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(71) Applicant *(for all designated States except US)*: **GUILFORD PHARMACEUTICALS INC.** [US/US]; Hansjorg Sauer, 6611 Tributary Street, Baltimore, MD 21224 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BELYAKOV, Sergei** [UA/US]; 9500 Midaro Court, Baltimore, MD 21236 (US). **KALISH, Vincent** [US/US]; 344 Dubois Road, Annapolis, MD 21401 (US). **FERRARIS, Dana** [US/US]; 1306 Hillcrest Drive, Eldersburg, MD 21784 (US).

(74) Agents: **SAUER, Hansjorg** et al.; Guilford Pharmaceuticals Inc., 6611 Tributary Street, Baltimore, MD 21224 (US).

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(54) Title: NOVEL INHIBITORS OF DIPEPTIDYL PEPTIDASE IV

(57) Abstract: Novel inhibitors of dipeptidyl peptidase IV (DPP IV), pharmaceutical compositions comprising therapeutically effective amounts of novel inhibitors of DPP IV, and novel methods of treating medical conditions are provided. The novel inhibitors of DPP IV described herein are useful in the treatment of neurological disorders, diabetes, inflammatory disorders such as arthritis, obesity, osteoporosis, and of such other enumerated conditions as can be treated with inhibitors of DPP IV.

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NOVEL INHIBITORS OF DIPEPTIDYL PEPTIDASE IV

The present invention relates to new and improved inhibitors of Dipeptidyl Peptidase IV, and new and improved treatment methods and related uses. The inhibitors according to the invention are useful for treating a wide variety of diseases and other abnormal conditions, including diseases impacting the central nervous system.

Dipeptidyl peptidase IV (DPP IV, EC 3.4.14.5) is a membrane-anchored aminopeptidase involved in the release of N-terminal dipeptides from proteins and other types or forms of peptides. The enzyme is a type II membrane serine peptidase, and has a substrate preference for proteins or peptides which carry a proline at the penultimate position of their N-termini. Since the peptide bonds before and after proline residues are known to be relatively resistant to cleavage by common proteases, it has been speculated that the presence of proline at the penultimate position of the peptide chain – a feature shared by a number of immunopeptides, neuropeptides, and peptide hormones - protects such peptides from degradation by unspecific exopeptidases. A physiological role for DPP IV has been assumed to be in the activation, inactivation, or degradation of its substrates through the specific release of a proline-containing dipeptide from the N-terminal region of the substrate peptide.

DPP IV has been found in the kidney, epithelial cells, endothelial cells, small intestine, prostate, brain, placenta, and liver. In T-cells, it has been shown to be identical to the memory cell surface antigen CD26. Other proteins which display DPP IV-like activity include fibroblast-activation protein (FAP), an inducible type-II cell-surface glycoprotein selectively expressed by reactive stromal fibroblasts of epithelial cancers and healing wounds [Niedermeyer, *et al.*, *Eur. J. Biochem.* 1998 254 (1998):650-4] and attractin/mahogany protein, which exists in membrane-bound and secreted forms and is implicated in control of pigmentation, energy metabolism, and CNS myelination [Tang *et al.*, *Proc. Natl. Acad. Sci. U. S. A.*. 97 (2000) 6025-30.].

DPP IV activity has also been found in serum, urine, seminal plasma, and amniotic fluid. It has been speculated that this soluble DPP IV activity can be attributed to cleavage of the membrane-bound form of DPP IV and release of its catalytic portion into the bloodstream [Augustyns, K., *et al.*, *Current Medicinal Chemistry*, 6 (1999) 311-327]. Additionally, a distinct form of DPP IV, which

appears to be a breakdown product of the T-cell surface antigen DPPT-L, has been described in human plasma. [Duke-Cohan, *et al., J. Immunol.* 156 (1996) 1714-21].

The physiological roles of DPP IV have not been completely elucidated. It has been thought that DPP IV plays a role, amongst others, in the regulation of fat intake, natriuresis, nociception, T-cell activation, regulation of blood glucose, and regulation of the digestive tract. DPP IV has been implicated in disease states such as HIV infection, diabetes, arthritis and certain cancers. For example, DPP IV activity and/or expression was found to be elevated in prostate [Wilson, *et al., J. Androl.* 21 (2000) 220-6], colon [Fric, *et al., Eur. J. Cancer Prev.* 9 (2000):265-8], skin [Van den Oord, *Br. J. Dermatol.* 138 (1998) 615-21] and lung cancer [Sedo, *et al., J. Cancer Res. Clin. Oncol.* 117 (1991) 249-53], and elevated DPP IV also has been found in patients having benign prostate hyperplasia. A high activity of DPP IV is also associated with membrane vesicles found in human, bovine, and equine ejaculate, where it is thought to play a role in the regulation of sperm motility and viability [Minelli A, *et al., J. Reprod. Fertil.* 114 (1998) 237-43; Agrawal, *et al., J. Reprod. Fertil.* 79 (1987) 409-19; Arienti, *et al., FEBS Lett.* 410 (1997) 343-6].

DPP IV also is being investigated for its role in type II diabetes because the glucagon-like peptide (GLP-1) can be a substrate for DPP IV cleavage, and some DPP IV inhibitors have demonstrated efficacy in animal models of diabetes. Additionally, DPP IV has been implicated in HIV infection due to its association with CD 26.

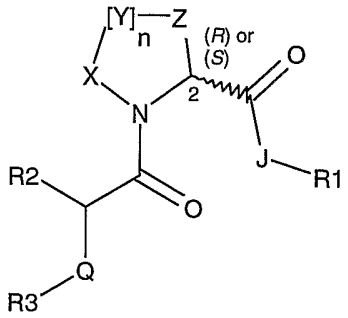
High levels of DPP IV expression have been reported for skin fibroblasts from human patients suffering from psoriasis, rheumatoid arthritis, and lichen planus [Raynaud, *et al., J. Cell Physiol.* 151 (1992) 378]. Inhibition of DPP IV has been shown to increase release of TGF-ß, a protein having neuroprotective properties. DPP IV inhibition itself has been implicated in cellular mechanisms relating to neurodegeneration [*see* PCT publication WO 01/34594].

It follows from the above that inhibitors of DPP IV may be useful as pharmaceuticals in the treatment of a range of medical conditions. In particular, they may be useful as immunosuppressants, anti-inflammatory agents, drugs that suppress tumor invasion and metastasis formation, drugs that inhibit HIV infectivity, regulators of blood glucose levels in patients suffering from diabetes, agents that affect sperm motility and viability useful both for contraception and in the reproduction of livestock, drugs for the treatment of dermatological disorders such as psoriasis, and as pharmaceuticals for the treatment of neurological disorders.

DPP IV inhibition has been studied in the treatment of autoimmune diseases such as diabetes, arthritis and multiple sclerosis. *See* PCT publications WO 97/40832 and WO 98/19998. Additionally, PCT publication WO 94/03055 discusses increasing production of hematopoietic cells with DPP IV inhibitors. PCT publication WO 95/11689 discloses the use of DPP IV inhibitors to block the entry of HIV into cells. U.S. Patent No. 5,543,396 discloses the use of inhibitors (certain proline phosphonate derivatives) to treat tumor invasion. PCT publication WO 95/34538 mentions the use of certain serine protease inhibitors (such as certain DPP IV and PEP inhibitors) to treat inflammation-related neurological/autoimmune diseases like multiple sclerosis. Efficacy in experimental models of inflammatory disorders has also been described for compounds with DPP IV inhibitory activity, suggesting that such compounds may be useful in the treatment of medical conditions such as rheumatoid arthritis and inflammatory bowel disorder. Augustyns *et al.* (*Curr. Med. Chem.*6 (1999) 311-327) and Hildebrandt *et al.* (*Clinical Science* 99 (2000) 93-104) review the wide therapeutic potential of various classes of DPP IV inhibitors.

DPP IV inhibitors based upon molecules that bear a resemblance to proline have been investigated in the field. For example, PCT publication WO 95/11689 discloses α-amino boronic acid analogs of proline. PCT publication WO 98/19998 discloses N-substituted 2-cyanopyrrolidines as DPP IV inhibitors. PCT publication WO 95/34538 discloses various proline containing compounds and phosphonate derivatives thereof. Proline phosphonate derivatives as inhibitors of DPP IV are also disclosed in U.S. Patent 5,543,396. U.S. Patent 6,172,081 discloses a series of tetrahydroisoquinoline 3-carboxaminde derivatives with potent DPP-IV inhibitory activity; U.S. Patents 6,166,063 and 6,107,317 disclose N-substituted 2-cyanopyrrolidines and 4-cyanothiazolidines, respectively. WO 95/15309 discloses various aminoacyl compounds as inhibitors of DPP IV. WO 01/68603 discloses a class of cyclopropyl-fused pyrrolidine derivatives as inhibitors of DPP IV. N-substituted 2-cyanopyrrole derivatives as inhibitors of DPP IV, and pharmaceutical compositions thereof, are taught for the treatment of various metabolic disorders in U.S. Patent Application Publication 2001/0031780.

In view of the needs of the art to provide new therapeutic products, methodologies, and uses, this invention provides novel inhibitors of dipetidyl peptidase, which comprise compounds of the following general Formula I:



or a pharmaceutically acceptable derivative thereof; wherein

n is 0, 1, or 2; forming a four, five- or six-membered nitrogen-containing ring; said nitrogen-containing ring is saturated or optionally contains one double bond;

X, and each Y, if present, are independently CH_2, CF_2, CH, S, O, NH, N, C=O, CH-W, or C-W; provided however that said nitrogen-containing ring may contain no more than one heteroatom in addition to said nitrogen;

Z is CH_2, CF_2, CH, C-W or CH-W;

W is halogen, hydroxy, sulfhydryl, alkyl or C_1-C_3 alkyloxy;

J is a single bond, C=O, or CH_2;

wherein, when J is CH_2:

R1 is halogen, cyano, -O-R4, -S-R4, or –NH-R5;

said R4 is phenyl or benzyl, said phenyl or benzyl optionally being substituted with one, two, three, or more substituents independently selected from the group consisting of hydrogen, hydroxy, sulfhydryl, trifluoromethyl, C_1-C_8 straight or branched alkyl, alkoxy, aralkoxy, and halogen;

said R5 is aryl- or heteroaryl-substituted $C_1 - C_6$ straight or branched chain lower alkyl or -alkanoyl;

wherein, when J is a single bond or C=O:

(i.) R1 is phenyl, which is optionally substituted at one, two, three, or more positions with a substituent independently selected from the group consisting of hydrogen, hydroxy, sulfhydryl, trifluoromethyl, cyano, C_1-C_8 straight or branched alkyl, C_1-C_8 straight or branched alkoxy, aralkoxy, and halogen; or

(ii.) R1 is a mono-, bi-, or tricyclic heteroaryl, which is optionally substituted with halogen, C_1-C_8 straight or branched alkyl, alkoxy, or aralkoxy; or

(iii.) R1 is cyano;

Q is NH, or CH_2;

wherein, when Q is NH:

(i.) one of R2 and R3 is hydrogen, and the other of R2 and R3 is a C_3-C_{12} straight or branched chain alkyl, or a saturated mono- bi- or tricyclic hydrocarbon wherein the individual rings comprise 3 – 12 carbon atoms; or

(ii.) R2 and R3, together with Q and the carbon atom to which they are attached, form a four- to twelve-membered saturated ring, said ring optionally having fused thereto one or two additional rings independently selected from C_4-C_{12} cycloalkyl, C_4-C_{12} cycloalkenyl, aryl, and heteroaryl; or

wherein, when Q is CH_2:

R2 and R3, together with Q and the carbon atom to which they are attached, form a four- to twelve-membered heterocyclic ring, said ring containing at least one nitrogen immediately adjacent to Q, said ring optionally having fused thereto one or two additional rings independently selected from C_4-C_{12} cycloalkyl, C_4-C_{12} cycloalkenyl, aryl, and heteroaryl.

In another aspect of this invention, there is provided a method of treating medical conditions which can be alleviated by inhibition of DPP IV, comprising administering

to a mammal in need of such treatment a therapeutically effective amount of a compound of Formula I, or of a pharmaceutically acceptable derivative thereof.

The present invention further provides a method of inhibiting DPP IV in a mammal, comprising administering to a mammal in need thereof a therapeutically effective amount of a compound of Formula I, or of a pharmaceutically acceptable derivative thereof.

Also included in the present invention are pharmaceutical compositions useful in inhibiting DPP IV, which comprise a therapeutically effective amount of one or several compounds of Formula I, or of a pharmaceutically acceptable derivative thereof, and a pharmaceutically acceptable carrier, diluent, or excipient.

Compounds of Formula I may be prepared or formulated as a salt or derivative for some uses, including pharmaceutical and tissue or cell culture uses. As used herein, the compounds of this invention are defined to include pharmaceutically acceptable derivatives. A "pharmaceutically acceptable derivative" denotes any pharmaceutically acceptable salt, ester, thioester, amide, or salt of such ester, thioester, or amide, of a compound of this invention or any other compound which, upon administration to an animal or human patient, is capable of providing (directly or indirectly) a compound of this invention, or a metabolite or residue thereof, characterized by the ability to inhibit DPP IV and/or its usefulness in treating or preventing a medical disorder. Examples of medical disorders within the scope of this aspect of the invention are given below. As stated above, the compounds of the invention can also be part of a composition comprising one or more compounds of Formula I

The term "alkyl" refers to optionally substituted straight or branched chain hydrocarbon groups having 1 to 12 carbon atoms, preferably 1 to 8, and more preferably 1-5 carbons. Exemplary unsubstituted alkyl groups include methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, the various branched chain isomers thereof, such as isopropyl, t-butyl, isobutyl, isohexyl, 4,4-dimethylpentyl, 2,2,4-trimethylpentyl and the like. Substituted alkyl groups include said alkyl groups substituted by one or more substituents selected from halogen, alkoxy, cycloalkyl, hydroxy, carboxy, $-CONR_6R_7$, $-NR_6R_7$ (where R_6 and R_7 are independently hydrogen or alkyl), nitro, cyano or sulfhydryl.

The term "alkoxy" refers to an alkyl group, such as any of the above alkyl groups, linked to an oxygen atom.

The term "cycloalkyl" refers to saturated cyclic hydrocarbon groups containing 3 - 12, preferably 4 – 8, and more preferably 5 - 6 ring carbons, with cyclopentyl and cyclohexyl being most preferred.

The terms "halogen" and "halo" are well-established in the chemical and pharmaceutical arts and are herein intended to have their common meaning. Preferred halo groups are fluoro-, chloro-, bromo-, and iodo-groups.

The term "aryl" refers to mono-, bi-, or tricyclic aromatic hydrocarbon groups having 6 to 14 carbon atoms in the ring portion, such as phenyl, naphthyl, tetrahydronaphthyl, biphenyl, indene, azulene, fluorene, and anthracene groups, each of which may optionally be substituted by one to four substituents such as alkyl, halo, hydroxy, alkoxy, amino, thiol, nitro, cyano, carboxy and the like.

The term "heteroaryl" refers to mono-, bi- or tricyclic unsaturated heterocyclic groups having 5-14 atoms in the ring portion, such as furan, thiophene, pyrrole, oxazole, thiazole, imidazole, pyrazole, isoxazole, isothiazole, oxadiazole, triazole, thiadiazole, pyran, pyridine, pyridazine, pyrimidine, pyrazine, triazine, indolizine, indole, isoindole, indoline, benzo[b]furan, benzo[b]thiophene, indazole, benzimidazole, benzthiazole, purine, 4H-quinolizine, quinoline, isoquinoline, cinnoline, phthalazine, quinazoline, quinoxaline, 1-8-naphthyridine, pteridine, carbazole, acridine, phenazine, phenothiazine, or phenoxazine, each of which may optionally be substituted by one, two, three, four, or more substituents such as alkyl, halo, hydroxy, alkoxy, amino, thiol, nitro, cyano, carboxy and the like.

The term "aralkoxy" refers to an aryl or heteroaryl group as defined above bonded to an alkoxy group.

Insofar as its preparation is not specifically mentioned or incorporated by reference herein, a compound used as a starting material for the synthesis of the compounds of this invention is known or may be prepared from known compounds, or in a known manner, or analogously to known methods, or analogously to the methods described herein, as will be appreciated by one skilled in the art. The compounds of the invention can be produced as a mixture of isomers or racemic mixtures or as optically pure compounds. Methods for separating stereoisomers known in the art can also be used to enrich mixtures for one or more compounds. The compositions of the invention may similarly contain mixtures of stereoisomers, mixtures of one or more stereoisomers, or be enriched for one or more stereoisomers.

All of these forms are specifically included in this invention and are within the scope of the claims.

The compounds of Formula I possess important utility as pharmaceuticals, especially in the treatment of medical conditions which can be alleviated by inhibition of DPP IV. Examples of such medical conditions are given below. However, the methods of the present invention are not limited to the treatment of such medical conditions alone. Thus, the ability of the compounds of the instant invention to bind to, and inhibit DPP IV further renders the compounds of Formula I useful in a variety of diagnostic and research applications. For example, *in vitro* techniques can be used to identify and characterize cellular components or chemical compounds that interact with DPP IV in a cell-free environment, as would be the case when a compound of Formula I is used to competitively bind to, or inhibit, DPP IV in the presence of such other chemical compound or cellular component. Further, compounds of Formula I may be labeled with a suitable radioisotope and in such form utilized for determining the cellular or tissue distribution of DPP IV in a given tissue sample, or utilized as a diagnostic medical imaging agent for the visualization of e.g. tumors which express high levels of DPP IV.

Another aspect of this invention provides methods for treating a medical condition in a patient in need of such treatment. Medical conditions to be treated with the compounds and compositions of this invention according to these methods include neurological disorders, mental illness, diabetes, hyperglycemia, obesity, atherosclerosis, polycystic ovary syndrome, arthritis, autoimmune disorders, AIDS, osteoporosis, chronic inflammatory bowel disease, metastatic cancer, and cutaneous disorders such as psoriasis and lichen planus. The instant compounds are further useful as immunosuppressants in allograft recipients, contraceptive agents affecting sperm function, and for the treatment of anorexia.

Neurological disorders to be treated according to the methods of this invention, when present in an animal, including humans, can be neurodegenerative disorders, neuropathic disorders, neurovascular disorders, traumatic injury of the brain, spinal cord, or peripheral nervous system, demyelinating disease of the central or peripheral nervous system, metabolic or hereditary metabolic disorder of the central or peripheral nervous system, or toxin-induced- or nutritionally related disorder of the central or peripheral nervous system. When present in a human, a neurodegenerative disorder can be, for example, Parkinson's disease, Alzheimer's

disease, amyotrophic lateral sclerosis (ALS), Huntington's disease, cerebellar ataxia, or multisystem atrophy including, for example, olivopontocerebellar degeneration, striatonigral degeneration, progressive supranuclear palsy, Shy-Drager syndrome, spinocerebellar degeneration and corticobasal degeneration. A demyelinating disease can be, for example, multiple sclerosis, Guillain-Barré syndrome, or chronic inflammatory demyelinating polyradiculoneuropathy. A neurovascular disorder can be global cerebral ischemia, spinal cord ischemia, ischemic stroke, cardiogenic cerebral embolism, hemorrhagic stroke, lacunar infarction, multiple infarct syndromes including multiple infarct dementia, or any disorder resulting in ischemia or ischemia/reperfusion injury of the central nervous system. Traumatic injury of the central or peripheral nervous system can be, for example, concussion, contusion, diffuse axonal injury, edema, and hematoma associated with craniocerebral or spinal trauma, or axonal or nerve sheath damage associated with laceration, compression, stretch, or avulsion of peripheral nerves or plexi, and further includes damage to central nervous tissue or peripheral or visceral nervous tissue caused during surgery, such as damage to the major pelvic ganglion and/or cavernous nerve caused during prostate surgery. A neuropathic disorder can be, for example, diabetic neuropathy, uremic neuropathy, neuropathy related to therapy with drugs such as phenytoin, suramin, taxol, thalidomide, vincristine or vinblastine; or neuropathy/encephalopathy associated with infectious disease, such as, for example, encephalopathy related to HIV, rubella virus, Epstein-Barr virus, herpes simplex virus, toxoplasmosis, prion infection. A metabolic disorder of the central nervous system can be, for example, status epilepticus, hypoglycemic coma, or Wilson's disease.

Mental illness to be treated according to the methods of this invention includes psychotic disorders such as schizophrenia or schizophreniform or schizoaffective disorder, delusional disorder, bipolar disorder or major depression when associated with psychotic symptoms, and other psychotic disorders of unclear etiology, as well as psychological disorders related to the use of psychoactive substances, such as central nervous system depressants, anxiolytics, stimulants, and hallucinogens (e.g. drugs such as cocaine, alcohol, barbiturates, amphetamines, "ecstasy", heroin, morphine, LSD, cannabis, tobacco, narcotics, natural and synthetic opiates, and others). The compounds of the invention can be used to treat not only the psychological and psychiatric symptoms associated with the use and abuse of such

psychoactive substances, but are also useful in treating the addiction to, and dependency on, such substances in addicted individuals.

A compound of this invention can be administered to an animal or human patient by itself or in pharmaceutical compositions where it is mixed with suitable carriers or excipients, at doses to treat or ameliorate various conditions. The compounds according to the present invention preferably have sufficient stability, potency, selectivity, solubility and availability to be safe and effective in treating diseases, injuries and other abnormal medical conditions or insults, including medical conditions of, and insults to, the central nervous system, the peripheral nerves, and other organs. A therapeutically effective dose refers to that amount of the compound sufficient to effect an activity in a nerve or neuronal cell, to produce a detectable change in a cell or organism, or to treat a disorder in a human or other mammal. The word "treat" in its various grammatical forms as used in relation to the present invention refers to preventing, curing, reversing, attenuating, alleviating, minimizing, suppressing, ameliorating or halting the deleterious effects of a disease state, disease progression, injury, wound, ischemia, disease causative agent (*e.g.*, bacteria, protozoans, parasites, fungi, viruses, viroids and/or prions), surgical procedure or other abnormal or detrimental condition (all of which are collectively referred to as "disorders," as will be appreciated by the person of skill in the art). A "therapeutically effective amount" of a compound according to the invention is an amount that can achieve effective treatment, and such amounts can be determined in accordance with the present teachings by one skilled in the art.

The methods of the present invention comprise (i.) administration of a compound of Formula I, where the compound is itself therapeutically active in the treatment of the targeted medical condition, or (ii.) administration of a prodrug of a compound of Formula I, wherein such prodrug is any compound which is capable of undergoing metabolic conversion to a compound of Formula I following administration, or (iii.) administration of a compound of Formula I where the compound is capable of undergoing metabolic conversion to a metabolite following administration, and where the metabolite is therapeutically active in the treatment of the targeted medical condition, or (iv.) administration of a metabolite of a compound of Formula I, where the metabolite is therapeutically active in the treatment of the targeted medical condition. Thus, the use of a compound of Formula I in the methods of the present invention explicitly includes not only the use of the compound itself,

but also the modifications ii, iii, and iv discussed in this paragraph, and all such modifications are explicitly intended to be within the scope of the following claims.

Therapeutically effective doses may be administered alone or as adjunctive therapy in combination with other treatments. Techniques for the formulation and administration of the compounds of the instant application may, for example, be found in *Remington's Pharmaceutical Sciences*, Mack Publishing Co., Easton, PA, 18th edition (1990), and subsequent editions thereof.

Suitable routes of administration may, for example, include oral, rectal, transmucosal, buccal, or intestinal administration; parenteral delivery, including intramuscular, subcutaneous, intramedullary injections, as well as intrathecal, direct intraventricular, intravenous, intraperitoneal, intranasal, or intraocular injections, and optionally in a depot or sustained release formulation. Furthermore, one may administer the agent of the present invention in a targeted drug delivery system, for example in a liposome coated with an antibody. The liposomes will be targeted to and taken up selectively by cells expressing the appropriate antigen.

The pharmaceutical compositions of the present invention may be manufactured in a manner that is itself known, e.g., by means of conventional mixing, dissolving, emulsifying, encapsulating, entrapping, or lyophilizing processes. Pharmaceutical compositions for use in accordance with the present invention thus may be formulated in a conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries, which facilitate processing of the active compounds into preparations, which can thus be used pharmaceutically.

For injection, the compounds of the invention may be formulated in aqueous solutions, preferably in physiologically compatible buffers, such as Hank's solution, Ringer's solution, or physiological saline buffer. For transmucosal or buccal administration, penetrants appropriate to the barrier to be permeated may be used in the formulation. Such penetrants are known in the art. Optionally, lyophilizates comprising one or more compounds of Formula I may be reconstituted in sterile saline, water, or buffer prior to injection.

For oral administration, the compounds can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers, well known to those in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, capsules, liquids, quick-dissolving preparations, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated.

Pharmaceutical preparations for oral use of the compounds of this invention can be obtained by employing a solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP).

In general, the pharmaceutical compositions also may comprise suitable solid or gel phase carriers or excipients. Examples of such carriers or excipients include but are not limited to calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols. If desired, disintegrating agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate or a number of others disintegrants (see, for example, *Remington's Pharmaceutical Sciences*, Mack Publishing Co., Easton, PA, 18th edition (1990), and subsequent editions thereof).

For administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide, pressurized air, or other suitable gas or mixture. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g. gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

The compounds may be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable

stabilizers or agents, which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions. Alternatively, the active ingredient may be in powder form for reconstitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

The compounds may also be formulated in rectal compositions such as suppositories, e.g., containing conventional suppository bases such as cocoa butter or other glycerides. In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

The compounds of the invention may further be formulated in pharmaceutical or cosmetic compositions for topical application to the skin in the form of an aqueous, alcoholic, aqueous/alcoholic or oily solution, or of a dispersion of the lotion or serum type, of an emulsion having a liquid or semi-liquid consistency of the milk type, obtained by dispersion of a fatty phase in an aqueous phase (O/W) or vice versa (W/O), or of a suspension or of an emulsion with a soft consistency of the aqueous or anhydrous gel, foam or cream type, or, alternatively, of microcapsules or microparticles, or of a vesicular dispersion of ionic and/or nonionic type, or may further be administered in the form of an aerosol composition comprising a pressurized propellent agent. The compounds of the invention, for use in the treatment of a cutaneous disorder such as, for example, psoriasis or lichen planus, can also be formulated into various compositions for hair care and, in particular, shampoos, hair-setting lotions, treating lotions, styling creams or gels, dye compositions (in particular oxidation dyes), optionally in the form of color-enhancing shampoos, hair-restructuring lotions, permanent-wave compositions, and the like. Pharmaceutical or cosmetic compositions comprising compounds of the invention can also contain additives and adjuvants which are conventional in the cosmetics field, such as gelling agents, preservatives, antioxidants, solvents, fragrances, fillers, screening agents, odor absorbers and colorants. The amounts of these different additives and adjuvants are those typically employed in the cosmetics field and range, for example, from 0.01% to 20% of the total weight of the composition, preferably 0.1% to 10%, and more

preferably 0.5% to 5%. In addition to one or several compounds of the invention, compositions for topical application may further contain additional agents known in the art to promote hair growth or to prevent or retard hair loss, such as, without limitation, tocopherol nicotinate, benzyl nicotinate or 2,4-diamino-6-piperidinopyrimidine 3-oxide, or may contain other active agents such as antibacterial agents, antiparasitic agents, antifungal agents, antiviral agents, anti-inflammatory agents, antipruriginous agents, anaesthetic agents, keratolytic agents, antiseborrhoeic agents, antidandruff agents, or antiacne agents. The cosmetic or pharmaceutical compositions according to the invention can be topically applied onto the affected areas of the scalp and skin of an individual and optionally maintained in contact for a number of hours and optionally rinsed. It is possible, for example, to apply the composition containing an effective amount of at least one compound of the invention in the evening, to retain the composition in contact overnight and optionally to shampoo in the morning. These applications can be repeated daily for one or a number of months, depending on the particular individuals involved.

Liposomes and emulsions are well known examples of delivery vehicles or carriers for hydrophobic drugs. Certain organic solvents such as dimethylsulfoxide also may be employed. Additionally, the compounds may be delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various sustained-release materials have been established and are well known by those skilled in the art. Sustained-release capsules may, depending on their chemical nature, release the compounds for a few weeks up to over 100 days. Depending on the chemical nature and the biological stability of the therapeutic reagent, additional strategies for stabilization may be employed.

The compounds of this invention may be administered in conjunction with, or formulated in pharmaceutical compositions together with, one or several additional therapeutic agents. Such additional therapeutic agents are themselves known in the art, and the specific agent employed together with the compounds of Formula I in this embodiment of the invention depend on the medical condition to be treated. Medical conditions wherein the compounds of Formula I are useful as therapeutic agents include diabetes, hyperglycemia, impaired glucose homeostasis, impaired glucose tolerance, infertility, polycystic ovary syndrome, growth disorders, frailty, arthritis, allograft rejection in transplantation, autoimmune diseases (such as scleroderma and

multiple sclerosis), various immunomodulatory diseases (such as lupus erythematosis or psoriasis), AIDS, intestinal diseases (such as necrotizing enteritis, microvillus inclusion disease or celiac disease), inflammatory bowel syndrome, chemotherapy-induced intestinal mucosal atrophy or injury, osteoporosis, Syndrome X, dysmetabolic syndrome, diabetic complications, hyperinsulinemia, obesity, atherosclerosis and related diseases, as well as inflammatory bowel disease (such as Crohn's disease and ulcerative colitis), neurological disorders and mental illness. The instant compounds are further useful as immunosuppressants in allograft recipients, contraceptive agents affecting sperm function, and for the treatment of anorexia. It follows that additional therapeutic agents to be used in combination with the compounds of this invention are selected from such agents known in the art to possess therapeutic utility in the medical condition to be treated. In the treatment of diabetes, for example, compounds of Formula I may be used in combination with one or more other types of antidiabetic agents which may be administered by any of the herein described routes in the same dosage form, or in a separate dosage form. Such other types of antidiabetic agents which may be used in combination with the compounds of this invention are themselves known in the art, and include, for example, biguanides, sulfonyl ureas such as glyburide, glucosidase inhibitors, thiazolidinediones such as troglitazone (Rezulin ®), glycogen phosphorylase inhibitors, and insulin. In the treatment of inflammatory disorders, for example, compounds of Formula I may be used in combination with one or several agents which themselves have therapeutic utility in that condition, such as aspirin, indomethacin, ibuprofen, ketoprofen, naproxen sodium, celecoxib (Celebrex ®), or rofexocib (Vioxx ®). In the treatment of mental illness, such as, for example, a psychotic disorder like schizophrenia, the antipsychotic compounds of Formula I may be administered in conjunction with one or several other antipsychotic agents such as neuroleptics from the butyrophenone or phenothiazine classes. Neuroleptic drugs are well-known in the art and include, for example, clozapine, olanzapine, risperidone, sertindole, quetiapine, ziprasadone, amisulpride, acetophenazine, chlorpromazine, chlorprothixene, fluphenazine, haloperidol, loxapine, mesoridazine, molindone, perphenazine, pimozide, piperacetazine, trifluoperazine, triflupromazine, thioridazine, and thiothixene.

Toxicity and therapeutic efficacy of the compounds or compositions can be determined by standard pharmaceutical, pharmacological, and toxicological procedures in cell cultures or experimental animals. For example, numerous methods

for determining the LD_{50} (the dose lethal to 50% of the population) and the ED_{50} (the dose therapeutically effective in 50% of the population) exist. The dose ratio between toxic and therapeutic effects is the therapeutic index, which can be expressed as the ratio between LD_{50} and ED_{50}. Compounds and compositions exhibiting high therapeutic indices are preferred. The data obtained from cell culture assays or animal studies can be used in formulating a range of dosages for use in humans, as has long been established in the art [*see, e.g.*, Fingl *et al.*, in *The Pharmacological Basis of Therapeutics*, Ch. 1 p. 1 (1975)].

The compounds of the present invention may be administered by a single dose, multiple discrete doses or continuous infusion. Dose levels on the order of about 0.1 mg to about 10,000 mg of the active ingredient are useful in the treatment of the above conditions, with preferred levels being about 0.1 mg to about 1,000 mg, and 1 mg to about 1000 mg. The specific dose level, and thus the therapeutically-effective amount, for any particular patient will vary depending upon a variety of factors, including the activity of the specific compound employed and its bioavailability at the site of drug action; 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 also are helpful. The considerations for determining the proper dose levels are available to the skilled person.

Suitable compounds of this invention can be administered in lyophilized form, as discussed above. In this case, 1 to 1000 mg, preferably 20 – 500 mg, of a compound of the present invention may be lyophilized in individual vials, together with a carrier and a buffer, such as mannitol and sodium phospshate. The compound may be reconstituted in the vials with bacteriostatic water before administration.

In treating a neurodegenerative disorder, for example, the compounds of the present invention are preferably administered orally, rectally, or parenterally 1 to 6 times daily, and may follow an initial bolus dose of higher concentration. In treating a cutaneous disorder, such as psoriasis or lichen planus, for example, the compounds of the present invention are preferably administered topically or orally one to four times daily.

For the compounds, methods, and uses of the present invention, any administration regimen regulating the timing and sequence of drug delivery can be

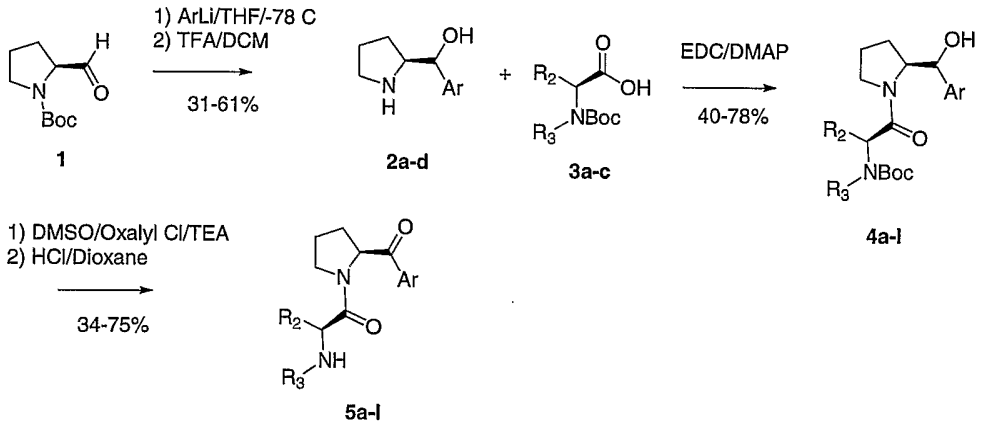
used and repeated as necessary to effect treatment. Such regimen may include pretreatment and/or co-administration with additional therapeutic agents.

The following description should not be taken as a limitation on the scope of the invention, and all embodiments and examples given are merely illustrative of the invention. Additional aspects of the invention can be devised by reference to this disclosure as a whole in combination with the references cited and listed throughout and at the end of the specification and the knowledge of one skilled in the art. All of the references cited and listed can be relied on, in their entirety, to allow one to make and use these additional aspects of the invention.

Synthetic pathways to the compounds of the invention

General synthesis of aryl ketones **5a-l.** Alcohols **2a-c** were synthesized as a mixture of diastereomers from L-Boc-prolinal **1** by methods which are themselves well-established in the art. [see, e.g.,Tsutsumi, S.; Okonogi, T.; Shibahara, S.; Ohuchi, S.; Hatsushiba, E. *et al.* Synthesis and structure-activity relationships of peptidyl alpha-keto heterocycles as novel inhibitors of prolyl endopeptidase. *J Med Chem* **1994**, *37*, 3492-3502.]

Scheme 1: general synthesis of aryl ketones 5a-l



Pyrrolidin-2-yl-thiazol-2-yl-methanol **(2a).** Yield = 42%; ^{1}H NMR ($CDCl_3$) δ 7.74 (d, 1H), 7.27 (d, 1H), 5.06 (d, 1H), 3.75 (m, 1H), 3.68 (bs, 1H), 3.00 (m, 2H), 1.88-1.59 (m, 4H).

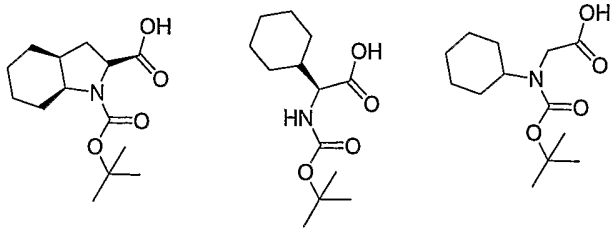
Benzothiazol-2-yl-pyrrolidin-2-yl-methanol **(2b).** Yield = 61%; ^{1}H NMR ($CDCl_3$) δ 7.98 (d, 1H), 7.89 (t, 1H), 7.46 (d, 1H), 7.37 (t, 1H), 5.17 (d, 0.5H), 4.92 (d, 0.5H), 4.05 (m, 0.5H), 3.91 (m, 0.5H), 3.09-2.90 (m, 2H), 2.17-1.69 (m, 4H).

Pyridin-2-yl-pyrrolidin-2-yl-methanol **(2c).** Yield = 35%; ^{1}H NMR ($CDCl_3$) δ 8.54 (d, 1H), 7.69 (t, 1H), 7.43 (d, 1H), 7.20 (t, 1H), 4.83 (d, 0.7H), 4.53 (d, 0.3H), 3.51 (m, 1H), 3.08 (bs, 1H), 3.04-2.86 (m, 2H), 1.84-1.38 (m, 4H).

(2,6-Dimethyl-phenyl)-pyrrolidin-2-yl-methanol **(2d).** This compound was also synthesized by the procedure described by Tsutsumi *et al.,* above. Yield = 31%; ^{1}H NMR ($CDCl_3$) δ 7.07-6.96 (m, 3H), 5.08 (d, 1H), 3.63 (m, 1H), 3.02 (bs, 1H), 2.96 (m, 2H), 2.46 (s, 6H), 1.93-1.82 (m, 4H).

General coupling procedure for synthesis of amido alcohols **4a-l**, exemplified for compound **4a.** Pyrrolidine **2a** (360 mg, 1.95 mmol) was suspended in a solution of dichloromethane (10 mL) with Boc-octahydroindole-2-carboxylic acid **3a** (525 mg, 1.95 mmol). The EDC (450 mg, 2.35 mmol) was added to this mixture followed by DMAP (~20 mg, catalyst) and the solution was stirred at room temperature overnight. The reaction was then quenched with water and the DCM layer was partitioned. The aqueous layer was washed two more times with DCM (10 mL). The combined organic layers were dried and concentrated *in vacuo* to yield the crude coupled product. This crude mixture was chromatographed on silica gel to yield the mixture of diastereomers **4a** as the major products (475 mg, 56%). ^{1}H NMR ($CDCl_3$) δ 7.71 (d, 1H), 7.35-7.27 (m, 3H), 5.16 (m, 1H), 4.70-4.33 (m, 2H), 3.73 (m, 2H), 3.04 (m, 1H), 2.25-1.80 (m, 6H), 1.75-1.00 (m, 8H), 1.44 (s, 5H), 1.38 (s, 4H).

Figure 1: Exemplary Boc-protected amino acids (3a-c)



3a **3b** **3c**

{1-Cyclohexyl-2-[2-(hydroxy-thiazol-2-yl-methyl)-pyrrolidin-1-yl]-2-oxo-ethyl}-carbamic acid *tert*-butyl ester (**4b**). (CHG) Yield = 64%; ^{1}H NMR ($CDCl_3$) δ 7.75-7.71 (m, 0.5H), 7.36 (d, 0.5H), 7.29 (d, 1H), 5.27 (m, 0.5H), 5.15 (s, 0.5H), 5.00 (m, 0.5H), 4.59 (m, 0.5H), 4.26 (m, 1H), 3.74-3.63 (m, 2H), 3.23 (m, 1H), 2.58 (m, 1H), 2.24-1.65 (m, 7H), 1.45 (s, 4.5H), 1.42 (s, 4.5H), 1.35-0.94 (m, 7H).

Cyclohexyl-{2-[2-(hydroxy-thiazol-2-yl-methyl)-pyrrolidin-1-yl]-2-oxo-ethyl}-carbamic acid *tert*-butyl ester (**4c**). (N-CHG) Yield = 77%; ^{1}H NMR ($CDCl_3$) δ 7.72 (d, 1H), 7.34 (m, 1H), 5.2 (m, 1H), 4.90 (m, 0.5H), 4.63 (m, 1H), 4.40 (m, 0.5H), 4.07-3.92 (m, 2H), 3.59-3.40 (m, 2H), 3.12 (m, 1H), 1.80-1.52 (m, 6H), 1.47 (s, 6H), 1.44 (s, 3H), 1.42-0.94 (m, 8H).

2-[2-(Benzothiazol-2-yl-hydroxy-methyl)-pyrrolidine-1-carbonyl]-octahydro-indole-1-carboxylic acid *tert*-butyl ester (**4d**). Yield = 40%; ^{1}H NMR ($CDCl_3$) δ 7.93 (m, 2H), 7.42 (m, 2H), 5.21 (m, 1H), 4.74 (m, 1H), 4.33 (m, 1H), 3.74 (m, 1H), 3.70 (m, 1H), 3.11 (m, 1H), 2.29 (m, 1H), 2.20-1.45 (m, 6H), 1.44 (s, 5H), 1.38 (s, 4H), 1.58-0.95 (m, 5H).

{2-[2-(Benzothiazol-2-yl-hydroxy-methyl)-pyrrolidin-1-yl]-1-cyclohexyl-2-oxo-ethyl}-carbamic acid *tert*-butyl ester (**4e**). Yield = 41%; ^{1}H NMR ($CDCl_3$) δ 7.95-7.86 (m, 2H), 7.45-7.37 (m, 2H), 7.21 (d, 1H), 5.18 (m, 1H), 4.59 (m, 1H), 4.22 (m, 1H), 3.78 (m, 1H), 3.33 (m, 1H), 2.74 (m, 1H), 2.32 (m, 1H), 2.0-1.59 (m, 4H), 1.41 (s, 9H), 1.45-0.82 (m, 10H).

{2-[2-(Benzothiazol-2-yl-hydroxy-methyl)-pyrrolidin-1-yl]-2-oxo-ethyl}-cyclohexyl-carbamic acid *tert*-butyl ester (**4f**). Yield = 65%; ^{1}H NMR ($CDCl_3$) δ 7.97 (t, 1H), 7.89 (d, 1H), 7.46 (t, 1H), 7.38 (d, 1H), 5.28 (m, 1H), 4.97 (m, 1H), 4.67 (m, 1H), 4.09-3.50 (m, 3H), 3.20 (m, 1H), 2.10 (m, 1H), 1.80-1.50 (m, 6H), 1.47 (s, 6H), 1.39 (s, 3H), 1.38-0.88 (m, 8H).

2-[2-(Hydroxy-pyridin-2-yl-methyl)-pyrrolidine-1-carbonyl]-octahydro-indole-1-carboxylic acid *tert*-butyl ester (**4g**). Yield = 44%; ^{1}H NMR ($CDCl_3$) δ 8.51 (d, 1H), 7.69 (dd, 1H), 7.48 (t, 1H), 7.10 (m, 1H), 5.72 (m, 1H), 5.26 (m, 1H), 4.45 (m, 2H),

3.76 (m, 2H), 3.30 (m, 1H), 2.28 (m, 1H), 2.05-1.62 (m, 8H), 1.45 (s, 4H), 1.38 (s, 5H), 1.24 (m, 4H).

1-Cyclohexyl-2-[2-(hydroxy-pyridin-2-yl-methyl)-pyrrolidin-1-yl]-2-oxo-ethyl}-carbamic acid *tert*-butyl ester (**4h**). Yield = 70%; ^{1}H NMR ($CDCl_3$) δ 8.52 (d, 1H), 7.68 (t, 1H), 7.45 (d, 1H), 7.20 (m, 1H), 5.44 (m, 1H), 5.28 (m, 1H), 4.48 (m, 1H), 4.31 (m, 1H), 3.72 (m, 1H), 3.42 (m, 1H), 1.90-1.50 (m, 8H), 1.43 (s, 9H), 1.18 (m, 6H).

Cyclohexyl-{2-[2-(hydroxy-pyridin-2-yl-methyl)-pyrrolidin-1-yl]-2-oxo-ethyl}-carbamic acid *tert*-butyl ester (**4i**). Yield = 67%; ^{1}H NMR ($CDCl_3$) δ 8.51 (d, 1H), 7.68 (dd, 1H), 7.48 (d, 1H), 7.18 (m, 1H), 5.59 (m, 0.5H), 5.30 (m, 1.5H), 4.48 (m, 1H), 4.09 (m, 1H), 4.04 (m, 2H), 3.44 (m, 1H), 2.04-1.52 (m, 8H), 1.49 (s, 4H), 1.44 (s, 5H), 1.28 (m, 6H).

2-{2-[(2,6-Dimethyl-phenyl)-hydroxy-methyl]-pyrrolidine-1-carbonyl}-octahydro-indole-1-carboxylic acid *tert*-butyl ester (**4j**). Yield = 50%; ^{1}H NMR ($CDCl_3$) δ 6.96 (m, 3H), 5.27 (m, 1H), 4.85 (m, 1H), 4.29 (m, 2H), 4.11 (m, 1H), 3.76 (m, 1H), 3.66 (m, 1H), 2.50 (s, 6H), 2.18-1.79 (m, 8H), 1.57 (m, 4H), 1.41 (s, 5H), 1.38 (s, 4H), 1.26 (m, 2H).

(1-Cyclohexyl-2-{2-[(2,6-dimethyl-phenyl)-hydroxy-methyl]-pyrrolidin-1-yl}-2-oxo-ethyl)-carbamic acid *tert*-butyl ester (**4k**). Yield = 78%; ^{1}H NMR ($CDCl_3$) δ 6.96 (m, 3H), 5.20 (m, 1H), 4.84 (m, 1H), 4.27 (m, 1H), 3.70 (m, 1H), 3.59 (m, 1H), 2.52 (s, 6H), 2.22 (m, 1H), 1.85-1.60 (m, 6H), 1.38 (s, 9H), 1.24-0.88 (m, 8H).

Cyclohexyl-(2-{2-[(2,6-dimethyl-phenyl)-hydroxy-methyl]-pyrrolidin-1-yl}-2-oxo-ethyl)-carbamic acid *tert*-butyl ester (**4l**). Yield = 59%; ^{1}H NMR ($CDCl_3$) δ 7.12 (t, 1H), 6.90 (d, 2H), 5.69 (m, 1H), 4.91 (m, 1H), 4.49 (m, 2H), 3.87 (m, 3H), 3.46 (m, 1H), 2.52 (s, 4H), 2.42 (s, 2H), 2.05 (m, 4H), 1.94-1.45 (m, 6H), 1.44 (s, 4H), 1.33 (s, 5H), 1.08 (m, 4H).

General procedure for the oxidation and deprotection of alcohols **4a-l**, exemplified for compound **5a**. Oxalyl chloride (185 μL, 2.06 mmol) was dissolved in dichloromethane (10 mL) and placed under nitrogen and cooled to –78 °C. The dimethylsulfoxide (322 mg, 4.13 mmol) was added to this solution of oxalyl chloride and the solution was stirred at –78 °C for 10 min. A solution of alcohol **4a** (450 mg, 1.03 mmol) in dichloromethane (3 mL) was then added and the mixture was stirred at –78 °C for an additional 30 min. The triethylamine (1.1 mL, 8.2 mmol) was added dropwise and the reaction mixture was warmed to 0 °C and stirred for 3 h at this temperature. The reaction was then quenched with EtOAc/satd. NaCl (1/1, 20 mL) and the organic layer was partitioned off. The aqueous layer was extracted with an additional amount of EtOAc (2x10 mL) and the combined organics were dried and concentrated *in vacuo* and the residue was run through a plug of silica gel to purify. The desired Boc protected ketone (273 mg, 63%) was dried *in vacuo* and then subjected to 4.0M HCl/Dioxane (4 mL) for 1 h. The dioxane was then removed *in vacuo* and the residue was dried on the high vac. After 10 min of drying, the solid was triturated with diethyl ether by stirring for 1 h. The resulting solid was collected by filtration and dried *in vacuo* for 10 min and immediately placed in the freezer. Dry yield = 203 mg, 81%. Overall yield from **4a** = 51%. ^{1}H NMR (D_2O) δ 8.13 (d, 1H), 8.09 (d, 1H), 5.58 (m, 1H), 4.71 (m, 1H), 3.77 (m, 3H), 3.19 (m, 2H), 2.65 (m, 1H), 2.52 (m, 2H), 2.11 (m, 4H), 1.90-1.25 (m, 8H). Anal Calcd. for $C_{17}H_{23}N_3O_2S$ (1.0 HCl)(0.85 H_2O): C, 53.00; H, 6.72; N, 10.91. Found: C, 53.31; H, 6.91; N, 10.88.

2-Amino-2-cyclohexyl-1-[2-(thiazole-2-carbonyl)-pyrrolidin-1-yl]-ethanone (**5b**). Yield = 36%; ^{1}H NMR (D_2O) δ 8.07 (m, 2H), 7.64 (m, 2H), 6.35 (d, 2H), 5.01 (m, 1H), 4.22 (bs, 0.5H), 4.18 (0.5H), 3.60 (m, 2H), 2.15 (m, 4H), 1.98-1.05 (m, 8H). Anal Calcd. for $C_{16}H_{23}N_3O_2S$ (1.0 HCl)(0.3 H_2O)(0.3 $C_4H_8O_2$): C, 53.11; H, 6.95; N, 10.93. Found: C, 53.29; H, 6.87; N, 11.04.

2-Cyclohexylamino-1-[2-(thiazole-2-carbonyl)-pyrrolidin-1-yl]-ethanone (**5c**). Yield = 53%; ^{1}H NMR (D_2O) δ 8.14 (m, 2H), 5.68 (m, 1H), 4.16 (m, 2H), 3.75 (m, 2H), 3.16 (m, 1H), 2.49 (m, 1H), 2.09-1.33 (m, 13H). Anal Calcd. for $C_{16}H_{23}N_3O_2S$ (1.15 HCl)(0.5 H_2O)(0.5 $C_4H_8O_2$): C, 51.24; H, 6.96; N, 9.96. Found: C, 51.10; H, 6.92; N, 9.87.

[2-(Benzothiazole-2-carbonyl)-pyrrolidin-1-yl]-(octahydro-indol-2-yl)-methanone (**5d**). Yield = 63%; ^{1}H NMR (D_2O) δ 8.16 (d, 1H), 8.05 (d, 1H), 7.64 (m, 2H), 5.51 (m, 1H), 4.65 (m, 1H), 3.73 (m, 3H), 2.58 (m, 2H), 2.42 (m, 1H), 2.16 (m, 3H), 1.93 (m, 1H), 1.75 (m, 1H), 1.48-0.9 (m, 7H). Anal Calcd. for $C_{21}H_{25}N_3O_2S$ (1.3 HCl)(0.25 H_2O)(0.25 $C_4H_8O_2$): C, 56.42; H, 6.20; N, 9.00. Found: C, 56.26; H, 6.12; N, 9.04.

2-Amino-1-[2-(benzothiazole-2-carbonyl)-pyrrolidin-1-yl]-2-cyclohexyl-ethanone (**5e**). Yield = 75%; ^{1}H NMR (D_2O) δ 8.07 (m, 2H), 7.64 (m, 2H), 6.35 (d, 2H), 5.01 (m, 1H), 4.22 (bs, 0.5H), 4.18 (0.5H), 3.60 (m, 2H), 2.15 (m, 4H), 1.98-1.05 (m, 8H). Anal Calcd. for $C_{20}H_{25}N_3O_2S$ (1.0 HCl)(1.5 H_2O)(0.5 $C_4H_8O_2$): C, 55.16; H, 6.94; N, 8.77. Found: C, 55.03; H, 7.04; N, 8.81.

1-[2-(Benzothiazole-2-carbonyl)-pyrrolidin-1-yl]-2-cyclohexylamino-ethanone (**5f**). Yield = 53%; ^{1}H NMR (D_2O) δ 8.11 (d, 1H), 8.04 (d, 1H), 7.57 (m, 2H), 5.63 (m, 1H), 4.05 (s, 2H), 3.64 (m, 2H), 3.02 (m, 1H), 2.44 (m, 1H), 2.10-1.25 (m, 13H). Anal Calcd. for $C_{20}H_{25}N_3O_2S$ (1.0 HCl)(0.35 H_2O)(0.25 $C_4H_8O_2$): C, 57.81; H, 6.63; N, 9.63. Found: C, 57.31; H, 6.52; N, 9.78.

(Octahydro-indol-2-yl)-[2-(pyridine-2-carbonyl)-pyrrolidin-1-yl]-methanone (**5g**). Yield = 57%; ^{1}H NMR (D_2O) δ 8.71 (d, 0.8H), 8.50 (d, 0.2H), 8.30 (m, 2H), 8.05 (d, 0.2H), 7.81 (d, 0.8Hz), 5.55 (m, 1H), 4.50 (t, 0.8H), 4.36 (t, 0.8H), 3.96 (t, 0.2H), 3.75 (t, 0.2H), 3.65 (m, 2H), 2.5-2.25 (m, 2H), 2.00-1.00 (m, 13H). Anal Calcd. for $C_{19}H_{25}N_3O_2$ (1.0 HCl)(3.0 H_2O)(0.5 $C_4H_8O_2$): C, 50.60; H, 7.38; N, 8.43. Found: C, 50.06; H, 7.41; N, 8.39.

2-Amino-2-cyclohexyl-1-[2-(pyridine-2-carbonyl)-pyrrolidin-1-yl]-ethanone (**5h**). Yield = 34%; ^{1}H NMR (D_2O) δ 8.83 (d, 0.6H), 8.54 (d, 0.4H), 8.39 (m, 1.6H), 7.98 (d, 0.4H), 7.97 (t, 0.6H), 7.71 (t, 0.4H), 5.82 (m, 1H), 4.25 (m, 1H), 4.00-3.83 (m, 1H), 3.70 (m, 0.6H), 3.21 (m, 0.4H), 2.5 (m, 0.6H), 2.25 (m, 0.4H), 2.11-1.10 (m, 14H). Anal Calcd. for $C_{18}H_{25}N_3O_2$ (1.5 HCl)(0.5 H_2O)(0.5 $C_4H_8O_2$): C, 54.42; H, 7.19; N, 9.52. Found: C, 54.13; H, 7.17; N, 9.65.

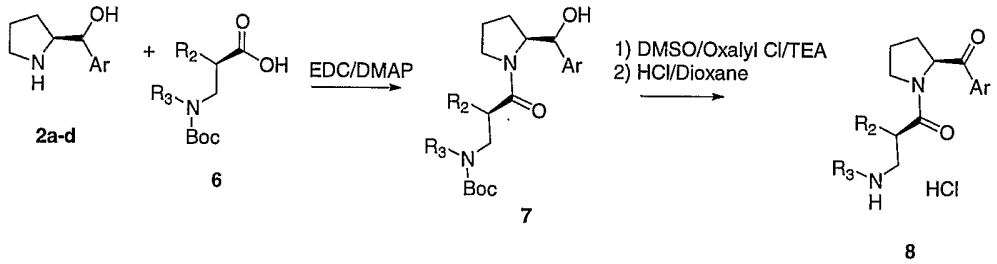
2-Cyclohexylamino-1-[2-(pyridine-2-carbonyl)-pyrrolidin-1-yl]-ethanone (**5i**). Yield = 36%; ^{1}H NMR (D_2O) δ 8.85 (d, 1H), 8.43 (m, 2H), 8.02 (t, 1H), 5.79 (m, 1H), 4.17 (d, 2H), 3.72 (m, 1H), 3.18 (m, 1H), 2.50 (m, 1H), 2.12-1.31 (m, 14H). Anal Calcd. for $C_{18}H_{25}N_3O_2$ (1.75 HCl)(0.5 H_2O)(1.0 $C_4H_8O_2$): C, 52.46; H, 7.15; N, 8.34. Found: C, 52.81; H, 7.26; N, 8.39.

[2-(2,6-Dimethyl-benzoyl)-pyrrolidin-1-yl]-(octahydro-indol-2-yl)-methanone (**5j**). Yield = 45%; ^{1}H NMR (D_2O) δ 7.30 (t, 1H), 7.15 (d, 1H), 5.31 (t, 1H), 4.65 (t, 1H), 3.81 (m, 1H), 3.66 (t, 2H), 2.62 (m, 1H), 2.46 (m, 1H), 2.29 (s, 6H), 2.18-1.34 (m, 13H). Anal Calcd. for $C_{22}H_{30}N_2O_2$ (1.15 HCl)(0.3 H_2O)(0.25 $C_4H_8O_2$): C, 62.78; H, 8.18; N, 6.66. Found: C, 62.42; H, 8.24; N, 6.74.

2-Amino-2-cyclohexyl-1-[2-(2,6-dimethyl-benzoyl)-pyrrolidin-1-yl]-ethanone (CHG) (**5k**). Yield = 54%; ^{1}H NMR (D_2O) δ 7.31 (t, 1H), 7.17 (d, 1H), 5.34 (m, 1H), 4.18 (m, 1H), 3.73 (m, 2H), 2.31 (s, 6H), 2.10-1.66 (m, 8H), 1.45-1.15 (m, 4H). Anal Calcd. for $C_{21}H_{30}N_2O_2$ (1.15 HCl)(0.5 H_2O)(0.25 $C_4H_8O_2$): C, 64.90; H, 7.98; N, 6.58. Found: C, 64.55; H, 7.98; N, 6.76.

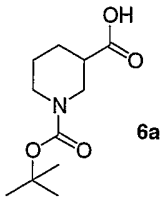
2-Cyclohexylamino-1-[2-(2,6-dimethyl-benzoyl)-pyrrolidin-1-yl]-ethanone (N-CHG) (**5l**). Yield = 50%; ^{1}H NMR (D_2O) δ 7.31 (t, 1H), 7.17 (d, 1H), 5.31 (m, 1H), 4.12 (dd, 2H), 3.72 (m, 1H), 3.15 (m, 1H), 2.31 (s, 6H), 2.06-1.25 (m, 14H). Anal Calcd. for $C_{21}H_{30}N_2O_2$ (1.2 HCl)(0.25 H_2O)(0.25 $C_4H_8O_2$): C, 62.91; H, 8.09; N, 6.67. Found: C, 62.72; H, 8.06; N, 6.70.

Scheme 2: General synthesis of prolylketo β-amino acids



Compound **7a** was synthesized in a manner analogous to the Boc alcohols **4a-l** from **6a** (Fig. 2, below) and oxidation of **7a** was carried out as indicated for compounds **5a-l**.

Figure 2: Example of Boc protected β-amino acids

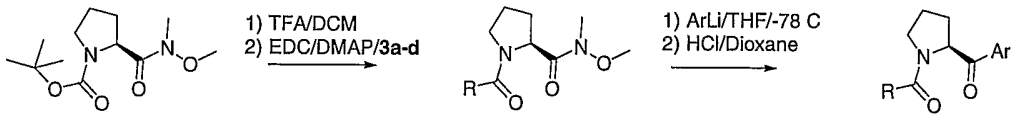


6a

3-[2-(Benzothiazol-2-yl-hydroxy-methyl)-pyrrolidine-1-carbonyl]-piperidine-1-carboxylic acid tert-butyl ester (**7a**). Yield = 58%; ^{1}H NMR ($CDCl_3$) δ 8.00-7.91 (m, 2H), 7.50-7.25 (m, 2H), 5.20 (m, 1H), 4.85 (m, 1H), 4.11 (m, 2H), 3.73-3.58 (m, 3H), 3.02-2.57 (m, 3H), 2.26 (m, 1H), 1.89-1.50 (m, 4H), 1.47 (s, 3H), 1.44 (s, 6H), 1.40 (m, 4H).

[2-(Benzothiazole-2-carbonyl)-pyrrolidin-1-yl]-piperidin-3-yl-methanone (**8a**). Yield = 54%; ^{1}H NMR (D_2O) δ 8.19 (d, 1H), 8.13 (d, 1H), 7.68 (m, 2H), 5.72 (m, 1H), 3.85 (m, 2H), 3.45-3.00 (m, 6H), 2.54 (m, 1H), 2.24-1.70 (m, 8H). Anal Calcd. for $C_{18}H_{21}N_3O_2S$ (1.0 HCl)(1.0 H_2O)(0.5 $C_4H_8O_2$): C, 54.35; H, 6.39; N, 9.51. Found: C, 54.35; H, 6.37; N, 9.57.

Scheme 3. Alternate synthesis of compounds 5 and 8.

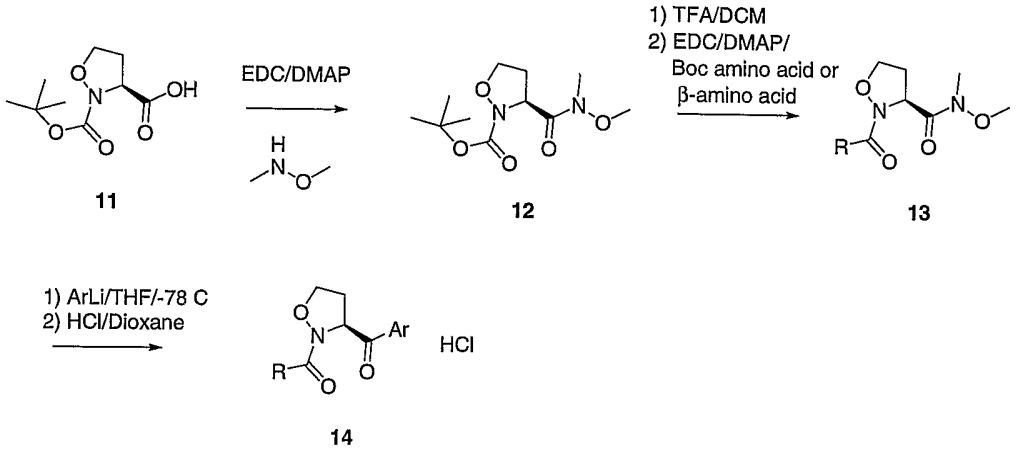


9 **10** **5 or 8**

Compound **9** is commercially available. The deprotection, coupling and arylation have been conducted according to methods which are themselves established in the art [for a description of deprotection, coupling and arylation of an analogous chemical series, *see, e.g.*, Joyeau, R. *et al.* Synthesis and activity of pyrrolidinyl- and

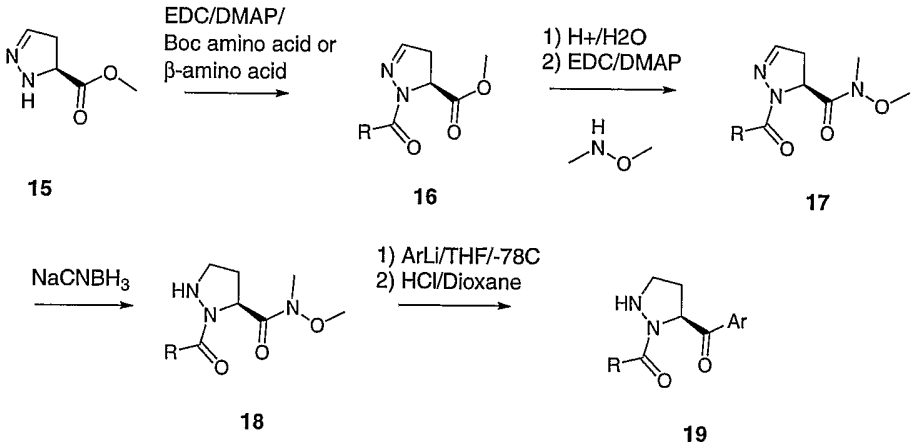
thiazolidinyl-dipeptide derivatives as inhibitors of the Tc80 prolyl oligopeptidase from *Trypanosoma cruzi*. *Eur J Med Chem* **2000**, *35*, 257-266].

*Scheme 4. Synthesis of 5-oxaprolylketones **14**.*

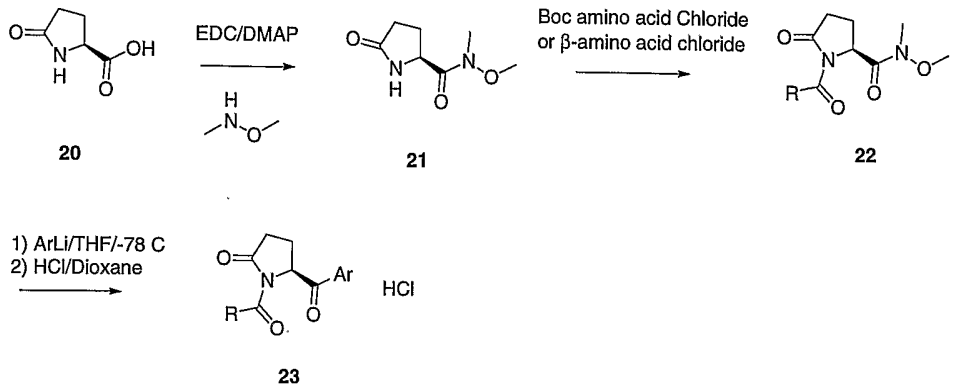


Compound **11** (Scheme 4) can be prepared according to established methods [*see, e.g.*, Vasella, A.; Voeffray, R.; Pless, J.; Huguenin, R. 121. Synthesis of D- and L-5-oxaproline and of a New Captopril Analogue. *Helv Chem Acta* 1983, 66, 1241-1252]. The deprotection, coupling and arylation can be accomplished as shown in Scheme 3, above.

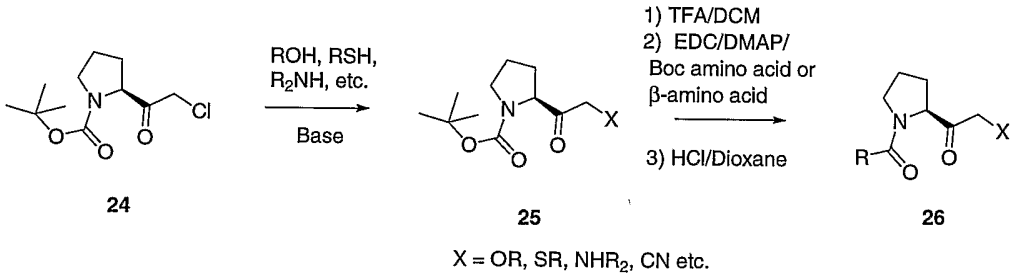
*Scheme 5. Synthesis of azaprolylketones **19**.*



Scheme 6. Synthesis of 5-oxo-prolylketones 23.

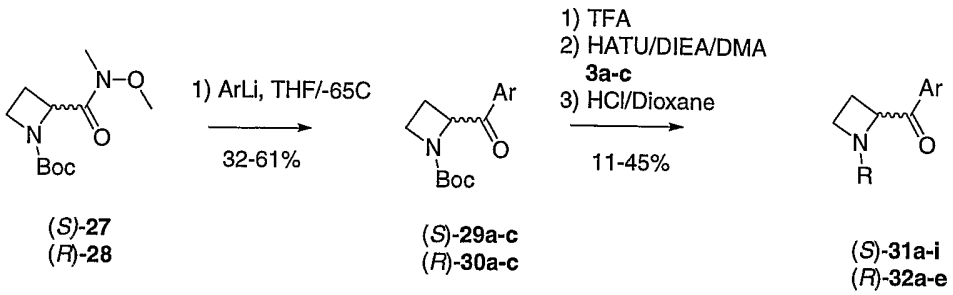


Scheme 7. Synthesis of ketones with leaving group in α position.



Synthesis of ketoazetidine compounds. The general synthesis of L- and D-ketoazetidines (or *S*- and *R*-, respectively) is outlined in Scheme 8, below. The Boc-protected amide (*S*)-**27** and (*R*)-**28** was synthesized according to the procedure of Balboni *et al.* [*see Eur. J. Med. Chem. Chim. Ther.* 35 (2000) 979-88]. The lithiation of this Weinreb amide led to the aryl ketones **29a-c** and **30a-c** in moderate yields (32-61%). The deprotection of these ketones with TFA led to the latent aminoketones which were immediately coupled with one of three representative, hydrophobic Boc-amino acids **3a-c** shown in Figure 1, above. The resulting Boc-ketoazetidines (*S*)-**31a-i** and (*R*)-**32a-e** were isolated in 11-45% yield after deprotection with HCl in dioxane. The amino ketones **31a-i** and **32a-e** were stored at 0°C to minimize decomposition.

Scheme 8. General Synthesis of ketoazetidines (S)-31a-i and (R)-32a-e



General procedure for the lithiation of amides (*S*)-**27** and (*R*)-**28**; 2-(Thiazole-2-carbonyl)-azetidine-1-carboxylic acid tert-butyl ester ((*R*)-**30a**). Thiazole (310 mg, 3.6 mmol) was dissolved in THF and cooled to –65 °C. nBuLi (1.47 mL of a 2.5 M solution) was added dropwise to the benzothiazole solution. The mixture was stirred for 30 min at –65 °C and a solution of (*R*)-**28** (600 mg, 2.45 mmol) was added in 1 mL of THF. The mixture was stirred and monitored for 1 hour at –60 °C. The starting material disappeared by TLC after 3 h at this temperature so the reaction was quenched with water (5 mL). The organics were extracted with EtOAc (3 x 10 mL) and the combined layers were dried, concentrated and chromatographed (hexanes → 25% EtOAc/hexanes) to afford 310 mg of (*R*)-**30a** (32%). ^{1}H NMR ($CDCl_3$) δ 8.01 (d, 1H), 7.72 (d, 1H), 5.75 (m, 1H), 4.10-3.94 (m, 2H), 2.69 (m, 1H), 2.21 (m, 1H), 1.36 (s, 9H). The other enantiomer (*S*)-**29a** had an identical ^{1}HNMR spectrum (yield = 39%). Spectroscopic data for **29a** were identical to **30a**.

2-(Benzothiazole-2-carbonyl)-azetidine-1-carboxylic acid tert-butyl ester ((*R*)-**30b**). Yield = 42%; ^{1}H NMR ($CDCl_3$) δ 8.12 (d, 1H), 7.92 (d, 1H), 7.49 (m, 2H), 5.83 (m, 1H), 4.10-3.92 (m, 2H), 2.70 (m, 1H), 2.19 (m, 1H), 1.30 (s, 9H). The other enantiomer (*S*)-**29b** had an identical ^{1}HNMR spectrum; (yield = 45%).

2-(Pyridine-2-carbonyl)-azetidine-1-carboxylic acid tert-butyl ester ((*R*)-**30c**). Yield = 35%; ^{1}H NMR ($CDCl_3$) δ 8.50 (d, 1H), 8.06 (d, 1H), 7.81 (t, 1H), 7.44 (t, 1H), 5.89 (m, 1H), 3.93 (m, 2H), 2.65 (m, 1H), 2.05 (m, 1H), 1.33 (s, 9H). The other enantiomer (*S*)-**29c** had an identical ^{1}HNMR spectrum; (yield = 61%).

General procedure for the synthesis of Boc keto-azetidines (*S*)-**31a-i** and (*R*)-**32a-e**.

2-(*R*)-[2-(Benzothiazole-2-carbonyl)-azetidin-1-yl]-(octahydro-indol-2-yl)-methanone hydrochloride (**32b**). Boc-OIC (600 mg, 2.22 mmol) was dissolved in DMA (3 mL). HATU (845 mg, 2.22 mmol) and DIEA were added to the mixture and the whole was stirred for 30 min. At the same time, (*R*)-**30b** (640, 2.0 mmol) was dissolved in TFA and stirred for 5 min at r.t. The TFA was removed and the crude aminoketone was concentrated *in vacuo* and pumped on high vac. The aminoketone was then suspended in DMA (1 mL) and immediately added to the coupling solution. The DMA was removed *in vacuo* and the crude residue was treated with water/EtOAc (5 mL each). The water was reextracted with EtOAc (2 x 5 mL) and the combined organics were treated with 10% $NaHCO_3$ followed by 5% $KHSO_4$ then brine (5 mL each). The organic layer was dried, concentrated and chromatographed to yield 440 mg (51%) of the Boc protected product. This material was dissolved in 3 mL of 4.0 M HCl in dioxane and stirred for 30 min. The dioxane was removed *in vacuo* and the crude solid was dried under high vac, then triturated with diethyl ether (10 mL) to remove traces of dioxane and water. The solid was filtered off and dried under high vacuum for 1 h to afford 274 mg (79%) of a yellow solid that was stable in the solid state for prolonged periods at 0 °C. ^{1}H NMR (MeOD), 300 MHz: δ 7.94 (d, J = 9Hz, 1H), 7.84 (d, J = 9Hz, 1H), 7.48 (t, J = 9Hz, 1H), 7.38 (t, J = 9Hz, 1H), 4.51 (m, 1H), 4.34 (m, 2H), 3.69 (m, 1H), 3.35 (m, 2H), 2.43 (m, 2H), 2.13 (m, 1H), 1.83-1.25 (m, 9H). Anal. Calcd for $C_{20}H_{23}N_3O_2S$ (0.8 H_2O)(1.0 $C_4H_8O_2$): C, 45.4; H, 5.6; N, 6.6. Found: C, 45.0; H, 5.4; N, 6.8.

2-(*S*)-(Octahydro-indol-2-yl)-[2-(thiazole-2-carbonyl)-azetidin-1-yl]-methanone (**31a**). Yield = 15%; ^{1}H NMR (D_2O) 300 MHz: δ 8.10 (s, 1H), 7.87 (s, 0.5H), 7.68 (s, 0.5H), 6.03 (m, 1H), 4.57 (m, 1H), 4.33 (m, 2H), 3.76 (m, 1H), 3.25 (m, 1H), 2.97 (m, 1H), 2.51-1.35 (m, 11H). Anal. Calcd for $C_{16}H_{21}N_3O_2S$ (1.2 HCl)(0.5 $C_4H_8O_2$)(1.0 H_2O): C, 50.0; H, 6.6; N, 9.7. Found: C, 50.0; H, 6.5; N, 9.8.

2-(*S*)-[2-(Benzothiazole-2-carbonyl)-azetidin-1-yl]-(octahydro-indol-2-yl)-methanone hydrochloride ((*S*)-**31b**). Yield = 25%. ^{1}H NMR (D_2O), 300 MHz: δ 7.94 (d, J = 6Hz, 1H), 7.75 (d, J = 6Hz, 1H), 7.41 (m, 2H), 5.88 (m, 1H), 4.33 (m, 1H), 4.10 (m, 2H), 3.46 (m, 1H), 3.02 (m, 1H), 2.77 (m, 1H), 2.35-1.00 (m, 11H).

2-(*S*)-(Octahydro-indol-2-yl)-[2-(pyridine-2-carbonyl)-azetidin-1-yl]-methanone (**31c**). Yield = 39%; ^{1}H NMR (D_2O), 300 MHz 8.75 (d, J = 6Hz, 0.3H), 8.58 (d, J = 6Hz, 0.7H), 8.43 (t, J = 6Hz, 0.7H), 8.21 (d, J = 6Hz, 0.3H), 8.15 (t, J = 6Hz, 0.3H), 7.81 (m, 1.4H), 4.66 (t, J = 6Hz, 1H), 4.46 (m, 2H), 3.80 (m, 1H), 3.48 (m, 1H), 2.56 (m, 2H), 2.20 (m, 1H), 1.91 (m, 1H), 1.67 (m, 5H), 1.41 (m, 5H). Anal. Calcd for $C_{18}H_{23}N_3O_2$ (1.4 HCl)(1.0 $C_4H_8O_2$)(1.8 H_2O): C, 53.0; H, 7.3; N, 8.4. Found: C, 52.7; H, 7.3; N, 8.6.

2-(*S*)-2-Amino-2-cyclohexyl-1-[2-(thiazole-2-carbonyl)-azetidin-1-yl]-ethanone ((S)-**31d**). Yield = 11%; ^{1}H NMR (D_2O) 300 MHz: δ 7.81 (d, J = 3Hz, 1H), 7.64 (d, J = 3Hz, 1H), 4.38 (m, 1H), 3.96 (m, 1H), 3.17 (m, 2H), 1.86 (m, 2H), 1.69 (m, 6H), 1.25-0.90 (m, 4H). Anal. Calcd for $C_{15}H_{21}N_3O_2S$ (1.2 HCl)(0.3 $C_4H_8O_2$)(1.3 EtOAc): C, 47.7; H, 6.7; N, 10.4. Found: C, 47.7; H, 6.7; N, 10.4.

2-(*S*)-2-Amino-2-cyclohexyl-1-[2-(1H-imidazole-2-carbonyl)-azetidin-1-yl]-ethanone hydrochloride (**31e**). White solid: ^{1}H NMR (MeOD, 11828-8620) 300 MHz 7.57 (m, 2H), 4.75-4.01 (m, 4H), 3.82 (d, J = 6Hz, 2H), 2.58-2.41 (m, 2H), 1.98-1.60 (m, 7H), 1.45-1.10 (m, 5H). Anal. Calcd for $C_{15}H_{22}N_4O_2$ (1.6 HCl)(1.0 $C_4H_8O_2$)(1.8 H_2O): C, 46.16; H, 7.4; N, 11.3. Found: C, 46.5; H, 7.3; N, 11.1.

2-(*S*)-2-Amino-1-(2-benzoyl-azetidin-1-yl)-2-cyclohexyl-ethanone hydrochloride (**31f**). White solid: ^{1}H NMR (MeOD, 11828-9530) 300 MHz 7.87 (t, J = 9Hz, 2H), 7.56 (t, J = 9Hz, 1H), 7.47 (d, J = 9Hz, 2H), 6.05 (m, 0.4H), 5.78 (m, 0.6H), 4.27 (m, 1H), 4.16 (m, 1H), 3.90 (t, J = 6Hz, 1H), 3.77 (d, J = 6Hz, 1.4H), 3.33 (d, J = 6Hz, 0.6H), 2.97 (m, 1H), 2.15 (m, 2H), 1.80-1.50 (m, 5H), 1.43-1.05 (m, 5H). Anal. Calcd for $C_{18}H_{24}N_2O_2$ (1.4 HCl)(0.3 $C_4H_8O_2$)(0.3 H_2O): C, 58.4; H, 7.2; N, 7.2. Found: C, 58.1; H, 7.3; N, 7.3.

2-(*S*)-L-1-[2-(Benzothiazole-2-carbonyl)-azetidin-1-yl]-2-cyclohexylamino-ethanone hydrochloride (**31g**). Yellow solid: m.p. 115-120 °C ^{1}H NMR ($CDCl_3$, 11820-10200): δ 7.95(dd, 1H), 7.81(dd, 1H), 7.44(m, 2H), 4.08(s, 1H), 3.77-3.85(m, 2H), 3.54(m, 2H) 3.08(t, 1H), 2.89(m, 1H), 2.31(m, 1H), 1.81(t, 2H), 1.58(bs, 2H), 1.39(bs, 1H), 1.08(m, 5H). Anal. calcd. for $C_{19}H_{23}N_3SO_2$ (1.4 HCl): (0.7 H_2O): C, 54.19; H, 6.17; N, 9.98; S, 7.61; Cl, 11.79. Found: C, 54.11; H, 6.18; N, 9.85; S, 7.61; Cl, 11.90.

2-(*S*)-2-Cyclohexylamino-1-[2-(pyridine-2-carbonyl)-azetidin-1-yl]-ethanone (**31h**). Yield = 39%; ^{1}H NMR (D_2O) 300 MHz: δ 8.65 (m, 0.5H), 8.57 (d, J = 6Hz, 0.5H), 8.42 (t, J = 6Hz, 0.5H), 8.23 (m, 0.5H), 8.08 (m, 0.5H), 7.79 (m, 1.5H), 4.40 (t, J = 6Hz, 2H), 4.12 (m, 2H), 3.44 (t, J = 6Hz, 1H), 3.21 (m, 1H), 2.07 (m, 2H), 1.82 (m, 2H), 1.64 (m, 1H), 1.33 (m, 7H). Anal. Calcd for $C_{17}H_{23}N_3O_2S$ (1.3 HCl)(0.5 $C_4H_8O_2$)(2.0 H_2O): C, 52.3; H, 9.6; N, 10.4. Found: C, 51.8; H, 7.4; N, 9.8.

2-(*S*)-L-*endo*-[1-(3-Amino-bicyclo[2.2.1]heptane-2-carbonyl)-azetidin-2-yl]-benzothiazol-2-yl-methanone hydrochloride (**31i**). Yellow solid: ^{1}H NMR (MeOD, 11828-10230) 300 MHz 7.97 (d, J = 6Hz, 1H), 7.83 (d, J = 6Hz, 1H), 7.51 (t, J = 6Hz, 1H), 7.43 (t, J = 6Hz, 1H), 4.34 (m, 2H), 3.24 (m, 1H), 3.20 (m, 2H), 2.78 (d, J = 6Hz, 1H), 2.49 (m, 1H), 2.31 (m, 1H), 2.08 (m, 1H), 1.61 (m, 2H), 1.33 (m, 4H). Anal. Calcd for $C_{19}H_{21}N_3O_2S$ (1.5 HCl)(1.8 H_2O): C, 49.6; H, 5.7; N, 9.1. Found: C, 50.0; H, 5.8; N, 9.1.

2-(*R*)-(Octahydro-indol-2-yl)-[2-(thiazole-2-carbonyl)-azetidin-1-yl]-methanone ((*R*)-**32a**). Yield = 45%; ^{1}H NMR (D_2O), 300 MHz 8.14 (m, 0.5H), 8.09 (m, 0.5H), 7.87 (m, 0.5H), 7.70 (m, 0.5H), 5.61 (m, 1H), 4.66-4.28 (m, 2H), 3.82 (m, 2H), 2.49 (m, 2H), 2.34 (m, 1H), 2.09 (m, 2H), 1.87 (m, 2H), 1.65-1.28 (m, 8H).

2-(*R*)-[1-(Octahydro-indole-2-carbonyl)-azetidin-2-yl]-pyridin-2-yl-methanone hydrochloride (**32c**). ^{1}H NMR (MeOD, 11828-7520) 300 MHz 8.56 (d, J = 6Hz, 1H), 8.41 (t, J = 6Hz, 1H), 8.03 (m, 1H), 7.79 (m, 2H), 4.57-4.39 (m, 2H), 3.69 (m, 1H), 3.20 (m, 2H), 2.46 (m, 4H), 2.15 (m, 1H), 1.86 (m, 1H), 1.66-1.19 (m, 7H). Anal. Calcd for $C_{18}H_{23}N_3O_2$ (2.3 HCl)(0.5 $C_4H_8O_2$) (1.3 H_2O): C, 47.3; H, 6.3; N, 8.3. Found: C, 47.1; H, 6.4; N, 8.2.

2-(*R*)-2-Amino-2-cyclohexyl-1-[2-(thiazole-2-carbonyl)-azetidin-1-yl]-ethanone hydrochloride (**32d**). Yellow solid: ^{1}H NMR (MeOD, 11828-7920) 300 MHz 7.99 (d, J = 3Hz, 1H), 7.88 (d, J = 3Hz, 1H), 4.48 (m, 1H), 4.39 (m, 1H), 3.91 (d, J = 6Hz, 2H), 3.17 (m, 2H), 1.90-1.51 (m, 7H), 1.32-1.00 (m, 6H). Anal. Calcd for $C_{15}H_{21}N_3O_2S$ (1.5 HCl)(0.5 $C_4H_8O_2$) (2.8 H_2O): C, 43.1; H, 6.8; N, 8.9. Found: C, 43.1; H, 6.8; N, 9.0.

2-(*R*)-2-Amino-1-[2-(benzothiazole-2-carbonyl)-azetidin-1-yl]-2-cyclohexyl-ethanone (**32e**). Yield = 42%; ^{1}H NMR (D_2O), 300 MHz 7.96 (d, J = 6Hz, 1H), 7.85 (d, J = 6Hz, 1H), 7.50 (t, J = 6Hz, 1H), 7.43 (t, J = 6Hz, 1H), 4.40 (m, 2H), 3.90 (d, J = 6Hz, 2H), 3.34 (m, 2H), 1.80-1.52 (m, 8H), 1.21-1.02 (m, 5H). Anal. Calcd for $C_{15}H_{21}N_3O_2S$ (1.8 HCl)(0.3 $C_4H_8O_2$): C, 47.7; H, 6.7; N, 10.4. Found: C, 47.7; H, 6.7; N, 10.4.

Additional compounds spanning the full scope of the aspect of this invention embodied in Formula I can be synthesized according to the methods described above, or according to the procedures outlined in Schemes 4 – 8, and according to other generally accepted synthetic procedures, with no more than routine experimentation, as will be appreciated by those of skill in the art.

Measuring the Bioactivity of the Compounds of the Invention:

As noted above, a number of methods can be used to assay for the bioactivity of the compounds of the invention. Appropriate assays can be *in vivo* or *in vitro* methods, which are themselves well-established in the art. For example, to determine the efficacy of the compounds of Formula I in the treatment or prevention of diabetes, the Zucker Diabetic rat model can be utilized, as will be appreciated by one skilled in the art. Rats of the Zucker strain are initially pre-diabetic, but develop a type II diabetes of varying severity as they mature. The literature cited herein discloses many such assays, and can be relied upon to make and practice aspects of the instant invention. The examples below illustrate assays for the ability of the compounds to protect neuronal cells from toxic treatments and the ability of the compounds to elicit neuronal cell growth, regeneration, or neurite extension.

Measuring DPP IV inhibition:

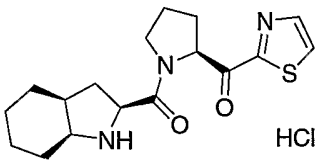
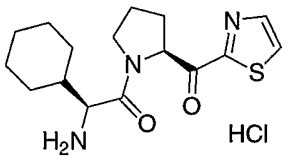
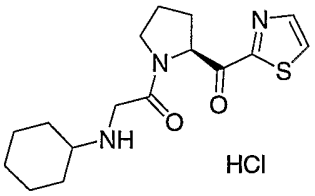
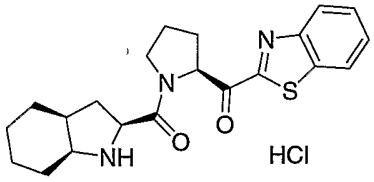
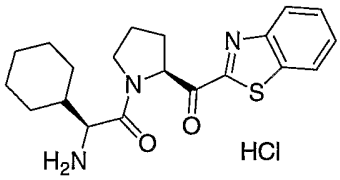
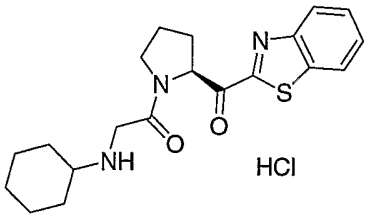
The inhibitory activity of the compounds of Formula I against DPP IV can be determined by *in vitro* assay systems, which are themselves well-established in the art. For example, inhibitory constants of the compounds of this invention can be determined by testing the compounds on purified porcine DPP IV according to the method taught at columns 23 – 24 of U.S. patent 6,395,762 to Robl *et al.*, which method is hereby incorporated by reference.

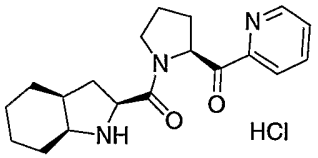
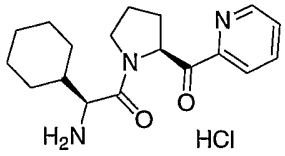
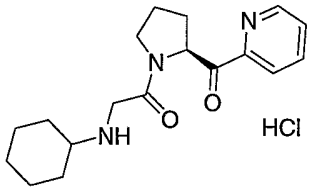
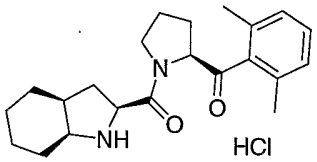
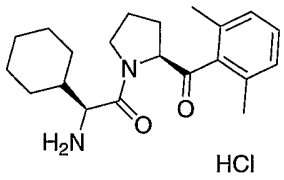
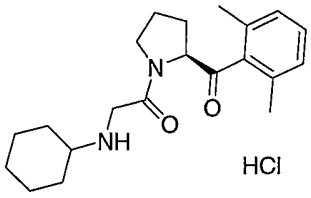
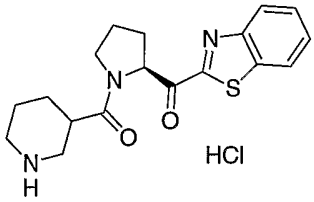
The assay results given in table 1, below, were obtained according to the following method:

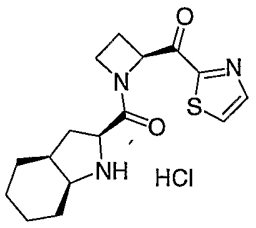
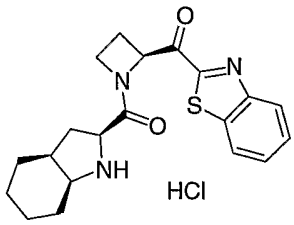
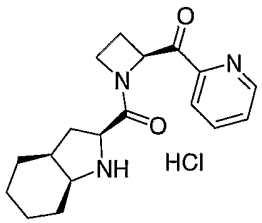
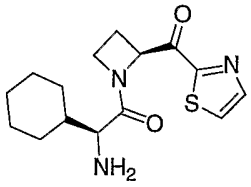
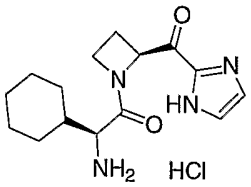
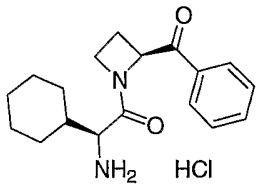
Dilute 1 volume of rat plasma (coagulated with sodium citrate) to 2.5 volumes assay buffer (25 mM HEPES, 140 mM NaCl, 1% BSA [added on the day of the assay]; pH 7.8) to yield approximately 350 micrograms total protein/well in a 96-well plate. Prepare 80 mM $MgCl_2$ solution in assay buffer (16.264 mg/mL). Dilute the peptide substrate (H-Gly-Pro-alpha methyl coumarin, 10 mM stock in 100% DMSO) 1:100 in assay buffer. Compounds of this invention are diluted in 100% DMSO. Add 10 microliter of diluted compounds or DMSO vehicle to wells. Add 25 uL of rat plasma or buffer to wells. Add 25 uL $MgCl_2$ to all wells. Vortex gently for 1 minute, then pre-incubate at room temp for 10 minutes. Start the reaction by adding 50 uL peptide substrate (no vortexing), and incubate the plate at room temp in the dark for 30 minutes. Stop the reaction by adding 25 uL of 25% glacial acetic acid. Read the plate at 380 nm (excitation) and 460 nm (emission). Plot absorbance vs. concentration of test compound to determine the concentration of test compound which yields a 50% inhibition of DPP IV enzymatic activity (IC50).

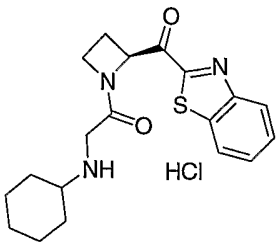
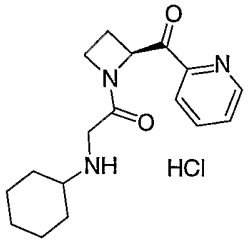
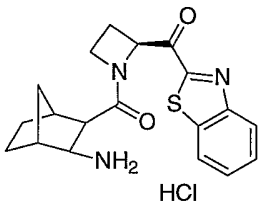
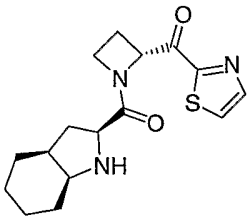
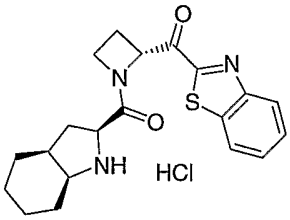
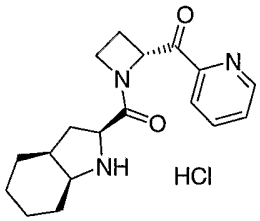
The following Table 1 expresses such IC50 values in nanomolar concentrations, as determined for exemplary compounds of this invention.

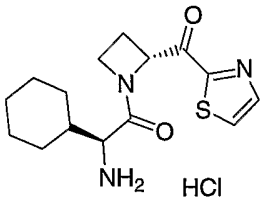
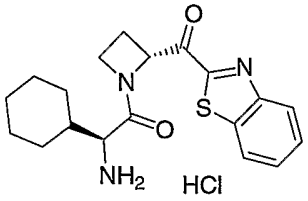
Table 1. Inhibitory potency of exemplary compounds against DPPIV.

Structure	Compound #	IC_{50}
	**5a**	44
	**5b**	50
	**5c**	300
	**5d**	30
	**5e**	2,000
	**5f**	300

Structure	Compound #	IC_{50}
	**5g**	2,000
	**5h**	900
	**5i**	>10,000
	**5j**	>10,000
	**5k**	>10,000
	**5l**	>10,000
	**8a**	>10,000

Structure	Compound #	IC_{50}(nM)
	**31a**	80
	**31b**	200
	**31c**	3000
	**31d**	50
	**31e**	70
	**31f**	100000

Structure	Compound #	IC_{50}(nM)
	**31g**	100
	**31h**	4000
	**31i**	75000
	**32a**	140
	**32b**	200
	**32c**	5000

Structure	Compound #	IC_{50}(nM)
	**32d**	30
	**32e**	70

Neuroprotection Assay in Spinal Cord Slice Preparations: All cultures are derived from postnatal day 8 (P8) Sprague-Dawley rat lumbar spinal cord slices of 325 micron thickness, prepared using a commercially available McIlwain tissue chopper. Experiments consist of two 6-well plates with 5 slices from 4 different animals per well; slices are cultured at the media/atmosphere interface on a commercially available permeable membrane culture well insert. Media changes are performed every 3 to 4 days. Cultures are treated with the neurotoxin THA [L(-)-threo-3-hydroxyaspartic acid; Tocris Cookson Inc., Ballwin, Missouri] at 200μM + compound (10μM) after one week in culture. The control is an untreated sample with 0.1% DMSO as vehicle. The THA control is a THA treated sample with 0.1% DMSO as vehicle. Two wells are used per condition. One media change with new THA and compounds is performed. The experiment is stopped 6 to 8 days following drug treatment (13-15 total days in vitro, DIV) as dictated by visual assessment of lesion, by fixation with 4% paraformaldehyde/0.1 M phosphate buffer for 30 minutes. Slices are permeabilized with 100% cold methanol for10 minutes and transferred to staining wells. The slices are blocked with 10% HS/TBS (horse serum/tris-buffered saline). Primary antibody incubation is overnight at 4°C with SMI-32 antibody 1:5000 in 2% HS/TBS. SMI-32 is specific towards the unphosphorylated H neurofilament subunit. Vectastain ABC Elite Kit with rat absorbed anti-mouse secondary antibody is used with 3,3-diaminobenzidine as a chromogen to stain the slices. The slices are mounted onto a slide and a coverslip is sealed with DPX mounting solution.

Quantification of surviving neurons is performed on a Zeiss Axiovert microscope. Neuronal survival is determined by observing an intact neuronal cell body with processes located ventrally of the central canal in each hemisphere. This correlates to laminae VII, VIII and IX. Each hemisphere is counted individually. Statistical analysis is performed with StatView™ software on a minimum of three different experiments per condition and significance is determined as compared to THA control. The percent of protection is determined from the average number of living neurons by the following equation: (drug treatment condition – THA control)/(Untreated control-THA control).

THA-treated control cultures display a significantly reduced average number of SMI-32 immunoreactive neurons per ventral hemisphere of the spinal cord slices at the end of the culturing interval, as compared to untreated control cultures. Addition of the compounds of this invention to THA-treated cultures causes a significant protection from THA-induced cell death.

In Vivo Reinnervation of the Denervated Striatum by Nigrostriatal Dopaminergic Fibers: The MPTP-lesioned mouse model of Parkinson's disease is utilized to demonstrate *in vivo* efficacy of the compounds of this invention. MPTP (N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) is a systemically available neurotoxin specific to nigrostriatal dopaminergic neurons, i.e. to the cells that degenerate in human Parkinson's disease. Administration of MPTP to mice leads to a selective partial destruction of the mesotelencephalic dopaminergic projection, and to a loss of dopamine and dopaminergic fibres in the corpus striatum, which is the main forebrain target of midbrain dopaminergic neurons.

Young adult male CD1 albino mice (Harlan - Sprague Dawley; 22-25g) are dosed i.p. with the dopamine cell-specific neurotoxin N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP hydrochloride, calculated as 34 mg/kg free base), dissolved in saline at a concentration of 3.4 mg/ml free base once daily on days one to five.

Experimental compounds are administered once daily on days 1-5 (10 mg/kg in Intralipid vehicle, s.c.), one hour prior to MPTP-administration. On day seven, animals are perfused transcardially with 10% neutral buffered formalin. Sagittal sections of striatal tissue are cut at 20 μm thickness on a freezing microtome and processed for free-floating tyrosine hydroxylase immunocytochemistry using a

polyclonal TH antibody (Pel Freeze, 1:2500 under refrigeration for 4 nights), further processed using the avidin:biotin peroxidase method (Vector Elite kit), and visualized with Diamino benzidine (DAB-HCl, Polysciences).

Blinded analysis of TH fiber density in the central striatum is performed at 630X magnification. For each mouse striatum, five representative 100 μm x 100 μm fields in the central striatum are photographed using a digital video camera. The percentage of sample field covered by TH positive processes and terminals is calculated using an image analysis program ("Simple," Compix Inc., Pittsburgh, PA). The mean striatal innervation density is calculated for each group. The magnitude of striatal deafferentation due to the MPTP lesion is assessed by dividing the observed striatal innervation values obtained in MPTP /vehicle treated cases by the mean striatal innervation density in the Vehicle/Vehicle group and expressed as %loss. The relative efficacy of the compounds of this invention is expressed as % protection of striatal innervation density, i.e., the degree to which the density of TH positive fibres in the striatum of lesioned/compound-treated animals exceeds the loss observed in lesioned-alone animals.

Administration of compounds of this invention leads to a significant protection of striatal dopaminergic innervation density from neurotoxin-induced lesion.

Antiinflammatory effects

The anti-inflammatory activity of the compounds of formula I can be assessed in the carrageenan-induced hindpaw inflammation model in the rat, which has long been established in the art [see, e.g., Winter, et al., Proc. Soc. Exp. Biol. Med. 111 (1962) 544-547]. Carrageenan is a naturally-occurring family of carbohydrates extracted from red seaweed, which commercially available for experimental purposes, and which is known to trigger a strong inflammatory and edema response following injection. Briefly, male albino rats of the Wistar or Sprague-Dawley strains are housed under a 12 h light/dark cycle with free access to food and water. For testing anti-inflammatory activity, the compound of formula I is dissolved in physiological saline or another pharmaceutically acceptable vehicle and dosed i.p. one hour before, and two hours following carrageenan injection. Control animals receive i.p. injections of vehicle only. Carrageenan is injected into the intraplantar region of the right hindpaw (0.75 mg per paw in 0.05 ml physiological saline). For intra-animal control, the contralateral hindpaw receives a similar injection of vehicle alone. At four hours

following carrageenan injection, animals are euthanized and the inflammatory response to carrageenan injection is assessed by volumetric measurement of hindpaw edema. Relative to control animals, animals treated with compounds of formula I display a dose-dependent attenuation of carrageenan-induced hindpaw swelling.

Analgesic effects

The analgesic effects of the compounds of this invention can be established by methods which are themselves well-established in the art [see, e.g., Hunskaar et al., J. neurosci. Methods 14 (1985) 69-76]. A simple analgesia assay useful in assessing efficacy of the compounds of formula I employs subcutaneous formalin injections in mice dosed with the compounds of this invention. Briefly, male albino NMRI mice (30-45 g) are housed under a 12h light/dark cycle with access to food and water *ad libitum*. The test compound of formula I is dissolved in sterile saline or other pharmaceutically suitable vehicles and dosed i.p. 30 min. prior to subcutaneous injection of a formalin solution under the dorsal surface of the right hindpaw (20 microliters of a 1 or 5% w/v solution in saline or another pharmaceutically suitable vehicle). The animal is then observed and the time spent licking the injected hindpaw is recorded. Control animals receive only vehicle injections. Pain intensity is rated using one single objective response: licking the injected paw, either the dorsal surface of the paw, the toes, or the leg.

Subcutaneous formalin injection results in a biphasic behavioral response, where the experimental animal spends time licking the injected hindpaw during the first 5-10 minutes following formalin injection, then displays diminished licking activity for the following 5 – 10 minutes, followed by a second, late pain response during the following 20 – 30 minutes.

Compared to animals dosed intraperitoneally with vehicle only, mice dosed with compounds of formula I display a dose-dependent reduction in both the early and late-phase licking response to subcutaneous formalin injection.

Antipsychotic effects

The antipsychotic effects of the compounds of the invention can be determined by established methods, such as, for example the mescaline-induced "scratching" model [*see, e.g.,* Cook *et al.,* J. Pharmacol. Exp. Ther. 263 (1992) 1159-66]: Young adult Swiss-Webster albino male mice receive parenteral injections of a compound of

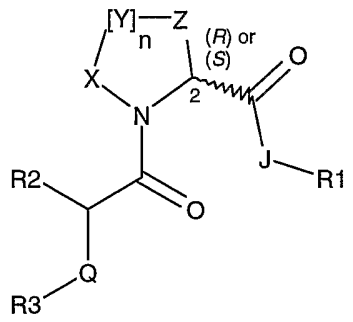
Formula I (1 – 100 mg/kg) or vehicle, followed 30 minutes later by i.p. injection of mescaline (50 mg/kg). Mice (n = 10 – 15/group) are then placed in individual cages and monitored for onset of scratching behavior. Beginning 20 minutes after the injection of mescaline, the numbers of back and neck scratching episodes are counted by a naïve observer over a 5 minute period. Compared to control animals, pretreatment with the compounds of the invention significantly reduces the number of compulsive scratching episodes induced by mescalin in mice.

Yet another model known in the art to be useful for assessing antipsychotic activity of experimental compounds is the amphetamine-induced locomotor hyperactivity model in mice: Young adult male albino mice receive parenteral injections of a compound of Formula I (1 – 100 mg/kg) or vehicle, followed 30 min. later by i.p. injections of a locomotor stimulatory dose of dexamphetamine sulphate (3 mg/kg i.p.). Immediately following amphetamine injection, mice are individually placed in automated behavioral activity chambers, and open-field locomotor activity is measured over a 30 min. period. Compared to amphetamine-treated animals that are pretreated with vehicle alone, amphetamine-treated mice that are pretreated with the compound of Formula I display a significant reduction in open-field activity, indicating that the compound of Formula I is capable of antagonizing the locomotor stimulatory effects of amphetamine *in vivo*.

The specific examples disclosed herein should not be interpreted as a limitation to the scope of the invention. Instead, they are merely exemplary embodiments one skilled in the art would understand from the entire disclosure of this invention. 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 included to be within the scope of the following claims.

We claim:

1. A compound according to the following Formula I:



or a pharmaceutically acceptable derivative thereof; wherein

n is 0, 1, or 2; forming a four, five- or six-membered nitrogen-containing ring; said nitrogen-containing ring is saturated or optionally contains one double bond;

X, and each Y, if present, are independently CH_2, CF_2, CH, S, O, NH, N, C=O, CH-W, or C-W; provided however that said nitrogen-containing ring may contain no more than one heteroatom in addition to said nitrogen;

Z is CH_2, CF_2, CH, C-W or CH-W;

W is halogen, hydroxy, sulfhydryl, alkyl or C_1-C_3 alkyloxy;

J is a single bond, C=O, or CH_2;

wherein, when J is CH_2:

R1 is halogen, cyano, -O-R4, -S-R4, or –NH-R5;

said R4 is phenyl or benzyl, said phenyl or benzyl optionally being substituted with one, two, three, or more substituents independently selected from the group consisting of hydrogen,

hydroxy, sulfhydryl, trifluoromethyl, C_1-C_8 straight or branched alkyl, alkoxy, aralkoxy, and halogen;

said R5 is aryl- or heteroaryl-substituted $C_1 - C_6$ straight or branched chain lower alkyl or -alkanoyl;

wherein, when J is a single bond or C=O:

(i) R1 is phenyl, which is optionally substituted at one, two, three, or more positions with a substituent independently selected from the group consisting of hydrogen, hydroxy, sulfhydryl, trifluoromethyl, cyano, C_1-C_8 straight or branched alkyl, C_1-C_8 straight or branched alkoxy, aralkoxy, and halogen; or

(ii) R1 is a mono-, bi-, or tricyclic heteroaryl, which is optionally substituted with halogen, C_1-C_8 straight or branched alkyl, alkoxy, or aralkoxy; or

(iii) R1 is cyano;

Q is NH, or CH_2;

wherein, when Q is NH:

(i) one of R2 and R3 is hydrogen, and the other of R2 and R3 is a C_3-C_{12} straight or branched chain alkyl, or a saturated mono- bi- or tricyclic hydrocarbon wherein the individual rings comprise 3 – 12 carbon atoms; or

(ii) R2 and R3, together with Q and the carbon atom to which they are attached, form a four- to twelve-membered saturated ring, said ring optionally having fused thereto one or two additional rings independently selected from C_4-C_{12} cycloalkyl, C_4-C_{12} cycloalkenyl, aryl, and heteroaryl; or

wherein, when Q is CH_2:

R2 and R3, together with Q and the carbon atom to which they are attached, form a four- to twelve-membered heterocyclic ring, said ring containing at least one nitrogen immediately adjacent to Q, said ring optionally having fused thereto one or two additional rings independently selected from C_4-C_{12} cycloalkyl, C_4-C_{12} cycloalkenyl, aryl, and heteroaryl.

2. The compound of **claim 1**, wherein n is 0 or 1, J is a single bond, and wherein R1 is phenyl which is optionally substituted at one, two, three, or more positions with a substituent independently selected from the group consisting of hydrogen, hydroxy, sulfhydryl, trifluoromethyl, cyano, C_1-C_8 straight or branched alkyl, alkoxy, aralkoxy, and halogen; or wherein R1 is a mono-, bi-, or tricyclic heteroaryl, which is optionally substituted with halogen, C_1-C_8 straight or branched alkyl, alkoxy, or aralkoxy.

3. The compound of **claim 2**, wherein n is 1, and X, Y, and Z are each CH_2.

4. The compound of **claim 3**, wherein the chiral carbon atom at position 2 of the five-membered ring formed by X, Y, Z, and the nitrogen and carbon atoms to which they are attached, is in the (*R*)-enantiomeric form.

5. The compound of **claim 3**, wherein the chiral carbon atom at position 2 of the five-membered ring formed by X, Y, Z, and the nitrogen and carbon atoms to which they are attached, is in the (*S*)-enantiomeric form.

6. The compound of **claim 2**, wherein n is 1, and X is O, S, NH, N, or C=O.

7. The compound of **claim 6**, wherein the chiral carbon atom at position 2 of the five-membered ring formed by X, Y, Z, and the nitrogen and carbon atoms to which they are attached, is in the (*R*)-enantiomeric form.

8. The compound of **claim 6**, wherein the chiral carbon atom at position 2 of the five-membered ring formed by X, Y, Z, and the nitrogen and carbon atoms to which they are attached, is in the (*S*)-enantiomeric form.

9. The compound of **claim 2**, wherein n is 1, and Y is O, S, C=O, CF_2, or CH-W.

10. The compound of **claim 9**, wherein the chiral carbon atom at position 2 of the five-membered ring formed by X, Y, Z, and the nitrogen and carbon atoms to which they are attached, is in the (*R*)-enantiomeric form.

11. The compound of **claim 9**, wherein the chiral carbon atom at position 2 of the five-membered ring formed by X, Y, Z, and the nitrogen and carbon atoms to which they are attached, is in the (*S*)-enantiomeric form.

12. The compound of **claim 9**, wherein W is fluoro or chloro.

13. The compound of **claim 2**, wherein n is 0, and X is CH_2, CF_2, or CH-W; said W being a halogen selected from fluoro and chloro.

14. The compound of **claim 13**, wherein X and Z are CH_2, and R1 is phenyl which is optionally substituted at one, two, three, or more positions with a substituent independently selected from the group consisting of hydrogen, hydroxy, sulfhydryl, trifluoromethyl, cyano, C_1-C_8 straight or branched alkyl, alkoxy, aralkoxy, and halogen.

15. The compound of **claim 14**, wherein the chiral carbon atom at position 2 of the four-membered ring formed by X, Z, and the nitrogen and carbon atoms to which they are attached, is in the (*R*)-enantiomeric form.

16. The compound of **claim 14**, wherein the chiral carbon atom at position 2 of the four-membered ring formed by X, Z, and the nitrogen and carbon atoms to which they are attached, is in the (*S*)-enantiomeric form.

17. The compound of **claim 13**, wherein X and Z are CH_2, and R1 is a mono-, bi-, or tricyclic heteroaryl, which is optionally substituted with halogen, C_1-C_8 straight or branched alkyl, alkoxy, or aralkoxy.

18. The compound of **claim 17**, wherein the chiral carbon atom at position 2 of the four-membered ring formed by X, Z, and the nitrogen and carbon atoms to which they are attached, is in the (*R*)-enantiomeric form.

19. The compound of **claim 17**, wherein the chiral carbon atom at position 2 of the four-membered ring formed by X, Z, and the nitrogen and carbon atoms to which they are attached, is in the (*S*)-enantiomeric form.

20. The compound of **claim 1**, wherein n is 0 or 1, J is CH_2, and R1 is phenoxy, benzyloxy, phenylthio, or benzylthio, said R1 optionally being substituted in one, two, or three positions with hydrogen, hydroxy, sulfhydryl, trifluoromethyl, C_1-C_8 straight or branched alkyl, C_1-C_8 straight or branched alkoxy, aralkoxy, and halogen.

21. The compound of **claim 1**, wherein n is 0 or 1, J is CH_2, and R1 is halogen or cyano.

22. The compound of **claim 1**, wherein n is 0 or 1, J is CH_2, and R1 is a $C_1 - C_6$ straight or branched chain alkylamino or alkylamido group, said alkylamino or alkylamido being substituted at one position with aryl or heteroaryl.

23. The compound of **claim 1**, wherein Q is NH, and R2 and R3, together with the nitrogen- and carbon-atoms to which they are attached, form a four to twelve-membered saturated ring, which optionally has fused thereto one or two additional rings independently selected from C_4-C_{12} cycloalkyl, C_4-C_{12} cycloalkenyl, aryl, and heteroaryl.

24. The compound of **claim 23**, wherein the chiral carbon atom at position 2 of the four, five- or six-membered nitrogen-containing ring formed by X, Y, Z, and the nitrogen- and carbon atoms to which they are attached, is in the (*S*)-enantiomeric form.

25. The compound of **claim 23**, wherein the chiral carbon atom at position 2 of the four, five- or six-membered nitrogen-containing ring formed by X, Y, Z, and the nitrogen- and carbon atoms to which they are attached, is in the (*R*)-enantiomeric form.

26. The compound of **claim 24** wherein n is 1, and X, Y, and Z are each CH_2.

27. The compound of **claim 25** wherein n is 1, and X, Y, and Z are each CH_2.

28. The compound of **claim 24** wherein n is 1, and X is O, S, NH, N, or C=O.

29. The compound of **claim 25** wherein n is 1, and X is O, S, NH, N, or C=O.

30. The compound of **claim 24** wherein n is 1, and Y is O, S, C=O, CF_2, or CH-W.

31. The compound of **claim 25** wherein n is 1, and Y is O, S, C=O, CF_2, or CH-W.

32. The compound of **claim 24** wherein n is 0, and X is CH_2, CF_2, or CH-W, said W being a halogen selected from fluoro and chloro.

33. The compound of **claim 25** wherein n is 0, and X is CH_2, CF_2, or CH-W, said W being a halogen selected from fluoro and chloro.

34. The compound of **claim 32**, wherein X and Z are CH_2, and R1 is phenyl which is optionally substituted at one, two, three, or more positions with a substituent independently selected from the group consisting of hydrogen, hydroxy, sulfhydryl, trifluoromethyl, cyano, C_1-C_8 straight or branched alkyl, alkoxy, aralkoxy, and halogen.

35. The compound of **claim 33**, wherein X and Z are CH_2, and R1 is phenyl which is optionally substituted at one, two, three, or more positions with a substituent independently selected from the group consisting of hydrogen, hydroxy, sulfhydryl, trifluoromethyl, cyano, C_1-C_8 straight or branched alkyl, alkoxy, aralkoxy, and halogen.

36. The compound of **claim 32**, wherein X and Z are CH_2, and R1 is a mono-, bi-, or tricyclic heteroaryl, which is optionally substituted with halogen, C_1-C_8 straight or branched alkyl, alkoxy, or aralkoxy.

37. The compound of **claim 33**, wherein X and Z are CH_2, and R1 is a mono-, bi-, or tricyclic heteroaryl, which is optionally substituted with halogen, C_1-C_8 straight or branched alkyl, alkoxy, or aralkoxy.

38. The compound of **claim 1**, wherein Q is NH, and wherein one of R2 and R3 is hydrogen, and the other of R2 and R3 is a C_3-C_{12} straight or branched chain alkyl, or a saturated mono- bi- or tricyclic hydrocarbon wherein the individual rings comprise 3 – 12 carbon atoms.

39. The compound of **claim 38**, wherein the chiral carbon atom at position 2 of the four, five- or six-membered nitrogen-containing ring formed by X, Y, Z, and the nitrogen- and carbon atoms to which they are attached, is in the (*S*)-enantiomeric form.

40. The compound of **claim 38**, wherein the chiral carbon atom at position 2 of the four, five- or six-membered nitrogen-containing ring formed by X, Y, Z, and the nitrogen- and carbon atoms to which they are attached, is in the (*R*)-enantiomeric form.

41. The compound of **claim 39** wherein n is 1, and X, Y, and Z are each CH_2.

42. The compound of **claim 40** wherein n is 1, and X, Y, and Z are each CH_2.

43. The compound of **claim 39** wherein n is 1, and X is O, S, NH, N, or C=O.

44. The compound of **claim 40** wherein n is 1, and X is O, S, NH, N, or C=O.

45. The compound of **claim 39** wherein n is 1, and Y is O, S, C=O, CF_2, or CH-W.

46. The compound of **claim 40** wherein n is 1, and Y is O, S, C=O, CF_2, or CH-W.

47. The compound of **claim 39** wherein n is 0, and X is CH_2, CF_2, or CH-W, said W being a halogen selected from fluoro and chloro.

48. The compound of **claim 40** wherein n is 0, and X is CH_2, CF_2, or CH-W, said W being a halogen selected from fluoro and chloro.

49. The compound of **claim 47**, wherein X and Z are CH_2, and R1 is phenyl which is optionally substituted at one, two, three, or more positions with a substituent independently selected from the group consisting of hydrogen, hydroxy, sulfhydryl, trifluoromethyl, cyano, C_1-C_8 straight or branched alkyl, alkoxy, aralkoxy, and halogen.

50. The compound of **claim 48**, wherein X and Z are CH_2, and R1 is phenyl which is optionally substituted at one, two, three, or more positions with a substituent independently selected from the group consisting of hydrogen, hydroxy, sulfhydryl, trifluoromethyl, cyano, C_1-C_8 straight or branched alkyl, alkoxy, aralkoxy, and halogen.

51. The compound of **claim 47**, wherein X and Z are CH_2, and R1 is a mono-, bi-, or tricyclic heteroaryl, which is optionally substituted with halogen, C_1-C_8 straight or branched alkyl, alkoxy, or aralkoxy.

52. The compound of **claim 48**, wherein X and Z are CH_2, and R1 is a mono-, bi-, or tricyclic heteroaryl, which is optionally substituted with halogen, C_1-C_8 straight or branched alkyl, alkoxy, or aralkoxy.

53. The compound of **claim 1**, wherein Q is CH_2, and R2 and R3, together with the carbon atoms to which they are attached, form a four to twelve-membered heterocyclic ring, said ring containing at least one nitrogen immediately adjacent to Q, said ring optionally having fused thereto one or two additional rings independently selected from C_4-C_{12} cycloalkyl, C_4-C_{12} cycloalkenyl, aryl, and heteroaryl.

54. The compound of **claim 53**, wherein the chiral carbon atom at position 2 of the four, five- or six-membered nitrogen-containing ring formed by X, Y, Z, and the nitrogen- and carbon atoms to which they are attached, is in the (*S*)-enantiomeric form.

55. The compound of **claim 53**, wherein the chiral carbon atom at position 2 of the four, five- or six-membered nitrogen-containing ring formed by X, Y, Z, and the nitrogen- and carbon atoms to which they are attached, is in the (*R*)-enantiomeric form.

56. The compound of **claim 54** wherein n is 1, and X, Y, and Z are each CH_2.

57. The compound of **claim 55** wherein n is 1, and X, Y, and Z are each CH_2.

58. The compound of **claim 54** wherein n is 1, and X is O, S, NH, N, or C=O.

59. The compound of **claim 55** wherein n is 1, and X is O, S, NH, N, or C=O.

60. The compound of **claim 54** wherein n is 1, and Y is O, S, C=O, CF_2, or CH-W.

61. The compound of **claim 55** wherein n is 1, and Y is O, S, C=O, CF_2, or CH-W.

62. The compound of **claim 54** wherein n is 0, and X is CH_2, CF_2, or CH-W, said W being a halogen selected from fluoro and chloro.

63. The compound of **claim 55** wherein n is 0, and X is CH_2, CF_2, or CH-W, said W being a halogen selected from fluoro and chloro.

64. The compound of **claim 62**, wherein X and Z are CH_2, and R1 is phenyl which is optionally substituted at one, two, three, or more positions with a substituent independently selected from the group consisting of hydrogen, hydroxy, sulfhydryl, trifluoromethyl, cyano, C_1-C_8 straight or branched alkyl, alkoxy, aralkoxy, and halogen.

65. The compound of **claim 63**, wherein X and Z are CH_2, and R1 is phenyl which is optionally substituted at one, two, three, or more positions with a substituent

independently selected from the group consisting of hydrogen, hydroxy, sulfhydryl, trifluoromethyl, cyano, C_1-C_8 straight or branched alkyl, alkoxy, aralkoxy, and halogen.

66. The compound of **claim 62**, wherein X and Z are CH_2, and R1 is a mono-, bi-, or tricyclic heteroaryl, which is optionally substituted with halogen, C_1-C_8 straight or branched alkyl, alkoxy, or aralkoxy.

67. The compound of **claim 63**, wherein X and Z are CH_2, and R1 is a mono-, bi-, or tricyclic heteroaryl, which is optionally substituted with halogen, C_1-C_8 straight or branched alkyl, alkoxy, or aralkoxy.

68. A pharmaceutical composition, comprising a compound of Formula I as defined in claim 1, and a pharmaceutically acceptable carrier, diluent, or excipient.

69. The pharmaceutical composition of **claim 68**, wherein n in said compound of Formula I is 0 or 1, J is a single bond, and wherein R1 is phenyl which is optionally substituted at one, two, three, or more positions with a substituent independently selected from the group consisting of hydrogen, hydroxy, sulfhydryl, trifluoromethyl, cyano, C_1-C_8 straight or branched alkyl, alkoxy, aralkoxy, and halogen; or wherein R1 is a mono-, bi-, or tricyclic heteroaryl, which is optionally substituted with halogen, C_1-C_8 straight or branched alkyl, alkoxy, or aralkoxy.

70. The pharmaceutical composition of **claim 69** wherein R1 is a mono-, bi-, or tricyclic heteroaryl, which is optionally substituted with halogen, C_1-C_8 straight or branched alkyl, alkoxy, or aralkoxy; Q is NH; and wherein one of R2 and R3 is hydrogen, and the other of R2 and R3 is a C_3-C_{12} straight or branched chain alkyl, or a saturated mono- bi- or tricyclic hydrocarbon wherein the individual rings comprise 3 – 12 carbon atoms.

71. The pharmaceutical composition of **claim 69** wherein R1 is a mono-, bi-, or tricyclic heteroaryl, which is optionally substituted with halogen, C_1-C_8

straight or branched alkyl, alkoxy, or aralkoxy; Q is NH; and wherein R2 and R3, together with Q and the carbon atom to which they are attached, form a four- to twelve-membered saturated ring, said ring optionally having fused thereto one or two additional rings independently selected from C_4-C_{12} cycloalkyl, C_4-C_{12} cycloalkenyl, aryl, and heteroaryl.

72. A method of treatment, comprising: administering to a patient in need thereof a therapeutically effective amount of a compound of Formula I as defined in claim 1, wherein said patient suffers from, or is at risk for, a medical condition which can be alleviated by inhibition of DPP IV.

73. A method of treatment, comprising: administering to a patient in need thereof a therapeutically effective amount of a compound of Formula I as defined in claim 1, wherein said patient suffers from, or is at risk for, a medical condition selected from the group consisting of neurological disorder, mental illness, inflammatory disorder, pain disorder, diabetes, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of free fatty acids or glycerol, obesity, hypertriglyceridemia, atherosclerosis, impaired glucose tolerance, impaired glucose homeostasis, polycystic ovary syndrome, arthritis, allograft rejection in organ or tissue transplantation, autoimmune disorder, AIDS, inflammatory bowel disease, osteoporosis, psoriasis, metastatic cancer, and rheumatoid arthritis.

74. The method according to **claim 73**, wherein the mental illness is a disorder selected from: schizophrenia; schizophreniform disorder; schizoaffective disorder; delusional disorder; bipolar disorder; major depression associated with psychotic symptoms; and psychological disorder related to the use of psychoactive substances.

75. A method of treatment, comprising: administering to a patient in need thereof a compound of Formula I as defined in claim I, wherein the patient suffers from pain or an inflammatory disorder, and wherein the compound is administered to the patient in an amount sufficient to produce an analgesic or anti-inflammatory effect.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/34388

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07D 277/64, 417/06; A61K 31/427, 31/428
US CL : 548/159, 180, 180; 514/365, 367

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 548/159, 180, 180; 514/365, 367

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6,448,281 B1 (BEAULIEU et al.) 10 September 2002 (10.9.2002), column 2, lines 26-67 and columns 3-11 in their entirety.	1, 3, 4, 5, 23-27, 32, 33, 36-42, 68, and 75

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
21 February 2004 (21.02.2004)

Date of mailing of the international search report
02 APR 2004

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimile No. (703)305-3230

Authorized officer
Sonya Wright

Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet) (July 1998)

Continuation of Box I Reason 2:
In these claims, the numerous variables (e.g. n, X, Y, Z, W, J, R1, R2, R3, etc. . .) and their voluminous complex meanings and their many permutations and combinations, make it difficult to determine the full scope and complete meaning of the claimed subject matter. As presented, the claimed subject matter cannot be regarded as being a clear and concise description for which protection is sought and as such the listed claims do not comply with the requirements of PCT article 6. Thus a meaningful search cannot be carried out on the same. A search will be made on the first discernable invention, which is compounds 5a-5f of Table 1 and their method of use in claim 75.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/34388

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claim Nos.: 2,6-22,28-31,34,35,43-67 and 69-74
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Please See Continuation Sheet

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.