to improving or increasing the mental faculty by which to register, retain or recall past experiences, knowledge, ideas, sensations, thoughts or impressions.

"Memory impairment" refers to a diminished mental registration, retention or recall of past experiences, knowledge, ideas, sensations, thoughts or impressions. Memory impairment may affect short and long-term information retention, facility with spatial relationships, memory (rehearsal) strategies, and verbal retrieval and production. Common causes of memory impairment are age, severe head trauma, brain anoxia or ischemia, alcoholic-nutritional diseases, and drug intoxications. Examples of memory impairment include, without limitation, benign forgetfulness, amnesia and any disorder in which memory deficiency is present, such as Korsakoff's amnesic psychosis, dementia and learning disorders.

"Neopsic factors" or "neopsics" refers to compounds useful in treating vision loss, preventing vision degeneration, or promoting vision regeneration.

"Neopsis" refers to the process of treating vision loss, preventing vision degeneration, or promoting vision regeneration.

"Ophthalmological" refers to anything about or concerning the eye, without limitation, and is used

interchangeably with "ocular," "ophthalmic," "ophthalmologic," and other such terms, without limitation.

"Pharmaceutically acceptable salt, ester, or solvate" refers to a salt, ester, or solvate of a subject compound which possesses the desired pharmacological activity and which is neither biologically nor otherwise undesirable. A salt, ester, or solvate 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, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, naphthylate, 2-naphthalenesulfonate, nicotinate, oxalate, sulfate, thiocyanate, tosylate and undecanoate. Examples of base salts, esters, or solvates 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, 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 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; aralkyl halides, such as benzyl and phenethyl bromides; and others. Water or oil-soluble or dispersible products are thereby obtained.

"Preventing vision degeneration" refers to the ability to prevent degeneration of vision in patients newly diagnosed as having a degenerative disease affecting vision, or at risk of developing a new degenerative disease affecting vision, and for preventing further degeneration of vision in patients

who are already suffering from or have symptoms of a degenerative disease affecting vision.

"Promoting vision regeneration" refers to maintaining, improving, stimulating or accelerating recovery of, or revitalizing one or more components of the visual system in a manner which improves or enhances vision, either in the presence or absence of any ophthalmologic disorder, disease, or injury.

"Treating" refers to:

(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.

"Vision" refers to the ability of humans and other animals to process images, and is used interchangeably with "sight", "seeing", and other such terms, without limitation.

"Vision disorder" refers to any disorder that affects or involves vision, including without limitation visual impairment, orbital disorders, disorders of the lacrimal apparatus, disorders of the eyelids, disorders of the conjunctiva, disorders of the cornea, cataracts, disorders of the uveal tract, disorders of the retina, disorders of the optic nerve or visual pathways, free radical induced eye disorders and diseases, immunologically-mediated eye disorders and diseases, eye injuries, and symptoms and complications of eye disease, eye disorder, or eye injury.

"Visual impairment" refers to any dysfunction in vision including without limitation disturbances or diminution in vision (e.g., binocular, central, peripheral, scotopic), visual acuity for objects near and far, visual field, ocular motility, color perception, adaptation to light and dark,

accommodation, refraction, and lacrimation. See Physician's Desk Reference (PDR) for Ophthalmology, 16th Edition, 6:47 (1988).

Methods of the Present Invention

The present invention relates to a method of treating a vision disorder, improving vision, treating memory impairment, or enhancing memory performance in an animal, which comprises administering to said animal an effective amount of a derivative.

The inventive methods are particularly useful for treating various eye disorders including but not limited to visual disorders, diseases, injuries, and complications, genetic disorders; disorders associated with aging or degenerative vision diseases; vision disorders correlating to physical injury to the eye, head, or other parts of the body resulting from external forces; vision disorders resulting from environmental factors; vision disorders resulting from a broad range of diseases; and combinations of any of the above.

In particular, the compositions and methods of the present invention are useful for improving vision, or correcting, treating, or preventing visual (ocular) impairment or dysfunction of the visual system, including permanent and temporary visual impairment, without limitation. The present invention is also useful in preventing and treating ophthalmologic diseases and disorders, treating damaged and injured eyes, and preventing and treating diseases, disorders, and injuries which result in vision deficiency, vision loss, or reduced capacity to see or process images, and the symptoms and complications resulting from same. The eye diseases and disorders which may be treated or prevented by the compositions and methods of the present invention are not limited with regard to the cause of said diseases or disorders. Accordingly, said

compositions and methods are applicable whether the disease or disorder is caused by genetic or environmental factors, as well as any other influences. The compositions and methods of the present invention are particularly useful for eye problems or vision loss or deficiency associated with all of the following, without limitation: aging, cellular or physiological degeneration, central nervous system or neurological disorder, vascular defects, muscular defects, and exposure to adverse environmental conditions or substances.

The compositions and methods of the present invention are particularly useful in correcting, treating, or improving visual impairment, without limitation. Visual impairment in varying degrees occurs in the presence of a deviation from normal in one or more functions of the eye, including (1) visual acuity for objects at distance and near; (2) visual fields; and (3) ocular motility without diplopia. *See Physicians' Desk Reference (PDR) for Ophthalmology, 16th Edition*, 6:47 (1988). Vision is imperfect without the coordinated function of all three. *Id.*

Said compositions and methods of use are also useful in correcting, treating, or improving other ocular functions including, without limitation, color perception, adaptation to light and dark, accommodation, metamorphopsia, and binocular vision. The compositions and methods of use are particularly useful in treating, correcting, or preventing ocular disturbances including, without limitation, paresis of accommodation, iridoplegia, entropion, ectropion, epiphora, lagophthalmos, scarring, vitreous opacities, non-reactive pupil, light scattering disturbances of the cornea or other media, and permanent deformities of the orbit.

The compositions and methods of use of the present invention are also highly useful in improving vision and treating vision loss. Vision loss ranging from slight loss to absolute loss may be treated or prevented using said

compositions and methods of use. Vision may be improved by the treatment of eye disorders, diseases, and injuries using the compositions and methods of the invention. However, improvements in vision using the compositions and methods of use are not so limited, and may occur in the absence of any such disorder, disease, or injury.

The compositions and methods of the present invention are also useful in the treatment or prevention of the following non-limiting exemplary diseases and disorders, and symptoms and complications resulting therefrom.

Vision disorders include but are not limited to the following:

visual impairment, such as diminished visual acuity for objects near and far, visual fields, and ocular motility;

orbital disorders, such as orbital cellulitis, periorbital cellulitis, cavernous sinus thrombosis, and exophthalmos (proptosis);

disorders of the lacrimal apparatus, such as dacryostenosis, congenital dacryostenosis, and dacryocystitis (acute or chronic);

disorders of the eyelids, such as lid edema, blepharitis, ptosis, Bell's palsy, blepharospasm, hordeolum (stye), external hordeolum, internal hordeolum (meibomian stye), chalazion, entropion (inversion of the eyelid), ectropion (eversion of the eyelid), tumors (benign and malignant), xanthelasma, basil cell carcinoma, squamous cell carcinoma, meibomian gland carcinoma, and melanoma;

disorders of the conjunctiva, such as pinguecula, pterygium, and other neoplasms, acute conjunctivitis, chronic conjunctivitis, adult gonococcal conjunctivitis, neonatal conjunctivitis, trachoma (granular conjunctivitis or Egyptian ophthalmia), inclusion conjunctivitis (inclusion blenorrhea or swimming pool conjunctivitis), neonatal inclusion conjunctivitis, adult inclusion conjunctivitis, vernal keratoconjunctivitis, keratoconjunctivitis sicca (keratitis

sicca or dry eye syndrome), episcleritis, scleritis, cicatricial pemphigoid (ocular cicatricial pemphigoid or benign mucous membrane pemphigoid), and subconjunctival hemorrhage;

disorders of the cornea, such as superficial punctate keratitis, corneal ulcer, indolent ulcer, recurrent corneal erosion, corneal epithelial basement membrane dystrophy, corneal endothelial cell dystrophy, herpes simplex keratitis (herpes simplex keratoconjunctivitis), dendritic keratitis, disciform keratitis, ophthalmic herpes zoster, phlyctenular keratoconjunctivitis (phlyctenular or eczematous conjunctivitis), interstitial keratitis (parenchymatous keratitis), peripheral ulcerative keratitis (marginal keratolysis or peripheral rheumatoid ulceration), keratomalacia (xerotic keratitis), xerophthalmia, keratoconus, bullous keratopathy;

cataracts, including developmental or congenital cataracts, juvenile or adult cataracts, nuclear cataract, posterior subcapsular cataracts;

disorders of the uveal tract, such as uveitis (inflammation of the uveal tract or retina), anterior uveitis, intermediate uveitis, posterior uveitis, iritis, cyclitis, choroiditis, ankylosing spondylitis, Reiter's syndrome, pars planitis, toxoplasmosis, cytomegalovirus (CMV), acute retinal necrosis, toxocariasis, birdshot choroidopathy, histoplasmosis (presumed ocular histoplasmosis syndrome), Behcet's syndrome, sympathetic ophthalmia, Vogt-Koyanagi-Harada syndrome, sarcoidosis, reticulum cell sarcoma, large cell lymphoma, syphilis, tuberculosis, juvenile rheumatoid arthritis, endophthalmitis, and malignant melanoma of the choroid;

disorders of the retina, such as vascular retinopathies (e.g., arteriosclerotic retinopathy and hypertensive retinopathy), central and branch retinal artery occlusion, central and branch retinal vein occlusion, diabetic

retinopathy (e.g., proliferative retinopathy and non-proliferative retinopathy), macular degeneration of the aged (age-related macular degeneration or senile macular degeneration), neovascular macular degeneration, retinal detachment, retinitis pigmentosa, retinal photic injury, retinal ischemia-induced eye injury, and glaucoma (e.g., primary glaucoma, chronic open-angle glaucoma, acute or chronic angle-closure, congenital (infantile) glaucoma, secondary glaucoma, and absolute glaucoma);

disorders of the optic nerve or visual pathways, such as papilledema (choked disk), papillitis (optic neuritis), retrobulbar neuritis, ischemic optic neuropathy, toxic amblyopia, optic atrophy, higher visual pathway lesions, disorders of ocular motility (e.g., third cranial nerve palsies, fourth cranial nerve palsies, sixth cranial nerve palsies, internuclear ophthalmoplegia, and gaze palsies);

free radical induced eye disorders and diseases; and

immunologically-mediated eye disorders and diseases, such as Graves' ophthalmopathy, conical cornea, dystrophia epithelialis corneae, corneal leukoma, ocular pemphigus, Mooren's ulcer, scleritis, and sarcoidosis (*See The Merck Manual*, Sixteenth Edition, 217:2365-2397 (1992) and *The Eye Book*, Cassel, Billig, and Randall, The Johns Hopkins University Press (1998)).

The compositions and methods of the present invention are also useful in the treatment of the following non-limiting eye injuries, and symptoms and complications resulting therefrom: conjunctival and corneal foreign body injuries, corneal abrasion, intraocular foreign body injuries, lacerations, lid lacerations, contusions, lid contusions (black eye), trauma to the globe, laceration of the iris, cataract, dislocated lens, glaucoma, vitreous hemorrhage, orbital-floor fractures, retinal hemorrhage or detachment, and rupture of the eyeball, anterior chamber hemorrhage (traumatic hyphema), burns, eyelid burns, chemical

burns, chemical burns of the cornea and conjunctiva, and ultraviolet light burns (sunburn). *See The Merck Manual, Sixteenth Edition*, *217*:2364-2365 (1992).

The compositions and methods of the present invention are also useful in treating and/or preventing the following non-limiting exemplary symptoms and complications of eye disease, eye disorder or eye injury: subconjunctival hemorrhages, vitreous hemorrhages, retinal hemorrhages, floaters, retinal detachments, photophobia, ocular pain, scotomas (negative and positive), errors of refraction, emmetropia, ametropia, hyperopia (farsightedness), myopia (nearsightedness), astigmatism, anisometropia, aniseikonia, presbyopia, bleeding, recurrent bleeding, sympathetic ophthalmia, inflammation, swelling, redness of the eye, irritation of the eye, corneal ulceration and scarring, iridocyclitis, perforation of the globe, lid deformities, exophthalmos, impaired mobility of the eye, lid swelling, chemosis, loss of vision, including partial or total blindness, optic neuritis, fever, malaise, thrombophlebitis, cavernous sinus thrombosis, panophthalmitis, infection of the meninges and brain, papilledema, severe cerebral symptoms (headache, decreased level of consciousness, and convulsions), cranial nerve palsies, epiphora (chronic or persistent tearing), copious reflux of mucus or pus, follicular subconjunctival hyperplasia, corneal vascularization, cicatrization of the conjunctiva, cornea, and lids, pannus, hypopyon, lagophthalmos, phlyctenules, rubeosis iridis, bitemporal hemianopia, and homonymous hemianopia. *See The Merck Manual, Sixteenth Edition*, *217*:2362-2363 (1992).

The derivative may be administered in combination with an effective amount of one or more factor(s) useful in treating vision disorder, improving vision, treating memory impairment, or enhancing memory performance.

In a preferred embodiment, the factor(s) to be combined

with the derivative is/are selected from the group consisting of immunosuppressants for treating autoimmune, inflammatory, and immunologically-mediated disorders; wound healing agents for treating wounds resulting from injury or surgery; antiglaucomatous medications for treating abnormally elevated intraocular pressure; neurotrophic factors and growth factors for treating neurodegenerative disorders or stimulating neurite outgrowth; compounds effective in limiting or preventing hemorrhage or neovascularization for treating macular degeneration; and antioxidants for treating oxidative damage to eye tissues.

Pharmaceutical Compositions of the Present Invention

The present invention also relates to a pharmaceutical composition comprising:

(i) an effective amount of a derivative for treating a vision disorder, improving vision, treating memory impairment, or enhancing memory performance in an animal; and

(ii) a pharmaceutically acceptable carrier.

The derivative may be administered in combination with an effective amount of one or more factor(s) useful in treating vision disorders, improving vision, treating memory impairment, or enhancing memory performance.

Non-Immunosuppressive Neuroimmunophilin FKBP Ligands

The non-immunosuppressive neuroimmunophilin FKBP ligand used in the method and pharmaceutical composition of the present invention is a low molecular weight, small molecule compound having an affinity for an FKBP-type immunophilin, such as FKBP12. When the compound binds to an FKBP-type immunophilin, it has been found to inhibit the prolyl-peptidyl *cis-trans* isomerase activity, or rotamase, activity of the binding protein.

As its name suggests, the compound is devoid of any

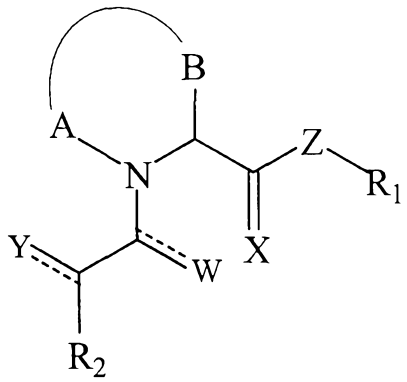
significant immunosuppressive activity.

Examples of a non-immunosuppressive neuroimmunophilin FKBP ligand that may be used in the inventive method and pharmaceutical composition are set forth below.

I. HETEROCYCLIC THIOESTERS AND KETONES

FORMULA I

The non-immunosuppressive neuroimmunophilin FKBP ligand may be a compound of formula I



I

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

A and B, together with the nitrogen and carbon atoms to which they are respectively attached, form a 5-7 membered saturated or unsaturated heterocyclic ring containing one or more heteroatom(s) independently selected from the group consisting of O, S, SO, SO_2, N, NH, and NR_2;

X is either O or S;

Z is either S, CH_2, CHR_1 or CR_1R_3;

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

R_1 and R_3 are independently C_1-C_6 straight or branched chain alkyl or C_2-C_6 straight or branched chain alkenyl, wherein said alkyl or alkenyl is substituted with one or more substituent(s) independently selected from the group consisting of $(Ar_1)_n$, C_1-C_6 straight or branched chain alkyl or C_2-C_6 straight or branched chain alkenyl substituted with $(Ar_1)_n$, C_3-C_8 cycloalkyl, C_1-C_6 straight or branched chain

alkyl or C_2-C_6 straight or branched chain alkenyl substituted with C_3-C_8 cycloalkyl, and Ar_2;

n is 1 or 2;

R_2 is either 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, or Ar_1, wherein said alkyl, alkenyl, cycloalkyl or cycloalkenyl is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of C_1-C_4 straight or branched chain alkyl, C_2-C_4 straight or branched chain alkenyl, and hydroxy; and

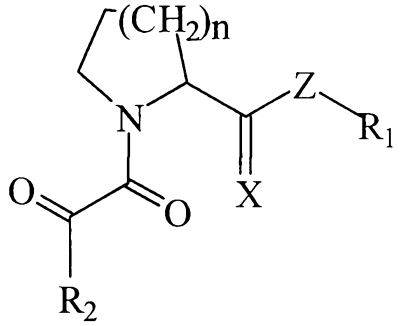
Ar_1 and Ar_2 are independently an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring, wherein said ring is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of halo, hydroxyl, nitro, trifluoromethyl, C_1-C_6 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, and amino; wherein the individual ring size is 5-8 members; and wherein the heterocyclic ring contains 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S.

Useful carbo- and heterocyclic rings include without limitation phenyl, benzyl, naphthyl, indenyl, azulenyl, fluorenyl, anthracenyl, indolyl, isoindolyl, indolinyl, benzofuranyl, benzothiophenyl, indazolyl, benzimidazolyl, benzthiazolyl, tetrahydrofuranyl, tetrahydropyranyl, pyridyl, pyrrolyl, pyrrolidinyl, pyridinyl, pyrimidinyl, purinyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, quinolizinyl, furyl, thiophenyl, imidazolyl, oxazolyl, benzoxazolyl, thiazolyl, isoxazolyl, isotriazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, trithianyl, indolizinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, thienyl, tetrahydroisoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, naphthyridinyl, pteridinyl,

carbazolyl, acridinyl, phenazinyl, phenothiazinyl, and phenoxazinyl.

FORMULA II

The non-immunosuppressive neuroimmunophilin FKBP ligand may also be a compound of formula II



II

or a pharmaceutically acceptable salt, ester, or solvate 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 CR_1R_3;

R_1 and R_3 are independently selected from the group consisting of C_1-C_5 straight or branched chain alkyl, C_2-C_5 straight or branched chain alkenyl, and Ar_1, wherein said alkyl, alkenyl or Ar_1 is unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of halo, nitro, C_1-C_6 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, and Ar_1;

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 one or more substituent(s) independently selected from the group consisting of halo, trifluoromethyl, 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, and amino.

Preferred compounds of formula II are presented in **TABLE A**.

TABLE A

No.	n	X	Z	R_1	R_2
1	1	O	CH_2	3-Phenylpropyl	1,1-Dimethylpropyl
2	1	O	CH_2	3-(3-Pyridyl)propyl	1,1-Dimethylpropyl
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	1,1-Dimethylpropyl
9	1	O	S	2-Phenethyl	1,1-Dimethylpropyl
10	2	O	S	2-Phenethyl	1,1-Dimethylpropyl
11	1	O	S	Methyl(2-thioindole)	1,1-Dimethylpropyl
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	1,1-Dimethylpropyl
16	2	O	CH_2	4-(4-Methoxy-phenyl)butyl	1,1-Dimethylpropyl
17	2	O	CH_2	4-Phenylbutyl	1,1-Dimethylpropyl
18	2	O	CH_2	4-Phenylbutyl	Phenyl
19	2	O	CH_2	4-Phenylbutyl	Cyclohexyl
20	1	S	CH_2	3-Phenylpropyl	1,1-Dimethylpropyl
21	1	S	S	2-Phenethyl	1,1-Dimethylpropyl

No.	n	X	Z	R_1	R_2
22	2	S	CH_2	3-Phenylpropyl	1,1-Dimethylpropyl
23	2	S	S	2-Phenethyl	1,1-Dimethylpropyl
24	2	O	CHR_1	3-Phenylpropyl	1,1-Dimethylpropyl
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-Trimethoxy-phenyl
28	1	O	S	2-Phenethyl	Cyclopentyl
29	2	O	S	3-Phenylpropyl	*tert*-Butyl
30	1	O	S	3-Phenylpropyl	1,1-Dimethylpropyl
31	1	O	S	3-(3-Pyridyl)propyl	1,1-Dimethylpropyl
32	1	O	S	3-Phenylpropyl	Cyclohexyl
33	1	O	S	4-Phenylbutyl	Cyclohexyl
34	1	O	S	4-Phenylbutyl	1,1-Dimethylpropyl
35	1	O	S	3-(3-Pyridyl)propyl	Cyclohexyl
36	1	O	S	3,3-Diphenylpropyl	1,1-Dimethylpropyl
37	1	O	S	3,3-Diphenylpropyl	Cyclohexyl
38	1	O	S	3-(4-Methoxyphenyl)-propyl	1,1-Dimethylpropyl
39	2	O	S	4-Phenylbutyl	*tert*-Butyl
40	2	O	S	1,5-Diphenylpentyl	1,1-Dimethylpropyl
41	2	O	S	1,5-Diphenylpentyl	Phenyl
42	2	O	S	3-(4-Methoxyphenyl)-propyl	1,1-Dimethylpropyl
43	2	O	S	3-(4-Methoxyphenyl)-propyl	Phenyl
44	2	O	S	3-(1-Naphthyl)propyl	1,1-Dimethylpropyl
45	1	O	S	3,3-Di(4-fluoro)phenylpropyl	1,1-Dimethylpropyl
46	1	O	S	4,4-Di(4-fluoro)-phenylbutyl	1,1-Dimethylpropyl

No.	n	X	Z	R_1	R_2
47	1	O	S	3-(1-Naphthyl)propyl	1,1-Dimethylpropyl
48	1	O	S	2,2-Diphenylethyl	1,1-Dimethylpropyl
49	2	O	S	2,2-Diphenylethyl	1,1-Dimethylpropyl
50	2	O	S	3,3-Diphenylpropyl	1,1-Dimethylpropyl
51	1	O	S	3-(4-{Trifluoro-methyl}phenyl)propyl	1,1-Dimethylpropyl
52	1	O	S	3-(2-Naphthyl)propyl	1,1-Dimethylpropyl
53	2	O	S	3-(1-Naphthyl)propyl	1,1-Dimethylpropyl
54	1	O	S	3-(3-Chloro)phenyl-propyl	1,1-Dimethylpropyl
55	1	O	S	3-(3-{Trifluoro-methyl}phenyl)propyl	1,1-Dimethylpropyl
56	1	O	S	3-(2-Biphenyl)propyl	1,1-Dimethylpropyl
57	1	O	S	3-(2-Fluorophenyl)-propyl	1,1-Dimethylpropyl
58	1	O	S	3-(3-Fluorophenyl)-propyl	1,1-Dimethylpropyl
59	2	O	S	4-Phenylbutyl	1,1-Dimethylpropyl
60	2	O	S	3-Phenylpropyl	1,1-Dimethylpropyl
61	1	O	S	3-(2-Chloro)phenyl-propyl	1,1-Dimethylpropyl
62	2	O	S	3-(3-Chloro)-phenylpropyl	1,1-Dimethylpropyl
63	2	O	S	3-(2-Fluoro)phenyl-propyl	1,1-Dimethylpropyl
64	2	O	S	3-(3-Fluoro)-phenylpropyl	1,1-Dimethylpropyl
65	1	O	S	3-(2,5-Dimethoxy-phenylpropyl	1,1-Dimethylpropyl
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

No.	n	X	Z	R_1	R_2
70	1	O	CH_2	3,3-Di(4-fluoro-phenyl)propyl	1,1-Dimethylpropyl
71	2	O	CH_2	3-Phenylpropyl	1,1-Dimethylpropyl

Preferred compounds of **TABLE A** 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 (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate

10 2-Phenyl-1-ethyl 1-(3,3-dimethyl-1,2-dioxopentyl)-2-piperidinecarbothioate

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-dioxoethyl)-2-pyrrolidinecarbothioate

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-dioxoethyl)-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-dioxoethyl)-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-dioxoethyl)-2-pyrrolidinecarbothioate

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

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

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*-Methoxyphenyl)-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-pyrrolidine-carbothioate

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-pyrrolidine-carbothioate

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

50 3,3-Diphenylpropyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarbothioate

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

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

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-pyrrolidine-carbothioate

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

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-(2-Cyclohexyl-1,2-dioxoethyl)piperidine

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

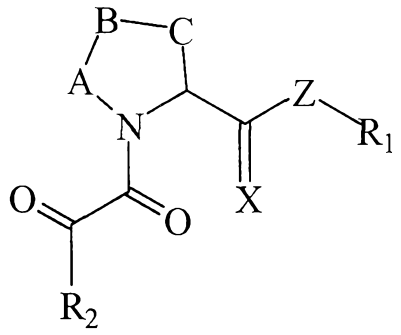
dimethyl-1,2-dioxobutyl)piperidine

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

Furthermore, the non-immunosuppressive neuroimmunophilin FKBP ligand may be a compound of formula III



III

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

A, B, and C 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 CR_1R_3;

R_1 and R_3 are independently C_1-C_6 straight or branched chain alkyl or C_2-C_6 straight or branched chain alkenyl, wherein said alkyl or alkenyl is substituted with one or more substituent(s) independently selected from the group consisting of $(Ar_1)_n$, C_1-C_6 straight or branched chain alkyl or C_2-C_6 straight or branched chain alkenyl substituted with $(Ar_1)_n$, C_3-C_8 cycloalkyl, C_1-C_6 straight or branched chain alkyl or C_2-C_6 straight or branched chain alkenyl substituted with C_3-C_8 cycloalkyl, and Ar_2;

n is 1 or 2;

R_2 is either 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 or Ar_1, wherein said alkyl, alkenyl, cycloalkyl or cycloalkenyl is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of C_1-C_4 straight or branched chain alkyl, C_2-C_4 straight or branched chain alkenyl, and hydroxyl; and

Ar_1 and Ar_2 are independently an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring, wherein said ring is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of halo, hydroxyl, nitro, trifluoromethyl, 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, and amino; wherein the individual ring size is 5-8 members; and wherein the heterocyclic ring contains 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S.

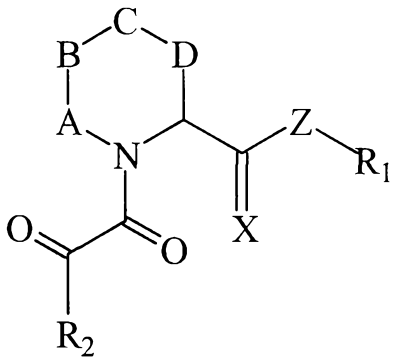
Preferred compounds of formula III are presented in TABLE B.

TABLE B

No.	A	B	C	X	Z	R_1	R_2
72	CH_2	S	CH_2	O	S	2-phenethyl	1,1-dimethyl-propyl
73	CH_2	S	CH_2	O	CH_2	3-phenyl-propyl	1,1-dimethyl-propyl
74	CH_2	CH_2	NH	O	S	2-phenethyl	1,1-dimethyl-propyl
75	CH_2	S	CH_2	S	S	2-phenethyl	1,1-dimethyl-propyl

FORMULA IV

Alternatively, the non-immunosuppressive neuroimmunophilin FKBP ligand may be a compound of formula IV



IV

or a pharmaceutically acceptable salt, ester, or solvate 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 CR_1R_3;

R_1 and R_3 are independently C_1-C_6 straight or branched chain alkyl or C_2-C_6 straight or branched chain alkenyl, wherein said alkyl or alkenyl is substituted with one or more substituent(s) independently selected from the group consisting of $(Ar_1)_n$, C_1-C_6 straight or branched chain alkyl or C_2-C_6 straight or branched chain alkenyl substituted with $(Ar_1)_n$, C_3-C_8 cycloalkyl, C_1-C_6 straight or branched chain alkyl or C_2-C_6 straight or branched chain alkenyl substituted with C_3-C_8 cycloalkyl, and Ar_2;

n is 1 or 2;

R_2 is either 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 or Ar_1, wherein said alkyl, alkenyl, cycloalkyl or cycloalkenyl is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of C_3-C_8 cycloalkyl, C_1-C_4 straight or branched chain alkyl, C_2-C_4 straight or branched chain alkenyl, and hydroxyl; and

Ar_1 and Ar_2 are independently an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring, wherein said ring is either unsubstituted or substituted with one or

more substituent(s) independently selected from the group consisting of halo, hydroxyl, nitro, trifluoromethyl, 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, and amino; wherein the individual ring size is 5-8 members; and wherein the heterocyclic ring contains 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S.

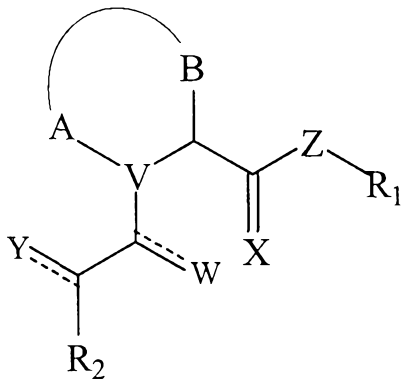
Preferred compounds of formula IV are presented in TABLE C.

TABLE C

No.	A	B	C	D	X	Z	R_1	R_2
76	CH_2	CH_2	O	CH_2	O	CH_2	3-phenyl-propyl	1,1-dimethylpropyl
77	CH_2	CH_2	O	CH_2	O	S	2-phen-ethyl	1,1-dimethylpropyl
78	CH_2	CH_2	S	CH_2	O	CH_2	3-phenyl-propyl	1,1-dimethylpropyl
79	CH_2	CH_2	S	CH_2	O	S	2-phen-ethyl	1,1-dimethylpropyl

FORMULA V

The non-immunosuppressive neuroimmunophilin FKBP ligand may further be a compound of formula V



V

or a pharmaceutically acceptable salt, ester, or solvate

thereof, wherein:

V is C, N, or S;

A and B, together with V and the carbon atom to which they are respectively attached, form a 5-7 membered saturated or unsaturated heterocyclic ring which may contain, in addition to V, one or more heteroatom(s) independently selected from the group consisting of O, S, SO, SO_2, N, NH, and NR_4;

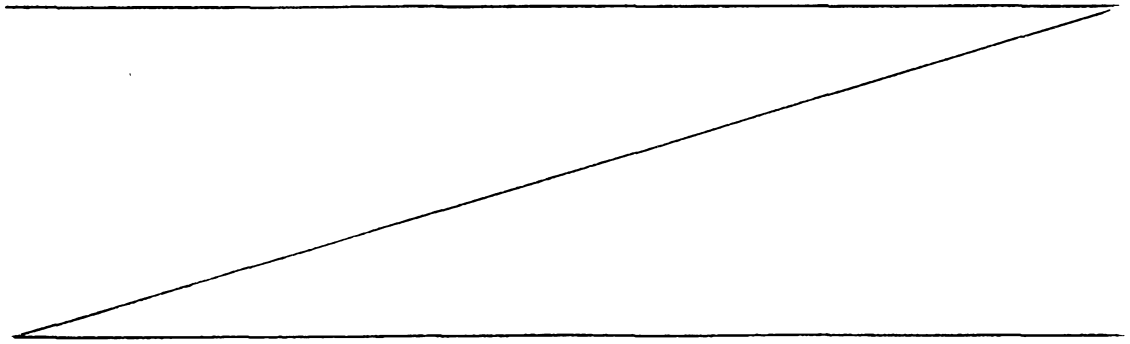
R_4 is either C_1-C_9 straight or branched chain alkyl, C_2-C_9 straight or branched chain alkenyl, C_3-C_9 cycloakyl, C_5-C_7 cycloalkenyl, or Ar_3, wherein R_4 is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of halo, haloalkyl, carbonyl, carboxy, hydroxy, nitro, trifluoromethyl, 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, thioalkyl, alkylthio, sulfhydryl, amino, alkylamino, aminoalkyl, aminocarboxyl, and Ar_4;

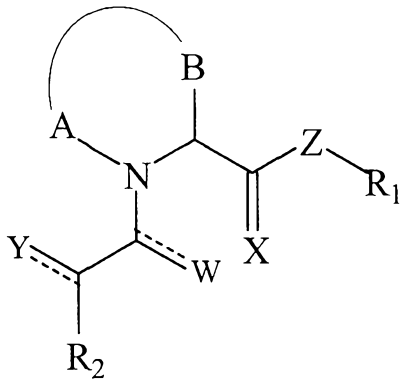
Ar_3 and Ar_4 are independently an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring; wherein the individual ring size is 5-8 members; wherein said heterocyclic ring contains 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S; and

R_1, R_2, W, X, Y, and Z are as defined in Formula I above.

II. HETEROCYCLIC ESTERS AND AMIDES FORMULA VI

Additionally, the non-immunosuppressive neuroimmunophilin FKBP ligand may be a compound of formula VI





VI

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

A and B, together with the nitrogen and carbon atoms to which they are respectively attached, form a 5-7 membered saturated or unsaturated heterocyclic ring which may contain, in addition to the nitrogen atom, one or more heteroatom(s) independently selected from the group consisting of O, S, SO, SO_2, N, NH, and NR_1;

X is O or S;

Z is O, NH or NR_1;

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 C_2-C_6 straight or branched chain alkenyl, which is substituted with one or more substituent(s) independently selected from the group consisting of $(Ar_1)_n$, C_1-C_6 straight or branched chain alkyl or C_2-C_6 straight or branched chain alkenyl substituted with $(Ar_1)_n$, C_3-C_8 cycloalkyl, C_1-C_6 straight or branched chain alkyl or C_2-C_6 straight or branched chain alkenyl substituted with C_3-C_8 cycloalkyl, and Ar_2;

n is 1 or 2;

R_2 is either C_1-C_9 straight or branched chain alkyl, C_2-C_9 straight or branched chain 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 with one or more substituent(s) independently selected from the group consisting of C_1-C_4 straight or branched chain alkyl,

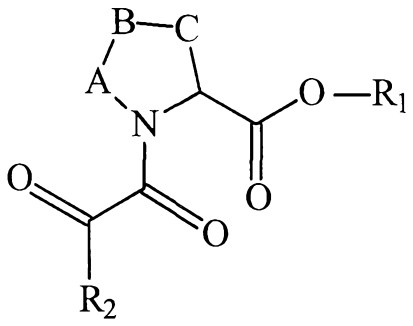
C_2-C_4 straight or branched chain alkenyl, and hydroxyl; and

Ar_1 and Ar_2 are independently an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring, wherein the ring is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of halo, hydroxyl, nitro, trifluoromethyl, 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, and amino; wherein the individual ring size is 5-8 members; and wherein the heterocyclic ring contains 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S.

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

FORMULA VII

The non-immunosuppressive neuroimmunophilin FKBP ligand may also be a compound of formula VII



VII

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

A, B and C are independently CH_2, O, S, SO, SO_2, NH or NR_1;

R_1 is C_1-C_5 straight or branched chain alkyl or C_2-C_5 straight or branched chain alkenyl, which is substituted with one or more substituent(s) independently selected from the group consisting of $(Ar_1)_n$ and C_1-C_6 straight or branched

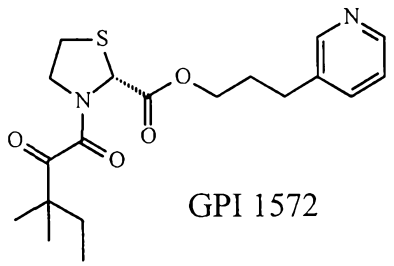
chain alkyl or C_2-C_6 straight or branched chain alkenyl substituted with $(Ar_1)_n$;

n is 1 or 2;

R_2 is either 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, or Ar_1; and

Ar_1 is an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring, wherein the ring is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of halo, hydroxyl, nitro, trifluoromethyl, 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, and amino; wherein the individual ring size is 5-8 members; and wherein the heterocyclic ring contains 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S.

In a preferred embodiment of the compounds of formula VII, the heterocyclic ester or amide is the Compound GPI 1572, of the formula



GPI 1572

In a particularly preferred embodiment of formula VII compounds:

A is CH_2;

B is CH_2 or S;

C is CH_2 or NH;

R_1 is selected from the group consisting of 3-phenylpropyl and 3-(3-pyridyl)propyl; and

R_2 is selected from the group consisting of 1,1-dimethylpropyl, cyclohexyl, and *tert*-butyl.

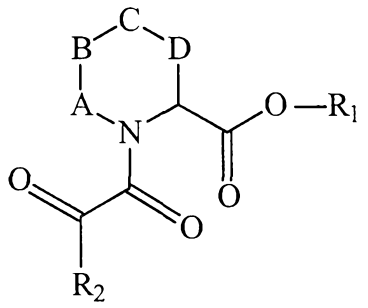
Specific examples of this embodiment are presented in TABLE D.

TABLE D

No.	A	B	C	R_1	R_2
80	CH_2	S	CH_2	3-phenylpropyl	1,1-dimethylpropyl
81	CH_2	S	CH_2	3-(3-pyridyl)propyl	1,1-dimethylpropyl
82	CH_2	S	CH_2	3-phenylpropyl	cyclohexyl
83	CH_2	S	CH_2	3-phenylpropyl	*tert*-butyl
84	CH_2	CH_2	NH	3-phenylpropyl	1,1-dimethylpropyl
85	CH_2	CH_2	NH	3-phenylpropyl	cyclohexyl
86	CH_2	CH_2	NH	3-phenylpropyl	*tert*-butyl

FORMULA VIII

In a further embodiment of this invention, the non-immunosuppressive neuroimmunophilin FKBP ligand may be a compound of formula VIII



VIII

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

A, B, C and D are independently CH_2, O, S, SO, SO_2, NH or NR_1;

R_1 is C_1-C_5 straight or branched chain alkyl or C_2-C_5 straight or branched chain alkenyl, which is substituted with one or more substituent(s) independently selected from the group consisting of $(Ar_1)_n$ and C_1-C_6 straight or branched chain alkyl or C_2-C_6 straight or branched chain alkenyl

substituted with $(Ar_1)_n$;

n is 1 or 2;

R_2 is either 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, or Ar_1; and

Ar_1 is an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring, wherein the ring is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of halo, hydroxyl, nitro, trifluoromethyl, 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, and amino; wherein the individual ring size is 5-8 members; and wherein the heterocyclic ring contains 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S.

In a particularly preferred embodiment of formula VIII compounds:

A is CH_2;

B is CH_2;

C is S, O or NH;

D is CH_2;

R_1 is selected from the group consisting of 3-phenylpropyl and (3,4,5-trimethoxy)phenylpropyl; and

R_2 is selected from the group consisting of 1,1-dimethylpropyl, cyclohexyl, *tert*-butyl, phenyl, and 3,4,5-trimethoxyphenyl.

Specific examples of this embodiment are presented in TABLE E.

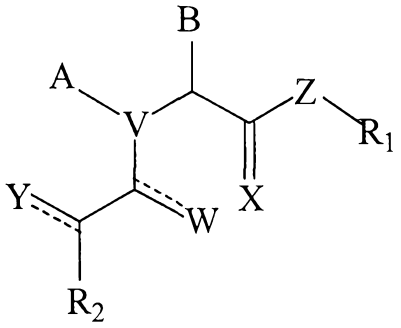
TABLE E

No.	A	B	C	D	R_1	R_2
87	CH_2	CH_2	S	CH_2	3-phenylpropyl	1,1-dimethylpropyl

No.	A	B	C	D	R_1	R_2
88	CH_2	CH_2	O	CH_2	3-phenylpropyl	1,1-dimethylpropyl
89	CH_2	CH_2	S	CH_2	3-phenylpropyl	cyclohexyl
90	CH_2	CH_2	O	CH_2	3-phenylpropyl	cyclohexyl
91	CH_2	CH_2	S	CH_2	3-phenylpropyl	phenyl
92	CH_2	CH_2	O	CH_2	3-phenylpropyl	phenyl
93	CH_2	CH_2	NH	CH_2	3-phenylpropyl	1,1-dimethylpropyl
94	CH_2	CH_2	NH	CH_2	3-phenylpropyl	phenyl

FORMULA IX

Additionally, the non-immunosuppressive neuroimmunophilin FKBP ligand may be a compound of formula IX



IX

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

V is C, N, or S;

A and B, together with V and the carbon atom to which they are respectively attached, form a 5-7 membered saturated or unsaturated heterocyclic ring which may contain, in addition to V, one or more heteroatom(s) independently selected from the group consisting of O, S, SO, SO_2, N, NH, and NR;

R is either C_1-C_9 straight or branched chain alkyl, C_2-C_9 straight or branched chain alkenyl, C_3-C_9 cycloakyl, C_5-C_7 cycloalkenyl, or Ar_3, wherein R is either unsubstituted or substituted with one or more substituent(s) independently

selected from the group consisting of halo, haloalkyl, carbonyl, carboxy, hydroxy, nitro, trifluoromethyl, 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, thioalkyl, alkylthio, sulfhydryl, amino, alkylamino, aminoalkyl, aminocarboxyl, and Ar_4;

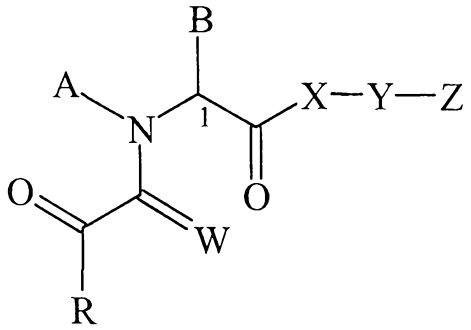
Ar_3 and Ar_4 are independently an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring; wherein the individual ring size is 5-8 members; wherein said heterocyclic ring contains 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S; and

R_1, R_2, W, X, Y, and Z are as defined in Formula VI above.

III. N-OXIDES OF HETEROCYCLIC ESTERS, AMIDES, THIOESTERS AND KETONES

FORMULA X

The non-immunosuppressive neuroimmunophilin FKBP ligand may further be a compound of formula X



X

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

A and B, together with the nitrogen and carbon atoms to which they are respectively attached, form a 5-7 membered saturated or unsaturated heterocyclic ring containing one or more heteroatom(s) independently selected from the group consisting of CH, CH_2, O, S, SO, SO_2, N, NH, and NR_1;

W is O, S, CH_2, or H_2;

R is C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, C_3-C_8 cycloalkyl, C_5-C_7 cycloalkenyl, or Ar_1, which is optionally substituted with one or more substituent(s) independently selected from the group consisting of C_1-C_4 alkyl, C_2-C_4 alkenyl, hydroxy, C_3-C_8 cycloalkyl, C_5-C_7 cycloalkenyl, and Ar_2;

Ar_1 and Ar_2 are independently selected from the group consisting of 1-napthyl, 2-napthyl, 1-indolyl, 2-indolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl and phenyl, having one or more substituent(s) independently selected from the group consisting of hydrogen, halo, hydroxy, nitro, trifluoromethyl, C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, C_2-C_4 alkenyloxy, phenoxy, benzyloxy, and amino;

X is O, NH, NR_1, S, CH, CR_1, or CR_1R_3;

Y is a direct bond, C_1-C_6 straight or branched chain alkyl, or C_2-C_6 straight or branched chain alkenyl; wherein said alkyl or alkenyl is optionally substituted with one or more substituent(s) independently selected from the group consisting of C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, C_3-C_8 cycloalkyl, C_5-C_7 cycloalkenyl, hydroxy, carbonyl oxygen, and Ar; wherein said alkyl, alkenyl, cycloalkyl, cycloalkenyl, or Ar is optionally substituted with C_1-C_4 alkyl, C_2-C_4 alkenyl, hydroxy, or carbonyl oxygen; wherein any carbon atom of said alkyl, alkenyl, cycloalkyl, cycloalkenyl, or Ar is optionally replaced with O, NH, NR_2, S, SO, or SO_2;

R_2 is selected from the group consisting of hydrogen, C_1-C_4 straight or branched chain alkyl, C_3-C_4 straight or branched chain alkenyl or alkynyl, and C_1-C_4 bridging alkyl wherein a bridge is formed between the nitrogen and a carbon atom of said alkyl or alkenyl chain containing said heteroatom to form a ring, wherein said ring is optionally fused to an Ar group;

Z is an aromatic amine or a tertiary amine oxidized to a corresponding N-oxide;

said aromatic amine is selected from the group consisting of pyridyl, pyrimidyl, quinolinyl, or isoquinolinyl, which is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of halo, hydroxy, nitro, trifluoromethyl, 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, and amino;

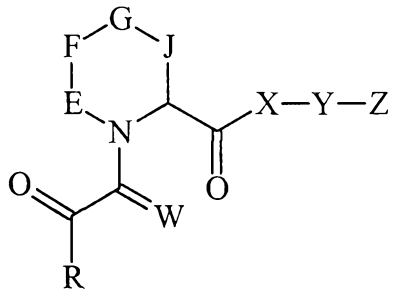
said tertiary amine is $NR_4R_5R_6$, wherein R_4, R_5, and R_6 are independently selected from the group consisting of C_1-C_6 straight or branched chain alkyl or C_2-C_6 straight or branched chain alkenyl optionally substituted with one or more substituent(s) independently selected from the group consisting of C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, C_3-C_8 cycloalkyl, C_5-C_7 cycloalkenyl, hydroxy, carbonyl oxygen, and Ar; wherein said alkyl, alkenyl, cycloalkyl, cycloalkenyl, or Ar is optionally substituted with C_1-C_4 alkyl, C_2-C_4 alkenyl, hydroxy, or carbonyl oxygen; wherein any carbon atom of said alkyl, alkenyl, cycloalkyl, cycloalkenyl, or Ar is optionally replaced with O, NH, NR_1, S, SO, or SO_2;

Ar is selected from the group consisting of pyrrolidinyl, pyridyl, pyrimidyl, pyrazyl, pyridazyl, quinolinyl, and isoquinolinyl; and

R_1 and R_3 are independently hydrogen, C_1-C_4 straight or branched chain alkyl, C_3-C_4 straight or branched chain alkenyl or alkynyl, or Y-Z.

FORMULA XI

Moreover, the non-immunosuppressive neuroimmunophilin FKBP ligand may be a compound of formula XI



XI

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

E, F, G and J are independently CH_2, O, S, SO, SO_2, NH or NR_1;

W is O, S, CH_2, or H_2;

R is C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, C_3-C_8 cycloalkyl, C_5-C_7 cycloalkenyl, or Ar_1, which is optionally substituted with one or more substituent(s) independently selected from the group consisting of C_1-C_4 alkyl, C_2-C_4 alkenyl, hydroxy, C_3-C_8 cycloalkyl, C_5-C_7 cycloalkenyl, and Ar_1;

Ar_1 is selected from the group consisting of 1-napthyl, 2-napthyl, 1-indolyl, 2-indolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, and phenyl, having one or more substituent(s) independently selected from the group consisting of hydrogen, halo, hydroxy, nitro, trifluoromethyl, C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, C_2-C_4 alkenyloxy, phenoxy, benzyloxy, and amino;

X is O, NH, NR_1, S, CH, CR_1, or CR_1R_3;

Y is a direct bond, C_1-C_6 straight or branched chain alkyl, or C_2-C_6 straight or branched chain alkenyl; wherein said alkyl or alkenyl is optionally substituted with one or more substituent(s) independently selected from the group consisting of C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, C_3-C_8 cycloalkyl, C_5-C_7 cycloalkenyl, hydroxy, carbonyl oxygen, and Ar; wherein said alkyl, alkenyl, cycloalkyl, cycloalkenyl, or Ar is optionally

substituted with C_1-C_4 alkyl, C_2-C_4 alkenyl, hydroxy, or carbonyl oxygen; wherein any carbon atom of said alkyl, alkenyl, cycloalkyl, cycloalkenyl, or Ar is optionally replaced with O, NH, NR_2, S, SO, or SO_2;

R_2 is selected from the group consisting of hydrogen, C_1-C_4 straight or branched chain alkyl, C_3-C_4 straight or branched chain alkenyl or alkynyl, and C_1-C_4 bridging alkyl wherein a bridge is formed between the nitrogen and a carbon atom of said alkyl or alkenyl chain containing said heteroatom to form a ring, wherein said ring is optionally fused to an Ar group;

Z is an aromatic amine or a tertiary amine oxidized to a corresponding N-oxide;

said aromatic amine is pyridyl, pyrimidyl, quinolinyl, and isoquinolinyl, which is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of halo, hydroxy, nitro, trifluoromethyl, 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, and amino;

said tertiary amine is $NR_4R_5R_6$, wherein R_4, R_5, and R_6 are independently selected from the group consisting of C_1-C_6 straight or branched chain alkyl and C_2-C_6 straight or branched chain alkenyl; wherein said alkyl or alkenyl is optionally substituted with one or more substituent(s) independently selected from the group consisting of C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, C_3-C_8 cycloalkyl, C_5-C_7 cycloalkenyl, hydroxy, carbonyl oxygen, and Ar; wherein said alkyl, alkenyl, cycloalkyl, cycloalkenyl, or Ar is optionally substituted with C_1-C_4 alkyl, C_2-C_4 alkenyl, hydroxy, or carbonyl oxygen; wherein any carbon atom of said alkyl, alkenyl, cycloalkyl, cycloalkenyl, or Ar is optionally replaced with O, NH, NR_1, S, SO, or SO_2;

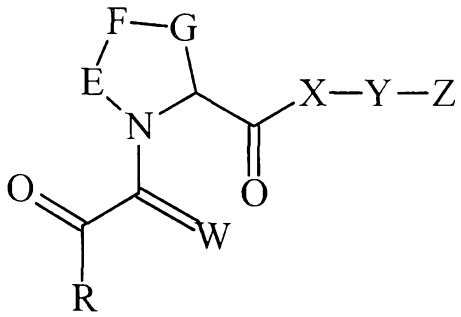
Ar is selected from the group consisting of

pyrrolidinyl, pyridyl, pyrimidyl, pyrazyl, pyridazyl, quinolinyl, and isoquinolinyl; and

R_1 and R_3 are independently hydrogen, C_1-C_4 straight or branched chain alkyl, C_3-C_4 straight or branched chain alkenyl or alkynyl, or Y-Z.

FORMULA XII

Furthermore, the non-immunosuppressive neuroimmunophilin FKBP ligand may be a compound of formula XII



XII

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

E, F, and G are independently CH_2, O, S, SO, SO_2, NH or NR_1;

W is O, S, CH_2, or H_2;

R is C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, C_3-C_8 cycloalkyl, C_5-C_7 cycloalkenyl, or Ar_1, which is optionally substituted with one or more substituent(s) independently selected from the group consisting of C_1-C_4 alkyl, C_2-C_4 alkenyl, hydroxy, C_3-C_8 cycloalkyl, C_5-C_7 cycloalkenyl, and Ar_1;

Ar_1 is selected from the group consisting of 1-napthyl, 2-napthyl, 1-indolyl, 2-indolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl and phenyl, having one or more substituent(s) independently selected from the group consisting of hydrogen, halo, hydroxy, nitro, trifluoromethyl, C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, C_2-C_4 alkenyloxy, phenoxy,

benzyloxy, and amino;

X is O, NH, NR_1, S, CH, CR_1, or CR_1R_3;

Y is a direct bond, C_1-C_6 straight or branched chain alkyl, or C_2-C_6 straight or branched chain alkenyl; wherein said alkyl or alkenyl is optionally substituted with one or more substituent(s) independently selected from the group consisting of C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, C_3-C_8 cycloalkyl, C_5-C_7 cycloalkenyl, hydroxy, carbonyl oxygen, and Ar; wherein said alkyl, alkenyl, cycloalkyl, cycloalkenyl, or Ar is optionally substituted with C_1-C_4 alkyl, C_2-C_4 alkenyl, hydroxy, or carbonyl oxygen; wherein any carbon atom of said alkyl, alkenyl, cycloalkyl, cycloalkenyl, or Ar is optionally replaced with O, NH, NR_2, S, SO, or SO_2;

R_2 is selected from the group consisting of hydrogen, C_1-C_4 straight or branched chain alkyl, C_3-C_4 straight or branched chain alkenyl or alkynyl, and C_1-C_4 bridging alkyl wherein a bridge is formed between the nitrogen and a carbon atom of said alkyl or alkenyl chain containing said heteroatom to form a ring, wherein said ring is optionally fused to an Ar group;

Z is an aromatic amine or a tertiary amine oxidized to a corresponding N-oxide;

said aromatic amine is pyridyl, pyrimidyl, quinolinyl, or isoquinolinyl, which is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of halo, hydroxy, nitro, trifluoromethyl, 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, and amino;

said tertiary amine is $NR_4R_5R_6$, wherein R_4, R_5, and R_6 are independently selected from the group consisting of C_1-C_6 straight or branched chain alkyl and C_2-C_6 straight or branched chain alkenyl; wherein said alkyl or alkenyl is optionally substituted with one or more substituent(s)

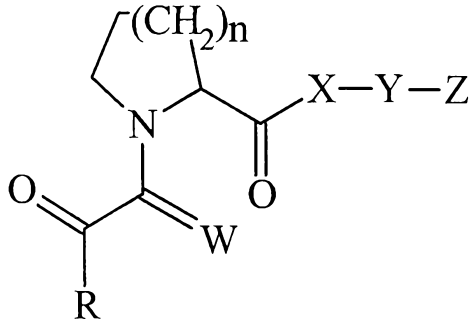
independently selected from the group consisting of C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, C_3-C_8 cycloalkyl, C_5-C_7 cycloalkenyl, hydroxy, carbonyl oxygen, and Ar; wherein said alkyl, alkenyl, cycloalkyl, cycloalkenyl, or Ar is optionally substituted with C_1-C_4 alkyl, C_2-C_4 alkenyl, hydroxy, or carbonyl oxygen; wherein any carbon atom of said alkyl, alkenyl, cycloalkyl, cycloalkenyl, or Ar is optionally replaced with O, NH, NR_1, S, SO, or SO_2;

Ar is selected from the group consisting of pyrrolidinyl, pyridyl, pyrimidyl, pyrazyl, pyridazyl, quinolinyl, and isoquinolinyl; and

R_1 and R_3 are independently hydrogen, C_1-C_4 straight or branched chain alkyl, C_3-C_4 straight or branched chain alkenyl or alkynyl, or Y-Z.

FORMULA XIII

The non-immunosuppressive neuroimmunophilin FKBP ligand may also be a compound of formula XIII



XIII

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

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

W is O, S, CH_2, or H_2;

R is C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, C_3-C_8 cycloalkyl, C_5-C_7 cycloalkenyl, or Ar_1, which is optionally substituted with one or more substituent(s) independently selected from the

group consisting of C_1-C_4 alkyl, C_2-C_4 alkenyl, hydroxy, C_3-C_8 cycloalkyl, C_5-C_7 cycloalkenyl, and Ar_1;

Ar_1 is selected from the group consisting of 1-napthyl, 2-napthyl, 1-indolyl, 2-indolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl and phenyl, having one or more substituent(s) independently selected from the group consisting of hydrogen, halo, hydroxy, nitro, trifluoromethyl, C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, C_2-C_4 alkenyloxy, phenoxy, benzyloxy, and amino;

X is O, NH, NR_1, S, CH, CR_1, or CR_1R_3;

Y is a direct bond, C_1-C_6 straight or branched chain alkyl, or C_2-C_6 straight or branched chain alkenyl; wherein said alkyl or alkenyl is optionally substituted with one or more substituent(s) independently selected from the group consisting of C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, C_3-C_8 cycloalkyl, C_5-C_7 cycloalkenyl, hydroxy, carbonyl oxygen, and Ar; wherein said alkyl, alkenyl, cycloalkyl, cycloalkenyl, or Ar is optionally substituted with C_1-C_4 alkyl, C_2-C_4 alkenyl, hydroxy, or carbonyl oxygen; wherein any carbon atom of said alkyl, alkenyl, cycloalkyl, cycloalkenyl, or Ar is optionally replaced with O, NH, NR_2, S, SO, or SO_2;

R_2 is selected from the group consisting of hydrogen, C_1-C_4 straight or branched chain alkyl, C_3-C_4 straight or branched chain alkenyl or alkynyl, and C_1-C_4 bridging alkyl wherein a bridge is formed between the nitrogen and a carbon atom of said alkyl or alkenyl chain containing said heteroatom to form a ring, wherein said ring is optionally fused to an Ar group;

Z is an aromatic amine or a tertiary amine oxidized to a corresponding N-oxide;

said aromatic amine is pyridyl, pyrimidyl, quinolinyl, or isoquinolinyl, which is either unsubstituted or substituted with one or more substituent(s) independently

selected from the group consisting of halo, hydroxy, nitro, trifluoromethyl, 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, and amino;

said tertiary amine is $NR_4R_5R_6$, wherein R_4, R_5, and R_6 are independently selected from the group consisting of C_1-C_6 straight or branched chain alkyl and C_2-C_6 straight or branched chain alkenyl; wherein said alkyl or alkenyl is optionally substituted with one or more substituent(s) independently selected from the group consisting of C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, C_3-C_8 cycloalkyl, C_5-C_7 cycloalkenyl, hydroxy, carbonyl oxygen, and Ar; wherein said alkyl, alkenyl, cycloalkyl, cycloalkenyl, or Ar is optionally substituted with C_1-C_4 alkyl, C_2-C_4 alkenyl, hydroxy, or carbonyl oxygen; wherein any carbon atom of said alkyl, alkenyl, cycloalkyl, cycloalkenyl, or Ar is optionally replaced with O, NH, NR_1, S, SO, or SO_2;

Ar is selected from the group consisting of pyrrolidinyl, pyridyl, pyrimidyl, pyrazyl, pyridazyl, quinolinyl, and isoquinolinyl; and

R_1 and R_3 hydrogen, C_1-C_4 straight or branched chain alkyl, C_3-C_4 straight or branched chain alkenyl or alkynyl, or Y-Z.

Examples of the compounds of formula XIII when W is O are presented in TABLE VI.

TABLE VI

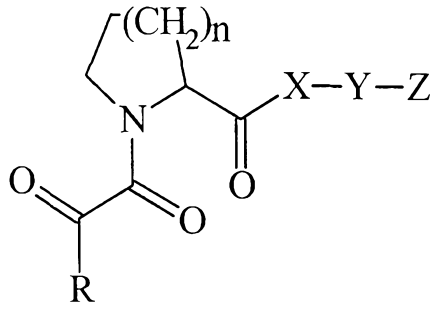


TABLE VI continued

No.	n	X	Y	Z	R
95	1	O	$(CH_2)_3$	3-Pyridyl N-oxide	1,1-dimethylpropyl
96	1	O	$(CH_2)_3$	2-Pyridyl N-oxide	1,1-dimethylpropyl
97	1	O	$(CH_2)_3$	4-Pyridyl N-oxide	1,1-dimethylpropyl
98	1	O	$(CH_2)_3$	2-Quinolyl N-oxide	1,1-dimethylpropyl
99	1	O	$(CH_2)_3$	3-Quinolyl N-oxide	1,1-dimethylpropyl
100	1	O	$(CH_2)_3$	4-Quinolyl N-oxide	1,1-dimethylpropyl

Preferred compounds of formula XIII may be selected from the group consisting of:

3-(2-Pyridyl)-1-propyl(2*S*)-1-(1,1-Dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate, N-oxide;

3-(3-Pyridyl)-1-propyl(2*S*)-1-(1,1-Dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate, N-oxide;

3-(4-Pyridyl)-1-propyl(2*S*)-1-(1,1-Dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate, N-oxide;

3-(2-Quinolyl)-1-propyl(2*S*)-1-(1,1-Dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate, N-oxide;

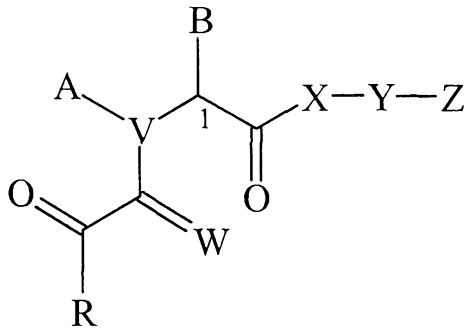
3-(3-Quinolyl)-1-propyl(2*S*)-1-(1,1-Dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate, N-oxide;

3-(4-Quinolyl)-1-propyl(2*S*)-1-(1,1-Dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate, N-oxide; and

pharmaceutically acceptable salts, esters, and solvates thereof.

FORMULA XIV

Additionally, the non-immunosuppressive neuroimmunophilin FKBP ligand may be a compound of formula XIV



XIV

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

V is C, N, or S;

A and B, together with V and the carbon atom to which they are respectively attached, form a 5-7 membered saturated or unsaturated heterocyclic ring which may contain, in addition to V, one or more heteroatom(s) independently selected from the group consisting of O, S, SO, SO_2, N, NH, and NR_7;

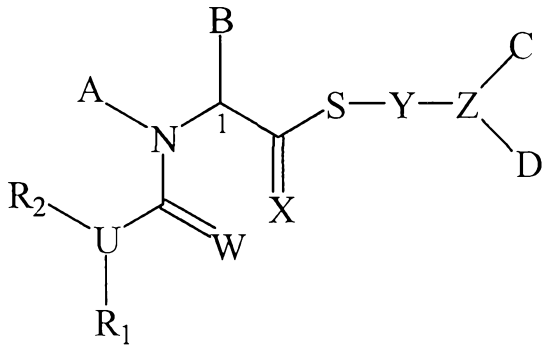
R_7 is either C_1-C_9 straight or branched chain alkyl, C_2-C_9 straight or branched chain alkenyl, C_3-C_9 cycloalkyl, C_5-C_7 cycloalkenyl, or Ar_3, wherein R_7 is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of halo, haloalkyl, carbonyl, carboxy, hydroxy, nitro, trifluoromethyl, 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, thioalkyl, alkylthio, sulfhydryl, amino, alkylamino, aminoalkyl, aminocarboxyl, and Ar_4;

Ar_3 and Ar_4 are independently an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring; wherein the individual ring size is 5-8 members; wherein said heterocyclic ring contains 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S; and

R, W, X, Y, and Z are as defined in Formula X above.

IV. N-LINKED UREAS AND CARBAMATES OF HETEROCYCLIC THIOESTERS

The non-immunosuppressive neuroimmunophilin FKBP ligand may further be a compound of formula XV



XV

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

A and B, together with the nitrogen and carbon atoms to which they are respectively attached, form a 5-7 membered saturated or unsaturated heterocyclic ring which may contain, in addition to the nitrogen atom, one or more additional heteroatom(s) independently selected from the group consisting of O, S, SO, SO_2, N, NH, and NR_3;

X is either O or S;

Y is a direct bond, C_1-C_6 straight or branched chain alkyl, or C_2-C_6 straight or branched chain alkenyl, wherein any carbon atom of said alkyl or alkenyl is optionally substituted in one or more position(s) with amino, halo, haloalkyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, or oxygen to form a carbonyl, or wherein any carbon atom of said alkyl or alkenyl is optionally replaced with O, NH, NR_3, S, SO, or SO_2;

R_3 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 a bridge is formed between the nitrogen and a carbon atom of said alkyl or alkenyl chain containing said

heteroatom to form a ring, wherein said ring is optionally fused to an Ar group;

Ar is an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring, wherein the ring is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of alkylamino, amido, amino, aminoalkyl, azo, benzyloxy, C_1-C_9 straight or branched chain alkyl, C_1-C_9 alkoxy, C_2-C_9 alkenyloxy, C_2-C_9 straight or branched chain alkenyl, C_3-C_8 cycloalkyl, C_5-C_7 cycloalkenyl, carbonyl, carboxy, cyano, diazo, ester, formanilido, halo, haloalkyl, hydroxy, imino, isocyano, isonitrilo, nitrilo, nitro, nitroso, phenoxy, sulfhydryl, sulfonylsulfoxy, thio, thioalkyl, thiocarbonyl, thiocyano, thioester, thioformamido, trifluoromethyl, and carboxylic and heterocyclic moieties, including alicyclic and aromatic structures; wherein the individual ring size is 5-8 members; wherein said heterocyclic ring contains 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S; and wherein said aromatic or tertiary alkyl amine is optionally oxidized to a corresponding N-oxide;

Z is a direct bond, C_1-C_6 straight or branched chain alkyl, or C_2-C_6 straight or branched chain alkenyl, wherein any carbon atom of said alkyl or alkenyl is optionally substituted in one or more position(s) with amino, halo, haloalkyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, or oxygen to form a carbonyl, or wherein any carbon atom of said alkyl or alkenyl is optionally replaced with O, NH, NR_3, S, SO, or SO_2;

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 said alkyl or alkenyl is optionally substituted with one or more substituent(s) independently selected from the group consisting of C_3-C_8 cycloalkyl, C_5-C_7

cycloalkenyl, hydroxy, carbonyl oxygen, and Ar; wherein said alkyl, alkenyl, cycloalkyl or cycloalkenyl is 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, sulfhydryl, thioalkyl, or sulfonyl; wherein any carbon atom of said alkyl or alkenyl is optionally substituted in one or more position(s) with oxygen to form a carbonyl; or wherein any carbon atom of said alkyl or alkenyl is optionally replaced with O, NH, NR_3, S, SO, or SO_2;

W is O or S; and

U is either O or N, provided that:

when U is O, then R_1 is a lone pair of electrons and R_2 is selected from the group consisting of Ar, C_3-C_8 cycloalkyl, C_1-C_6 straight or branched chain alkyl, and C_2-C_6 straight or branched chain alkenyl, wherein said alkyl or alkenyl is optionally substituted with one or more substituent(s) independently selected from the group consisting of Ar and C_3-C_8 cycloalkyl; and

when U is N, then R_1 and R_2 are independently selected from the group consisting of hydrogen, Ar, C_3-C_8 cycloalkyl, C_1-C_6 straight or branched chain alkyl, and C_2-C_6 straight or branched chain alkenyl, wherein said alkyl or alkenyl is substituted with one or more substituent(s) independently selected from the group consisting of Ar and C_3-C_8 cycloalkyl; or R_1 and R_2 are taken together to form a heterocyclic 5 or 6 membered ring selected from the group consisting of pyrrolidine, imidazolidine, pyrazolidine, piperidine, and piperazine.

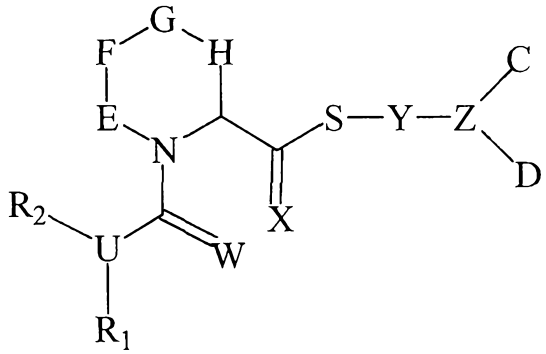
Useful carbo- and heterocyclic rings include without limitation phenyl, benzyl, naphthyl, indenyl, azulenyl, fluorenyl, anthracenyl, indolyl, isoindolyl, indolinyl, benzofuranyl, benzothiophenyl, indazolyl, benzimidazolyl, benzthiazolyl, tetrahydrofuranyl, tetrahydropyranyl, pyridyl, pyrrolyl, pyrrolidinyl, pyridinyl, pyrimidinyl, purinyl,

quinolinyl, isoquinolinyl, tetrahydroquinolinyl, quinolizinyl, furyl, thiophenyl, imidazolyl, oxazolyl, benzoxazolyl, thiazolyl, isoxazolyl, isotriazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, trithianyl, indolizinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, thienyl, tetrahydroisoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, naphthyridinyl, pteridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, and phenoxazinyl.

In a preferred embodiment of formula XV, Ar is selected from the group consisting of phenyl, benzyl, naphthyl, indolyl, pyridyl, pyrrolyl, pyrrolidinyl, pyridinyl, pyrimidinyl, purinyl, quinolinyl, isoquinolinyl, furyl, fluorenyl, thiophenyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, and thienyl.

FORMULA XVI

Moreover, the non-immunosuppressive neuroimmunophilin FKBP ligand may be a compound of formula XVI



XVI

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

E, F, G and J are independently CH_2, O, S, SO, SO_2, NH, or NR_3;

X is either O or S;

Y is a direct bond, C_1-C_6 straight or branched chain alkyl, or C_2-C_6 straight or branched chain alkenyl, wherein

any carbon atom of said alkyl or alkenyl is optionally substituted in one or more position(s) with amino, halo, haloalkyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, or oxygen to form a carbonyl, or wherein any carbon atom of said alkyl or alkenyl is optionally replaced with O, NH, NR_3, S, SO, or SO_2;

R_3 is selected from the group consisting of hydrogen, C_1-C_4 straight or branched chain alkyl, C_3-C_4 straight or branched chain alkenyl or alkynyl, and C_1-C_4 bridging alkyl wherein a bridge is formed between the nitrogen and a carbon atom of said alkyl or alkenyl chain containing said heteroatom to form a ring, wherein said ring is optionally fused to an Ar group;

Ar is an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring, wherein the ring is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of alkylamino, amido, amino, aminoalkyl, azo, benzyloxy, C_1-C_9 straight or branched chain alkyl, C_1-C_9 alkoxy, C_2-C_9 alkenyloxy, C_2-C_9 straight or branched chain alkenyl, C_3-C_8 cycloalkyl, C_5-C_7 cycloalkenyl, carbonyl, carboxy, cyano, diazo, ester, formanilido, halo, haloalkyl, hydroxy, imino, isocyano, isonitrilo, nitrilo, nitro, nitroso, phenoxy, sulfhydryl, sulfonylsulfoxy, thio, thioalkyl, thiocarbonyl, thiocyano, thioester, thioformamido, trifluoromethyl, and carboxylic and heterocyclic moieties, including alicyclic and aromatic structures; wherein the individual ring size is 5-8 members; wherein said heterocyclic ring contains 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S; and wherein said aromatic or tertiary alkyl amine is optionally oxidized to a corresponding N-oxide;

Z is a direct bond, C_1-C_6 straight or branched chain alkyl, or C_2-C_6 straight or branched chain alkenyl, wherein

any carbon atom of said alkyl or alkenyl is optionally substituted in one or more position(s) with amino, halo, haloalkyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, or oxygen to form a carbonyl, or wherein any carbon atom of said alkyl or alkenyl is optionally replaced with O, NH, NR_3, S, SO, or SO_2;

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 said alkyl or alkenyl is optionally substituted with one or more substituent(s) independently selected from the group consisting of C_3-C_8 cycloalkyl, C_5-C_7 cycloalkenyl, hydroxy, carbonyl oxygen, and Ar; wherein said alkyl, alkenyl, cycloalkyl or cycloalkenyl is 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, sulfhydryl, thioalkyl, or sulfonyl; wherein any carbon atom of said alkyl or alkenyl is optionally substituted in one or more position(s) with oxygen to form a carbonyl; or wherein any carbon atom of said alkyl or alkenyl is optionally replaced with O, NH, NR_3, S, SO, or SO_2;

W is O or S; and

U is either O or N, provided that:

when U is O, then R_1 is a lone pair of electrons and R_2 is selected from the group consisting of Ar, C_3-C_8 cycloalkyl, C_1-C_6 straight or branched chain alkyl, and C_2-C_6 straight or branched chain alkenyl, wherein said alkyl or alkenyl is optionally substituted with one or more substituent(s) independently selected from the group consisting of Ar and C_3-C_8 cycloalkyl; and

when U is N, then R_1 and R_2 are independently selected from the group consisting of hydrogen, Ar, C_3-C_8 cycloalkyl, C_1-C_6 straight or branched chain alkyl, and C_2-C_6 straight or branched chain alkenyl, wherein

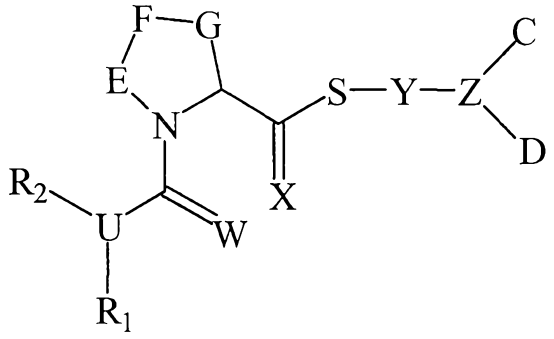
said alkyl or alkenyl is optionally substituted with one or more substituent(s) independently selected from the group consisting of Ar and C_3-C_8 cycloalkyl; or R_1 and R_2 are taken together to form a heterocyclic 5 or 6 membered ring selected from the group consisting of pyrrolidine, imidazolidine, pyrazolidine, piperidine, and piperazine.

Useful carbo- and heterocyclic rings include without limitation phenyl, benzyl, naphthyl, indenyl, azulenyl, fluorenyl, anthracenyl, indolyl, isoindolyl, indolinyl, benzofuranyl, benzothiophenyl, indazolyl, benzimidazolyl, benzthiazolyl, tetrahydrofuranyl, tetrahydropyranyl, pyridyl, pyrrolyl, pyrrolidinyl, pyridinyl, pyrimidinyl, purinyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, quinolizinyl, furyl, thiophenyl, imidazolyl, oxazolyl, benzoxazolyl, thiazolyl, isoxazolyl, isotriazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, trithianyl, indolizinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, thienyl, tetrahydroisoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, naphthyridinyl, pteridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, and phenoxazinyl.

In a preferred embodiment of formula XVI, 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.

FORMULA XVII

The non-immunosuppressive neuroimmunophilin FKBP ligand may also be a compound of formula XVII



XVII

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

E, F, and G are independently CH_2, O, S, SO, SO_2, NH, and NR_3;

X is either O or S;

Y is a direct bond, C_1-C_6 straight or branched chain alkyl, or C_2-C_6 straight or branched chain alkenyl, wherein any carbon atom of said alkyl or alkenyl is optionally substituted in one or more position(s) with amino, halo, haloalkyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, or oxygen to form a carbonyl, or wherein any carbon atom of said alkyl or alkenyl is optionally replaced with O, NH, NR_3, S, SO, or SO_2;

R_3 is selected from the group consisting of hydrogen, C_1-C_4 straight or branched chain alkyl, C_3-C_4 straight or branched chain alkenyl or alkynyl, and C_1-C_4 bridging alkyl wherein a bridge is formed between the nitrogen and a carbon atom of said alkyl or alkenyl chain containing said heteroatom to form a ring, wherein said ring is optionally fused to an Ar group;

Ar is an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring, wherein the ring is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of alkylamino, amido, amino, aminoalkyl, azo, benzyloxy, C_1-C_9 straight or branched chain alkyl, C_1-C_9 alkoxy, C_2-C_9

alkenyloxy, C_2-C_9 straight or branched chain alkenyl, C_3-C_8 cycloalkyl, C_5-C_7 cycloalkenyl, carbonyl, carboxy, cyano, diazo, ester, formanilido, halo, haloalkyl, hydroxy, imino, isocyano, isonitrilo, nitrilo, nitro, nitroso, phenoxy, sulfhydryl, sulfonylsulfoxy, thio, thioalkyl, thiocarbonyl, thiocyano, thioester, thioformamido, trifluoromethyl, and carboxylic and heterocyclic moieties, including alicyclic and aromatic structures; wherein the individual ring size is 5-8 members; wherein said heterocyclic ring contains 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S; and wherein said aromatic or tertiary alkyl amine is optionally oxidized to a corresponding N-oxide;

Z is a direct bond, C_1-C_6 straight or branched chain alkyl, or C_2-C_6 straight or branched chain alkenyl, wherein any carbon atom of said alkyl or alkenyl is optionally substituted in one or more position(s) with amino, halo, haloalkyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, or oxygen to form a carbonyl, or wherein any carbon atom of said alkyl or alkenyl is optionally replaced with O, NH, NR_3, S, SO, or SO_2;

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 said alkyl or alkenyl is optionally substituted with one or more substituent(s) independently selected from the group consisting of C_3-C_8 cycloalkyl, C_5-C_7 cycloalkenyl, hydroxy, carbonyl oxygen, and Ar; wherein said alkyl, alkenyl, cycloalkyl or cycloalkenyl is 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, sulfhydryl, thioalkyl, or sulfonyl; wherein any carbon atom of said alkyl or alkenyl is optionally substituted in one or more position(s) with oxygen to form a carbonyl; or wherein

any carbon atom of said alkyl or alkenyl is optionally replaced with O, NH, NR_3, S, SO, or SO_2;

W is O or S; and

U is either O or N, provided that:

when U is O, then R_1 is a lone pair of electrons and R_2 is selected from the group consisting of Ar, C_3-C_8 cycloalkyl, C_1-C_6 straight or branched chain alkyl, and C_2-C_6 straight or branched chain alkenyl, wherein said alkyl or alkenyl is optionally substituted with one or more substituent(s) independently selected from the group consisting of Ar and C_3-C_8 cycloalkyl; and

when U is N, then R_1 and R_2 are independently selected from the group consisting of hydrogen, Ar, C_3-C_8 cycloalkyl, C_1-C_6 straight or branched chain alkyl, and C_2-C_6 straight or branched chain alkenyl, wherein said alkyl or alkenyl is optionally substituted with one or more substituent(s) independently selected from the group consisting of Ar and C_3-C_8 cycloalkyl; or R_1 and R_2 are taken together to form a heterocyclic 5 or 6 membered ring selected from the group consisting of pyrrolidine, imidazolidine, pyrazolidine, piperidine, and piperazine.

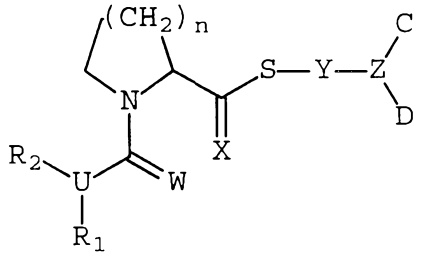
Useful carbo- and heterocyclic rings include without limitation phenyl, benzyl, naphthyl, indenyl, azulenyl, fluorenyl, anthracenyl, indolyl, isoindolyl, indolinyl, benzofuranyl, benzothiophenyl, indazolyl, benzimidazolyl, benzthiazolyl, tetrahydrofuranyl, tetrahydropyranyl, pyridyl, pyrrolyl, pyrrolidinyl, pyridinyl, pyrimidinyl, purinyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, quinolizinyl, furyl, thiophenyl, imidazolyl, oxazolyl, benzoxazolyl, thiazolyl, isoxazolyl, isotriazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, trithianyl, indolizinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, thienyl, tetrahydroisoquinolinyl, cinnolinyl, phthalazinyl,

quinazolinyl, quinoxalinyl, naphthyridinyl, pteridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, and phenoxazinyl.

In a preferred embodiment of formula XVII, 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.

FORMULA XVIII

The non-immunosuppressive neuroimmunophilin FKBP ligand may further be a compound of formula XVIII



XVIII

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

n is 1, 2 or 3;

X is either O or S;

Y is a direct bond, C_1-C_6 straight or branched chain alkyl, or C_2-C_6 straight or branched chain alkenyl, wherein any carbon atom of said alkyl or alkenyl is optionally substituted in one or more position(s) with amino, halo, haloalkyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, or oxygen to form a carbonyl, or wherein any carbon atom of said alkyl or alkenyl is optionally replaced with O, NH, NR_3, S, SO, or SO_2;

R_3 is selected from the group consisting of hydrogen, C_1-C_4 straight or branched chain alkyl, C_3-C_4 straight or branched chain alkenyl or alkynyl, and C_1-C_4 bridging alkyl wherein a bridge is formed between the nitrogen and a carbon

atom of said alkyl or alkenyl chain containing said heteroatom to form a ring, wherein said ring is optionally fused to an Ar group;

Ar is an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring, wherein the ring is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of alkylamino, amido, amino, aminoalkyl, azo, benzyloxy, C_1-C_9 straight or branched chain alkyl, C_1-C_9 alkoxy, C_2-C_9 alkenyloxy, C_2-C_9 straight or branched chain alkenyl, C_3-C_8 cycloalkyl, C_5-C_7 cycloalkenyl, carbonyl, carboxy, cyano, diazo, ester, formanilido, halo, haloalkyl, hydroxy, imino, isocyano, isonitrilo, nitrilo, nitro, nitroso, phenoxy, sulfhydryl, sulfonylsulfoxy, thio, thioalkyl, thiocarbonyl, thiocyano, thioester, thioformamido, trifluoromethyl, and carboxylic and heterocyclic moieties, including alicyclic and aromatic structures; wherein the individual ring size is 5-8 members; wherein said heterocyclic ring contains 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S; and wherein said aromatic or tertiary alkyl amine is optionally oxidized to a corresponding N-oxide;

Z is a direct bond, C_1-C_6 straight or branched chain alkyl, or C_2-C_6 straight or branched chain alkenyl, wherein any carbon atom of said alkyl or alkenyl is optionally substituted in one or more position(s) with amino, halo, haloalkyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, or oxygen to form a carbonyl, or wherein any carbon atom of said alkyl or alkenyl is optionally replaced with O, NH, NR_3, S, SO, or SO_2;

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 said alkyl or alkenyl is optionally substituted with one or more substituent(s) independently

selected from the group consisting of C_3-C_8 cycloalkyl, C_5-C_7 cycloalkenyl, hydroxy, carbonyl oxygen, and Ar; wherein said alkyl, alkenyl, cycloalkyl or cycloalkenyl is 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, sulfhydryl, thioalkyl, or sulfonyl; wherein any carbon atom of said alkyl or alkenyl is optionally substituted in one or more position(s) with oxygen to form a carbonyl; or wherein any carbon atom of said alkyl or alkenyl is optionally replaced with O, NH, NR_3, S, SO, or SO_2;

W is O or S; and

U is either O or N, provided that:

when U is O, then R_1 is a lone pair of electrons and R_2 is selected from the group consisting of Ar, C_3-C_8 cycloalkyl, C_1-C_6 straight or branched chain alkyl, and C_2-C_6 straight or branched chain or alkenyl, wherein said alkyl or alkenyl is optionally substituted with one or more substituent(s) independently selected from the group consisting of Ar and C_3-C_8 cycloalkyl; and

when U is N, then R_1 and R_2 are independently selected from the group consisting of hydrogen, Ar, C_3-C_8 cycloalkyl, C_1-C_6 straight or branched chain alkyl, and C_2-C_6 straight or branched chain alkenyl, wherein said alkyl or alkenyl is optionally substituted with one or more substituent(s) independently selected from the group consisting of Ar and C_3-C_8 cycloalkyl; or R_1 and R_2 are taken together to form a heterocyclic 5 or 6 membered ring selected from the group consisting of pyrrolidine, imidazolidine, pyrazolidine, piperidine, and piperazine.

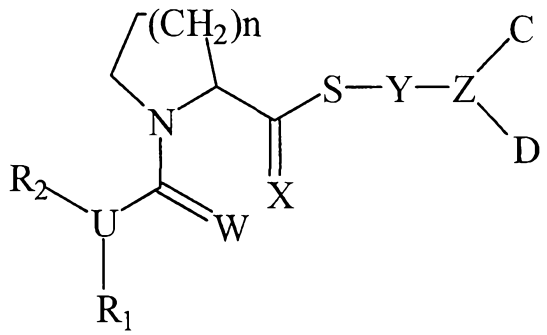
Useful carbo- and heterocyclic rings include without limitation phenyl, benzyl, naphthyl, indenyl, azulenyl, fluorenyl, anthracenyl, indolyl, isoindolyl, indolinyl, benzofuranyl, benzothiophenyl, indazolyl, benzimidazolyl,

benzthiazolyl, tetrahydrofuranyl, tetrahydropyranyl, pyridyl, pyrrolyl, pyrrolidinyl, pyridinyl, pyrimidinyl, purinyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, quinolizinyl, furyl, thiophenyl, imidazolyl, oxazolyl, benzoxazolyl, thiazolyl, isoxazolyl, isotriazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, trithianyl, indolizinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, thienyl, tetrahydroisoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, naphthyridinyl, pteridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, and phenoxazinyl.

In a preferred embodiment of formula XVIII, 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.

Exemplary compounds of formula XVIII are presented in TABLE VII.

TABLE VII



No.	n	W	Y	Z	C	D	R_1	R_2
101	1	O	$(CH_2)_2$	CH	3-Pyridyl	H	H	2-Methyl-butyl
102	1	O	$(CH_2)_2$	CH	3-Pyridyl	H	H	1,1-dimethyl-propyl

TABLE VII (continued)

No.	n	W	Y	Z	C	D	R_1	R_2
103	1	O	$(CH_2)_2$	CH	4-Methoxy-phenyl	H	H	1,1-dimethyl-propyl
104	1	O	CH_2	CH	Phenyl	H	H	1,1-dimethyl-propyl
105	1	S	$(CH_2)_2$	CH	4-Methoxy-phenyl	H	H	Cyclohexyl
106	1	O	$(CH_2)_2$	CH	3-Pyridyl	H	H	Cyclohexyl
107	1	S	$(CH_2)_2$	CH	3-Pyridyl	H	H	Cyclohexyl
108	1	S	$(CH_2)_2$	CH	3-Pyridyl	H	H	1-Adamantyl
109	1	S	$(CH_2)_2$	CH	3-Pyridyl	H	H	1,1-dimethyl-propyl
110	1	O	$(CH_2)_2$	CH	Phenyl	Phenyl	H	1,1-dimethyl-propyl
111	2	O	$(CH_2)_2$	CH	Phenyl	H	H	1,1-dimethyl-propyl
112	2	O	$(CH_2)_2$	CH	Phenyl	H	H	Phenyl
113	2	O	Direct bond	CH	2-Phenyl-ethyl	2-Phenyl-ethyl	H	Phenyl
114	2	O	Direct bond	CH	2-Phenyl-ethyl	2-Phenyl-ethyl	H	Cyclohexyl
115	2	S	Direct bond	CH	2-Phenyl-ethyl	2-Phenyl-ethyl	H	Cyclohexyl

TABLE VII (continued)

No.	n	W	Y	Z	C	D	R_1	R_2
116	2	O	$(CH_2)_2$	CH	4-Methoxy-phenyl	H	H	Cyclohexyl

The most preferred compounds of formula XVIII are selected from the group consisting of:

3-(3-Pyridyl)-1-propyl-2S-1-[(2-methylbutyl) carbamoyl]pyrrolidine-2-carboxylate;

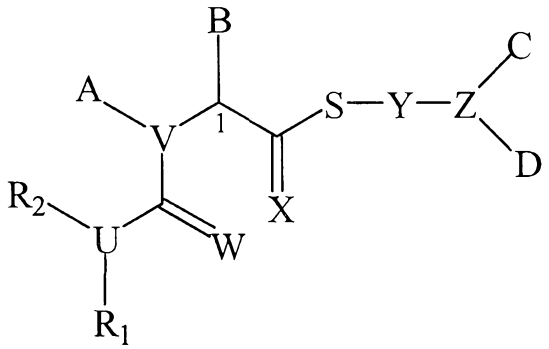
3-(3-Pyridyl)-1-propyl-2S-1-[(1',1'-Dimethylpropyl) carbamoyl]pyrrolidine-2-carboxylate;

3-(3-Pyridyl)-1-propyl-2S-1-[(cyclohexyl) thiocarbamoyl]pyrrolidine-2-carboxylate; and

pharmaceutically acceptable salts, esters, and solvates thereof.

FORMULA XIX

Additionally, the non-immunosuppressive neuroimmunophilin FKBP ligand may be a compound of formula XIX



XIX

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

V is C, N, or S;

Y is a direct bond, C_1-C_6 straight or branched chain alkyl, or C_2-C_6 straight or branched chain alkenyl, wherein any carbon atom of said alkyl or alkenyl is optionally

substituted in one or more position(s) with amino, halo, haloalkyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, or oxygen to form a carbonyl, or wherein any carbon atom of said alkyl or alkenyl is optionally replaced with O, NH, NR_3, S, SO, or SO_2;

R_3 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 a bridge is formed between the nitrogen and a carbon atom of said alkyl or alkenyl chain containing said heteroatom to form a ring, wherein said ring is optionally fused to an Ar group;

Ar is an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring, wherein the ring is either unsubstituted or substituted with one or more substituent(s); wherein the individual ring size is 5-8 members; wherein said heterocyclic ring contains 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S; and wherein said aromatic or tertiary alkyl amine is optionally oxidized to a corresponding N-oxide;

Z is a direct bond, C_1-C_6 straight or branched chain alkyl, or C_2-C_6 straight or branched chain alkenyl, wherein any carbon atom of said alkyl or alkenyl is optionally substituted in one or more position(s) with amino, halo, haloalkyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, or oxygen to form a carbonyl, or wherein any carbon atom of said alkyl or alkenyl is optionally replaced with O, NH, NR_3, S, SO, or SO_2;

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 said alkyl or alkenyl is optionally substituted with one or more substituent(s) independently selected from the group consisting of C_3-C_8 cycloalkyl, C_5-C_7

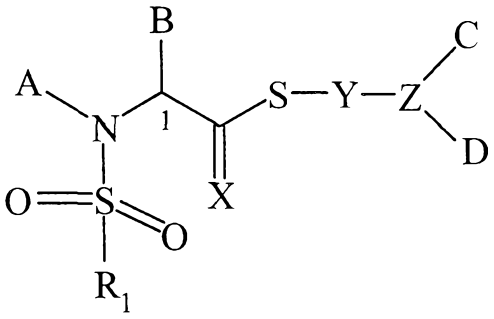
cycloalkenyl, hydroxy, carbonyl oxygen, and Ar; wherein said alkyl, alkenyl, cycloalkyl or cycloalkenyl is optionally substituted with C_1-C_6 alkyl, C_2-C_6 alkenyl, hydroxy, amino, halo, haloalkyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, or sulfonyl; wherein any carbon atom of said alkyl or alkenyl is optionally substituted in one or more position(s) with oxygen to form a carbonyl; or wherein any carbon atom of said alkyl or alkenyl is optionally replaced with O, NH, NR_3, S, SO, or SO_2; and

A, B, R_1, R_2, U, W, and X are as otherwise defined in formula XV.

V. N-LINKED SULFONAMIDES OF HETEROCYCLIC THIOESTERS

FORMULA XX

The non-immunosuppressive neuroimmunophilin FKBP ligand may further be a compound of formula XX



XX

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

A and B, together with the nitrogen and carbon atoms to which they are respectively attached, form a 5-7 membered saturated or unsaturated heterocyclic ring which may contain, in addition to the nitrogen atom, one or more heteroatom(s) independently selected from the group consisting of O, S, SO, SO_2, N, NH, and NR_2;

X is either O or S;

Y is a direct bond, C_1-C_6 straight or branched chain

alkyl, or C_2-C_6 straight or branched chain alkenyl, wherein any carbon atom of said alkyl or alkenyl is optionally substituted in one or more position(s) with amino, halo, haloalkyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, or oxygen to form a carbonyl, or wherein any carbon atom of said alkyl or alkenyl is optionally replaced with O, NH, NR_3, S, SO, or SO_2;

R_2 is selected from the group consisting of hydrogen, C_1-C_4 straight or branched chain alkyl, C_3-C_4 straight or branched chain alkenyl or alkynyl, and C_1-C_4 bridging alkyl wherein a bridge is formed between the nitrogen and a carbon atom of said alkyl or alkenyl chain containing said heteroatom to form a ring, wherein said ring is optionally fused to an Ar group;

Ar is an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring, wherein the ring is either unsubstituted or substituted with one or more substituent(s); wherein the individual ring size is 5-8 members; wherein the heterocyclic ring contains 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S; wherein an aromatic or tertiary alkyl amine is optionally oxidized to a corresponding N-oxide;

Z is a direct bond, C_1-C_6 straight or branched chain alkyl, or C_2-C_6 straight or branched chain alkenyl, wherein any carbon atom of said alkyl or alkenyl is optionally substituted in one or more position(s) with amino, halo, haloalkyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, or oxygen to form a carbonyl, or wherein any atom of said alkyl or alkenyl is optionally replaced with O, NH, NR_2, S, SO, or SO_2;

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 said alkyl or alkenyl is optionally

substituted with one or more substituent(s) independently selected from the group consisting of C_3-C_8 cycloalkyl, C_5-C_7 cycloalkenyl, hydroxy, carbonyl oxygen, and Ar; wherein said alkyl, alkenyl, cycloalkyl or cycloalkenyl is 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, sulfhydryl, thioalkyl, or sulfonyl; wherein any carbon atom of said alkyl or alkenyl is optionally substituted in one or more position(s) with oxygen to form a carbonyl; or wherein any carbon atom of said alkyl or alkenyl is optionally replaced with O, NH, NR_3, S, SO, or SO_2; 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, and C_2-C_6 straight or branched chain alkenyl, wherein said alkyl or alkenyl is optionally substituted with one or more substituent(s) independently selected from the group consisting of Ar, C_3-C_8 cycloalkyl, 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, and sulfonyl, wherein any carbon atom of said alkyl or alkenyl is optionally replaced with O, NH, NR_3, S, SO, or SO_2.

Useful carbo- and heterocyclic rings include without limitation phenyl, benzyl, naphthyl, indenyl, azulenyl, fluorenyl, anthracenyl, indolyl, isoindolyl, indolinyl, benzofuranyl, benzothiophenyl, indazolyl, benzimidazolyl, benzthiazolyl, tetrahydrofuranyl, tetrahydropyranyl, pyridyl, pyrrolyl, pyrrolidinyl, pyridinyl, pyrimidinyl, purinyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, quinolizinyl, furyl, thiophenyl, imidazolyl, oxazolyl, benzoxazolyl, thiazolyl, isoxazolyl, isotriazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, trithianyl, indolizinyl,

pyrazolyl, pyrazolinyl, pyrazolidinyl, thienyl, tetrahydroisoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, naphthyridinyl, pteridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, and phenoxazinyl.

In a preferred embodiment of formula XX, Ar is selected from the group consisting of phenyl, benzyl, naphthyl, indolyl, pyridyl, pyrrolyl, pyrrolidinyl, pyridinyl, pyrimidinyl, purinyl, quinolinyl, isoquinolinyl, furyl, fluorenyl, thiophenyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, and thienyl.

In another preferred embodiment of formula XX, A and B, together with the nitrogen and carbon atoms to which they are respectfully attached, form a 6 membered saturated or unsaturated heterocyclic ring; and R_2 is C_4-C_7 branched chain alkyl, C_4-C_7 cycloalkyl, phenyl, or 3,4,5-trimethoxyphenyl.

In the most preferred embodiment of formula XX, the compound is selected from the group consisting of:

3-(*para*-Methoxyphenyl)-1-propylmercaptyl(2*S*)-N-(benzenesulfonyl)pyrrolidine-2-carboxylate;

3-(*para*-Methoxyphenyl)-1-propylmercaptyl(2*S*)-N-(α-toluenesulfonyl)pyrrolidine-2-carboxylate;

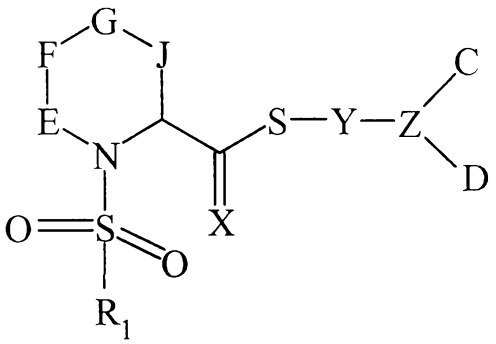
3-(*para*-Methoxyphenyl)-1-propylmercaptyl(2*S*)-N-(α-toluenesulfonyl)pyrrolidine-2-carboxylate;

1,5-Diphenyl-3-pentylmercaptyl N-(*para*-toluenesulfonyl)pipecolate; and

pharmaceutically acceptable salts, esters, and solvates thereof.

FORMULA XXI

Moreover, the non-immunosuppressive neuroimmunophilin FKBP ligand may be a compound of formula XXI



XXI

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

E, F, G and J are independently CH_2, O, S, SO, SO_2, NH or NR_2;

X is either O or S;

Y is a direct bond, C_1-C_6 straight or branched chain alkyl, or C_2-C_6 straight or branched chain alkenyl, wherein any carbon atom of said alkyl or alkenyl is optionally substituted in one or more position(s) with amino, halo, haloalkyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, or oxygen to form a carbonyl, or wherein any carbon atom of said alkyl or alkenyl is optionally replaced with O, NH, NR_3, S, SO, or SO_2;

R_2 is selected from the group consisting of hydrogen, C_1-C_4 straight or branched chain alkyl, C_3-C_4 straight or branched chain alkenyl or alkynyl, and C_1-C_4 bridging alkyl wherein a bridge is formed between the nitrogen and a carbon atom of said alkyl or alkenyl chain containing said heteroatom to form a ring, wherein said ring is optionally fused to an Ar group;

Z is a direct bond, C_1-C_6 straight or branched chain alkyl, or C_2-C_6 straight or branched chain alkenyl, wherein any carbon atom of said alkyl or alkenyl is optionally substituted in one or more position(s) with amino, halo, haloalkyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl,

thioalkyl, sulfonyl, or oxygen to form a carbonyl, or wherein any atom of said alkyl or alkenyl is optionally replaced with O, NH, NR_2, S, SO, or SO_2;

Ar is an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring, wherein the ring is either unsubstituted or substituted with one or more substituent(s); wherein the individual ring size is 5-8 members; wherein the heterocyclic ring contains 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S; wherein an aromatic or tertiary alkyl amine is optionally oxidized to a corresponding N-oxide;

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 said alkyl or alkenyl is optionally substituted with one or more substituent(s) independently selected from the group consisting of C_3-C_8 cycloalkyl, C_5-C_7 cycloalkenyl, hydroxy, carbonyl oxygen, and Ar; wherein said alkyl, alkenyl, cycloalkyl or cycloalkenyl is 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, sulfhydryl, thioalkyl, or sulfonyl; wherein any carbon atom of said alkyl or alkenyl is optionally substituted in one or more position(s) with oxygen to form a carbonyl; or wherein any carbon atom of said alkyl or alkenyl is optionally replaced with O, NH, NR_3, S, SO, or SO_2; 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, and C_2-C_6 straight or branched chain alkenyl, wherein said alkyl or alkenyl is optionally substituted with one or more substituent(s) independently selected from the group consisting of Ar, C_3-C_8 cycloalkyl, 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,

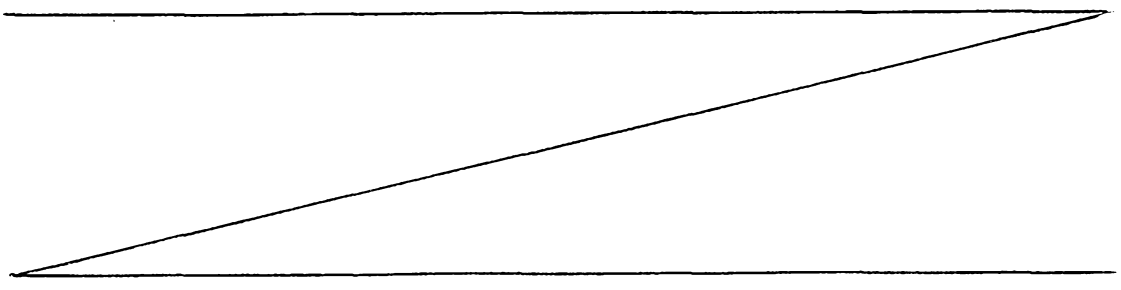
nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, and sulfonyl, wherein any carbon atom of said alkyl or alkenyl is optionally replaced with O, NH, NR_3, S, SO, or SO_2.

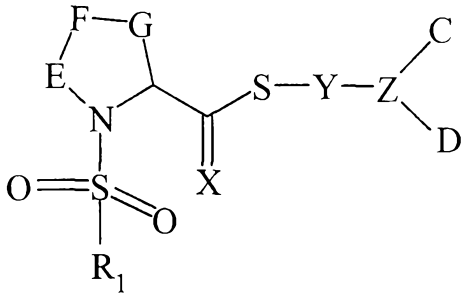
Useful carbo- and heterocyclic rings include without limitation phenyl, benzyl, naphthyl, indenyl, azulenyl, fluorenyl, anthracenyl, indolyl, isoindolyl, indolinyl, benzofuranyl, benzothiophenyl, indazolyl, benzimidazolyl, benzthiazolyl, tetrahydrofuranyl, tetrahydropyranyl, pyridyl, pyrrolyl, pyrrolidinyl, pyridinyl, pyrimidinyl, purinyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, quinolizinyl, furyl, thiophenyl, imidazolyl, oxazolyl, benzoxazolyl, thiazolyl, isoxazolyl, isotriazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, trithianyl, indolizinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, thienyl, tetrahydroisoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, naphthyridinyl, pteridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, and phenoxazinyl.

In a preferred embodiment of formula XXI, Ar is selected from the group consisting of phenyl, benzyl, naphthyl, indolyl, pyridyl, pyrrolyl, pyrrolidinyl, pyridinyl, pyrimidinyl, purinyl, quinolinyl, isoquinolinyl, furyl, fluorenyl, thiophenyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, and thienyl.

FORMULA XXII

The non-immunosuppressive neuroimmunophilin FKBP ligand may also be a compound of formula XXII





XXII

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

E, F, and G are independently CH_2, O, S, SO, SO_2, NH or NR_2;

X is either O or S;

Y is a direct bond, C_1-C_6 straight or branched chain alkyl, or C_2-C_6 straight or branched chain alkenyl, wherein any carbon atom of said alkyl or alkenyl is optionally substituted in one or more position(s) with amino, halo, haloalkyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, or oxygen to form a carbonyl, or wherein any carbon atom of said alkyl or alkenyl is optionally replaced with O, NH, NR_2, S, SO, or SO_2;

R_2 is selected from the group consisting of hydrogen, C_1-C_4 straight or branched chain alkyl, C_3-C_4 straight or branched chain alkenyl or alkynyl, and C_1-C_4 bridging alkyl wherein a bridge is formed between the nitrogen and a carbon atom of said alkyl or alkenyl chain containing said heteroatom to form a ring, wherein said ring is optionally fused to an Ar group;

Ar is an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring, wherein the ring is either unsubstituted or substituted with one or more substituent(s); wherein the individual ring size is 5-8 members; wherein the heterocyclic ring contains 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S; wherein an aromatic or tertiary alkyl amine is optionally oxidized to a

corresponding N-oxide;

Z is a direct bond, C_1-C_6 straight or branched chain alkyl, or C_2-C_6 straight or branched chain alkenyl, wherein any carbon atom of said alkyl or alkenyl is optionally substituted in one or more position(s) with amino, halo, haloalkyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, or oxygen to form a carbonyl, or wherein any atom of said alkyl or alkenyl is optionally replaced with O, NH, NR_2, S, SO, or SO_2;

R_2 is selected from the group consisting of hydrogen, C_1-C_4 straight or branched chain alkyl, C_3-C_4 straight or branched chain alkenyl or alkynyl, and C_1-C_4 bridging alkyl wherein a bridge is formed between the nitrogen and a carbon atom of said alkyl or alkenyl chain containing said heteroatom to form a ring, wherein said 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 C_2-C_6 straight or branched chain alkenyl, wherein said alkyl or alkenyl is optionally substituted with one or more substituent(s) independently selected from the group consisting of C_3-C_8 cycloalkyl, C_5-C_7 cycloalkenyl, hydroxy, carbonyl oxygen, and Ar; wherein said alkyl, alkenyl, cycloalkyl or cycloalkenyl is optionally substituted with C_1-C_4 alkyl, C_2-C_4 alkenyl, or hydroxy; wherein any carbon atom of said alkyl or alkenyl is optionally substituted in one or more position(s) with oxygen to form a carbonyl, or wherein any carbon atom of said alkyl or alkenyl is optionally replaced with O, NH, NR_2, S, SO, or SO_2; 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, and C_2-C_6 straight or branched chain alkenyl, wherein said alkyl or alkenyl is optionally substituted with one or more substituent(s) independently selected from the group

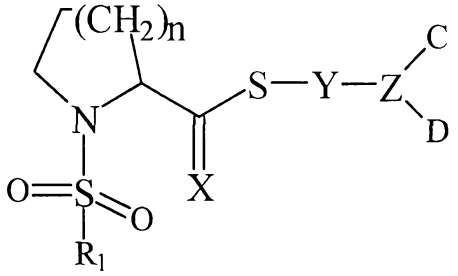
consisting of Ar, C_3-C_8 cycloalkyl, amino, halo, haloalkyl, hydroxy, trifluoromethyl, C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, carbonyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, and sulfonyl, wherein any carbon atom of said alkyl or alkenyl is optionally replaced with O, NH, NR_3, S, SO, or SO_2.

Useful carbo- and heterocyclic rings include without limitation phenyl, benzyl, naphthyl, indenyl, azulenyl, fluorenyl, anthracenyl, indolyl, isoindolyl, indolinyl, benzofuranyl, benzothiophenyl, indazolyl, benzimidazolyl, benzthiazolyl, tetrahydrofuranyl, tetrahydropyranyl, pyridyl, pyrrolyl, pyrrolidinyl, pyridinyl, pyrimidinyl, purinyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, quinolizinyl, furyl, thiophenyl, imidazolyl, oxazolyl, benzoxazolyl, thiazolyl, isoxazolyl, isotriazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, trithianyl, indolizinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, thienyl, tetrahydroisoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, naphthyridinyl, pteridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, and phenoxazinyl.

In a preferred embodiment of formula XXII, Ar is selected from the group consisting of phenyl, benzyl, naphthyl, indolyl, pyridyl, pyrrolyl, pyrrolidinyl, pyridinyl, pyrimidinyl, purinyl, quinolinyl, isoquinolinyl, furyl, fluorenyl, thiophenyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, and thienyl.

FORMULA XXIII

Additionally, the non-immunosuppressive neuroimmunophilin FKBP ligand may be a compound of formula XXIII



XXIII

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

n is 1, 2 or 3;

X is either O or S;

Y is a direct bond, C_1-C_6 straight or branched chain alkyl, or C_2-C_6 straight or branched chain alkenyl, wherein any carbon atom of said alkyl or alkenyl is optionally substituted in one or more position(s) with amino, halo, haloalkyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, or oxygen to form a carbonyl, or wherein any carbon atom of said alkyl or alkenyl is optionally replaced with O, NH, NR_2, S, SO, or SO_2;

R_2 is selected from the group consisting of hydrogen, C_1-C_4 straight or branched chain alkyl, C_3-C_4 straight or branched chain alkenyl or alkynyl, and C_1-C_4 bridging alkyl wherein a bridge is formed between the nitrogen and a carbon atom of said alkyl or alkenyl chain containing said heteroatom to form a ring, wherein said ring is optionally fused to an Ar group;

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

O, NH, NR_2, S, SO, or SO_2;

R_2 is selected from the group consisting of hydrogen, C_1-C_4 straight or branched chain alkyl, C_3-C_4 straight or branched chain alkenyl or alkynyl, and C_1-C_4 bridging alkyl wherein a bridge is formed between the nitrogen and a carbon atom of said alkyl or alkenyl chain containing said heteroatom to form a ring, wherein said ring is optionally fused to an Ar group;

Ar is an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring, wherein the ring is either unsubstituted or substituted with one or more substituent(s); wherein the individual ring size is 5-8 members; wherein the heterocyclic ring contains 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S; wherein an aromatic or tertiary alkyl amine is optionally oxidized to a corresponding N-oxide;

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 said alkyl or alkenyl is optionally substituted with one or more substituent(s) independently selected from the group consisting of C_3-C_8 cycloalkyl, C_5-C_7 cycloalkenyl, hydroxy, carbonyl oxygen, and Ar; wherein said alkyl, alkenyl, cycloalkyl or cycloalkenyl is optionally substituted with C_1-C_4 alkyl, C_2-C_4 alkenyl, or hydroxy; wherein any carbon atom of said alkyl or alkenyl is optionally substituted in one or more position(s) with oxygen to form a carbonyl, or wherein any carbon atom of said alkyl or alkenyl is optionally replaced with O, NH, NR_2, S, SO, or SO_2; 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, and C_2-C_6 straight or branched chain alkenyl, wherein said alkyl or alkenyl is optionally substituted with one or more substituent(s) independently selected from the group consisting of Ar, C_3-C_8 cycloalkyl, amino, halo, haloalkyl,

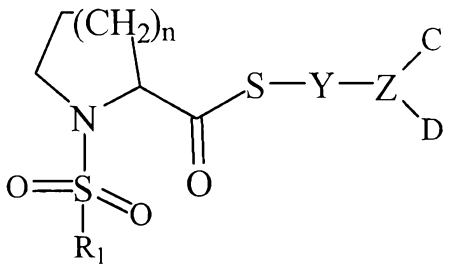
hydroxy, trifluoromethyl, C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, carbonyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, and sulfonyl, wherein any carbon atom of said alkyl or alkenyl is optionally replaced with O, NH, NR_3, S, SO, or SO_2.

Useful carbo- and heterocyclic rings include without limitation phenyl, benzyl, naphthyl, indenyl, azulenyl, fluorenyl, anthracenyl, indolyl, isoindolyl, indolinyl, benzofuranyl, benzothiophenyl, indazolyl, benzimidazolyl, benzthiazolyl, tetrahydrofuranyl, tetrahydropyranyl, pyridyl, pyrrolyl, pyrrolidinyl, pyridinyl, pyrimidinyl, purinyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, quinolizinyl, furyl, thiophenyl, imidazolyl, oxazolyl, benzoxazolyl, thiazolyl, isoxazolyl, isotriazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, trithianyl, indolizinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, thienyl, tetrahydroisoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, naphthyridinyl, pteridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, and phenoxazinyl.

In a preferred embodiment of formula XXIII, Ar is selected from the group consisting of phenyl, benzyl, naphthyl, indolyl, pyridyl, pyrrolyl, pyrrolidinyl, pyridinyl, pyrimidinyl, purinyl, quinolinyl, isoquinolinyl, furyl, fluorenyl, thiophenyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, and thienyl.

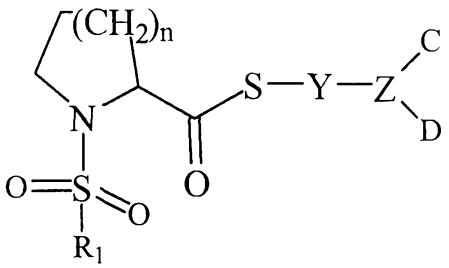
Exemplary compounds of formula XXIII are presented in TABLE VIII.

TABLE VIII



No.	n	Y	Z	C	D	R1
117	1	CH_2	CH	Phenyl	H	Phenyl
118	1	CH_2	CH	Phenyl	H	α-Methyl-phenyl
119	1	CH_2	CH	Phenyl	H	4-Methylphenyl
120	1	$(CH_2)_2$	CH	*p*-Methoxy-phenyl	H	Phenyl
121	1	$(CH_2)_2$	CH	*p*-Methoxy-phenyl	H	α-Methyl-phenyl
122	1	$(CH_2)_2$	CH	*p*-Methoxy-phenyl	H	4-Methyl-phenyl
123	1	$(CH_2)_2$	CH	Phenyl	Phenyl	Phenyl
124	1	$(CH_2)_2$	CH	Phenyl	Phenyl	α-Methyl-phenyl
125	1	$(CH_2)_2$	CH	Phenyl	Phenyl	4-Methyl-phenyl
126	2	$(CH_2)_3$	CH	Phenyl	H	Phenyl
127	2	$(CH_2)_3$	CH	Phenyl	H	α-Methyl-phenyl
128	2	$(CH_2)_3$	CH	Phenyl	H	4-Methyl-phenyl
129	2	$(CH_2)_3$	CH	Phenyl	H	3,4,5-tri-methoxyphenyl
130	2	$(CH_2)_3$	CH	Phenyl	H	Cyclohexyl

TABLE VIII (continued)



No.	n	Y	Z	C	D	R1
131	2	Direct bond	CH	3-Phenyl-propyl	3-Phenyl-propyl	Phenyl
132	2	Direct bond	CH	3-Phenyl-propyl	3-Phenyl-propyl	α-Methyl-phenyl
133	2	Direct bond	CH	3-Phenyl-propyl	3-Phenyl-propyl	4-Methyl-phenyl
134	2	Direct bond	CH	3-Phenyl-ethyl	3-Phenyl-ethyl	4-Methyl-phenyl
135	2	Direct bond	CH	3-(4-Methoxy-phenyl)-propyl	3-Phenyl-propyl	4-Methyl-phenyl
136	2	Direct bond	CH	3-(2-Pyridyl)-propyl	3-Phenyl-propyl	4-Methyl-phenyl

The most preferred compounds of formula XXIII are selected from the group consisting of:

3-(*para*-Methoxyphenyl)-1-propylmercaptyl(2*S*)-N-(benzenesulfonyl)pyrrolidine-2-carboxylate;

3-(*para*-Methoxyphenyl)-1-propylmercaptyl(2*S*)-N-(α-toluenesulfonyl)pyrrolidine-2-carboxylate;

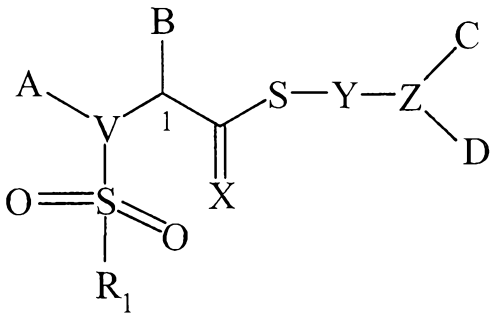
3-(*para*-Methoxyphenyl)-1-propylmercaptyl(2*S*)-N-(α-toluenesulfonyl)pyrrolidine-2-carboxylate;

1,5-Diphenyl-3-pentylmercaptyl N-(*para*-toluenesulfonyl)pipecolate; and

pharmaceutically acceptable salts, esters, and solvates thereof.

FORMULA XXIV

Moreover, the non-immunosuppressive neuroimmunophilin FKBP ligand may be a compound of formula XXIV



XXIV

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

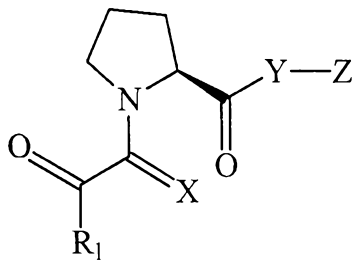
V is C, N, or S;

A, B, C, D, R_1, X, Y, and Z are as defined in formula XX above.

VI. PYRROLIDINE DERIVATIVES

FORMULA XXV

The non-immunosupressive neuroimmunophilin FKBP ligand may also be a compound of formula XXV



XXV

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

R_1 is 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 or Ar_1, wherein said R_1 is unsubstituted or

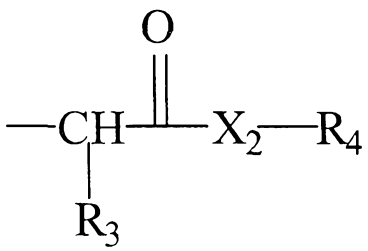
substituted with one or more substituents independently selected from the group consisting of C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, C_5-C_7 cycloalkenyl, hydroxy, and Ar_2;

Ar_1 and Ar_2 are independently selected from the group consisting of 1-naphthyl, 2-napthyl, 2-indolyl, 3-indolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl and phenyl, wherein said Ar_1 is unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of hydrogen, halo, hydroxy, nitro, trifluoromethyl, 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, and amino;

X is O, S, CH_2 or H_2;

Y is a direct bond, O, or NR_2, wherein R_2 is hydrogen or C_1-C_6 alkyl; and

Z is C_1-C_6 straight or branched chain alkyl, or C_2-C_6 straight or branched chain alkenyl, wherein said Z is substituted with one or more substituent(s) independently selected from the group consisting of Ar_1, C_3-C_8 cycloalkyl, and C_1-C_6 straight or branched chain alkyl or C_2-C_6 straight or branched chain alkenyl substituted with C_3-C_8 cycloalkyl; or Z is fragment



wherein:

R_3 is C_1-C_9 straight or branched chain alkyl which is unsubstituted or substituted with C_3-C_8 cycloalkyl or Ar_1;

X_2 is O or NR_5, wherein R_5 is selected from the group consisting of hydrogen, C_1-C_6 straight or branched chain alkyl, and C_2-C_6 straight or branched chain alkenyl; and

R_4 is selected from the group consisting of phenyl, benzyl, C_1-C_5 straight or branched chain alkyl, C_2-C_5 straight or branched chain alkenyl, C_1-C_5 straight or branched chain alkyl substituted with phenyl, and C_2-C_5 straight or branched chain alkenyl substituted with phenyl.

In a preferred embodiment of formula XXV, Z and R_1 are lipophilic.

In a more preferred embodiment of formula XXV, the compound is selected from the group consisting of:

3-phenyl-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate;

3-phenyl-1-prop-2-(E)-enyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate;

3-(3,4,5-trimethoxyphenyl)-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate;

3-(3,4,5-trimethoxyphenyl)-1-prop-2-(E)-enyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate;

3-(4,5-dichlorophenyl)-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate;

3-(4,5-dichlorophenyl)-1-prop-2-(E)-enyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate;

3-(4,5-methylenedioxyphenyl)-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate;

3-(4,5-methylenedioxyphenyl)-1-prop-2-(E)-enyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate;

3-cyclohexyl-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate;

3-cyclohexyl-1-prop-2-(E)-enyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate;

(1*R*)-1,3-diphenyl-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate;

(1*R*)-1,3-diphenyl-1-prop-2-(E)-enyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate;

(1*R*)-1-cyclohexyl-3-phenyl-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate;

(1*R*)-1-cyclohexyl-3-phenyl-1-prop-2-(E)-enyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate;

(1*R*)-1-(4,5-dichlorophenyl)-3-phenyl-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate;

3-phenyl-1-propyl (2*S*)-1-(1,2-dioxo-2-cyclohexyl)ethyl-2-pyrrolidinecarboxylate;

3-phenyl-1-propyl (2*S*)-1-(1,2-dioxo-4-cyclohexyl)butyl-2-pyrrolidinecarboxylate;

3-phenyl-1-propyl (2*S*)-1-(1,2-dioxo-2-[2-furanyl])ethyl-2-pyrrolidinecarboxylate;

3-phenyl-1-propyl (2*S*)-1-(1,2-dioxo-2-[2-thienyl])ethyl-2-pyrrolidinecarboxylate;

3-phenyl-1-propyl (2*S*)-1-(1,2-dioxo-2-[2-thiazolyl])ethyl-2-pyrrolidinecarboxylate;

3-phenyl-1-propyl (2*S*)-1-(1,2-dioxo-2-phenyl)ethyl-2-pyrrolidinecarboxylate;

1,7-diphenyl-4-heptyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate;

3-phenyl-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxo-4-hydroxybutyl)-2-pyrrolidinecarboxylate;

3-phenyl-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxamide;

1-[1-(3,3-dimethyl-1,2-dioxopentyl)-L-proline]-L-phenylalanine ethyl ester;

1-[1-(3,3-dimethyl-1,2-dioxopentyl)-L-proline]-L-leucine ethyl ester;

1-[1-(3,3-dimethyl-1,2-dioxopentyl)-L-proline]-L-phenylglycine ethyl ester;

1-[1-(3,3-dimethyl-1,2-dioxopentyl)-L-proline]-L-phenylalanine phenyl ester;

1-[1-(3,3-dimethyl-1,2-dioxopentyl)-L-proline]-L-phenylalanine benzyl ester;

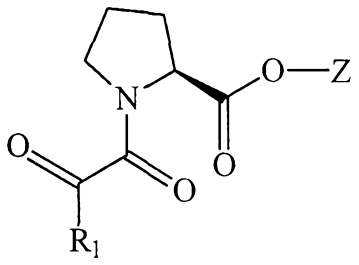
1-[1-(3,3-dimethyl-1,2-dioxopentyl)-L-proline]-L-isoleucine ethyl ester; and

pharmaceutically acceptable salts, esters, and solvates

thereof.

FORMULA XXVI

Additionally, the non-immunosuppressive neuroimmunophilin FKBP ligand may be a compound of formula XXVI



XXVI

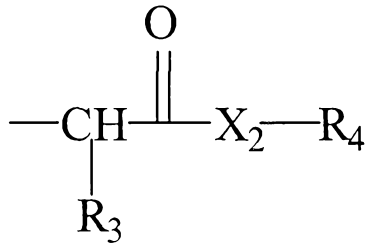
or a pharmaceutically acceptable salt, ester, or solvate thereof, wherein:

R_1 is 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 or Ar_1, wherein said R_1 is unsubstituted or substituted with one or more substituents independently selected from the group consisting of C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, C_5-C_7 cycloalkenyl, hydroxy, and Ar_2;

Ar_1 and Ar_2 are independently selected from the group consisting of 1-naphthyl, 2-napthyl, 2-indolyl, 3-indolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl and phenyl, wherein said Ar_1 is unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of hydrogen, halo, hydroxy, nitro, trifluoromethyl, 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, and amino;

Z is C_1-C_6 straight or branched chain alkyl, or C_2-C_6 straight or branched chain alkenyl, wherein said Z is substituted with one or more substituent(s) independently selected from the group consisting of Ar_1, C_3-C_8 cycloalkyl, and C_1-C_6 straight or branched chain alkyl or C_2-C_6 straight

or branched chain alkenyl substituted with C_3-C_8 cycloalkyl; or Z is fragment



wherein:

R_3 is C_1-C_9 straight or branched chain alkyl which is unsubstituted or substituted with C_3-C_8 cycloalkyl or Ar_1;

X_2 is O or NR_5, wherein R_5 is selected from the group consisting of hydrogen, C_1-C_6 straight or branched chain alkyl, and C_2-C_6 straight or branched chain alkenyl; and

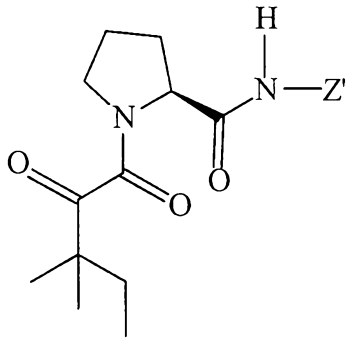
R_4 is selected from the group consisting of phenyl, benzyl, C_1-C_5 straight or branched chain alkyl, C_2-C_5 straight or branched chain alkenyl, C_1-C_5 straight or branched chain alkyl substituted with phenyl, and C_2-C_5 straight or branched chain alkenyl substituted with phenyl.

In a preferred embodiment of formula XXVI, R_1 is selected from the group consisting of C_1-C_9 straight or branched chain alkyl, 2-cyclohexyl, 4-cyclohexyl, 2-furanyl, 2-thienyl, 2-thiazolyl, and 4-hydroxybutyl.

In another preferred embodiment of formula XXVI, Z and R_1 are lipophilic.

FORMULA XXVII

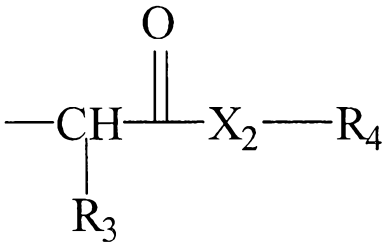
The non-immunosuppressive neuroimmunophilin FKBP ligand may also be a compound of formula XXVII



XXVII

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

Z' is fragment



wherein:

R_3 is C_1-C_9 straight or branched chain alkyl or unsubstituted Ar_1, wherein said alkyl is unsubstituted or substituted with C_3-C_8 cycloalkyl or Ar_1;

X_2 is O or NR_5, wherein R_5 is selected from the group consisting of hydrogen, C_1-C_6 straight or branched chain alkyl, and C_2-C_6 straight or branched chain alkenyl;

R_4 is selected from the group consisting of phenyl, benzyl, C_1-C_5 straight or branched chain alkyl, C_2-C_5 straight or branched chain alkenyl, C_1-C_5 straight or branched chain alkyl substituted with phenyl, and C_2-C_5 straight or branched chain alkenyl substituted with phenyl; and

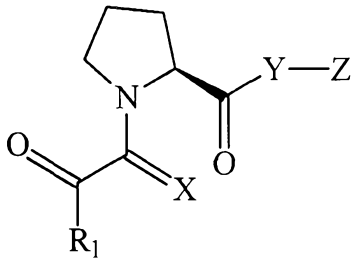
Ar_1 is as defined in formula XXVI.

In a preferred embodiment of formula XXVII, Z' is lipophilic.

FORMULA XXVIII

The non-immunosuppressive neuroimmunophilin FKBP ligand

may also be a compound of formula XXVIII



XXVIII

wherein:

R_1 is C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, C_3-C_6 cycloalkyl or Ar_1, wherein said alkyl or alkenyl is unsubstituted or substituted with C_3-C_6 cycloalkyl or Ar_2;

Ar_1 and Ar_2 are independently selected from the group consisting of 2-furyl, 2-thienyl, and phenyl;

X is O, S, CH_2 or H_2;

Y is oxygen;

Z is C_1-C_6 straight or branched chain alkyl, or C_2-C_6 straight or branched chain alkenyl, wherein said Z is substituted with one or more substituent(s) independently selected from the group consisting of 2-furyl, 2-thienyl, C_3-C_6 cycloalkyl, pyridyl, and phenyl, each having one or more substituent(s) independently selected from the group consisting of hydrogen and C_1-C_4 alkoxy.

In a preferred embodiment of formula XXVIII, Z and R_1 are lipophilic.

In another preferred embodiment of formula XXVIII, the compound is selected from the group consisting of:

3-(2,5-dimethoxyphenyl)-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate;

3-(2,5-dimethoxyphenyl)-1-prop-2-(E)-enyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate;

2-(3,4,5-trimethoxyphenyl)-1-ethyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate;

3-(3-pyridyl)-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-

dioxopentyl)-2-pyrrolidinecarboxylate;

3-(2-pyridyl)-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate;

3-(4-pyridyl)-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate;

3-phenyl-1-propyl (2*S*)-1-(2-*tert*-butyl-1,2-dioxoethyl)-2-pyrrolidinecarboxylate;

3-phenyl-1-propyl (2*S*)-1-(2-cyclohexylethyl-1,2-dioxoethyl)-2-pyrrolidinecarboxylate;

3-(3-pyridyl)-1-propyl (2*S*)-1-(2-cyclohexylethyl-1,2-dioxoethyl)-2-pyrrolidinecarboxylate;

3-(3-pyridyl)-1-propyl (2*S*)-1-(2-*tert*-butyl-1,2-dioxoethyl)-2-pyrrolidinecarboxylate;

3,3-diphenyl-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate;

3-(3-pyridyl)-1-propyl (2*S*)-1-(2-cyclohexyl-1,2-dioxoethyl)-2-pyrrolidinecarboxylate;

3-(3-pyridyl)-1-propyl (2*S*)-N-([2-thienyl]glyoxyl)pyrrolidinecarboxylate;

3,3-diphenyl-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxobutyl)-2-pyrrolidinecarboxylate;

3,3-diphenyl-1-propyl (2*S*)-1-cyclohexylglyoxyl-2-pyrrolidinecarboxylate;

3,3-diphenyl-1-propyl (2*S*)-1-(2-thienyl)glyoxyl-2-pyrrolidinecarboxylate; and

pharmaceutically acceptable salts, esters, and solvates thereof.

In a more preferred embodiment of formula XXVIII, the compound is selected from the group consisting of:

3-(3-pyridyl)-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate;

3-(2-pyridyl)-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate;

3-(3-pyridyl)-1-propyl (2*S*)-1-(2-cyclohexyl-1,2-

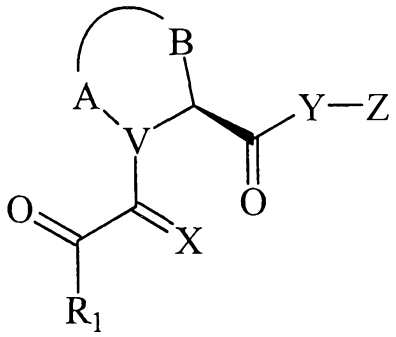
dioxoethyl)-2-pyrrolidinecarboxylate; and

pharmaceutically acceptable salts, esters, and solvates thereof.

In the most preferred embodiment of formula XXVIII, the compound is 3-(3-pyridyl)-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate, and pharmaceutically acceptable salts, esters, and solvates thereof.

FORMULA XXIX

Additionally, the non-immunosuppressive neuroimmunophilin FKBP ligand may be a compound of formula XXIX



XXIX

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

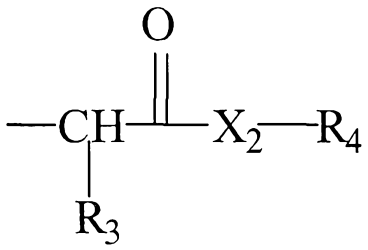
unsubstituted or substituted with one or more substituent(s); wherein the individual ring size is 5-8 members; wherein said heterocyclic ring contains 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S;

X is O, S, CH_2 or H_2;

Y is a direct bond, O, or NR_2, wherein R_2 is hydrogen or C_1-C_6 alkyl; and

Z is C_1-C_6 straight or branched chain alkyl, or C_2-C_6 straight or branched chain alkenyl, wherein said Z is substituted with one or more substituent(s) independently selected from the group consisting of Ar_1, C_3-C_8 cycloalkyl, and C_1-C_6 straight or branched chain alkyl or C_2-C_6 straight or branched chain alkenyl substituted with C_3-C_8 cycloalkyl;

or Z is fragment



wherein:

R_3 is C_1-C_9 straight or branched chain alkyl which is unsubstituted or substituted with C_3-C_8 cycloalkyl or Ar_1;

X_2 is O or NR_5, wherein R_5 is selected from the group consisting of hydrogen, C_1-C_6 straight or branched chain alkyl, and C_2-C_6 straight or branched chain alkenyl; and

R_4 is selected from the group consisting of phenyl, benzyl, C_1-C_5 straight or branched chain alkyl, C_2-C_5 straight or branched chain alkenyl, C_1-C_5 straight or branched chain alkyl substituted with phenyl, and C_2-C_5 straight or branched chain alkenyl substituted with phenyl.

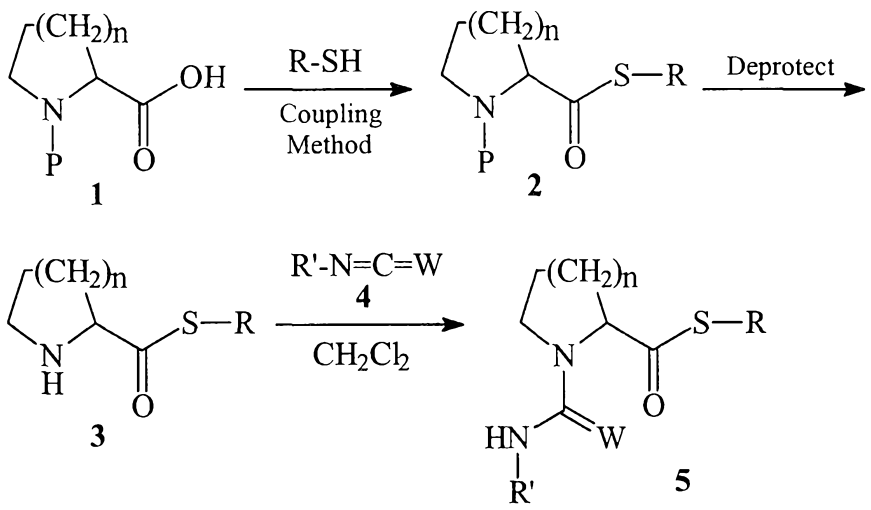
All the compounds of Formulas I-XXIX possess asymmetric centers and thus can be produced as mixtures of stereoisomers or as individual R- and S- stereoisomers. The individual stereoisomers may be obtained by using an optically active starting material, by resolving a racemic or non-racemic mixture of an intermediate at some appropriate stage of the synthesis, or by resolving the compounds of Formulas I-XXIX. It is understood that the compounds of Formulas I-XXIX encompass individual stereoisomers as well as mixtures (racemic and non-racemic) of stereoisomers. Preferably, S-stereoisomers are used in the pharmaceutical compositions and methods of the present invention.

Synthesis of Non-Immunosuppressive Neuroimmunophilin FKBP ligands

The compounds of formulas XV to XIX may be readily prepared by standard techniques of organic chemistry,

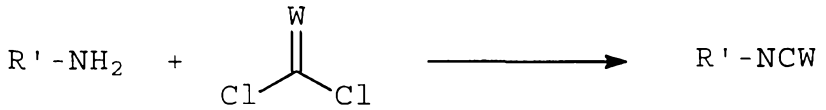
utilizing the general synthetic pathway depicted below. As described by Scheme I, cyclic amino acids **1** protected by suitable blocking groups P on the amino acid nitrogen may be reacted with thiols RSH to generate thioesters **2**. After removal of the protecting group, the free amine **3** may be reacted with a variety of isocyanates or isothiocyanates to provide the final ureas or thioureas, respectively.

SCHEME I



Isocyanates (R'NCO) or isothiocyanates (R'NCS) **4** may be conveniently prepared from the corresponding readily available amines by reaction with phosgene or thiophosgene, as depicted in Scheme II.

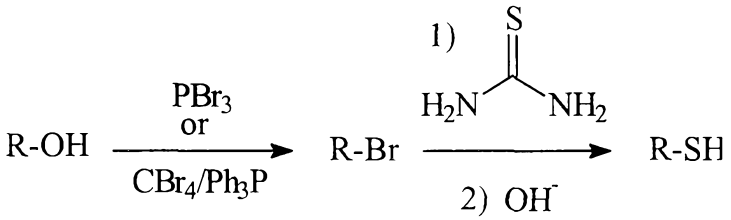
SCHEME II



Thiols R-SH may be conveniently prepared from the corresponding readily available alcohols or halides via a two step replacement of halide by sulfur, as described in Scheme III. Halides may be reacted with thiourea, and the corresponding alkyl thiouronium salts hydrolyzed to provide

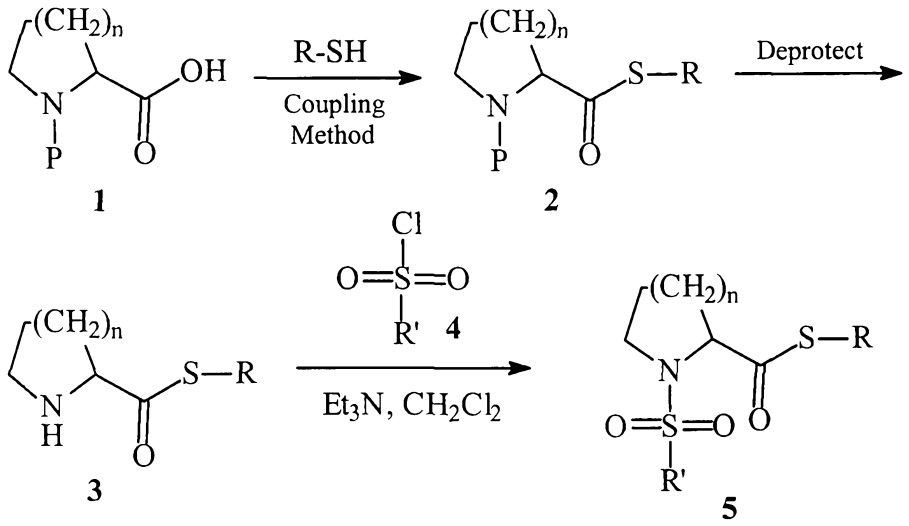
thiols RSH. If alcohols are used as the starting materials, they may be first converted to the corresponding halides by standard methods.

SCHEME III



The compounds of formulas XX to XXIV may be readily prepared by standard techniques of organic chemistry, utilizing the general synthetic pathway depicted below. As described by Scheme IV, 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.

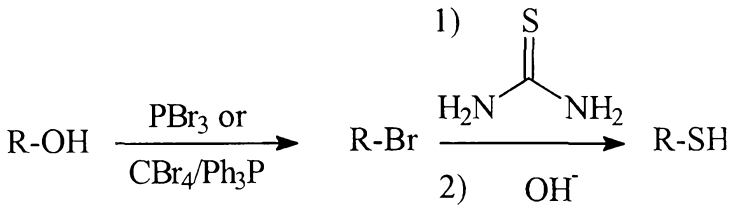
SCHEME IV



Thiols R-SH may be conveniently prepared from the corresponding readily available alcohols or halides via a two

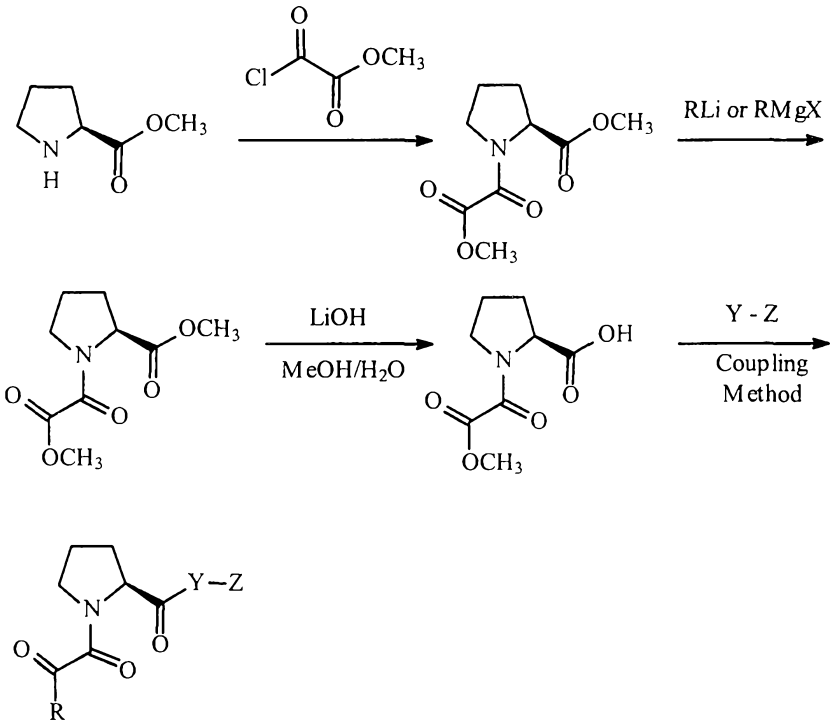
step replacement of halogen by sulfur, as described in Scheme V. Halides may be reacted with thiourea, and the corresponding alkyl thiouronium salts hydrolyzed to provide thiols RSH. If alcohols are used as the starting materials, they may be first converted to the corresponding halides by standard methods.

SCHEME V



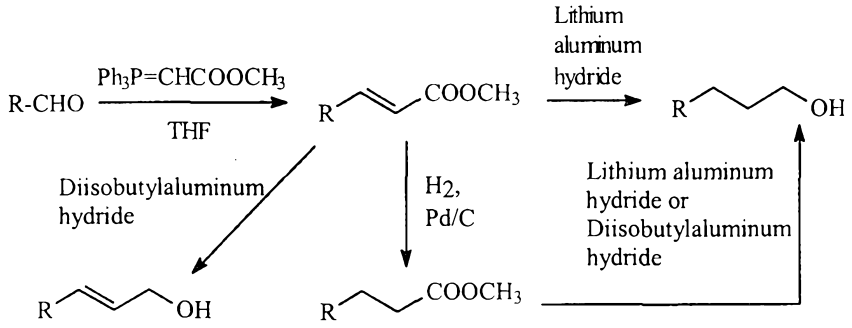
The compounds of formulas XXV to XXIX may be prepared by a variety of synthetic sequences that utilize established chemical transformations. The general pathway to the present compounds is described in Scheme VI. N-glyoxylproline derivatives may be prepared by reacting L-proline methyl ester with methyl oxalyl chloride as shown in Scheme VI. The resulting oxamates may be reacted with a variety of carbon nucleophiles to obtain intermediates compounds. These intermediates are then reacted with a variety of alcohols, amides, or protected amino acid residues to obtain the propyl esters and amides of the invention.

SCHEME VI



The substituted alcohols may be prepared by a number of methods known to those skilled in the art of organic synthesis. As described in Scheme VII, alkyl or aryl aldehydes may be homologated to phenyl propanols by reaction with methyl(triphenyl-phosphoranylidene)acetate to provide a variety of *trans*-cinnamates; these latter may be reduced to the saturated alcohols by reaction with excess lithium aluminum hydride, or sequentially by reduction of the double bond by catalytic hydrogenation and reduction of the saturated ester by appropriate reducing agents. Alternatively, the *trans*-cinnamates may be reduced to (E)-allylic alcohols by the use of diisobutylaluminum hydride.

SCHEME VII



Longer chain alcohols may be prepared by homologation of benzylic and higher aldehydes. Alternatively, these aldehydes may be prepared by conversion of the corresponding phenylacetic and higher acids, and phenethyl and higher alcohols.

Affinity for FKBP12

The compounds used in the inventive methods and pharmaceutical compositions 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.

K_i Test Procedure

Inhibition of the peptidyl-prolyl isomerase (rotamase) activity of the compounds used in the inventive methods and pharmaceutical compositions 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.

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.

TABLE IX

In Vitro Test Results - Formulas I to V

Compound	K_i (nM)
1	31
2	210
3	85
9	104
10	12
11	299
12	442
14	313
28	108
29	59
30	11
31	8.7
32	362
33	1698

TABLE IX (continued)

Compound	K_i (nM)
34	34
35	62
36	7
37	68
38	8.9
39	347
40	1226
41	366
42	28
43	259
44	188
45	31
46	757
47	21
48	127
49	1334
50	55
51	33
52	6
53	261
54	37
55	30
56	880
57	57
58	79
59	962
60	90
61	139
62	196

TABLE IX (continued)

Compound	K_i (nM)
63	82
64	163
65	68
66	306
67	177
68	284
69	49
70	457
71	788

TABLE X

In Vitro Test Results - Formulas VI to IX

Compound	K_i (nM)
80	215
81	638

Table XI

In Vitro Test Results - Formulas X to XIV

Compound	K_i (nM)
Parent (unoxidized) compound of Example 6	7.5
95 (Example 6)	225

TABLE XII

In Vitro Test Results - Formulas XV to XIX

Compound	K_i (nM)
101	+++
102	++
103	++

TABLE XII (continued)

Compound	K_i (nM)
104	++
105	++
106	+
107	++
108	+++
109	+++
110	+++
111	++
112	+++
113	+++
114	+++
115	+++
116	++

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

TABLE XIII

In Vitro Test Results - Formulas XX to XXIV

Compound	K_i (nM)
117	+++
118	++
119	++
120	++
121	++
122	+
123	++

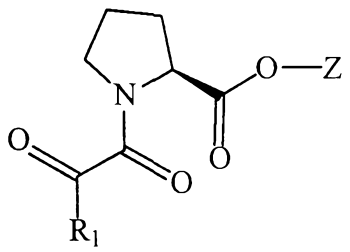
TABLE XIII (continued)

Compound	K_i (nM)
124	+++
125	+++
126	+++
127	++
128	+++
129	+++
130	+++
131	+++
132	++

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

TABLE XIV

In Vitro Test Results - Formulas XXV to XXIX



No.	Z	R'	K_i
137	1,1-dimethylpropyl	3-phenylpropyl	42
138	"	3-phenyl-prop-2-(E)-enyl	125
139	"	3-(3,4,5-trimethoxy-phenyl)propyl	200
140	"	3-(3,4,5-trimethoxy-phenyl)-prop-2-(E)-enyl	65

TABLE XIV (continued)

No.	Z	R'	K_i
141	"	3-(4,5-methylenedioxy)-phenylpropyl	170
142	"	3-(4,5-methylenedioxy)-phenylprop-2-(E)-enyl	160
143	"	3-cyclohexylpropyl	200
144	"	3-cyclohexylprop-2-(E)-enyl	600
145	"	(1*R*)-1,3-diphenyl-1-propyl	52
146	2-furanyl	3-phenylpropyl	4000
147	2-thienyl	"	92
148	2-thiazolyl	"	100
149	phenyl	"	1970
150	1,1-dimethylpropyl	3-(2,5-dimethoxy)-phenylpropyl	250
151	"	3-(2,5-dimethoxy)-phenylprop-2-(E)-enyl	450
152	"	2-(3,4,5-trimethoxy-phenyl)ethyl	120
153	"	3-(3-pyridyl)propyl	5
154	"	3-(2-pyridyl)propyl	195
155	"	3-(4-pyridyl)propyl	23
156	cyclohexyl	3-phenylpropyl	82
157	*tert*-butyl	"	95
158	cyclohexylethyl	"	1025
159	cyclohexylethyl	3-(3-pyridyl)propyl	1400
160	*tert*-butyl	3-(3-pyridyl)propyl	3
161	1,1-dimethylpropyl	3,3-diphenylpropyl	5
162	cyclohexyl	3-(3-pyridyl)propyl	9
163	2-thienyl	3-(3-pyridyl)propyl	1000
164	*tert*-butyl	3,3-diphenylpropyl	5

TABLE XIV (continued)

No.	Z	R'	K_i
165	cyclohexyl	"	20
166	2-thienyl	"	150

Route of Administration

To effectively treat vision loss or promote vision regeneration, the compounds used in the inventive methods and pharmaceutical compositions must readily affect the targeted areas.

Other routes of administration known in the pharmaceutical art are also contemplated by this invention.

Dosage

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 specific dose level for any particular patient will vary depending 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. Typically, *in vitro* dosage-effect results provide useful guidance on the proper doses for patient administration. Studies in animal models are also helpful. The considerations for determining the proper dose levels are well known in the art.

The compounds can be administered with other agents for treating vision loss, preventing vision degeneration, or promoting vision regeneration. Specific dose levels for such other agents will depend upon the factors previously stated and the effectiveness of the drug combination.

EXAMPLES

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

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 ($CDCl_3$; 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 as a clear oil, 120 mg. ^1H 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). Analysis calculated for $C_{22}H_{31}NO_3 \cdot H_2O$: 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 (10)

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. ^1H NMR ($CDCl_3$): δ 1.93 (dm, 2H); 2.17 (m, 2H); 3.62 (m, 2H); 3.71 (s, 3H); 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. ^1H 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 (10)

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 dicyclohexylcarbo-diimide (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 compound 10 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). Analysis calculated for $C_{20}H_{27}NO_3S$ - 0.4 H_2O: C, 65.15; H, 7.60; N, 3.80. Found: C, 65.41; H, 7.49; N, 3.72.

Example 3

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

(9)

Methyl 1-(1,2-dioxo-2-methoxyethyl)-2-piperidine-carboxylate

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-piperidine-carboxylate

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 -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. ^1H 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 (9)

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 compound 9 as an oil. ^{1}H 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). Analysis calculated 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.

Example 4

Synthesis of 3-phenyl-1-propyl(2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-(4-thiazolidine)carboxylate (80)

1-(1,2-dioxo-2-methoxyethyl)2-(4-thiazolidine)-carboxylate

A solution of L-thioproline (1.51 g; 11.34 mmol)in 40 mL

of dry methylene chloride was cooled to 0°C and treated with 3.3 mL (2.41 g; 23,81 mmol) of triethylamine. After stirring this mixture for 30 minutes, a solution of methyl oxalyl chloride (1.81 g; 14.74 mmol) was added dropwise. The resulting mixture was stirred at 0°C for 1.5 hours, filtered through Celite to remove solids, dried and concentrated. The crude material was purified on a silic gel column, eluting with 10% MeOH in methylene chloride, to obtain 2.0 g of the oxamate as an orange-yellow solid.

3-phenyl-1-propyl(2*S*)-1-(1,2-dioxo-2-methoxyethyl)2-(4-thiazolidine)carboxylate

1-(1,2-dioxo-2-methoxyethyl)2-(4-thiazolidine)-carboxylate (500 mg; 2.25 mmol), 3-phenyl-1-propanol (465 mg; 3.42 mmol), dicyclohexylcarbodiimide (750 mg; 3.65 mmol), 4-dimethylaminopyridine (95 mg; 0.75 mmol) and camphorsulfonic acid (175 mg; 0.75 mmol) in 30 mL of methylene chloride were stirred together overnight. The mixture was filtered through Celite to remove solids and chromatographed (25% ethyl acetate/hexane) to obtain 690 mg of material. ^{1}H NMR ($CDCl_3$, 300 MHz): δ1.92-2.01 (m, 2H); 2.61-2.69 (m, 2H); 3.34 (m, 1H); 4.11-4.25 (m, 2H); 4.73 (m, 1H); 5.34 (m, 1H); 7.12 (m, 3H); 7.23 (m, 2H).

3-phenyl-1-propyl(2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-(4-thiazolidine)carboxylate (80)

A solution of 3-phenyl-1-propyl(2*S*)-1-(1,2-dioxo-2-methoxyethyl)2-(4-thiazolidine)carboxylate (670 mg; 1.98 mmol) in tetrahydrofuran (10 mL) was cooled to -78°C and treated with 2.3 mL of a 1.0 M solution of 1,1-dimethylpropylmagnesium chloride in ether. After stirring the mixture for 3 hours, it was poured into saturated ammonium chloride, extracted into ethyl acetate, and the organic phase was washed with water, dried and concentrated. The crude material was purified on a silica gel column, eluting with 25% ethyl acetate in hexane, to obtain 380 mg of the compound of Example 4 as a yellow oil. ^{1}H NMR ($CDCl_3$, 300

MHz): d 0.86 (t, 3H); 1.21 (s, 3H); 1.26 (s, 3H); 1.62-1.91 (m, 3H); 2.01 (m, 2H); 2.71 (m, 2H); 3.26-3.33 (m, 2H); 4.19 (m, 2H); 4.58 (m, 1H); 7.19 (m, 3H); 7.30 (m, 2H). Analysis calculated for $C_{20}H_{27}NO_4S$: C, 63.63; H, 7.23; N, 3.71. Found: C, 64.29; H, 7.39; N, 3.46.

Example 5

Synthesis of 3-(3-pyridyl)-1-propyl(2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-(4-thiazolidine) carboxylate (81)

The compound of Example 5 was prepared according to the procedure of Example 4, using 3-(3-pyridyl)-1-propanol in the final step, to yield 3-(3-pyridyl)-1-propyl(2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-(4-thiazolidine)carboxylate. ^1H NMR ($CDCl_3$, 300 MHz): δ 0.89 (t, 3H, J = 7.3); 1.25 (s, 3H); 1.28 (s, 3H); 1.77 (q, 2H, J = 7.3); 2.03 (tt, 2H, J = 6.4, 7.5); 2.72 (t, 2H, J = 7.5); 3.20 (dd, 1H, J = 4.0, 11.8); 3.23 (dd, 1H, J = 7.0, 11.8); 4.23 (t, 2H, J = 6.4); 4.55 (d, 2H, J = 8.9); 5.08 (dd, 1H, J = 4.0, 7.0); 7.24 (m, 1H); 8.48 (m, 2H). Analysis calculated for $C_{19}H_{26}N_2O_4S$ - 0.5 H_2O: C, 58.89; H, 7.02; N, 7.23. Found: C, 58.83; H, 7.05; N, 7.19.

Example 6

Synthesis of 3-(3-pyridyl)-1-propyl (2*S*)-1-(3,3-Dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate, N-oxide (95)

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 minutes, 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. ^1H NMR ($CDCl_3$): δ 1.93 (dm, 2H); 2.17 (m, 2H); 3.62 (m, 2H); 3.71 (s, 3H); 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. ^1H 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-pyrrolidinecarboxylic acid

A mixture of methyl (2*S*)-1-(1,2-dioxo-3,3-dimethylpentyl-2-pyrrolidine-carboxylate (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. ^1H NMR ($CDCl_3$): d 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).

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

A mixture of (2*S*)-1-(1,2-dioxo-3,3-dimethylpentyl)-2-pyrrolidinecarboxylic acid (4.58 g; 19 mmol), 3-pyridinepropanol (3.91 g; 28.5 mmol), dicyclohexylcarbodiimide (6.27 g; 30.4 mmol), camphorsulfonic acid (1.47 g; 6.33 mmol) and 4-dimethyl aminopyridine (773 mg; 6.33 mmol) in methylene chloride (100 mL) was stirred overnight under a nitrogen atmosphere. The reaction mixture was filtered through Celite to remove solids and concentrated in vacuo. The crude material was triturated with several portions of ether, and the ether portions were filtered through Celite to remove solids and concentrated in vacuo. The concentrated filtrate was purified on a flash column (gradient elution, 25% ethyl acetate in hexane to pure ethyl acetate) to obtain 5.47 g (80%) of GPI 1046 as a colorless oil (partial hydrate). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.85 (t, 3H); 1.23, 1.26 (s, 3H each); 1.63-1.89 (m, 2H); 1.90-2.30 (m, 4H); 2.30-2.50 (m, 1H); 2.72 (t, 2H); 3.53 (m, 2H); 4.19 (m, 2H); 4.53 (m, 1H); 7.22 (m, 1H); 7.53 (dd, 1H); 8.45. Analysis calculated for $C_{20}H_{28}NO_4$ - 0.25 H_2O: C, 65.82; H, 7.87; N, 7.68. Found: C, 66.01; H, 7.85; N, 7.64.

3-(3-Pyridyl)-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate, N-oxide (95)

A solution of 3-(3-pyridyl)-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate (190 mg; 0.52 mmol) and m-chloroperbenzoic acid (160 mg of 57%-86% material, 0.53 mmol) was stirred in methylene chloride (20 mL) at room temperature for 3 hours. The reaction mixture was diluted with methylene chloride and washed twice with 1 N NaOH. The organic extract was dried and concentrated, and the crude material was chromatographed, eluting with 10%

methanol in ethyl acetate, to obtain 130 mg of the Compound 95 of Example 6. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.83 (t, 3H); 1.21 (s, 3H); 1.25 (s, 3H); 1.75-2.23 (m, 8H); 2.69 (t, 2H, J = 7.5); 3.52 (t, 2H, J = 6.3); 4.17 (dd, 2H, J = 6.3); 4.51 (m, 1H); 7.16-7.22 (m, 2H); 8.06-8.11 (m, 2H). Analysis calculated for $C_{20}H_{28}N_2O_5$ - 0.75 H_2O: C, 61.60; H, 7.63; N, 7.18. Found: C, 61.79; H, 7.58; N, 7.23.

Example 7

Synthesis of 3-(3-Pyridyl)-1-propylmercaptyl 2S-1-[(2-methylbutyl)carbamoyl]pyrrolidine-2-carboxylate (101)

3-(3-Pyridyl)-1-propylchloride

To a solution of 3-(3-pyridyl)-1-propanol (10 g; 72.4 mmol) in chloroform (100 mL) was added dropwise a solution of thionyl chloride (12.9 g; 108.6 mmol) in chloroform (50 mL). The resulting mixture was refluxed for 1 hour, then poured into ice-cold 50% aqueous potassium hydroxide (150 mL). The layers were separated, and the organic phase was dried, concentrated, and purified on a silica gel column, eluting with 40% ethylacetate in hexane, to obtain 10 g (65%) of the chloride as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.02-2.11 (m, 2H); 2.77 (m, 2H); 3.51 (m, 2H); 7.20 (m, 1H); 7.49 (m, 1H); 8.45 (m, 2H).

3-(3-Pyridyl)-1-propylmercaptan

A mixture of 3-(3-pyridyl)-1-propylchloride (3 g; 19.4 mmol) and thiourea (1.48 g; 19.4 mmol) in ethanol (10 mL) was refluxed for 24 hours. Aqueous sodium hydroxide, 15 mL of a 0.75 N solution, was added, and the mixture was refluxed for an additional 2 hours. After cooling to room temperature, the solvent was removed *in vacuo*. Chromatographic purification of the crude thiol on a silica gel column eluting with 50% ethyl acetate in hexane delivered 1.2 g of 3-(3-Pyridyl)-1-propylmercaptan as a clear liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.34 (m, 1H); 1.90 (m, 2H); 2.52 (m, 2H); 2.71 (m, 2H); 7.81 (m, 1H); 7.47 (m, 1H); 8.42 (m, 2H).

3-(3-Pyridyl)-1-propylmercaptyl N-(*tert*-butyloxycarbonyl)pyrrolidine-2-carboxylate

A mixture of N-(*tert*-butyloxycarbonyl)-(*S*)-proline (3.0 g; 13.9 mmol); 3-(3-Pyridyl)-1-propylmercaptan (3.20 g; 20.9 mmol), dicyclohexylcarbodiimide (4.59 g; 22.24 mmol), camphorsulfonic acid (1.08 g; 4.63 mmol), and 4-dimethylaminopyridine (0.60 g; 4.63 mmol) in dry methylene chloride (100 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, and the crude residue was purified on a silica gel column eluting with ethyl acetate to obtain 4.60 g (95%) of the thioester as a thick oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.45 (s, 9H); 1.70-2.05 (m, 5H); 2.32 (m, 1H); 2.71 (t, 2H); 2.85 (m, 2H); 3.50 (m, 2H); 4.18 (m, 1H); 7.24 (m, 1H); 7.51 (m, 1H); 8.48 (m, 2H).

3-(3-Pyridyl)-1-propylmercaptyl pyrrolidine-2-carboxylate

A solution of 3-(3-Pyridyl)-1-mercaptyl N-(*tert*-butyloxycarbonyl)pyrrolidine-2-carboxylate (4.60 g; 13.1 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 2.36 g (75%) of the free amine as a thick oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.87-2.20 (m, 6H); 2.79 (m, 2H); 3.03-3.15 (m, 4H total); 3.84 (m, 1H); 7.32 (m, 1H); 7.60 (m, 1H); 8.57 (m, 2H).

3-(3-Pyridyl)-1-propylmercaptyl 2S-1-[(2-methylbutyl)carbamoyl]pyrrolidine-2-carboxylate (101)

A solution of 2-methylbutylamine (113 mg; 1.3 mmol) and triethylamine (132 mg; 1.3 mmol) in methylene chloride (5 mL) was added to a solution of triphosgene (128 mg; 0.43 mmol) in methylene chloride (5 mL). The resulting mixture was

refluxed for 1 hour and then cooled to room temperature. 3-(3-Pyridyl)-1-propylmercaptyl pyrrolidine-2-carboxylate (300 mg; 1.3 mmol) in 5 mL of methylene chloride was added and the resulting mixture was stirred for 1 hour and then partitioned between water and a 1:1 mixture of ethyl acetate and hexane. The organic phase was dried, concentrated and purified by column chromatography (50% ethyl acetate/hexane) to obtain 250 mg (55%) of the compound of Example 7 (Compound 101, Table VII) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$): d ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.89-0.93 (m, 6H); 1.10-1.20 (m, 1H); 1.27 (s, 1H); 1.36-1.60 (m, 2H); 1.72 (s, 2H); 1.97-2.28 (m, 6H); 2.70-2.75 (m, 2H); 2.92-3.54 (m, 6H); 4.45-4.47 (m, 1H); 7.21-7.29 (m, 1H); 7.53-7.56 (dd, 1H); 8.46-8.48 (s, 2H).

Example 8

Synthesis of 3-(3-Pyridyl)-1-propyl 2S-1-[(1',1'-Dimethylpropyl)carbamoyl]pyrrolidine-2-carboxylate (102)

Reaction of 3-(3-pyridyl)-1-propylmercaptyl pyrrolidine-2-carboxylate with the isocyanate generated from *tert*-amylamine and triphosgene, as described for Example 7, provided the compound of Example 8 (Compound 102, Table VII) in 62% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.83 (t, 3H); 1.27 (s, 6H); 1.64-1.71 (m, 2H); 1.91-2.02 (m, 7H); 2.66-2.71 (t, 2H); 2.85 (m, 2H); 3.29-3.42 (m, 2H); 4.11 (br, 1H); 4.37-4.41 (m, 1H).

Example 9

Synthesis of 3-(3-pyridyl)-1-propylmercaptyl 2S-1-[(cyclohexyl)thiocarbamoyl]-pyrrolidine-2-carboxylate (107)

A mixture of cyclohexylisothiocyanate (120 mg; 0.9 mmol), 3-(3-pyridyl)-1-propylmercaptyl pyrrolidine-2-carboxylate (200 mg; 0.9 mmol) and triethylamine (90 mg; 0.9 mmol) in 20 mL of methylene chloride was stirred for 1 hour and then partitioned between water and a 1:1 mixture of ethyl

acetate and hexane. The organic phase was dried, concentrated and purified by column chromatography (50% ethyl acetate/hexane) to obtain 160 mg (47%) of the compound of Example 9 (Compound 107, Table VII). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.16-1.40 (m, 6H); 1.50-1.71 (m, 4H); 1.95-2.08 (m, 7H); 2.70-2.75 (t, 2H); 3.03 (m, 2H); 3.40-3.60 (m, 2H); 4.95-4.98 (d, 1H); 5.26-5.29 (d, 1H); 7.17-7.25 (m, 1H).

Example 10

Synthesis of 3-(*para*-Methoxyphenyl)-1-propylmercaptyl(2*S*)-N-(benzenesulfonyl)pyrrolidine-2-carboxylate (120)

3-(*p*-Methoxyphenyl)-1-propylbromide

To a solution of 3-(*p*-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-(*p*-methoxyphenyl)-1-propylbromide.

3-(*p*-Methoxyphenyl)-1-propylmercaptan

A mixture of 3-(*p*-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 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 brine, dried, and concentrated. Chromatographic purification of the crude thiol on a silica gel column eluting with 2% either in hexane delivered 10.2 g of 3-(*p*-

methoxyphenyl)- 1-propylmercaptan as a clear liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.34 (t, 1H); 1.88-1.92 (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).

3-(*p*-Methoxyphenyl)-1-mercaptyl N-(*tert*-butyloxycarbonyl)pyrrolidine-2-carboxylate

A mixture of N-(*tert*-butyloxycarbonyl)-(*S*)-proline (2.0 g; 9.29 mmol), 3-(*p*-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 (100%) as a thick oil. ^{1}H NMR (300 MHz, $CDCl_3$): 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-(*p*-Methoxyphenyl)-1-mercaptyl pyrrolidine-2-carboxylate

A solution of 3-(*p*-methoxyphenyl)-mercaptyl N-(*tert*-butyloxycarbonyl)pyrrolidine-2-carboxylate (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. ^{1}H NMR (300 MHz, $CDCl_3$): 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-(*para*-Methoxyphenyl)-1-propylmercaptyl (2*S*)-N-(benzenesulfonyl)pyrrolidine-2-carboxylate (120)

A solution of 3-(*p*-methoxyphenyl)-1-mercaptyl pyrrolidine-2-carboxylate (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 120 (Table VIII) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$): 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).

Example 11

Synthesis of 3-(*para*-Methoxyphenyl)-1-propylmercaptyl(2*S*)-N-(α-toluenesulfonyl)pyrrolidine-2-carboxylate (121)

A solution of 3-(*p*-Methoxyphenyl)-1-mercaptyl pyrrolidine-2-carboxylate (645 mg; 2.30 mmol) and α-toluenesulfonyl 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 10 provided the compound of Example 11 (Compound 121, Table VIII) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.65-2.25 (m, 8H); 2.65 (t, 2H); 2.89-2.96 (m, 2H); 3.55-3.73 (m, 2H); 3.80 (s, 3H); 4.32 (s, 2H); 4.70-4.81 (m, 1H); 6.83 (d, 2H); 7.09 (d, 2H); 7.14 (m, 3H); 7.26 (m, 2H).

Example 12

Synthesis of 3-(*para*-Methoxyphenyl)-1-propylmercaptyl(2*S*)-N-(α-toluenesulfonyl)pyrrolidine-2-carboxylate (122)

A solution of 3-(*p*-methoxyphenyl)-1-mercaptyl pyrrolidine-2-carboxylate (567 mg; 2.30 mmol) and *p*-toluenesulfonyl chloride (425 mg; 2.23 mmol) in methylene chloride (5 mL) was stirred overnight at room temperature.

Purification as described for Example 10 provided the compound of Example 12 (Compound 122, Table VIII) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 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).

Example 13

Synthesis of 1,5-Diphenyl-3-pentylmercaptyl N-(para-toluenesulfonyl)pipecolate (134)

3-Phenyl-1-propanal

Oxalyl chloride (2.90 g; 2.29 mmol) in methylene chloride (50 mL), cooled to -78°C, was treated with dimethylsulfoxide (3.4 mL) in 10 mL of methylene chloride. After stirring for 5 min, 3-phenyl-1-propanol (2.72 g; 20 mmol) in 20 mL of methylene chloride was added, and the resulting mixture was stirred at -78°C for 15 min, treated with 14 mL of triethylamine, stirred an additional 15 min, and poured into 100 mL of water. The layers were separated, the organic phase was dried and concentrated, and the crude residue was purified on a silica gel column, eluting with 10% ethyl acetate in hexane, to obtain 1.27 g (47%) of the aldehyde as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.80 (m, 2H); 2.98 (m, 2H); 7.27 (m, 5H); 9.81 (2, 1H).

1,5-Diphenyl-3-pentanol

A solution of 2-(bromoethyl)benzene (1.73 g; 9.33 mmol) in diethylether (10 mL) was added to a stirred slurry of magnesium turnings (250 mg; 10.18 mmol) in 5 mL of ether. The reaction was initiated with a heat gun, and after the addition was complete the mixture was heated on an oil bath for 30 min. 3-Phenyl-1-propanal (1.25 g; 9.33 mmol) was added in 10 mL of ether, and reflux was continued for 1 hour. The reaction was cooled and quenched with saturated ammonium chloride, extracted into 2x ethyl acetate, and the combined

organic portions were dried and concentrated. Chromatographic purification on a silica gel column (10% ethyl acetate in hexane) delivered 1.42 g(63%) of the diphenyl alcohol. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.84 (m, 4H); 2.61-2.76(m, 4H); 3.65 (m, 1H); 7.19-7.29 (m, 10H).

1,5-Diphenyl-3-bromopentane

To a solution of 1,5-diphenyl-3-pentanol (1.20 g (5 mmol) and carbon tetrabromide (1.67 g; 5 mmol) in methylene chloride (20 mL) was added triphenylphosphine (1.31 g; 5 mmol) portionwise, at 0°C. After stirring at room temperature for 18 hours, the mixture was concentrated, triturated with ether, and the solids removed by filtration. The filtrate was passed through a plug of silica gel, eluting with hexane:methylene chloride, 10:1, to give 1.35 g (90%) of the bromide as an oil which was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.11-2.18 (m, 4H); 2.73 (m, 2H); 2.86 (m, 2H); 3.95 (m, 1H); 7.16-7.30 (m, 10H).

1,5-Diphenyl-3-pentylmercaptan

Using the procedure described in Example 10 for the conversion of bromides to thiols, 1,5-diphenyl-3-bromopentane was converted to 1,5-diphenyl-3-pentylmercaptan in 35% overall yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.79 (m, 2H); 1.98 (m, 2H); 2.71 (m, 3H); 2.80 (m, 2H); 7.16-7.28 (m, 10H).

1,5-Diphenyl-3-pentylmercaptyl N-(*tert*-butyloxycarbonyl)pyrrolidine-2-carboxylate

A mixture of N-(*tert*-butyloxycarbonyl)-(*S*)-pipecolic acid (2.11 g; 9.29 mmol), 1,5-diphenyl-3-pentylmercaptan (2.58 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 870 mg (20%) of the product as a

thick oil, which was used without further purification.

1,5-Diphenyl-3-pentylmercaptyl pyrrolidine-2-carboxylate

A solution of 1,5-diphenyl-3-pentylmercaptyl N-(*tert*-butyloxycarbonyl)pyrrolidine-2-carboxylate (850 mg; 1.8 mmol) in methylene chloride (10 mL) and trifluoroacetic acid (1 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. The combined organic extracts were dried and concentrated to yield 480 mg (72%) of the free amine as a thick oil, which was used without further purification.

1,5-Diphenyl-3-pentylmercaptyl N-(*para*-toluenesulfonyl)pipecolate (134)

1,5-Diphenyl-3-pentylmercaptyl N-(*para*-toluenesulfonyl)pipecolate(18) was prepared from 1,5-diphenyl-3-pentylmercaptyl pyrrolidine-2-carboxylate and *para*-toluenesulfonyl chloride as described for Example 12, in 65% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.80 (m, 4H); 1.23-1.97 (m, 5H); 2.15 (d, 1H); 2.61-2.69 (m, 4H); 3.23 (m, 1H); 3.44 (dm, 1H); 4.27 (s, 2H); 4.53 (d, 1H, J = 4.5); 5.06 (m, 1H); 7.16-7.34 (m, 15H).

Example 14

Synthesis of 3-phenyl-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate (137)

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. ^1H NMR ($CDCl_3$): d 1.93 (dm, 2H); 2.17 (m, 2H); 3.62 (m, 2H); 3.71 (s, 3H); 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. ^1H NMR ($CDCl_3$): d 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).

Synthesis of (2*S*)-1-(1,2-dioxo-3,3-dimethylpentyl)-2-pyrrolidinecarboxylic 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. ^1H NMR ($CDCl_3$): d 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).

3-Phenyl-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate (137)

A mixture of (2*S*)-1-(1,2-dioxo-3,3-dimethylpentyl)-2-pyrrolidine-carboxylic acid (600 mg; 2.49 mmol), 3-phenyl-1-propanol (508 mg; 3.73 mmol), dicyclohexylcarbodiimide (822 mg; 3.98 mmol), camphorsulfonic acid (190 mg; 0.8 mmol) and 4-dimethylaminopyridine (100 mg; 0.8 mmol) in methylene chloride (20 mL) was stirred overnight under a nitrogen atmosphere. The reaction mixture was filtered through Celite to remove solids and concentrated in vacuo, and the crude material was purified on a flash column (25% ethyl acetate in hexane) to obtain 720 mg (80%) of Example 14 as a colorless oil. ^{1}H NMR ($CDCl_3$): d 0.84 (t, 3H); 1.19 (s, 3H); 1.23 (s, 3H); 1.70 (dm, 2H); 1.98 (m, 5H); 2.22 (m, 1H); 2.64 (m, 2H); 3.47 (m, 2H); 4.14 (m, 2H); 4.51 (d, 1H); 7.16 (m, 3H); 7.26 (m, 2H).

Example 15

The method of Example 14 was utilized to prepare the following illustrative compounds.

Compound 138: 3-phenyl-1-prop-2-(E)-enyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate, 80%. ^{1}H NMR (360 Mhz, $CDCl_3$): d 0.86 (t, 3H); 1.21 (s, 3H); 1.25 (s, 3H); 1.54-2.10 (m, 5H); 2.10-2.37 (m, 1H); 3.52-3.55 (m, 2H); 4.56 (dd, 1H, J = 3.8, 8.9); 4.78-4.83 (m, 2H); 6.27 (m, 1H); 6.67 (dd, 1H, J = 15.9); 7.13-7.50 (m, 5H).

Compound 139: 3-(3,4,5-trimethoxyphenyl)-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidine- carboxylate, 61%. ^{1}H NMR ($CDCl_3$): d 0.84 (t, 3H); 1.15 (s, 3H); 1.24 (s, 3H); 1.71 (dm, 2H); 1.98 (m, 5H); 2.24 (m, 1H); 2.63 (m, 2H);

3.51 (t, 2H); 3.79 (s, 3H); 3.83 (s, 3H); 4.14 (m, 2H); 4.52 (m, 1H); 6.36 (s, 2H).

Compound 140: 3-(3,4,5-trimethoxyphenyl)-1-prop-2-(E)-enyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidine carboxylate, 66%. ^{1}H NMR ($CDCl_3$): d 0.85 (t, 3H); 1.22 (s, 3H); 1.25 (s, 3H); 1.50-2.11 (m, 5H); 2.11-2.40 (m, 1H); 3.55 (m, 2H); 3.85 (s, 3H); 3.88 (s, 6H); 4.56 (dd, 1H); 4.81 (m, 2H); 6.22 (m, 1H); 6.58 (d, 1H, J = 16); 6.63 (s, 2H).

Compound 141: 3-(4,5-methylenedioxyphenyl)-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidine- carboxylate, 82%. ^{1}H NMR (360 MHz, $CDCl_3$): d 0.86 (t, 3H); 1.22 (s, 3H); 1.25 (s, 3H); 1.60-2.10 (m, 5H); 3.36-3.79 (m, 2H); 4.53 (dd, 1H, J = 3.8, 8.6); 4.61-4.89 (m, 2H); 5.96 (s, 2H); 6.10 (m, 1H); 6.57 (dd, 1H, J = 6.2, 15.8); 6.75 (d, 1H, J = 8.0); 6.83 (dd, 1H, J = 1.3, 8.0); 6.93 (s, 1H).

Compound 142: 3-(4,5-methylenedioxyphenyl)-1-prop-2-(E)-enyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate, 82%. ^{1}H NMR (360 MHz, $CDCl_3$): d 0.86 (t, 3H); 1.22 (s, 3H); 1.25 (s, 3H); 1.60-2.10 (m, 5H); 2.10-2.39 (m, 1H); 3.36-3.79 (m, 2H); 4.53 (dd, 1H, J = 3.8, 8.6); 4.61-4.89 (m, 2H); 5.96 (s, 2H); 6.10 (m, 1H); 6.57 (dd, 1H, J = 6.2, 15.8); 6.75 (d, 1H, J = 8.0); 6.83 (dd, 1H, J = 1.3, 8.0); 6.93 (s, 1H).

Compound 144: 3-cyclohexyl-1-prop-2-(E)-enyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidine-carboxylate, 92%. ^{1}H NMR (360 MHz, $CDCl_3$): d 0.86 (t, 3H); 1.13-1.40 (m + 2 singlets, 9H total); 1.50-1.87 (m, 8H); 1.87-2.44 (m, 6H); 3.34-3.82 (m, 2H); 4.40-4.76 (m, 3H); 5.35-5.60 (m, 1H); 5.60-5.82 (dd, 1H, J = 6.5, 16).

Compound 145: (1*R*)-1,3-Diphenyl-1-propyl (2*S*)-1-(3,3-

dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate, 90%. ^{1}H NMR (360 MHz, $CDCl_3$): d 0.85 (t, 3H); 1.20 (s, 3H); 1.23 (s, 3H); 1.49-2.39 (m, 7H); 2.46-2.86 (m, 2H); 3.25-3.80 (m, 2H); 4.42-4.82 (m, 1H); 5.82 (td, 1H, J = 1.8, 6.7); 7.05-7.21 (m, 3H); 7.21-7.46 (m, 7H).

Compound 146: 3-phenyl-1-propyl (2*S*)-1-(1,2-dioxo-2-[2-furanyl])ethyl-2-pyrrolidinecarboxylate, 99%. ^{1}H NMR (300 MHz, $CDCl_3$): d 1.66-2.41 (m, 6H); 2.72 (t, 2H, J = 7.5); 3.75 (m, 2H); 4.21 (m, 2H); 4.61 (m, 1H); 6.58 (m, 1H); 7.16-7.29 (m, 5H); 7.73 (m, 2H).

Compound 147: 3-phenyl-1-propyl (2*S*)-1-(1,2-dioxo-2-[2-thienyl])ethyl-2-pyrrolidinecarboxylate, 81%. ^{1}H NMR (300 MHz, $CDCl_3$): d 1.88-2.41 (m, 6H); 2.72 (dm, 2H); 3.72 (m, 2H); 4.05 (m, 1H); 4.22 (m, 1H); 4.64 (m, 1H); 7.13-7.29 (m, 6H); 7.75 (dm, 1H); 8.05 (m, 1H).

Compound 149: 3-phenyl-1-propyl (2*S*)-1-(1,2-dioxo-2-phenyl)ethyl-2-pyrrolidinecarboxylate, 99%. ^{1}H NMR (300 MHz, $CDCl_3$): d 1.97-2.32 (m, 6H); 2.74 (t, 2H, J = 7.5); 3.57 (m, 2H); 4.24 (m, 2H); 4.67 (m, 1H); 6.95-7.28 (m, 5H); 7.51-7.64 (m, 3H); 8.03-8.09 (m, 2H).

Compound 150: 3-(2,5-dimethoxyphenyl)-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidine- carboxylate, 99%. ^{1}H NMR (300 MHz, $CDCl_3$): d 0.87 (t, 3H); 1.22 (s, 3H); 1.26 (s, 3H); 1.69 (m, 2H); 1.96 (m, 5H); 2.24 (m, 1H); 2.68 (m, 2H); 3.55 (m, 2H); 3.75 (s, 3H); 3.77 (s, 3H); 4.17 (m, 2H); 4.53 (d, 1H); 6.72 (m, 3H).

Compound 151: 3-(2,5-dimethoxyphenyl)-1-prop-2-(E)-enyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidine-carboxylate, 99%. ^{1}H NMR (300 MHz, $CDCl_3$): d 0.87 (t, 3H); 1.22 (s, 3H); 1.26 (s, 3H); 1.67 (m, 2H); 1.78 (m, 1H); 2.07

(m, 2H); 2.26 (m, 1H); 3.52 (m, 2H); 3.78 (s, 3H); 3.80 (s, 3H); 4.54 (m, 1H); 4.81 (m, 2H); 6.29 (dt, 1H, J = 15.9); 6.98 (s, 1H).

Compound 152: 2-(3,4,5-trimethoxyphenyl)-1-ethyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidine- carboxylate, 97%. ^{1}H NMR (300 MHz, $CDCl_3$): d 0.84 (t, 3H); 1.15 (s, 3H); 1.24 (s, 3H); 1.71 (dm, 2H); 1.98 (m, 5H); 2.24 (m, 1H); 2.63 (m, 2H); 3.51 (t, 2H); 3.79 (s, 3H); 3.83 (s, 3H); 4.14 (m, 2H); 4.52 (m, 1H); 6.36 (s, 2H).

Compound 153: 3-(3-Pyridyl)-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate, 80%. ^{1}H NMR ($CDCl_3$, 300 MHz): d 0.85 (t, 3H); 1.23, 1.26 (s, 3H each); 1.63-1.89 (m, 2H); 1.90-2.30 (m, 4H); 2.30-2.50 (m, 1H); 2.72 (t, 2H); 3.53 (m, 2H); 4.19 (m, 2H); 4.53 (m, 1H); 7.22 (m, 1H); 7.53 (dd, 1H); 8.45.

Compound 154: 3-(2-Pyridyl)-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate, 88%. ^{1}H NMR ($CDCl_3$, 300 MHz): d 0.84 (t, 3H); 1.22, 1.27 (s, 3H each); 1.68-2.32 (m, 8H); 2.88 (t, 2H, J = 7.5); 3.52 (m, 2H); 4.20 (m, 2H); 4.51 (m, 1H); 7.09-7.19 (m, 2H); 7.59 (m, 1H); 8.53 (d, 1H, J = 4.9).

Compound 155: 3-(4-Pyridyl)-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate, 91%. ^{1}H NMR ($CDCl_3$, 300 MHz): d 6.92-6.80 (m, 4H); 6.28 (m, 1H); 5.25 (d, 1H, J = 5.7); 4.12 (m, 1H); 4.08 (s, 3H); 3.79 (s, 3H); 3.30 (m, 2H); 2.33 (m, 1H); 1.85-1.22 (m, 7H); 1.25 (s, 3H); 1.23 (s, 3H); 0.89 (t, 3H, J = 7.5).

Compound 156: 3-phenyl-1-propyl (2*S*)-1-(2-cyclohexyl-1,2-dioxoethyl)-2-pyrrolidinecarboxylate, 91%. ^{1}H NMR ($CDCl_3$, 300

MHz): d 1.09-1.33 (m, 5H); 1.62-2.33 (m, 12H); 2.69 (t, 2H, J = 7.5); 3.15 (dm, 1H); 3.68 (m, 2H); 4.16 (m, 2H); 4.53, 4.84 (d, 1H total); 7.19 (m, 3H); 7.29 (m, 2H).

Compound 157: 3-phenyl-1-propyl (2*S*)-1-(2-*tert*-butyl-1,2-dioxoethyl)-2-pyrrolidinecarboxylate, 92%. ^{1}H NMR ($CDCl_3$, 300 MHz): d 1.29 (s, 9H); 1.94-2.03 (m, 5H); 2.21 (m, 1H); 2.69 (m, 2H); 3.50-3.52 (m, 2H); 4.16 (m, 2H); 4.53 (m, 1H); 7.19 (m, 3H); 7.30 (m, 2H).

Compound 158: 3-phenyl-1-propyl (2*S*)-1-(2-cyclohexyl- ethyl-1,2-dioxoethyl)-2-pyrrolidinecarboxylate, 97%. ^{1}H NMR ($CDCl_3$, 300 MHz): d 0.88 (m, 2H); 1.16 (m, 4H); 1.43-1.51 (m, 2H); 1.67 (m, 5H); 1.94-2.01 (m, 6H); 2.66-2.87 (m, 4H); 3.62-3.77 (m, 2H); 4.15 (m, 2H); 4.86 (m, 1H); 7.17-7.32 (m, 5H).

Compound 159: 3-(3-pyridyl)-1-propyl (2*S*)-1-(2-cyclo-hexylethyl-1,2-dioxoethyl)-2-pyrrolidinecarboxylate, 70%. ^{1}H NMR ($CDCl_3$, 300 MHz): d 0.87 (m, 2H); 1.16 (m, 4H); 1.49 (m, 2H); 1.68 (m, 4H); 1.95-2.32 (m, 7H); 2.71 (m, 2H); 2.85 (m, 2H); 3.63-3.78 (m, 2H); 4.19 (m, 2H); 5.30 (m, 1H); 7.23 (m, 1H); 7.53 (m, 1H); 8.46 (m, 2H).

Compound 160: 3-(3-pyridyl)-1-propyl (2*S*)-1-(2-*tert*-butyl-1,2-dioxoethyl)-2-pyrrolidinecarboxylate, 83%. ^{1}H NMR ($CDCl_3$, 300 MHz): d 1.29 (s, 9H); 1.95-2.04 (m, 5H); 2.31 (m, 1H); 2.72 (t, 2H, J = 7.5); 3.52 (m, 2H); 4.18 (m, 2H); 4.52 (m, 1H); 7.19-7.25 (m, 1H); 7.53 (m, 1H); 8.46 (m, 2H).

Compound 161: 3,3-diphenyl-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate, 99%. ^{1}H NMR ($CDCl_3$, 300 MHz): d 0.85 (t, 3H); 1.21, 1.26 (s, 3H each); 1.68-2.04 (m, 5H); 2.31 (m, 1H); 2.40 (m, 2H); 3.51 (m, 2H); 4.08 (m, 3H); 4.52 (m, 1H); 7.18-7.31 (m, 10H).

Compound 162: 3-(3-pyridyl)-1-propyl (2*S*)-1-(2-cyclo- hexyl-1,2-dioxoethyl)-2-pyrrolidinecarboxylate, 88%. ^{1}H NMR ($CDCl_3$, 300 MHz): d 1.24-1.28 (m, 5H); 1.88-2.35 (m, 11H); 2.72 (t, 2H, J = 7.5); 3.00-3.33 (dm, 1H); 3.69 (m, 2H); 4.19 (m, 2H); 4.55 (m, 1H); 7.20-7.24 (m, 1H); 7.53 (m, 1H); 8.47 (m, 2H).

Compound 163: 3-(3-Pyridyl)-1-propyl (2*S*)-N-([2-thienyl] glyoxyl)pyrrolidinecarboxylate, 49%. ^{1}H NMR ($CDCl_3$, 300 MHz): d 1.81-2.39 (m, 6H); 2.72 (dm, 2H); 3.73 (m, 2H); 4.21 (m, 2H); 4.95 (m, 1H); 7.19 (m, 2H); 7.61 (m, 1H); 7.80 (d, 1H); 8.04 (d, 1H); 8.46 (m, 2H).

Compound 164: 3,3-Diphenyl-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxobutyl)-2-pyrrolidinecarboxylate, 99%. ^{1}H NMR ($CDCl_3$, 300 MHz): d 1.27 (s, 9H); 1.96 (m, 2H); 2.44 (m, 4H); 3.49 (m, 1H); 3.64 (m, 1H); 4.08 (m, 4H); 4.53 (dd, 1H); 7.24 (m, 10H).

Compound 165: 3,3-Diphenyl-1-propyl (2*S*)-1-cyclohexyl glyoxyl-2-pyrrolidinecarboxylate, 91%. ^{1}H NMR ($CDCl_3$, 300 MHz): d 1.32 (m, 6H); 1.54-2.41 (m, 10H); 3.20 (dm, 1H); 3.69 (m, 2H); 4.12 (m, 4H); 4.52 (d, 1H); 7.28 (m, 10H).

Compound 166: 3,3-Diphenyl-1-propyl (2*S*)-1-(2-thienyl) glyoxyl-2-pyrrolidinecarboxylate, 75%. ^{1}H NMR ($CDCl_3$, 300 MHz): d 2.04 (m, 3H); 2.26 (m, 2H); 2.48 (m, 1H); 3.70 (m, 2H); 3.82-4.18 (m, 3H total); 4.64 (m, 1H); 7.25 (m, 11H); 7.76 (dd, 1H); 8.03 (m, 1H).

Example 16

General procedure for the synthesis of acrylic esters, exemplified for methyl (3,3,5-trimethoxy)-*trans*-cinnamate.

A solution of 3,4,5-trimethoxybenzaldehyde (5.0 g; 25.48 mmol) and methyl (triphenyl- phosphoranylidene)acetate (10.0 g; 29.91 mmol) in tetrahydrofuran (250 mL) was refluxed

overnight. After cooling, the reaction mixture was diluted with 200 mL of ethyl acetate and washed with 2 x 200 mL of water, dried, and concentrated in vacuo. The crude residue was chromatographed on a silica gel column, eluting with 25% ethyl acetate in hexane, to obtain 5.63 g (88%) of the cinnamate as a white crystalline solid. ^{1}H NMR (300 Mhz; $CDCl_3$): d 3.78 (s, 3H); 3.85 (s, 6H); 6.32 (d, 1H, J = 16); 6.72 (s, 2H); 7.59 (d, 1H, J = 16).

Example 17

General procedure for the synthesis of saturated alcohols from acrylic esters, exemplified for (3,4,5-trimethoxy) phenylpropanol.

A solution of methyl (3,3,5-trimethoxy)-*trans*-cinnamate (1.81 g; 7.17 mmol) in tetrahydrofuran (30 mL) was added in a dropwise manner to a solution of lithium aluminum hydride (14 mmol) in THF (35 mL), with stirring and under an argon atmosphere. After the addition was complete, the mixture was heated to 75°C for 4 hours. After cooling, it was quenched by the careful addition of 15 mL of 2 N NaOH followed by 50 mL of water. The resulting mixture was filtered through Celite to remove solids, and the filter cake was washed with ethyl acetate. The combined organic fractions were washed with water, dried, concentrated in vacuo, and purified on a silica gel column, eluting with ethyl acetate to obtain 0.86 g (53%) of the alcohol as a clear oil. ^{1}H NMR (300 Mhz; $CDCl_3$): d 1.23 (br, 1H); 1.87 (m, 2H); 2.61 (t, 2H, J = 7.1); 3.66 (t, 2H); 3.80 (s, 3H); 3.83 (s, 6H); 6.40 (s, 2H).

Example 18

General procedure for the synthesis of *trans*-allylic alcohols from acrylic esters, exemplified for (3,4,5-trimethoxy)phenylprop-2-(E)-enol.

A solution of methyl (3,3,5-trimethoxy)-*trans*-cinnamate (1.35 g; 5.35 mmol) in toluene (25 mL) was cooled to -10°C

and treated with a solution of diisobutylaluminum hydride in toluene (11.25 mL of a 1.0 M solution; 11.25 mmol). The reaction mixture was stirred for 3 hours at 0°C and then quenched with 3 mL of methanol followed by 1 N HCl until the pH was 1. The reaction mixture was extracted into ethyl acetate and the organic phase was washed with water, dried and concentrated. Purification on a silica gel column eluting with 25% ethyl acetate in hexane furnished 0.96 g (80%) of a thick oil. ^{1}H NMR (360 Mhz; $CDCl_3$): d 3.85 (s, 3H); 3.87 (s, 6H); 4.32 (d, 2H, J = 5.6); 6.29 (dt, 1H, J = 15.8, 5.7), 6.54 (d, 1H, J = 15.8); 6.61 (s, 2H).

Example 19

Synthesis of 3-phenyl-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate (1)

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 ($CDCl_3$): d 1.93 (dm, 2H); 2.17 (m, 2H); 3.62 (m, 2H); 3.71 (s, 3H); 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 ($CDCl_3$): d 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).

Synthesis of (2*S*)-1-(1,2-dioxo-3,3-dimethylpentyl)-2-pyrrolidinecarboxylic 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 ($CDCl_3$): d 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).

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

A mixture of (2*S*)-1-(1,2-dioxo-3,3-dimethylpentyl)-2-pyrrolidine-carboxylic acid (600 mg; 2.49 mmol), 3-phenyl-1-propanol (508 mg; 3.73 mmol), dicyclohexylcarbodiimide (822 mg; 3.98 mmol), camphorsulfonic acid (190 mg; 0.8 mmol) and 4-dimethylaminopyridine (100 mg; 0.8 mmol) in methylene

chloride (20 ml) was stirred overnight under a nitrogen atmosphere. The reaction mixture was filtered through Celite to remove solids and concentrated in vacuo, and the crude material was purified on a flash column (25% ethyl acetate in hexane) to obtain 720 mg (80%) of Example 1 as a colorless oil. ^{1}H NMR ($CDCl_3$): d 0.84 (t, 3H); 1.19 (s, 3H); 1.23 (s, 3H); 1.70 (dm, 2H); 1.98 (m, 5H); 2.22 (m, 1H); 2.64 (m, 2H); 3.47 (m, 2H); 4.14 (m, 2H); 4.51 (d, 1H); 7.16 (m, 3H); 7.26 (m, 2H).

Figure 1. GPI 1046 protects retinal ganglion cells against degeneration following retinal ischemia.

Retinal ganglion cells were retrogradely labeled in adult rats by bilateral injection of fluorogold in their lateral geniculate nuclei. Labeled ganglion cells in the normal rat retina appear as white profiles against the dark background (Figure 1A). Complete retinal ischemia was produced by infusing normal saline solution into the retinal vitreous cavity of each eye until the intraocular pressure exceeded arterial blood pressure. 28 days after the ischemic episode extensive degeneration of retinal ganglion cell was evidenced by massive reduction in the density of fluorogold labeled cells (Figure 1B). Administration of GPI 1046 (10mg/kg, s.c.) 1 hour prior to the ischemic episode and at 10mg/kg/day for the next four days produced noticeable protection of a large proportion of the vulnerable ganglion cell population (Figure 1C).

Figure 2. GPI 1046 prevents degeneration of optic nerve axons and myelin following retinal ischemia

Examination of the optic nerves from the same retinal ischemia cases reveals that GPI 1046 produces dramatic protection of optic nerve element from ischemic degeneration. Toluidine blue staining of epon embedded optic nerve cross sections revealed the detail of myelin sheaths (white

circles) and optic nerve axons (black centers) in the normal rat optic nerve. Optic nerves from vehicle treated cases examined 28 days after a 1 hour retinal ischemic episode are characterized by a decreased density of optic nerve axons and the appearance of numerous degenerating myelin figures (bright white filled circles). Treatment with GPI 1046 protected the majority of optic nerve axons from degeneration and also dramatically decreased the density of degenerating myelin figures.

Figure 3. GPI 1046 provides moderate protection against retinal ganglion cell death after optic nerve transection

Complete transection of the optic nerve 5 mm from the eyeball produces massive degeneration of retinal ganglion cells, representing loss of >87% of the normal ganglion cell population 90 days after the injury (Table 1). Few spared fluorogold pre labeled ganglion cells are present in vehicle treated cases (large white figures) among a population of small microglia that digest the debris of the degenerating cells and take up the fluorogold label (Figure 3A). Treatment with GPI 1046 for 14 days resulted in a small but not significant increase in the density of retinal ganglion cells that survived 90 days after transection (Table 1) but treatment with GPI 1046 for the first 28 days after transection produced moderate but significant protection of 12.6% of the vulnerable ganglion cell population (Table 1, Figure 3B).

Figure 4. GPI 1046 treatment duration significantly affects the process of optic nerve axonal degeneration after transection.

Examination of optic nerve axon density in the proximal stump of the optic nerve from the same cases revealed a more dramatic protection afforded by GPI 1046 treatment. 90 days

after transection few ganglion cell axons remain within the optic nerve (Figure 4B), representing only 5.6% of the normal population. The loss of axons reflects both the death of retinal ganglion cells and the regression or "dying back" of the axons of ~ 70% of the small surviving ganglion cell population into the retina itself (Table 1). Treatment with GPI 1046 for the first 14 days after optic nerve transection produced a small but significant 5.3% protection of optic nerve axons (Figure 4D, Table 1), but treatment with the same dose of GPI 1046 for 28 days resulted in the protection of optic nerve axons for the vast majority (81.4%) of spared retinal ganglion cells (Figure 4C, Table 1).

Figure 5. GPI 1046 treatment produces a greater effect on optic nerve axons than ganglion cell bodies

This summary figure shows data from Figure 3 ganglion cell protection and higher power photomicrographs of optic nerve axon protection (Figure 5A&B, upper panels). 28 day treatment with GPI 1046 produced a significant increase in the density of large, and particularly medium and small caliber optic nerve axons (Figure 5C&D, lower panels).

Figure 6. GPI 1046 treatment for 28 days after optic nerve transection prevents myelin degeneration in the proximal stump

Myelin basic protein immunohistochemistry labels fascicles (darker labeled 'islands') of myelinated axons in the normal optic nerve (Figure 6A, upper left). 90 days after transection extensive degeneration of myelin is evident in vehicle treated cases, characterized by the loss of fascicular organization and the appearance of numerous large dense degenerating myelin figures (Figure 6B, upper right). Treatment with GPI 1046 for the first 14 days after optic nerve transection did not alter the pattern of myelin degeneration (Figure 6C, lower left panel), and yielded an

insignificant 1.6% quantitative recovery in myelin density (Table 1). Extending the GPI 1046 treatment course through the first 28 days after optic nerve transection produced a dramatic preservation of the fascicular staining pattern for myelin basic protein in the proximal stump of the optic nerve and decreased the density of degenerating myelin figures (Figure 6D, lower right panel), representing a '70% recovery of myelin density (Table 1).

Figure 7. FKBP-12 immunohistochemistry labels oligodendroglia (large dark cells with fibrous processes), the cells which produce myelin, located between the fascicles of optic nerve fibers, and also some optic nerve axons.

Figure 8. GPI 1046 treatment for 28 days after optic nerve transection prevents myelin degeneration in the distal stump. Complete transection of the optic nerve leads to degeneration of the distal segments (axon fragments disconnected from the ganglion cell bodies), and the degeneration of their myelin sheaths. 90 days after transection (Figure 8B) myelin basic protein immunohistochemistry reveals the near total loss of fascicular organization (present in the normal optic nerve, Figure 8A) and the presence of numerous dense degenerating myelin figures. Quantitation reveals that the cross sectional area of the transected distal stump shrinks by 31% and loses approximately 1/2 of its myelin (Table 1). Treatment with GPI 1046 for the first 14 days after transection did not protect against shrinkage of the distal stump but did slightly increase the density of myelin, though the density of degenerating myelin figures remained high (Figure 8C, Table 1). GPI 1046 treatment through the first 28 days produced dramatic protection of the fascicular pattern of myelin labeling, decreased the density of degenerating myelin figures, prevented cross sectional

shrinkage of the distal stump of the transected nerve and maintained the myelin levels at ~99% of normal levels (Figure 8D, Table 1).

Figure 9. 28 day treatment with GPI 1046 treatment beginning 8 weeks after onset of streptozotocin induced diabetes decreases the extent of neovascularization in the inner and outer retina and protects neurons in the inner nuclear layer (INL) and ganglion cell layer (GCL) from degeneration.

Negative images of cresyl violet stained tangential retinal sections reveals perikarya in the three cellular layers (Figure 9A). The retinae of streptozotocin treated animals administered only vehicle (Figure 9B) exhibited loss of cells from the ONL and INL, decreased thickness of the Outer plexiform layer (the dark area between ONL and INL) and a dramatic increase in the size and density of retinal blood vessels (large black circular outlines) in the INL, OPL, ONL and the photoreceptor layer (PR, the gray fuzzy area above the ONL). GPI 1046 treatment reduced neovascularization (i.e. prevented the proliferation of blood vessels) in the PR, ONL, OPL and INL. Although GPI 1046 did not appear to protect against neuronal loss in the ONL, it appeared to decrease the loss of neurons in both the INL and GCL compared to streptozotocin/vehicle treated controls.

Example 20

In Vivo Retinal Ganglion Cell and Optic Nerve Axon Tests

The extent of degeneration reduction or prevention in retinal ganglion cells and optic nerve axons was determined in a vision loss model utilizing surgical optic nerve transection to simulate mechanical damage to the optic nerve. The effects of several neuroimmunophilin FKBP ligands on retinal ganglion cells neuroprotection and optic nerve axon

density was determined experimentally, comparing 14 day and 28 day neuroimmunophilin FKBP ligand treatments. The effects of treatment with neuroimmunophilin FKBP ligands on retinal ganglion cells and optic nerve axons was correlated.

Surgical Procedures

Adult male Sprague Dawley rats (3 months old, 225-250 grams) were anesthetized with a ketamine (87mg/kg) and xylazine (13mg/kg) mixture. Retinal ganglion cells were pre-labeled by bilateral stereotaxic injection of the fluorescent retrogradely transported marker fluoro-gold (FG, 0.5 microliters of 2.5% solution in saline) at the coordinates of the LGNd (4.5 millimeters post β, 3.5 millimeters lateral, 4.6 millimeters below dura). Four days later, FG labeled rats underwent a second surgery for microsurgical bilateral intraorbital optic nerve transection 4-5 millimeters behind the orbit.

Experimental animals were divided into six experimental groups of six rats (12 eyes) per group. One group received a neuroimmunophilin FKBP ligand (10 milligrams per kg per day sc in PEG vehicle (20 percent propylene glycol, 20 percent ethanol, and 60 percent saline)) for 14 days. A second group received the same neuroimmunophilin FKBP ligand dose for 28 days. Each treated group had a corresponding sham/surgery and transection control group which received corresponding 14 or 28 day dosing with the vehicle only.

All animals were sacrificed 90 days after optic nerve transection and perfused pericardially with formalin. All eyes and optic nerves stumps were removed. Cases were excluded from the study if the optic nerve vasculature was damaged or if FG labeling was absent in the retina.

Retinal Ganglion Cell Counts

Retinas were removed from eyes and prepared for wholemount analysis. For each group, five eyes with dense and intense FG labeling were selected for quantitative analysis using a 20 power objective. Digital images were

obtained from five fields in the central retina (3-4 millimeters radial to optic nerve head). FG labeled Large (>18 μm), medium (12-16 μm), and small (<10 μm) ganglion cells and microglia were counted in five 400 μm by 400 μm fields per case, 5 cases per group.

Examination of Optic Nerves

Proximal and distal optic nerve stumps were identified, measured, and transferred to 30% sucrose saline. The proximal stumps of five nerves were blocked and affixed to a chuck, and 10 micron cross sections were cut on a cryostat; one in ten sections were saved per set. Sections including the region 1-2 mm behind the orbit were reacted for RT97 neurofilament immunohistochemistry. Analysis of optic nerve axon density was performed using a 63 power oil immersion lens, a Dage 81 camera, and the Simple Image Analysis program. RT97 positive optic nerve axons were counted in three 200 μm by 200 μm fields per nerve. The area of the nerve was also determined for each case at 10 power.

As depicted graphically in Table I & II, the 14 day course of treatment with a neuroimmunophilin FKBP ligand provided moderate neuroprotection of retinal ganglion cells observed 28 days after optic nerve transection. However, by 90 days after transection, only 5% of the ganglion cell population remained viable.

90 days after optic nerve transection the number of axons persisting in the proximal stump of the optic nerve represented approximately one half of the number of surviving ganglion cells in groups of animals that received vehicle alone or the 14 day course of treatment with a neuroimmunophilin FKBP ligand. These results indicate that over half of the transected ganglion cell axons retract beyond the optic nerve head, and that treatment with a neuroimmunophilin FKBP ligand during the first 14 days after optic nerve transection is not sufficient to arrest this retraction.

As depicted graphically in Table I & II, more prolonged treatment with a neuroimmunophilin FKBP ligand during the 28 day course of treatment produced a moderate increase in retinal ganglion cell neuroprotection. Approximately 12% of the vulnerable retinal ganglion cell population was protected. A similar proportion (~50%) of optic nerve axon density sparing was also observed. These results demonstate the startling result that extending the duration of treatment with a neuroimmunophilin FKBP ligands to 28 days after transection completely arrests the regression of damaged axons for essentially the entire surviving population of retinal ganglion cells.

Additional results are set forth in Tables III and IV.

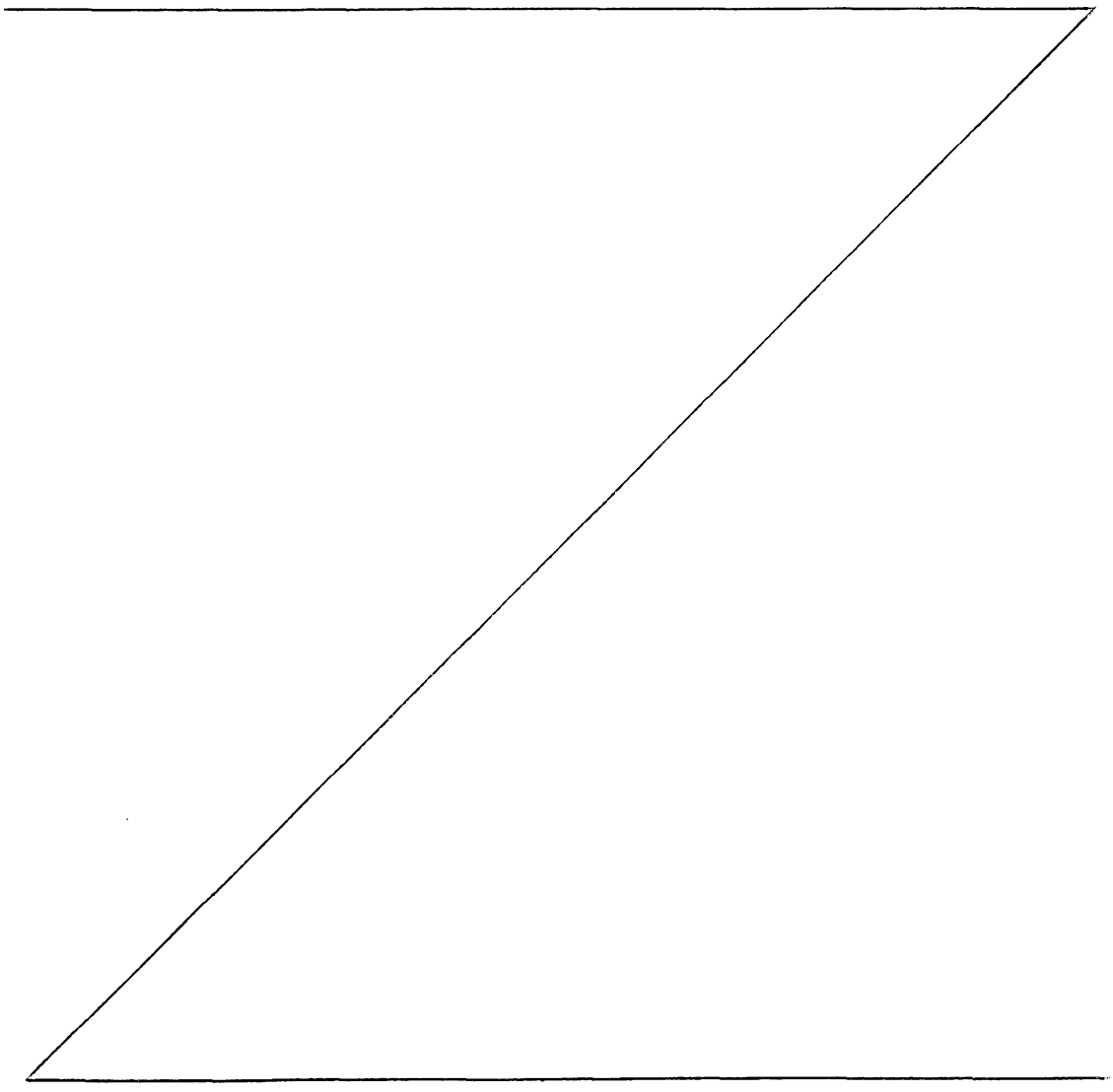


Table 1

Effect of prolonged GPI 1046 treatment on retinal ganglion cell survival, optic nerve axon perservation, and myelination 90 days after optic nerve transection

GROUP	RGC Counts[1]	ON Axon density[2]	ON head area (%sham)	% RGCs Rescued	increased ON axon density[3]	Spared RGC population	ON axon Count[4]	% surviving RGCs with ON axons	Proximal optic nerve myelin basic protein Density [5]
Sham	290 ± 14.8	7600*	100%	-		120,000*	120,000	100%	**normal**
ONT/Vehicle	35.9 ± 2.8	428 ± 34	68%	*(87% loss)*		14,855	*4593*	*30.9%*	*52+ 5.2 SEM % loss*
ONT/ 14 days GPI 1046	49 ± 5.3	569 ± 23	76%	**5.3%**	**1.5X**	20,275	**6820**	**33.6%**	**1.6 ± 3.0SEM %recovery**
ONT/ 28 days GPI 1046	67.9 + 5.8*	1526 ± 120*	95%*	**12.6%***	**5.0X**	28,096*	**22,861***	**81.4%**	**70 ± 6.3 SEM %recovery***

*significance p<.001

[1] Mean density + SEM of Fluoro-gold labeled retinal ganglion cells (RGC) in 400 μm x 400 μm sample gridfields.

[2] mean density + SEM of RT97 neurofilament antibody labeled optic nerve (ON) axons in 200 μm x 200μm region of interest

*estimate for 200 μm x 200μm region in normal optic nerve assuming 120,000 RGC axons in normal rat optic nerve, measured to be 0.630 mm^2 mean cross sectional area

[3] adjusted for optic nerve diameter

[4] calculated by multiplying axonal density by ON area

[5] determined from 20X analysis of % areal coverage of optic nerve cross section

Table II

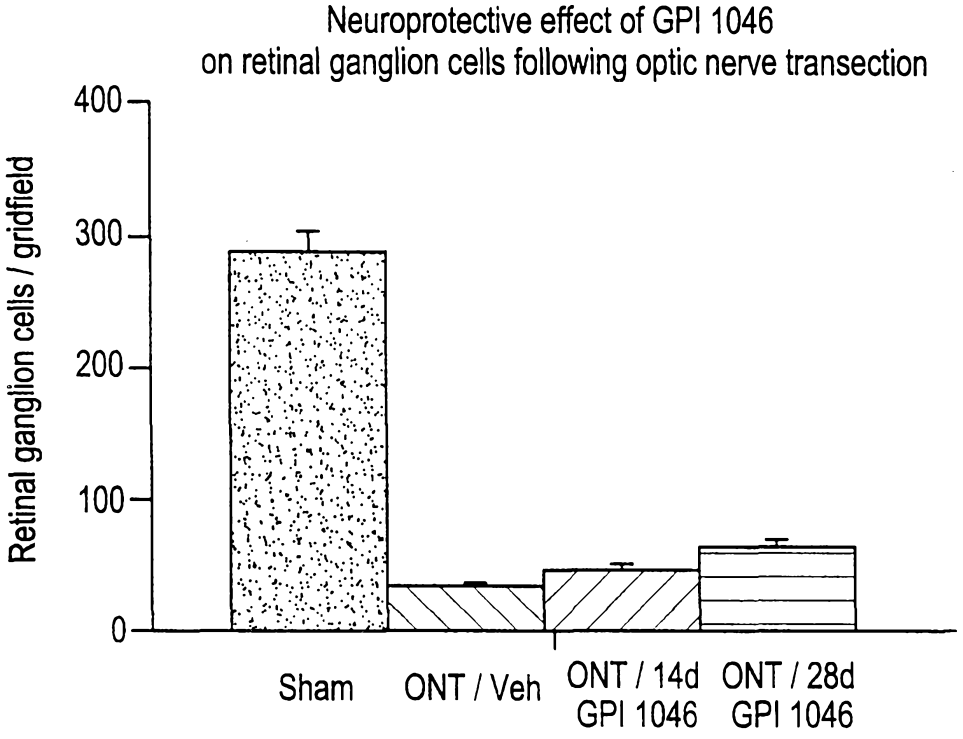

Neuroprotective effect of GPI 1046
on retinal ganglion cells following optic nerve transection
Retinal ganglion cells / gridfield
400
300
200
100
0
Sham
ONT / Veh
ONT / 14d GPI 1046
ONT / 28d GPI 1046

Table III

Correlation between Retinal Ganglion Cell and Optic Nerve Axon Sparing at 90 days following optic nerve transection and 14 or 28 day GPI 1046 treatment

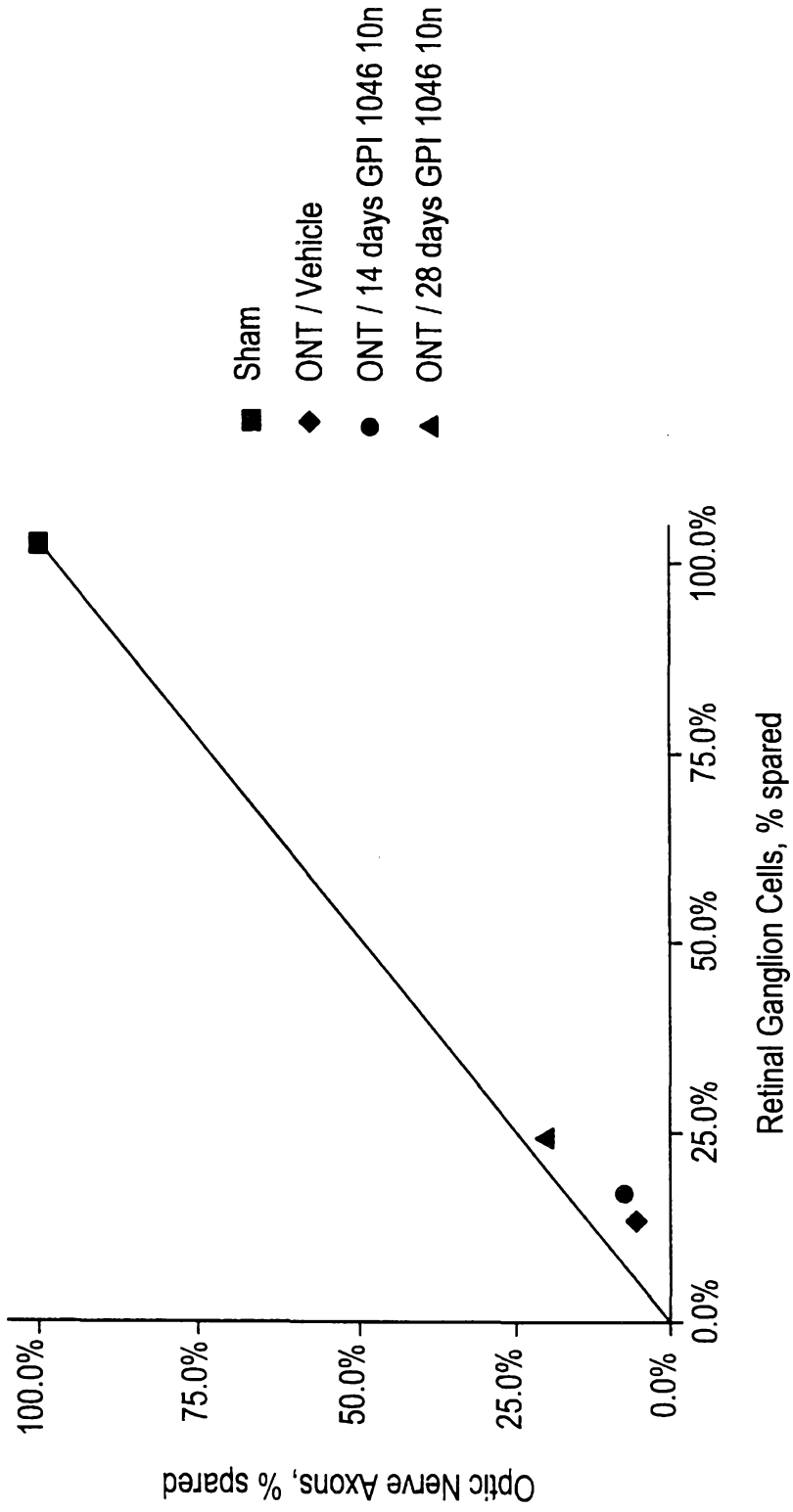
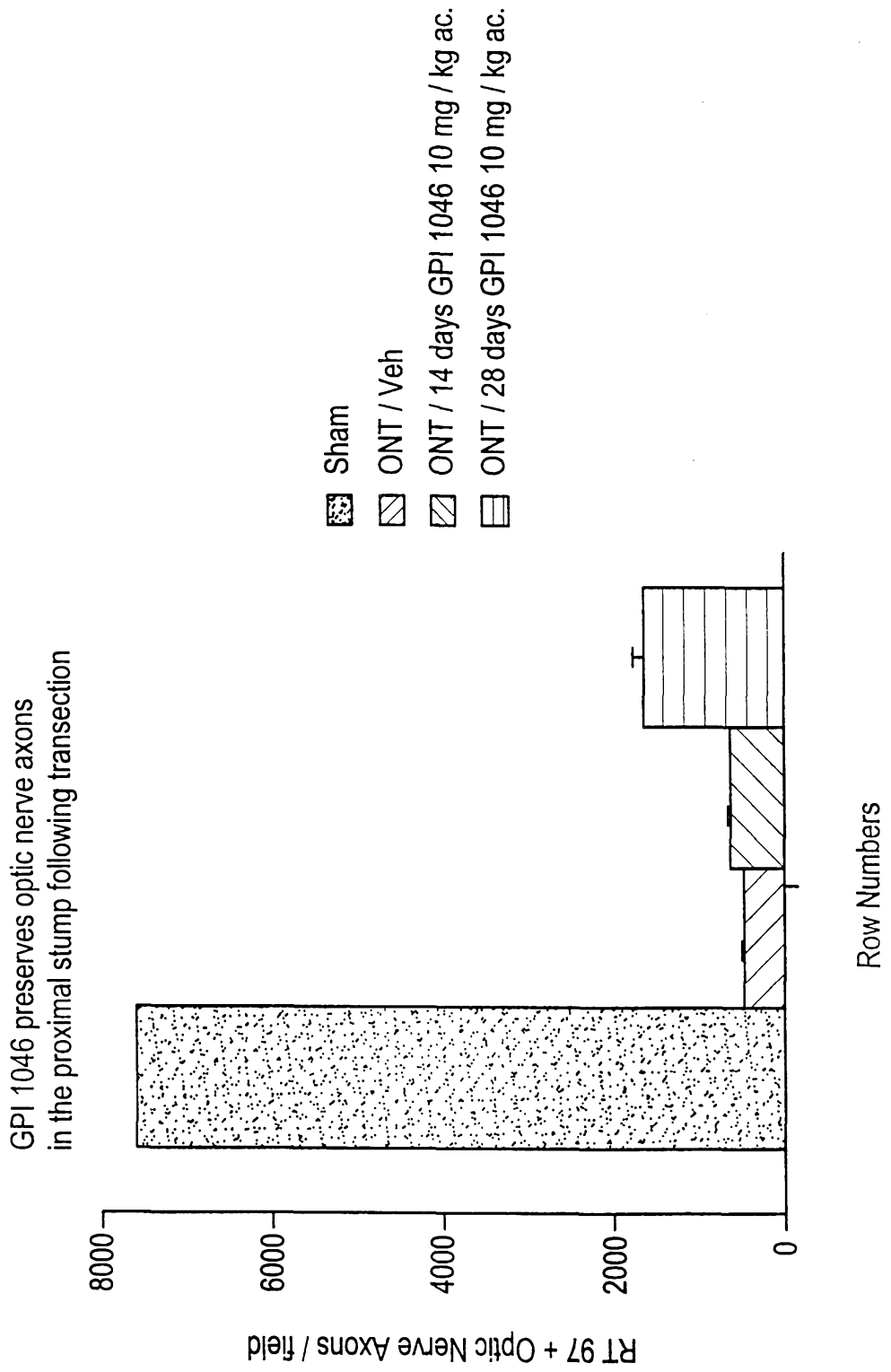


Table IV


GPI 1046 preserves optic nerve axons
in the proximal stump following transection
Sham
ONT / Veh
ONT / 14 days GPI 1046 10 mg / kg ac.
ONT / 28 days GPI 1046 10 mg / kg ac.
RT 97 + Optic Nerve Axons / field
8000
6000
4000
2000
0
Row Numbers

Example 21

A patient is suffering from macular degeneration. A derivative as identified above, alone or in combination with one or more other neopsic factors, or a pharmaceutical composition comprising the same, may be administered to the patient. A reduction in vision loss, prevention of vision degeneration, and/or promotion of vision regeneration are/is expected to occur following treatment.

Example 22

A patient is suffering from glaucoma, resulting in cupping of the optic nerve disc and damage to nerve fibers. A derivative as identified above, alone or in combination with one or more other neopsic factors, or a pharmaceutical composition comprising the same, may be administered to the patient. A reduction in vision loss, prevention of vision degeneration, and/or promotion of vision regeneration are/is expected to occur following treatment.

Example 23

A patient is suffering from cataracts requiring surgery. Following surgery, a derivative as identified above, alone or in combination with one or more other neopsic factors, or a pharmaceutical composition comprising the same, may be administered to the patient. A reduction in vision loss, prevention of vision degeneration, and/or promotion of vision regeneration are/is expected to occur following treatment.

Example 24

A patient is suffering from an impairment or blockage of retinal blood supply relating to diabetic retinopathy, ischemic optic neuropathy, or retinal artery or vein blockage. A derivative as identified above, alone or in combination with one or more other neopsic factors, or a pharmaceutical composition comprising the same, may be

administered to the patient. A reduction in vision loss, prevention of vision degeneration, and/or promotion of vision regeneration are/is expected to occur following treatment.

Example 25

A patient is suffering from a detached retina. A derivative as identified above, alone or in combination with one or more other neopsic factors, or a pharmaceutical composition comprising the same, may be administered to the patient. A reduction in vision loss, prevention of vision degeneration, and/or promotion of vision regeneration are/is expected to occur following treatment.

Example 26

A patient is suffering from tissue damage caused by inflammation associated with uveitis or conjunctivitis. A derivative as identified above, alone or in combination with one or more other neopsic factors, or a pharmaceutical composition comprising the same, may be administered to the patient. A reduction in vision loss, prevention of vision degeneration, and/or promotion of vision regeneration are/is expected to occur following treatment.

Example 27

A patient is suffering from photoreceptor damage caused by chronic or acute exposure to ultraviolet light. A derivative as identified above, alone or in combination with one or more other neopsic factors, or a pharmaceutical composition comprising the same, may be administered to the patient. A reduction in vision loss, prevention of vision degeneration, and/or promotion of vision regeneration are/is expected to occur following treatment.

Example 28

A patient is suffering from optic neuritis. A

derivative as identified above, alone or in combination with one or more other neopsic factors, or a pharmaceutical composition comprising the same, may be administered to the patient. A reduction in vision loss, prevention of vision degeneration, and/or promotion of vision regeneration are/is expected to occur following treatment.

Example 29

A patient is suffering from tissue damage associated with a "dry eye" disorder. A derivative as identified above, alone or in combination with one or more other neopsic factors, or a pharmaceutical composition comprising the same, may be administered to the patient. A reduction in vision loss, prevention of vision degeneration, and/or promotion of vision regeneration are/is expected to occur following treatment.

Example 30

Efficacy of representative compounds from different immunophilin ligand series in protecting retinal ganglion cell axons from degeneration following optic nerve transection is set forth in Table V.

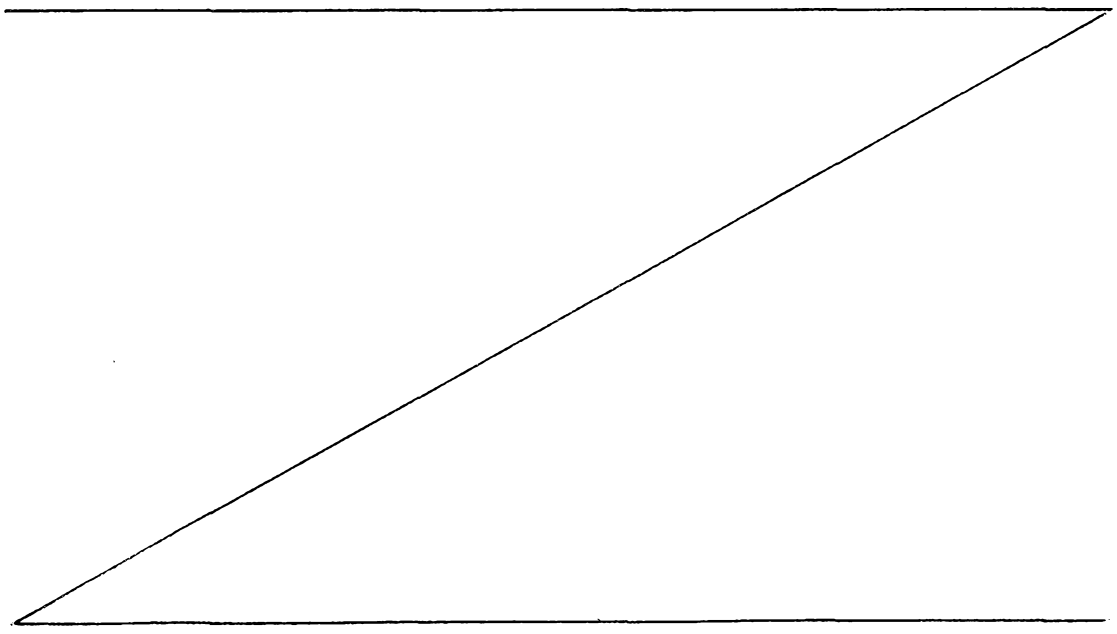


Table V

Efficacy of representative compounds from different immunophilin ligand series in protecting retinal ganglion cell axons from degeneration following optic nerve transection

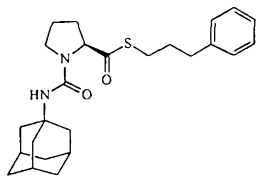
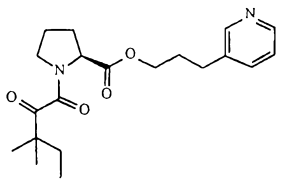
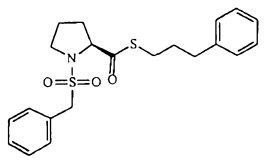
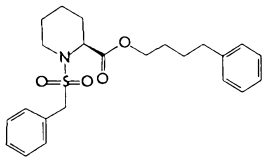
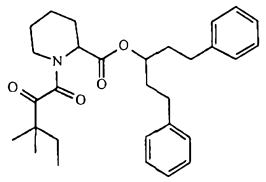
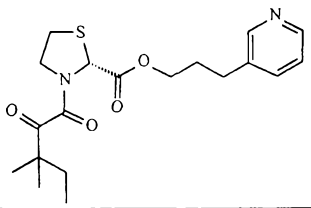
Compound	Structure	Comments	RT97+RGC axon density 14 days after ON transection (% ON axons rescued)
B		Adamantyl Thioester of urea Ki rotamase=149 nM Clearance=? µl/min.	100.0% ±5.2% SEM
A GPI 1046		Ester Ki rotamase=7.5 nM Clearance=63.8 µl/min.	60.5% ±3.9SEM
C		Sulfonamide Ki rotamase=107 nM Clearance=31.1 µl/min.	60.4% ±3.1% SEM
D		Pipecolic sulfonamide Ki rotamase= nM Clearance= µl/min.	58.4% ±6.4% SEM
E		Ester of pipecolic acid Ki rotamase=20 nM Clearance=41.8 µl/min.	56.6% ±9.4% SEM
F		Proline heterocycle Analog of GPI 1046 Ki rotamase=272 nM Clearance=? µl/min.	55.1% ±5.9% SEM

TABLE V continued

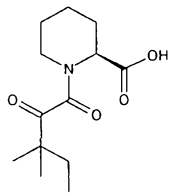
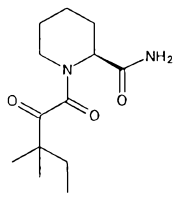
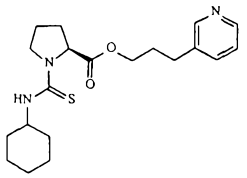
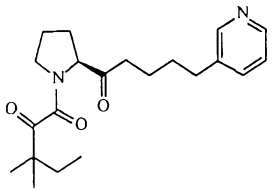
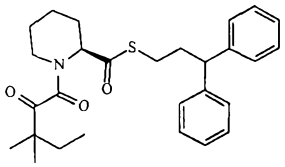
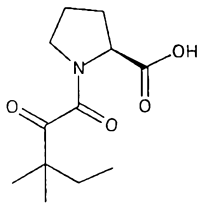
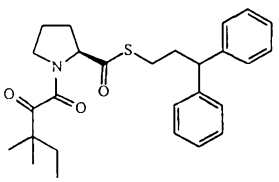
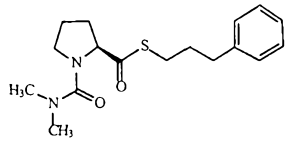
Compound	Structure	Comments	RT97+RGC axon density 14 days after ON transection (% ON axons rescued)
G		Pipecolic acid dimethyl ketone Ki rotamase>10,000 nM Clearance=? µl/min.	34.0% ±4.8% SEM
H		Ki rotamase= nM Clearance= ? µl/min.	30.3% ±8.0% SEM
I		Ester of Thiourea Ki rotamase=131 nM Clearance=8.0 µl/min.	23.8% ±5.3 SEM
J		Ketone analog of GPI 1046 Ki rotamase=210 nM Clearance=1.5 µl/min.	15.8% ±4.8% SEM
K		Pipecolic acid Thioester Ki rotamase=86 nM Clearance=4.5 µl/min.	13.0% ±4.2% SEM
L		Prolyl acid Ki rotamase= >7743 nM Clearance=5.2 µl/min.	7.8% ±3.0% SEM
M		Thioester Ki rotamase=7 nM Clearance=12.5 µl/min.	-6.3% +3.9% SEM

TABLE V continued

Compound	Structure	Comments	RT97+RGC axon density 14 days after ON transection (% ON axons rescued)
N		Ki rotamase=722 nM Clearance=21.9 μl/min.	

Example 31

THE FKBP NEUROIMMUNOPHILIN LIGAND GPI-1046 ENHANCES RETINAL GANGLION CELL SURVIVAL AND ARRESTS AXONAL DYING BACK FOLLOWING OPTIC NERVE TRANSECTION

Transection of the mammalian optic nerve results in a brief period of abortive regeneration, but the majority of axotomized neurons die and the axons from many persisting ganglion cells die back beyond the optic nerve head. The present Example was designed to examine the neuroprotective effects of GPI-1046 following optic nerve transection.

Retinal ganglion cells in adult male Sprague Dawley rats were retrogradely labeled by fluorogold injection in the LGNd and four days later the optic nerves were transected 5 mm behind the globe. Groups of animals received either GPI-1046 10mg/kg/day s.c. or vehicle for 28 days. All experimental animals and controls were sacrificed 90 days after transection.

By 90 days only - 10% of the FG labeled ganglion cell population survived but less than half of these neurons maintained axons that extended past the optic nerve head, as detected with RT97 neurofilament immunohistochemisty. GPI-1046 treatment produced a moderate degree of perikaryal

neuroprotection, sparing 25% of the ganglion cell population, and preserved the axons of virtually all protected neurons in the proximal stump of the transected nerve. These results indicate that treatment with the FKBP neuroimmunophilin ligand GPI-1046 produces a fundamental alteration in the pathological process following injury to CNS tracts.

These results also demonstrate that the small molecule FKBP neuroimmunophilin ligand GPI 1046 enhances neurite outgrowth in culture, enhance peripheral nerve regeneration, and stimulate sprouting within the CNS following partial deafferentation.

Example 32

NEUROIMMUNOPHILIN LIGANDS PROMOTE RECOVERY FROM THE PERIPHERAL SENSORY NEUROPATHY ASSOCIATED WITH STREPTOZOTOCIN-INDUCED DIABETES

Peripheral neuropathy is a common debilitating complication of Type 2 diabetes in some 30-40% of diabetic patients. Neurotrophic factors such as nerve growth factor (NGF) are known to promote survival of developing and adult neurons of the peripheral nervous system (PNS), and have also been evaluated as treatments for diabetic peripheral neuropathy. Some of the selective ligands of the neuroimmunophilin FKBP-12 such as the small molecule GPI-1046, have also been shown to promote repair and regeneration in the central and peripheral nervous systems (Proc. Nat'l. Acad. Sci. USA 94, 2019-2024, 1997).

In this Example the potential therapeutic effects of GPI-1046 were evaluated for its ability to improve sensory function in the streptozotocin-induced diabetic rat. The procedure involved using Male Wistar rats which were given a single injection of streptozotocin (65 mg/kg i.v.). Blood glucose levels were determined weekly for the first three weeks and on the last week of the experiment. Animals were

evaluated weekly for signs of sensory neuropathy using the conventional hot plate and tail flick apparatus test procedures. After six weeks, treatment either with GPI-1046 or vehicle was initiated.

The results demonstrated that behavioral testing using the hot plate and the tail flick apparatus indicated improvement in latency in lesioned animals treated for 6 weeks with GPI-1046 at 10 mg/kg s.c. The results also showed that GPI-1046 ameliorates the behavioral sequelae of diabetic sensory neuropathy and may offer some relief for patients suffering from diabetic peripheral neuropathy.

Morris Watermaze/Aging and Memory Test Procedure

Aged rodents exhibit marked individual differences in performance on a variety of behavioral tasks, including two-choice spatial discrimination in a modified T-maze, spatial discrimination in a circular platform task, passive avoidance, radial maze tasks, and spatial navigation in a water pool.

In all of these tasks, a proportion of aged rats or mice perform as well as the vast majority of young control animals, while other animals display severe impairments in memory function compared to young animals. For example, Fischer and colleagues showed that the proportion of rats displaying significant impairments in spatial navigation increases with age, (Fischer et al. 1991b) with 8% of all 12 month old, 45% of 18 month old, 53% of 24 month old, and 90% of all 30 month old rats displaying impairments in spatial acquisition of the Morris watermaze task relative to young controls.

Specifically, rodent spatial learning and memory decline during aging has been accepted by many investigators as an intriguing correlative animal model of human senile dementia. Cholinergic function in the hippocampus has been extensively studied as a component of spatial learning in rodents, and

declining hippocampal cholinergic function has been noted in parallel with the development of learning and memory impairments. In addition, other neurotransmitter systems have been shown to contribute to spatial learning, and to decline with age, such as the dopaminergic and noradrenergic, serotonergic, and glutamatergic systems.

Also, reports on age-related deficits of hippocampal long-term potentiation (LTP)-induction, a reduction in theta rhythm frequency, a loss of experience-dependent plasticity of hippocampal place-units, and reductions in hippocampal protein kinase C are in keeping with the concept that no single underlying pathology can be identified as the cause of age-related behavioral impairment in rodents. However, the various experimental therapeutic approaches that have been undertaken to improve memory function in aged rodents have been somewhat slanted towards the cholinergic hypothesis.

The Morris watermaze is widely used for assessing spatial memory formation and retention in experimental animals. The test depends on the animal's ability to utilize spatial visual information in order to locate a submerged escape platform in a water tank. It is important that the tank itself be as devoid of specific visual features as possible - thus, it is always circular in shape, the sides are kept smooth and in uniform dull colors, and the water is rendered opaque with nontoxic watercolour pigment or powdered milk. This is to ensure that the animal navigates only by the use of more distant visual cues, or by the use of intra-maze cues specifically provided by the experimenter.

The tank is filled to a level which forces the animal to swim actively. Normal mice and rats react aversively to the swimming part of the test and will climb onto, and remain on, an escape platform from which they are removed to a heated resting cage.

If the platform is visible (i.e. above the surface), animals placed in the tank will quickly learn to home in on

the platform and climb out onto it. Testing with a visible platform will also ensure that the experimental animals are not blind and show sufficient motivation and stamina to perform the task, which can be important in experiments involving aged rodents. If the platform is invisible (i.e. submerged just below the surface), normal animals learn to use distant visual cues in the test room for orientation in the test tank, and, when placed in the tank, will quickly home in on the approximate location of the platform and circle in that area until the platform is found. The animals' path, speed, and swim time are tracked with a ceiling camera for later computerized analysis. Over the course of several successive trials, spatial learning can therefore be defined as a drop of distance swum, or time elapsed, from placement in the tank until escape onto the invisible platform.

The test can be adapted to assess several aspects of spatial memory: a) acquisition of a cued task, where the animal's ability to link one visual cue directly with the escape platform depends on cortical function (i.e. a ball is suspended over the escape platform and the animal learns to follow this cue to find the platform); b) acquisition of a spatial task, where the animal's ability to learn the location of a submerged escape platform based on a combination of distant visual cues is dependent upon hippocampal function (i.e. the animal learns to triangulate its position in the tank by visually aligning the paper-tower dispenser with the door and ceiling lamp); c) retention of a successfully acquired spatial task, which is predominantly dependant on cortical function (i.e. the animal must remember the spatial location of the platform over several weeks); d) a hippocampus-dependant reversal task where the animals must reacquire a new spatial platform location (i.e. the platform is moved to a new location between swim trials and the animal must abandon its previous search strategy and acquire a new

one).

These different modifications of the Morris watermaze procedure can be applied in sequence to the same set of experimental animals and allow for a thorough characterization of their spatial memory performance and its decline with normal ageing. Moreover, such a series of sequential memory tests sheds some light on the functional integrity of the specific brain systems involved in the acquisition and retention of spatial memory (e.g. rats with cholinergic lesions of the hippocampus may remember a platform location acquired weeks before, but persevere over the old platform location after the platform is moved).

Example 33

EFFECTS OF CHRONIC GPI-1046 ADMINISTRATION ON SPATIAL LEARNING AND MEMORY IN AGED RODENTS

This Example shows the effects of chronic treatment with the systemically available FKBP-ligand GPI-1046 on spatial learning and memory in aged rodents.

The procedure involved using three-month old (young) and 18-19 month old male C57BL/6N-Nia (aged) mice which habituated to the well known and conventional Morris watermaze during a 4 trials/day, 3-4 day visible platform training phase. Subsequent spatial acquisition testing was conducting as follows: All mice were given 4 trials/day (block), for 5 days. Maximum swim time was 90 seconds. Aged mice were allocated to an "aged impaired" group if their performance during blocks 4 or 5 of the acquisition phase was >1 S.D. above the mean of "young" mice, and to an "aged non-impaired" group if their performance was < 0.5 S.D. above the mean of "young" mice. Aged groups were then split into statistically similar "GPI-1046" and "vehicle" groups.

Daily treatment with 10mg/kg GPI-1046 was initiated 3 days after the end of acquisition training, and continued

through retention testing. Retention testing began after 3 weeks of dosing using the same methods as the acquisition phase. Swim Distances (cm) were analyzed in a 7 X 5 ANOVA including Groups and Blocks (1-5) as factors in the analysis, treating Blocks as a repeated measure.

The results showed that planned contrasts revealed that there were significant differences between the "young", and "aged impaired-vehicle and GPI-1046" treated groups at the end of the acquisition phase, $F_{1,58}$ = 26.75, P=0.0001, and $F_{1,58}$ = 17.70, P=0.0001 respectively. While there were no significant differences between the two "aged impaired" groups, $F_{1,58}$ = 0.67, P = 0.42. During retention testing, however, "aged impaired-vehicle" treated animals performed significantly poorer than "aged impaired - GPI-1046", and "young" animals, $F_{1,69}$ = 8.11, P = 0.006, and $F_{1,69}$ = 25.45, P = 0.0001 respectively. There was no longer any statistically significant difference between the "young" and "aged impaired" - GPI-1046" treated groups during the retention phase, $F_{1,69}$ = 3.09, P = 0.08. In summary, systemic treatment with GPI-1046 significantly enhanced spatial memory performance of mice with age-related spatial memory impairments.

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 method for treating a vision disorder, improving vision, treating memory impairment or enhancing memory performance in an animal, which comprises administering to said animal an effective amount of a non-immunosuppressive FKBP neuroimmunophilin ligand.

2. The method of claim 1, wherein the FKBP neuroimmunophilin is FKBP-12.

3. A pharmaceutical composition for treating a vision disorder, improving vision, treating memory impairment or enhancing memory performance in an animal, comprising:

a) an effective amount for treating a vision disorder, improving vision, treating memory impairment or enhancing memory performance in an animal of a non-immunosuppressive FKBP neuroimmunophilin ligand; and

b) a pharmaceutically acceptable carrier.

4. The pharmaceutical composition of claim 3, wherein the FKBP neuroimmunophilin is FKBP-12.

FIG. 1A

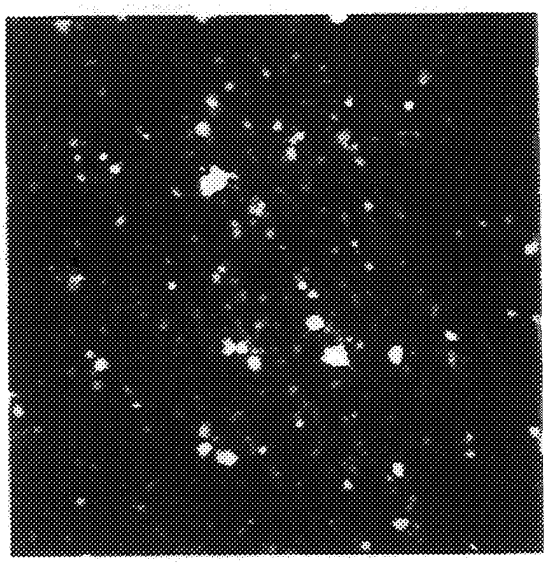


FIG. 1B

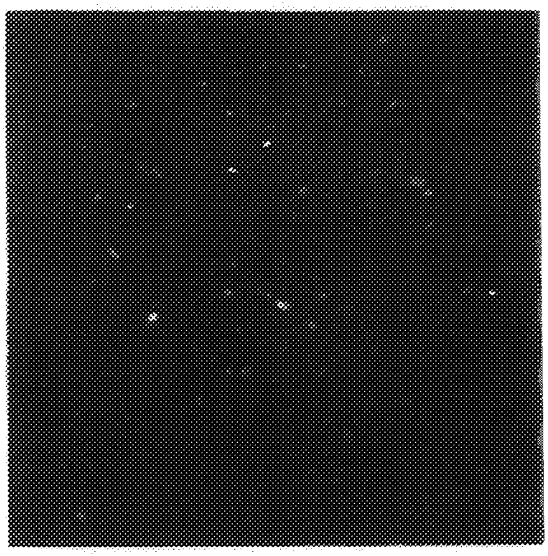


FIG. 1C

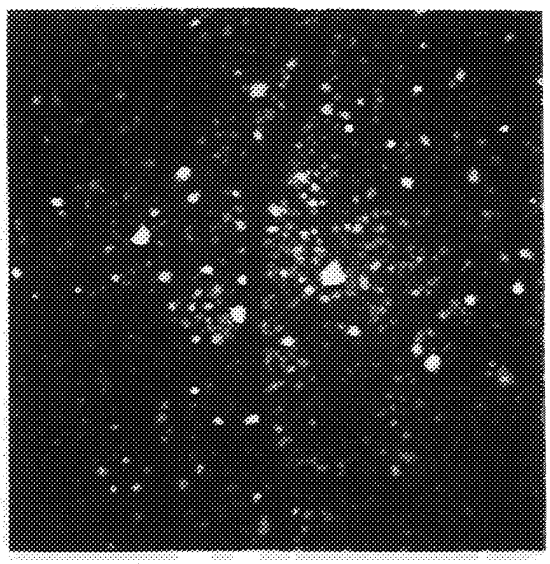


FIG. 2A

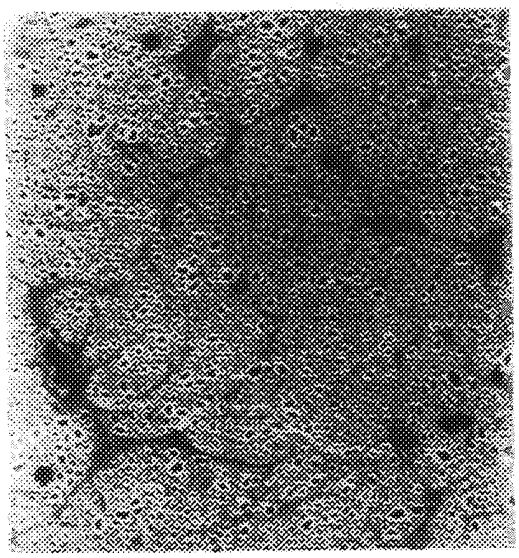


FIG. 2B

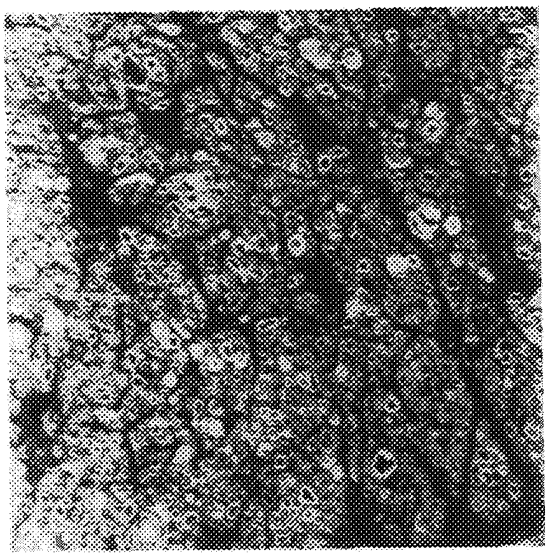


FIG. 2C

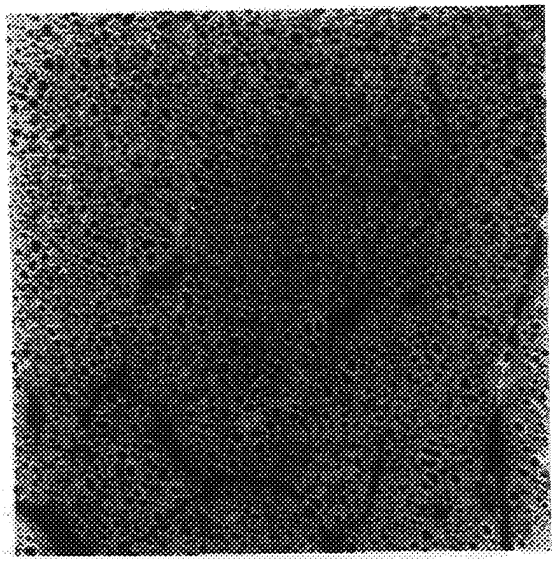


FIG. 3A

FIG. 3B

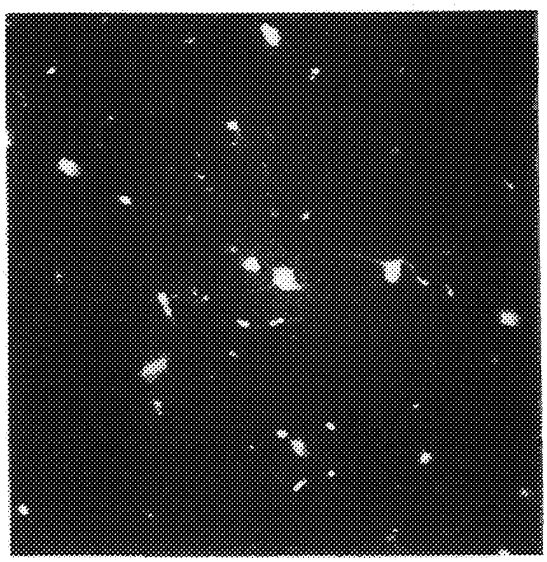


FIG. 4A

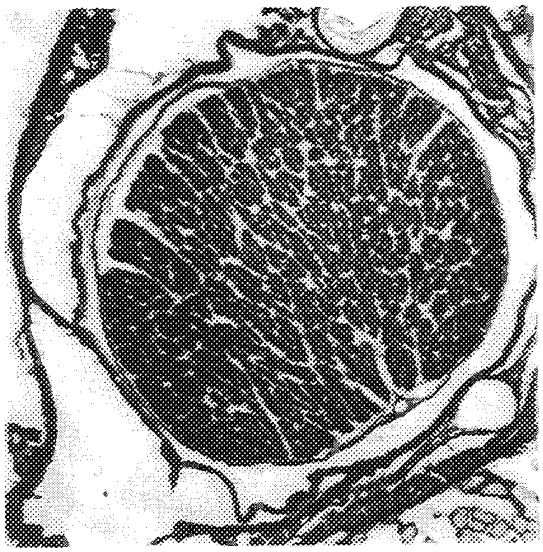


FIG. 4B

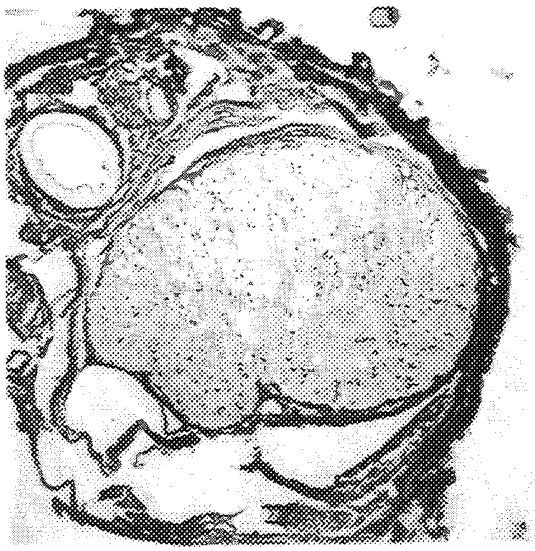


FIG. 4C

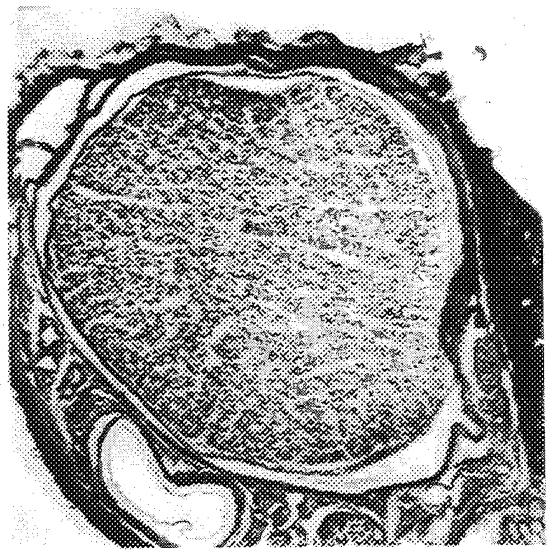


FIG. 4D

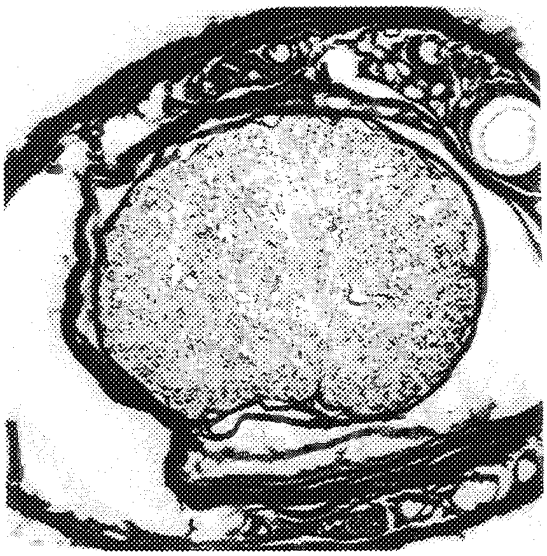


FIG. 5A

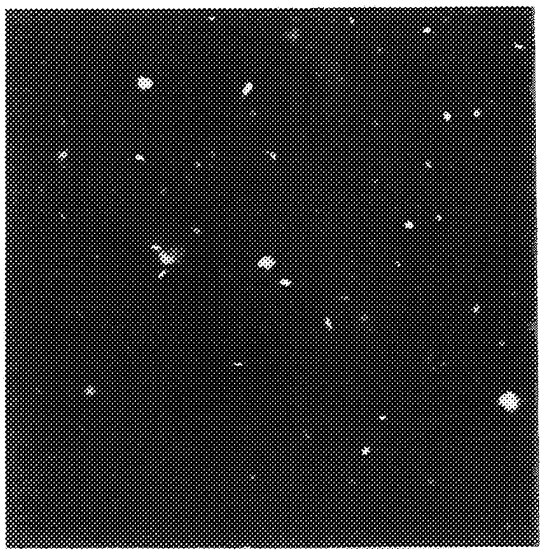


FIG. 5B

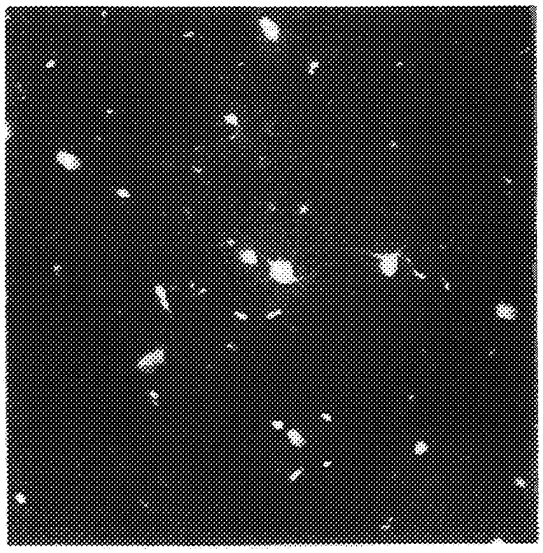


FIG. 5C

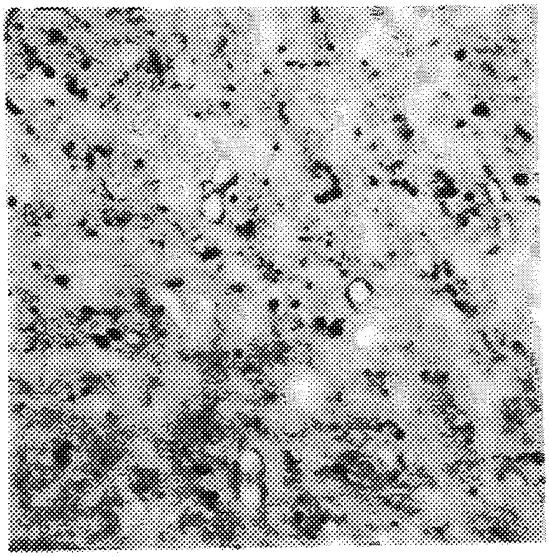


FIG. 5D

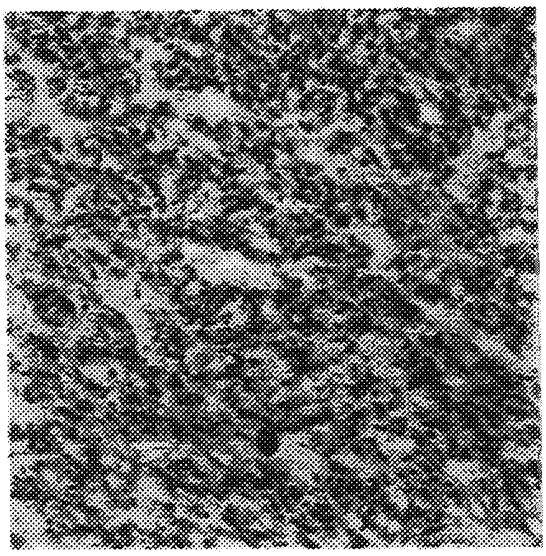


FIG. 6A

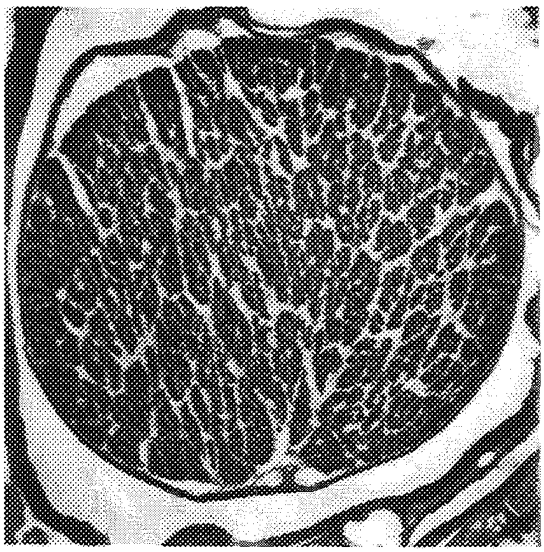


FIG. 6B

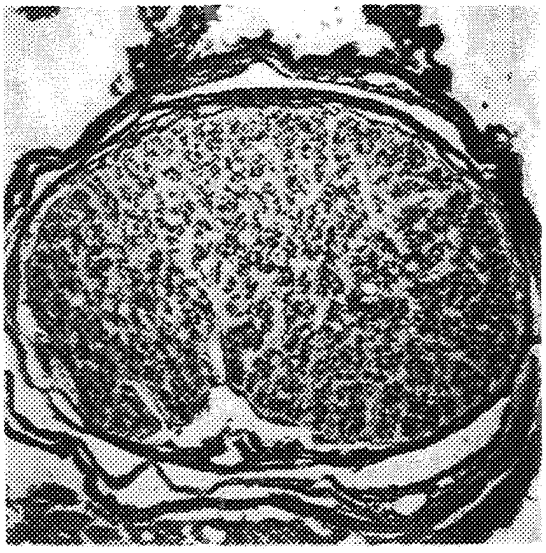


FIG. 6C

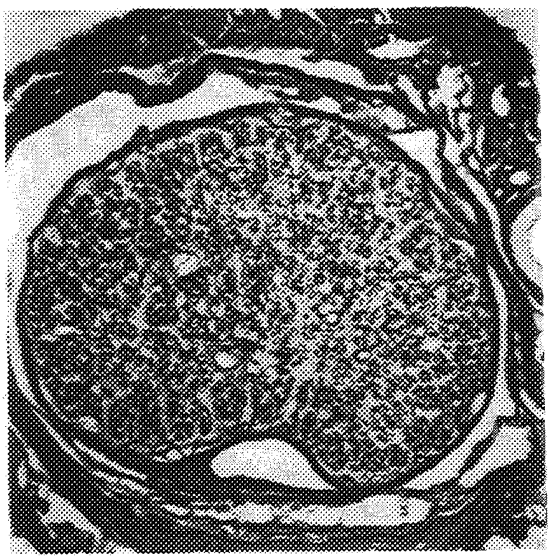


FIG. 6D

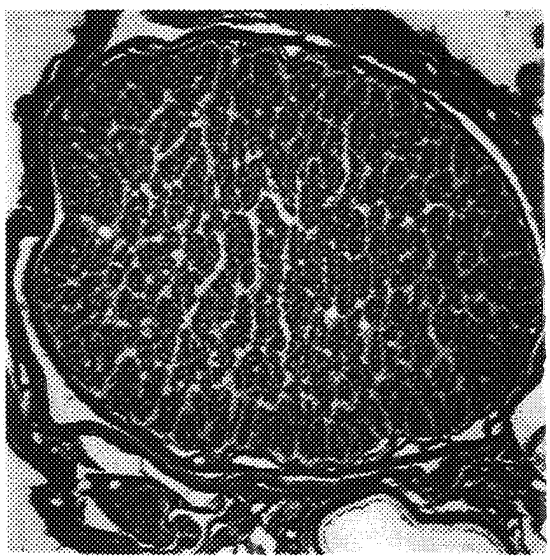


FIG. 7

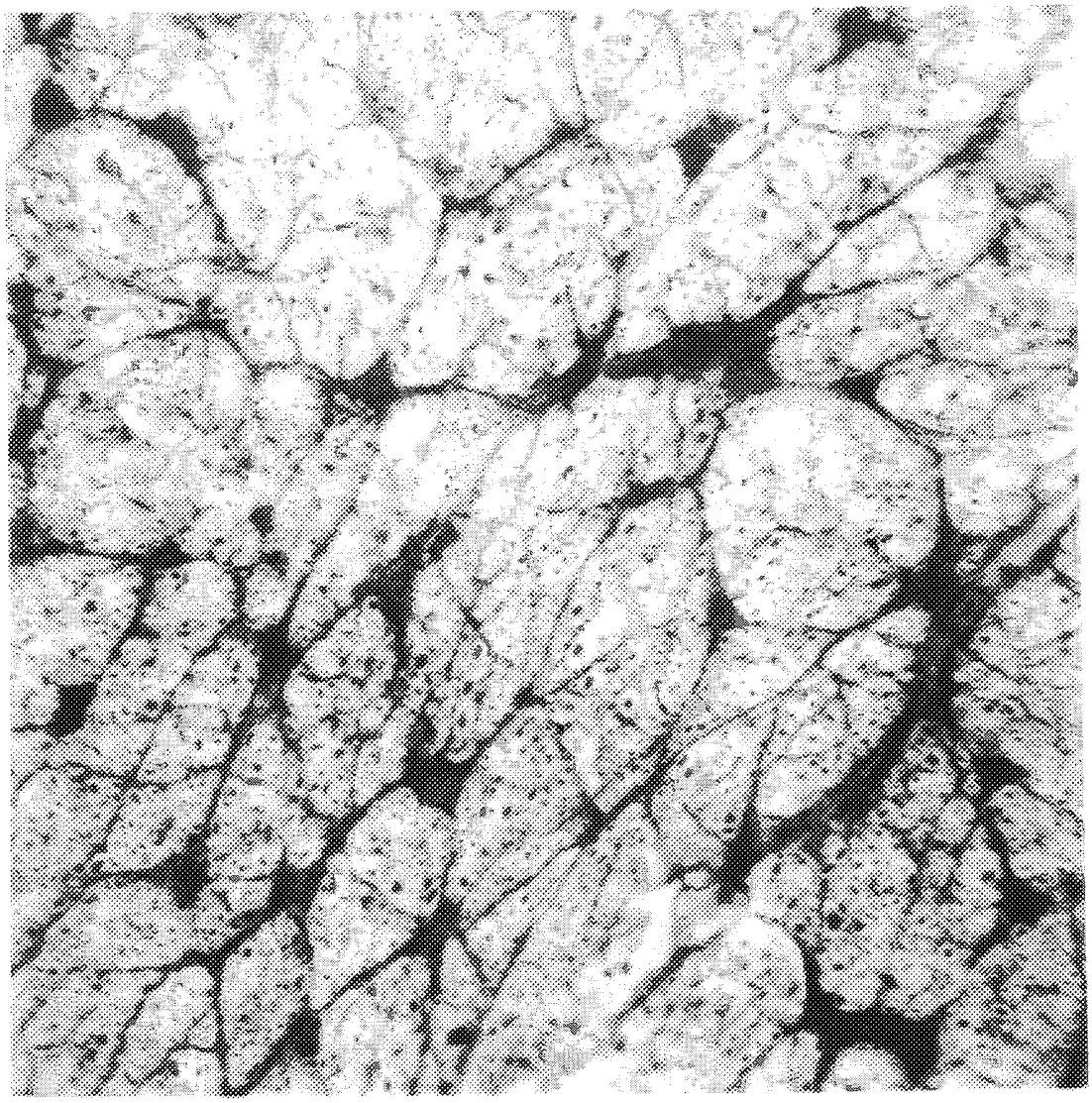


FIG. 8A

FIG. 8B

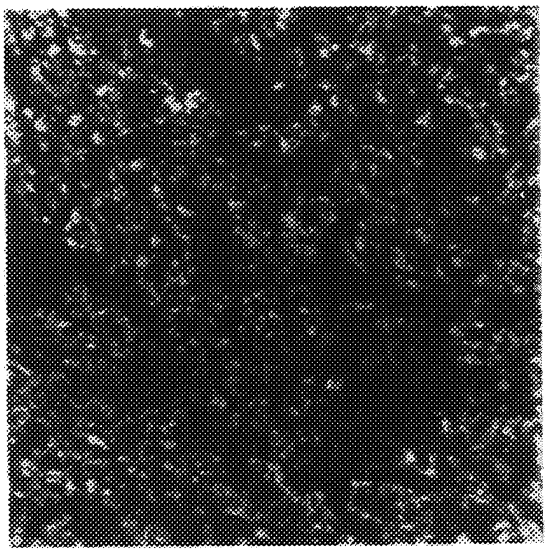


FIG. 8C

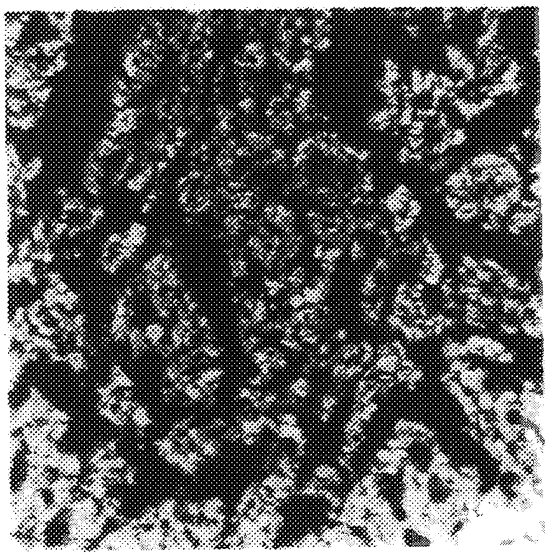


FIG. 8D

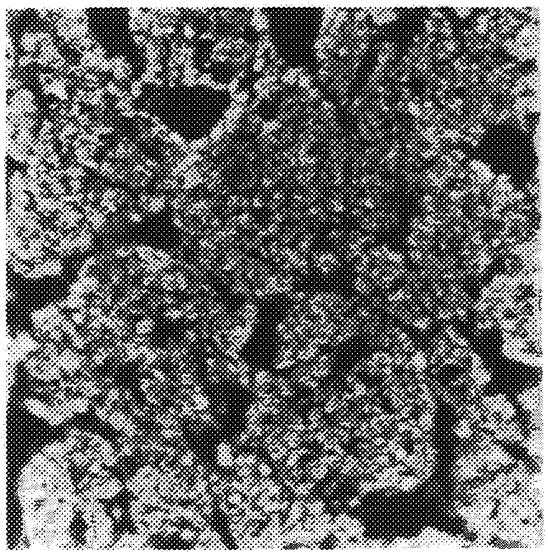


FIG. 9A

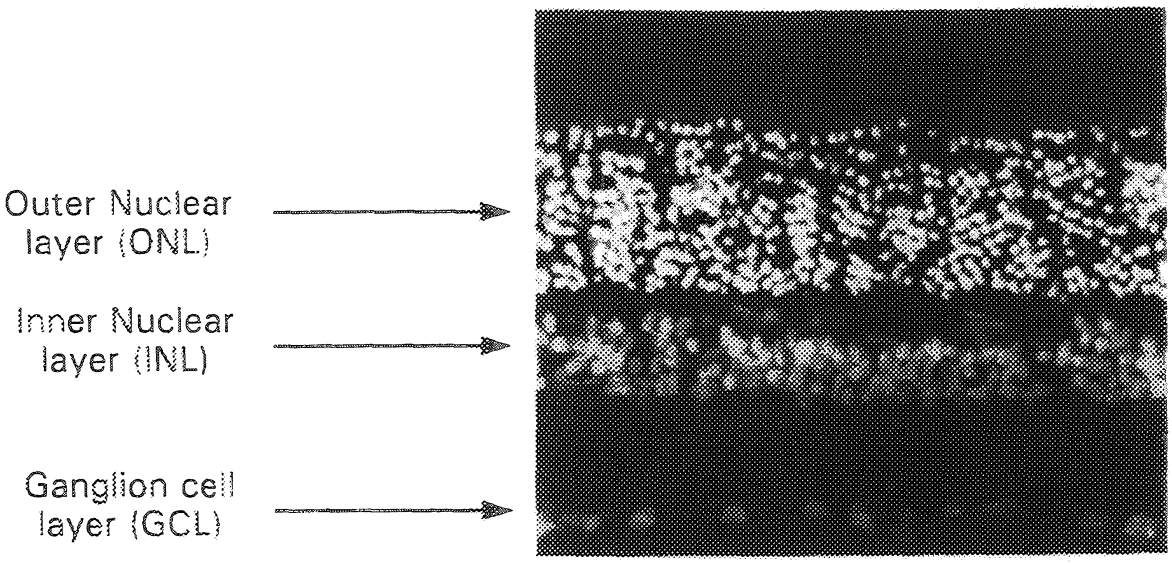


FIG. 9B

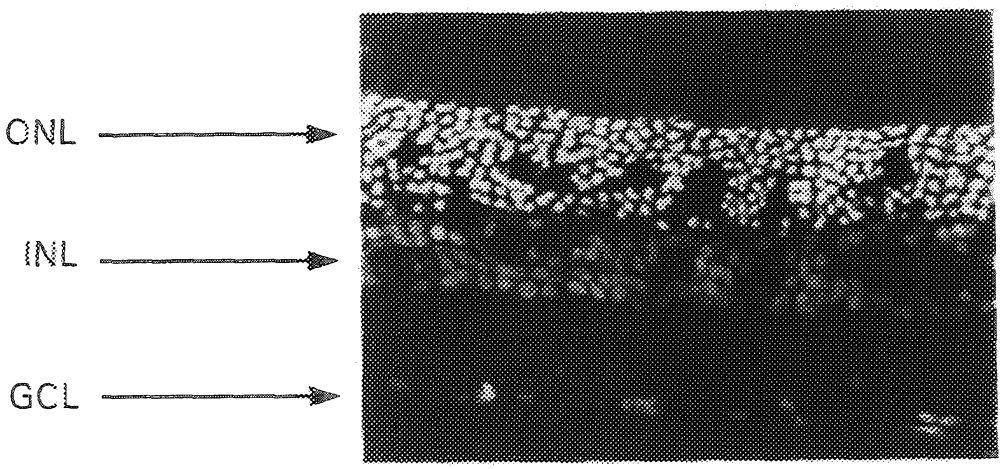


FIG. 9C