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(54) Title: PROTEASOME INHIBITORS

(57) Abstract: The present invention is directed to compounds that are proteasome inhibitors, pharmaceutical composition comprising such compounds and methods of treating diseases mediated by unregulated proteasome activity.

PROTEASOME INHIBITORS

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention is directed to compounds that are proteasome inhibitors, pharmaceutical composition comprising such compounds and methods of treating diseases mediated by unregulated proteasome activity.

State of the Art

The proteasome is the main nonlysosomal proteolytic system in the cell and resides in the cytoplasm as well as in the nucleus. It possesses up to five different peptidase activities, in different catalytic domains and the best characterized ones are chymotrypsin-like, trypsin-like, and peptidylglutamyl-peptide hydrolyzing activities.

Proteasome plays an active role in regulating different cellular functions. It participates in the rapid elimination and post-translational processing of proteins involved in cellular regulation. For example, the degradation of several important regulators of cell proliferation such as cyclin 2, cyclin 3, cyclin B, p53 and $p27^{kip1}$ are mediated by proteasome. The activities of several important regulators involved in cell activation are also controlled by proteasome. For example IκBα and IκBβ are degraded via the proteasome pathway and the p50 component of a transacting nuclear factor NF-κβ matures after cotranslational processing of its precursor peptide by proteasome. In addition, proteasome activity is essential for the induction of nitric oxide synthase.

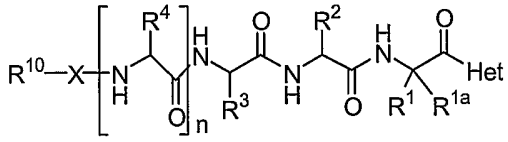
It has been demonstrated that proteasome inhibitors can reduce the cellular content and activity of NF-κβ which is required for the expression of a number of genes involved in the inflammatory response such as TNF-α gene and genes encoding the cell adhesion molecules E-selectin, P-selectin, ICAM, and VCAM (*see* Palombella et al. WO 95/25533). Proteasome inhibitors can also inhibit induction of nitric oxide synthase, and hence production of nitric oxide which is implicated in initiating and exacerbating symptoms of acute and chronic inflammation (*see* Lundberg et al., Nature Medicine, 3:30-31, 1997). Furthermore, it is known that

inhibitors of proteasome can treat conditions mediated by proteolytic function of the proteasome such as rapid elimination and post-translational processing of proteins involved in cellular regulation, intercellular communication, and immune response.

The present invention provides novel compounds that are proteasome inhibitors and accordingly provide a means for the treatment of diseases mediated by proteolytic function of the proteasome such as inflammatory diseases, autoimmune diseases and proliferative diseases such as cancer.

SUMMARY OF THE INVENTION

In one aspect, this invention is directed to a compound of Formula I:



I

wherein:

n is 0 or 1;

R^{1a} is hydrogen or alkyl;

R^1 is alkyl, haloalkyl, hydroxyalkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylthioalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, alkoxyalkyl, aminoalkyl, or aralkyl; or

R^1 and R^{1a} together with the carbon atom to which they are attached form cycloalkyl or heterocycloalkyl;

R^2 is alkyl, hydroxyalkyl, alkylthioalkyl, or alkoxyalkyl;

R^3 is $-(C_{1-3})$-CONH-CHR^6R^7 (where R^6 is hydrogen or alkyl and R^7 is branched (C_{4-10})alkyl or cycloalkyl), $-(C_{1-3})$-$COOR^8$ (where R^8 is branched (C_{4-10})alkyl or cycloalkyl), or $-(C_{1-3})$-Y-$(C_{1-3})_{n1}$Ar (where Y is –O-, -NH-, or $-S(O)_{n2}$- where n2 is 0 to 2, n1 is 0 or 1, and Ar is aryl);

R^4 is alkyl or haloalkyl;

X is –CO-, -OCO-, $-SO_2$-, $-NR^9CO$-, $-NR^9CS$-, or $-NR^9SO_2$- where R^9 is hydrogen or alkyl;

R^{10} is alkyl, aryl, aralkyl, or heteroaryl; or

R^9 and R^{10} together with the nitrogen atom to which they are attached form heterocycloamino; and

Het is a heteroaryl ring; or

a pharmaceutically acceptable salt thereof.

In a second aspect, this invention is directed to a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I and a pharmaceutically acceptable excipient.

In a third aspect, this invention is directed to a method of treating a disorder mediated by the proteolytic function of the proteasome in an animal suffering said disorder, comprising administering to said animal a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient.

Preferably, the disorder is a cancer, autoimmune disease such as asthma and multiple sclerosis, graft rejection, inflammatory diseases, and septic shock. Preferably, the disorder is haemotological malignancies such as multiple myeloma and solid tumors such as lung, prostate, pancreatic, breast, and colon cancers.

In a fourth aspect, this invention is directed to a method of treating cancer in an animal which method comprises administering to said animal a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I and a pharmaceutically acceptable excipient in combination with radiation therapy and optionally in combination with one or more chemotherapeutic compound(s) independently selected from an estrogen receptor modulator, an androgen receptor modulator, retinoid receptor modulator, a cytotoxic agent, another antiproliferative agent, a prenyl-protein transferase inhibitor, an HMG-CoA reductase inhibitor, an HIV protease inhibitor, a reverse transcriptase inhibitor, or an angiogenesis inhibitor.

Preferably, the chemotherapeutic compound(s) is independently selected from Taxol®, Taxotere®, epothilone A, epothilone B, desoxyepothilone A, desoxyepothilone B or their derivatives); epidophyllotoxin; procarbazine; mitoxantrone; the mitomycins, discodermolide, podophyllotoxins, doxorubicin, carminomycin, daunorubicin, aminopterin, methotrexate, methopterin, dichloromethotrexate, mitomycin C, porfiromycin, Herceptin®, Rituxan®, 5-fluorouracil, 6-mercaptopurine, gemcitabine, cytosine arabinoside, colchicines,

etoposide, etoposide phosphate, teniposide, melphalan, vinblastine, vincristine, leurosidine, vindesine, leurosine, estramustine, cisplatin, carboplatin, cyclophosphamide, bleomycin, tamoxifen, ifosamide, melphalan, hexamethyl melamine, thiotepa, cytarabin, idatrexate, trimetrexate, dacarbazine, L-asparaginase, camptothecin, CPT-11, topotecan, ara-C, bicalutamide, flutamide, leuprolide, pyridobenzoindole derivatives, interferons, and interleukins.

DETAILED DESCRIPTION OF THE INVENTION

Definitions:

Unless otherwise stated, the following terms used in the specification and claims are defined for the purposes of this Application and have the following meanings:

"Alkyl" means a linear saturated monovalent hydrocarbon radical of one to six carbon atoms or a branched saturated monovalent hydrocarbon radical of three to six carbon atoms unless otherwise specified, e.g., methyl, ethyl, propyl, 2-propyl, butyl (including all isomeric forms), pentyl (including all isomeric forms), and the like.

"Alkylene" means a linear saturated divalent hydrocarbon radical of one to six carbon atoms or a branched saturated monovalent hydrocarbon radical of three to six carbon atoms unless otherwise specified, e.g., methylene, ethylene, propylene, 2-propylene, butylene (including all isomeric forms), pentylene (including all isomeric forms), and the like.

"Acyl" means a radical –COR where R is hydrogen, alkyl or haloalkyl, e.g., methylcarbonyl, trifluoromethylcarbonyl, and the like.

"Acylamino" means a radical –NHCOR where R is alkyl or haloalkyl, e.g., methylcarbonylamino, trifluoromethylcarbonylamino, and the like.

"Alkylamino" means a radical –NHR where R is alkyl as defined above, or an N-oxide derivative, or a protected derivative thereof, e.g., methylamino, ethylamino, *n*-, *iso*-propylamino, *n*-, *iso*-, *tert*-butylamino, methylamino-N-oxide, and the like.

"Aminosulfonyl" means a radical $-SO_2NH_2$.

"Aminoalkyl" means a radical –(alkylene)-NR^aR^b where R^a and R^b are independently hydrogen or alkyl, e.g., aminomethyl, aminoethyl, aminopropyl, and the like.

"Alkylaminosulfonyl" means a radical $–SO_2NHR$ where R is alkyl as defined above, e.g, methylaminosulfonyl, ethylaminosulfonyl, and the like.

"Alkoxy" means a radical -OR where R is alkyl as defined above, e.g., methoxy, ethoxy, propoxy, or 2-propoxy, *n*-, *iso*-, or *tert*-butoxy, and the like.

"Alkoxycarbonyl" means a radical -COOR where R is alkyl as defined above, e.g., methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, or 2-propoxycarbonyl, *n*-, *iso*-, or *tert*-butoxycarbonyl, and the like.

"Alkylthio" means a radical -SR where R is alkyl as defined above, e.g., methylthio, ethylthio, propylthio (including all isomeric forms), butylthio (including all isomeric forms), and the like.

"Alkylthioalkyl" means a radical –(alkylene)-SR where R is alkyl as defined above, e.g., methylthioethyl, ethylthiopropyl, (including all isomeric forms), and the like.

"Alkylsulfinyl" means a radical –S(O)R where R is alkyl as defined above, e.g., methylsulfinyl, ethylsulfinyl, propylsulfinyl (including all isomeric forms), butylsulfinyl (including all isomeric forms), and the like.

"Alkylsulfinylalkyl" means a radical –(alkylene)-S(O)R where R is alkyl as defined above, e.g., methylsulfinylethyl, ethylsulfinylpropyl, (including all isomeric forms), and the like.

"Alkylsulfonyl" means a radical $–S(O)_2R$ where R is alkyl as defined above, e.g., methylsulfonyl, ethylsulfonyl, propylsulfonyl (including all isomeric forms), butylsulfonyl (including all isomeric forms), and the like.

"Alkylsulfonylalkyl" means a radical –(alkylene)-$S(O)_2R$ where R is alkyl as defined above, e.g., methylsulfonylethyl, ethylsulfonylpropyl, (including all isomeric forms), and the like.

"Alkoxyalkyl" means a linear monovalent hydrocarbon radical of one to six carbon atoms or a branched monovalent hydrocarbon radical of three to six carbons substituted with at least one alkoxy group, preferably one or two alkoxy groups, as defined above, e.g., 2-methoxyethyl, 1-, 2-, or 3-methoxypropyl, 2-ethoxyethyl, and the like.

"Aryl" means a monovalent monocyclic or bicyclic aromatic hydrocarbon radical of 6 to 12 ring atoms e.g., phenyl, naphthyl or anthracenyl. The aryl ring may be optionally fused to a saturated or unsaturated heterocycloalkyl ring and optionally substituted on any of the rings with one, two, or three substituents independently selected from the group consisting of alkyl, alkoxy, alkylthio, haloalkyl, haloalkoxy, halo, hydroxy, amino, alkylamino, dialkylamino, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, nitro, acyl, acylamino, alkoxycarbonyl, alkoxyalkyl, cyano, hydroxyalkyl, optionally substituted heteroaryl, or when two substituents are adjacent to each other they can combine to form methylenedioxy group or aryl is pentafluorophenyl.

"Aralkyl" means a radical –(alkylene)-R where R is aryl as defined above, e.g., benzyl, phenethyl, and the like.

"Cycloalkyl" means a cyclic saturated monovalent hydrocarbon radical of three to seven carbon atoms, e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl.

"Dialkylamino" means a radical –NRR' where R and R' are independently alkyl as defined above, or an N-oxide derivative, or a protected derivative thereof, e.g., dimethylamino, diethylamino, methylpropylamino, methylethylamino, *n*-, *iso*-, or *tert*-butylamino, and the like.

"Dialkylaminosulfonyl" means a radical $-SO_2NRR'$ where R and R' are independently alkyl as defined above, or R and R' together with the nitrogen atom to which they are attached form heterocycloamino, e.g, dimethylaminosulfonyl, methylethylaminosulfonyl, piperazin-1-ylsulfonyl, piperidin-1-ylsulfonyl, and the like.

"Halo" means fluoro, chloro, bromo, and iodo, preferably fluoro or chloro.

"Haloalkyl" means alkyl substituted with one or more halogen atoms, preferably one to three halogen atoms, preferably fluorine or chlorine, including those substituted with different halogens, e.g., $-CH_2Cl$, $-CF_3$, $-CHF_2$, and the like.

"Haloalkoxy" means a radical -OR where R is haloalkyl as defined above, e.g., trifluoromethoxy, 2,2,2-trifluoroethoxy, and the like.

"Hydroxyalkyl" means a linear monovalent hydrocarbon radical of one to six carbon atoms or a branched monovalent hydrocarbon radical of three to six carbons substituted with one or two hydroxy groups, provided that if two hydroxy groups are present they are not both on the same carbon atom. Representative

examples include, but are not limited to, hydroxymethyl, 2-hydroxyethyl, 2-hydroxypropyl, 3-hydroxypropyl, 1-(hydroxymethyl)-2-methylpropyl, 2-hydroxybutyl, 3-hydroxybutyl, 4-hydroxybutyl, 2,3-dihydroxypropyl, 1-(hydroxymethyl)-2-hydroxyethyl, 2,3-dihydroxybutyl, 3,4-dihydroxybutyl and 2-(hydroxymethyl)-3-hydroxypropyl, preferably 2-hydroxyethyl, 2,3-dihydroxypropyl, and 1-(hydroxymethyl)-2-hydroxyethyl.

"Heteroaryl" means a monovalent monocyclic or bicyclic aromatic radical of 5 to 10 ring atoms containing one or more, preferably one, two, three, or four ring heteroatoms selected from N, O, or S, the remaining ring atoms being carbon. More specifically the term heteroaryl includes, but is not limited to, pyridyl, pyrrolyl, 1,3,4-oxadiazolyl, imidazolyl, thienyl, furanyl, indolyl, quinolyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isoxazolyl, benzoxazolyl, quinolinyl, isoquinolinyl, benzopyranyl, triazolyl, oxazolyl, tetrazolyl, and thiazolyl, and the derivatives thereof, or N-oxide or a protected derivative thereof. The heteroaryl ring may be optionally substituted with one, two, or three substituents independently selected from the group consisting of alkyl, alkoxy, alkylthio, haloalkyl, haloalkoxy, halo, hydroxy, amino, alkylamino, dialkylamino, nitro, acyl, acylamino, alkoxycarbonyl, alkoxyalkyl, cyano, hydroxyalkyl, optionally substituted phenyl, or optionally substituted heteroaryl.

"Heteroaralkyl" means a radical –(alkylene)-R where R is a heteroaryl group as defined above e.g., pyridylmethyl, furanylmethyl, indolylmethyl, pyrimidinylmethyl, and the like.

"Heterocycloalkyl" means a saturated or unsaturated monovalent cyclic group of 3 to 8 ring atoms in which one or two ring atoms are heteroatoms selected from N, O, or S(O)n, where n is an integer from 0 to 2, the remaining ring atoms being C. The heterocycloalkyl ring may be optionally substituted with one or more substituents, preferably one or two substituents, independently selected from alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, halo, haloalkyl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, halo, cyano, carboxy, or –COOR where R is alkyl as define above or a protected derivative thereof. More specifically the term heterocycloalkyl includes, but is not limited to, pyrrolidino, piperidino, morpholino, piperazino, tetrahydropyranyl, and thiomorpholino.

"Heterocycloamino" means a saturated or unsaturated monovalent cyclic group of 3 to 8 ring atoms in which one or two ring atoms are heteroatoms selected

from N, O, or S(O)n, where n is an integer from 0 to 2, the remaining ring atoms being C provided that the at least one of the heteroatom is N. The heterocycloalkyl ring may be optionally substituted with one or more substituents, preferably one or two substituents, independently selected from alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, halo, haloalkyl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, halo, cyano, carboxy, or –COOR where R is alkyl as define above or a protected derivative thereof. More specifically the term heterocycloalkyl includes, but is not limited to, pyrrolidino, piperidino, morpholino, piperazino, tetrahydropyranyl, and thiomorpholino.

The present invention also includes the prodrugs of compounds of Formula I. The term prodrug is intended to represent covalently bonded carriers, which are capable of releasing the active ingredient of Formula I when the prodrug is administered to a mammalian subject. Release of the active ingredient occurs *in vivo*. Prodrugs can be prepared by techniques known to one skilled in the art. These techniques generally modify appropriate functional groups in a given compound. These modified functional groups however regenerate original functional groups by routine manipulation or *in vivo*. Prodrugs of compounds of Formula I include compounds wherein a hydroxy, amidino, guanidino, amino, carboxylic, or a similar group is modified. Examples of prodrugs include, but are not limited to esters (e.g., acetate, formate, and benzoate derivatives), carbamates (e.g., *N,N*-dimethylaminocarbonyl) of hydroxy or amino functional groups in compounds of Formula I), amides (e.g, trifluoroacetylamino, acetylamino, and the like), and the like. Prodrugs of compounds of Formula I are also within the scope of this invention.

The present invention also includes N-oxide derivatives and protected derivatives of compounds of Formula I. For example, when compounds of Formula I contain an oxidizable nitrogen atom, the nitrogen atom can be converted to an N-oxide by methods well known in the art. Also when compounds of Formula I contain groups such as hydroxy, carboxy, thiol or any group containing a nitrogen atom(s), these groups can be protected with a suitable protecting groups. A comprehensive list of suitable protective groups can be found in T.W. Greene, *Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc. 1981, the disclosure of which is incorporated herein by reference in its entirety.

The protected derivatives of compounds of Formula I can be prepared by methods well known in the art.

A "pharmaceutically acceptable salt" of a compound means a salt that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. Such salts include:

acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or

salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like. It is understood that the pharmaceutically acceptable salts are non-toxic. Additional information on suitable pharmaceutically acceptable salts can be found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, 1985, which is incorporated herein by reference.

The compounds of the present invention may have asymmetric centers. Compounds of the present invention containing an asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of materials. All chiral, diastereomeric, racemic forms are within the scope of this invention, unless the specific stereochemistry or isomeric form is specifically indicated.

"Optional" or "optionally" means that the subsequently described event or circumstance may but need not occur, and that the description includes instances

where the event or circumstance occurs and instances in which it does not. For example, "heteroaryl group optionally mono- or di-substituted with an alkyl group" means that the alkyl may but need not be present, and the description includes situations where the heteroaryl group is mono- or disubstituted with an alkyl group and situations where the heteroaryl group is not substituted with the alkyl group.

"Optionally substituted phenyl" means a phenyl ring optionally substituted with one, two, or three substituents independently selected from alkyl, halo, alkoxy, alkylthio, trifluoromethyl, trifluoromethoxy, amino, alkylamino, dialkylamino, hydroxy, cyano, nitro, methylenedioxy, aminocarbonyl, hydroxyalkyl, alkoxycarbonyl, or carboxy or optionally substituted with five fluorine atoms.

"Optionally substituted heteroaryl" means a heteroaryl ring as defined above which is optionally substituted with one, two, or three substituents independently selected from alkyl, halo, alkoxy, trifluoromethyl, trifluoromethoxy, amino, alkylamino, dialkylamino, hydroxy, cyano, nitro, aminocarbonyl, hydroxyalkyl, or alkoxycarbonyl. More specifically the term optionally substituted heteroaryl includes, but is not limited to, pyridyl, pyrrolyl, imidazolyl, thienyl, furanyl, indolyl, quinolyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isoxazolyl, benzoxazolyl, quinolinyl, isoquinolinyl, benzopyranyl, and thiazolyl, and the derivatives thereof, or N-oxide or a protected derivative thereof.

A "pharmaceutically acceptable carrier or excipient" means a carrier or an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes a carrier or an excipient that is acceptable for veterinary use as well as human pharmaceutical use. "A pharmaceutically acceptable carrier/excipient" as used in the specification and claims includes both one and more than one such excipient.

"Treating" or "treatment" of a disease includes:

(1) preventing the disease, i.e. causing the clinical symptoms of the disease not to develop in a mammal that may be exposed to or predisposed to the disease but does not yet experience or display symptoms of the disease;

(2) inhibiting the disease, i.e., arresting or reducing the development of the disease or its clinical symptoms; or

(3) relieving the disease, i.e., causing regression of the disease or its clinical symptoms.

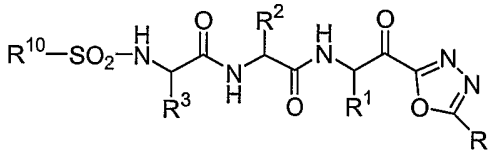
The term "treating cancer" or "treatment of cancer" refers to administration to a mammal afflicted with a cancerous condition and refers to an effect that alleviates the cancerous condition by killing the cancerous cells, but also to an effect that results in the inhibition of growth and/or metastasis of the cancer.

A "therapeutically effective amount" means the amount of a compound of Formula I that, when administered to a mammal for treating a disease, is sufficient to effect such treatment for the disease. The "therapeutically effective amount" will vary depending on the compound, the disease and its severity and the age, weight, etc., of the mammal to be treated.

Representative compounds of the invention are disclosed in Tables I, II, and III below:

Table I

Compounds of Formula I where n is 0, R^{1a} is hydrogen, Het is 1,3,4-oxadiazol-2yl, X is $-SO_2-$ and other groups are as disclosed below are:

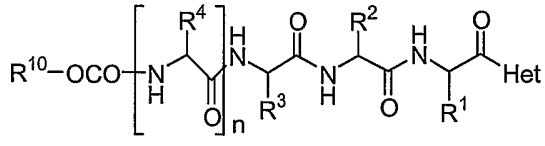


Cpd #	R	R^1	R^2	R^3	R^{10}
1	phenyl	*S*-2-methylpropyl	*S*-methyl	*S*-$CH_2CONHCH_2C(CH_3)_3$	4-methylphenyl
2	ethyl	*RS*-2-methylpropyl	*S*-methyl	*S*-$CH_2CONHCH_2C(CH_3)_3$	4-methylphenyl
3	phenyl	*S*-2-methylpropyl	*S*-CH_2O-$C(CH_3)_3$	*S*-$CH_2CONHCH_2C(CH_3)_3$	4-methylphenyl
4	phenyl	*RS*-2-methylpropyl	*S*-CH_2OH	*S*-$CH_2CONHCH_2C(CH_3)_3$	4-methylphenyl
5	phenyl	*S*-2-methylpropyl	*S*-methyl	*S*-$CH_2CONHCH_2C(CH_3)_3$	3-methylphenyl
6	4-$(CH_3)_2N$-phenyl	*S*-2-methylpropyl	*S*-methyl	*S*-$CH_2CONHCH_2C(CH_3)_3$	4-methylphenyl
7	2-propyl	*S*-2-methylpropyl	*S*-methyl	*S*-$CH_2CONHCH_2C(CH_3)_3$	4-methylphenyl
8	pyridin-4-yl	*S*-methylpropyl	*S*-methyl	*S*-$CH_2CONHCH_2C(CH_3)_3$	4-methylphenyl

9	phenyl	*S*-2-methylpropyl	*S*-CH_2OCH_3	*S*-$CH_2CONHCH_2C(CH_3)_3$	4-methylphenyl
10	phenyl	*S*-2-methylpropyl	*S*-$CH(OH)CH_3$	*S*-$CH_2CONHCH_2C(CH_3)_3$	4-methylphenyl
11	furan-2-yl	*S*-2-methylpropyl	*S*-methyl	*S*-$CH_2CONHCH_2C(CH_3)_3$	4-methylphenyl
12	4-$(CH_3)_2N$-phenyl	*S*-2-methylpropyl	*S*-CH_2OCH_3	*S*-$CH_2CONHCH_2C(CH_3)_3$	4-methylphenyl
13	phenyl	*S*-1-methylpropyl	*S*-methyl	*S*-$CH_2CONHCH_2C(CH_3)_3$	4-methylphenyl
14	4-methyl-phenyl	*S*-2-methylpropyl	*S*-methyl	*S*-$CH_2CONHCH_2C(CH_3)_3$	4-methylphenyl
15	4-CF_3-phenyl	*S*-2-methylpropyl	*S*-methyl	*S*-$CH_2CONHCH_2C(CH_3)_3$	4-methylphenyl
16	phenyl	*S*-2-methylpropyl	*S*-methyl	*S*-$(CH_2)_2COOC(CH_3)_3$	4-methylphenyl
17	phenyl	*S*-2-methylpropyl	*S*-CH_2OCH_3	*S*-CH_2OCH_2phenyl	4-methylphenyl
18	phenyl	*S*-2-methylpropyl	*S*-CH_2OCH_3	*S*-$CH_2CONHCH_2C(CH_3)_3$	4-SO_2NH_2-phenyl
19	phenyl	*S*-2-methylpropyl	*S*-CH_2OCH_3	*S*-CH_2OCH_2(2-Clphenyl)	4-methylphenyl
20	phenyl	*S*-2-methylpropyl	*S*-CH_2OCH_3	*S*-CH_2OCH_2(3,5-diCH_3phenyl)	4-methylphenyl
21	phenyl	*S*-2-methylpropyl	*S*-CH_3	*S*-CH_2OCH_2(2-CH_3phenyl)	4-methylphenyl
22	phenyl	*S*-2-methylpropyl	*S*-methyl	*S*-$CH_2CONHCH_2C(CH_3)_3$	4-methylphenyl
23	phenyl	*S*-2-methylpropyl	*S*-methyl	*S*-$CH_2CONHCH_2C(CH_3)_3$	1-methylimidazol-4-yl
24	phenyl	*S*-2-methylpropyl	*S*-methyl	*S*-$CH_2CONHCH_2C(CH_3)_3$	3,5-dimethyl-isoxazol-4-yl
25	phenyl	*S*-2-methylpropyl	*S*-methyl	*S*-$CH_2CONHCH_2C(CH_3)_3$	1,3,5-trimethyl-pyrazol-4-yl
26	phenyl	*S*-2-methylpropyl	*S*-methyl	*S*-$CH_2CONHCH_2C(CH_3)_3$	4-trifluoromethoxy-phenyl

Table II

Compounds of Formula I where R^{1a} is hydrogen, X is –OC(O)- and other groups are as disclosed below are:

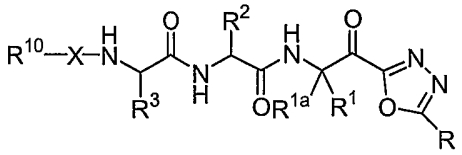


Cpd #	n	Het	R^1	R^2	R^3	R^4	R^{10}
1	1	benzoxazol-2-yl	*S*-2-methylpropyl	*S*-methyl	*S*-$(CH_2)_2COOC(CH_3)_3$	*S*-1*S*-methylpropyl	benzyl
2	0	benzoxazol-2-yl	*S*-2-	*S*-methyl	*S*-$(CH_2)_2COOC(CH_3)_3$	-	benzyl

			methylpropyl				
3	1	5-phenyl-1,3,4-oxadiazol-2-yl	*S*-propyl	*S*-methyl	*S*-$(CH_2)_2COOC(CH_3)_3$	*S*-1*S*-methylpropyl	benzyl

Table III

Compounds of Formula I where n is 0, Het is 1,3,4-oxadiazol-2yl, and other groups are as disclosed below are:

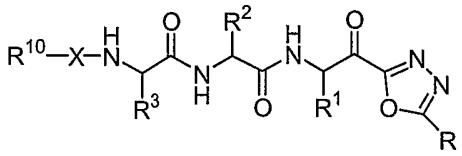


Cpd #	R	R^1	R^{1a}	R^2	R^3	X-R^{10}
1	phenyl	methyl	methyl	*S*-methyl	*S*-$CH_2CONHCH_2C(CH_3)_3$	-SO_2-(4-methylphenyl)
2	2-propyl	*S*-2-methylpropyl	hydrogen	*S*-methyl	*S*-$CH_2CONHCH_2C(CH_3)_3$	-SO_2-$N(CH_3)_2$
3	phenyl	*S*-2-methylpropyl	hydrogen	*S*-CH_2OCH_3	*S*-$CH_2CONHCH_2C(CH_3)_3$	-SO_2-$N(CH_3)_2$
4	phenyl	*S*-2-methylpropyl	hydrogen	*S*-CH_2OCH_3	*S*-$CH_2CONHCH_2C(CH_3)_3$	-CO-(4-aminosulfonyl-phenyl)

Presently Preferred Embodiments

While the broadest definition of this invention is set forth in the Summary of the Invention, certain compounds of Formula I are preferred. For example:

A preferred group of compounds is represented by Formula II below:



II

wherein:

R is alkyl, haloalkyl, alkoxyalkyl, optionally substituted phenyl, or optionally substituted heteroaryl;

R^1 is alkyl or aralkyl;

R^2 is alkyl, hydroxyalkyl, alkylthio, alkylthioalkyl, or alkoxyalkyl;

R^3 is $-(C_{1-3})$-$CONHCHR^5R^6$ where R^5 is hydrogen or alkyl and R^6 is branched (C_{4-10})alkyl or cycloalkyl, $-(C_{1-3})$-$COOR^8$ (where R^8 is branched (C_{4-10})alkyl or

cycloalkyl), or $-(C_{1-3})$-Y-$(C_{1-3})_{n1}$Ar (where Y is –O-, -NH-, or $-S(O)_{n2}$- where n2 is 0 to 2, n1 is 0 or 1, and Ar is aryl);

X is –CO-, -OC(O)-, $-SO_2$-, or $-NR^9SO_2$- where R^9 is alkyl;

R^{10} is alkyl, aryl, or heteroaryl; or

a pharmaceutically acceptable salt thereof.

Within this group of compounds, a more preferred group of compound is that wherein

X is –CO-.

Within this group of compounds, another more preferred group of compound is that wherein X is $-SO_2$-.

Within this group of compounds, another more preferred group of compound is that wherein X is -OC(O)-.

Within this group of compounds, another more preferred group of compound is that wherein X is $-NR^9SO_2$-, preferably $-N(CH_3)SO_2$-.

Within these preferred groups, a more preferred group of compound is that wherein:

R is methyl, ethyl, 2-propyl, trifluoromethyl, methoxy, optionally substituted phenyl, or optionally substituted heteroaryl, more preferably methyl, ethyl, 2-propyl, trifluoromethyl, methoxy, 4-dimethylaminophenyl, pyridin-4-yl, furan-2-yl, 4-methylphenyl, 4-trifluoromethylphenyl, or phenyl, most preferably phenyl;

R^1 is methyl, ethyl, 1-methylpropyl, 2-methylpropyl, 2,2-dimethylpropyl, benzyl, more preferably 1-methylpropyl or 2-methylpropyl;

R^2 is methyl, ethyl, methoxymethyl, *tert*-butoxymethyl, hydroxymethyl, 1-hydroxyethyl, methylthiomethyl; preferably methyl or methoxymethyl, most preferably methyl;

R^3 is $-CH_2CONHCH_2C(CH_3)_3$ or $-(CH_2)_2CONHC(CH_3)_3$; more preferably $-CH_2CONHCH_2C(CH_3)_3$; or

R^3 is $-(C_{1-3})$-Y-$(C_{1-3})_{n1}$Ar (where Y is –O-, NH-, or $-S(O)_{n2}$- where n2 is 0 to 2, n1 is 1, and Ar is aryl), preferably R^3 is $-(CH_2)$-O-(CH_2)-Ar, more preferably $-(CH_2)$-O-(CH_2)-(3,5-dimethylphenyl), $-(CH_2)$-O-(CH_2)-(2-methylphenyl) or $-(CH_2)$-O-(CH_2)-(2-chlorophenyl); or

R^3 is $-(CH_2)_2$COO-*tert*-butyl; and

R^{10} is aryl, preferably phenyl optionally substituted with alkyl or aminosulfonyl, preferably R^{10} is 4-methylphenyl, 3-methylphenyl, or 4-aminosulfonylphenyl, more preferably 4-methylphenyl; or

R^{10} is alkyl, preferably methyl when X is $-NR^9SO_2-$; or

R^{10} is alkyl, preferably *tert*-butyl when X is –OC(O)-; or

R^{10} is heteroaryl.

A number of different preferences have been given above, and following any one of these preferences results in a compound of this invention that is more presently preferred than a compound in which that particular preference is not followed. However, these preferences are generally independent [although some (alternative) preferences are mutually exclusive], and additive; and following more than one of these preferences may result in a more presently preferred compound than one in which fewer of the preferences are followed.

Presently preferred classes of compounds of this invention include those wherein:

(a) n is 0, R^1 is alkyl; R^{1a} is hydrogen; R^2 is alkyl, hydroxyalkyl, or alkoxyalkyl; R^3 is $-(C_{1-3})$-CONH-CHR^5R^6 where R^5 is hydrogen or alkyl and R^6 is branched (C_{4-10})alkyl or cycloalkyl; X is –CO-; and R^{10} is aryl.

(b) n is 0, Het is 1,3,4-oxadiazol-2-yl which is substituted at the 5-position with methyl, ethyl, 2-propyl, trifluoromethyl, methoxy, or optionally substituted phenyl; R^1 is methyl, ethyl, 1-methylpropyl, 2-methylpropyl, 2,2-dimethylpropyl, or benzyl; R^{1a} is hydrogen; R^2 is methyl, ethyl, methoxymethyl, *tert*-butoxymethyl, hydroxymethyl, 1-hydroxyethyl, or methylthiomethyl; R^3 is $-CH_2CONHCH_2C(CH_3)_3$ or $-(CH_2)_2CONHC(CH_3)_3$; X is –CO-; and R^{10} is aryl.

(c) n is 0, Het is 1,3,4-oxadiazol-2-yl which is substituted at the 5-position with methyl, ethyl, 2-propyl, trifluoromethyl, methoxy, 4-dimethylaminophenyl, pyridin-4-yl, furanyl, 4-methylphenyl, 4-trifluoromethylphenyl, or phenyl; R^1 is methyl, ethyl, 1-methylpropyl, 2-methylpropyl, 2,2-dimethylpropyl, or benzyl; R^{1a} is hydrogen; R^2 is methyl, ethyl, methoxymethyl, *tert*-butoxymethyl, hydroxymethyl, 1-hydroxyethyl, or methylthiomethyl; R^3 is $-CH_2CONHCH_2C(CH_3)_3$ or $-(CH_2)_2CONHC(CH_3)_3$; X is –CO-; and R^{10} is phenyl optionally substituted with alkyl or aminosulfonyl.

(d) n is 0, R^1 is alkyl; R^{1a} is hydrogen; R^2 is alkyl, hydroxyalkyl, or alkoxyalkyl; R^3 is $-(C_{1-3})$-CONH-CHR^5R^6 where R^5 is hydrogen or alkyl and R^6 is branched (C_{4-10})alkyl or cycloalkyl; X is $-SO_2-$; and R^{10} is aryl.

(e) n is 0, Het is 1,3,4-oxadiazol-2-yl which is substituted at the 5-position with methyl, ethyl, 2-propyl, trifluoromethyl, methoxy, or optionally substituted phenyl; R^1 is methyl, ethyl, 1-methylpropyl, 2-methylpropyl, 2,2-dimethylpropyl, or benzyl; R^{1a} is hydrogen; R^2 is methyl, ethyl, methoxymethyl, *tert*-butoxymethyl, hydroxymethyl, 1-hydroxyethyl, or methylthiomethyl; R^3 is $-CH_2CONHCH_2C(CH_3)_3$ or $-(CH_2)_2CONHC(CH_3)_3$; X is $-SO_2-$; and R^{10} is aryl.

(f) n is 0, Het is 1,3,4-oxadiazol-2-yl which is substituted at the 5-position with methyl, ethyl, 2-propyl, trifluoromethyl, methoxy, 4-dimethylaminophenyl, pyridin-4-yl, furanyl, 4-methylphenyl, 4-trifluoromethylphenyl, or phenyl; R^1 is methyl, ethyl, 1-methylpropyl, 2-methylpropyl, 2,2-dimethylpropyl, or benzyl; R^{1a} is hydrogen; R^2 is methyl, ethyl, methoxymethyl, *tert*-butoxymethyl, hydroxymethyl, 1-hydroxyethyl, or methylthiomethyl; R^3 is $-CH_2CONHCH_2C(CH_3)_3$ or $-(CH_2)_2CONHC(CH_3)_3$; X is $-SO_2-$; and R^{10} is phenyl optionally substituted with alkyl.

(g) n is 0, Het is 1,3,4-oxadiazol-2-yl which is substituted at the 5-position with methyl, ethyl, 2-propyl, trifluoromethyl, methoxy, 4-dimethylaminophenyl, pyridin-4-yl, furanyl, 4-methylphenyl, 4-trifluoromethylphenyl, or phenyl; R^1 is methyl, ethyl, 1-methylpropyl, 2-methylpropyl, 2,2-dimethylpropyl, or benzyl; R^{1a} is hydrogen; R^2 is methyl, ethyl, methoxymethyl, *tert*-butoxymethyl, hydroxymethyl, 1-hydroxyethyl, or methylthiomethyl; R^3 is $-CH_2CONHCH_2C(CH_3)_3$ or $-(CH_2)_2CONH(CH_3)_3$; X is $-SO_2-$; and R^{10} is 4-methylphenyl, or 3-methylphenyl.

(h) n is 0, Het is 1,3,4-oxadiazol-2-yl which is substituted at the 5-position with 4-dimethylaminophenyl, pyridin-4-yl, furanyl, 4-methylphenyl, 4-trifluoromethylphenyl, or phenyl; R^1 is 2-methylpropyl; R^{1a} is hydrogen; R^2 is methyl; R^3 is $-CH_2CONHCH_2C(CH_3)_3$; X is $-SO_2-$; and R^{10} is 4-methylphenyl.

(i) n is 0, R^1 is alkyl; R^{1a} is hydrogen; R^2 is alkyl, hydroxyalkyl, or alkoxyalkyl; R^3 is $-(C_{1-3})$-Y-(C_{1-3})n1-Ar; X is $-SO_2-$; and R^{10} is aryl.

(j) n is 0, Het is 1,3,4-oxadiazol-2-yl which is substituted at the 5-position with methyl, ethyl, 2-propyl, trifluoromethyl, methoxy, or optionally substituted phenyl; R^1 is methyl, ethyl, 1-methylpropyl, 2-methylpropyl, 2,2-dimethylpropyl, or benzyl; R^{1a} is hydrogen; R^2 is methyl, ethyl, methoxymethyl, *tert*-butoxymethyl, hydroxymethyl, 1-hydroxyethyl, or methylthiomethyl; R^3 is $-CH_2OCH_2$-Ar where Ar is aryl; X is $-SO_2-$; and R^{10} is aryl.

(k) n is 0, Het is 1,3,4-oxadiazol-2-yl which is substituted at the 5-position with methyl, ethyl, 2-propyl, trifluoromethyl, methoxy, 4-dimethylaminophenyl, pyridin-4-yl, furanyl, 4-methylphenyl, 4-trifluoromethylphenyl, or phenyl; R^1 is methyl, ethyl, 1-methylpropyl, 2-methylpropyl, 2,2-dimethylpropyl, or benzyl; R^{1a} is hydrogen; R^2 is methyl, ethyl, methoxymethyl, *tert*-butoxymethyl, hydroxymethyl, 1-hydroxyethyl, or methylthiomethyl; R^3 is $-CH_2OCH_2$-Ar where Ar is aryl optionally substituted with one, two or three groups independently selected from alkyl, halo, alkoxy, or hydroxy; X is $-SO_2$-; and R^{10} is phenyl optionally substituted with alkyl.

(l) n is 0, Het is 1,3,4-oxadiazol-2-yl which is substituted at the 5-position with 4-dimethylaminophenyl, pyridin-4-yl, furan-2-yl, 4-methylphenyl, 4-trifluoromethylphenyl, or phenyl; R^1 is methyl, ethyl, 1-methylpropyl, 2-methylpropyl, 2,2-dimethylpropyl, or benzyl; R^{1a} is hydrogen; R^2 is methyl, ethyl, methoxymethyl, *tert*-butoxymethyl, hydroxymethyl, 1-hydroxyethyl, or methylthiomethyl; R^3 is $-CH_2OCH_2$-Ar where Ar is phenyl optionally substituted with one, two or three groups independently selected from methyl, chloro, fluoro, methoxy, or hydroxy; X is $-SO_2$-; and R^{10} is 4-methylphenyl, or 3-methylphenyl.

(m) n is 0, Het is 1,3,4-oxadiazol-2-yl which is substituted at the 5-position with 4-dimethylaminophenyl, pyridin-4-yl, furan-2-yl, 4-methylphenyl, 4-trifluoromethylphenyl, or phenyl; R^1 is 1-methylpropyl; R^{1a} is hydrogen; R^2 is methyl; R^3 is $-CH_2OCH_2$-Ar where Ar is phenyl optionally substituted with one, two or three groups independently selected from methyl, chloro, fluoro, methoxy, or hydroxy; X is $-SO_2$-; and R^{10} is 4-methylphenyl, or 3-methylphenyl.

(n) n is 0, R^1 is alkyl; R^{1a} is hydrogen; R^2 is alkyl, hydroxyalkyl, or alkoxyalkyl; R^3 is $-(C_{1-3})$-CONH-CHR^5R^6 where R^5 is hydrogen or alkyl and R^6 is branched (C_{4-10})alkyl or cycloalkyl; X is $-NR^9SO_2$- where R^9 is alkyl; and R^{10} is alkyl.

(o) n is 0, Het is 1,3,4-oxadiazol-2-yl which is substituted at the 5-position with 4-dimethylaminophenyl, pyridin-4-yl, furan-2-yl, 4-methylphenyl, 4-trifluoromethylphenyl, or phenyl; R^1 is methyl, ethyl, 1-methylpropyl, 2-methylpropyl, 2,2-dimethylpropyl, or benzyl; R^{1a} is hydrogen; R^2 is methyl, ethyl, methoxymethyl, *tert*-butoxymethyl, hydroxymethyl, 1-hydroxyethyl, or methylthiomethyl, R^3 is $-CH_2CONHCH_2C(CH_3)_3$ or $-(CH_2)_2CONH(CH_3)_3$, X is $-NR^9SO_2$- where R^9 is alkyl; and R^{10} is alkyl.

(p) n is 0, R^1 is alkyl; R^{1a} is hydrogen; R^2 is alkyl, hydroxyalkyl, or alkoxyalkyl; R^3 is $-(C_{1-3})$-Y-(C_{1-3})n1-Ar where Ar is aryl, X is $-NR^9SO_2-$ where R^9 is alkyl; and R^{10} is alkyl.

(q) n is 0, Het is 1,3,4-oxadiazol-2-yl which is substituted at the 5-position with 4-dimethylaminophenyl, pyridin-4-yl, furan-2-yl, 4-methylphenyl, 4-trifluoromethylphenyl, or phenyl; R^1 is methyl, ethyl, 1-methylpropyl, 2-methylpropyl, 2,2-dimethylpropyl, or benzyl; R^{1a} is hydrogen; R^2 is methyl, ethyl, methoxymethyl, *tert*-butoxymethyl, hydroxymethyl, 1-hydroxyethyl, or methylthiomethyl, R^3 is $-CH_2OCH_2$-Ar where Ar is aryl optionally substituted with one, two or three groups independently selected from alkyl, halo, alkoxy, or hydroxy, X is $-NR^9SO_2-$ where R^9 is alkyl; and R^{10} is alkyl.

(r) n is 0, R^1 is alkyl; R^{1a} is hydrogen; R^2 is alkyl, hydroxyalkyl, or alkoxyalkyl; R^3 is $-(C_{1-3})$-CONH-CHR^5R^6 where R^5 is hydrogen or alkyl and R^6 is branched (C_{4-10})alkyl or cycloalkyl; X is $-OC(O)-$; and R^{10} is alkyl.

(s) Yet another preferred group of compounds of Formula I is that wherein n is 1, R^4 is alkyl or haloalkyl and other groups are as defined in compounds of Formula II above.

GENERAL SYNTHESIS

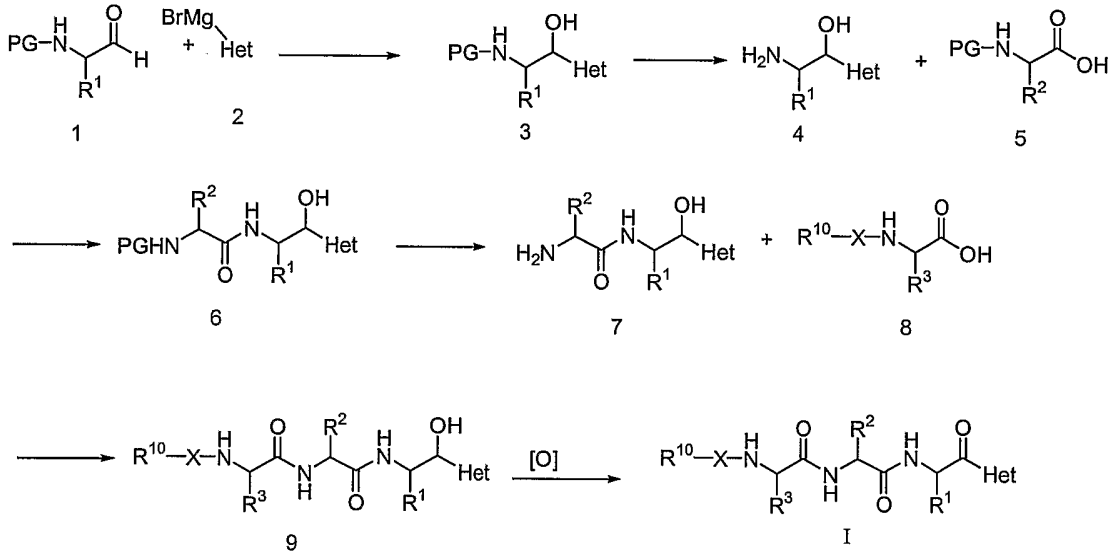
Compounds of this invention can be made by the methods depicted in the reaction schemes shown below.

The starting materials and reagents used in preparing these compounds are either available from commercial suppliers such as Aldrich Chemical Co., (Milwaukee, Wis.), or Bachem (Torrance, Calif.), or are prepared by methods known to those skilled in the art following procedures set forth in references such as Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-17 (John Wiley and Sons, 1991); Rodd's Chemistry of Carbon Compounds, Volumes 1-5 and Supplementals (Elsevier Science Publishers, 1989); Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991), March's Advanced Organic Chemistry, (John Wiley and Sons, 4th Edition) and Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989). These schemes are merely illustrative of some methods by which the compounds of this invention can be synthesized, and various modifications to these schemes can be made and will be suggested to one skilled in the art having referred to this disclosure.

The starting materials and the intermediates of the reaction may be isolated and purified if desired using conventional techniques, including but not limited to filtration, distillation, crystallization, chromatography and the like. Such materials may be characterized using conventional means, including physical constants and spectral data.

Unless specified to the contrary, the reactions described herein take place at atmospheric pressure over a temperature range from about –78 °C to about 150 °C, more preferably from about 0 °C to about 125 °C and most preferably at about room (or ambient) temperature, e.g., about 20 ° C.

A compound of Formula I where n is 0 and other groups are as defined in the Summary of the Invention can be prepared by the procedure illustrated and described in Scheme A below.



Reaction of an alpha amino aldehyde of formula 1 where R^1 is as defined in the Summary of the Invention and PG is a suitable amino protecting group such as *tert*-butoxycarbonyl, benzyloxycarbonyl, and the like, preferably *tert*-butoxycarbonyl, with a Grignard reagent of formula 2 where Het is a heteroaryl ring provides a compound of formula 3. The reaction is carried out by first preparing the Grignard reagent by treating the heteroaryl with *n*-butyllithium at approximately –78 °C in an ethereal solvent such as tetrahydrofuran, and the like, followed by treatment of the resulting lithiated compound with magnesium bromide diethyl etherate and then

reacting the resulting Grignard reagent with the alpha amino aldehyde. The aldehyde of formula 1 is prepared by the synthetic procedure described in Falkiewicz, B., et al, Nucleosides and Nucleotides, 20, 1393, 2001.

Deprotection of the amino group in 3 provides the alpha amino alcohol compound of formula 4. The reaction conditions employed for the removal of the amino protecting group depend on the nature of the amino protecting group. For example, removal of the *tert*-butoxycarbonyl group can be carried out using a strong acid such as trifluoroacetic acid or hydrochloric acid with or without the presence of a cosolvent such as dichloromethane, methanol, and the like. Benzyloxycarbonyl group can be removed by a number of methods including, catalytic hydrogenation with hydrogen in the presence of a palladium or platinum catalyst in a protic solvent such as methanol, ethanol, and the like. Other suitable reaction conditions for their removal can be found in T.W. Greene, *Protecting Groups in Organic Synthesis*, John Wiley & Sons, Inc. 1981.

Coupling of 4 with an N-protected alpha amino acid of formula 5 provides a compound of formula 6. The reaction is typically carried out in the presence of a suitable coupling agent such as benzotriazole-1-yloxytrispyrrolidinophosphonium hexafluorophosphate (PyBOP®), *O*-benzotriazol-1-yl-*N*,*N*,*N'*,*N'*-tetramethyluronium hexafluorophosphate (HBTU), *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU), or 1-hydroxybenzotriazole (HOBT) in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), or 1,3-dicyclohexylcarbodiimide (DCC), a base such as *N*,*N*-diisopropylethylamine, triethylamine, or N-methylmorpholine. The reaction is typically carried out at 20 to 30 ° C, preferably at about 25° C, and requires 2 to 4 hours to complete. Suitable reaction solvents are inert organic solvents such as halogenated organic solvents (e.g., methylene chloride, chloroform, and the like), acetonitrile, dimethylformamide, ethereal solvents such as tetrahydrofuran, dioxane, and the like.

Removal of the amino protecting group in 6, followed by reaction of the resulting amino compound 7 with an acid compound of formula 8 under the coupling conditions described above provides a compound of formula 9.

Oxidation of the hydroxy group in 9 then provides a compound of Formula I. The reaction is carried out at room temperature. Suitable solvents are halogenated organic solvent such as methylene chloride, chloroform, carbon tetrachloride, and the

like. Suitable oxidizing agent are Dess-Martin Periodinane (DMP) (supplier Lancaster), and the like.

Compounds of formula 8 can be prepared by methods well known in the art. For example, syntheses of a compound of formula 8 where R^3 is $-CH_2$-CONH-$CH_2C(CH_3)_3$, X is $-SO_2$- and R^{10} is 4-methylphenyl or X is –OC(O)- and R^{10} is *tert*-butyl are described in Working Example1 below.

Pharmacology and Utility

The compounds of the invention are inhibitors of proteasome and hence are useful in the treatment of diseases mediated by the proteolytic function of the proteasome. For example, the compounds of the invention are useful in treating cancer such as multiple myeloma, leukemia, colorectal, prostate, breast and lung cancers, allergic disorders, including, but not limited to asthma; allogeneic immune reponses, including, but not limited to, organ transplants or tissue grafts, autoimmune disorders, including, but not limited to multiple sclerosis, inflammatory diseases, and septic shock.

Testing

The proteasome inhibitory activities of the compounds of the invention can be determined by methods known to those of ordinary skill in the art. Details of assays for measuring proteasome inhibitory activity *in vitro*, are set forth in Biological Examples 1 and 2, infra.

Administration and Pharmaceutical Compositions

In general, compounds of Formula I will be administered in therapeutically effective amounts via any of the usual and acceptable modes known in the art, either singly or in combination with another therapeutic agent. A therapeutically effective amount may vary widely depending on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors. For example, therapeutically effective amounts of a compound of Formula I may range from 0.1 micrograms per kilogram body weight (μg/kg) per day to 10 milligram per kilogram body weight (mg/kg) per day, typically 1 μg/kg/day to 1 mg/kg/day. Therefore, a therapeutically effective amount for a 80 kg human patient may range from 8 μg/day to 800 mg/day. In general, one of ordinary skill in the art, acting in

reliance upon personal knowledge and the disclosure of this Application, will be able to ascertain a therapeutically effective amount of a compound of Formula I for treating a given disease.

The compounds of Formula I can be administered as pharmaceutical compositions by one of the following routes: oral, systemic (e.g., transdermal, intranasal or by suppository) or parenteral (e.g., intramuscular, intravenous or subcutaneous). Compositions can take the form of tablets, pills, capsules, semisolids, powders, sustained release formulations, solutions, suspensions, elixirs, aerosols, or any other appropriate composition and are comprised of, in general, a compound of Formula I in combination with at least one pharmaceutically acceptable excipient. Acceptable excipients are non-toxic, aid administration, and do not adversely affect the therapeutic benefit of the active ingredient. Such excipient may be any solid, liquid, semisolid or, in the case of an aerosol composition, gaseous excipient that is generally available to one of skill in the art.

Solid pharmaceutical excipients include starch, cellulose, talc, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride, dried skim milk, and the like. Liquid and semisolid excipients may be selected from water, ethanol, glycerol, propylene glycol and various oils, including those of petroleum, animal, vegetable or synthetic origin (e.g., peanut oil, soybean oil, mineral oil, sesame oil, or the like). Preferred liquid carriers, particularly for injectable solutions, include water, saline, aqueous dextrose and glycols.

The amount of a compound of Formula I in the composition may vary widely depending upon the type of formulation, size of a unit dosage, kind of excipients and other factors known to those of skill in the art of pharmaceutical sciences. In general, a composition of a compound of Formula I for treating a given disease will comprise from 0.01%w to 10%w, preferably 0.3%w to 1%w, of active ingredient with the remainder being the excipient or excipients. Preferably the pharmaceutical compositions are administered in a single unit dosage form for continuous treatment or in a single unit dosage form *ad libitum* when relief of symptoms is specifically required.

As stated previously, the compounds of this invention can be administered in combination with known anti-cancer agents. Such known anti-cancer agents include the following: estrogen receptor modulators, androgen receptor

modulators, retinoid receptor modulators, cytotoxic agents, antiproliferative agents, prenyl-protein transferase inhibitors, HMG-CoA reductase inhibitors, HIV protease inhibitors, reverse transcriptase inhibitors, and other angiogenesis inhibitors. The compound of the present invention compounds are particularly useful when administered in combination with radiation therapy. Preferred angiogenesis inhibitors are selected from the group consisting of a tyrosine kinase inhibitor, an inhibitor of epidermal-derived growth factor, an inhibitor of fibroblast-derived growth factor, an inhibitor of platelet derived growth factor, an MMP (matrix metalloprotease) inhibitor, an integrin blocker, interferon-α, interleukin-12, pentosan polysulfate, a cyclooxygenase inhibitor, carboxyamidotriazole, combretastatin A-4, squalamine, 6-O-chloroacetyl-carbonyl)-fumagillol, thalidomide, angiostatin, troponin-1, and an antibody to VEGF.

Preferred estrogen receptor modulators are tamoxifen and raloxifene.

"Estrogen receptor modulators" refers to compounds that interfere or inhibit the binding of estrogen to the receptor, regardless of mechanism. Examples of estrogen receptor modulators include, but are not limited to, tamoxifen, raloxifene, idoxifene, LY353381, LY117081, toremifene, fulvestrant, 4-[7-(2,2-dimethyl-1-oxopropoxy-4-methyl-2-[4-[2-(1-piperidinyl)ethoxy]phenyl]-2H-1-benzopyran-3-yl]-phenyl-2,2-dimethylpropanoate, 4,4'-dihydroxybenzophenone-2,4-dinitrophenyl-hydrazone, and SH646.

"Androgen receptor modulators" refers to compounds, which interfere or inhibit the binding of androgens to the receptor, regardless of mechanism. Examples of androgen receptor modulators include finasteride and other 5α-reductase inhibitors, nilutamide, flutamide, bicalutamide, liarozole, and abiraterone acetate.

"Retinoid receptor modulators" refers to compounds, which interfere or inhibit the binding of retinoids to the receptor, regardless of mechanism. Examples of such retinoid receptor modulators include bexarotene, tretinoin, 13-cis-retinoic acid, 9-cis-retinoic acid, α-difluoromethylornithine, ILX23-7553, trans-N-(4'-hydroxyphenyl) retinamide, and N-4-carboxyphenyl retinamide.

"Cytotoxic agents" refer to compounds which cause cell death primarily by interfering directly with the cell's functioning or inhibit or interfere with cell

myosis, including alkylating agents, tumor necrosis factors, intercalators, microtubulin inhibitors, and topoisomerase inhibitors.

Examples of cytotoxic agents include, but are not limited to, tirapazimine, sertenef, cachectin, ifosfamide, tasonermin, lonidamine, carboplatin, altretamine, prednimustine, dibromodulcitol, ranimustine, fotemustine, nedaplatin, oxaliplatin, temozolomide, heptaplatin, estramustine, improsulfan tosilate, trofosfamide, nimustine, dibrospidium chloride, pumitepa, lobaplatin, satraplatin, profiromycin, cisplatin, irofulven, dexifosfamide, cis-aminedichloro(2-methyl-pyridine) platinum, benzylguanine, glufosfamide, GPX100, (trans, trans, trans)-bis-mu-(hexane-1,6-diamine)-mu-[diamine-platinum(II)]bis[diamine(ch loro)platinum(II)]-tetrachloride, diarizidinylspermine, arsenic trioxide, 1-(11-dodecylamino-10-hydroxyundecyl)-3,7-dimethylxanthine, zorubicin, idarubicin, daunorubicin, bisantrene, mitoxantrone, pirarubicin, pinafide, valrubicin, amrubicin, antineoplaston, 3'-deamino-3'-morpholino-13-deoxo-10-hydroxycarminomycin, annamycin, galarubicin, elinafide, MEN10755, and 4-demethoxy-3-deamino-3-aziridinyl-4-methylsulphonyl-daunorubicin (*see* WO 00/50032).

Examples of microtubulin inhibitors include paclitaxel, vindesine sulfate, 3',4'-didehydro-4'-deoxy-8'-norvincaleukoblastine, docetaxol, rhizoxin, dolastatin, mivobulin isethionate, auristatin, cemadotin, RPR109881, BMS184476, vinflunine, cryptophycin, 2,3,4,5,6-pentafluoro-N-(3-fluoro-4-methoxyphenyl)benzene sulfonamide, anhydrovinblastine, N,N-dimethyl-L-valyl-L-valyl-N-methyl-L-valyl-L-prolyl-L-proline-t-butylamide, TDX258, and BMS188797.

Some examples of topoisomerase inhibitors are topotecan, hycaptamine, irinotecan, rubitecan, 6-ethoxypropionyl-3',4'-O-exo-benzylidene-chartreusin, 9-methoxy-N,N-dimethyl-5-nitropyrazolo[3,4,5-kl]acridine-2-(6H)propanamine, 1-amino-9-ethyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo[de]pyrano[3',4':b,7]-indolizino[1,2b]quinoline-10,13(9H,15H)dione, lurtotecan, 7-[2-(N-isopropylamino)-ethyl]-(20S)camptothecin, BNP1350, BNPI1100, BN80915, BN80942, etoposide phosphate, teniposide, sobuzoxane, 2'-dimethylamino-2'-deoxy-etoposide, GL331, N-[2-(dimethylamino)ethyl]-9-hydroxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide, asulacrine, (5a, 5aB, 8aa,9b)-9-[2-[N-[2-(dimethylamino)ethyl]-N-methylamino]ethyl]-5-[4-

hydroxy –3,5-dimethoxyphenyl]-5,5a,6,8,8a,9-hexohydrofuro(3',4': 6,7)colchic(2,3-d)-1,3-dioxol-6-one, 2,3-(methylenedioxy)-5-methyl-7-hydroxy-8-methoxybenzo[c]-phenanthridinium, 6,9-bis[(2-aminoethyl)-amino]benzo[g]isoguinoline-5,10-dione, 5-(3-aminopropylamino)-7,10-dihydroxy-2-(2-hydroxyethylaminomethyl)-6H-pyrazolo[4,5,1-de]acridin-6-one, N-[1-[2(diethylamino)ethylamino]-7-methoxy-9-oxo-9H-thioxanthen-4-ylmethyl]formamide, N-(2-(dimethylamino)ethyl)acridine-4-carboxamide, 6-[[2-(dimethylamino)ethyl]amino]-3-hydroxy-7H-indeno[2, 1-c]quinolin-7-one, and dimesna.

"Antiproliferative agents" includes antisense RNA and DNA oligonucleotides such as G3139, ODN698, RVASKRAS, GEM231, and INX3001, and antimetabolites such as enocitabine, carmofur, tegafur, pentostatin, doxifluridine, trimetrexate, fludarabine, capecitabine, galocitabine, cytarabine ocfosfate, fosteabine sodium hydrate, raltitrexed, paltitrexid, emitefur, tiazofurin, decitabine, nolatrexed, pemetrexed, nelzarabine, 2'-deoxy-2'-methylidenecytidine, 2'-fluoromethylene-2'-deoxycytidine, N-[5-(2,3-dihydro-benzofuryl)-sulfonyl]-N'-(3,4-dichlorophenyl)urea, N6-[4-deoxy-4-[N2-[2(E),4(E)-tetradecadienoyl]-glycylamino]-L-glycero-B-L-manno-heptopyranosyl]adenine, aplidine, ecteinascidin, troxacitabine, 4-[2-amino-4-oxo-4,6,7,8-tetrahydro-3H-pyrimidino[5,4-b][1,4]thiazin-6-yl- (S)-ethyl]-2,5-thienoyl-L-glutamic acid, aminopterin, 5-flurouracil, alanosine, 11-acetyl-8-(carbamoyloxymethyl)-4-formyl-6-methoxy-14-oxa-1,11-diazatetra cyclo(7.4.1.0.0)-tetradeca-2,4,6-trien-9-yl acetic acid ester, swainsonine, lometrexol, dexrazoxane, methioninase, 2'-cyano-2'-deoxy-N4-palmitoyl-1-B-D-arabino furanosyl cytosine, and 3-aminopyridine-2-carboxaldehyde thiosemicarbazone. "Antiproliferative agents" also includes monoclonal antibodies to growth factors, other than those listed under "angiogenesis inhibitors", such as trastuzumab, and tumor suppressor genes, such as p53, which can be delivered via recombinant virus-mediated gene transfer (see U.S. Pat. No. 6,069,134, for example).

"HMG-CoA reductase inhibitors" refers to inhibitors of 3-hydroxy-3-methylglutaryl-CoA reductase. Compounds which have inhibitory activity for HMG-CoA reductase can be readily identified by using assays well-known in the art. For example, see the assays described or cited in U.S. Pat. No. 4,231,938 at col. 6, and WO 84/02131 at pp. 30-33. The terms "HMG-CoA reductase inhibitor"

and "inhibitor of HMG-CoA reductase" have the same meaning when used herein. It has been reported that (Int. J. Cancer, 20;97(6):746-50, 2002) combination therapy with lovastatin, a HMG-CoA reductase inhibitor, and butyrate, an inducer of apoptosis in the Lewis lung carcinoma model in mice showed potentiating antitumor effects

Examples of HMG-CoA reductase inhibitors that may be used include but are not limited to lovastatin (MEVACOR®; see U.S. Pat. Nos. 4,231,938; 4,294,926; 4,319,039), simvastatin (ZOCOR®; see U.S. Pat. Nos. 4,444,784; 4,820,850; 4,916,239), pravastatin (PRAVACHOL®; see U.S. Pat. Nos. 4,346,227; 4,537,859; 4,410,629; 5,030,447 and 5,180,589), fluvastatin (LESCOL®; see U.S. Pat. Nos. 5,354,772; 4,911,165; 4,929,437; 5,189,164; 5,118,853; 5,290,946; 5,356,896), atorvastatin (LIPITOR®; see U.S. Pat. Nos. 5,273,995; 4,681,893; 5,489,691; 5,342,952) and cerivastatin (also known as rivastatin and BAYCHOL®; see U.S. Pat. No. 5,177,080). The structural formulas of these and additional HMG-CoA reductase inhibitors that may be used in the instant methods are described at page 87 of M. Yalpani, "Cholesterol Lowering Drugs", Chemistry & Industry, pp. 85-89 (Feb. 5, 1996) and U.S. Pat. Nos. 4,782,084 and 4,885,314. The term HMG-CoA reductase inhibitor as used herein includes all pharmaceutically acceptable lactone and open-acid forms (i.e., where the lactone ring is opened to form the free acid) as well as salt and ester forms of compounds which have HMG-CoA reductase inhibitory activity, and □olchicin the use of such salts, esters, open-acid and lactone forms is included within the scope of this invention.

In HMG-CoA reductase inhibitors where an open-acid form can exist, salt and ester forms may preferably be formed from the open-acid, and all such forms are included within the meaning of the term "HMG-CoA reductase inhibitor" as used herein. Preferably, the HMG-CoA reductase inhibitor is selected from lovastatin and simvastatin, and most preferably simvastatin.

Herein, the term "pharmaceutically acceptable salts" with respect to the HMG-CoA reductase inhibitor shall mean non-toxic salts of the compounds employed in this invention which are generally prepared by reacting the free acid with a suitable organic or inorganic base, particularly those formed from cations such as sodium, potassium, aluminum, calcium, lithium, magnesium, zinc and

tetramethylammonium, as well as those salts formed from amines such as ammonia, ethylenediamine, N-methylglucamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine, chloroprocaine, diethanolamine, procaine, N-benzylphenethylamine, 1-p-chlorobenzyl-2-pyrrolidine-1'-yl-methylbenzimidazole, diethylamine, piperazine, and tris(hydroxymethyl) aminomethane. Further examples of salt forms of HMG-CoA reductase inhibitors may include, but are not limited to, acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynapthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylsulfate, mucate, napsylate, nitrate, oleate, oxalate, pamaote, palmitate, panthothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide, and valerate.

Ester derivatives of the described HMG-CoA reductase inhibitor compounds may act as prodrugs which, when absorbed into the bloodstream of a warm-blooded animal, may cleave in such a manner as to release the drug form and permit the drug to afford improved therapeutic efficacy.

"Prenyl-protein transferase inhibitor" refers to a compound which inhibits any one or any combination of the prenyl-protein transferase enzymes, including farnesyl-protein transferase (FPTase), geranylgeranyl-protein transferase type I (GGPTase-I), and geranylgeranyl-protein transferase type-II (GGPTase-II, also called Rab GGPTase). Examples of prenyl-protein transferase inhibiting compounds include (±)-6-[amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methyl-2(1H)-quinolinone, (-)-6-[amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl)methyl]-4-(3-chloro phenyl)-1-methyl-2(1H)-quinolinone, (+)-6-[amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl)methyl]-4-(3-chloro phenyl)-1-methyl-2(1H)-quinolinone, 5(S)-n-butyl-1-(2,3-dimethylphenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethy l]-2-piperazinone, (S)-1-(3-chlorophenyl)-4-[1-(4-cyano-benzyl)-5-imidazolylmethyl]-5-[2-(ethanesulfonyl)-methyl)-2-piperazinone, 5(S)-n-butyl-1-(2-methylphenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2 –piperazinone, 1-(3-chlorophenyl) –4-[1-

(4-cyanobenzyl)-2-methyl-5-imidazolylmethyl]-2-piperazinone, 1-(2,2-diphenylethyl)-3-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl]piperidine, 4-{5-[4-hydroxymethyl-4-(4-chloropyridin-2-ylmethyl)-piperidine-1-ylmethyl]-2-methylimidazol-1-ylmethyl}-benzonitrile, 4-{5-[4-hydroxymethyl-4-(3-chlorobenzyl)-piperidine-1-ylmethyl]-2-methylimidazol-1-ylmethyl}benzonitrile, 4-{3-[4-(2-oxo-2H-pyridin-1-yl)benzyl]-3H-imidazol-4-ylmethyl}benzonitrile, 4-{3-[4-(5-chloro-2-oxo-2H-[1,2']bipyridin-5'-ylmethyl]-3H-imidazol-4-ylmethyl}benzonitrile, 4-{3-[4-(2-oxo-2H-[1,2']bipyridin-5'-ylmethyl]-3H-imidazol-4-ylmethyl}benzonitrile, 4-[3-(2-oxo-1-phenyl-1,2-dihydropyridin-4-ylmethyl)-3H-imidazol-4-ylmethyl}benzonitrile, 18,19-dihydro-19-oxo-5H,17H-6,10: 12,16-dimetheno-1H-imidazo[4,3-c][1,11,4]dioxa-azacyclononadecine-9-carbonitrile, (±)-19,20-dihydro-19-oxo-5H-18,21-ethano-12,14-etheno-6,10-metheno-22H-benzo[d]imidazo[4,3-k][1,6,9,12]-oxatriaza-cyclooctadecine-9-carbonitrile, 19,20-dihydro-19-oxo-5H,17H-18,21-ethano-6,10: 12,16-dimetheno-22H-imidazo[3,4-h][1,8,11,14]oxatriazacyclo-eicosine-9-carbonitrile, and (±)-19,20-dihydro-3-methyl-19-oxo-5H-18,21-ethano-12,14-etheno-6,10-met heno-22H-benzo[d]imidazo[4,3-k][1,6,9,12]oxa-triazacyclooctadecine-9-carbonitrile.

Other examples of prenyl-protein transferase inhibitors can be found in the following publications and patents: WO 96/30343, WO 97/18813, WO 97/21701, WO 97/23478, WO 97/38665, WO 98/28980, WO 98/29119, WO 95/32987, U.S. Pat. Nos. 5,420,245, 5,523,430, 5,532,359, 5,510,510, 5,589,485, 5,602,098, European Patent Publ. 0 618 221, European Patent Publ. 0 675 112, European Patent Publ. 0 604 181, European Patent Publ. 0 696 593, WO 94/19357, WO 95/08542, WO 95/11917, WO 95/12612, WO 95/12572, WO 95/10514, U.S. Pat. No. 5,661,152, WO 95/10515, WO 95/10516, WO 95/24612, WO 95/34535, WO 95/25086, WO 96/05529, WO 96/06138, WO 96/06193, WO 96/16443, WO 96/21701, WO 96/21456, WO 96/22278, WO 96/24611, WO 96/24612, WO 96/05168, WO 96/05169, WO 96/00736, U.S. Pat. No. 5,571,792, WO 96/17861, WO 96/33159, WO 96/34850, WO 96/34851, WO 96/30017, WO 96/30018, WO 96/30362, WO 96/30363, WO 96/31111, WO 96/31477, WO 96/31478, WO 96/31501, WO 97/00252, WO 97/03047, WO 97/03050, WO 97/04785, WO 97/02920, WO 97/17070, WO 97/23478, WO 97/26246, WO 97/30053, WO 97/44350, WO 98/02436, and U.S. Pat. No. 5,532,359. For an example of the role

of a prenyl-protein transferase inhibitor on angiogenesis see J. of Cancer, Vol. 35, No. 9, pp.1394-1401 (1999).

Examples of HIV protease inhibitors include amprenavir, abacavir, CGP-73547, CGP-61755, DMP-450, indinavir, nelfinavir, tipranavir, ritonavir, saquinavir, ABT-378, AG 1776, and BMS-232,632. Examples of reverse transcriptase inhibitors include delaviridine, efavirenz, GS-840, HB Y097, lamivudine, nevirapine, AZT, 3TC, ddC, and ddI. It has been reported (Nat. Med.;8(3):225-32, 2002) that HIV protease inhibitors, such as indinavir or saquinavir, have potent anti-angiogenic activities and promote regression of Kaposi sarcoma

"Angiogenesis inhibitors" refers to compounds that inhibit the formation of new blood vessels, regardless of mechanism. Examples of angiogenesis inhibitors include, but are not limited to, tyrosine kinase inhibitors, such as inhibitors of the tyrosine kinase receptors Flt-1 (VEGFR1) and Flk-1/KDR (VEGFR20), inhibitors of epidermal-derived, fibroblast-derived, or platelet derived growth factors, MMP (matrix metalloprotease) inhibitors, integrin blockers, interferon-∝, interleukin-12, pentosan polysulfate, cyclooxygenase inhibitors, including nonsteroidal anti-inflammatories (NSAIDs) like aspirin and ibuprofen as well as selective cyclooxygenase-2 inhibitors like celecoxib, valdecoxib, and rofecoxib (PNAS, Vol. 89, p. 7384 (1992); JNCI, Vol. 69, p. 475 (1982); Arch. Opthalmol., Vol. 108, p.573 (1990); Anat. Rec., Vol. 238, p. 68 (1994); FEBS Letters, Vol. 372, p. 83 (1995); Clin., Orthop. Vol. 313, p. 76 (1995); J. Mol. Endocrinol., Vol. 16, p.107 (1996); Jpn. J. Pharmacol., Vol. 75, p. 105 (1997); Cancer Res., Vol. 57, p. 1625 (1997); Cell, Vol. 93, p. 705 (1998); Intl. J. Mol. Med., Vol. 2, p. 715 (1998); J. Biol. Chem., Vol. 274, p. 9116 (1999)), carboxyamidotriazole, combretastatin A-4, squalamine, 6-O-chloroacetyl-carbonyl)-fumagillol, thalidomide, angiostatin, troponin-1, angiotensin II antagonists (see Fernandez et al., J. Lab. Clin. Med. 105:141-145 (1985)), and antibodies to VEGF (see, Nature Biotechnology, Vol. 17, pp.963-968 (October 1999); Kim et al., Nature, 362, 841-844 (1993); WO 00/44777; and WO 00/61186).

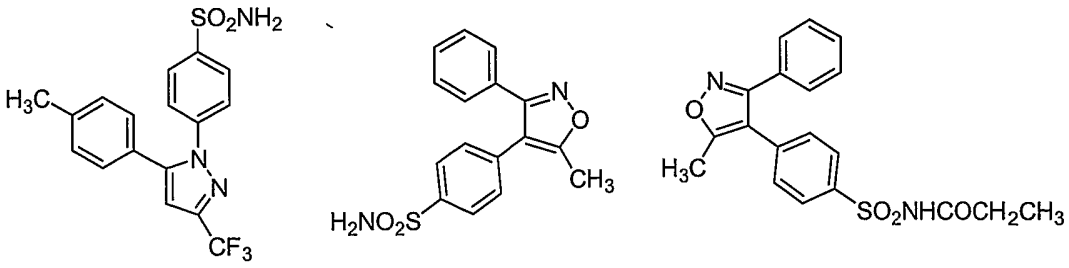
As described above, the combinations with NSAID's are directed to the use of NSAID's which are potent COX-2 inhibiting agents. For purposes of this

specification an NSAID is potent if it possess an IC_{50} for the inhibition of COX-2 of 1 μM or less as measured by the cell or microsomal assay known in the art.

The invention also encompasses combinations with NSAID's which are selective COX-2 inhibitors. For purposes of this specification NSAID's which are selective inhibitors of COX-2 are defined as those which possess a specificity for inhibiting COX-2 over COX-1 of at least 100 fold as measured by the ratio of IC_{50} for COX-2 over IC_{50} for COX-1 evaluated by the cell or microsomal assay disclosed herein under. Such compounds include, but are not limited to those disclosed in U.S. Pat. No. 5,474,995, issued Dec. 12, 1995, U.S. Pat. No. 5,861,419, issued Jan. 19, 1999, U.S. Pat. No. 6,001,843, issued Dec. 14, 1999, U.S. Pat. No. 6,020,343, issued Feb. 1, 2000, U.S. Pat. No. 5,409,944, issued Apr. 25, 1995, U.S. Pat. No. 5,436,265, issued Jul. 25, 1995, U.S. Pat. No. 5,536,752, issued Jul. 16, 1996, U.S. Pat. No. 5,550,142, issued Aug. 27, 1996, U.S. Pat. No. 5,604,260, issued Feb. 18, 1997, U.S. Pat. No. 5,698,584, issued Dec. 16, 1997, U.S. Pat. No. 5,710,140, issued Jan. 20, 1998, WO 94/15932, published Jul. 21, 1994, U.S. Pat. No. 5,344,991, issued Jun. 6, 1994, U.S. Pat. No. 5,134,142, issued Jul. 28, 1992, U.S. Pat. No. 5,380,738, issued Jan. 10, 1995, U.S. Pat. No. 5,393,790, issued Feb. 20, 1995, U.S. Pat. No. 5,466,823, issued Nov. 14, 1995, U.S. Pat. No. 5,633,272, issued May 27, 1997, and U.S. Pat. No. 5,932,598, issued Aug. 3, 1999, all of which are hereby incorporated by reference. Other examples of specific inhibitors of COX-2 include those disclosed in U.S. Patent 6,313,138 the disclosure of which is incorporated herein by reference in its entirety.

General and specific synthetic procedures for the preparation of the COX-2 inhibitor compounds described above are found in U.S. Pat. No. 5,474,995, issued Dec. 12, 1995, U.S. Pat. No. 5,861,419, issued Jan. 19, 1999, and U.S. Pat. No. 6,001,843, issued Dec. 14, 1999, all of which are herein incorporated by reference.

Compounds that have been described as specific inhibitors of COX-2 and are therefore useful in the present invention include, but are not limited to, the following:



or a pharmaceutically acceptable salt thereof.

Compounds which are described as specific inhibitors of COX-2 and are therefore useful in the present invention, and methods of synthesis thereof, can be found in the following patents, pending applications and publications, which are herein incorporated by reference: WO 94/15932, published Jul. 21, 1994, U.S. Pat. No. 5,344,991, issued Jun. 6, 1994, U.S. Pat. No. 5,134,142, issued Jul. 28, 1992, U.S. Pat. No. 5,380,738, issued Jan. 10, 1995, U.S. Pat. No. 5,393,790, issued Feb. 20, 1995, U.S. Pat. No. 5,466,823, issued Nov. 14, 1995, U.S. Pat. No. 5,633,272, issued May 27, 1997, and U.S. Pat. No. 5,932,598, issued Aug. 3, 1999.

Compounds which are specific inhibitors of COX-2 and are therefore useful in the present invention, and methods of synthesis thereof, can be found in the following patents, pending applications and publications, which are herein incorporated by reference: U.S. Pat. No. 5,474,995, issued Dec. 12, 1995, U.S. Pat. No. 5,861,419, issued Jan. 19, 1999, U.S. Pat. No. 6,001,843, issued Dec. 14, 1999, U.S. Pat. No. 6,020,343, issued Feb. 1, 2000, U.S. Pat. No. 5,409,944, issued Apr. 25, 1995, U.S. Pat. No. 5,436,265, issued Jul. 25, 1995, U.S. Pat. No. 5,536,752, issued Jul. 16, 1996, U.S. Pat. No. 5,550,142, issued Aug. 27, 1996, U.S. Pat. No. 5,604,260, issued Feb. 18, 1997, U.S. Pat. No. 5,698,584, issued Dec. 16, 1997, and U.S. Pat. No. 5,710,140, issued Jan. 20, 1998.

Other examples of angiogenesis inhibitors include, but are not limited to, endostatin, ukrain, ranpirnase, IM862, 5-methoxy-4-[2-methyl-3-(3-methyl-2-butenyl)oxiranyl]-1-oxaspiro[2,5]oct-6 –yl(chloroacetyl)carbamate, acetyldinanaline, 5-amino-1-[[3,5-dichloro-4-(4-chlorobenzoyl)phenyl]-methyl]-1H-1,2,3-triazo le-4-carboxamide, CM101, squalamine, combretastatin, RPI4610, NX31838, sulfated mannopentose phosphate, 7,7-(carbonyl-bis[imino-N-methyl-4,2-pyrrolocarbonyl-imino[N-methyl-4,2-pyrrole]-carbonylimino]-bis-(1,3-

naphthalene disulfonate), and 3-[(2,4-dimethylpyrrol-5-yl)methylene]-2-indolinone (SU5416).

As used above, "integrin blockers" refers to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the $\alpha_v\beta_3$ integrin, to compounds which selectively antagonize, inhibit or counter-act binding of a physiological ligand to the $\alpha_v\beta_5$ integrin, to compounds which antagonize, inhibit or counteract binding of a physiological ligand to both the $\alpha_v\beta_3$ integrin and the $\alpha_v\beta_5$ integrin, and to compounds which antagonize, inhibit or counteract the activity of the particular integrin(s) expressed on capillary endothelial cells. The term also refers to antagonists of the $\alpha_v\beta_6$, $\alpha_v\beta_8$, $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$ and $\alpha_6\beta_4$ integrins. The term also refers to antagonists of any combination of $\alpha_v\beta_3$, $\alpha_v\beta_5$, $\alpha_v\beta_6$, $\alpha_v\beta_8$, $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$ and $\alpha_6\beta_4$ integrins.

Some specific examples of tyrosine kinase inhibitors include N-(trifluoromethyl-phenyl)-5-methylisoxazol-4-carboxamide, 3-[(2,4-dimethylpyrrol-5-yl)methylidenyl)indolin-2-one, 17-(allylamino)-17-demethoxygeldanamycin, 4-(3-chloro-4-fluorophenylamino)-7-methoxy-6-[3-(4-morpholinyl)propoxyl]quinazoline, N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, BIBX1382, 2,3,9,10,11,12-hexahydro-10-(hydroxymethyl)-10-hydroxy-9-methyl-9,12-epoxy –1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocin-1-one, SH268, genistein, ST1571, CEP2563, 4-(3-chlorophenylamino)-5,6-dimethyl-7H-pyrrolo [2,3-d]pyrimidinemethane sulfonate, 4-(3-bromo-4-hydroxyphenyl)amino-6,7-dimethoxyquinazoline, 4-(4'-hydroxyphenyl)amino-6,7-dimethoxyquinazoline, SU6668, SU11248, STI571A, N-4-chlorophenyl-4-(4-pyridylmethyl)-1-phthalazinamine, and EMD121974.

The instant compounds are also useful, alone or in combination with platelet fibrinogen receptor (GP IIb/IIIa) antagonists, such as tirofiban, to inhibit metastasis of cancerous cells. Tumor cells can activate platelets largely via thrombin generation. This activation is associated with the release of VEGF. The release of VEGF enhances metastasis by increasing extravasation at points of adhesion to vascular endothelium (Amirkhosravi, Platelets 10, 285-292, 1999). Therefore, the present compounds can serve to inhibit metastasis, alone or in combination with GP IIb/IIIa) antagonists. Examples of other fibrinogen receptor

antagonists include abciximab, eptifibatide, sibrafiban, lamifiban, lotrafiban, cromofiban, and CT50352.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described above and the other pharmaceutically active agent(s) within its approved dosage range. Compounds of the instant invention may alternatively be used sequentially with known pharmaceutically acceptable agent(s) when a combination formulation is inappropriate.

The term administration and variants thereof (e.g., "administering" a compound) in reference to a compound of the invention means introducing the compound or a prodrug of the compound into the system of the animal in need of treatment. When a compound of the invention or prodrug thereof is provided in combination with one or more other active agents (e.g., a cytotoxic agent, etc.), "administration" and its variants are each understood to include concurrent and sequential introduction of the compound or prodrug thereof and other agents.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

The compounds of the instant invention may also be co-administered with other well known therapeutic agents that are selected for their particular usefulness against the condition that is being treated. For example, the compounds of the instant invention may also be co-administered with other well known cancer therapeutic agents that are selected for their particular usefulness against the condition that is being treated. Included in such combinations of therapeutic agents are combinations of the farnesyl-protein transferase inhibitors disclosed in US Patent 6,313,138 and an antineoplastic agent. It is also understood that such a combination of antineoplastic agent and inhibitor of farnesyl-protein transferase may be used in conjunction with other methods of treating cancer and/or tumors, including radiation therapy and surgery.

Examples of an antineoplastic agent include, in general, microtubule-stabilizing agents (such as paclitaxel (also known as Taxol®), docetaxel (also known as Taxotere®epothilone A, epothilone B, desoxyepothilone A,

desoxyepothilone B or their derivatives); microtubule-disruptor agents; alkylating agents, anti-metabolites; epidophyllotoxin; an antineoplastic enzyme; a topoisomerase inhibitor; procarbazine; mitoxantrone; platinum coordination complexes; biological response modifiers and growth inhibitors; hormonal/anti-hormonal therapeutic agents and haematopoietic growth factors.

Example classes of antineoplastic agents include, for example, the anthracycline family of drugs, the vinca drugs, the mitomycins, the bleomycins, the cytotoxic nucleosides, the taxanes, the epothilones, discodermolide, the pteridine family of drugs, diynenes and the podophyllotoxins. Particularly useful members of those classes include, for example, doxorubicin, carminomycin, daunorubicin, aminopterin, methotrexate, methopterin, dichloro-methotrexate, mitomycin C, porfiromycin, Herceptin®, Rituxan®, 5-fluorouracil, 6-mercaptopurine, gemcitabine, cytosine arabinoside, podophyllotoxin or podo-phyllotoxin derivatives such as colchicines, etoposide, etoposide phosphate or teniposide, melphalan, vinblastine, vincristine, leurosidine, vindesine, leurosine, paclitaxel and the like. Other useful antineoplastic agents include estramustine, cisplatin, carboplatin, cyclophosphamide, bleomycin, tamoxifen, ifosamide, melphalan, hexamethyl melamine, thiotepa, cytarabin, idatrexate, trimetrexate, dacarbazine, L-asparaginase, camptothecin, CPT-11, topotecan, ara-C, bicalutamide, flutamide, leuprolide, pyridobenzoindole derivatives, interferons and interleukins. The preferred class of antineoplastic agents is the taxanes and the preferred antineoplastic agent is paclitaxel.

Radiation therapy, including x-rays or gamma rays which are delivered from either an externally applied beam or by implantation of tiny radioactive sources, may also be used in combination with the compounds of this invention alone to treat cancer.

Representative pharmaceutical formulations containing a compound of Formula I are described below.

EXAMPLES

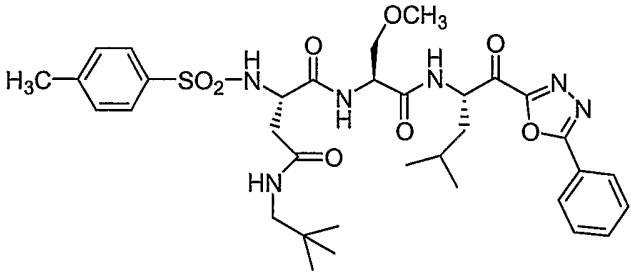
The following preparations and examples are given to enable those skilled in the art to more clearly understand and to practice the present invention. They should not be considered as limiting the scope of the invention, but merely as

being illustrative and representative thereof.

Synthetic Examples

Example 1

Synthesis of N4-(2,2-dimethylpropyl)-N1-{2-methoxy-1*S*-[3-methyl-1*S*-(5-phenyl-[1,3,4]oxadiazol-2-ylcarbonyl)butylcarbamoyl]ethyl}-2*S*-(toluene-4-sulfonylamino)succinamide



Step 1

N-α-Boc-L-aspartic acid α-t-butyl ester (3.00g, 10.4 mmol), neopentylamine (1.22 mL, 10.4 mmol), N-methylmorpholine (2.3 mL, 21.0 mmol) and 2-(1-H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU, 3.95 g, 10.4 mmol) were dissolved in anhydrous DMF (25 mL). The yellow solution was stirred at ambient temperature under an atmosphere of dry nitrogen. After 4 hr, the solvent was removed by rotary evaporation and the oily residue was partitioned between ethyl acetate and 0.5N aqueous HCl. The organic phase was separated, washed with water, saturated sodium bicarbonate, and brine, then dried over anhydrous magnesium sulfate. Filtration and solvent evaporation furnished 2-*tert*-butoxycarbonylamino-N-(2,2-dimethylpropyl)succinamic acid *tert*-butyl ester as a colorless oil (3.02 g, 81%) that was used without further purification for the next step.

Step 2

2-*tert*-Butoxycarbonylamino-N-(2,2-dimethylpropyl)-succinamic acid *tert*-butyl ester from above (2.90 g, 8.09 mmol) was dissolved in 20.2 mL 4.0M HCl in 1,4-dioxane (80.9 mmol). After stirring for 2 hr at ambient temperature, the solvent was removed by rotary evaporation. Toluene was added to the residue and rotary evaporation was continued. After vacuum pumping 2-amino-N-(2,2-dimethylpropyl)succinamic acid hydrochloride was obtained as a white solid (1.93 g, 100%) and used without purification for the reaction below.

Step 3

2-Amino-N-(2,2-dimethylpropyl)succinamic acid hydrochloride from above (1.50 g, 6.28 mmol) was dissolved in 25 mL of a chilled 0.5N aqueous NaOH solution. p-Toluenesulfonyl chloride (1.20 g, 6.28 mmol) was added to the vigorously stirred solution in portions and the pH of the reaction mixture was frequently adjusted to >=9 by addition of 4M aqueous NaOH as necessary. After 2 hr, the reaction mixture was acidified with 6M HCl and extracted thrice with ethyl acetate. The combined organic phase was washed with 1M aqueous HCl, water, and brine. The resulting solution was dried over anhydrous magnesium sulfate. Filtration and solvent evaporation furnished a colorless oil. Chloroform was added and rotary evaporation was continued. Upon vacuum pumping of the residue N-(2,2-dimethy-propyl)-2-(toluene-4-sulfonylamino)succinamic acid was obtained as a white solid (2.24 g, 60%), mp 163.5 – 165 °C.

Step 4

Benzoic hydrazide (54.4 g, 400 mmol), p-toluenesulfonic acid monohydrate (1.1g, 5.78 mmol), and trimethylorthoformate (66 mL, 600 mmol) were heated to reflux for 30 min. The reaction mixture was then vacuum distilled, with fractions boiling between 90C and 120C at 4 torr being combined to afford 2-phenyl-[1,3,4]oxadiazole as a colorless liquid (44.4 g, 76%) which crystallized upon standing, mp 34 – 36 °C.

Step 5

A solution of 2-phenyl-[1,3,4]oxadiazole (3.34g, 16.0 mmol) in anhydrous THF (100 mL) was cooled with a dry ice bath and maintained under an atmosphere of dry nitrogen. A solution of 1.6M *n*-butyllithium in hexanes (10.0 mL, 16.0 mmol) was added via syringe. After 1 hr, magnesium bromide diethyl etherate (4.13g, 16.0 mmol) was added in one portion. After another hr, a solution of freshly prepared (1-formyl-3-methylbutyl)-carbamic acid *tert*-butyl ester (BOC-Leu-H, 1.94g, 8.0 mmol, prepared by the procedure described in Falkiewicz, B. *et al. Nucleosides and Nucleotides* **20** 1393, 2001) was added. After an additional 1.5 hr at low temperature, 1.0 N aqueous HCl was added and the cold bath was removed. Upon warming to room temperature the mixture was transferred to a separatory funnel and 100 ml diethyl ether was added. The organic phase was separated and the aqueous phase was extracted twice more with 50 mL portions of ether. The combined organic phase was washed with water, saturated sodium bicarbonate, and brine, then dried over

anhydrous magnesium sulfate. Filtration and solvent evaporation gave an oily residue that was flash chromatographed on silica gel, eluting with a gradient of 25% to 50% ethyl acetate in hexane, to give {1-[hydroxy-(5-phenyl-[1,3,4]oxadiazol-2-yl)methyl]-3-methylbutyl}carbamic acid *tert*-butyl ester (1.61g, 70% yield).

Step 6

{1-[Hydroxy-(5-phenyl-[1,3,4]oxadiazol-2-yl)methyl]-3-methylbutyl}carbamic acid *tert*-butyl ester (11.9g, 32.9 mmol) was dissolved in 25 mL dichloromethane. A 4.0M solution of HCl in 1,4-dioxane (100 mL, 400 mmol) was added with stirring. After 2 hr, diethyl ether (400 mL) was added, which caused an oil to form. The supernatant was decanted and the oil was triturated with more ether to afford 2-amino-4-methyl-1-(5-phenyl-[1,3,4]oxadiazol-2-yl)-pentan-1-ol hydrochloride as a pale yellow solid (9.73 g, 100% yield).

Step 7

N-α-Boc-O-methyl-L-serine (2.19g, 10.0 mmol), HOBt (1.62g, 12.0 mmol), 1-ethyl-3-(3'-dimethylamino-propyl)carbodiimide hydrochloride (EDC, 2.01g, 10.5 mmol), and N-methylmorpholine (1.4 mL, 12.5 mmol) were stirred in 150 mL anhydrous dichloromethane. After 5 min, 2-amino-4-methyl-1-(5-phenyl-[1,3,4]oxadiazol-2-yl)-pentan-1-ol hydrochloride (2.61g, 10.0 mmol) dissolved in dichloromethane (50 mL)and more N-methylmorpholine (1.4 mL, 12.5 mmol) were added. After 3 hr, the reaction mixture was transferred to a separatory funnel and washed twice with 100 mL portions of 0.5N aqueous HCl. The organic phase was separated and once with water (50 mL) and twice with saturated aqueous sodium bicarbonate (100 mL). The organic phase was dried over anhydrous magnesium sulfate. Filtration and solvent evaporation gave a tan foam. This was flash chromatographed on silica gel, eluting with 5% methanol in dichloromethane to give (1-{1-[hydroxy-(5-phenyl-[1,3,4]oxadiazol-2-yl)methyl]-3-methyl-butylcarbamoyl}-2-methoxyethyl)carbamic acid *tert*-butyl ester as a brittle, pale yellow foam, (3.65g, 79%) as a mixture of diastereomers.

Step 8

(1-{1-[Hydroxy-(5-phenyl-[1,3,4]oxadiazol-2-yl)methyl]-3-methylbutylcarbamoyl}-2-methoxyethyl)carbamic acid *tert*-butyl ester (3.55g, 7.68 mmol) was dissolved in 4.0N HCl (36 mL, 144 mmol) in 1,4-dioxane and stirred at ambient temperature. After 97 min, the volatiles were removed by rotary evaporation

and the residue was triturated with diethyl ether (15 mL). Filtration and drying gave 2-amino-N-{1-[hydroxy-(5-phenyl-[1,3,4]oxadiazol-2-yl)-methyl]-3-methyl-butyl}-3-methoxy-propionamide hydrochloride as a beige solid (3.06g, 100%), a mixture of diastereomers.

Step 9

N-(2,2-Dimethylpropyl)-2-(toluene-4-sulfonylamino)succinamic acid (2.68g, 7.52 mmol) and hydroxybenzotriazole (HOBt, 3.00g, 7.52 mmol) were stirred at ambient temperature in dichloromethane (130 mL). 1-Ethyl-3-(3'-dimethylamino-propyl)carbodiimide hydrochloride (EDC, 1.51g, 7.90 mmol) and N-methylmorpholine (1.65g, 15.0 mmol) were added. After 8 min., 2-amino-N-{1-[hydroxy-(5-phenyl-[1,3,4]oxadiazol-2-yl)-methyl]-3-methyl-butyl}-3-methoxy-propionamide hydrochloride (3.00g, 7.52 mmol) and more N-methylmorpholine (1.65g, 15.0 mmol) were added. After 2.5 hr, the reaction mixture was transferred to a separatory funnel and washed thrice with 0.5N aqueous HCl. The organic phase was washed with water, saturated aqueous sodium bicarbonate, and brine. Drying over anhydrous magnesium sulfate followed by filtration and solvent evaporation gave a sticky brown oil. Trituration with diethyl ether (25 mL) followed by filtration and drying of the precipitate gave N-4-(2,2-dimethylpropyl)-N1-(1-{1-[hydroxy-(5-phenyl-[1,3,4]oxadiazol-2-yl)-methyl]-3-methylbutylcarbamoyl}-2-methoxyethyl)-2-(toluene-4-sulfonylamino)succinamide (1.93g, 37% yield) as a mixture of diastereomers, mp 109-112 °C.

Step 10

N-4-(2,2-Dimethylpropyl)-N1-(1-{1-[hydroxy-(5-phenyl-[1,3,4]oxadiazol-2-yl)-methyl]-3-methylbutylcarbamoyl}-2-methoxyethyl)-2-(toluene-4-sulfonylamino)succinamide (2.20g, 3.14 mmol) was dissolved in 50 mL water-saturated dichloromethane and was vigorously stirred at ambient temperature under an atmosphere of nitrogen. Dess Martin periodinane (2.00g, 4.71 mmol) was added in one portion and stirring was continued. After 2 hr, additional Dess Martin periodinane (0.67g, 1.57 mmol) was added. After another 4 hr, a solution of 0.26M sodium thiosulfate in saturated aqueous sodium bicarbonate (300 mL) was added with vigorous stirring. After 30 min., the reaction mixture was transferred to a separatory funnel and 50 mL dichloromethane was added. The organic phase was separated and washed twice with the previously described sodium thiosulfate solution, then was washed once with saturated aqueous sodium bicarbonate, water, and brine. Drying

over anhydrous magnesium sulfate followed by filtration and solvent evaporation afforded 1.93g of a pale yellow solid. This was flash chromatographed on silica gel, eluting with 2.5/5.0/92.5 methanol /acetone /dichloromethane to give N4-(2,2-dimethylpropyl)-N1-{2-methoxy-1*S*-[3-methyl-1*S*-(5-phenyl-[1,3,4]oxadiazol-2-ylcarbonyl)butylcarbamoyl]ethyl}-2*S*-(toluene-4-sulfonylamino)succinamide (1.73 g, 79%) as a pale yellow solid, mp 161-163 °C.

400MHz ^{1}H-NMR (DMSO-d6) δ 8.56 (d, J= 6.4Hz, 1H), 8.16 (d, J= 7.6Hz, 1H), 8.06 (d, J= 8Hz, 2H), 7.92 (d, J= 8.8Hz, 1H), 7.77 (t, J= 6Hz, 1H), 7.65 (m, 5H), 7.29 (d, J= 8Hz, 2H), 5.13 (m, 1H), 4.15 (m, 2H), 3.42 (m, 1H), 3.25 (m, 1H), 3.13 (s, 3H), 2.79 (m, 2H), 2.35 (s, 3H), 2.31 (m, 2H), 1.71 (m, 3H), 0.93 (br s, 6H), 0.78 (s, 9H). LCMS (electrospray) $(mH)^+$ 699.6 (100%).

Proceeding as described in Example 1 above, and using appropriate starting materials the following compounds of Formula I were prepared:

4-{1-[3-Methyl-1-(5-phenyl-[1,3,4]oxadiazol-2-ylcarbonyl)-butylcarbamoyl]-ethylcarbamoyl}-4-(toluene-4-sulfonylamino)butyric acid *tert*-butyl ester. 400MHz ^{1}H-NMR (DMSO-d6) δ 8.2 (d, 2H), 7.8 (d, 1H), 7.7 (d, 2H), 7.5 (m, 2H), 7.2 (m, 3H), 7.0 (d, 1H), 6.8 (d, 1H), 5.4 (m, 1H), 4.4 (m, 1H), 3.5 (m, 1H), 2.39 (m, 5H), 1.9-1.6 (m, 3H), 1.4 (s, 9H), 1.3 (d, 3H), 0.9 (m, 6H), 0.8 (m, 2H). MS (electrospray): mH^+ 670.2 (100%).

N4-(2,2-Dimethylpropyl)-N1-{1-[3-methyl-1-(5-phenyl-[1,3,4]oxadiazol-2-ylcarbonyl)-butylcarbamoyl]ethyl}-2-(toluene-4-sulfonylamino)succinamide. Prepared by the method of Example 1 using t-BOC alanine in place of t-BOC OMe serine. 400MHz ^{1}H-NMR (DMSO-d6) δ 8.45 (d, 1H), 8.1 (d, 1H), 8.05 (d, 2H), 7.9 (d, 1H), 7.8 (t, 1H), 7.6 (m, 5H), 7.2 (d, 2H), 5.1 (m, 1H), 4.05 (m, 1H), 3.95 (m, 1H), 2.6 (m, 2H), 2.6-2.5 (m, 5H), 1.75 (m, 3H), 1.0 (d, 3H), 0.9 (m, 6H), 0.8 (s, 9H). MS (electrospray): mH^+ 669.4 (100%).

N4-(2,2-Dimethylpropyl)-N1-{1-[1-(5-ethyl-[1,3,4]oxadiazol-2-ylcarbonyl)-3-methyl-butylcarbamoyl]ethyl}-2-(toluene-4-sulfonylamino)succinamide. Prepared by the method of Example 1 using 2-ethyl-1,3,4-oxadiazole in place of 2-phenyl-1,3,4-oxadiazole and t-BOC alanine in place of t-BOC OMe serine. 400MHz ^{1}H-NMR (DMSO-d6) δ 8.2 (d, 1H), 8.1 (m, 1H), 8.00 (d, 1H), 7.95 (m, 1H), 7.6 (d, 2H), 7.3 (d, 2H), 5.01 (m, 1H), 4.05 (m, 1H), 3.95 (m, 1H), 2.95 (q, 2H), 2.9 (m, 1H), 2.3 (s, 3H), 1.6 (m, 3H), 1.3 (t, 3H), 1.0-0.8 (m, 21H). MS (electrospray): mH^+ 621.7 (100%).

N1-{2-*tert*-Butoxy-1-[3-methyl-1-(5-phenyl-[1,3,4]oxadiazol-2-ylcarbonyl)-butylcarbamoyl]-ethyl}-N4-(2,2-dimethylpropyl)-2-(toluene-4-sulfonylamino)-succinamide. Prepared by the method of Example 1 using t-BOC O-t-butyl serine in place of t-BOC OMe serine. 400MHz ^{1}H-NMR (DMSO-d6) δ 8.4 (d, 1H), 8.1 (d, 2H), 7.99 (d, 1H), 7.92 (d, 1H), 7.8 (t, 1H), 7.7-7.6 (m, 5H), 7.3 (d, 2H), 5.15 (m, 1H), 4.2 (m, 1H), 4.05 (m, 1H), 3.4 (m, 1H), 3.2 (m, 1H), 2.8 (m, 2H), 2.5 (m, 1H), 2.35 (s, 3H), 2.3 (m, 1H), 1.7 (m, 3H), 1.05 (s, 9H), 0.98 (d, 6H), 0.8 (s, 9H). MS (electrospray): mH^+ 741.8 (100%).

N4-(2,2-Dimethylpropyl)-N1-{2-hydroxy-1-[3-methyl-1-(5-phenyl-[1,3,4]oxadiazol-2-ylcarbonyl)-butylcarbamoyl]ethyl}-2-(toluene-4-sulfonylamino)succinamide. Prepared by the trifluoroacetic acid deprotection of N1-{2-*tert*-butoxy-1-[3-methyl-1-(5-phenyl-[1,3,4]oxadiazol-2-ylcarbonyl)-butylcarbamoyl]-ethyl}-N4-(2,2-dimethylpropyl)-2-(toluene-4-sulfonylamino)-succinamide. Prepared by the method of Example 1 using *tert*-BOC O-*tert*-butyl serine in place of t-BOC OMe above. 400MHz ^{1}H-NMR (DMSO-d6) δ 8.61, 8.59 (2d, 1H), 8.41 (d, 1H), 8.1 (d, 2H), 7.92 (d, 1H), 7.85 (t, 1H), 7.5 (m, 5H), 7.3 (d, 2H), 5.2 (m, 1H), 4.4 (m, 1H), 4.1 (m, 1H), 3.5 (m, 2H), 3.5 (m, 1H), 2.8 (m, 2H), 2.4 (m, 2H), 2.3 (s, 3H), 1.7 (m, 3H), 0.9 (m, 6H), 0.75 (s, 9H). MS (electrospray): mH^+ 685.8 (100%).

N4-(2,2-Dimethylpropyl)-N1-{1-[3-methyl-1-(5-phenyl-[1,3,4]oxadiazol-2-ylcarbonyl)-butylcarbamoyl]ethyl}-2-(toluene-3-sulfonylamino)succinamide. Prepared by the methods described in Scheme I and Example 1, using 3-toluenesulfonyl chloride in place of 4-toluenesulfonyl chloride in Scheme I and t-BOC alanine in place of t-BOC-OMe serine in Example 1. 400MHz ^{1}H-NMR (DMSO-d6) δ 8.4 (d, 1H), 8.15 (d, 1H), 8.05 (d, 1H), 8.00 (d, 1H), 7.9 (t, 1H), 7.5 (m, 7H), 7.3 (d, 1H), 5.1 (m, 1H), 4.05 (m, 1H), 3.9 (t, 1H), 2.9 (m, 2H), 2.5-2.35 (m, 2H), 2.35 (s, 3H), 1.75 (m, 3H), 1.0 (d, 3H), 0.95 (m, 6H), 0.8 (s, 9H). MS (electrospray): mH^+ 669.3 (100%).

N1-(1-{1-[5-(4-Dimethylaminophenyl)-[1,3,4]oxadiazol-2-ylcarbonyl]-3-methyl-butylcarbamoyl}ethyl)-N4-(2,2-dimethylpropyl)-2-(toluene-4-sulfonylamino)-succinamide. Prepared by the method of Example 1 using 2-(4-dimethylaminophenyl)-1,3,4-oxadiazole in place of 2-phenyl-1,3,4-oxadiazole. 400MHz ^{1}H-NMR (DMSO-d6) δ 8.35 (d, 1H), 8.05 (d, 1H), 7.9 (d, 1H), 7.8 (d, 2H),

7.7 (t, 1H), 7.55 (d, 2H), 7.25 (d, 2H), 6.8 (d, 2H), 5.05 (m, 1H), 4.0 (m, 1H), 3.9 (t, 1H), 3.0 (s, 6H), 2.7 – 2.9 (m, 4H), 2.35 (s, 3H), 1.7 (m, 3H), 1.0 (d, 3H), 0.95 (m, 6H), 0.8 (s, 9H). MS (electrospray): mH^+ 712.5.

N4-(2,2-Dimethylpropyl)-N1-{1-[1-(5-isopropyl-[1,3,4]oxadiazol-2-ylcarbonyl)-3-methyl-butylcarbamoyl]ethyl}-2-(toluene-4-sulfonylamino)-succinamide. Prepared by the method of Example 1 using t-BOC alanine in place of t-BOD OMe serine and 2-isopropyl-1,3,4-oxadiazole in place of 2-phenyl-1,3,4-oxadiazole. 400MHz ^{1}H-NMR (DMSO-d6) δ 8.35 (d, 1H), 8.1 (d, 1H), 7.9 (d, 1H), 7.75 (t, 1H), 7.55 – 7.65 (d, 2H), 7.3 (d, 2H), 5.0 (m, 1H), 4.0 (m, 1H), 3.9 (t, 1H), 3.35 (m, 1H), 2.7 – 2.9 (m, 4H), 2.35 (s, 3H), 1.65 – 1.8 (m, 1H), 1.5 – 1.65 (t, 2H), 1.3 (d, 6H), 0.7 – 1.0 (m, 18H). LCMS (electrospray) $(mH)^+$ 635.5 (100%).

N4-(2,2-Dimethylpropyl)-N1-{1-[3-methyl-1-(5-pyridin-4-yl-[1,3,4]oxadiazol-2-ylcarbonyl)-butylcarbamoyl]ethyl}-2-(toluene-4-sulfonylamino)succinamide. Prepared by the method of Example 1 using t-BOC alanine in place of t-BOC OMe serine and 2-(4-pyridyl)-1,3,4-oxadiazole in place of 2-phenyl-1,3,4-oxadiazole. 400MHz ^{1}H-NMR (DMSO-d6) δ 8.8 (m, 2H), 8.4 (d, 1H), 8.1 (d, 1H), 7.95 – 8.0 (m, 2H), 7.9 (m, 1H), 7.8 (t, 1H), 7.6 (d, 2H), 7.2 – 7.35 (d, 2H), 5.1 (m, 1H), 4.0 (m, 1H), 3.95 (t, 1H), 2.7 – 2.9 (m, 4H), 2.35 (s, 3H), 1.6 – 1.8 (m, 3H), 1.0 (d, 3H), 0.9 (m, m, 6H), 0.75 (s, 9H). LCMS (electrospray) $(mH)^+$ 670.3 (100%).

N4-(2,2-Dimethylpropyl)-N1-{1-[1-(5-isopropyl-[1,3,4]oxadiazol-2-ylcarbonyl)-3-methylbutylcarbamoyl]ethyl}-2-(dimethylaminosulfonylamino)succinamide. Prepared by the methods of Scheme I and Example 1 using dimethylsulfamoyl chloride in place of p-toluenesulfonyl chloride in Scheme I, t-BOC alanine in place of t-BOC OMe serine and 2-isopropyl-1,3,4-oxadiazole in place of 2-phenyl-1,3,4-oxadiazole in Example 1. 400MHz ^{1}H-NMR (DMSO-d6) δ 8.4 (d, 1H), 8.15 (d, 1H), 7.8 (t, 1H), 7.4 (d, 1H), 5.1 (m, 1H), 4.2 (t, 1H), 4.0 (m, 1H), 2.8 (d, 3H), 2.4 (s, 6H), 1.7 (m, 1H), 1.6 (m, 2H), 1.35 (d, 6H), 1.2 (d, 3H), 0.9 (m, 6H), 0.8 (s, 9H). LCMS (electrospray) $(mH)^+$ 588.5 (100%).

N4-(2,2-Dimethylpropyl)-N1-{2-methoxy-1-[3-methyl-1-(5-phenyl-[1,3,4]oxadiazol-2-ylcarbonyl)butylcarbamoyl]ethyl}-2-(4-sulfamoylbenzoylamino)succinamide. Prepared by the methods of Scheme I and Example 1 using HBTU coupling of 4-sulfonamido benzoic acid in place of the

coupling of p-toluenesulfonyl chloride in Scheme I. Proton NMR (400 MHz, DMSO-d6): δ 8.8 (d, 1H), 8.7 (d, 1H), 8.2 (d, 1H), 8.1 (d, 2H), 7.95 (d, 2H), 7.85 (d, 2H), 7.8 (d, 1H), 7.6 (m, 3H), 7.5 (s, 2H), 5.2 (m, 1H), 4.8 (m, 1H), 4.45 (m, 1H), 3.45 (m, 2H), 3.1 (s, 3H), 2.8 (m, 2H), 2.65 (m, 2H), 1.75 (m, 3H), 0.95 (d, 6H), 0.8 (s, 9H). MS (electrospray): mH^+ 728.5 (100%).

N4-(2,2-Dimethylpropyl)-N1-{2-hydroxy-1-[3-methyl-1-(5-phenyl-[1,3,4]oxadiazol-2-ylcarbonyl)butylcarbamoyl]propyl}-2-(toluene-4-sulfonylamino)succinamide. Prepared by the method of Example 1 using t-BOC threonine in place of t-BOC OMe serine and using trifluoroacetic acid deprotection as the final step. 400MHz ^{1}H-NMR (DMSO-d6) δ 8.35 (d, 1H), 8.0 (d, 2H), 7.95 (m, 1H), 7.75 – 7.85 (m, 2H), 7.7 (m, 5H), 7.3 (d, 2H), 5.15 (m, 1H), 4.1 (m, 1H), 3.95 (m, 2H), 2.8 (m, 4H), 2.35 (s, 3H), 1.6 – 1.8 (m, 3H), 0.9 (m, 9H), 0.8 (s, 9H). LCMS (electrospray) $(mH)^+$ 699.2 (100%).

N4-(2,2-Dimethylpropyl)-N1-{2-methoxy-1-[3-methyl-1-(5-phenyl-[1,3,4]oxadiazol-2-ylcarbonyl)butylcarbamoyl]ethyl}-2-(dimethylaminosulfonylamino)succinamide. Prepared by the methods of Scheme I and Example 1 using dimethylsulfamoyl chloride in place of p-toluenesulfonyl chloride in Scheme I. 400MHz ^{1}H-NMR (DMSO-d6) δ 8.6 (d, 1H), 8.2 (d, 1H), 8.05 (d, 2H), 7.9 (t, 1H), 7.6 (m, 3H), 7.4 (d, 1H), 5.1 (m, 1H), 4.4 (m, 1H), 4.1 (m, 1H), 3.4 – 3.6 (m, 2H), 3.15 (s, 3H), 2.8 (d, 4H), 2.4 (s, 6H), 1.6 – 1.9 (m, 3H), 0.9 (d, 6H), 0.8 (s, 9H). LCMS (electrospray) $(mH)^+$ 652.5 (100%).

N4-(2,2-Dimethylpropyl)-N1-{1-[1-(5-furan-2-yl-[1,3,4]oxadiazol-2-ylcarbonyl)-3-methylbutylcarbamoyl]ethyl}-2-(toluene-4-sulfonylamino)succinamide. Prepared by the method of Example 1 using t-BOC alanine in place of t-BOC OMe serine and 2-(2-furanyl)-1,3,4-oxadiazole in place of 2-phenyl-1,3,4-oxadiazole. 400MHz ^{1}H-NMR (DMSO-d6) δ 8.42 (d, 1H), 8.13 (d, 1H), 7.92 (d, 1H), 7.8 (t, 1H), 7.62 (d, 2H), 7.53 (m, 1H), 7.27 (d, 2H), 6.82 (m, 2H), 5.1 (m, 1H), 4.05 (m, 1H), 3.95 (t, 1H), 2.75 – 2.95 (m, 4H), 2.3 (s, 3H), 1.6 – 1.8 (m, 3H), 1.0 (d, 3H), 0.95 (m, 6H), 0.8 (s, 9H). LCMS (electrospray) $(mH)^+$ 659.6.

N1-(1-{1-[5-(4-Dimethylaminophenyl)-[1,3,4]oxadiazol-2-ylcarbonyl]-3-methyl-butylcarbamoyl}-2-methoxyethyl)-N4-(2,2-dimethylpropyl)-2-(toluene-4-sulfonylamino)succinamide. Prepared by the method of Example 1 using 2-(4-dimethylaminophenyl)-1,3,4-oxadiazole in place of 2-phenyl-1,3,4-oxadiazole.

400MHz ^{1}H-NMR (DMSO-d6) δ 8.5 (d, 1H), 8.17 (d, 1H), 7.92 (d, 1H), 7.82 (d, 2H), 7.77 (t, 1H), 7.62 (d, 2H), 7.27 (d, 2H), 6.82 (d, 2H), 5.15 (m, 1H), 4.2 (m, 4H), 3.18 (s, 3H), 3.05 (s, 6H), 2.78 (d, 4H), 2.35 (s, 3H), 1.6 – 1.8 (m, 3H), 1.0 (m, 6H), 0.8 (s, 9H). LCMS (electrospray) $(mH)^+$ 742.6.

N4-(2,2-Dimethylpropyl)-N1-{1-[2-methyl-1-(5-phenyl-[1,3,4]oxadiazol-2-ylcarbonyl)-butylcarbamoyl]ethyl}-2-(toluene-4-sulfonylamino)succinamide. Prepared by the method of Example 1 using t-BOC alanine in place of t-BOC OMe serine and t-BOC isoleucinal in place of t-BOC leucinal. 400MHz ^{1}H-NMR (DMSO-d6) δ 8.2 (d, 2H), 7.8 (d, 2H), 7.75 (m, 1H), 7.65 (m, 1H), 7.60 (m, 3H), 7.3 (m, 2H), 7.2 (m, 1H), 6.8 (d, 1H), 5.8 (m, 1H), 5.3 (m, 1H), 4.0 (m, 1H), 3.0 (m, 2H), 2.8 (m, 2H), 2.4 (s, 3H), 1.4 (m, 3H), 1.05 (d, 3H), 1.0 (m, 6H), 0.8 (s, 9H). LCMS (electrospray) $(mH)^+$ 669.4 (100%).

N4-(2,2-Dimethylpropyl)-2-methanesulfonylamino-N1-{1-[3-methyl-1-(5-phenyl-[1,3,4]oxadiazol-2-ylcarbonyl)butylcarbamoyl]ethyl}succinamide. Prepared by the methods of Scheme I and Example 1 using methanesulfonyl chloride in place of p-toluenesulfonyl chloride in Scheme I and t-BOC alanine in place of t-BOC OMe serine in Example 1. 400MHz ^{1}H-NMR (DMSO-d6) δ 8.5 (d, 1H), 8.2 (d, 1H), 7.8 (t, 1H), 7.6 (m, 3H), 7.4 (d, 1H), 5.15 (m, 1H), 4.25 (m, 1H), 4.1 (m, 1H), 2.8 (m, 5H), 2.6 (m, 2H), 1.75 (m, 3H), 1.2 (d, 3H), 0.95 (m, 6H), 0.8 (s, 9H). LCMS (electrospray) $(mH)^+$ 593.6 (100%).

N4-(2,2-Dimethylpropyl)-N1-{1-[3-methyl-1-(5-*p*-tolyl-[1,3,4]oxadiazol-2-ylcarbonyl)-butylcarbamoyl]ethyl}-2-(toluene-4-sulfonylamino)succinamide. Prepared by the method of Example 1 using t-BOC alanine in place of t-BOC OMe serine and 2-(4-methylphenyl)-1,3,4-oxadiazole in place of 2-phenyl-1,3,4-oxadiazole. 400MHz ^{1}H-NMR (DMSO-d6) δ 8.45 (m, 1H), 8.1 – 8.3 (m, 2H), 7.97 (d, 2H), 7.8 (m, 1H), 7.6 (d, 2H), 7.45 (d, 2H), 7.34 (d, 2H), 5.15 (m, 1H), 4.0 (m, 1H), 3.95 (t, 1H), 2.7 – 2.9 (m, 4H), 2.42 (s, 3H), 2.35 (s, 3H), 1.6 – 1.8 (m, 3H), 1.05 (d, 3H), 0.95 (m, 6H), 0.8 (s, 9H). LCMS (electrospray) $(mH)^+$ 683.6 (100%).

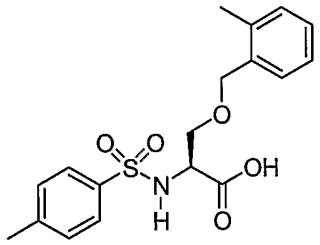
N4-(2,2-Dimethylpropyl)-N1-(1-{3-methyl-1-[5-(4-trifluoromethylphenyl)-[1,3,4]oxadiazol-2-ylcarbonyl]butylcarbamoyl}ethyl)-2-(toluene-4-sulfonylamino)-succinamide. Prepared by the method of Example 1 using t-BOC alanine in place of t-BOC OMe serine and 2-(4-trifluoromethylphenyl)-1,3,4-oxadiazole in place of 2-phenyl-1,3,4-oxadiazole. 400MHz ^{1}H-NMR (DMSO-d6) δ 8.45 (m, 1H), 8.24 (d,

2H), 8.15 (m, 1H), 7.98 (d, 2H), 7.8 – 8.0 (m, 2H), 7.45 (d, 2H), 7.3 (m, 2H), 5.15 (m, 1H), 4.05 (m, 1H), 3.95 (t, 1H), 2.7 – 2.9 (m, 4H), 2.35 (s, 3H), 1.7 (m, 3H), 1.0 (d, 3H), 0.95 (m, 6H), 0.8 (s, 9H). LCMS (electrospray) $(mH)^+$ 737.4.

In the compounds listed above, all the chiral carbons in the molecules have S-stereochemistry.

Example 2

Synthesis of 3-(2-methylbenzyloxy)-2*S*-(toluene-4-sulfonylamino)propionic acid



Step 1

BOC-Ser-OH (2.05 g, 10.0 mmol) was dissolved in dry *N,N'*-dimethylformamide (50 mL) with stirring and cooled to 0 °C under nitrogen. To the solution was added NaH (0.880g of 60% mineral oil dispersion, 22.0 mmol) batchwise over 30 minutes. The solution was stirred cold for 10 minutes and then stirred at room temperature for 40 minutes, and then cooled to 0 °C again. 2-Methylbenzyl bromide (1.58 mL, 11.8 mmol) in DMF (10 mL) was added dropwise by addition funnel to the stirring cold solution under nitrogen. After the addition was complete, the reaction was allowed to stir at room temperature overnight. The reaction was quenched by the addition of 1.0 N HCl (150 mL) and transferred to a separatory funnel. The turbid solution was extracted three times, each with 20 mL of ethyl acetate. The total volume of ethyl acetate was washed once with 1.0 N HCl (10 mL) and once with brine (10 mL). The organic solution was dried over magnesium sulfate and filtered over sintered glass. The filtrate was concentrated *in vacuo*. Analytical LCMS of the residual syrup indicated the presence of *2-tert*-butoxycarbonylamino-3-(2-methyl-benzyloxy)propionic acid in 60% yield. The crude material was used as is.

Step 2

2-tert-Butoxycarbonylamino-3-(2-methylbenzyloxy)propionic acid was mixed with 4.0 N HCl (20 mL) in dioxane with vigorous agitation. The solution was stirred

for 20 minutes after which time LCMS indicated the reaction was complete. The solution was concentrated *in vacuo* to give 2-amino-3-(2-methylbenzyloxy)propionic acid hydrochloride which was used without purification.

Step 3

The thick syrup described above was taken up with vigorous stirring in 20 mL tetrahydrofuran (20 mL) and water (40 mL). Pellets of sodium hydroxide (1.2 g, 30 mmol) were added to the clear, colorless solution with vigorous stirring. After all the pellets dissolved, *p*-toluenesulfonyl chloride (1.91 g, 10.0 mmol) was added batchwise over thirty minutes with continued stirring. More tetrahydrofuran was added as needed to maintain a homogeneous solution. NaOH pellets were added one at a time to keep the pH 9 or higher. After stirring for two hours, the reaction was quenched by the addition of 4.0 N HCl(aq) (200 mL). The reaction mixture was transferred to a separatory funnel. The turbid solution was extracted three times, each with 30 mL of ethyl acetate. The total volume of ethyl acetate was washed once with 1.0 N HCl (20 mL) and once with brine. The organic solution was dried over magnesium sulfate and filtered through sintered glass. The filtrate was concentrated *in vacuo*. Analytical LCMS of the residual syrup indicated the presence of 3-(2-methylbenzyloxy)-2-(toluene-4-sulfonylamino)propionic acid in 50% yield.

Proceeding as described in Example 2 above, but substituting 2-methylbenzyl bromide with benzyl bromide, 2-chlorobenzyl bromide, and 3,5-dimethylbenzyl bromide gave 3-(2-benzyloxy)-2-(toluene-4-sulfonylamino)propionic acid, 3-(2-chlorobenzyloxy)-2-(toluene-4-sulfonylamino)propionic acid, and 3-(3,5-dimethylbenzyloxy)-2-(toluene-4-sulfonylamino)propionic acid respectively.

Proceeding as described in Example 1 above, but substituting *N*-(2,2-dimethylpropyl)-2-(toluene-4-sulfonylamino)succinamic acid with 3-(2-methylbenzyloxy)-2-(toluene-4-sulfonylamino)propionic acid, 3-(2-benzyloxy)-2-(toluene-4-sulfonylamino)propionic acid, 3-(2-chlorobenzyloxy)-2-(toluene-4-sulfonylamino)propionic acid, and 3-(3,5-dimethylbenzyloxy)-2-(toluene-4-sulfonylamino)propionic acid gave:

3-(2-Methyl-benzyloxy)-N-{1-[3-methyl-1-(5-phenyl-[1,3,4]oxadiazol-2-ylcarbonyl)-butylcarbamoyl]ethyl}-2-(toluene-4-sulfonylamino)propionamide. 400MHz ^{1}H-NMR (DMSO-d6) δ 8.4 (d, 1H), 8.2 (d, 1H), 8.05 (d, 2H), 8.0 (d, 1H), 7.6 (m, 5H), 7.2 (d, 2H), 7.1 (m, 4H), 5.05 (m, 1H), 4.3 (s, 2H), 4.1 (m, 1H),

4.05 (m, 1H), 3.4 (m, 2H), 2.3 (s, 3H), 2.1 (s, 3H), 1.7 (m, 2H), 1.45 (m, 1H), 1.0 (m, 3H), 1.0 (m, 6H). MS (electrospray): mH^+ 676.6 (100%);

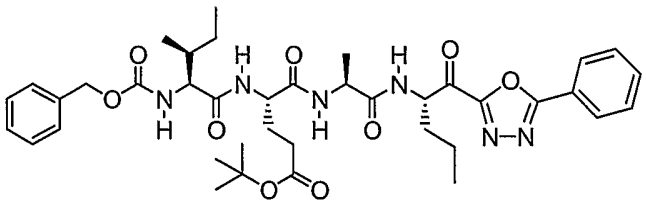
3-Benzyloxy-N-{2-methoxy-1-[3-methyl-1-(5-phenyl-[1,3,4]oxadiazol-2-ylcarbonyl)-butylcarbamoyl]ethyl}-2-(toluene-4-sulfonylamino)propionamide. 400MHz ^{1}H-NMR (DMSO-d6) δ 8.55 (d, 1H), 8.2 (d, 1H), 8.1 (d, 2H), 8.05 (d, 1H), 7.6 (m, 5H), 7.2 (m, 7H), 5.15 (m, 1H), 4.35 (m, 1H), 4.25 (s, 2H), 4.1 (m, 1H), 3.4 (m, 2H), 3.2 (m, 2H), 3.1 (s, 3H), 2.3 (s, 3H), 1.7 (m, 2H), 1.5 (m, 1H), 0.9 (m, 6H). MS (electrospray): mH^+ 692.4 (100%);

3-(2-Chlorobenzyloxy)-N-{2-methoxy-1-[3-methyl-1-(5-phenyl-[1,3,4]oxadiazol-2-ylcarbonyl)-butylcarbamoyl]-ethyl}-2-(toluene-4-sulfonylamino)-propionamide. 400MHz ^{1}H-NMR (DMSO-d6) δ 8.2 (d, 2H), 7.8 (d, 2H), 7.6 (m, 1H), 7.55 (m, 4H), 7.5 (m, 1H), 7.3 (m, 1H), 7.2 (m, 5H), 5.6 (m, 1H), 5.5 (m, 1H), 4.6 (m, 1H), 4.4 (m, 2H), 3.8 (m, 2H), 3.4 (m, 2H), 3.25 (s, 3H), 2.4 (s, 3H), 1.0 (m, 6H), 0.95 (m, 3H). MS (electrospray): mH^+ 726.4 (100%); and

3-(3,5-Dimethylbenzyloxy)-N-{2-methoxy-1-[3-methyl-1-(5-phenyl-[1,3,4]oxadiazol-2-ylcarbonyl)-butylcarbamoyl]ethyl}-2-(toluene-4-sulfonylamino)propionamide. 400MHz ^{1}H-NMR (DMSO-d6) δ 8.2 (d, 2H), 7.7 (d, 1H), 7.6 (m, 5H), 7.4 (m, 1H), 7.3 (m, 2H), 6.9 (s, 1H), 6.8 (s, 2H), 5.5 (m, 1H), 4.3 (m, 2H), 3.8 (m, 2H), 3.35 (s, 2H), 2.4 (s, 3H), 2.3 (s, 6H), 0.95 (m, 6H), 0.8 (s, 9H). MS (electrospray): mH^+ 720.5 (100%), respectively.

Example 3

Synthesis of 4-(2-benzyloxycarbonylamino-3*S*-methylpentanoylamino)-4*S*-{1*S*-[1*S*-(5-phenyl-[1,3,4]-oxadiazol-2-ylcarbonyl)butylcarbamoyl]ethylcarbamoyl}butyric acid *tert*-butyl ester



Step 1

Carbobenzyloxy-L-isoleucine succinate ester (2.17 g, 6.0 mmol), L-glutamic acid γ-t-butyl ester (1.22 g, 6.0 mmol) and triethylamine (1.67 mL, 12.0 mmol) were

stirred at ambient temperature in a mixture of THF (98 mL) and water (9 mL) for 16 hr. The reaction mixture was poured into 0.2N aqueous HCl (200 mL) and extracted twice with dichloromethane. The combined organic phase was washed with water and brine, then dried over anhydrous magnesium sulfate. Filtration and solvent evaporation gave a sticky white foam that was triturated with a mixture of diethyl ether (15 mL) and n-hexane (20 mL). The white precipitate was collected and dried to give 1.84g of 2-(2-benzyloxycarbonylamino-3-methylpentanoylamino)-pentanedioic acid 5-*tert*-butyl ester (68% yield).

Step 2

2-(2-Benzyloxycarbonylamino-3-methylpentanoylamino)pentanedioic acid 5-*tert*-butyl ester (1.73 g, 3.84 mmol) and N-hydroxysuccinimide (442 mg, 3.84 mmol) were dissolved in dry THF (30 mL). Dicyclohexylcarbodiimide (792 mg, 3.84 mmol) was added at ambient temperature. After 30 min., the reaction mixture was cooled to 0-5 °C and left for 14 hr. The precipitate was filtered and rinsed with 5 ml THF. The combined filtrate was rotary evaporated and the resulting sticky white foam was triturated with diethyl ether. Filtration and drying gave 2.06 g of 2-(2-benzyloxycarbonylamino-3-methyl-pentanoylamino)-pentanedioic acid 5-*tert*-butyl ester 5-(2,5-dioxopyrrolidin-1-yl) ester (96% yield).

Step 3

2-(2-Benzyloxycarbonylamino-3-methyl-pentanoylamino)-pentanedioic acid 5-*tert*-butyl ester 5-(2,5-dioxopyrrolidin-1-yl) ester (2.01g, 3.67 mmol) was dissolved in THF (40 mL) at ambient temperature. Triethylamine (0.51 mL, 7.34 mmol) was added. A suspension of L-alanine (327 mg, 3.67 mmol) in 50% aqueous THF (10 mL) was then added with stirring. The pH of the reaction mixture was adjusted to 8 by occasional addition of more triethylamine. The reaction mixture was stirred at ambient temperature for 14.5 hr, then poured into 200 mL 0.2N aqueous HCl. The product was extracted twice with 100 mL portions of dichloromethane. The combined organic phase was washed with water and brine, then dried over anhydrous magnesium sulfate. Filtration and solvent evaporation gave a sticky white foam that was triturated with diethyl ether. Filtration and drying gave 1.35g of 4-(2-benzyloxycarbonylamino-3-methyl-pentanoylamino)-4-(1-carboxy-ethylcarbamoyl)-butyric acid *tert*-butyl ester as a white solid (a 71% yield).

Step 4

4-(2-Benzyloxycarbonylamino-3-methylpentanoylamino)-4-(1-carboxyethylcarbamoyl)-butyric acid *tert*-butyl ester (202 mg, 0.39 mmol) was dissolved in anhydrous THF (10 mL) and stirred under an atmosphere of dry nitrogen in a methanol-ice bath. N-methyl morpholine (64 μL, 0.585 mmol) and isobutyl chloroformate (50 μL, 0.39 mmol) were added. After 10 minutes, 2-amino-1-(5-phenyl-[1,3,4]oxadiazol-2-yl)pentan-1-ol hydrochloride (110 mg, 0.39 mmol), which had been prepared according to the method detailed in Reference 12 of WO 00/55144, substituting (S)-2-*tert*-butoxycarbonylamino-4-methylpentanoic acid for (*S*)-2-*tert*-butoxycarbonylamino-4-phenylbutyric acid, was added in one portion, followed by the addition of N-methylmorpholine (64 μL, 0.585 mmol). After 1 hr, the reaction mixture was partitioned between 0.5N aq. HCl and dichloromethane in a separatory funnel. The organic phase was separated and washed with water, sat. aq. sodium bicarbonate, and brine. Drying over magnesium sulfate followed by filtration and solvent evaporation gave a residue that was flash chromatographed on silica gel, eluting with 2.5/5.0/92.5 methanol/ acetone/ dichloromethane to give 96.7 mg of 4-(2-benzyloxy-carbonylamino-3-methyl-pentanoylamino)-4-(1-{1-[hydroxy-(5-phenyl-[1,3,4]oxadiazol-2-yl)methyl]butylcarbamoyl}ethylcarbamoyl)butyric acid *tert*-butyl ester as a foam (a 33% yield).

Step 5

4-(2-Benzyloxy-carbonylamino-3-methyl-pentanoylamino)-4-(1-{1-[hydroxy-(5-phenyl-[1,3,4]oxadiazol-2-yl)methyl]butylcarbamoyl}ethylcarbamoyl)butyric acid *tert*-butyl *ester* (90.0 mg, 0.12 mmol) was dissolved in 6 mL of water-saturated dichloromethane. The solution was stirred at ambient temperature and the Dess-Martin periodinane (76 mg, 0.18 mmol) was added. After 3.5 hr, an additional 76 mg of the Dess-Martin periodinane was added and the solution was stirred for 14 hr. A solution of 0.26M sodium thiosulfate (20 mL) dissolved in sat. aq. sodium bicarbonate was added and the reaction mixture was stirred vigorously for 30 min. The organic phase was separated, washed with sat. aq. sodium bicarbonate and brine, then dried over magnesium sulfate. Filtration and solvent evaporation gave a residue that was flash chromatographed on silica, eluting with 2.5/5.0/92.5 methanol/ acetone/dichloromethane to give 49 mg of the title compound (55% yield).

270MHz ^{1}H-NMR (CD_3OD) δ 8.16 (m, 1H), 8.14 (m, 2H), 7.60 (m, 4H), 7.33 (m, 7H), 5.28 (dd, 1H), 5.1 (m, 2H), 4.1 – 4.5 (m, 3H), 3.8 – 4.0 (m, 1H), 2.15 – 2.40 (m, 2H), 1.6 – 2.15 (m, 4H), 1.1 – 1.6 (m, 19H), 0.89 (dt, 6H).

Proceeding as described in Example 3 above, and using appropriate starting materials the following compounds of Formula I were prepared:

4-{1-[1-(Benzooxazol-2-ylcarbonyl)-3-methylbutylcarbamoyl]ethylcarbamoyl}-4-(2-benzyloxycarbonylamino-3-methylpentanoylamino)butyric acid *tert*-butyl ester. 270MHz ^{1}H-NMR (DMSO-d6) δ 8.51 (bt, 1H), 7.95 (m, 3H), 7.65 (t, 1H), 7.55 (t, 1H), 7.35 (m, 7H), 5.36 (m, 1H), 5.03 (s, 2H), 4.2 – 4.4 (m, 2H), 3.89 (t, 1H), 2.21 (m, 2H), 1.5 – 2.0 (m, 7H), 1.35 (m, 9H), 0.7 – 1.3 (m, 16H).

4-{1-[1-(Benzooxazol-2-ylcarbonyl)-3-methylbutylcarbamoyl]ethylcarbamoyl}-4-benzyloxycarbonylaminobutyric acid *tert*-butyl ester. 400MHz ^{1}H-NMR (DMSO-d6) δ 8.5 (d, 1H), 8.0 (m, 2H), 7.9 (d, 1H), 7.5 (m, 2H), 7.4 (d, 1H), 7.3 (m, 5H), 5.3 (m, 1H), 5.0 (s, 2H), 4.3 (m, 1H), 4.0 (m, 1H), 2.1 (m, 2H), 1.8-1.6 (m, 5H), 1.2 (s, 9H), 1.2 (d, 3H), 0.9 (m, 6H). MS (electrospray): mH^+ 623.6 (100%).

In the compounds listed above, all the chiral carbons in the molecules have S-stereochemistry.

Biological Assays

Determination of the efficacy of the compounds of this invention, *in vitro*

The efficacy of the compounds of this invention was evaluated by determining their effect on human tumor cell proliferation. Then, a cell-associated p21 accumulation assay was carried out to demonstrate that the effects on cell proliferation were mediated by the inhibition of the 26S proteasome.

a. Cell proliferation assay: The effects of the compounds of this invention on human tumor cell proliferation were monitored in an alamar Blue™ fluorometric assay as described by de Fries and Mitsuhashi (*see.*, "Quantification of mitrogen induced lymphocyte proliferation:comparison of alamar Blue™ assay to ^{3}H-thymidine incorporation assay" J. Clin. Invest., 9:89-95).

Briefly, 5000 cells per well were plated in 96-well plates in complete media and each cell line was exposed to the test compound for a period of 48 hr (two

doubling times). Each well, including the controls, contained 0.2 % DMSO. The alamar Blue™ reagent was added to cells at 44 hr and the plates were incubated for 4 hr at 37°C. At 48 hr, the fluorescence was determined using the plate reader and IC_{50} values were calculated for each compound. Compounds of the invention tested by the above-described assay inhibited cell proliferation.

b. Cell-associated p21 accumulation immunoblotting assay: Human tumor cell-associated p21 levels were detected by western blot analysis. Briefly, cells were cultured in 24-well plates to 80% confluence. Media was changed and replaced with media containing increasing concentrations of the compounds of the invention and the cells were cultured in the presence of compound for 16 hr. At the end of the 16 hr incubation period, cells were washed with PBS, lysed with lysis buffer (1X SDS-PAGE/BME) and boiled for 5 min. Samples were electrophoresed through 12% Tris-glycine SDS-PAGE gels (NOVEX). Proteins in the gel were transferred to nitrocellulose membranes and probed with mouse monoclonal antibodies against p21 (Pharmingen). The blots were washed and incubated with a peroxidase-conjugated affinipure donkey anti-mouse secondary antibody (Jackson ImmunoResearch Laboratories, Inc., PA). Antigen-antibody complexes were visualized by chemiluminescence with the Pierce SuperSignal West Pico Kit (Rockford, IL) and imaged by autoradiography. Compounds of the invention tested by the above-described assay demonstrated that the effects on cell proliferation were mediated by the inhibition of the 26S proteasome.

Example 2

Inhibition of human 20S proteasome, *in vitro*

Human 20S proteasome (from Affiniti Research Products Ltd., Mamhead, Exeter, U.K., final concentration 1 to 3 nM) and test compounds (present at variable concentrations, final DMSO concentration 5%) were incubated for 60 minutes at room temperature in assay medium (50 mM Tris, 50 mM NaCl, 0.5 mM EDTA, 0.05% Tween-20, 0.035% SDS, pH = 7.4). Reactions were initiated with the addition of Suc-Leu-Leu-Val-Tyr-AMC substrate (Bachem Bioscience Inc., King of Prussia, PA USA, final concentration 50 μM) following the 60-minute incubation phase. Hydrolysis of the substrate was measured using an fMax plate reader (Molecular Devices, Sunnyvale, CA) for 10 minutes at room temperature with a 355 +/- 38 nm excitation filter and a 460 +/- 25 nm emission filter. Initial velocity measurements

calculated from the progress curves using the kinetic analysis program Batch Ki (Biokin, Ltd., Pullman, WA USA) were used to determine apparent inhibition constants (Ki app).

Compounds of the invention tested by the above-described assay exhibited inhibition of human 20S proteasome.

Pharmaceutical Composition Examples

The following are representative pharmaceutical formulations containing a compound of Formula I.

Tablet Formulation

The following ingredients are mixed intimately and pressed into single scored tablets.

Ingredient	Quantity per tablet, mg
compound of this invention	400
cornstarch	50
croscarmellose sodium	25
lactose	120
magnesium stearate	5

Capsule Formulation

The following ingredients are mixed intimately and loaded into a hard-shell gelatin capsule.

Ingredient	Quantity per capsule, mg
compound of this invention	200
lactose, spray-dried	148
magnesium stearate	2

Suspension Formulation

The following ingredients are mixed to form a suspension for oral administration.

Ingredient	Amount
compound of this invention	1.0 g
fumaric acid	0.5 g
sodium chloride	2.0 g
methyl paraben	0.15 g
propyl paraben	0.05 g
granulated sugar	25.5 g
sorbitol (70% solution)	12.85 g
Veegum K (Vanderbilt Co.)	1.0 g

flavoring	0.035 ml
colorings	0.5 mg
distilled water	q.s. to 100 ml

Injectable Formulation

The following ingredients are mixed to form an injectable formulation.

Ingredient	Amount
compound of this invention	1.2 g
sodium acetate buffer solution,	0.4 M 2.0 ml
HCl (1 N) or NaOH (1 N)	q.s. to suitable pH
water (distilled, sterile)	q.s.to 20 ml

All of the above ingredients, except water, are combined and heated to 60-70 °C with stirring. A sufficient quantity of water at 60 °C is then added with vigorous stirring to emulsify the ingredients, and water then added q.s. to 100 g.

Suppository Formulation

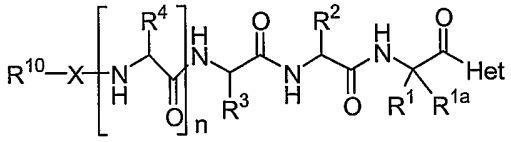
A suppository of total weight 2.5 g is prepared by mixing the compound of the invention with Witepsol® H-15 (triglycerides of saturated vegetable fatty acid; Riches-Nelson, Inc., New York), and has the following composition:

compound of the invention	500 mg
Witepsol® H-15	balance

The foregoing invention has been described in some detail by way of illustration and example, for purposes of clarity and understanding. It will be obvious to one of skill in the art that changes and modifications may be practiced within the scope of the appended claims. Therefore, it is to be understood that the above description is intended to be illustrative and not restrictive. The scope of the invention should, therefore, be determined not with reference to the above description, but should instead be determined with reference to the following appended claims, along with the full scope of equivalents to which such claims are entitled.

What is Claimed:

1. A compound of Formula I:



I

wherein:

n is 0 or 1;

R^{1a} is hydrogen or alkyl;

R^1 is alkyl, haloalkyl, hydroxyalkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylthioalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, alkoxyalkyl, or aralkyl; or

R^1 and R^{1a} together with the carbon atom to which they are attached form cycloalkyl or heterocycloalkyl;

R^2 is alkyl, hydroxyalkyl, alkylthioalkyl, or alkoxyalkyl;

R^3 is $-(C_{1-3})$-CONH-CHR^{6}R^7 (where R^6 is hydrogen or alkyl and R^7 is branched (C_{4-10})alkyl or cycloalkyl), $-(C_{1-3})$-COOR^8 (where R^8 is branched (C_{4-10})alkyl or cycloalkyl), or $-(C_{1-3})$-Y-$(C_{1-3})_{n1}$Ar (where Y is –O-, NH-, or $-S(O)_{n2}$- where n2 is 0 to 2, n1 is 0 or 1, and Ar is aryl);

R^4 is alkyl or haloalkyl;

X is –CO-, -OCO-, $-SO_2$-, -NR^{9}CO-, -NR^{9}CS-, or -NR$^9SO_2$- where R^9 is hydrogen or alkyl;

R^{10} is alkyl, aryl, aralkyl, or heteroaryl; or

R^9 and R^{10} together with the nitrogen atom to which they are attached form heterocycloamino; and

Het is a heteroaryl ring; or

a pharmaceutically acceptable salt thereof.

2. The compound of Claim 1 where:

n is 0;

R^{1a} is hydrogen;

R^1 is alkyl or aralkyl;

R^2 is alkyl, hydroxyalkyl, alkylthio, alkylthioalkyl, or alkoxyalkyl;

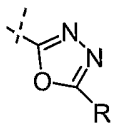
R^3 is $-(C_{1-3})$-CONHCHR^{5}R^6 where R^5 is hydrogen or alkyl and R^6 is branched (C_{4-10})alkyl or cycloalkyl, $-(C_{1-3})$-COOR^8 (where R^8 is branched (C_{4-10})alkyl or

cycloalkyl), or $-(C_{1-3})$-Y-$(C_{1-3})_{n1}$Ar (where Y is –O-, -NH-, or $-S(O)_{n2}$- where n2 is 0 to 2, n1 is 0 or 1, and Ar is aryl);

X is –CO-, -OC(O)-, $-SO_2$-, or $-NR^9SO_2$- where R^9 is alkyl;

R^{10} is alkyl, aryl, or heteroaryl; and

Het is a ring of the formula:



where R is alkyl, haloalkyl, alkoxyalkyl, optionally substituted aryl, or optionally substituted heteroaryl.

3. The compound of Claim 1 where n is 0, R^{1a} is hydrogen; R^1 is alkyl; R^2 is alkyl, hydroxyalkyl, or alkoxyalkyl; R^3 is $-(C_{1-3})$-CONH-CHR^5R^6 where R^5 is hydrogen or alkyl and R^6 is branched (C_{4-10})alkyl or cycloalkyl; X is $-SO_2$-; and R^{10} is aryl.

4. The compound of Claim 1 where n is 0, Het is 1,3,4-oxadiazol-2-yl which is substituted at the 5-position with methyl, ethyl, 2-propyl, trifluoromethyl, methoxy, or optionally substituted phenyl; R^{1a} is hydrogen; R^1 is methyl, ethyl, 1-methylpropyl, 2-methylpropyl, 2,2-dimethylpropyl, or benzyl; R^2 is methyl, ethyl, methoxymethyl, *tert*-butoxymethyl, hydroxymethyl, 1-hydroxyethyl, or methylthiomethyl; R^3 is $-CH_2CONHCH_2C(CH_3)_3$ or $-(CH_2)_2CONHC(CH_3)_3$; X is $-SO_2$-; and R^{10} is aryl.

5. The compound of Claim 1 where n is 0, Het is 1,3,4-oxadiazol-2-yl which is substituted at the 5-position with methyl, ethyl, 2-propyl, trifluoromethyl, methoxy, 4-dimethylaminophenyl, pyridin-4-yl, furanyl, 4-methylphenyl, 4-trifluoromethylphenyl, or phenyl; R^{1a} is hydrogen;

R^1 is methyl, ethyl, 1-methylpropyl, 2-methylpropyl, 2,2-dimethylpropyl, or benzyl; R^2 is methyl, ethyl, methoxymethyl, *tert*-butoxymethyl, hydroxymethyl, 1-hydroxyethyl, or methylthiomethyl; R^3 is $-CH_2CONHCH_2C(CH_3)_3$ or $-(CH_2)_2CONHC(CH_3)_3$; X is $-SO_2$-; and R^{10} is phenyl optionally substituted with alkyl.

6. The compound of Claim 1 where n is 0, Het is 1,3,4-oxadiazol-2-yl which is substituted at the 5-position with methyl, ethyl, 2-propyl, trifluoromethyl, methoxy, 4-

dimethylaminophenyl, pyridin-4-yl, furanyl, 4-methylphenyl, 4-trifluoromethylphenyl, or phenyl; R^{1a} is hydrogen;

R^1 is methyl, ethyl, 1-methylpropyl, 2-methylpropyl, 2,2-dimethylpropyl, or benzyl;

R^2 is methyl, ethyl, methoxymethyl, *tert*-butoxymethyl, hydroxymethyl, 1-hydroxyethyl, or methylthiomethyl; R^3 is $-CH_2CONHCH_2C(CH_3)_3$ or $-(CH_2)_2CONHCH_2C(CH_3)_3$; X is $-SO_2-$; and R^{10} is 4-methylphenyl or 3-methylphenyl.

7. A compound selected from the group consisting of:

N4-(2,2-dimethylpropyl)-N1-{2-methoxy-1*S*-[3-methyl-1*S*-(5-phenyl-[1,3,4]oxadiazol-2-ylcarbonyl)butylcarbamoyl]ethyl}-2*S*-(toluene-4-sulfonylamino)succinamide;

4-{1-[3-Methyl-1-(5-phenyl-[1,3,4]oxadiazol-2-ylcarbonyl)-butylcarbamoyl]-ethylcarbamoyl}-4-(toluene-4-sulfonylamino)butyric acid *tert*-butyl ester;

N4-(2,2-Dimethylpropyl)-N1-{1-[3-methyl-1-(5-phenyl-[1,3,4]oxadiazol-2-ylcarbonyl)-butylcarbamoyl]ethyl}-2-(toluene-4-sulfonylamino)succinamide;

N4-(2,2-Dimethyl-propyl)-N1-{1-[1-(5-ethyl-[1,3,4]oxadiazol-2-ylcarbonyl)-3-methyl-butylcarbamoyl]-ethyl}-2-(toluene-4-sulfonylamino)-succinamide;

N1-{2-*tert*-Butoxy-1-[3-methyl-1-(5-phenyl-[1,3,4]oxadiazol-2-ylcarbonyl)-butylcarbamoyl]ethyl}-N4-(2,2-dimethylpropyl)-2-(toluene-4-sulfonylamino)-succinamide;

N4-(2,2-Dimethylpropyl)-N1-{2-hydroxy-1-[3-methyl-1-(5-phenyl-[1,3,4]oxadiazol-2-ylcarbonyl)butylcarbamoyl]-ethyl}-2-(toluene-4-sulfonylamino)-succinamide;

N4-(2,2-Dimethylpropyl)-N1-{1-[3-methyl-1-(5-phenyl-[1,3,4]oxadiazol-2-ylcarbonyl)-butylcarbamoyl]ethyl}-2-(toluene-3-sulfonylamino)succinamide;

N1-(1-{1-[5-(4-Dimethylaminophenyl)-[1,3,4]oxadiazol-2-ylcarbonyl]-3-methyl-butylcarbamoyl}ethyl)-N4-(2,2-dimethylpropyl)-2-(toluene-4-sulfonylamino)succinamide;

N4-(2,2-Dimethylpropyl)-N1-{1-[1-(5-isopropyl-[1,3,4]oxadiazol-2-ylcarbonyl)-3-methyl-butylcarbamoyl]ethyl}-2-(toluene-4-sulfonylamino)succinamide;

N4-(2,2-Dimethylpropyl)-N1-{1-[3-methyl-1-(5-pyridin-4-yl-[1,3,4]oxadiazol-2-ylcarbonyl)butylcarbamoyl]ethyl}-2-(toluene-4-sulfonylamino)succinamide;

N4-(2,2-Dimethylpropyl)-N1-{1-[1-(5-isopropyl-[1,3,4]oxadiazol-2-ylcarbonyl)-3-methylbutylcarbamoyl]ethyl}-2-(dimethylaminosulfonylamino)succinamide;

N4-(2,2-Dimethylpropyl)-N1-{2-methoxy-1-[3-methyl-1-(5-phenyl-[1,3,4]oxadiazol-2-ylcarbonyl)butylcarbamoyl]ethyl}-2-(4-sulfamoylbenzoylamino)-succinamide;

N4-(2,2-Dimethylpropyl)-N1-{2-hydroxy-1-[3-methyl-1-(5-phenyl-[1,3,4]oxadiazol-2-ylcarbonyl)butylcarbamoyl]propyl}-2-(toluene-4-sulfonylamino)succinamide;

N4-(2,2-Dimethylpropyl)-N1-{2-methoxy-1-[3-methyl-1-(5-phenyl-[1,3,4]oxadiazol-2-ylcarbonyl)butylcarbamoyl]ethyl}-2-(dimethylaminosulfonylamino)succinamide;

N4-(2,2-Dimethylpropyl)-N1-{1-[1-(5-furan-2-yl-[1,3,4]oxadiazol-2-ylcarbonyl)-3-methylbutylcarbamoyl]ethyl}-2-(toluene-4-sulfonylamino)succinamide;

N1-(1-{1-[5-(4-Dimethylaminophenyl)-[1,3,4]oxadiazol-2-ylcarbonyl]-3-methyl-butylcarbamoyl}-2-methoxyethyl)-N4-(2,2-dimethylpropyl)-2-(toluene-4-sulfonylamino)-succinamide;

N4-(2,2-Dimethylpropyl)-N1-{1-[2-methyl-1-(5-phenyl-[1,3,4]oxadiazol-2-ylcarbonyl)-butylcarbamoyl]ethyl}-2-(toluene-4-sulfonylamino)succinamide;

N4-(2,2-Dimethylpropyl)-2-methanesulfonylamino-N1-{1-[3-methyl-1-(5-phenyl-[1,3,4]oxadiazol-2-ylcarbonyl)butylcarbamoyl]ethyl}succinamide;

N4-(2,2-Dimethylpropyl)-N1-{1-[3-methyl-1-(5-*p*-tolyl-[1,3,4]oxadiazol-2-ylcarbonyl)-butylcarbamoyl]ethyl}-2-(toluene-4-sulfonylamino)succinamide;

N4-(2,2-Dimethylpropyl)-N1-(1-{3-methyl-1-[5-(4-trifluoromethylphenyl)-[1,3,4]oxadiazol-2-ylcarbonyl]butylcarbamoyl}ethyl)-2-(toluene-4-sulfonylamino)-succinamide;

3-(2-Methylbenzyloxy)-N-{1-[3-methyl-1-(5-phenyl-[1,3,4]oxadiazol-2-ylcarbonyl)-butylcarbamoyl]ethyl}-2-(toluene-4-sulfonylamino)propionamide;

3-Benzyloxy-N-{2-methoxy-1-[3-methyl-1-(5-phenyl-[1,3,4]oxadiazol-2-ylcarbonyl)-butylcarbamoyl]ethyl}-2-(toluene-4-sulfonylamino)propionamide;

3-(2-Chlorobenzyloxy)-N-{2-methoxy-1-[3-methyl-1-(5-phenyl-[1,3,4]oxadiazol-2-ylcarbonyl)-butylcarbamoyl]-ethyl}-2-(toluene-4-sulfonylamino)-propionamide;

3-(3,5-Dimethylbenzyloxy)-N-{2-methoxy-1-[3-methyl-1-(5-phenyl-[1,3,4]oxadiazol-2-ylcarbonyl)-butylcarbamoyl]ethyl}-2-(toluene-4-sulfonylamino)propionamide;

4-(2-benzyloxycarbonylamino-3-methyl-pentanoylamino)-4-{1-[1-(5-phenyl-[1,3,4]-oxadiazol-2-ylcarbonyl)-butylcarbamoyl]-ethylcarbamoyl}-butyric acid *tert*-butyl ester;

4-{1-[1-(Benzooxazol-2-ylcarbonyl)-3-methylbutylcarbamoyl]ethylcarbamoyl}-4-(2-benzyloxycarbonylamino-3-methylpentanoylamino)butyric acid *tert*-butyl ester; and

4-{1-[1-(Benzooxazol-2-ylcarbonyl)-3-methylbutylcarbamoyl]ethylcarbamoyl}-4-benzyloxycarbonylaminobutyric acid *tert*-butyl ester; and individual stereoisomers and mixture of stereoisomers; or a pharmaceutically acceptable salt thereof.

8. The compounds of Claim 7 where all the chiral carbons have S stereochemistry.

9. A pharmaceutical composition comprising a therapeutically effective amount of a compound of any of the Claims 1-8 and a pharmaceutically acceptable excipient.

9. A method of treating a disorder mediated by the proteolytic function of the proteasome in an animal suffering said disorder, comprising administering to said animal a pharmaceutical composition comprising a therapeutically effective amount of a compound of any of the Claims 1-8 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient.

10. The method of Claim 9 wherein the disorder is a cancer, autoimmune disease such as asthma and multiple sclerosis, graft rejection, inflammatory diseases, and septic shock.

11. A method of treating cancer in an animal which method comprises administering to said animal a pharmaceutical composition comprising a therapeutically effective amount of a compound of any of the Claims 1-8 and a pharmaceutically acceptable excipient in combination with radiation therapy and optionally in combination with one or more chemotherapeutic compound(s) independently selected from an estrogen receptor modulator, an androgen receptor modulator, retinoid receptor modulator, a cytotoxic agent, another antiproliferative agent, a prenyl-protein transferase inhibitor, an HMG-CoA reductase inhibitor, an

HIV protease inhibitor, a reverse transcriptase inhibitor, or an angiogenesis inhibitor.

12. The method of Claim 11 wherein the chemotherapeutic compound(s) is independently selected from Taxol®, Taxotere®, epothilone A, epothilone B, desoxyepothilone A, desoxyepothilone B or their derivatives); epidophyllotoxin; procarbazine; mitoxantrone; the mitomycins, discodermolide, podophyllotoxins, doxorubicin, carminomycin, daunorubicin, aminopterin, methotrexate, methopterin, dichloromethotrexate, mitomycin C, porfiromycin, Herceptin®, Rituxan®, 5-fluorouracil, 6-mercaptopurine, gemcitabine, cytosine arabinoside, colchicines, etoposide, etoposide phosphate, teniposide, melphalan, vinblastine, vincristine, leurosidine, vindesine, leurosine, estramustine, cisplatin, carboplatin, cyclophosphamide, bleomycin, tamoxifen, ifosamide, melphalan, hexamethyl melamine, thiotepa, cytarabin, idatrexate, trimetrexate, dacarbazine, L-asparaginase, camptothecin, CPT-11, topotecan, ara-C, bicalutamide, flutamide, leuprolide, pyridobenzoindole derivatives, interferons, and interleukins.