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(54) Title: CYSTEINE PROTEASE INHIBITORS

(57) Abstract: The present invention relates to compounds, compositions and methods for treating diseases associated with cysteine protease activity, particularly diseases associated with activity of cathepsins B, K, L or S.The present invention thus provides compounds of Formula I: pharmaceutical compositions comprising compounds of Formula I and methods of treating diseases associated with cysteine protease activity using pharmaceutical compositions comprising compounds of Formula I.

CYSTEINE PROTEASE INHIBITORS

THE INVENTION

The present invention relates to compounds, compositions and methods for treating diseases associated with cysteine protease activity, particularly diseases associated with activity of cathepsins B, K, L or S.

DESCRIPTION OF THE FIELD

Cysteine proteases represent a class of peptidases characterized by the presence of a cysteine residue in the catalytic site of the enzyme. Cysteine proteases are associated with the normal degradation and processing of proteins. The aberrant activity of cysteine proteases, e.g., as a result of increase expression or enhanced activation, however, may have pathological consequences. In this regard, certain cysteine proteases are associated with a number of disease states, including arthritis, muscular dystrophy, inflammation, tumor invasion, glomerulonephritis, malaria, periodontal disease, metachromatic leukodystrophy and others. For example, increased cathepsin B levels and redistribution of the enzyme are found in tumors; thus, suggesting a role for the enzyme in tumor invasion and metastasis. In addition, aberrant cathepsin B activity is implicated in such disease states as rheumatoid arthritis, osteo arthritis, pneumocystis carinii, acute pancreatitis, inflammatory airway disease and bone and joint disorders.

The prominent expression of cathepsin K in osteoclasts and osteoclast-related multinucleated cells and its high collagenolytic activity suggest that the enzyme is involved in ososteoclast-mediated bone resorption and, hence, in bone abnormalities such as occurs in osteoporosis. In addition, cathepsin K expression in the lung and its elastinolytic activity suggest that the enzyme plays a role in pulmonary disorders as well.

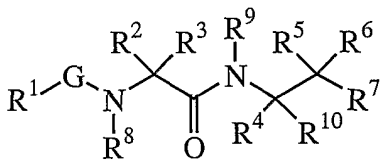
Cathepsin L is implicated in normal lysosomal proteolysis as well as several disease states, including, but not limited to, metastasis of melanomas. Cathepsin S is implicated in Alzheimer's disease and certain autoimmune disorders, including, but not

limited to juvenile onset diabetes, multiple sclerosis, pemphigus vulgaris, Graves' disease, myasthenia gravis, systemic lupus erythemotasus, rheumatoid arthritis and Hashimoto's thyroiditis; allergic disorders, including, but not limited to asthma; and allogeneic immune reponses, including, but not limited to, rejection of organ transplants or tissue grafts.

In view of the number of diseases wherein it is recognized that an increase in cysteine protease activity contributes to the pathology and/or symptomatology of the disease, molecules which are shown to inhibit the activity of this class of enzymes, in particular molecules which are inhibitors of cathepsins B, K, L and/or S, will be useful as therapeutic agents.

SUMMARY OF THE INVENTION

An aspect of the present invention are compounds of Formula I:



I

wherein:

R^1 represents (C_{1-6})alkyl or $-(CH_2)_{0-2}-Z^1-X^1$;

R^2 and R^3 together with the carbon atom to which both R^2 and R^3 are attached form a monocyclic or bridged polycyclic cycloalkylene moiety having from three to eight ring atoms or a monocyclic or bridged polycyclic heterocycloalkylene moiety having from three to eight ring atoms;

R^4 represents a group selected from (C_{1-6})alkyl, $-Y^1NR^{11}R^{11}$, $-Y^1NR^{11}C(O)OR^{11}$, $-Y^1NR^{11}C(O)NR^{11}R^{11}$, $-Y^1NR^{11}C(NR^{11})NR^{11}R^{11}$, $-Y^1OR^{11}$, $-Y^1SR^{11}$, $-Y^1C(O)OR^{11}$, $-Y^1C(O)NR^{11}R^{11}$, $-Y^1S(O)_2NR^{11}R^{11}$, $-Y^1P(O)(OR^{11})OR^{11}$, $-Y^1OP(O)(OR^{11})OR^{11}$, $-Y^1NR^{11}C(O)R^{12}$, $-Y^1S(O)R^{12}$, $-Y^1S(O)_2R^{12}$, $-Y^1C(O)R^{12}$, $-R^{13}$, $-Y^1OR^{13}$, $-Y^1SR^{13}$, $-Y^1S(O)R^{13}$, $-Y^1S(O)_2R^{13}$, $-Y^1C(O)R^{13}$, $-Y^1C(O)OR^{13}$, $-Y^1OC(O)R^{13}$, $-Y^1NR^{13}R^{14}$, $-Y^1NR^{14}C(O)R^{13}$, $-Y^1NR^{14}C(O)OR^{13}$, $-Y^1C(O)NR^{13}R^{14}$, $-Y^1S(O)_2NR^{13}R^{14}$, $-Y^1NR^{14}C(O)NR^{13}R^{14}$ and $-Y^1NR^{14}C(NR^{14})NR^{13}R^{14}$, wherein Y^1 is (C_{1-6})alkylene, R^{11} at

each occurrence independently is hydrogen, (C_{1-6})alkyl or halo-substituted (C_{1-3})alkyl, R^{12} is (C_{1-6})alkyl or halo-substituted (C_{1-3})alkyl, R^{13} is cycloalkyl(C_{0-6})alkyl, heterocycloalkyl(C_{0-6})alkyl, aryl(C_{0-6})alkyl or heteroaryl(C_{0-6})alkyl and R^{14} is hydrogen or (C_{1-6})alkyl and wherein within R^4 any alicyclic or aromatic ring may be substituted further with one to three groups independently selected from (C_{1-6})alkyl, (C_{1-6})alkylidene, (C_{1-6})alkylimino, cyano, halo, halo-substituted (C_{1-4})alkyl, imino, nitro, oxo, thioxo, $-Y^2NR^{11}R^{11}$, $-Y^2NR^{11}C(O)OR^{11}$, $-Y^2NR^{11}C(O)NR^{11}R^{11}$, $-Y^2NR^{11}C(NR^{11})NR^{11}R^{11}$, $-Y^2OR^{11}$, $-Y^2SR^{11}$, $-Y^2C(O)OR^{11}$, $-Y^2C(O)NR^{11}R^{11}$, $-Y^2S(O)_2NR^{11}R^{11}$, $-Y^2P(O)(OR^{11})OR^{11}$, $-Y^2OP(O)(OR^{11})OR^{11}$, $-Y^2NR^{11}C(O)R^{12}$, $-Y^2S(O)R^{12}$, $-Y^2S(O)_2R^{12}$ and $-Y^2C(O)R^{12}$, wherein Y^2 is a bond or (C_{1-6})alkylene and R^{11} and R^{12} are as defined above;

R^{10} represents hydrogen or (C_{1-6})alkyl; or

R^4 and R^{10} together with the carbon atom to which both R^4 and R^{10} are attached form a monocyclic or bridged polycyclic cycloalkylene moiety having from three to eight ring atoms or a monocyclic or bridged polycyclic heterocycloalkylene moiety having from three to eight ring atoms;

R^5 represents hydrogen and R^6 represents hydroxy; or

R^5 and R^6 together with the carbon atom to which both R^5 and R^6 are attached form a -C(O)- group;

R^7 represents a heteroaryl moiety having five to ten ring atoms or a heterocycloalkyl moiety having a five to ten ring atoms, wherein said heteroaryl or heterocycloalkyl moieties may be substituted with a group selected from $-R^{13}$, $-Y^2OR^{13}$, $-Y^2SR^{13}$, $-Y^2S(O)R^{13}$, $-Y^2S(O)_2R^{13}$, $-Y^2C(O)R^{13}$, $-Y^2C(O)OR^{13}$, $-Y^2OC(O)R^{13}$, $-Y^2NR^{13}R^{14}$, $-Y^2NR^{14}C(O)R^{13}$, $-Y^2NR^{14}C(O)OR^{13}$, $-Y^2C(O)NR^{13}R^{14}$, $-Y^2S(O)_2NR^{13}R^{14}$, $-Y^2NR^{14}C(O)NR^{13}R^{14}$ and $-Y^2NR^{14}C(NR^{14})NR^{13}R^{14}$, wherein Y^2 is a bond or (C_{1-6})alkylene, R^{13} is cycloalkyl(C_{0-6})alkyl, heterocycloalkyl(C_{0-6})alkyl, aryl(C_{0-6})alkyl or heteroaryl(C_{0-6})alkyl and R^{14} is hydrogen or (C_{1-6})alkyl and wherein within R^7 any alicyclic or aromatic ring may be substituted further with one to three groups independently selected from (C_{1-6})alkyl, (C_{1-6})alkylidene, (C_{1-6})alkylimino, cyano, halo, halo-substituted (C_{1-4})alkyl, imino, nitro, oxo, thioxo, $-Y^2NR^{11}R^{11}$, $-Y^2NR^{11}C(O)OR^{11}$, $-Y^2NR^{11}C(O)NR^{11}R^{11}$, $-Y^2NR^{11}C(NR^{11})NR^{11}R^{11}$, $-Y^2OR^{11}$, $-Y^2SR^{11}$, $-Y^2C(O)OR^{11}$,

$-Y^2C(O)NR^{11}R^{11}$, $-Y^2S(O)_2NR^{11}R^{11}$, $-Y^2P(O)(OR^{11})OR^{11}$, $-Y^2OP(O)(OR^{11})OR^{11}$, $-Y^2NR^{11}C(O)R^{12}$, $-Y^2S(O)R^{12}$, $-Y^2S(O)_2R^{12}$ and $-Y^2C(O)R^{12}$, wherein Y^2 is as defined above, R^{11} at each occurrence independently is hydrogen, (C_{1-6})alkyl or halo-substituted (C_{1-3})alkyl and R^{12} is (C_{1-6})alkyl or halo-substituted (C_{1-3})alkyl;

G represents –C(O)-, -C(S)-, $–C(CH_2)$-, -S(O)- or $–S(O)_2$-;

Z^1 represents arylene, heteroarylene, cycloalkylene or heterocycloalkylene;

X^1 represents hydrogen or $-(CH_2)_{0-3}$-L-$(CH_2)_{0-3}$-Z^2-X^2;

R^8 and R^9 independently represent hydrogen or (C_{1-6})alkyl;

n represents an integer from zero to two;

Z^2 represents arylene, heteroarylene, cycloalkylene or heterocycloalkylene;

X^2 represents hydrogen or $-(CH_2)_{0-3}$-L-$(CH_2)_{0-3}$-Z^3-X^3;

Z^3 represents arylene, heteroarylene, cycloalkylene or heterocycloalkylene;

X^3 represents hydrogen or $-(CH_2)_{0-3}$-L-$(CH_2)_{0-3}$-Z^4;

L represents a bond, -O-, $-S(O)_n$-, -C(O)O-, -OC(O)-, $-NR^{15}S(O)_2$-, $-C(O)NR^{15}$-$S(O)_2NR^{15}$-, $-NR^{15}C(O)$-, -C(O)-, $-NR^{15}C(O)O$-, $-C(O)ONR^{15}$-, $-NR^{15}$- or $-NR^{15}C(NR^{15})$-, wherein R^{15} represents hydrogen or (C_{1-4})alkyl; and

Z^4 represents aryl, heteroaryl, cycloalkyl or heterocycloalkyl; wherein within R^1 any alicyclic or aromatic ring may be substituted further with one to three groups independently selected from (C_{1-6})alkyl, (C_{1-6})alkylidene, (C_{1-6})alkylimino, cyano, halo, halo-substituted (C_{1-4})alkyl, imino, nitro, oxo, thioxo, $-Y^2NR^{11}R^{11}$, $-Y^2NR^{11}C(O)OR^{11}$, $-Y^2NR^{11}C(O)NR^{11}R^{11}$, $-Y^2NR^{11}C(NR^{11})NR^{11}R^{11}$, $-Y^2OR^{11}$, $-Y^2SR^{11}$, $-Y^2C(O)OR^{11}$, $-Y^2C(O)NR^{11}R^{11}$, $-Y^2S(O)_2NR^{11}R^{11}$, $-Y^2P(O)(OR^{11})OR^{11}$, $-Y^2OP(O)(OR^{11})OR^{11}$, $-Y^2NR^{11}C(O)R^{12}$, $-Y^2S(O)R^{12}$, $-Y^2S(O)_2R^{12}$ and $-Y^2C(O)R^{12}$, wherein Y^2 is a bond or (C_{1-6})alkylene, R^{11} at each occurrence independently is hydrogen, (C_{1-6})alkyl or halo-substituted (C_{1-3})alkyl and R^{12} is (C_{1-6})alkyl or halo-substituted (C_{1-3})alkyl; with the proviso that no more than one of Z^1, Z^2, Z^3 and Z^4 is a fused polycyclic moiety; and the prodrug derivatives, individual isomers and mixtures of isomers; and the pharmaceutically acceptable salts thereof.

Another aspect of the present invention is a pharmaceutical composition which contains a compound of Formula I or II, or a *N*-oxide derivative, prodrug derivative,

individual isomer or mixture of isomers, or a pharmaceutically acceptable salt thereof in admixture with one or more suitable excipients.

Another aspect of the present invention is method of treating a disease in an animal in which inhibition of a cysteine protease can prevent, inhibit or ameliorate the pathology and/or symptomatology of the disease, which method comprises administering to the animal a therapeutically effective amount of compound of Formula I or an individual isomer or mixture of isomers thereof, or prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

Another aspect of the present invention are the processes for preparing compounds of Formula I and the *N*-oxide derivatives, prodrug derivative, protected derivatives, individual isomers and mixtures of isomers and pharmaceutically acceptable salts thereof as set forth.

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 meanings given this Section:

"Alicyclic" means a moiety characterized by arrangement of the carbon atoms in closed non-aromatic ring structures having properties resembling those of aliphatics and may be saturated or partially unsaturated with two or more double or triple bonds.

"Aliphatic" means a moiety characterized by straight or branched chain arrangement of the constituent carbon atoms and may be saturated or partially unsaturated with two or more double or triple bonds.

"Alkyl" represented by itself means a straight or branched, saturated or unsaturated, aliphatic radical having the number of carbon atoms indicated (e.g. (C_{1-6})alkyl includes methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, isobutyl, *tert*-butyl, vinyl, allyl, 1-propenyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methylallyl, ethynyl, 1-propynyl, 2-propynyl, and the like). Alkyl represented along with another radical (e.g. as in arylalkyl) means a straight or branched, saturated or unsaturated

aliphatic divalent radical having the number of atoms indicated or when no atoms are indicated means a bond (e.g. (C_{6-12})aryl(C_{0-6})alkyl includes phenyl, benzyl, phenethyl, 1-phenylethyl 3-phenylpropyl, and the like).

"Alkylene", unless indicated otherwise, means a straight or branched, saturated or unsaturated, aliphatic, divalent radical having the number of carbon atoms indicated (e.g. (C_{1-6})alkylene includes methylene ($-CH_2-$), ethylene ($-CH_2CH_2-$), trimethylene ($-CH_2CH_2CH_2-$), 2-methyltrimethylene ($-CH_2CH(CH_3)CH_2-$), tetramethylene ($-CH_2CH_2CH_2CH_2-$), 2-butenylene ($-CH_2CH=CHCH_2-$), 2-methyltetramethylene ($-CH_2CH(CH_3)CH_2CH_2-$), pentamethylene ($-CH_2CH_2CH_2CH_2CH_2-$) and the like).

"Alkylidene" means a straight or branched saturated or unsaturated, aliphatic, divalent radical having the number of carbon atoms indicated (e.g. (C_{1-6})alkylidene includes methylene ($=CH_2$), ethylidene ($=CHCH_3$), isopropylidene ($=C(CH_3)_2$), propylidene ($=CHCH_2CH_3$), allylidene ($=CHCH=CH_2$), and the like).

"Amino" means the radical $-NH_2$. Unless indicated otherwise, the compounds of the invention containing amino moieties include *N*-oxide and protected derivatives thereof. Suitable protecting groups for amino moieties include acetyl, *tert*-butoxycarbonyl, benzyloxycarbonyl, and the like.

"Animal" includes humans, non-human mammals (e.g. dogs, cats, rabbits, cattle, horses, sheep, goats, swine, deer, or the like) and non-mammals (e.g. birds, or the like).

"Aryl" and means an aromatic monocyclic ring or fused polycyclic (i.e., fused bicyclic or tricyclic) ring system having, unless indicated otherwise, from six (6) to fourteen (14) ring carbon atoms. For example, aryl as used in this Application includes phenyl, naphthyl and anthracenyl. Aryl groups may be substituted with one to three groups independently select from (C_{1-6})alkyl, cyano, halo, halo-substituted (C_{1-4})alkyl, nitro, $-Y^2NR^{11}R^{11}$, $-Y^2NR^{11}C(O)OR^{11}$, $-Y^2NR^{11}C(O)NR^{11}R^{11}$, $-Y^2NR^{11}C(NR^{11})NR^{11}R^{11}$, $-Y^2OR^{11}$, $-Y^2SR^{11}$, $-Y^2C(O)OR^{11}$, $-Y^2C(O)NR^{11}R^{11}$, $-Y^2S(O)_2NR^{11}R^{11}$, $-Y^2P(O)(OR^{11})OR^{11}$, $-Y^2OP(O)(OR^{11})OR^{11}$, $-Y^2NR^{11}C(O)R^{12}$, $-Y^2S(O)R^{12}$, $-Y^2S(O)_2R^{12}$ and $-Y^2C(O)R^{12}$, wherein Y^2 is a bond or (C_{1-6})alkylene, R^{11} at each occurrence independently is hydrogen, (C_{1-6})alkyl or halo-substituted (C_{1-3})alkyl and R^{12} is (C_{1-6})alkyl or halo-substituted (C_{1-3})alkyl.

"Arylene" means an aromatic divalent monocyclic ring or fused polycyclic (i.e., bicyclic or tricyclic) ring system having, unless indicated otherwise, from six (6) to fourteen (14) ring carbon atoms. For example, arylene as used in this Application includes phenylene, naphthylene and anthracenylene. Aryl groups may be substituted with one to three groups independently select from (C_{1-6})alkyl, cyano, halo, halo-substituted (C_{1-4})alkyl, nitro, $-Y^2NR^{11}R^{11}$, $-Y^2NR^{11}C(O)OR^{11}$, $-Y^2NR^{11}C(O)NR^{11}R^{11}$, $-Y^2NR^{11}C(NR^{11})NR^{11}R^{11}$, $-Y^2OR^{11}$, $-Y^2SR^{11}$, $-Y^2C(O)OR^{11}$, $-Y^2C(O)NR^{11}R^{11}$, $-Y^2S(O)_2NR^{11}R^{11}$, $-Y^2P(O)(OR^{11})OR^{11}$, $-Y^2OP(O)(OR^{11})OR^{11}$, $-Y^2NR^{11}C(O)R^{12}$, $-Y^2S(O)R^{12}$, $-Y^2S(O)_2R^{12}$ and $-Y^2C(O)R^{12}$, wherein Y^2 is a bond or (C_{1-6})alkylene, R^{11} at each occurrence independently is hydrogen, (C_{1-6})alkyl or halo-substituted (C_{1-3})alkyl and R^{12} is (C_{1-6})alkyl or halo-substituted (C_{1-3})alkyl.

"Aromatic" means a moiety wherein the constituent atoms make up an unsaturated ring system, all atoms in the ring system are sp2 hybridized and the total number of pi electrons is equal to 4n + 2.

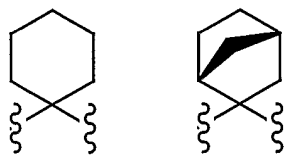
"Carbamoyl" means the radical $-C(O)NH_2$. Unless indicated otherwise, the compounds of the invention containing carbamoyl moieties include the *N*-oxide and protected derivatives thereof. Suitable protecting groups for carbamoyl moieties include acetyl, *tert*-butoxycarbonyl, benzyloxycarbonyl.

"Carboxy" means the radical -C(O)OH. Unless indicated otherwise, the compounds of the invention containing carboxy moieties include protected derivatives thereof. Suitable protecting groups for carboxy moieties include benzyl, *tert*-butyl, and the like.

"Cycloalkyl" means a saturated or partially unsaturated monocyclic ring or fused polycyclic (i.e., fused bicyclic or tricyclic) ring system or bridged polycyclic ring system having, unless indicated otherwise, from three (3) to fourteen (14) carbon atoms. For example, cycloalkyl as used in this Application includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, 2,5-cyclohexadienyl, bicyclo[2.2.2]octyl, adamantan-1-yl, decahydronaphthalenyl, oxocyclohexyl, dioxocyclohexyl, thiooxocyclohexyl, 2-oxobicyclo[2.2.1]hept-1-yl, and the like). Cycloalkyl groups may be substituted with one to three groups independently select from (C_{1-6})alkyl, (C_{1-6})alkylidene, (C_{1-6})alkylimino, cyano, halo, halo-substituted (C_{1-4})alkyl, imino, nitro,

oxo, thioxo, $-Y^2NR^{11}R^{11}$, $-Y^2NR^{11}C(O)OR^{11}$, $-Y^2NR^{11}C(O)NR^{11}R^{11}$, $-Y^2NR^{11}C(NR^{11})NR^{11}R^{11}$, $-Y^2OR^{11}$, $-Y^2SR^{11}$, $-Y^2C(O)OR^{11}$, $-Y^2C(O)NR^{11}R^{11}$, $-Y^2S(O)_2NR^{11}R^{11}$, $-Y^2P(O)(OR^{11})OR^{11}$, $-Y^2OP(O)(OR^{11})OR^{11}$, $-Y^2NR^{11}C(O)R^{12}$, $-Y^2S(O)R^{12}$, $-Y^2S(O)_2R^{12}$ and $-Y^2C(O)R^{12}$, wherein Y^2 is a bond or (C_{1-6})alkylene, R^{11} at each occurrence independently is hydrogen, (C_{1-6})alkyl or halo-substituted (C_{1-3})alkyl and R^{12} is (C_{1-6})alkyl or halo-substituted (C_{1-3})alkyl.

"Cycloalkylene" means a saturated or partially unsaturated divalent monocyclic ring or fused polycyclic (i.e., bicyclic or tricyclic) ring system or bridged polycyclic ring system containing from three (3) to fourteen (14) carbon atoms, unless indicated otherwise. For example, (e.g. (C_{3-12})cycloalkylene includes cyclopropylene, cyclobutylene, cyclopentylene, cyclohexylene, cyclohexenylene, 2,5-cyclohexadienylene, bicyclo[2.2.2]octylene, adamantanylene, decahydronaphthalenylene, oxocyclohexylene, dioxocyclohexylene, thiooxocyclohexylene, 2-oxobicyclo[2.2.1]hept-1-ylene, and the like). Cycloalkylene groups may be substituted with one to three groups independently select from (C_{1-6})alkyl, (C_{1-6})alkylidene, (C_{1-6})alkylimino, cyano, halo, halo-substituted (C_{1-4})alkyl, imino, nitro, oxo, thioxo, $-Y^2NR^{11}R^{11}$, $-Y^2NR^{11}C(O)OR^{11}$, $-Y^2NR^{11}C(O)NR^{11}R^{11}$, $-Y^2NR^{11}C(NR^{11})NR^{11}R^{11}$, $-Y^2OR^{11}$, $-Y^2SR^{11}$, $-Y^2C(O)OR^{11}$, $-Y^2C(O)NR^{11}R^{11}$, $-Y^2S(O)_2NR^{11}R^{11}$, $-Y^2P(O)(OR^{11})OR^{11}$, $-Y^2OP(O)(OR^{11})OR^{11}$, $-Y^2NR^{11}C(O)R^{12}$, $-Y^2S(O)R^{12}$, $-Y^2S(O)_2R^{12}$ and $-Y^2C(O)R^{12}$, wherein Y^2 is a bond or (C_{1-6})alkylene, R^{11} at each occurrence independently is hydrogen, (C_{1-6})alkyl or halo-substituted (C_{1-3})alkyl and R^{12} is (C_{1-6})alkyl or halo-substituted (C_{1-3})alkyl. For example, the instance wherein R^2 and R^3 together with the carbon atom to which both R^2 and R^3 are attached form a monocyclic or bridged polycyclic cycloalkylene moiety having from three to eight ring atoms includes, but is not limited to, the following:



"Disease" specifically includes any unhealthy condition of an animal or part thereof and includes an unhealthy condition which may be caused by, or incident to,

medical or veterinary therapy applied to that animal, i.e., the "side effects" of such therapy.

"Guanidino" means the radical -NHC(NH)NH_2. Unless indicated otherwise, the compounds of the invention containing guanidino moieties include the *N*-oxide and protected derivatives thereof. Suitable protecting groups for amino moieties include acetyl, *tert*-butoxycarbonyl, benzyloxycarbonyl, and the like and both the unprotected and protected derivatives fall within the scope of the invention.

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

"Halo-substituted alkyl", as a group or part of a group, means "alkyl" substituted by one or more "halo" atoms, as such terms are defined in this Application. Halo-substituted alkyl includes haloalkyl, dihaloalkyl, trihaloalkyl, perhaloalkyl and the like (e.g. halo-substituted (C_{1-3})alkyl includes chloromethyl, dicloromethyl, difluoromethyl, trifluromethyl, 2,2,2-trifluoroethyl, perfluoroethyl, 2,2,2-trifluoro-1,1-dichloroethyl, and the like).

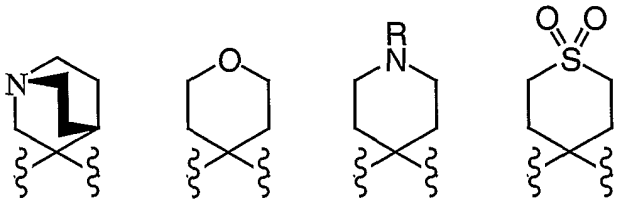
"Heteroaryl" means an aromatic monocyclic ring or fused polycyclic (i.e.,bicyclic, or tricyclic) ring system having, unless indicated otherwise, from five (5) to fourteen (14) ring atoms, wherein one or more of the ring atoms is a heteroatom moiety selected from -N=, -NR-, -O- or -S-, wherein R is hydrogen, (C_{1-6})alkyl, a protecting group or oxygen forming the *N*-oxide derivative. Suitable protecting groups include *tert*-butoxycarbonyl, benzyloxycarbonyl, benzyl, 4-methoxybenzyl, 2-nitrobenzyl, and the like. For example, heteroaryl as used in this Application includes benzofuryl, benzooxazolyl, benzothiazolyl, carbazolyl, carbolinyl, chromenyl, cinnolinyl, furazanyl, furyl, imidazolyl, indazolyl, indolyl, indolizinyl, isobenzofuryl, isochromenyl, isooxazolyl, isoquinolyl, isothiazolyl, naphthyridinyl, oxazolyl, perimidinyl, phthalazinyl, pteridinyl, purinyl, pyrazinyl, pyradazinyl, pyrazolyl, pyridyl, pyrimidinyl, pyrrolizinyl, pyrrolidinyl, pyrrolyl, pyranyl, quinazolinyl, quinolizinyl, quinolyl, quinoxalinyl, tetrazolyl, thiazolyl, thienyl, xanthenyl, and the like. Heteroaryl groups may be substituted with one to three groups independently select from (C_{1-6})alkyl, cyano, halo, halo-substituted (C_{1-4})alkyl, nitro, $-Y^2NR^{11}R^{11}$, $-Y^2NR^{11}C(O)OR^{11}$, $-Y^2NR^{11}C(O)NR^{11}R^{11}$, $-Y^2NR^{11}C(NR^{11})NR^{11}R^{11}$, $-Y^2OR^{11}$, $-Y^2SR^{11}$, $-Y^2C(O)OR^{11}$, $-Y^2C(O)NR^{11}R^{11}$, $-Y^2S(O)_2NR^{11}R^{11}$, $-Y^2P(O)(OR^{11})OR^{11}$, $-Y^2OP(O)(OR^{11})OR^{11}$, $-Y^2NR^{11}C(O)R^{12}$, $-Y^2S(O)R^{12}$, $-Y^2S(O)_2R^{12}$ and $-Y^2C(O)R^{12}$,

wherein Y^2 is a bond or (C_{1-6})alkylene, R^{11} at each occurrence independently is hydrogen, (C_{1-6})alkyl or halo-substituted (C_{1-3})alkyl and R^{12} is (C_{1-6})alkyl or halo-substituted (C_{1-3})alkyl.

"Heterocycloalkyl" means a saturated or partially unsaturated monocyclic ring or polycyclic (i.e., bicyclic or tricyclic) ring system or bridged polycyclic ring system having, unless indicated otherwise, from three (3) to fourteen (14) ring atoms, wherein one or more of the ring atoms is a heteroatom moiety selected from -N=, -NR-, -O- or -S-, wherein R is hydrogen, (C_{1-6})alkyl, a protecting group or oxygen forming the *N*-oxide derivative. Suitable protecting groups include *tert*-butoxycarbonyl, benzyloxycarbonyl, benzyl, 4-methoxybenzyl, 2-nitrobenzyl, and the like. For example, heterocycloalkyl as used in this Application includes includes dihydrooxazolyl, morpholinyl, piperazinyl, piperidyl, pirazolidinyl, pirazolinyl, pyrrolinyl, pyrrolidinyl, quinuclidinyl, and the like. Cycloalkyl groups may be substituted with one to three groups independently select from (C_{1-6})alkyl, (C_{1-6})alkylidene, (C_{1-6})alkylimino, cyano, halo, halo-substituted (C_{1-4})alkyl, imino, nitro, oxo, thioxo, $-Y^2NR^{11}R^{11}$, $-Y^2NR^{11}C(O)OR^{11}$, $-Y^2NR^{11}C(O)NR^{11}R^{11}$, $-Y^2NR^{11}C(NR^{11})NR^{11}R^{11}$, $-Y^2OR^{11}$, $-Y^2SR^{11}$, $-Y^2C(O)OR^{11}$, $-Y^2C(O)NR^{11}R^{11}$, $-Y^2S(O)_2NR^{11}R^{11}$, $-Y^2P(O)(OR^{11})OR^{11}$, $-Y^2OP(O)(OR^{11})OR^{11}$, $-Y^2NR^{11}C(O)R^{12}$, $-Y^2S(O)R^{12}$, $-Y^2S(O)_2R^{12}$ and $-Y^2C(O)R^{12}$, wherein Y^2 is a bond or (C_{1-6})alkylene, R^{11} at each occurrence independently is hydrogen, (C_{1-6})alkyl or halo-substituted (C_{1-3})alkyl and R^{12} is (C_{1-6})alkyl or halo-substituted (C_{1-3})alkyl.

"Heterocycloalkylene" means a saturated or partially unsaturated divalent monocyclic ring or polycyclic (i.e., bicyclic or tricyclic) ring system or bridged polycyclic ring system containing from three (3) to fourteen (14) carbon atoms, unless indicated otherwise. For example, heterocycloalkylene as used in this Application includes cyclopropylene, cyclobutylene, cyclopentylene, cyclohexylene, cyclohexenylene, 2,5-cyclohexadienylene, bicyclo[2.2.2]octylene, adamantanylene, decahydronaphthalenylene, oxocyclohexylene, dioxocyclohexylene, thiooxocyclohexylene, 2-oxobicyclo[2.2.1]hept-1-ylene, and the like). Cycloalkylene groups may be substituted with one to three groups independently select from (C_{1-6})alkyl, (C_{1-6})alkylidene, (C_{1-6})alkylimino, cyano, halo, halo-substituted (C_{1-4})alkyl, imino, nitro, oxo, thioxo, $-Y^2NR^{11}R^{11}$, $-Y^2NR^{11}C(O)OR^{11}$, $-Y^2NR^{11}C(O)NR^{11}R^{11}$,

$-Y^2NR^{11}C(NR^{11})NR^{11}R^{11}$, $-Y^2OR^{11}$, $-Y^2SR^{11}$, $-Y^2C(O)OR^{11}$, $-Y^2C(O)NR^{11}R^{11}$, $-Y^2S(O)_2NR^{11}R^{11}$, $-Y^2P(O)(OR^{11})OR^{11}$, $-Y^2OP(O)(OR^{11})OR^{11}$, $-Y^2NR^{11}C(O)R^{12}$, $-Y^2S(O)R^{12}$, $-Y^2S(O)_2R^{12}$ and $-Y^2C(O)R^{12}$, wherein Y^2 is a bond or (C_{1-6})alkylene, R^{11} at each occurrence independently is hydrogen, (C_{1-6})alkyl or halo-substituted (C_{1-3})alkyl and R^{12} is (C_{1-6})alkyl or halo-substituted (C_{1-3})alkyl. For example, the instance wherein R^2 and R^3 together with the carbon atom to which both R^2 and R^3 are attached form a monocyclic or bridged polycyclic heterocycloalkylene moiety having from three to eight ring atoms includes, but is not limited to, the following:



"Hydroxy" means the radical -OH. Unless indicated otherwise, the compounds of the invention containing hydroxy radicals include protected derivatives thereof. Suitable protecting groups for hydroxy moieties include benzyl and the like and both the unprotected and protected derivatives fall within the scope of the invention.

"Imino" means the radical =N. Unless indicated otherwise, the compounds of the invention containing imino radicals include *N*-oxide and protected derivatives thereof. Suitable protecting groups for imino moieties include acetyl, *tert*-butoxycarbonyl, benzyloxycarbonyl, and the like.

"Isomers" mean compounds of Formula I having identical molecular formulae but differ in the nature or sequence of bonding of their atoms or in the arrangement of their atoms in space. Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers". Stereoisomers that are not mirror images of one another are termed "diastereomers" and stereoisomers that are nonsuperimposable mirror images are termed "enantiomers" or sometimes "optical isomers". A carbon atom bonded to four nonidentical substituents is termed a "chiral center". A compound with one chiral center has two enantiomeric forms of opposite chirality is termed a "racemic mixture". A compound that has more than one chiral center has 2^{n-1} enantiomeric pairs, where *n* is the

number of chiral centers. Compounds with more than one chiral center may exist as ether an individual diastereomer or as a mixture of diastereomers, termed a "diastereomeric mixture". When one chiral center is present a stereoisomer may be characterized by the absolute configuration of that chiral center. Absolute configuration refers to the arrangement in space of the substituents attached to the chiral center. Enantiomers are characterized by the absolute configuration of their chiral centers and described by the *R*- and *S*-sequencing rules of Cahn, Ingold and Prelog. Conventions for stereochemical nomenclature, methods for the determination of stereochemistry and the separation of stereoisomers are well known in the art (e.g. see "Advanced Organic Chemistry", 3rd edition, March, Jerry, John Wiley & Sons, New York, 1985). It is understood that the names and illustration used in this Application to describe compounds of Formula I are meant to be encompassed all possible stereoisomers and any mixture, racemic or otherwise, thereof.

"Nitro" means the radical $-NO_2$.

"*N*-oxide derivatives" means a derivatives of compound of Formula I in which nitrogens are in an oxidized state (i.e., O←N) and which possess the desired pharmacological activity.

"Oxo" means the radical=O.

"Pathology" of a disease means the essential nature, causes and development of the disease as well as the structural and functional changes that result from the disease processes.

"Pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary use as well as human pharmaceutical use.

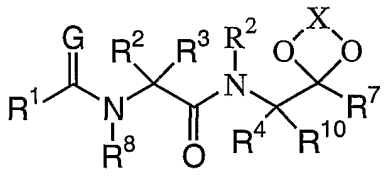
"Pharmaceutically acceptable salts" means salts of compounds of Formula I which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological activity. Such salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or with organic acids such as acetic acid, propionic acid, hexanoic acid, heptanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid,

malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartatic acid, citric acid, benzoic acid, *o*-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, madelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, *p*-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, *p*-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylic 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.

Pharmaceutically acceptable salts also include base addition salts which may be formed when acidic protons present are capable of reacting with inorganic or organic bases. Acceptable inorganic bases include sodium hydroxide, sodium carbonate, potassium hydroxide, ammonium hydroxide, aluminum hydroxide and calcium hydroxide. Acceptable organic bases include ethanolamine, diethanolamine, triethanolamine, tromethamine, *N*-methylglucamine and the like.

"Prodrug" means a compound which is convertible in vivo by metabolic means (e.g. by hydrolysis) to a compound of Formula (I). For example an ester of a compound of Formula (I) containing a hydroxy group may be convertible by hydrolysis *in vivo* to the parent molecule. Alternatively an ester of a compound of Formula (I) containing a carboxy group may be convertible by hydrolysis *in vivo* to the parent molecule. Suitable esters of compounds of Formula (I) containing a hydroxy group, are for example acetates, citrates, lactates, tartrates, malonates, oxalates, salicylates, propionates, succinates, fumarates, maleates, methylene-bis-b-hydroxynaphthoates, gentisates, isethionates, di-*p*-toluoyltartrates, methanesulphonates, ethanesulphonates, benzenesulphonates, p-toluenesulphonates, cyclohexylsulphamates and quinates. Suitable esters of compounds of Formula (I) containing a carboxy group, are for example those described by F.J.Leinweber, Drug Metab. Res., 1987, 18, page 379. An especially useful class of esters of compounds of Formula (I) containing a hydroxy group, may be formed from acid moieties selected from those described by Bundgaard et. al., J. Med. Chem., 1989, 32 , page 2503-2507, and include substituted (aminomethyl)-benzoates, for example, dialkylamino-methylbenzoates in which the two alkyl groups may be joined together

and/or interrupted by an oxygen atom or by an optionally substituted nitrogen atom, e.g. an alkylated nitrogen atom, more especially (morpholino-methyl)benzoates, e.g. 3- or 4-(morpholinomethyl)-benzoates, and (4-alkylpiperazin-1-yl)benzoates, e.g. 3- or 4-(4-alkylpiperazin-1-yl)benzoates. A prodrug derivative of a compound of Formula I wherein R^5 and R^6 together are oxo is depicted by the following formula:



in which X is a bond, straight, saturated ethylene or (-$CH_2CR^{16}R^{17}CH_2$-), wherein R^{16} and R^{17} independently are hydrogen, halo or (C_{1-3})alkyl or taken together form methylene.

"Protected derivatives" means derivatives of compounds of Formula I in which a reactive site or sites are blocked with protecting groups. Protected derivatives of compounds of Formula I are useful in the preparation of compounds of Formula I or in themselves may be active cysteine protease inhibitors. A comprehensive list of suitable protecting groups can be found in T.W. Greene, *Protecting Groups in Organic Synthesis*, John Wiley & Sons, Inc. 1981.

"Sulfamoyl" means the radical -$S(O)_2NH_2$. Unless indicated otherwise, the compounds of the invention containing sulfamoyl radicals include *N*-oxide and protected derivatives thereof. Suitable protecting groups for sulfamoyl radicals include acetyl, *tert*-butoxycarbonyl, benzyloxycarbonyl, and the like.

"Therapeutically effective amount" means that amount which, when administered to an animal for treating a disease, is sufficient to effect such treatment for the disease.

"Thioxo" means a the radical =S.

"Treatment" or "treating" means any administration of a compound of the present invention and includes:

(1) preventing the disease from occurring in an animal which may be predisposed to the disease but does not yet experience or display the pathology or symptomatology of the disease,

(2) inhibiting the disease in an animal that is experiencing or displaying the pathology or symptomatology of the diseased (i.e., arresting further development of the pathology and/or symptomatology), or

(3) ameliorating the disease in an animal that is experiencing or displaying the pathology or symptomatology of the diseased (i.e., reversing the pathology and/or symptomatology).

Specific Embodiments of the Invention:

While the broadest definition of the invention is set forth in the Summary of the Invention, certain aspects of the invention are preferred.

Preferred are those compounds of Formula I in which G is -C(O)-; L is a bond, -O- or -NR^{15}-, wherein R^{15} is hydrogen or (C_{1-4})alkyl; Z^1, Z^2 and Z^3 independently are selected from phenylene, heteroarylene having from five to nine ring atoms and heterocycloalkylene having five to six ring atoms, wherein each said phenylene, heteroarylene and heterocycloalkylene may be substituted further with one to three groups independently selected from (C_{1-6})alkyl, (C_{1-6})alkylidene, (C_{1-6})alkylimino, cyano, halo, halo-substituted (C_{1-4})alkyl, imino, nitro, oxo, thioxo, $-Y^2NR^{11}R^{11}$, $-Y^2NR^{11}C(O)OR^{11}$, $-Y^2NR^{11}C(O)NR^{11}R^{11}$, $-Y^2NR^{11}C(NR^{11})NR^{11}R^{11}$, $-Y^2OR^{11}$, $-Y^2SR^{11}$, $-Y^2C(O)OR^{11}$, $-Y^2C(O)NR^{11}R^{11}$, $-Y^2S(O)_2NR^{11}R^{11}$, $-Y^2P(O)(OR^{11})OR^{11}$, $-Y^2OP(O)(OR^{11})OR^{11}$, $-Y^2NR^{11}C(O)R^{12}$, $-Y^2S(O)R^{12}$, $-Y^2S(O)_2R^{12}$ and $-Y^2C(O)R^{12}$, wherein Y^2 is a bond or (C_{1-6})alkylene, R^{11} at each occurrence independently is hydrogen, (C_{1-6})alkyl or halo-substituted (C_{1-3})alkyl and R^{12} is (C_{1-6})alkyl or halo-substituted (C_{1-3})alkyl; R^2 and R^3 together with the carbon atom to which both R^2 and R^3 are attached form a monocyclic cycloalkylene moiety having three to six ring atoms; R^4 is (C_{1-6}) alkyl or phenyethyl; R^5 and R^6 together with the carbon atom to which both R^5 and R^6 are attached form a -C(O)- group; R^7 represents a heteroaryl moiety having five to nine ring atoms, wherein said heteroaryl moiety may be substituted with aryl, wherein within R^7 any aromatic ring may be substituted further with one to three groups independently selected from (C_{1-6})alkyl, cyano, halo, halo-substituted (C_{1-4})alkyl, nitro, $-Y^2NR^{11}R^{11}$, $-Y^2NR^{11}C(O)OR^{11}$, $-Y^2NR^{11}C(O)NR^{11}R^{11}$, $-Y^2NR^{11}C(NR^{11})NR^{11}R^{11}$, $-Y^2OR^{11}$, $-Y^2SR^{11}$, $-Y^2C(O)OR^{11}$, $-Y^2C(O)NR^{11}R^{11}$, $-Y^2S(O)_2NR^{11}R^{11}$, $-Y^2P(O)(OR^{11})OR^{11}$, $-Y^2OP(O)(OR^{11})OR^{11}$,

$-Y^2NR^{11}C(O)R^{12}$, $-Y^2S(O)R^{12}$, $-Y^2S(O)_2R^{12}$ and $-Y^2C(O)R^{12}$, wherein Y^2 is as defined above, R^{11} at each occurrence independently is hydrogen, (C_{1-6})alkyl or halo-substituted (C_{1-3})alkyl and R^{12} is (C_{1-6})alkyl or halo-substituted (C_{1-3})alkyl; and R^8, R^9 and R^{10} each are hydrogen.

More preferred are those compounds of Formula I in which L is a bond, -O- or -NH-; Z^1, Z^2 and Z^3 independently are selected from phenylene, heteroarylene having from five to nine ring atoms or heterocycloalkylene having five to six ring atoms, wherein each said phenylene, heteroarylene and heterocycloalkylene may be substituted with 1 to 2 groups independently selected from (C_{1-6})alkyl, halo, nitro, halo-substituted (C_{1-4})alkyl, oxo, $-Y^2OR^{11}$, $-Y^2NR^{11}R^{11}$, $-Y^2C(O)OR^{11}$ and $-Y^2S(O)_2R^{12}$; and R^7 represents a heteroaryl moiety having five to nine ring atoms, wherein said heteroaryl moiety may be substituted with phenyl or one to two substitutents independently selected from (C_{1-6})alkyl, halo and $-Y^2OR^{11}$, wherein said phenyl may be substituted further with one to two substitutents independently selected from halo-substituted (C_{1-4})alkyl or $-Y^2OR^{11}$.

Particularly preferred are those compounds of Formula I in which R^7 is is selected from benzooxazol-2-yl, benzofuran-2-yl, benzo[*b*]thiophen-2-yl wherein said benzooxazol-2-yl, benzofuran-2-yl or benzo[*b*]thiophen-2-yl may be substituted with one to two groups selected from halo and $-Y^2OR^{11}$.

More particularly preferred are those compounds of Formula I in which R^1 is a group selected from 4-[2-(4-methyl-piperazin-1-yl)-thiazol-4-yl]-phenyl, 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-yl, 4-morpholin-4-yl-phenyl, pyridin-3-yl, pyridin-4-yl, pyrazin-2-yl, benzofuran-2-yl, benzo[*b*]thiophen-2-yl, 5-methoxy-benzofuran-2-yl, [1,4']bipiperidinyl-1'-yl, 4-isopropylamino-piperidin-1-yl, 4-{2-[1-(*tert*-butoxycarbonyl)-piperidin-4-ylamino]-thiazol-4-yl}-phenyl, 4-(2-morpholin-4-ylmethyl-thiazol-4-yl)-phenyl, 4-dimethylaminophenyl, 3-dimethylaminophenyl, 4-isopropylpiperazin-1-yl-phenyl, 4-(4-oxopiperidin-1-yl)phenyl, 4-[2-(piperidin-4-ylamino)-thiazol-4-yl]-phenyl, 4-*tert*-butylpiperazin-1-yl-phenyl, methyl, 4-*tert*-butylphenyl, 3,5-dimethoxyphenyl, 3,6-dimethoxyphenyl, 2-chlorophenyl, 2,5-dichlorophenyl, 4-nitrophenyl, 4-fluorophenyl, 4-trifluoromethoxyphenyl, 4-isobutylphenyl, 4-trifluoromethylphenyl, 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-yl, 4-chlorophenyl, 4-methylsufonylphenyl, 4-methoxyphenyl, 4-methylpiperazin-1-yl,

4-morpholin-4-ylpiperazin-1-yl, and 4-*tert*-butylpiperazin-1-yl; R^2 and R^3 together with the carbon atom to which both R^2 and R^3 are attached form cyclohexylene; R^4 is butyl, phenethyl, propyl, isobutyl or ethyl; and R^7 is selected from benzooxazol-2-yl, benzofuran-2-yl, benzo[*b*]thiophen-2-yl, 5-chlorobenzooxazol-2-yl and 5-methoxy-benzofuran-2-yl.

Particularly preferred are those compounds of Formula I in which R^7 is [1,3,4]oxadiazol-2-yl wherein said [1,3,4]oxadiazol-2-yl may be substituted with phenyl or one to two substitutents independently selected from (C_{1-6})alkyl and $-Y^2OR^{11}$, wherein said phenyl may be substituted further with one to two substitutents independently selected from halo-substituted (C_{1-4})alkyl or $-Y^2OR^{11}$.

More particularly preferred are those compounds of Formula I in which R^1 is a group selected from 4-[2-(4-methyl-piperazin-1-yl)-thiazol-4-yl]-phenyl, 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-yl, 4-morpholin-4-yl-phenyl, pyridin-3-yl, pyridin-4-yl, pyrazin-2-yl, benzofuran-2-yl, benzo[*b*]thiophen-2-yl, 5-methoxy-benzofuran-2-yl, [1,4']bipiperidinyl-1'-yl, 4-isopropylamino-piperidin-1-yl, 4-{2-[1-(*tert*-butoxycarbonyl)-piperidin-4-ylamino]-thiazol-4-yl}-phenyl, 4-(2-morpholin-4-ylmethyl-thiazol-4-yl)-phenyl, 4-dimethylaminophenyl, 3-dimethylaminophenyl, 4-isopropylpiperazin-1-yl-phenyl, 4-(4-oxopiperidin-1-yl)phenyl, 4-[2-(piperidin-4-ylamino)-thiazol-4-yl]-phenyl, 4-*tert*-butylpiperazin-1-yl-phenyl, methyl, 4-*tert*-butylphenyl, 3,5-dimethoxyphenyl, 3,6-dimethoxyphenyl, 2-chlorophenyl, 2,5-dichlorophenyl, 4-nitrophenyl, 4-fluorophenyl, 4-trifluoromethoxyphenyl, 4-isobutylphenyl, 4-trifluoromethylphenyl, 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-yl, 4-chlorophenyl, 4-methylsufonylphenyl, 4-methoxyphenyl, 4-methylpiperazin-1-yl, 4-morpholin-4-ylpiperazin-1-yl, and 4-*tert*-butylpiperazin-1-yl; R^2 and R^3 together with the carbon atom to which both R^2 and R^3 are attached form cyclohexylene; R^4 is butyl, phenethyl, propyl, isobutyl or ethyl; R^7 is a group selected from 5-phenyl-[1,3,4]oxadiazol-2-yl, 5-(3-methoxyphenyl)-[1,3,4]oxadiazol-2-yl, 5-(4-methoxyphenyl)-[1,3,4]oxadiazol-2-yl, 5-(4-trifluoromethylphenyl)-[1,3,4]oxadiazol-2-yl, 5-(3-trifluoromethylphenyl)-[1,3,4]oxadiazol-2-yl, 5-(4-methoxyphenyl)-[1,3,4]oxadiazol-2-yl, 5-ethyl-[1,3,4]oxadiazol-2-yl, 5-methoxymethyl-[1,3,4]oxadiazol-2-yl and 5-*tert*-butyl-[1,3,4]oxadiazol-2-yl.

Most preferred those compounds selected from:

5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid {1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-3-phenyl-propylcarbamoyl]-cyclohexyl}-amide;

5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid {1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-pentylcarbamoyl]-cyclohexyl}-amide;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-3-phenyl-propylcarbamoyl]-cyclohexyl}-4-[2-(4-methyl-piperazin-1-yl)-thiazol-4-yl]-benzamide;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-pentylcarbamoyl]-cyclohexyl}-4-[2-(4-methyl-piperazin-1-yl)-thiazol-4-yl]-benzamide;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-4-morpholin-4-yl-benzamide;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-nicotinamide;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-isonicotinamide;

pyrazine-2-carboxylic acid {1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-amide;

benzofuran-2-carboxylic acid {1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-amide;

benzo[*b*]thiophene-2-carboxylic acid {1-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-amide;

5-methoxy-benzofuran-2-carboxylic acid {1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-amide;

[1,4']bipiperidinyl-1'-carboxylic acid {1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-amide;

4-isopropylamino-piperidine-1-carboxylic acid {1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-amide;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-4-[2-(4-methyl-piperazin-1-yl)-thiazol-4-yl]-benzamide;

4-[4-(4-{1-[1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexylcarbamoyl}-phenyl)-thiazol-2-ylamino]-piperidine-1-carboxylic acid *tert*-butyl ester;

N-{1-[1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-4-(2-morpholin-4-ylmethyl-thiazol-4-yl)-benzamide;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-4-dimethylamino-benzamide;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-3-dimethylamino-benzamide;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-4-(4-isopropyl-piperazin-1-yl)-benzamide;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-4-(4-oxo-piperidin-1-yl)-benzamide;

N-{1-[1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-4-[2-(piperidin-4-ylamino)-thiazol-4-yl]-benzamide;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-4-(4-*tert*-butyl-piperazin-1-yl)-benzamide;

1-acetylamino-cyclohexanecarboxylic acid [(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butyl]-amide;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-4-*tert*-butyl-benzamide;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-3-methyl-butylcarbamoyl]-cyclohexyl}-4-*tert*-butyl-benzamide;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-3,5-dimethoxy-benzamide;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-3,4-dimethoxy-benzamide;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-2-chloro-benzamide;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-2,5-dichloro-benzamide;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-4-nitro-benzamide;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-4-fluoro-benzamide;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-4-trifluoromethoxy-benzamide;

N-{1-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-4-isobutyl-benzamide;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-4-trifluoromethyl-benzamide;

5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid {1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-amide;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-4-chloro-benzamide;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-4-methanesulfonyl-benzamide;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-propylcarbamoyl]-cyclohexyl}-4-trifluoromethoxy-benzamide;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-4-methoxy-benzamide;

N-(1-{(*S*)-1-[1-(5-phenyl-[1,3,4]oxadiazol-2-yl)-methanoyl]-pentylcarbamoyl}-cyclohexyl)-4-trifluoromethoxy-benzamide;

4-*tert*-butyl-*N*-(1-{(*S*)-1-[1-(5-chloro-benzooxazol-2-yl)-methanoyl]-butylcarbamoyl}-cyclohexyl)-benzamide;

N-(1-{(*S*)-1-[1-(5-phenyl-[1,3,4]oxadiazol-2-yl)-methanoyl]-butylcarbamoyl}-cyclohexyl)-4-trifluoromethoxy-benzamide;

N-[1-((*S*)-1-{1-[5-(3-methoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-methanoyl}-butylcarbamoyl)-cyclohexyl]-4-trifluoromethoxy-benzamide;

N-[1-((*S*)-1-{1-[5-(4-methoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-methanoyl}-butylcarbamoyl)-cyclohexyl]-4-trifluoromethoxy-benzamide;

4-trifluoromethoxy-*N*-[1-((*S*)-1-{1-[5-(4-trifluoromethyl-phenyl)-[1,3,4]oxadiazol-2-yl]-methanoyl}-butylcarbamoyl)-cyclohexyl]-benzamide;

4-trifluoromethoxy-*N*-[1-((*S*)-1-{1-[5-(3-trifluoromethyl-phenyl)-[1,3,4]oxadiazol-2-yl]-methanoyl}-butylcarbamoyl)-cyclohexyl]-benzamide;

4-methyl-piperazine-1-carboxylic acid [1-((*S*)-1-{1-[5-(4-methoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-methanoyl}-butylcarbamoyl)-cyclohexyl]-amide;

4-morpholin-4-yl-piperidine-1-carboxylic acid [1-((*S*)-1-{1-[5-(4-methoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-methanoyl}-butylcarbamoyl)-cyclohexyl]-amide;

4-*tert*-butyl-piperazine-1-carboxylic acid [1-((*S*)-1-{1-[5-(4-methoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-methanoyl}-butylcarbamoyl)-cyclohexyl]-amide;

N-(1-{(*S*)-1-[1-(5-ethyl-[1,3,4]oxadiazol-2-yl)-methanoyl]-butylcarbamoyl}-cyclohexyl)-4-trifluoromethoxy-benzamide;

N-(1-{(*S*)-1-[1-(5-methoxymethyl-[1,3,4]oxadiazol-2-yl)-methanoyl]-butylcarbamoyl}-cyclohexyl)-4-trifluoromethoxy-benzamide;

N-(1-{(*S*)-1-[1-(5-*tert*-butyl-[1,3,4]oxadiazol-2-yl)-methanoyl]-butylcarbamoyl}-cyclohexyl)-4-trifluoromethoxy-benzamide;

4-*tert*-butyl-piperazine-1-carboxylic acid (1-{(*S*)-1-[1-(5-ethyl-[1,3,4]oxadiazol-2-yl)-methanoyl]-butylcarbamoyl}-cyclohexyl)-amide;

4-*tert*-butyl-piperazine-1-carboxylic acid (1-{(*S*)-1-[1-(5-methoxymethyl-[1,3,4]oxadiazol-2-yl)-methanoyl]-butylcarbamoyl}-cyclohexyl)-amide; and

4-*tert*-butyl-piperazine-1-carboxylic acid (1-{(*S*)-1-[1-(5-*tert*-butyl-[1,3,4]oxadiazol-2-yl)-methanoyl]-butylcarbamoyl}-cyclohexyl)-amide.

Nomenclature:

The compounds of Formula I and the intermediates and starting materials used in their preparation named by AutoNom 4.0 (Beilstein Information Systems, Inc.) or in accordance with IUPAC rules of nomenclature in which the characteristic groups have decreasing priority for citation as the principle group as follows: acids, esters, amides, etc.

Administration and Pharmaceutical Compositions:

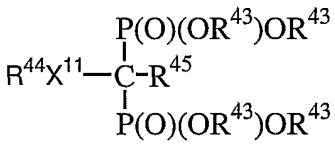
In general, compounds of Formula I will be administered in therapeutically effective amounts via any of the usual and acceptable modes known in the art, either singly or in combination with another therapeutic agent. A therapeutically effective amount may vary widely depending on the severity of the 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 10 μg/day to 100 mg/day, typically 0.1 mg/day to 10 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 composition is 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.

The compounds of Formula I can be administered alone or in combination with other compounds of Formula I or in combination with one or more other active ingredient(s). For example, the compounds of Formula I can be administered in combination with a therapeutically active amount of a bisphosphonic acid or acid ester derivative or any pharmaceutically acceptable salt thereof. Suitable bisphosphonic acids and acid ester derivatives include compounds corresponding to the following formula:



wherein X^{11} is a bond or (C_{1-7})alkylene, each R^{43} independently is hydrogen or (C_{1-30})alkyl, R^{44} and R^{45} are selected independently from a group consisting of hydrogen, halo, optionally substituted (C_{1-30})alkyl, (C_{3-30})cycloalkyl, hetero(C_{5-30})cycloalkyl, optionally substituted (C_{6-10})aryl, hetero(C_{6-10})aryl, $-NR^{46}R^{46}$, $-OR^{46}$, $-SR^{46}$, wherein each R^{46} independently is hydrogen, (C_{1-10})alkyl, (C_{3-10})cycloalkyl, optionally substituted (C_{6-10})aryl, provided that both R^{44} and R^{45} are not selected from hydrogen or hydroxy when X^{11} is a bond; or R^{44} and R^{45} taken together form (C_{2-9})alkylene; wherein (C_{3-10})cycloalkyl includes adamantyl and the like, hetero(C_{5-10})cycloalkyl includes pyrrolidinyl and the like, (C_{6-10})aryl includes phenyl and naphthyl, and hetero(C_{6-10})aryl includes quinolyl, isoquinolyl, pyridyl, furyl, imidazolyl, imidazopyridyl and the like.

Instances wherein R^{44} and/or R^{45} are substituted (C_{1-30})alkyl may include, but are not limited to, (C_{1-30})alkyl substituted by hetero(C_{5-10})cycloalkyl, (C_{6-10})aryl,

hetero(C_{6-10})aryl, -$NR^{47}R^{47}$, -OR^{47} and -SR^{47}, wherein each R^{47} is independently hydrogen or (C_{1-10})alkyl; wherein hetero(C_{5-10})cycloalkyl includes pyrrolidinyl and the like, (C_{6-10})aryl includes phenyl and naphthyl, and hetero(C_{6-10})aryl includes quinolyl, isoquinolyl, pyridyl, furyl, imidazolyl, imidazopyridyl and the like. Suitable optionally substituted aryl groups include, but are not limited to, halo-substituted phenyl.

A non-limiting class of bisphosphonic acids and acid ester derivatives thereof suitable for administration in combination with compounds of Formula I include those in which R^{44} is selected from the group consisting of hydrogen, hydroxy or halo, and R^{45} is selected from the group consisting of optionally substituted (C_{1-30})alkyl, halo and -SR^{46}, wherein R^{46} is (C_{1-10})alkyl or phenyl.

A non-limiting subclass of bisphosphonic acids and acid ester derivatives thereof suitable for administration in combination with compounds of Formula I include those in which R^{44} is selected from the group consisting of hydrogen, hydroxy and chloro and R^{45} is selected from the group consisting of optionally substituted (C_{1-30})alkyl, chloro and chlorophenylthio.

A non-limiting example of a bisphosphonic acid suitable for administration in combination with compounds of Formula I include that in which X^{11} is a bond, each R^{43} is hydrogen, R^{44} is hydroxy and R^{45} is 3-aminopropyl, namely 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid (aka alendronic acid), or the monosodium trihydrate salt thereof, namely 4-amino-1-hydroxybutylidene-1,1-bisphosphonate monosodium trihydrate (aka alendronate monosodium trihydrate), described in U.S. Patents 4,922,007, to Kieczykowski et al., issued May 1, 1990; 5,019,651, to Kieczykowski et al., issued May 28, 1991; 5,510,517, to Dauer et al., issued April 23, 1996; 5,648,491, to Dauer et al., issued July 15, 1997, all of which patents are incorporated by reference herein in their entirety.

Further non-limiting examples of bisphosphonic acids suitable for administration in combination with compounds of Formula I include the following:

cycloheptylaminomethylene-1,1-bisphosphonic acid (aka cimadronic acid), described in U.S. Patent 4,970,335, to Isomura et al., issued November 13, 1990;

1,1-dichloromethylene-1,1-diphosphonic acid (aka clodronic acid) and the disodium salt thereof, namely clodronate disodium, described in Belgium Patent 672,205 (1966) and *J. Org. Chem 32*, 4111 (1967);

1-hydroxy-3-pyrrolidin-1-ylpropylidene-1,1-bisphosphonic acid (aka EB-1053);

1-hydroxyethylidene-1,1-diphosphonic acid (aka etidronic acid);

1-hydroxy-3-(*N*-methyl-*N*-pentylamino)propylidene-1,1-bisphosphonic acid (aka ibandronic acid), described in U.S. Patent No. 4,927,814, issued May 22, 1990;

6-amino-1-hydroxyhexylidene-1,1-bisphosphonic acid (aka neridronic acid);

3-(dimethylamino)-1-hydroxypropylidene-1,1-bisphosphonic acid (aka olpadronic acid);

3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid (aka pamidronic acid);

2-pyrid-2-ylethylidene-1,1-bisphosphonic acid (aka piridronic acid), described in U.S. Patent No. 4,761,406;

1-hydroxy-2-pyrid-3-ylethylidene-1,1-bisphosphonic acid (aka risedronic acid);

4-chlorophenylthiomethylenebisphosphonic acid (aka tiludronic acid), described in U.S. Patent 4,876,248, to Breliere et al., October 24, 1989; and

1-hydroxy-2-(1*H*-imidazol-1-yl)ethylidene-1,1-bisphosphonic acid (aka zoledronic acid); all of which patents and other documents referred to above are incorporated by reference herein in their entirety.

A non-limiting subclass of bisphosphonic acids suitable for administration in combination with compounds of Formula I include those selected from the group consisting of alendronic acid, cimadronic acid, clodronic acid, tiludronic acid, etidronic acid, ibandronic acid, risedronic acid, piridronic acid, pamidronic acid, zolendronic acid, pharmaceutically acceptable salts thereof, and mixtures thereof. A further example of a bisphosphonic acid suitable for administration in combination with compounds of Formula I is alendronic acid or a pharmaceutically acceptable salt thereof, and mixtures thereof. A further non-limiting example is alendronate monosodium trihydrate.

Compounds of Formula I can be administered in combination with a therapeutically active amount of an estrogen receptor agonist. Non-limiting examples of estrogen receptor agonists suitable for administration in combination with the compounds of Formula I include naturally occurring estrogens such as estradiol, estrone and estroil, or

synthetic estrogen receptor agonists such as [6-hydroxy-2-(4-hydroxyphenyl)benzo[*b*]thien-3-yl][4-(2-piperidin-1-ylethoxy)phenyl]methanone (aka raloxifene) and {2-[4-(1,2-diphenylbut-1-enyl)phenoxy]ethyl}dimethylamine (aka tamoxifen). A non-limiting subclass of estrogen receptor agonists suitable for administration in combination with the compounds of Formula I include estrogen receptor partial agonists (i.e., estrogen receptor agonists with mixed agonist/antagonist properties), sometimes referred to as estrogen receptor modulators. Estrogen receptor partial agonists can exert tissue-selective estrogen agonist effects. Tamoxifen, for example, selectively exerts an estrogen agonist effect on the bone, in humans. Additional suitable estrogen receptor partial agonists are described in Tissue-Selective Actions Of Estrogen Analogs, Bone Vol. 17, No. 4, October 1995, 181S-190S. Certain 3-[4-(2-phenylindol-1-ylmethyl)phenyl]acrylamides, described in U.S. Patent 5,985,910 to Miller *et al.*, November 16, 1999; benzothiphene compounds, described in U.S. Patent 5,985,897 to Meuhl *et al.*, November 16, 1999; naphthyl compounds, described in U.S. Patent 5,952,350 to Cullinan *et al.*, September 14, 1999; substituted benzothiophene compounds, described in U.S. Patent 5,962,475 to Schmid *et al.*, October 4, 1999, are suitable estrogen receptor partial agonists for administration with the compounds of Formula I; all of which patents and other documents referred to above are incorporated by reference herein in their entirety.

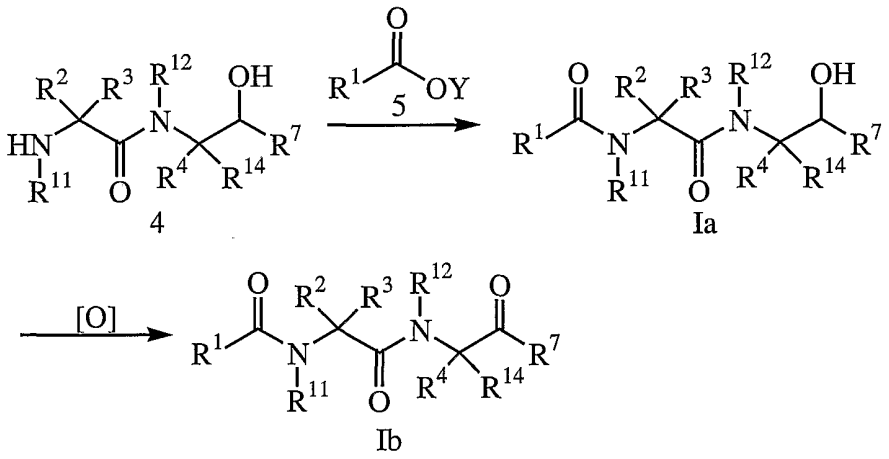
More particularly a pharmaceutical composition of this invention may comprise a therapeutically effect amount of a compound of Formula I in combination with one or more active ingredient(s) selected from the group consisting of (i) a therapeutically effect amount of a bisphosphonic acid or acid ester thereof or a pharmaceutically acceptable salt thereof and (ii) a therapeutically effect amount of an estrogen receptor agonist or a pharmaceutically acceptable salt thereof; and one or more pharmaceutically acceptable excipient(s). Non-limiting examples of such bisphosphonic acids include 1,1-dichloromethylene-1,1-diphosphonic acid, 1-hydroxy-3-pyrrolidin-1-ylpropylidene-1,1-bisphosphonic acid, 1-hydroxyethylidene-1,1-diphosphonic acid, 1-hydroxy-3-(*N*-methyl-*N*-pentylamino)propylidene-1,1-bisphosphonic acid, 6-amino-1-hydroxyhexylidene-1,1-bisphosphonic acid, 3-(dimethylamino)-1-hydroxypropylidene-

1,1-bisphosphonic acid, 3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid, 2-pyrid-2-ylethylidene-1,1-bisphosphonic acid, 1-hydroxy-2-pyrid-3-ylethylidene-1,1-bisphosphonic acid, 4-chlorophenylthiomethylenebisphosphonic acid and 1-hydroxy-2-(1*H*-imidazol-1-yl)ethylidene-1,1-bisphosphonic acid or acid ester thereof or a pharmaceutically acceptable salt thereof; particularly 1,1-dichloromethylene-1,1-diphosphonic acid or a pharmaceutically acceptable salt thereof and preferably 1,1-dichloromethylene-1,1-diphosphonate monosodium trihydrate.

Chemistry:

Compounds of Formula I in which G is -C(O)- can be prepared by proceeding as in the following Scheme I:

Scheme I



in which Y is hydrogen or an activating group (e.g. 2,5-dioxopyrrolidin-1-yl (NBS), or the like) and each R^1, R^2, R^3, R^7, R^{11}, R^{12} and R^{14} are as defined in the Summary of the Invention.

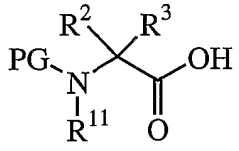
Compounds of Formula I in which G is –C(O)- and R^5 and R^6 together from oxo (Formula Ib) can be prepared by condensing an amine of Formula 4 with a carboxylic acid of Formula 5 to give a compound of Formula I in which R^5 is hydrogen and R^6 is hydroxy (Formula Ia) and then oxidizing to give the corresponding compound of Formula Ib. The condensation reaction is carried out in a suitable base (e.g. triethylamine,

diisopropylethylamine, or the like) and in a suitable solvent (e.g. acetonitrile, *N*,*N*-dimethylformamide (DMF), dichloromethane, or any suitable combination thereof, or the like) at 10 to 30°C, preferably at about 25°C, and requires 24 to 30 hours to complete.

When Y is hydrogen a suitable coupling agent (e.g. benzotriazole-1-yloxytrispyrrolidinophosphonium hexafluorophosphate (PyBOP®), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), *O*-benzotriazol-1-yl-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate (HBTU), *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU), 1,3-dicyclohexylcarbodiimide (DCC), or the like) and base (e.g. *N*,*N*-diisopropylethylamine, triethylamine, or the like) is required and the reaction requires 2 to 3 hours to complete.

The oxidation can be carried out with a suitable oxidizing agent (e.g. Dess-Martin periodinate, or the like) in a suitable solvent (e.g. dichloromethane, or the like) at 15 to 25° C and requires 10 to 20 hours to complete.

Compounds of Formula 4 can be prepared by condensing compound of Formula 1:



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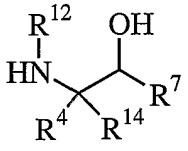
in which PG is a protecting group, with a compound of Formula 2:



2

and then deprotecting. The condensation reaction is carried out in a manner analogous that set forth for Scheme 1.

Deprotection can be effected by any means which removes the protecting group and gives the desired product in reasonable yield. A detailed description of the techniques applicable to the creation of protecting groups and their removal can be found in T.W. Greene, *Protecting Groups in Organic Synthesis*, John Wiley & Sons, Inc. 1981. For example, deprotection can be effected by treating the compound of Formula 3 with an excess amount of HCl in dioxane for 8 to 12 hours.

A compound of Formula I can be prepared as a pharmaceutically acceptable acid addition salt by reacting the free base form of the compound with a pharmaceutically acceptable inorganic or organic acid. Alternatively, a pharmaceutically acceptable base addition salt of a compound of Formula I can be prepared by reacting the free acid form of the compound with a pharmaceutically acceptable inorganic or organic base. Inorganic and organic acids and bases suitable for the preparation of the pharmaceutically acceptable salts of compounds of Formula I are set forth in the definitions section of this application. Alternatively, the salt forms of the compounds of Formula I can be prepared using salts of the starting materials or intermediates.

The free acid or free base forms of the compounds of Formula I can be prepared from the corresponding base addition salt or acid addition salt form. For example, a compound of Formula I in an acid addition salt form can be converted to the corresponding free base by treating with a suitable base (e.g. ammonium hydroxide solution, sodium hydroxide, or the like). A compound of Formula I in a base addition salt form can be converted to the corresponding free acid by treating with a suitable acid (e.g. hydrochloric acid, etc).

The *N*-oxides of compounds of Formula I can be prepared by methods known to those of ordinary skill in the art. For example, *N*-oxides can be prepared by treating an unoxidized form of the compound of Formula I with an oxidizing agent (e.g. trifluoroperacetic acid, permaleic acid, perbenzoic acid, peracetic acid, *meta*-chloroperoxybenzoic acid, or the like) in a suitable inert organic solvent (e.g. a halogenated hydrocarbon such as dichloromethane) at approximately 0°C. Alternatively, the *N*-oxides of the compounds of Formula I can be prepared from the *N*-oxide of an appropriate starting material.

Compounds of Formula I in unoxidized form can be prepared from *N*-oxides of compounds of Formula I by treating with a reducing agent (e.g. sulfur, sulfur dioxide, triphenyl phosphine, lithium borohydride, sodium borohydride, phosphorus trichloride, tribromide, or the like) in an suitable inert organic solvent (e.g. acetonitrile, ethanol, aqueous dioxane, or the like) at 0 to 80°C.

Prodrug derivatives of the compounds of Formula I can be prepared by methods known to those of ordinary skill in the art (e.g. for further details see Saulnier *et al.*(1994), *Bioorganic and Medicinal Chemistry Letters.* **4**:1985). For example, appropriate prodrugs can be prepared by reacting a non-derivatized compound of Formula I with a suitable carbamylating agent (e.g. 1,1-acyloxyalkylcarbonochloridate, *para*-nitrophenyl carbonate, or the like).

Protected derivatives of the compounds of Formula I can be made by means known to those of ordinary skill in the art. A detailed description of the techniques applicable to the creation of protecting groups and their removal can be found in T.W. Greene, *Protecting Groups in Organic Synthesis*, John Wiley & Sons, Inc. 1981.

Compounds of Formula I can be prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers and recovering the optically pure enantiomer. While resolution of enantiomers can be carried out using covalent diasteromeric derivatives of compounds of Formula I, dissociable complexes are preferred (e.g. crystalline diastereoisomeric salts). Diastereomers have distinct physical properties (e.g. melting points, boiling points, solubilities, reactivity, and the like) and can be readily separated by taking advantage of these dissimilarities. The diastereomers can be separated by chromatography or, preferably, by separation/resolution techniques based upon differences in solubility. The optically pure enantiomer is then recovered, along with the resolving agent, by any practical means that would not result in racemization. A more detailed description of the techniques applicable to the resolution of stereoisomers of compounds from their racemic mixture can be found in Jean Jacques Andre Collet, Samuel H. Wilen, Enantiomers, Racemates and Resolutions, Honh Wiley & Sons, Inc. (1981).

Examples:

REFERENCE 1

4-Methyl-piperazine-1-carbothioic acid amide

Thiocarbonyldiimidazole (2.0 g) was dissolved in THF (30 mL) and the solution was stirred at room temperature while *N*-methyl piperazine (1.1 gm) was added. The reaction mixture was stirred at room temperature for 1 hour and then at 55 °C for 1 hour. The reaction mixture was cooled to room temperature and approximately 20 ml of THF was removed under vacuum. Ammonia in ethanol (2.0 M soln, 20 mL) was added and the mixture was stirred overnight. The mixture was heated at 55 °C for 2 hours and then cooled to room temperature. A solid material was isolated by filtration, washed with ether and dried to give 4-methyl-piperazine-1-carbothioic acid amide (1.0 gm, 60% yield). LC-MS and PMR. ^{1}H NMR (DMSO-d_6, ppm):): 2.13 (s, 3 H), 2.23 (m, 4 H), 3.68 (m, 4 H), 7.5 (br. s. 2 H).

REFERENCE 2

4-Bromoacetylbenzoic acid

4-Acetyl benzoic acid (20 gms, 128.2 mmol) was taken up into acetic acid (200 ml) and dissolved by heating to 80 ° C. Bromine (7.0 mL, 128.2 mmol) was added to the solution and the mixture was stirred for 1 hour while cooling to room temperature. A solid material was isolated by filtration, washed with ether and dried to give 4-bromoacetylbenzoic acid (20 gms, 67%). ^{1}H NMR (DMSO-d_6, ppm): 5.51 (s, 2 H), 7.81 (m, 4 H), 10.1 (br. S. 1 H).

REFERENCE 3

4-[2-(4-Methyl-piperazin-1-yl)-thiazol-4-yl]-benzoic acid

4-Bromoacetylbenzoic acid (2.44 g, 10.0 mmol), prepared as in Reference 2, was dissolved in ethanol (50 mL) and then 4-methyl-piperazine-1-carbothioic acid amide (1.59 g, 10 mmol), prepared as in Reference 1, was added to the solution. The mixture

was refluxed for 3 hours and the solids were isolated by filtration, washed with acetone and ether and dried to give 4-[2-(4-methyl-piperazin-1-yl)-thiazol-4-yl]-benzoic acid (3.90 g, 100% yield). FAB LC-MS. 304.2 ($M+H^+$).

REFERENCE 4

1-Amino-cyclohexanecarboxylic acid [1-(benzooxazol-2-yl-hydroxymethyl)-3-phenyl-propyl]-amide

1-*tert*-Butoxycarbonylamino-cyclohexanecarboxylic acid (1.00 g, 4.11 mmol), (*S*)-2-amino-1-benzooxazol-2-yl-4-phenyl-butan-1-ol (1.16 g, 4.11 mmol, 16.05 mL of a 0.256 M solution in CH_2Cl_2) and HATU (1.563 g, 4.11 mmol) were dissolved in DMF (20 mL). The mixture was cooled to 0 °C and then triethylamine (1.72 mL, 12.33 mmol) was added. The mixture was stirred at ambient temperature for about 8-12 hours and then combined with 4:1:2:3 ethyl acetate/THF/water/brine (150 mL). The organic phase was isolated, sequentially washed with 1M HCl (50 mL), saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (0-50% ethyl acetate/hexane) to give {1-[1-(1-benzooxazol-2-yl-1-hydroxy-methyl)-3-phenyl-propylcarbamoyl]-cyclohexyl}-carbamic acid *tert*-butyl ester (1.78 g, 85% yield).

The {1-[1-(1-benzooxazol-2-yl-1-hydroxy-methyl)-3-phenyl-propylcarbamoyl]-cyclohexyl}-carbamic acid *tert*-butyl ester was dissolved in CH_2Cl_2 (5 mL) and the solution was mixed with HCl in dioxane (9 mL, 36 mmol). The resulting mixture was agitated at ambient temperature for about 8 to 12 hours and then was diluted with ethyl ether (200 mL) forming a suspension. The solids were isolated, washed with hexane and dried to give 1-amino-cyclohexanecarboxylic acid [1-(benzooxazol-2-yl-hydroxymethyl)-3-phenyl-propyl]-amide (1.25 g, 80% yield).

REFERENCE 5

(1-{1-[hydroxy-(5-phenyl-[1,3,4]oxadiazol-2-yl)-methyl]-pentylcarbamoyl}-cyclohexyl)-carbamic acid tert-butyl ester

{1-[Hydroxy-(5-phenyl-[1,3,4]oxadiazol-2-yl)-methyl]-pentyl}-carbamic acid *tert*-butyl ester (0.416 g, 1.15 mmol) was dissolved in CH_2Cl_2 (3 mL) and HCl/dioxane (2.87 mL of a 4.0 M solution) was added. The mixture was stirred at room temperature overnight and then ether (75 mL) was added. The mixture was stirred/triturated for 2 hours and the supernatant was removed. The residue was triturated once more with ether (75 mL) and then dried *in vacuo* to give 2-amino-1-(5-phenyl-[1,3,4]oxadiazol-2-yl)-hexan-1-ol hydrochloride (0.304, 74% yield).

1-*tert*-Butoxycarbonylaminocyclohexanecarboxylic acid (0.243 g, 1.00 mmol), 2-amino-1-(5-phenyl-[1,3,4]oxadiazol-2-yl)-hexan-1-ol hydrochloride (0.304 g, 1.02 mmol) and HATU (0.380 g, 1.00 mmol, PerSeptive Biosystems) were dissolved in DMF (5 mL) and then diisopropylethylamine (DIPEA, 0.533 mL, 3.00 mmol) was added to the solution. The mixture was stirred for 3 hours at room temperature and 10% aqueous Na_2CO_3 (5 mL) was added. The mixture was stirred for 10 minutes and then extracted with ethyl acetate (50 mL). The extract was washed with water (10 mL), 1M HCl (10 mL), saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated to dryness to give (1-{1-[hydroxy-(5-phenyl-[1,3,4]oxadiazol-2-yl)-methyl]-pentylcarbamoyl}-cyclohexyl)-carbamic acid tert-butyl ester (0.46 g) as a mixture of diastereomers. TLC (50% ethyl acetate/CH_2Cl_2) $R_f = 0.48, 0.41$.

REFERENCE 6

1-(4-Trifluoromethoxybenzoylamino)-cyclohexanecarboxylic acid

1-*tert*-Butoxycarbonylamino-cyclohexanecarboxylic acid (14.66 g, 60.25 mmol), phenyl-methanol (6.24 mL, 60.25 mmol) and 4-dimethylaminopyridine (0.736 g, 6.025 mmol) were dissolved in CH_2Cl_2 (200 mL) and then diisopropylcarbodiimide (9.43 mL, 60.25 mmol) was added to the solution. The mixture was stirred at room temperature for 16 hours and then the solvent was removed under reduced pressure. The residue was combined with ethyl acetate (200 mL) to form a suspension which was cooled to -20°C, filtered, washed with 1M HCl (100 mL), saturated aqueous $NaHCO_3$ (100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and evaporated to dryness to give 1-*tert*-butoxycarbonylamino-cyclohexanecarboxylic acid benzyl ester.

The 1-*tert*-butoxycarbonylamino-cyclohexanecarboxylic acid benzyl ester was dissolved in CH_2Cl_2 (60 mL) and then HCl/dioxane (125 mL of a 4.0M solution) was added to the solution. The mixture was stirred for 2 hours at room temperature and then ether (30 mL) was added to form a precipitate. The solid was isolated by filtration, washed with ether (3 x 100 mL) and hexane (100 mL) and dried in vacuo to give 10.66 g of 1-amino-cyclohexanecarboxylic acid benzyl ester hydrochloride (10.66 g, 66% yield from 1-*tert*-butoxycarbonylamino-cyclohexanecarboxylic acid).

4-Trifluoromethoxy-benzoyl chloride (2.07 g, 9.23 mmol) was dissolved in THF (50 mL) and then 1-amino-cyclohexanecarboxylic acid benzyl ester hydrochloride (2.48 g, 9.23 mmol) and DIPEA (6.42 mL, 36.9 mmol) were added to the solution. The mixture was stirred at room temperature for 3 hours and then ethyl acetate (100 mL) was added. The mixture was washed with 1M HCl (50 mL), saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered and evaporated to dryness to give an oil which upon standing crystallized to give (1-(4-trifluoromethoxybenzoylamino)-cyclohexanecarboxylic acid benzyl ester.

The (1-(4-trifluoromethoxybenzoylamino)-cyclohexanecarboxylic acid benzyl ester was dissolved in ethanol (100 mL) and then 10% Pd on carbon (0.4 g) was added to the solution. The mixture was hydrogenated on a Parr shaker at room temperature (50 PSI H_2) for 16 hours and then the solution was filtered and evaporated to dryness. The residue

was crystallized from CH_2Cl_2/hexane to give 1-(4-trifluoromethoxybenzoylamino)-cyclohexanecarboxylic acid (2.23 g, 73% from 1-*tert*-butoxycarbonylamino-cyclohexanecarboxylic acid).

REFERENCE 7

(S)-2-Amino-1-[5-(4-methoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-pentan-1-ol hydrochloride

Methyl 4-methoxybenzoate (25.0 g, 150 mmol), hydrazine hydrate (11.0 mL, 225mmol), toluene (10 mL) and dioxane (10 mL) were added to a 100 mL round-bottomed flask equipped with a stir bar and reflux condenser. The mixture was stirred for 24 hours at 100 °C and then concentrated by rotary evaporation. The residue was dissolved in methylene chloride and the solution was extracted with a saturated aqueous solution of sodium chloride. The aqueous phase was extracted with methylene chloride. The combined organic phases were dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated by rotary evaporation and then dried overnight under reduced pressure to give 4-methoxybenzoic acid hydrazide (23.21g, 140 mmol, 93% yield) as a white solid.

4-Methoxybenzoic acid hydrazide (23.21g, 140mmol), trimethyl orthoformate (23 mL, 210mmol) and p-toluenesulfonic acid monohydrate (0.40g, 210 mmol) were combined in a 100 mL round-bottomed flask equipped with a standard distillation apparatus and the mixture was heated at 80-120 °C until methanol ceased to be collected by distillation. The remaining solid residue was dissolved in warm 2-propanol and precipitated by addition of water. The solid was washed with a mixture (ca. 1:1) of 2-propanol and water and then with water. The off-white solid was dried overnight under reduced pressure to give 2-(4-methoxyphenyl)-1,3,4-oxadiazole (17.36g, 98.5 mmol, 70.4% yield). TLC R_f=0.32, EtOAc/hexane (1/1). MS: m/z = 176.8 $(M + H)^+$.

2-(4-Methoxyphenyl)-1,3,4-oxadiazole (17.36 g, 98.5 mmol) was dissolved in THF (300 mL) and the solution was cooled to -70 °C. *n*-Butyllithium (39.4 mL of a 2.5 M solution in hexane, 98.5 mmol) was added dropwise under nitrogen to the stirring cooled solution and the mixture was stirred for 40 minutes. $MgBr_2 \cdot OEt_2$ (25.4g, 98.5 mmol) was added and the mixture was allowed to warm to -45 °C. The resulting slurry was stirred at

-45 °C for another 1.5 hours and then (*S*)-(1-formyl-propyl)-carbamic acid *tert*-butyl ester (7.24 g, 36 mmol) in THF (19 mL) of was added. The reaction temperature was raised to -20 °C and stirred for 3.5 hours. The reaction was quenched with saturated NH_4Cl and the mixture extracted with ethyl acetate. The organic layer was washed with water (x3) and then brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated by rotary evaporation. The residue was tritiated with hot hexane. The hexane was decanted and upon cooling a white precipitate formed. The hexane was filtered removing the precipitate and the filtrate was recombined with the residue. The mixture was concentrated by rotary evaporation. Product was purified from the residue by column chromatography on silica gel (Merck 60, EtOAc/hexane (1/1-4/1) to give ((*S*)-1-{1-hydroxy-1-[5-(4-methoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-methyl}-butyl)-carbamic acid *tert*-butyl ester (1.82 g, 4.83 mmol, 13.4% yield). TLC R_f=0.18, EtOAc/hexane (1/1). MS: m/z = 377.0 $(M + H)^+$, 400.0 $(M + Na)^+$.

((*S*)-1-{1-Hydroxy-1-[5-(4-methoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-methyl}-butyl)-carbamic acid *tert*-butyl ester (1.82 g, 4.83 mmol) was dissolved in 4N HCl in dioxane (12 mL) and the solution was stirred at room temperature for 15 hours. The mixture was concentrated by rotary evaporation and then dried by azeotropic removal of water with toluene to give (*S*)-2-amino-1-[5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl] pentan-1-ol hydrochloride quantitatively. MS m/z = 278.4 $(M + H)^+$.

Proceeding as in Reference 7 provided the following intermediates:

(*S*)-2-amino-1-(5-phenyl-[1,3,4]oxadiazol-2-yl)-pentan-1-ol; MS m/z = 248.4 $(M + H)^+$;

(*S*)-2-amino-1-[5-(3-methoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-pentan-1-ol; MS m/z = 278.2 $(M + H)^+$;

(*S*)-2-amino-1-[5-(4-trifluoromethyl-phenyl)-[1,3,4]oxadiazol-2-yl]-pentan-1-ol; MS m/z = 316.2 $(M + H)^+$;

(*S*)-2-amino-1-[5-(3-trifluoromethyl-phenyl)-[1,3,4]oxadiazol-2-yl]-pentan-1-ol;

(*S*)-2-amino-1-(5-*tert*-butyl-[1,3,4]oxadiazol-2-yl)-pentan-1-ol; MS m/z = 278.4 $(M + H)^+$;

(*S*)-2-amino-1-(5-ethyl-[1,3,4]oxadiazol-2-yl)-pentan-1-ol; MS m/z = 278.4 $(M + H)^+$; and

(*S*)-2-amino-1-(5-methoxymethyl-[1,3,4]oxadiazol-2-yl)-pentan-1-ol.

REFERENCE 8

(*S*)-2-Amino-1-(5-phenyl-[1,3,4]oxadiazol-2-yl)-hexan-1-ol trifluoroacetic acid

Benzoylhydrazide (22.5 g, 165 mmol) and triethylorthoformate (150 ml) and *p*-toluenesulfonic acid (300 mg) were combined and the mixture heated at 120 °C for 12 hours. The mixture was concentrated under vacuum and was product was purified from the residue by silica gel column chromatography to give 2-phenyloxadiazole (14.5 g). H^1 NMR (DMSO-□): 9.34 (1H, s), 8.05-7.98 (2H, m), 7.68-7.55 (3H, m). MS: 147.4 (M+1)

Oxadiazole (1.46 g, 10 mmol) was dissolved in THF (40 ml) and the mixture was cooled to -78 °C. *n*-Buthyl lithium (1.6M solution in 6.2 ml of hexane) was added to the cooled solution dropwise under nitrogen. The mixture was stirred for 1 hour and then $MgBr.Et_2O$ (2.58 g, 10 mmol) was added. The mixture was allowed to warm to -45 °C and then was treated with ((*S*)-1-formyl-pentyl)-carbamic acid *tert*-butyl ester (1.07 g, 5 mmol) in THF (20 ml). The mixture was stirred for 1 hour, quenched with saturated NH_4Cl and extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography to give {(*S*)-1-[1-hydroxy-1-(5-phenyl-[1,3,4]oxadiazol-2-yl)-methyl]-pentyl}-carbamic acid *tert*-butyl ester; (800 mg). MS: 360.2 (M-1), 362.6 (M+1), 364.6 (M+23).

{(*S*)-1-[1-Hydroxy-1-(5-phenyl-[1,3,4]oxadiazol-2-yl)-methyl]-pentyl}-carbamic acid *tert*-butyl ester (260 mg, 0.72 mmol) and CH_2Cl_2 (5ml) were combined and the mixture was treated with trifluoroacetic acid (1ml) at room temperature. The mixture was stirred for 1 hour and then concentrated under vacuum to give (*S*)-2-amino-1-(5-phenyl-[1,3,4]oxadiazol-2-yl)-hexan-1-ol trifluoroacetic acid.

REFERENCE 9

1-{[1-(4-Morpholin-4-yl-piperidin-1-yl)-methanoyl]-amino}-cyclohexanecarboxylic acid

1-Amino-cyclohexanecarboxylic acid benzyl ester hydrochloride (5.16 g, 19.13 mmol) and pyridine (6.19 mL, 76.51 mmol) were dissolved in CH_2Cl_2 (100 mL) and the solution was cooled to 0°C. Phosgene (12.88 mL of a 20% toluene solution (approx. 1.93 mmol, Fluka)) was added to the cooled solution and then the mixture was stirred for 2 hours while warming to room temperature. The mixture was quickly washed with ice-cold 0.5 M HCl (100 mL then 50 mL) and ice-cold brine (100 mL), dried over $MgSO_4$, filtered and concentrated to dryness to give 1-formylamino-cyclohexanecarboxylic acid benzyl ester (4.58 g, 92% yield).

1-Formylamino-cyclohexanecarboxylic acid benzyl ester (1.00 g, 3.86 mmol) was dissolved in THF and then *tert*-butylpiperazine dihydrobromide (1.17 g, 3.86 mmol) and DIPEA (2.69 mL, 15.43 mmol) were added to the solution. The mixture was stirred overnight at room temperature and then diluted with ethyl acetate (50 mL). The mixture was washed with saturated aqueous $NaHCO_3$ (25 mL) and brine (25 mL), dried over $MgSO_4$, filtered and concentrated to give 1-{[1-(4-*tert*-butyl-piperazin-1-yl)-methanoyl]-amino}-cyclohexanecarboxylic acid benzyl ester.

The 1-{[1-(4-*tert*-butyl-piperazin-1-yl)-methanoyl]-amino}-cyclohexanecarboxylic acid benzyl ester was dissolved in ethanol (30-40 mL) and subjected to hydrogenolysis on a Parr shaker in the presence of 10% Pd on C (0.2-0.3 g) for 24 hours. The zwitterionic products were isolated by filtration, evaporation to dryness and precipitation from CH_2Cl_2/hexane to give 1-{[1-(4-*tert*-butyl-piperazin-1-yl)-methanoyl]-amino}-cyclohexanecarboxylic acid (0.816 g, 90%).

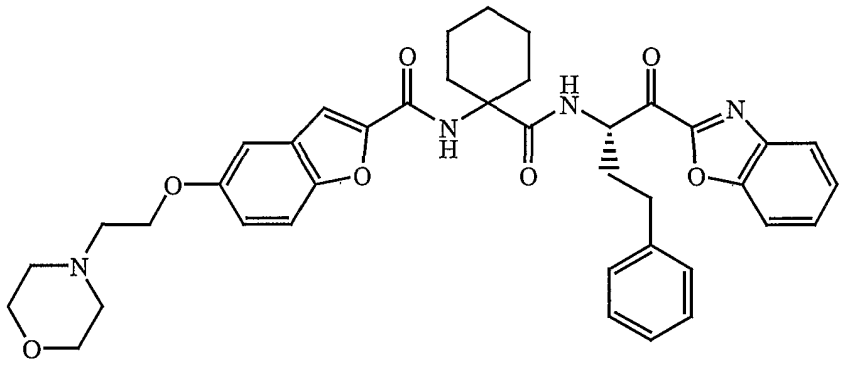
Proceeding as in Reference 9 provided the following intermediates:

1-{[1-(4-methyl-piperazin-1-yl)-methanoyl]-amino}-cyclohexanecarboxylic acid; and

1-{[1-(4-morpholin-4-yl-piperidin-1-yl)-methanoyl]-amino}-cyclohexanecarboxylic acid; MS $M^{+1} = 338$.

EXAMPLE 1

5-(2-Morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid {1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-3-phenyl-propylcarbamoyl]-cyclohexyl}-amide (Compound 1)



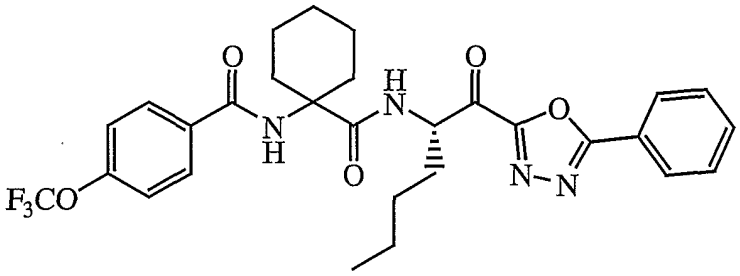
A solution of 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid hydrochloride (0.147 g, 0.449 mmol), (*S*)-1-amino-cyclohexanecarboxylic acid [1-(benzooxazol-2-yl-hydroxy-methyl)-3-phenylpropyl]-amide, prepared as in Reference 4, (0.200 g, 0.449 mmol) and HATU (0.171 g, 0.449 mmol) in DMF (2 mL) was treated with triethylamine (0.251 mL, 1.78 mmol) at room temperature overnight. Potassium carbonate (10%, 5 mL) was added. The mixture was stirred vigorously for 10 minutes, whereupon the suspension was diluted with ethyl acetate/THF/brine (4:1:3, 15 mL). The organic phase was separated, washed with saturated aqueous $NaHCO_3$ (5 mL), brine (5 mL), dried over $MgSO_4$, filtered, and evaporated to give 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid {1-[(*S*)-1-(1-benzooxazol-2-yl-1-hydroxy-methyl)-3-phenyl-propylcarbamoyl]-cyclohexyl}-amide (0.32 grams, 100% yield).

The 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid {1-[(*S*)-1-(1-benzooxazol-2-yl-1-hydroxy-methyl)-3-phenyl-propylcarbamoyl]-cyclohexyl}-amide was dissolved in CH_2Cl_2 (5 mL) at room temperature and then treated with Dess-Martin periodinane (0.382 g, 0.90 mmol). The mixture was stirred overnight. Saturated aqueous $NaHCO_3$ (10 mL) was added. The mixture was stirred vigorously for 10 minutes, extracted with ethyl acetate (50 mL), washed with brine (10 mL), dried over $MgSO_4$,

filtered, evaporated, and purified by preparative HPLC to give 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid {1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-3-phenyl-propylcarbamoyl]-cyclohexyl}-amide (10 mg). MS ($M+1^+$): 679.

EXAMPLE 2

N-(1-{(*S*)-1-[1-(5-Phenyl-[1,3,4]oxadiazol-2-yl)-methanoyl]-pentylcarbamoyl}-cyclohexyl)-4-trifluoromethoxy-benzamide (Compound 40);



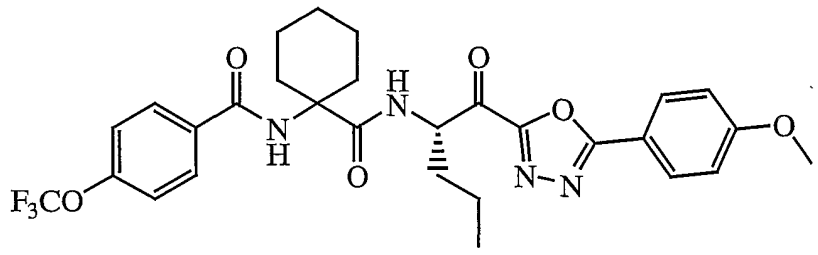
(1-{(*S*)-1-[1-Hydroxy-1-(5-phenyl-[1,3,4]oxadiazol-2-yl)-methyl]-pentylcarbamoyl}-cyclohexyl)-carbamic acid *tert*-butyl ester (0.46 g, 0.94 mmol), prepared as in Reference 5, was dissolved in CH_2Cl_2 (2.5 mL) and the solution was treated with HCl/dioxane (2.5 mL of a 4.0 M solution) at room temperature overnight. The mixture was diluted with ether (200 mL) and solids were isolated by filtration, washed with ether (2x 30 mL) and dried *in vacuo*. The residue was dissolved in THF (10 mL) at room temperature and then 4-trifluoromethoxybenzoyl chloride (0.157 g, 1.00 mmol) and DIPEA (0.533 mL, 1.00 mmol) were added sequentially. The mixture was stirred for 3 hours and then 1M HCl (10 mL) was added. The mixture was extracted with ethyl acetate (30 mL) and the extract washed with saturated aqueous $NaHCO_3$ (10 mL), dried over $MgSO_4$, filtered and concentrated to dryness to give *N*-(1-{1-[hydroxy-(5-phenyl-[1,3,4]oxadiazol-2-yl)-methyl]-pentylcarbamoyl}-cyclohexyl)-4-trifluoromethoxybenzamide as a mixture of diastereomers. TLC (50% ethyl acetate/CH_2Cl_2) R_f = 0.66, 0.50.

The *N*-(1-{1-[hydroxy-(5-phenyl-[1,3,4]oxadiazol-2-yl)-methyl]-pentylcarbamoyl}-cyclohexyl)-4-trifluoromethoxybenzamide (0.53 g, 0.92 mmol) was dissolved in CH_2Cl_2 (5 mL) and the solution was treated with Dess-Martin periodinane

(DMP, Lancaster Synthesis, 0.424 g, 1.00 mmol) for 30 minutes at room temperature. Isopropanol (0.5 mL) was added to the solution. The mixture was stirred for 10 minutes and saturated aqueous $NaHCO_3$ (10 mL) was added. The mixture stirred for another 30 minutes and then extracted with ethyl acetate (50 mL). The extract was dried over $MgSO_4$, filtered and concentrated to dryness. The residue was purified by chromatography on silica gel (20-50% ethyl acetate/hexane) and product was isolated by precipitation from ether and hexane to give *N*-(1-{(*S*)-1-[1-(5-phenyl-[1,3,4]oxadiazol-2-yl)-methanoyl]-pentylcarbamoyl}-cyclohexyl)-4-trifluoromethoxy-benzamide (16 mg, 3% yield). MS (M^{+1}) = 573.

EXAMPLE 3

N-[1-((*S*)-1-{1-[5-(4-Methoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-methanoyl}-butylcarbamoyl)-cyclohexyl]-4-trifluoromethoxy-benzamide (Compound 46)



1-(4-Trifluoromethoxybenzoylamino)-cyclohexanecarboxylic acid (0.20 g, 0.60 mmol), prepared as in Reference 6, (*S*)-2-amino-1-[5-(4-methoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-pentan-1-ol hydrochloride (0.170 g, 0.60 mmol) and HATU (0.23 g, 0.60 mmol) were dissolved in DMF (3 mL) and then DIPEA (0.315 mL, 1.80 mmol) was added to the solution. The mixture was stirred until the reaction was complete and then 10% Na_2CO_3 (2 mL) was added. The mixture was stirred for 1 hour and then ethyl acetate (10 mL) and water (2 mL) were added. The mixture was stirred for 15 minutes and then the organic phase was separated, washed with 1M HCl (3 mL), saturated aqueous $NaHCO_3$ (3 mL) and brine (3 mL), dried over $MgSO_4$, filtered and evaporated to give *N*-[1-((*S*)-1-{1-hydroxy-1-[5-(4-methoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-methyl}-butylcarbamoyl)-cyclohexyl]-4-trifluoromethoxy-benzamide as a mixture of

diastereomers. The mixture was used directly in the next step without intermediate purification. TLC (50% ethyl acetate/hexane) showed two spots, Rf = 0.27, 0.19.

The diastereomeric mixture was dissolved in CH_2Cl_2 (8 mL) at room temperature and then DMP (0.424 g, 1.00 mmol) was added. The mixture was stirred for 1 hour and then IPA (0.5 mL) was added. The mixture was allowed 10 minutes and then saturated aqueous $NaHCO_3$ (10 mL) and ethyl acetate (50 mL) were sequentially added. The organic phase was separated, washed with 1M HCl (10 mL), saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered and evaporated to dryness. The residue was purified by chromatography on a short plug of silica gel, using a 10-30% ethyl acetate/hexane gradient. The pure fractions were collected, concentrated, and isolated as a gelatinous precipitate from CH_2Cl_2/hexane to provide *N*-[1-((*S*)-1-{1-[5-(4-methoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-methanoyl}-butylcarbamoyl)-cyclohexyl]-4-trifluoromethoxy-benzamide. MS (M^{+1}): 589. ^{1}H NMR ($CDCl_3$): 0.95 (3H, t, J = 7 Hz), 1.3-2.31 (14H, m*), 3.87 (3H, s), 5.38 (1H, ddd), 6.21 (1H, s), 6.99 (2H, d, J = 8.9 Hz), 7.25 (2H, d, J = 7.9 Hz), 7.79 (2H, d, J = 8.9 Hz), 7.9 (1H, d, J = 7 Hz), 8.03 (2H, d, J = 9 Hz). ^{13}C NMR ($CDCl_3$): 13.7, 10.1, 21.7, 25.2, 32.3, 33.9, 55.6, 56.8, 60.7, 114.8, 115.1, 120.8, 129.0, 129.8, 133.1, 151.8, 159.5, 163.4, 166.2, 111.9, 174.0, 186.0.

Proceeding as in Example 3 provided the following compounds of Formula I:

N-(1-{(*S*)-1-[1-(5-phenyl-[1,3,4]oxadiazol-2-yl)-methanoyl]-butylcarbamoyl}-cyclohexyl)-4-trifluoromethoxy-benzamide (Compound 44); MS (M^{+1}): 559; ^{1}H NMR ($CDCl_3$): 0.954 (3H, t, J = 7.4 Hz), 1.3-2.3 (14H, m*); 5.38 (ddd, 1H); 6.06 (1H, s), 7.26 (2H, d, J = 8.6 Hz), 7.46-7.7.62 (3H, m), 7.81 (2H, d, J = 8.6 Hz); 7.92 (1H, d, J = 7 Hz); 8.10 (2H, J = 6.9 Hz). ^{13}C ($CDCl_3$ (partial)): 21.75, 32.36, 120.92, 127.87, 128.96, 128.32, 167, 174, 186);

N-[1-((*S*)-1-{1-[5-(3-methoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-methanoyl}-butylcarbamoyl)-cyclohexyl]-4-trifluoromethoxy-benzamide (Compound 45) MS (M^{+1}): 588; ^{1}H NMR ($CDCl_3$): 0.96 (3H, t, J = 7 Hz), 1.38-2.31 (14H, m*), 3.86 (3H, s), 5.37 (1H, m), 6.12 (1H, s), 7.13 (1H, ddd), 7.25 (2H, J = 10 Hz), 7.41 (1H, t, J = 8 Hz), 7.61 (1H, t), 7.69 (1H, dt), 7.78 (2H, dt), 7.92 (1H, d, J = 6.7 Hz). ^{13}C NMR ($CDCl_3$): 13.7,

19.1, 21.7, 25.2, 32.3, 33.8, 55.6, 56.9, 60.7, 112.1, 119.7, 120.3, 120.9, 123.8, 129.0, 130.5, 133.0, 160.1, 167.0, 174.1, 186.1;

4-trifluoromethoxy-*N*-[1-((*S*)-1-{1-[5-(4-trifluoromethyl-phenyl)-[1,3,4]oxadiazol-2-yl]-methanoyl}-butylcarbamoyl)-cyclohexyl]-benzamide (Compound 47); MS (M^{+1}): 627. ^{1}H NMR ($CDCl_3$): 0.96 (3H, t, J = 7 Hz), 1.2-2.33 (14H, m*), 5.35 (1H, m), 6.08 (1H, s), 7.25 (2H, d, J = 8.4 Hz), 7.77 (4H, 2xd), 7.96 (1H, d, J = 6.7 Hz), 8.24 (2H, d, J = 8 Hz). ^{13}C NMR ($CDCl_3$, partial): 13.6, 19.0, 21.6, 25.1, 32.3, 33.5, 56.9, 60.6, 120.8, 126.3, 126.3, 128.1, 128.9, 132.9, 167.0, 174.0, 186;

4-trifluoromethoxy-*N*-[1-((*S*)-1-{1-[5-(3-trifluoromethyl-phenyl)-[1,3,4]oxadiazol-2-yl]-methanoyl}-butylcarbamoyl)-cyclohexyl]-benzamide (Compound 48); MS (M^{+1}): 627. NMR ($CDCl_3$): 0.96 (3H, t, J = 7 Hz), 1.3-2.35 (14H, m*), 5.36 (1H, ddd), 6.07 (1H, s), 7.27 (2H, d, J = 8 Hz), 7.67 (1H, t, J = 8 Hz), 7.81 (2H, m*), 7.96 (1H, d, J = 6.4 Hz), 8.31 (1H, d, J = 8 Hz), 8.38 (1H, s). ^{13}C NMR (partial, $CDCl_3$): 13.6, 19.3, 21.7, 25.4, 32.4, 33.8, 57.0, 60.4, 120.9, 128.9, 129.3, 130.2, 130.7, 133.1, 165, 166.7, 174.1, 186;

N-(1-{(*S*)-1-[1-(5-ethyl-[1,3,4]oxadiazol-2-yl)-methanoyl]-butylcarbamoyl}-cyclohexyl)-4-trifluoromethoxy-benzamide (Compound 52); MS (M^{+1}): 511; ^{1}H NMR ($CDCl_3$): 0.93 (3H, t, J = 7 Hz), 1.25-2.1 (15H, m* incl. t, J = 7.7 Hz), 2.23 (2H, br. t), 2.93 (2H, q, J = 7.7 Hz), 5.33 (1H, m), 6.11 (1H, s), 7.26 (2H, J = 8.4 Hz), 7.80 (2H, d, J = 8.4 Hz), 7.9 (2H, d, J = 6.7 Hz). ^{13}C NMR: 10.6, 13.7, 19.1, 19.3, 21.7, 25.2, 32.3, 32.4, 33.7, 56.8, 60.7, 120.9, 129.0, 133.1, 152.1, 160.2, 167.0, 170.1, 174.0, 186.2;

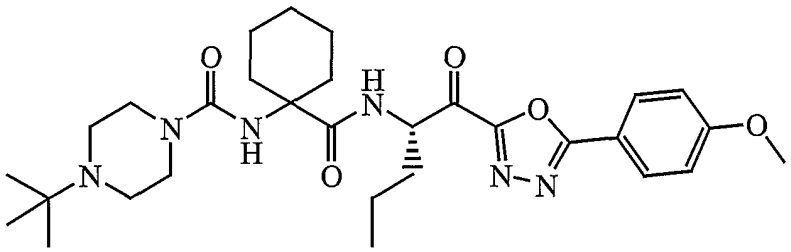
N-(1-{(*S*)-1-[1-(5-methoxymethyl-[1,3,4]oxadiazol-2-yl)-methanoyl]-butylcarbamoyl}-cyclohexyl)-4-trifluoromethoxy-benzamide (Compound 53); MS (M^{+1}): 527; ^{1}H NMR ($CDCl_3$): 0.94 (3H, t, J = 7 Hz), 1.3-1.85 (9H, m*), 1.87-2.1 (3H, m*), 2.25 (2H, br. t), 3.44 (3H, s), 4.67 (2H, s), 5.32 (1H, ddd), 6.09 (1H, s), 7.27 (2H, d, J = 8.6 Hz), 7.79 (2H, d, J = 8.7 Hz), 7.91 (1H, d, J = 6.4 Hz). ^{13}C ($CDCl_3$): 186 (C=O signal); and

N-(1-{(*S*)-1-[1-(5-*tert*-butyl-[1,3,4]oxadiazol-2-yl)-methanoyl]-butylcarbamoyl}-cyclohexyl)-4-trifluoromethoxy-benzamide (Compound 54); MS (M^{+1}): 539; ^{1}H NMR ($CDCl_3$): 0.93 (3H, t, J = 7 Hz), 1.42 (9H, s), 1.35-2.04 (12H, m*), 2.24 (2H, br. t), 5.35 (1H, ddd), 6.18 (1H, s), 7.26 (2H, d), 7.8 (2H, d), 8.17 (1H, d). ^{13}C NMR (partial, $CDCl_3$):

13.7, 19.1, 21.7, 27.2, 28.2, 32.3, 33.8, 56.7, 60.7, 120.9, 129.0, 133.5, 137.0, 167.3, 174.1, 186.2.

EXAMPLE 4

4-*tert*-butyl-piperazine-1-carboxylic acid [1-((*S*)-1-{1-[5-(4-methoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-methanoyl}-butylcarbamoyl)-cyclohexyl]-amide (Compound 51)



1-{[1-(4-*tert*-Butyl-piperazin-1-yl)-methanoyl]-amino}-cyclohexanecarboxylic acid (213 mg, 0.685 mmol), prepared as in Reference 9, (*S*)-2-amino-1-[5-(4-methoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-pentan-1-one hydrochloride (0.215 g, 0.685 mmol), prepared as in Reference 7, and HATU (0.266 g, 0.685 mmol) were dissolved in DMF (3 mL) was then DIPEA (0.358 mL, 2.06 mmol) was added to the solution. The mixture was stirred at room temperature for 72 hours and then 10% Na_2CO_3 (5 mL) was added. The mixture was stirred for 20 minutes and partitioned between 2:1 ethyl acetate and water (100 mL). The organic layer was washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated to dryness to give 4-*tert*-butyl-piperazine-1-carboxylic acid [1-((*S*)-1-{1-hydroxy-1-[5-(4-methoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-methyl}-butylcarbamoyl)-cyclohexyl]-amide as a mixture of stereoisomers. TLC (2 diastereomers, 10% CH_3OH/CH_2Cl_2): 0.60, 0.49.).

The 4-*tert*-butyl-piperazine-1-carboxylic acid [1-((*S*)-1-{1-hydroxy-1-[5-(4-methoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-methyl}-butylcarbamoyl)-cyclohexyl]-amide was dissolved in an alcohol mixture in CH_2Cl_2 (10 mL) and the solution was treated with DMP (0.424 g, 1.00 mmol) at room temperature for 1 hour. Isopropanol (0.5 mL) was added to quench excess oxidant and the mixture was partitioned between ethyl acetate

(50 mL) and saturated aqueous $NaHCO_3$ (70 mL, 50:20). The organic layer was washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated to dryness. Product was purified from the residue by flash chromatography on a short plug of silica gel, eluting with 10% methanol/ethyl acetate then 5-10% methanol/CH_2Cl_2) to give 4-morpholin-4-yl-piperidine-1-carboxylic acid [1-((S)-1-{1-[5-(4-methoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-methanoyl}-butylcarbamoyl)-cyclohexyl]-amide (80 mg, 20% yield). MS (M^{+1}): 569. ^1H NMR (DMSO-d^6): 0.86 (3H, t, J = 7 Hz): 1.01 (9H, s), 1.1-2.02 (14H m*), 2.44 (4H, m), 3.25 (4H, m), 3.84 (3H, s), 4.96 (1H, m), 5.95 (1H, s), 7.17 (2H, d, J = 8.9 Hz), 8.02 (2H, d*), 8.06 (1H, d).

Proceeding as in Example 4 provided the following compounds of Formula I:

4-morpholin-4-yl-piperidine-1-carboxylic acid [1-((*S*)-1-{1-[5-(4-methoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-methanoyl}-butylcarbamoyl)-cyclohexyl]-amide (Compound 50); MS (M^{+1}): 597; ^1H NMR (DMSO-d^6): 0.86 (3H, t, J = 7 Hz), 1.2-2.02 (18H, m*), 2.25 (2H, t*), 2.48 (4H, br. s), 2.63 (2H, t*), 3.55 (4H, br. s), 3.86 (3H, s), 4.95 (1H, m), 5.98 (1H, s), 7.16 (2H, d, J = 8.9 Hz), 8.02 (2H, d, J = 8.9 Hz), 8.07 (1H, d, J = 6.7 Hz).

4-methyl-piperazine-1-carboxylic acid [1-((*S*)-1-{1-[5-(4-methoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-methanoyl}-butylcarbamoyl)-cyclohexyl]-amide (Compound 49); MS (M^{+1}): 527. ^1H NMR (DMSO-d^6): 0.86 (1H, t, J = 7 Hz): 1.15-2.02 (14H, M*), 2.16 (3H, s). 2.24 (4H, m), 3.26 (4H, m), 3.84 (3H, s), 4.96 (1H, m), 5.99 (1H, s), 7.16 (2H, d, J = 9 Hz), 8.04 (3H, d* + d*);

4-*tert*-butyl-piperazine-1-carboxylic acid (1-{(*S*)-1-[1-(5-methoxymethyl-[1,3,4]oxadiazol-2-yl)-methanoyl]-butylcarbamoyl}-cyclohexyl)-amide (Compound 56); MS (M^{+1}): 507;

4-*tert*-butyl-piperazine-1-carboxylic acid (1-{(*S*)-1-[1-(5-ethyl-[1,3,4]oxadiazol-2-yl)-methanoyl]-butylcarbamoyl}-cyclohexyl)-amide (Compound 55); MS (M^{+1}): 491; and

4-*tert*-butyl-piperazine-1-carboxylic acid (1-{(*S*)-1-[1-(5-*tert*-butyl-[1,3,4]oxadiazol-2-yl)-methanoyl]-butylcarbamoyl}-cyclohexyl)-amide (Compound 57); MS (M^{+1}): 519.

Proceeding by procedures analogous to those set forth in this Application provided the following compounds of Formula I:

5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid {1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-pentylcarbamoyl]-cyclohexyl}-amide (Compound 2); ^{1}H NMR (partial assignment) (d^6-DMSO): 0.78 (3H, t, J= 6.4 Hz); 1.2-2.0 (16H, m); 2.05 (m); 3.2 (m); 3.5-3.8 (m); 3.97 (m); 4.39 (2H, t); 5.19 (1H); 7.15 (1H, dd, J = 9,2.4 Hz); 7.34 (1H, d), 7.46 (1H, s); 7.5 (1H, d, J=8 Hz); 7.59-7.66 (2H, m); 7.83-7.94 (2H, m); 8.14 (1H, d, J=7 Hz); MS ($M+1^+$): 631;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-3-phenyl-propylcarbamoyl]-cyclohexyl}-4-[2-(4-methyl-piperazin-1-yl)-thiazol-4-yl]-benzamide trifluoroacetic acid salt (Compound 3); NMR (d^6-DMSO): 1.3-2.3 (14H, m); 2.4-2.7 (4H, m); 2.89 (3H, s); 3.2 (2H, m) 4.1 (2H, d); 5.15 (1H, m); 7.1-7.3 (5H, m); 7.49-7.67 (3H, s); 7.85-7.95 (7H, dd); 8.27 (1H, d, J=5 Hz); 9.85 (1H, br s); MS ($M+1^+$): 691;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-pentylcarbamoyl]-cyclohexyl}-4-[2-(4-methyl-piperazin-1-yl)-thiazol-4-yl]-benzamide (Compound 4); MS ($M+1^+$): 643;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-4-morpholin-4-yl-benzamide (Compound 5); ^{1}H NMR ($CDCl_3$): 0.93 (3H, t, J = 7Hz), 1.25-2.38 (14H, m*), 3.26 (4H, dd, J = 4.9, 4.7 Hz) 3.87 (4H, t, J = 4.7 Hz), 5.58 (1H, m), 6.00 (1H, s), 6.90 (2H, d, J = 8.4 Hz), 7.38-7.85 (6H total, 1H, t, 1H, t, 1H, d, 2H, d, J = 8.4 Hz, 1H, d), 8.0 (1H, d, J = 6.9 Hz);

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-nicotinamide (Compound 6); 1H NMR ($CDCl_3$): 0.94 (3H, t, J = 7 Hz), 1.35-2.38 (14H, m*), 5.61 (1H, m), 6.55 (1H, br.s), 7.41 (1H, t), 7.44 (1H, t), 7.61 (1H, d), 7.78 (2H, d + br.s), 8.2 (1H, br. d), 8.73 (1H, d), 9.12 (1H, br.s);

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-isonicotinamide (Compound 7); ^{1}H NMR ($CDCl_3$): 0.937 (3H, t, J = 7 Hz); 1.33-2.37

(14H, m*), 5.59 (1H, m), 6.49 (1H, s), 7.41 (1H, t), 7.51 (1H, t), 7.65 (4H, 2xd, J = 9 Hz), 7.78 (1H, d, J = 6.9 Hz), 8.72 (1H, d, J = 5.4 Hz);

pyrazine-2-carboxylic acid {1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-amide (Compound 8); MS (M^{+23}, M+Na+H): 472. ^{1}H NMR ($CDCl_3$); 0.93 (3H, t, J = 7 Hz), 1.3-2.28 (14H, m*), 5.59 (1H, m), 7.39 (1H, t), 7.50 (1H, t), 7.75 (2H, m), 7.98 (1H, s), 8.54 (1H, d, J = 1 Hz), 8.77 (1H, d, J = 2.4 Hz), 9.32 (1H, d, J = 1 Hz);

benzofuran-2-carboxylic acid {1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-amide (Compound 9); MS: M^{+23} (M+Na)) 510, M^{-1}, 486. ^{1}H NMR ($CDCl_3$): 0.93 (3H, t, J = 7 Hz), 1.25-2.5 (14H, m*), 5.56 (1H, m), 6.64 (1H, s), 7.25-7.74 (9H, m*), 7.85 (1H, d, J = 7 Hz);

benzo[*b*]thiophene-2-carboxylic acid {1-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-amide (Compound 10); ^{1}H NMR ($CDCl_3$): 0.94 (3H, t, J = 7 Hz), 1.35-2.35 (14H, m*), 5.56 (1H, m), 6.12 (1H, br. s), 7.41-7.5 (4H, m*), 7.6 (1H, d), 7.72-7.9 (5H, m*);

5-methoxy-benzofuran-2-carboxylic acid {1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-amide (Compound 11); ^{1}H NMR ($CDCl_3$): 0.93 (3H, t, J = 7 Hz),1.26-2.38 (14H, m*), 3.84 (3H, s), 5.58 (1H, m), 6.60 (1H, s), 7.05 (2H, m), 7.29-7.51 (4H, m*), 7.59 (1H, d), 7.71 (1H, d), 7.88 (1H, d);

[1,4']bipiperidinyl-1'-carboxylic acid {1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-amide (Compound 12); MS (M^{+1}): 538;

4-isopropylamino-piperidine-1-carboxylic acid {1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-amide (Compound 13); MS (M^{+1}): 512;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-4-[2-(4-methyl-piperazin-1-yl)-thiazol-4-yl]-benzamide (Compound 14); MS (M^{+1}): 629. ^{1}H NMR (DMSO-d^6): 0.86 (3H, t, J = 7 Hz), 1.25-2.0 (12H, m*), 2.15 (2H, m*), 2.25 (3H, s), 2.49 (4H, m), 3.48 (4H, m), 5.22 (1H, m), 7.43 (1H, s), 7.52 (1H, t), 7.62 (1H, t), 7.79-8.0 (7H, m*), 8.05 (1H, d);

4-[4-(4-{1-[1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexylcarbamoyl}-phenyl)-thiazol-2-ylamino]-piperidine-1-carboxylic acid *tert*-butyl ester (Compound 15);

N-{1-[1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-4-(2-morpholin-4-ylmethyl-thiazol-4-yl)-benzamide (Compound 16);

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-4-methylamino-benzamide (Compound 17); ^{1}H NMR ($CDCl_3$), 0.87 (3H, br.t), 1.19-2.05 (12H, m*), 2.22 (2H, br.t), 2.96 (6H, s), 5.50 (1H, m), 5.95 (1H, br.s), 6.58 (2H, d), 7.34 (1H, t), 7.36 (1H, t), 7.59 (3H, m*), 7.73 (1H, d, J = 7 Hz), 8.18 (1H, d, J = 5 Hz);

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-3-methylamino-benzamide (Compound 18); MS (M^{+23}, M+Na+H): 513 ^{1}H NMR ($CDCl_3$): 0.93 (3H, t, J = 7 Hz), 1.25-2.15 (12H, m*), 2.27 (2H, br. t), 2.93 (3H, s), 2.98 (3H, s), 5.57 (1H, m), 6.11 (1H, s), 6.87 (1H, d), 6.99 (1H, d), 7.15 (1H, s), 7.27 (1H, t), 7.4 (1H, t), 7.49 (1H, t), 7.60 (1H, d), 7.76 (1H, d), 8.02 (1H, d);

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-4-(4-isopropyl-piperazin-1-yl)-benzamide (Compound 19);

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-4-(4-oxo-piperidin-1-yl)-benzamide (Compound 20);

N-{1-[1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-4-[2-(piperidin-4-ylamino)-thiazol-4-yl]-benzamide (Compound 21);

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-4-(4-*tert*-butyl-piperazin-1-yl)-benzamide (Compound 22);

1-acetylamino-cyclohexanecarboxylic acid [(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butyl]-amide (Compound 23); MS (M^{+23}, M+Na+H): 408;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-4-*tert*-butyl-benzamide Compound 24); MS (M^{+1}): 504;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-3-methyl-butylcarbamoyl]-cyclohexyl}-4-*tert*-butyl-benzamide (Compound 25); MS (M^{+23}, M+Na+H): 540;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-3,5-dimethoxy-benzamide (Compound 26); MS (M^{-1}): 506;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-3,4-dimethoxy-benzamide (Compound 27); MS (M^{+23}, M+Na+H): 530. M^{-1}: 506. ^{1}H NMR ($CDCl_3$): 0.93 (3H, t, J = 7 Hz), 1.31-2.36 (14H, m*), 3.89 (3H, s), 3.92 (3H, s),

5.57 (1H, m), 6.07 (1H, s), 6.85 (1H, d), 7.26 (1H, dd), 7.35 (1H, d), 7.39 (1H, dt), 7.49 (1H, dt), 7.61 (1H, d), 7.75 (1H, d, J = 8.1 Hz), 7.99 (1H, d, J = 7 Hz);

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-2-chloro-benzamide (Compound 28); MS (M^{+23}, M+Na+H): 504. ^{1}H NMR ($CDCl_3$): 0.94 (3H, t, J = 7 Hz). 1.27-2.23 (12H, m*), 2.37 (2H, d, J = 14 Hz), 5.67 (1H, m), 6.20 (1H, s), 7.38-7.68 (8H, m*), 7.87 (2H, d);

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-2,5-dichloro-benzamide (Compound 29); MS (M^{+23}, M+Na+H): 539, M^{+1}: 517. ^{1}H NMR ($CDCl_3$): 0.94 (3H, t, J = 7 Hz), 1.24-2.25 (12H, m*), 2.32 (2H, d, J = 13 Hz), 5.65 (1H, m), 6.24 (1H, s), 7.34 (2H, d), 7.43 (1H, dt), 7.51 (1H, dt), 7.62 (1H, t*), 7.65 (2H, d*), 7.85 (1H, J = 8 Hz);

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-4-nitro-benzamide (Compound 30); MS (M^{+1}): 493;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-4-fluoro-benzamide (Compound 31); MS (M^{+1}): 466;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-4-trifluoromethoxy-benzamide (Compound 32); MS (M^{+1}): 532. ^{1}H NMR ($CDCl_3$): 0.88 (3H, t, J = 7 Hz), 1.15-2.3 (14H, m*), 5.53 (1H, m), 6.34 (1H, s), 7.16 (2H, d), 7.35 (1H, t), 7.45 (1H, t), 7.55 (1H, d), 7.72 (4H, m*). ^{13}C NMR ($CDCl_3$): 13.8, 14.2, 19.0, 21.7, 22.7, 25.2, 31.6, 32.3, 34.3, 56.3, 60.7, 111.9, 120.8, 122.5, 125.9, 128.8, 129.0, 133.1, 140.5, 150.6, 151.7, 155.9, 166.8, 174.2, 188.8.l;

N-{1-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-4-isobutyl-benzamide (Compound 33); MS (M^{+23}, M+Na+H): 554: M^{-1}: 530;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-4-trifluoromethyl-benzamide (Compound 34); MS (M^{+1}): 516;

5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid {1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-amide (Compound 35); MS (M^{+1}): 617;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-4-chloro-benzamide (Compound 36); MS (M^{+23}, M+Na+H): 504, M^{-1}: 480;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-4-methanesulfonyl-benzamide (Compound 37); MS (M^{+1}): 526;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-propylcarbamoyl]-cyclohexyl}-4-trifluoromethoxy-benzamide (Compound 38); MS (M^{+1}): 518;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-4-methoxy-benzamide (Compound 39); MS (M^{+1}): 478; and

4-*tert*-butyl-*N*-(1-{(*S*)-1-[1-(5-chloro-benzooxazol-2-yl)-methanoyl]-butylcarbamoyl}-cyclohexyl)-benzamide (Compound 43).

EXAMPLE 5

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

ORAL FORMULATION

Compound of Formula I	10-100 mg
Citric Acid Monohydrate	105 mg
Sodium Hydroxide	18 mg
Flavoring	
Water	q.s. to 1oo ml

INTRAVENOUS FORMULATION

Compound of Formula I	0.1 to 10 mg
Dextrose Monohydrate	q.s. to make isotonic
Citric Acid Monohydrate	1.05 mg
Sodium Hydroxide	0.18 mg
Water for Injection	q.s. to 1.0 mL

TABLET FORMULATION

Compound of Formula I	1 %
Microcrystalline Cellulose	73 %
Stearic Acid	25 %
Colloidal Silica	1 %

EXAMPLE 6

Cathepsin B Assay

Solutions of test compounds (varying concentrations in 10 μL of DMSO) were diluted into assay buffer (40 μL, comprising: BES, 50 mM (pH 6); polyoxyethylenesorbitan monolaurate, 0.05%; and DTT, 2.5 mM). Human cathepsin B (0.025 pMoles in 25 μL of assay buffer) was added to the dilutions. The assay solutions were mixed for 5-10 seconds on a shaker plate, covered and incubated for 30 minutes at room temperature. Z-FR-AMC (20 nMoles in 25 μL of assay buffer) was added to the assay solutions and hydrolysis was followed spectrophotometrically at (λ 460 nm) for 5 minutes. Apparent inhibition constants (K_i) were calculated from the enzyme progress curves using standard mathematical models.

Compounds of the invention were tested by the above-described assay and observed to exhibit cathepsin B inhibitory activity.

EXAMPLE 7

Cathepsin K Assay

Solutions of test compounds (varying concentrations in 10 μL of DMSO) were diluted into assay buffer (40 μL, comprising: MES, 50 mM (pH 5.5); EDTA, 2.5 mM; and DTT, 2.5 mM). Human cathepsin K (0.0906 pMoles in 25 μL of assay buffer) was added to the dilutions. The assay solutions were mixed for 5-10 seconds on a shaker plate, covered and incubated for 30 minutes at room temperature. Z-Phe-Arg-AMC (4 nMoles in 25 μL of assay buffer) was added to the assay solutions and hydrolysis was followed

spectrophotometrically at (λ 460 nm) for 5 minutes. Apparent inhibition constants (K_i) were calculated from the enzyme progress curves using standard mathematical models.

Compounds of the invention were tested by the above-described assay and observed to exhibit cathepsin K inhibitory activity.

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EXAMPLE 8

Cathepsin L Assay

Solutions of test compounds (varying concentrations in 10 μL of DMSO) were
10 diluted into assay buffer (40 μL, comprising: MES, 50 mM (pH 5.5); EDTA, 2.5 mM; and DTT, 2.5 mM). Human cathepsin L (0.05 pMoles in 25 μL of assay buffer) was added to the dilutions. The assay solutions were mixed for 5-10 seconds on a shaker plate, covered and incubated for 30 minutes at room temperature. Z-Phe-Arg-AMC (1 nMoles in 25 μL of assay buffer) was added to the assay solutions and hydrolysis was followed
15 spectrophotometrically at (λ 460 nm) for 5 minutes. Apparent inhibition constants (K_i) were calculated from the enzyme progress curves using standard mathematical models.

Compounds of the invention were tested by the above-described assay and observed to exhibit cathepsin L inhibitory activity.

20 EXAMPLE 9

Cathepsin S Assay

Solutions of test compounds (varying concentrations in 10 μL of DMSO) were diluted into assay buffer (40 μL, comprising: MES, 50 mM (pH 6.5); EDTA, 2.5 mM; and
25 NaCl, 100 mM). Human cathepsin S (0.158 pMoles in 25 μL of assay buffer) was added to the dilutions. The assay solutions were mixed for 5-10 seconds on a shaker plate, covered and incubated for 30 minutes at room temperature. Z-Val-Val-Arg-AMC (9 nMoles in 25 μL of assay buffer) was added to the assay solutions and hydrolysis was followed spectrophotometrically at (λ 460 nm) for 5 minutes. Apparent inhibition
30 constants (K_i) were calculated from the enzyme progress curves using standard mathematical models.

Compounds of the invention were tested by the above-described assay and observed to exhibit cathepsin S inhibitory activity.

EXAMPLE 10

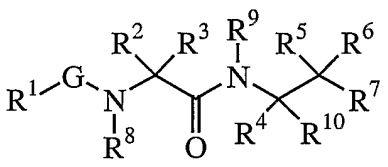
Cathepsin K Assay

Solutions of test compounds (varying concentrations in 10 μL of DMSO) were diluted into assay buffer (40 μL, comprising: MES, 50 mM (pH 5.5); EDTA, 2.5 mM; and DTT, 2.5 mM). Human cathepsin K (0.0906 pMoles in 25 μL of assay buffer) was added to the dilutions. The assay solutions were mixed for 5-10 seconds on a shaker plate, covered and incubated for 30 minutes at room temperature. Z-Phe-Arg-AMC (4 nMoles in 25 μL of assay buffer) was added to the assay solutions and hydrolysis was followed spectrophotometrically at (λ 460 nm) for 5 minutes. Apparent inhibition constants (K_i) were calculated from the enzyme progress curves using standard mathematical models.

Compounds of the invention were tested by the above-described assay and observed to exhibit cathepsin K inhibitory activity.

CLAIMS

1. A compound of Formula I:



I

wherein:

R^1 represents (C_{1-6})alkyl or $-(CH_2)_{0-2}-Z^1-X^1$;

R^2 and R^3 together with the carbon atom to which both R^2 and R^3 are attached form a monocyclic or bridged polycyclic cycloalkylene moiety having from three to eight ring atoms or a monocyclic or bridged polycyclic heterocycloalkylene moiety having from three to eight ring atoms;

R^4 represents a group selected from (C_{1-6})alkyl, $-Y^1NR^{11}R^{11}$, $-Y^1NR^{11}C(O)OR^{11}$, $-Y^1NR^{11}C(O)NR^{11}R^{11}$, $-Y^1NR^{11}C(NR^{11})NR^{11}R^{11}$, $-Y^1OR^{11}$, $-Y^1SR^{11}$, $-Y^1C(O)OR^{11}$, $-Y^1C(O)NR^{11}R^{11}$, $-Y^1S(O)_2NR^{11}R^{11}$, $-Y^1P(O)(OR^{11})OR^{11}$, $-Y^1OP(O)(OR^{11})OR^{11}$, $-Y^1NR^{11}C(O)R^{12}$, $-Y^1S(O)R^{12}$, $-Y^1S(O)_2R^{12}$, $-Y^1C(O)R^{12}$, $-R^{13}$, $-Y^1OR^{13}$, $-Y^1SR^{13}$, $-Y^1S(O)R^{13}$, $-Y^1S(O)_2R^{13}$, $-Y^1C(O)R^{13}$, $-Y^1C(O)OR^{13}$, $-Y^1OC(O)R^{13}$, $-Y^1NR^{13}R^{14}$, $-Y^1NR^{14}C(O)R^{13}$, $-Y^1NR^{14}C(O)OR^{13}$, $-Y^1C(O)NR^{13}R^{14}$, $-Y^1S(O)_2NR^{13}R^{14}$, $-Y^1NR^{14}C(O)NR^{13}R^{14}$ and $-Y^1NR^{14}C(NR^{14})NR^{13}R^{14}$, wherein Y^1 is (C_{1-6})alkylene, R^{11} at each occurrence independently is hydrogen, (C_{1-6})alkyl or halo-substituted (C_{1-3})alkyl, R^{12} is (C_{1-6})alkyl or halo-substituted (C_{1-3})alkyl, R^{13} is cycloalkyl(C_{0-6})alkyl, heterocycloalkyl(C_{0-6})alkyl, aryl(C_{0-6})alkyl or heteroaryl(C_{0-6})alkyl and R^{14} is hydrogen or (C_{1-6})alkyl and wherein within R^4 any alicyclic or aromatic ring may be substituted further with one to three groups independently selected from (C_{1-6})alkyl, (C_{1-6})alkylidene, (C_{1-6})alkylimino, cyano, halo, halo-substituted (C_{1-4})alkyl, imino, nitro, oxo, thioxo, $-Y^2NR^{11}R^{11}$, $-Y^2NR^{11}C(O)OR^{11}$, $-Y^2NR^{11}C(O)NR^{11}R^{11}$, $-Y^2NR^{11}C(NR^{11})NR^{11}R^{11}$, $-Y^2OR^{11}$, $-Y^2SR^{11}$, $-Y^2C(O)OR^{11}$, $-Y^2C(O)NR^{11}R^{11}$, $-Y^2S(O)_2NR^{11}R^{11}$, $-Y^2P(O)(OR^{11})OR^{11}$, $-Y^2OP(O)(OR^{11})OR^{11}$, $-Y^2NR^{11}C(O)R^{12}$, $-Y^2S(O)R^{12}$, $-Y^2S(O)_2R^{12}$

and $-Y^2C(O)R^{12}$, wherein Y^2 is a bond or (C_{1-6})alkylene and R^{11} and R^{12} are as defined above;

R^{10} represents hydrogen or (C_{1-6})alkyl; or

R^4 and R^{10} together with the carbon atom to which both R^4 and R^{10} are attached form a monocyclic or bridged polycyclic cycloalkylene moiety having from three to eight ring atoms or a monocyclic or bridged polycyclic heterocycloalkylene moiety having from three to eight ring atoms;

R^5 represents hydrogen and R^6 represents hydroxy; or

R^5 and R^6 together with the carbon atom to which both R^5 and R^6 are attached form a -C(O)- group;

R^7 represents a heteroaryl moiety having five to ten ring atoms or a heterocycloalkyl moiety having a five to ten ring atoms, wherein said heteroaryl or heterocycloalkyl moieties may be substituted with a group selected from $-R^{13}$, $-Y^2OR^{13}$, $-Y^2SR^{13}$, $-Y^2S(O)R^{13}$, $-Y^2S(O)_2R^{13}$, $-Y^2C(O)R^{13}$, $-Y^2C(O)OR^{13}$, $-Y^2OC(O)R^{13}$, $-Y^2NR^{13}R^{14}$, $-Y^2NR^{14}C(O)R^{13}$, $-Y^2NR^{14}C(O)OR^{13}$, $-Y^2C(O)NR^{13}R^{14}$, $-Y^2S(O)_2NR^{13}R^{14}$, $-Y^2NR^{14}C(O)NR^{13}R^{14}$ and $-Y^2NR^{14}C(NR^{14})NR^{13}R^{14}$, wherein Y^2 is a bond or (C_{1-6})alkylene, R^{13} is cycloalkyl(C_{0-6})alkyl, heterocycloalkyl(C_{0-6})alkyl, aryl(C_{0-6})alkyl or heteroaryl(C_{0-6})alkyl and R^{14} is hydrogen or (C_{1-6})alkyl and wherein within R^7 any alicyclic or aromatic ring may be substituted further with one to three groups independently selected from (C_{1-6})alkyl, (C_{1-6})alkylidene, (C_{1-6})alkylimino, cyano, halo, halo-substituted (C_{1-4})alkyl, imino, nitro, oxo, thioxo, $-Y^2NR^{11}R^{11}$, $-Y^2NR^{11}C(O)OR^{11}$, $-Y^2NR^{11}C(O)NR^{11}R^{11}$, $-Y^2NR^{11}C(NR^{11})NR^{11}R^{11}$, $-Y^2OR^{11}$, $-Y^2SR^{11}$, $-Y^2C(O)OR^{11}$, $-Y^2C(O)NR^{11}R^{11}$, $-Y^2S(O)_2NR^{11}R^{11}$, $-Y^2P(O)(OR^{11})OR^{11}$, $-Y^2OP(O)(OR^{11})OR^{11}$, $-Y^2NR^{11}C(O)R^{12}$, $-Y^2S(O)R^{12}$, $-Y^2S(O)_2R^{12}$ and $-Y^2C(O)R^{12}$, wherein Y^2 is as defined above, R^{11} at each occurrence independently is hydrogen, (C_{1-6})alkyl or halo-substituted (C_{1-3})alkyl and R^{12} is (C_{1-6})alkyl or halo-substituted (C_{1-3})alkyl;

G represents –C(O)-, -C(S)-, $–C(CH_2)$-, -S(O)- or $–S(O)_2$-;

Z^1 represents arylene, heteroarylene, cycloalkylene or heterocycloalkylene;

X^1 represents hydrogen or $-(CH_2)_{0-3}$-L-$(CH_2)_{0-3}$-Z^2-X^2;

R^8 and R^9 independently represent hydrogen or (C_{1-6})alkyl;

n represents an integer from zero to two;

Z^2 represents arylene, heteroarylene, cycloalkylene or heterocycloalkylene;

X^2 represents hydrogen or $-(CH_2)_{0-3}-L-(CH_2)_{0-3}-Z^3-X^3$;

Z^3 represents arylene, heteroarylene, cycloalkylene or heterocycloalkylene;

X^3 represents hydrogen or $-(CH_2)_{0-3}-L-(CH_2)_{0-3}-Z^4$;

L represents a bond, -O-, $-S(O)_n-$, -C(O)O-, -OC(O)-, $-NR^{15}S(O)_2-$, $-C(O)NR^{15}-S(O)_2NR^{15}-$, $-NR^{15}C(O)-$, -C(O)-, $-NR^{15}C(O)O-$, $-C(O)ONR^{15}-$, $-NR^{15}-$ or $-NR^{15}C(NR^{15})-$, wherein R^{15} represents hydrogen or (C_{1-4})alkyl; and

Z^4 represents aryl, heteroaryl, cycloalkyl or heterocycloalkyl; wherein within R^1 any alicyclic or aromatic ring may be substituted further with one to three groups independently selected from (C_{1-6})alkyl, (C_{1-6})alkylidene, (C_{1-6})alkylimino, cyano, halo, halo-substituted (C_{1-4})alkyl, imino, nitro, oxo, thioxo, $-Y^2NR^{11}R^{11}$, $-Y^2NR^{11}C(O)OR^{11}$, $-Y^2NR^{11}C(O)NR^{11}R^{11}$, $-Y^2NR^{11}C(NR^{11})NR^{11}R^{11}$, $-Y^2OR^{11}$, $-Y^2SR^{11}$, $-Y^2C(O)OR^{11}$, $-Y^2C(O)NR^{11}R^{11}$, $-Y^2S(O)_2NR^{11}R^{11}$, $-Y^2P(O)(OR^{11})OR^{11}$, $-Y^2OP(O)(OR^{11})OR^{11}$, $-Y^2NR^{11}C(O)R^{12}$, $-Y^2S(O)R^{12}$, $-Y^2S(O)_2R^{12}$ and $-Y^2C(O)R^{12}$, wherein Y^2 is a bond or (C_{1-6})alkylene, R^{11} at each occurrence independently is hydrogen, (C_{1-6})alkyl or halo-substituted (C_{1-3})alkyl and R^{12} is (C_{1-6})alkyl or halo-substituted (C_{1-3})alkyl; with the proviso that no more than one of Z^1, Z^2, Z^3 and Z^4 is a fused polycyclic moiety; and the prodrug derivatives, individual isomers and mixtures of isomers; and the pharmaceutically acceptable salts thereof.

2. The compound of Claim 1 Formula I in which G is -C(O)-; L is a bond, -O- or $-NR^{15}-$, wherein R^{15} is hydrogen or (C_{1-4})alkyl; Z^1, Z^2 and Z^3 independently are selected from phenylene, heteroarylene having from five to nine ring atoms and heterocycloalkylene having five to six ring atoms, wherein each said phenylene, heteroarylene and heterocycloalkylene may be substituted further with one to three groups independently selected from (C_{1-6})alkyl, (C_{1-6})alkylidene, (C_{1-6})alkylimino, cyano, halo, halo-substituted (C_{1-4})alkyl, imino, nitro, oxo, thioxo, $-Y^2NR^{11}R^{11}$, $-Y^2NR^{11}C(O)OR^{11}$, $-Y^2NR^{11}C(O)NR^{11}R^{11}$, $-Y^2NR^{11}C(NR^{11})NR^{11}R^{11}$, $-Y^2OR^{11}$, $-Y^2SR^{11}$, $-Y^2C(O)OR^{11}$, $-Y^2C(O)NR^{11}R^{11}$, $-Y^2S(O)_2NR^{11}R^{11}$, $-Y^2P(O)(OR^{11})OR^{11}$, $-Y^2OP(O)(OR^{11})OR^{11}$, $-Y^2NR^{11}C(O)R^{12}$, $-Y^2S(O)R^{12}$, $-Y^2S(O)_2R^{12}$ and $-Y^2C(O)R^{12}$, wherein Y^2 is a bond or (C_{1-6})alkylene, R^{11} at each occurrence independently is hydrogen, (C_{1-6})alkyl or

halo-substituted (C_{1-3})alkyl and R^{12} is (C_{1-6})alkyl or halo-substituted (C_{1-3})alkyl; R^2 and R^3 together with the carbon atom to which both R^2 and R^3 are attached form a monocyclic cycloalkylene moiety having three to six ring atoms; R^4 is (C_{1-6}) alkyl or phenyethyl; R^5 and R^6 together with the carbon atom to which both R^5 and R^6 are attached form a -C(O)- group; R^7 represents a heteroaryl moiety having five to nine ring atoms, wherein said heteroaryl moiety may be substituted with aryl, wherein within R^7 any aromatic ring may be substituted further with one to three groups independently selected from (C_{1-6})alkyl, cyano, halo, halo-substituted (C_{1-4})alkyl, nitro, $-Y^2NR^{11}R^{11}$, $-Y^2NR^{11}C(O)OR^{11}$, $-Y^2NR^{11}C(O)NR^{11}R^{11}$, $-Y^2NR^{11}C(NR^{11})NR^{11}R^{11}$, $-Y^2OR^{11}$, $-Y^2SR^{11}$, $-Y^2C(O)OR^{11}$, $-Y^2C(O)NR^{11}R^{11}$, $-Y^2S(O)_2NR^{11}R^{11}$, $-Y^2P(O)(OR^{11})OR^{11}$, $-Y^2OP(O)(OR^{11})OR^{11}$, $-Y^2NR^{11}C(O)R^{12}$, $-Y^2S(O)R^{12}$, $-Y^2S(O)_2R^{12}$ and $-Y^2C(O)R^{12}$, wherein Y^2 is as defined above, R^{11} at each occurrence independently is hydrogen, (C_{1-6})alkyl or halo-substituted (C_{1-3})alkyl and R^{12} is (C_{1-6})alkyl or halo-substituted (C_{1-3})alkyl; and R^8, R^9 and R^{10} each are hydrogen; and the prodrug derivatives, individual isomers and mixtures of isomers; and the pharmaceutically acceptable salts thereof.

3. The compound of Claim 2 in which L is a bond, -O- or -NH-; Z^1, Z^2 and Z^3 independently are selected from phenylene, heteroarylene having from five to nine ring atoms or heterocycloalkylene having five to six ring atoms, wherein each said phenylene, heteroarylene and heterocycloalkylene may be substituted with 1 to 2 groups independently selected from (C_{1-6})alkyl, halo, nitro, halo-substituted (C_{1-4})alkyl, oxo, $-Y^2OR^{11}$, $-Y^2NR^{11}R^{11}$, $-Y^2C(O)OR^{11}$ and $-Y^2S(O)_2R^{12}$; and R^7 represents a heteroaryl moiety having five to nine ring atoms, wherein said heteroaryl moiety may be substituted with phenyl or one to two substitutents independently selected from (C_{1-6})alkyl, halo and $-Y^2OR^{11}$, wherein said phenyl may be substituted further with one to two substitutents independently selected from halo-substituted (C_{1-4})alkyl or $-Y^2OR^{11}$; and the prodrug derivatives, individual isomers and mixtures of isomers; and the pharmaceutically acceptable salts thereof.

4. The compound of Claim 3 in which R^7 is is selected from benzooxazol-2-yl, benzofuran-2-yl, benzo[*b*]thiophen-2-yl wherein said benzooxazol-2-yl,

benzofuran-2-yl or benzo[*b*]thiophen-2-yl may be substituted with one to two groups selected from halo and $-Y^2OR^{11}$; and the prodrug derivatives, individual isomers and mixtures of isomers; and the pharmaceutically acceptable salts thereof.

5. The compound of Claim 4 in which R^1 is a group selected from 4-[2-(4-methyl-piperazin-1-yl)-thiazol-4-yl]-phenyl, 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-yl, 4-morpholin-4-yl-phenyl, pyridin-3-yl, pyridin-4-yl, pyrazin-2-yl, benzofuran-2-yl, benzo[*b*]thiophen-2-yl, 5-methoxy-benzofuran-2-yl, [1,4']bipiperidinyl-1'-yl, 4-isopropylamino-piperidin-1-yl, 4-{2-[1-(*tert*-butoxycarbonyl)-piperidin-4-ylamino]-thiazol-4-yl}-phenyl, 4-(2-morpholin-4-ylmethyl-thiazol-4-yl)-phenyl, 4-dimethylaminophenyl, 3-dimethylaminophenyl, 4-isopropylpiperazin-1-yl-phenyl, 4-(4-oxopiperidin-1-yl)phenyl, 4-[2-(piperidin-4-ylamino)-thiazol-4-yl]-phenyl, 4-*tert*-butylpiperazin-1-yl-phenyl, methyl, 4-*tert*-butylphenyl, 3,5-dimethoxyphenyl, 3,6-dimethoxyphenyl, 2-chlorophenyl, 2,5-dichlorophenyl, 4-nitrophenyl, 4-fluorophenyl, 4-trifluoromethoxyphenyl, 4-isobutylphenyl, 4-trifluoromethylphenyl, 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-yl, 4-chlorophenyl, 4-methylsufonylphenyl, 4-methoxyphenyl, 4-methylpiperazin-1-yl, 4-morpholin-4-ylpiperazin-1-yl, and 4-*tert*-butylpiperazin-1-yl; R^2 and R^3 together with the carbon atom to which both R^2 and R^3 are attached form cyclohexylene; R^4 is butyl, phenethyl, propyl, isobutyl or ethyl; and R^7 is selected from benzooxazol-2-yl, benzofuran-2-yl, benzo[*b*]thiophen-2-yl, 5-chlorobenzooxazol-2-yl and 5-methoxy-benzofuran-2-yl; and the prodrug derivatives, individual isomers and mixtures of isomers; and the pharmaceutically acceptable salts thereof.

6. The compound of Claim 3 in which R^7 is [1,3,4]oxadiazol-2-yl in which R^7 is [1,3,4]oxadiazol-2-yl wherein said [1,3,4]oxadiazol-2-yl may be substituted with phenyl or one to two substitutents independently selected from (C_{1-6})alkyl and $-Y^2OR^{11}$, wherein said phenyl may be substituted further with one to two substitutents independently selected from halo-substituted (C_{1-4})alkyl or $-Y^2OR^{11}$; and the prodrug derivatives, individual isomers and mixtures of isomers; and the pharmaceutically acceptable salts thereof.

7. The compound of Claim 6 in which R^1 is a group selected from 4-[2-(4-methyl-piperazin-1-yl)-thiazol-4-yl]-phenyl, 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-yl, 4-morpholin-4-yl-phenyl, pyridin-3-yl, pyridin-4-yl, pyrazin-2-yl, benzofuran-2-yl, benzo[*b*]thiophen-2-yl, 5-methoxy-benzofuran-2-yl, [1,4']bipiperidinyl-1'-yl, 4-isopropylamino-piperidin-1-yl, 4-{2-[1-(*tert*-butoxycarbonyl)-piperidin-4-ylamino]-thiazol-4-yl}-phenyl, 4-(2-morpholin-4-ylmethyl-thiazol-4-yl)-phenyl, 4-dimethylaminophenyl, 3-dimethylaminophenyl, 4-isopropylpiperazin-1-yl-phenyl, 4-(4-oxopiperidin-1-yl)phenyl, 4-[2-(piperidin-4-ylamino)-thiazol-4-yl]-phenyl, 4-*tert*-butylpiperazin-1-yl-phenyl, methyl, 4-*tert*-butylphenyl, 3,5-dimethoxyphenyl, 3,6-dimethoxyphenyl, 2-chlorophenyl, 2,5-dichlorophenyl, 4-nitrophenyl, 4-fluorophenyl, 4-trifluoromethoxyphenyl, 4-isobutylphenyl, 4-trifluoromethylphenyl, 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-yl, 4-chlorophenyl, 4-methylsufonylphenyl, 4-methoxyphenyl, 4-methylpiperazin-1-yl, 4-morpholin-4-ylpiperazin-1-yl, and 4-*tert*-butylpiperazin-1-yl; R^2 and R^3 together with the carbon atom to which both R^2 and R^3 are attached form cyclohexylene; R^4 is butyl, phenethyl, propyl, isobutyl or ethyl; R^7 is a group selected from 5-phenyl-[1,3,4]oxadiazol-2-yl, 5-(3-methoxyphenyl)-[1,3,4]oxadiazol-2-yl, 5-(4-methoxyphenyl)-[1,3,4]oxadiazol-2-yl, 5-(4-trifluoromethylphenyl)-[1,3,4]oxadiazol-2-yl, 5-(3-trifluoromethylphenyl)-[1,3,4]oxadiazol-2-yl, 5-(4-methoxyphenyl)-[1,3,4]oxadiazol-2-yl, 5-ethyl-[1,3,4]oxadiazol-2-yl, 5-methoxymethyl-[1,3,4]oxadiazol-2-yl and 5-*tert*-butyl-[1,3,4]oxadiazol-2-yl; and the prodrug derivatives, individual isomers and mixtures of isomers; and the pharmaceutically acceptable salts thereof.

8. The compound of Claim 5 selected from:

5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid {1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-3-phenyl-propylcarbamoyl]-cyclohexyl}-amide;

5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid {1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-pentylcarbamoyl]-cyclohexyl}-amide;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-3-phenyl-propylcarbamoyl]-cyclohexyl}-4-[2-(4-methyl-piperazin-1-yl)-thiazol-4-yl]-benzamide;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-pentylcarbamoyl]-cyclohexyl}-4-[2-(4-methyl-piperazin-1-yl)-thiazol-4-yl]-benzamide;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-4-morpholin-4-yl-benzamide;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-nicotinamide;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-isonicotinamide;

pyrazine-2-carboxylic acid {1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-amide;

benzofuran-2-carboxylic acid {1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-amide;

benzo[*b*]thiophene-2-carboxylic acid {1-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-amide;

5-methoxy-benzofuran-2-carboxylic acid {1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-amide;

[1,4']bipiperidinyl-1'-carboxylic acid {1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-amide;

4-isopropylamino-piperidine-1-carboxylic acid {1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-amide;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-4-[2-(4-methyl-piperazin-1-yl)-thiazol-4-yl]-benzamide;

4-[4-(4-{1-[1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexylcarbamoyl}-phenyl)-thiazol-2-ylamino]-piperidine-1-carboxylic acid *tert*-butyl ester;

N-{1-[1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-4-(2-morpholin-4-ylmethyl-thiazol-4-yl)-benzamide;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-4-methylamino-benzamide;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-3-methylamino-benzamide;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-4-(4-isopropyl-piperazin-1-yl)-benzamide;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-4-(4-oxo-piperidin-1-yl)-benzamide;

N-{1-[1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-4-[2-(piperidin-4-ylamino)-thiazol-4-yl]-benzamide;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-4-(4-*tert*-butyl-piperazin-1-yl)-benzamide;

1-acetylamino-cyclohexanecarboxylic acid [(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butyl]-amide;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-4-*tert*-butyl-benzamide;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-3-methyl-butylcarbamoyl]-cyclohexyl}-4-*tert*-butyl-benzamide;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-3,5-dimethoxy-benzamide;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-3,4-dimethoxy-benzamide;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-2-chloro-benzamide;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-2,5-dichloro-benzamide;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-4-nitro-benzamide;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-4-fluoro-benzamide;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-4-trifluoromethoxy-benzamide;

N-{1-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-4-isobutyl-benzamide;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-4-trifluoromethyl-benzamide;

5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid {1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-amide;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-4-chloro-benzamide;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-4-methanesulfonyl-benzamide;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-propylcarbamoyl]-cyclohexyl}-4-trifluoromethoxy-benzamide;

N-{1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butylcarbamoyl]-cyclohexyl}-4-methoxy-benzamide; and

4-*tert*-butyl-*N*-(1-{(*S*)-1-[1-(5-chloro-benzooxazol-2-yl)-methanoyl]-butylcarbamoyl}-cyclohexyl)-benzamide; and the prodrug derivatives, individual isomers and mixtures of isomers; and the pharmaceutically acceptable salts thereof.

9. The compound of Claim 7 selected from:

N-(1-{(*S*)-1-[1-(5-phenyl-[1,3,4]oxadiazol-2-yl)-methanoyl]-pentylcarbamoyl}-cyclohexyl)-4-trifluoromethoxy-benzamide;

N-(1-{(*S*)-1-[1-(5-phenyl-[1,3,4]oxadiazol-2-yl)-methanoyl]-butylcarbamoyl}-cyclohexyl)-4-trifluoromethoxy-benzamide;

N-[1-((*S*)-1-{1-[5-(3-methoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-methanoyl}-butylcarbamoyl)-cyclohexyl]-4-trifluoromethoxy-benzamide;

N-[1-((*S*)-1-{1-[5-(4-methoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-methanoyl}-butylcarbamoyl)-cyclohexyl]-4-trifluoromethoxy-benzamide;

4-trifluoromethoxy-*N*-[1-((*S*)-1-{1-[5-(4-trifluoromethyl-phenyl)-[1,3,4]oxadiazol-2-yl]-methanoyl}-butylcarbamoyl)-cyclohexyl]-benzamide;

4-trifluoromethoxy-*N*-[1-((*S*)-1-{1-[5-(3-trifluoromethyl-phenyl)-[1,3,4]oxadiazol-2-yl]-methanoyl}-butylcarbamoyl)-cyclohexyl]-benzamide;

4-methyl-piperazine-1-carboxylic acid [1-((*S*)-1-{1-[5-(4-methoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-methanoyl}-butylcarbamoyl)-cyclohexyl]-amide;

4-morpholin-4-yl-piperidine-1-carboxylic acid [1-((*S*)-1-{1-[5-(4-methoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-methanoyl}-butylcarbamoyl)-cyclohexyl]-amide;

4-*tert*-butyl-piperazine-1-carboxylic acid [1-((*S*)-1-{1-[5-(4-methoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-methanoyl}-butylcarbamoyl)-cyclohexyl]-amide;

N-(1-{(*S*)-1-[1-(5-ethyl-[1,3,4]oxadiazol-2-yl)-methanoyl]-butylcarbamoyl}-cyclohexyl)-4-trifluoromethoxy-benzamide;

N-(1-{(*S*)-1-[1-(5-methoxymethyl-[1,3,4]oxadiazol-2-yl)-methanoyl]-butylcarbamoyl}-cyclohexyl)-4-trifluoromethoxy-benzamide;

N-(1-{(*S*)-1-[1-(5-*tert*-butyl-[1,3,4]oxadiazol-2-yl)-methanoyl]-butylcarbamoyl}-cyclohexyl)-4-trifluoromethoxy-benzamide;

4-*tert*-butyl-piperazine-1-carboxylic acid (1-{(*S*)-1-[1-(5-ethyl-[1,3,4]oxadiazol-2-yl)-methanoyl]-butylcarbamoyl}-cyclohexyl)-amide;

4-*tert*-butyl-piperazine-1-carboxylic acid (1-{(*S*)-1-[1-(5-methoxymethyl-[1,3,4]oxadiazol-2-yl)-methanoyl]-butylcarbamoyl}-cyclohexyl)-amide; and

4-*tert*-butyl-piperazine-1-carboxylic acid (1-{(*S*)-1-[1-(5-*tert*-butyl-[1,3,4]oxadiazol-2-yl)-methanoyl]-butylcarbamoyl}-cyclohexyl)-amide; and the prodrug derivatives, individual isomers and mixtures of isomers; and the pharmaceutically acceptable salts thereof.

10. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Claim 1 in combination with one or more pharmaceutically acceptable excipient(s).

11. The composition of Claim 10 which further comprises one or more active ingredient(s) selected from the group consisting of (i) a therapeutically effective amount of a bisphosphonic acid or acid ester thereof or a pharmaceutically acceptable salt thereof and (ii) a therapeutically effective amount of an estrogen receptor agonist or a pharmaceutically acceptable salt thereof.

12. The composition of Claim 11 wherein the bisphosphonic acid is selected from the group consisting of 1,1-dichloromethylene-1,1-diphosphonic acid, 1-hydroxy-3-pyrrolidin-1-ylpropylidene-1,1-bisphosphonic acid, 1-hydroxyethylidene-1,1-diphosphonic acid, 1-hydroxy-3-(*N*-methyl-*N*-pentylamino)propylidene-1,1-bisphosphonic acid, 6-amino-1-hydroxyhexylidene-1,1-bisphosphonic acid, 3-(dimethylamino)-1-hydroxypropylidene-1,1-bisphosphonic acid, 3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid, 2-pyrid-2-ylethylidene-1,1-bisphosphonic acid, 1-hydroxy-2-pyrid-3-ylethylidene-1,1-bisphosphonic acid, 4-chlorophenylthiomethylenebisphosphonic acid and 1-hydroxy-2-(1*H*-imidazol-1-yl)ethylidene-1,1-bisphosphonic acid or acid ester thereof or a pharmaceutically acceptable salt thereof.

13. The composition of Claim 12 wherein the bisphosphonic acid is 1,1-dichloromethylene-1,1-diphosphonic acid or a pharmaceutically acceptable salt thereof.

14. The composition of Claim 13 which comprises 1,1-dichloromethylene-1,1-diphosphonate monosodium trihydrate.

15. A method for treating a disease in an animal in which inhibition of a cysteine protease can prevent, inhibit or ameliorate the pathology and/or symptomatology of the disease, which method comprises administering to the animal a therapeutically effective amount of compound of Claim 1 or a prodrug derivative, individual isomer or mixture of isomers; or a pharmaceutically acceptable salt thereof.

16. The method of Claim 15 wherein the disease is osteoporosis.

17. The method of Claim 16 wherein the animal is a human.

18. The method of Claim 17 wherein the human is a post-menopausal woman.

19. The method of Claim 18 wherein the cysteine protease is cathepsin K activity.