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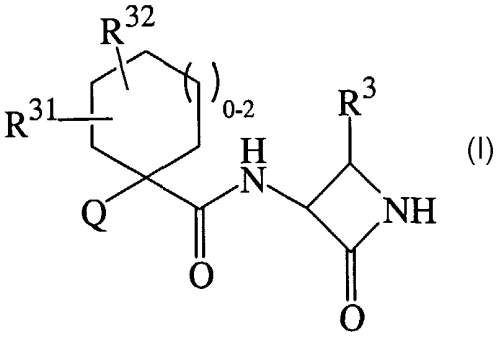

(I)

(57) Abstract: This Invention relates to monobactam derivatives that are cysteine protease inhibitors of Formula I: and are therefore useful for treating diseases associated with cysteine protease activity, particularly diseases associated with activity of cathepsin K.

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MONOBACTAMS AS CATHEPSIN K INHIBITORS

BACKGROUND OF INVENTION

Field of Invention

This invention relates to monobactam derivatives that are cysteine protease inhibitors and are therefore useful for treating diseases associated with cysteine protease activity, particularly diseases associated with activity of cathepsin K.

State of the Art

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 increased 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 osteoclast-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.

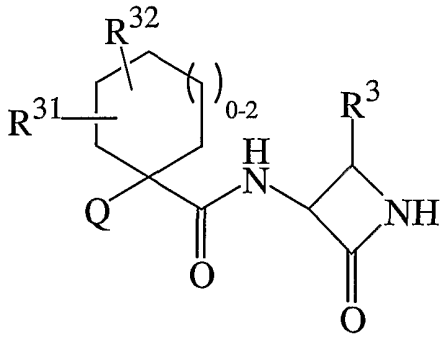
Cathepsin L is implicated in normal lysosomal proteolysis as well as several disease states, including, but not limited to, metastasis of melanomas. Cathepsin S is implicated in Alzheimer's disease and certain autoimmune disorders, including, but not

limited to juvenile onset diabetes, multiple sclerosis, pemphigus vulgaris, Graves' disease, myasthenia gravis, systemic lupus erythemotasus, rheumatoid arthritis and Hashimoto's thyroiditis. In addition, cathepsin S is implicated in: allergic disorders, including, but not limited to asthma; and allogenic immune responses, 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 INVENTION

This Application relates to compounds of Formula I:



Formula I

wherein:

Q is selected from a group consisting of -Z^1-(C_{6-10})aryl, -Z^1-(C_{3-10})cycloalkyl, -Z^1-C_1 alkyl, -Z^1-hetero(C_{3-10})cycloalkyl, -Z^1-hetero(C_{5-10})aryl, -Z^1-(C_{9-10})bicycloaryl and -Z^1-hetero(C_{8-10}) bicycloaryl, wherein said (C_{6-10})aryl, (C_{3-10})cycloalkyl, C_1 alkyl, hetero(C_{3-10})cycloalkyl, hetero(C_{5-10})aryl, (C_{9-10})bicycloaryl and hetero(C_{8-10}) bicycloaryl groups are substituted with R^1;

R^1 is selected from a group consisting of H, -$X^3NR^8R^{21}$, -$X^3NR^8C(O)R^{21}$, -$X^3NR^8C(O)OR^{21}$, -$X^3NR^8C(O)NR^8R^{21}$, -$X^3NR^8C(NR^8)NR^8R^{21}$, -X^3OR^{21}, -X^3SR^{21}, -$X^3S(O)R^{21}$, -$X^3S(O)_2R^{21}$, -$X^3C(O)R^{21}$, -$X^3C(O)OR^{21}$, -$X^3OC(O)R^{21}$, -$X^3C(O)NR^8R^{21}$, -$X^3OC(O)NR^8R^{21}$, -$X^3S(O)_2NR^8R^{21}$, -$X^3P(O)(OR^8)OR^{21}$, -X^3OR^{52}, -$X^3CONR^8R^{52}$,

$-X^3SO_2NR^8R^{52}$, $-X^3OP(O)(OR^8)OR^{21}$, and R^{21} wherein:

X^3 is a bond or (C_{1-6})alkylene, R^8 at each occurrence independently is hydrogen or (C_{1-6})alkyl, R^{52} represents $-CH_2CH_2-N(CH_2CH_2OH)_2$, $-CH(CH_3)CH_2N(CH_3)_2$, $-CH_2CH_2OH$, $-CH_2CH_2N(CH_3)_2$ or $-CH_2CN$, and R^{21} is (C_{1-8})alkyl or X^4R^{22} wherein X^4 is a bond or (C_{1-6})alkylene and R^{22} is selected from a group consisting of (C_{3-10})cycloalkyl, hetero(C_{5-10})cycloalkyl, (C_{6-10})aryl, hetero(C_{5-10})aryl, (C_{9-10})bicycloaryl and hetero(C_{8-10})bicycloaryl wherein the cyclic group contained within R^{22} may be substituted further by a radical selected from a group consisting of $-X^3NR^8R^{23}$, $-X^3NR^8C(O)R^{23}$, $-X^3NR^8C(O)OR^{23}$, $-X^3NR^8C(O)NR^8R^{23}$, $-X^3OR^{23}$, $-X^3NR^8C(NR^8)NR^8R^{23}$, $-X^3SR^{23}$, $-X^3S(O)R^{23}$, $-X^3S(O)_2R^{23}$, $-X^3C(O)R^{23}$, $-X^3OC(O)R^{23}$, $-X^3C(O)OR^{23}$, $-X^3C(O)NR^8R^{23}$, $-X^3OC(O)NR^8R^{23}$, $-X^3S(O)_2NR^8R^{23}$, $-X^3OR^{52}$, $-X^3CONR^8R^{52}$, $-X^3SO_2NR^8R^{52}$, $-X^3P(O)(OR^8)OR^{23}$, $-X^3OP(O)(OR^8)OR^{23}$ and R^{23} wherein:

X^3, R^8 and R^{52} are as defined above, and R^{23} is (C_{1-8})alkyl or $-X^5R^{24}$ wherein X^5 is a bond or (C_{1-6})alkylene and R^{24} is selected from a group consisting of (C_{3-10})cycloalkyl, hetero(C_{5-10})cycloalkyl, (C_{6-10})aryl, hetero(C_{5-10})aryl, (C_{9-10})bicycloaryl and hetero(C_{8-10})bicycloaryl wherein:

R^{24} may be substituted further by a radical selected from a group consisting of $-X^3NR^8R^{25}$, $-X^3NR^8C(O)R^{25}$, $-X^3NR^8C(O)OR^{25}$, $-X^3OR^{25}$, $-X^3NR^8C(O)NR^8R^{25}$, $-X^3NR^8C(NR^8)NR^8R^{25}$, $-X^3SR^{25}$, $-X^3S(O)R^{25}$, $-X^3S(O)_2R^{25}$, $-X^3C(O)R^{25}$, $-X^3OC(O)R^{25}$, $-X^3C(O)OR^{25}$, $-X^3C(O)NR^8R^{25}$, $-X^3OC(O)NR^8R^{25}$, $-X^3S(O)_2NR^8R^{25}$, $-X^3P(O)(OR^8)OR^{25}$, $-X^3OR^{52}$, $-X^3CONR^8R^{52}$, $-X^3SO_2NR^8R^{52}$, $-X^3OP(O)(OR^8)OR^{25}$ and R^{25} wherein:

X^3, R^8 and R^{52} are as defined above, and R^{25} is (C_{1-8})alkyl or X^6R^{26}, wherein X^6 is a bond or (C_{1-6})alkylene and R^{26} is selected from a group consisting of (C_{3-10})cycloalkyl, hetero(C_{5-10})cycloalkyl, (C_{6-10})aryl, hetero(C_{5-10})aryl, (C_{9-10})bicycloaryl and hetero(C_{8-10})bicycloaryl wherein any of the (C_{3-10})cycloalkyl, hetero(C_{5-10})cycloalkyl, (C_{6-10})aryl, hetero(C_{5-10})aryl, (C_{9-10})bicycloaryl and hetero(C_{8-10})bicycloaryl contained within R^3, R^{22}, R^{24} and R^{26} may be substituted further with up to five substituents selected from a group consisting of (C_{1-6})alkyl, (C_{1-6})alkylidene, cyano, halo, nitro, halo-substituted (C_{1-3})alkyl, $-X^3NR^{16}R^{16}$, $-X^3NR^{16}C(O)OR^{16}$, $-X^3NR^{16}C(O)NR^{16}R^{16}$, $-X^3NR^{16}C(NR^{16})NR^{16}R^{16}$, $-X^3OR^{16}$,

$-X^3SR^{16}$, $X^3C(O)OR^{16}$, $-X^3C(O)NR^{16}R^{16}$, $-X^3S(O)_2NR^{16}R^{16}$, $-X^3P(O)(OR^8)OR^{16}$; $-X^3OR^{52}$, $-X^3CONR^8R^{52}$, $-X^3C(O)R^{16}$, $-X^3SO_2NR^8R^{52}$, $-X^3S(O)R^{17}$, $-X^3OP(O)(OR^8)OR^{16}$, $-X^3NR^{16}C(O)R^{17}$, $-X^3S(O)_2R^{17}$ and $-X^3C(O)R^{16}$ wherein:

X^3, R^8 and R^{52} are as defined above, R^{16} at each occurrence independently is selected from a group consisting of hydrogen, (C_{1-3})alkyl or halo-substituted (C_{1-3})alkyl and R^{17} is $-(C_{1-3})$alkyl or halo-substituted (C_{1-3})alkyl;

R^{31} and R^{32} independently represent hydrogen or hydroxy, alternatively R^{31} and R^{32} can be taken together to represent an oxo (=O) group;

R^3 is $-OCOC_{1-8}$ alkyl, -S-aryl, $-COOC_{1-8}$ alkyl, or $-SO_2$-aryl;

Z^1 is $-NHCO-(C_{0-6})$alkylene-, or $-NHCOO-(C_{0-6})$alkylene-; or

pharmaceutically acceptable salts thereof.

In a second aspect, this invention is directed to a pharmaceutical comprising a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient. The pharmaceutical composition can also comprise one or more active ingredient(s) selected from the group consisting of (i) a therapeutically effective amount of a bisphosphonic acid or an 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.

The bisphosphonic acid(s) used in the composition of the present invention is/are 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.

Particularly preferred pharmaceutical compositions of the present invention comprise 1,1-dichloromethylene-1,1-diphosphonic acid, 1,1-dichloromethylene-

1,1-diphosphonate monosodium trihydrate or a pharmaceutically acceptable salt thereof.

In a third aspect, this invention is directed to a method of treating a disease in an animal in which inhibition of a cysteine protease, in particular cathepsin K, can prevent, inhibit or ameliorate the pathology and/or symptomatology of the disease, which method comprises administering to the animal a pharmaceutical composition comprising a therapeutically effective amount of compound of Formula I, an individual isomer, mixture of isomers or a pharmaceutically acceptable salt thereof. A preferred method is one wherein the disease is osteoporosis and the animal being treated is a human. Particularly preferred method comprises a post-menopausal woman as the animal being treated and wherein the cysteine protease is cathepsin K activity.

The above method can also be carried out by administering to said human a pharmaceutical composition comprising a compounds of Formula I, an individual isomer, mixture of isomers or a pharmaceutically acceptable salt thereof in combination with one or more active ingredient(s) selected from the group consisting of (i) a therapeutically effective amount of a bisphosphonic acid or an 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.

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, preferably one or two 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, preferably one or two 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, 2-methylpropyl, butyl, vinyl, allyl, 1-propenyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methylallyl, ethynyl, 1-propynyl, 2-propynyl, and the like). An alkyl group can be optionally substituted with one or more groups selected from $-NH_2$, $-NH(CH_3)_{1-4}$, $-N[(CH_3)_{1-4}]_2$, -OH and $-OCH_3$.

"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_{2-5})alkylene includes ethylene ($-CH_2CH_2-$ or $-CH(CH_3)-$), 1-methylethylene ($-CH(CH_3)CH_2-$), trimethylene ($-CH_2CH_2CH_2-$), tetramethylene ($-CH_2CH_2CH_2CH_2-$), 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 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, non-human primates such as monkeys, apes, etc., or the like) and non-mammals (e.g., birds, or the like).

"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.

"Aryl" means a monocyclic or fused bicyclic aromatic ring assembly containing the total number of ring carbon atoms indicated. For example, optionally substituted (C_{6-10})aryl as used in this Application includes phenyl, 3-bromophenyl, 3-carbamoylphenyl, 4-carbamoylphenyl, 3-[2-(1-methylpyrrolidin-2-yl)-ethoxycarbonylamino]phenyl, morpholin-4-ylcarbonylmethyl, 3-(2-morpholin-4-ylethoxycarbonylamino)phenyl, 3-[3-(3-morpholin-4-ylpropyl)ureido]phenyl,

naphth-1-yl, naphth-2-yl, 3-nitrophenyl, 4-nitrophenyl, 2-methoxyphenyl, 4-methoxyphenyl, 3-phenoxyphenyl, 4-phenoxyphenyl, phenyl, 4-(3-pyrid-3-ylmethylureido)phenyl, 4-(3-pyrid-4-ylmethylureido)phenyl, 3-pyrid-3-ylphenyl, 4-(3-pyrid-4-ylureido)phenyl, 4'-sulfamoylbiphenyl-3-yl, 3-thien-3-ylphenyl, and the like.

"Bicycloaryl" means a bicyclic ring assembly containing the number of ring carbon atoms indicated, wherein the rings are fused and one, but not both, of the rings comprising the assembly is aromatic, and any carbocyclic ketone, thioketone or iminoketone derivative thereof (e.g., (C_{9-10})bicycloaryl includes 1,2-dihydronaphthyl, 5,6,7,8-tetrahydronaphth-1-yl, 2,4-dioxo-1,2,3,4-tetrahydronaphthyl, indanyl, indenyl, 1,2,3,4-tetrahydronaphthyl, and the like).

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

"Carbocyclic ketone, thioketone or iminoketone derivative" means an alicyclic derivative wherein one or more ring members are substituted by an oxo (=O), thioxo (=S) or imino (=NR) group, wherein R is hydrogen, (C_{1-6})alkyl or a protecting group (e.g., 1-oxoindan-5-yl, 3-thioxocyclohexyl, 5-iminopiperidin-3-yl, and the like).

"Cycloalkyl" means a saturated or partially unsaturated, monocyclic ring, or bridged polycyclic ring assembly containing the number of ring carbon atoms indicated, and any carbocyclic ketone, thioketone or iminoketone derivative thereof (e.g., (C_{3-10})cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, 2,5-cyclohexadienyl, bicyclo[2.2.2]octyl, adamantan-1-yl, decahydronaphthyl, oxocyclohexyl, dioxocyclohexyl, thiocyclohexyl, 2-oxobicyclo[2.2.1]hept-1-yl, and the like).

"Disease" specifically includes any unhealthy condition of an animal or part thereof and includes an unhealthy condition that may be caused by, or incident to, medical or veterinary therapy applied to that animal, i.e., the "side effects" of such therapy.

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

"Halo substituted alkyl" means alkyl group as defined above that is substituted with one to five, preferably one to three fluoro, chloro, bromo or iodo atoms e.g., trifluoromethyl, and the like.

"Heteroaryl" means aryl, as defined in this Application, provided that one or more of the ring carbon atoms indicated are replaced by a hetero atom moiety selected from N, NR, O or S, wherein R is hydrogen, (C_{1-6})alkyl or a protecting group, and each ring is comprised of 5 or 6 ring atoms. For example, optionally substituted hetero(C_{5-10})aryl as used in this Application includes 4-(3-aminophenyl)thiazol-2-yl, 3-(6-aminopyrid-3-yl)phenyl, 2-dimethylaminothiazol-4-yl, 3-(4,6-dimethylpyrid-2-yl)-phenyl, 6-methoxypyrid-3-yl, 2-(4-morpholin-4-ylphenyl)thiazol-4-yl, 4-(3-nitrophenyl)thiazol- 2-yl, 2-phenylthiazol-4-yl, 4-phenylthiazol-2-yl, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, 2-pyrid-4-ylaminothiazol-4-yl, 3-pyrid-2-ylphenyl, 3-pyrid-3-ylphenyl, 3-pyrid-4-ylphenyl, 2-pyrid-4-ylthiazol-4-yl, 4-pyrid-4-ylthiazol-2-yl, 4-(4-pyrrolidin-1-ylphenyl)thiazol-2-yl, thien-2-yl, thien-3-yl, thien-2-ylphenyl, thiazol-2-ylphenyl, 6-bromopyrid-2-ylphenyl, 6-bromopyrid-3-ylphenyl, 3-(2,3-dihydrobenzo[1,4]dioxin-6-yl)phenyl, 3-(2,3-dihydrobenzo[1,3]dioxol-5-yl)-phenyl, indol-1-yl, and the like. Suitable protecting groups include *tert*-butoxycarbonyl, benzyloxycarbonyl, benzyl, 4-methoxybenzyl, 2-nitrobenzyl, and the like.

"Heterobicycloaryl" means bicycloaryl, as defined in this Application, provided that one or more of the ring carbon atoms indicated are replaced by a hetero atom moiety selected from N, NR, O, S or B, wherein R is hydrogen, (C_{1-6})alkyl or a protecting group, and any carbocyclic ketone, thioketone or iminoketone derivative thereof. In general, the term heterobicycloaryl as used in this Application includes, for example, benzo[1,3]dioxol-5-yl, 3,4-dihydro-2*H*-[1,8]naphthyridinyl, 3,4-dihydro-2*H*-quinolinyl, 2,4-dioxo-3,4-dihydro-2*H*-quinazolinyl, 3-oxo-2,3-dihydrobenzo[1,4]oxazinyl, 5,6,7,8-tetrahydroquinolinyl, and the like. Suitable protecting groups include *tert*-butoxycarbonyl, benzyloxycarbonyl, benzyl, 4-methoxybenzyl, 2-nitrobenzyl, and the like.

"Heterocycloalkyl" means cycloalkyl, as defined in this Application, provided that one or more of the ring carbon atoms indicated are replaced by a hetero atom moiety selected from N, NR, O, S or B, wherein R is hydrogen, (C_{1-6})alkyl or a

protecting group, and any carbocyclic ketone, thioketone or iminoketone derivative thereof (e.g., the term heterocyclo(C_{5-10})alkyl includes imidazolidinyl, morpholinyl, piperazinyl, piperidyl, pyrrolidinyl, pyrrolinyl, quinuclidinyl, and the like). For example, optionally substituted hetero(C_{5-10})cycloalkyl as used in this Application to define R^1 includes morpholin-4-yl, 1-methylpyrrolidin-2-yl, pyrrolidin-1-yl, tetrahydrofur-2-yl, and the like. Suitable protecting groups include acetyl, *tert*-butoxycarbonyl, benzyloxycarbonyl, benzyl, 4-methoxybenzyl, 2-nitrobenzyl, and the like.

"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.

"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.

"Leaving group" has the meaning conventionally associated with it in synthetic organic chemistry, i.e., an atom or group displaceable under alkylating conditions, and includes, halogen, hydroxy, alkyloxy, alkylsulfonloxy (e.g., mesyloxy, ethanesulfonyloxy, or the like), arylsulfonyloxy (e.g., benzenesulfonyloxy and tosyloxy, thienyloxy), dihalophosphinoyloxy, tetrahalophosphaoxy, and the like.

"Nitro" means the radical NO_2.

"Optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, the phrase "R^1 can be optionally substituted " means that the moiety referred to may or may not contain substituents in order to fall within the scope of the invention.

"*N*-oxide derivatives" means derivatives of compounds of Formula I in which nitrogens are in an oxidized state (i.e., N→O) 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, tartaric 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, aluminum hydroxide, ammonium hydroxide and calcium hydroxide. Acceptable organic bases include ethanolamine, diethanolamine, triethanolamine, tromethamine, *N*-methylglucamine and the like.

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

The present invention also includes N-oxide derivatives and protected derivatives of compounds of Formula I. For example, when compounds of Formula I contain an oxidizable nitrogen atom, the nitrogen atom can be converted to an N-oxide by methods well known in the art. Also when compounds of Formula I contain groups such as hydroxy, carboxy, thiol or any group containing a nitrogen atom(s), these

groups can be protected with a suitable protecting groups. A comprehensive list of suitable protective groups can be found in T.W. Greene, *Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc. 1981, the disclosure of which is incorporated herein by reference in its entirety. The protected derivatives of compounds of Formula I can be prepared by methods well known in the art.

"Protected derivatives" means derivatives of compounds of Formula I in which a reactive site or sites are blocked with Pg* (i.e., a protecting group) as illustrated in Scheme II. Protected derivatives of compounds of Formula I are useful in the preparation of other 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, *Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc. 1981.

"Therapeutically effective amount" means that amount which, when administered to an animal for treating a disease, is, by itself or in combination with additional active ingredients, sufficient to effect such treatment for the disease.

"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).

Nomenclature

The compounds of Formula I and the intermediates and starting materials used in their preparation are named 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. or by using the "Autonom", a Beilstein Commander 2.1 Application, distributed by Beilstein.

Presently Preferred Embodiments

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

A preferred embodiment of the present invention provides a compound of Formula I wherein:

Q represents -NHCO-(C_{6-10})aryl or -NHCO-hetero(C_{5-10})aryl wherein said C_{6-10} aryl and hetero(C_{5-10})aryl groups are further substituted with R^1 wherein R^1 is selected from a group consisting of H, $-X^3NR^8R^{21}$, $-X^3NR^8C(O)R^{21}$, $-X^3NR^8C(O)OR^{21}$, $-X^3NR^8C(O)NR^8R^{21}$, $-X^3OR^{21}$, $-X^3SR^{21}$, $-X^3C(O)R^{21}$, $-X^3C(O)OR^{21}$, $-X^3OC(O)R^{21}$, $-X^3C(O)NR^8R^{21}$, $-X^3OR^{52}$, $-X^3CONR^8R^{52}$ and R^{21} wherein:

X^3 is a bond or (C_{1-6})alkylene, R^8 at each occurrence independently is hydrogen or (C_{1-6})alkyl, R^{52} represents $-CH_2CH_2-N(CH_2CH_2OH)_2$, hydrogen, $-CH(CH_3)CH_2N(CH_3)_2$, $-CH_2CH_2OH$, CH_2CN or $-CH_2CH_2N(CH_3)_2$, and R^{21} is (C_{1-8})alkyl or X^4R^{22} wherein:

X^4 is a bond or (C_{1-6})alkylene; and

R^{22} is selected from a group consisting of hetero(C_{5-10})cycloalkyl, (C_{6-10})aryl, hetero(C_{5-10})aryl and hetero(C_{8-10})bicycloaryl wherein R^{22} may be substituted further by a radical selected from a group consisting of (C_{1-4})alkyl, $-X^3NR^8R^{23}$, $-X^3C(O)NR^8R^{52}$, $-X^3OR^{23}$, $-X^3NR^8C(O)OR^{23}$, $-X^3SO_2NR^8R^{52}$, $-X^3C(O)NR^8R^{23}$, $-X^3SO_2NR^8R^{23}$, $-X^3COR^{23}$, $-X^3OR^{52}$, $-X^3S(O)_2R^{23}$, $-X^3N(R^8)_2$ and R^{23} wherein X^3, R^8 and R^{52} are as defined above and R^{23} is (C_{1-8})alkyl or X^5R^{24} wherein:

X^5 is a bond or (C_{1-6})alkylene; and

R^{24} is selected from a group consisting of hetero(C_{5-10})cycloalkyl and hetero(C_{5-10})aryl wherein R^{24} may be substituted further with R^{25}, $-X^3OR^{52}$, $-X^3NR^8R^{25}$, $-X^3NHC(O)OR^{25}$, $-X^3COOR^{25}$ and $-X^3SO_2NR^8R^{52}$ wherein X^3, R^{52} and R^8 are as defined above, and R^{25} is (C_{1-8})alkyl or X^6R^{26} wherein:

X^6 is a bond or (C_{1-6})alkylene; and

R^{26} is hetero(C_{5-10})cycloalkyl; and wherein any of the (C_{3-10})cycloalkyl, hetero(C_{5-10})cycloalkyl, (C_{6-10})aryl, hetero(C_{5-10})aryl, (C_{9-10})bicycloaryl and hetero(C_{8-10})bicycloaryl contained within R^3, R^{22}, R^{24} and R^{26} may be substituted further with up to five substituents selected from a group consisting of (C_{1-6})alkyl,

cyano, halo, nitro, halo-substituted (C_{1-3})alkyl, $-X^3NR^{16}R^{16}$, $-X^3OR^{52}$ and $-X^3C(O)R^{16}$, wherein X^3 and R^{52} are as defined above and R^{16} at each occurrence independently is selected from a group consisting of hydrogen, (C_{1-3})alkyl or halo-substituted (C_{1-3})alkyl and R^{17} is $-(C_{1-3})$alkyl or halo-substituted (C_{1-3})alkyl; and

R^3 represents -COO-*t*-butyl, -S-Ph, or $-SO_2$-Ph.

Another preferred embodiment provides a compound of Formula I wherein: Q is -NHCO-phenyl or -NHCO-hetero(C_{5-6})aryl wherein said phenyl and hetero(C_{5-6})aryl groups are substituted with R^1 wherein R^1 is selected from a group consisting of $-X^3NR^8R^{21}$, $-X^3NR^8C(O)R^{21}$, $-X^3NR^8C(O)OR^{21}$ and R^{21} where X^3 is a bond or (C_{1-6})alkylene, R^8 at each occurrence independently is hydrogen or (C_{1-6})alkyl, and R^{21} is X^4R^{22} where:

X^4 is a bond or (C_{1-6})alkylene; and

R^{22} is selected from a group consisting of hetero(C_{5-6})cycloalkyl, (C_6)aryl, hetero(C_{5-10})aryl and hetero(C_{8-9})bicycloaryl wherein R^{22} can be optionally substituted further by a radical selected from a group consisting of (C_{1-4})alkyl, $-X^3OR^{23}$, $-X^3NR^8R^{23}$, $-X^3C(O)NR^8R^{23}$, $-X^3C(O)NR^8R^{52}$, $-X^3NR^8C(O)OR^{23}$, $-X^3SO_2NR^8R^{23}$ and R^{23} wherein X^3, R^{52} represents $-CH_2CH_2$-$N(CH_2CH_2OH)_2$, hydrogen, $-CH(CH_3)CH_2N(CH_3)_2$, $-CH_2CH_2OH$, CH_2CN or $-CH_2CH_2N(CH_3)_2$, and R^8 are as defined above, and R^{23} is (C_{1-8})alkyl or X^5R^{24} wherein:

X^5 is a bond or (C_{1-6})alkylene; and

R^{24} is selected from a group consisting of hetero(C_{5-6})cycloalkyl and hetero(C_{5-6})aryl, wherein R^{24} may be substituted further with R^{25}, $-X^3OR^{52}$, $-X^3NR^8R^{25}$, $-X^3NHC(O)OR^{25}$, $-X^3COOR^{25}$ and $-X^3SO_2NR^8R^{52}$; wherein X^3, R^{52} and R^8 are as defined above, and R^{25} is (C_{1-4})alkyl or X^6R^{26} wherein:

X^6 is a bond or (C_{1-6})alkylene; and

R^{26} is hetero(C_{5-10})cycloalkyl; and wherein the (C_{3-10})cycloalkyl contained within R^{26} may be substituted further with up to three groups selected from a group consisting of (C_{1-2})alkyl.

In a further preferred embodiment is provided a compound of Formula I wherein:

R^1 represents R^{21} where R^{21} is X^4R^{22} where:

X^4 is a bond; and

R^{22} is hetero(C_5)aryl or hetero(C_{5-6})cycloalkyl wherein R^{22} is substituted further by R^{23} where R^{23} is X^5R^{24} wherein:

X^5 is a bond; and

R^{24} is hetero(C_5)aryl or hetero(C_{5-6})cycloalkyl wherein R^{24} may be substituted further with R^{25}, $-X^3OR^{52}$, $-X^3NR^8R^{25}$, $-X^3COOR^{25}$ or $-X^3SO_2NR^8R^{52}$; wherein X^3 is a bond or (C_{1-6})alkylene, R^{52} represents $-CH_2CH_2OH$, $-CH_2CN$, $-CH_2CH_2-N(CH_2CH_2OH)_2$, $-CH(CH_3)CH_2N(CH_3)_2$, or $-CH_2CH_2N(CH_3)_2$, R^8 at each occurrence independently is hydrogen or (C_{1-6})alkyl and R^{25} is (C_{1-6})alkyl or $-X^6R^{26}$ wherein:

X^6 is a bond; and

R^{26} is hetero(C_{5-6})cycloalkyl substituted with up to two (0-2) groups selected from a group consisting of (C_{1-2})alkyl.

In yet another preferred embodiment is provided a compound of Formula I wherein:

Q is -NHCO-phenyl wherein said phenyl is substituted with R^{21} where R^{21} is X^4R^{22} where X^4 is a bond; and R^{22} is hetero(C_{5-6})aryl wherein R^{22} is substituted further by R^{23} where:

R^{23} is $-X^5R^{24}$, wherein X^5 is a bond and R^{24} is hetero(C_5)aryl or hetero(C_{5-6})cycloalkyl substituted with up to two (0-2) groups selected from a group consisting of (C_{1-2})alkyl.

A particularly preferred compound of the present invention is selected from:

Acetic acid 3-[(1-*tert*-butoxycarbonylamino-cyclohexanecarbonyl)-amino]-4-oxo-azetidin-2-yl ester;

Acetic acid 3-[(1-benzyloxycarbonylamino-cyclohexanecarbonyl)-amino]-4-oxo-azetidin-2-yl ester;

Acetic acid 3-[(1-{4-[2-(4-methyl-piperazin-1-yl)-thiazol-4-yl]-benzoylamino}-cyclohexanecarbonyl)-amino]-4-oxo-azetidin-2-yl ester;

Acetic acid 3-[1-(1-{4-[2-(4-methyl-piperazin-1-yl)-thiazol-4-yl]-benzoylamino}-cyclohexyl)-vinylamino]-4-oxo-azetidin-2-yl ester;

Acetic acid 3-[(1-{4-[2-(3-tert-butoxycarbonylamino-pyrrolidin-1-yl)-thiazol-4-yl]-benzoylamino}-cyclohexanecarbonyl)-amino]-4-oxo-azetidin-2-yl ester;

[1-(2-Oxo-4-phenylsulfanyl-azetidin-3-ylcarbamoyl)-cyclohexyl]-carbamic acid benzyl ester;

Acetic acid 3-{[1-(4-dimethylamino-benzoylamino)-cyclohexanecarbonyl]-amino}-4-oxo-azetidin-2-yl ester;

Acetic acid 3-({1-[4-(2-dimethylamino-thiazol-4-yl)-benzoylamino]-cyclohexanecarbonyl}-amino)-4-oxo-azetidin-2-yl ester;

Acetic acid 3-[(1-{4-[2-(4-methyl-piperazin-1-ylamino)-thiazol-4-yl]-benzoylamino}-cyclohexanecarbonyl)-amino]-4-oxo-azetidin-2-yl ester;

Acetic acid 3-{[1-(4-morpholin-4-yl-benzoylamino)-cyclohexanecarbonyl]-amino}-4-oxo-azetidin-2-yl ester;

Acetic acid 3-({1-[4-(2-morpholin-4-ylmethyl-thiazol-4-yl)-benzoylamino]-cyclohexanecarbonyl}-amino)-4-oxo-azetidin-2-yl ester;

N-[1-(2-Benzenesulfonyl-4-oxo-azetidin-3-ylcarbamoyl)-cyclohexyl]-4-(4-methyl-piperazin-1-yl)-benzamide; and

[1-(2-Benzenesulfonyl-4-oxo-azetidin-3-ylcarbamoyl)-cyclohexyl]-carbamic acid benzyl ester.

Pharmacology and Utility

The compounds of this invention are cysteine protease inhibitors. In particular the compounds of this invention inhibit the activity of cathepsins K and, as such, are useful for treating diseases in which cathepsin K activity contributes to the pathology and/or symptomatology of the disease. For example, the compounds of this invention are useful in treating rheumatoid arthritis, osteo arthritis and bone and joint disorders. Furthermore, the compounds of this invention are useful in treating bone resorption disorders, e.g., osteoporosis. In particular, the compounds of this invention are useful in treating osteoporosis in humans by inhibition of cathepsin K, particularly in treating post-menopausal women.

The cysteine protease inhibitory activities of the compounds of the invention can be determined by methods known to those of ordinary skill in the art. Suitable *in vitro* assays for measuring protease activity and the inhibition thereof by test compounds are known. Typically, the assay measures protease induced hydrolysis of a peptide based substrate. Details of assays for measuring protease inhibitory activity are set forth below.

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. 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.

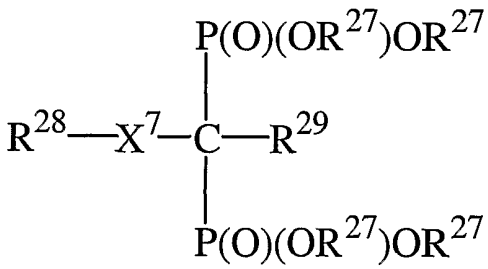
The compounds of Formula I can be administered as pharmaceutical compositions by one of the following routes: oral, systemic (e.g., transdermal, intranasal or by suppository) or parenteral (e.g., intramuscular, intravenous or subcutaneous). Compositions can take the form of tablets, pills, capsules, 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 compositions 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. Representative pharmaceutical formulations containing a compound of Formula I are described below.

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^7 is a bond or (C_{1-7})alkylene, each R^{27} independently is hydrogen or (C_{1-30})alkyl, R^{28} and R^{29} 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, $NR^{30}R^{30}$, OR^{30}, SR^{30}, wherein each R^{30} independently is hydrogen, (C_{1-10})alkyl, (C_{3-10})cycloalkyl, optionally substituted (C_{6-10})aryl, provided that both R^{28} and R^{29} are not selected from hydrogen or

hydroxy when X^7 is a bond; or R^{28} and R^{29} 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^{28} and/or R^{29} 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, $NR^{31}R^{31}$, OR^{31} and SR^{31}, wherein each R^{31} 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^{28} is selected from the group consisting of hydrogen, hydroxy or halo, and R^{29} is selected from the group consisting of optionally substituted (C_{1-30})alkyl, halo and SR^{30}, wherein R^{30} 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^{28} is selected from the group consisting of hydrogen, hydroxy and chloro and R^{29} 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^7 is a bond, each R^{27} is hydrogen, R^{28} is hydroxy and R^{29} 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.

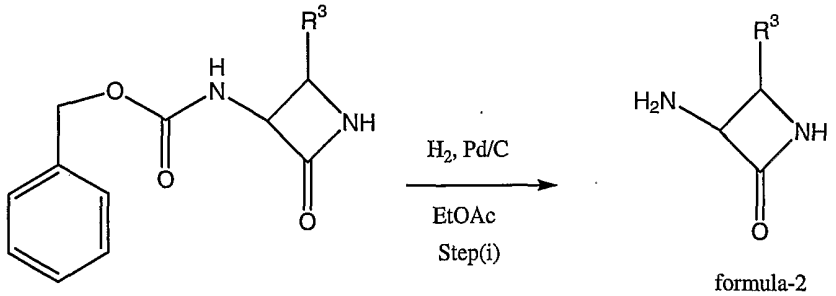
EXAMPLES

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

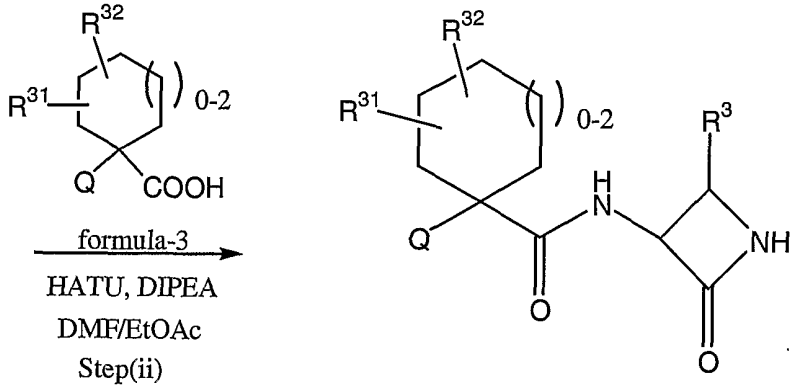
General Synthetic Procedures:

Compounds of the present invention can be prepared by the procedures outlined in synthetic Schemes I-IV below.

Scheme I



formula-1 formula-2



Formula-I

Step (i)

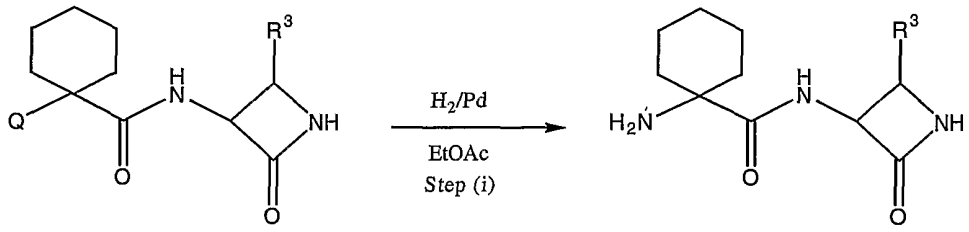
A mixture of a compound of formula-1 (1 eq.) and 10% Pd/C (catalyst) in ethyl acetate (EtOAc) is hydrogenated at 50 psi at ambient temperature for about 8 hours. The reaction mixture then is filtered through Celite, and the filtrate then is concentrated under reduced pressure to yield a compound of formula-2. The compound of formula-2 (the free amine) can be unstable hence it is used as its acid salt.

Step (ii)

A mixture of a compound of formula-2 and a neutral solvent such as EtOAc is combined with a mixture of a compound of formula-3 (1 eq.), in the presence of a coupling agent such as HATU (1 eq.), organic base such as DIPEA (1.2 eq) and a neutral solvent such as DMF. The resulting reaction mixture is agitated, at ambient temperature, from about 10 hours to about 20 hours. The agitated reaction mixture then is concentrated under reduced pressure to yield a residue. The residue is diluted with EtOAc, sequentially washed with an aqueous solution of sodium bicarbonate and brine, dried (Na_2SO_4) and concentrated under reduced pressure to yield the compound of Formula I. The compound of Formula I can be purified, if desired, using silica gel column chromatography, using 1:1 ethyl acetate:hexane as eluant.

Alternatively, a compound of Formula I can be prepared as described in Scheme II below.

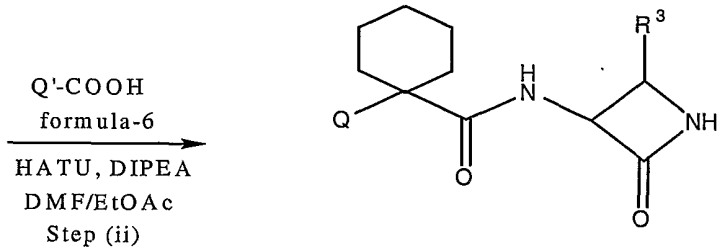
Scheme II



Formula-I formula-5

where Q = -NHCO$_2$CH$_2$-aryl
or -NH-Pg*

Pg* represents a protecting group



Formula-I

Q' = -(CH$_2$)$_{0-6}$- (C$_{6-10}$)aryl, -(CH$_2$)$_{0-6}$-(C$_{3-10}$)cycloalkyl, -C$_{1-4}$ alkyl, -(CH$_2$)$_{0-6}$-hetero(C$_{5-10}$)aryl, -(CH$_2$)$_{0-6}$-(C$_{3-10}$)heterocycloalkyl, -(CH$_2$)$_{0-6}$-(C$_{9-10}$)bicycloaryl or hetero(C$_{8-10}$) bicycloaryl

Step (i)

A compound of Formula I (wherein Q = -NHCOOCH$_2$aryl or –NHPg*) (1 eq.) is hydrogenated, as described in Scheme I, Step (i) above, to yield a compound of formula-5.

Step (ii)

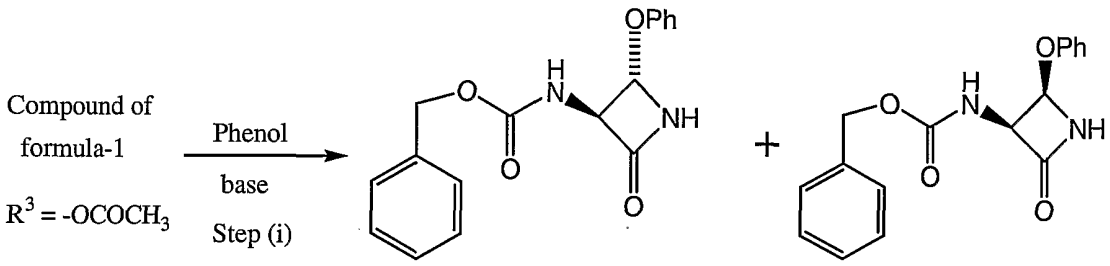
A mixture of a compound of formula-5 and a neutral solvent such as EtOAc is combined with a mixture of a compound of formula-6 (1 eq.), in the presence of a coupling agent such as HATU (1 eq.), DIPEA (2 eq.) and a neutral solvent (DMF). The resulting reaction mixture then is agitated at ambient temperature from about 10 to about 20 hours. The agitated reaction mixture then is concentrated under reduced pressure to yield a residue. The residue is diluted with EtOAc, sequentially washed with a saturated aqueous solution of Na_2CO_3 and brine. The washed EtOAc layer then is dried (Na_2SO_4) and concentrated under reduced pressure to yield a compound of Formula I. This compound of Formula I can be purified, if necessary using purification

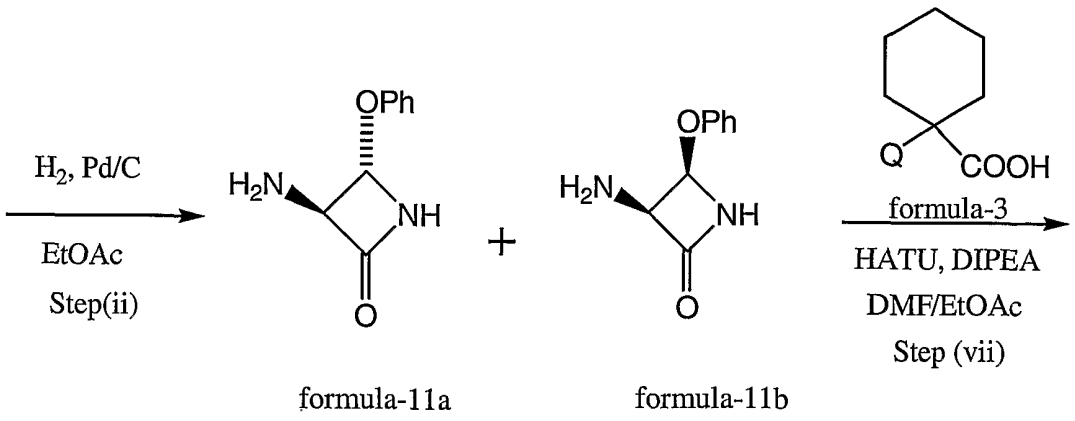
techniques known to one skilled in the art. Thus, for example HPLC can be used to yield a purer form of the compound of Formula I.

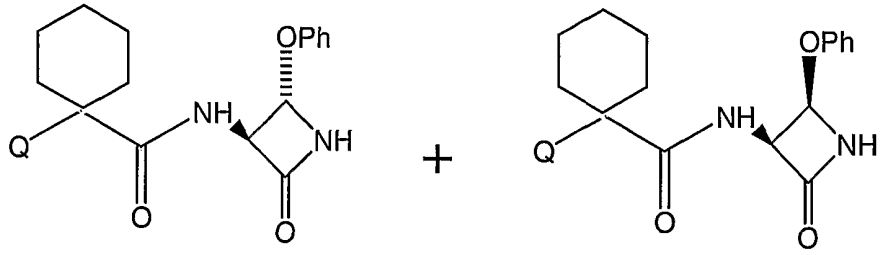
Compound of formula –6 are either commercially available or they can be prepared by methods well known in the art. Some such methods are described in WO 00/55126 the disclosure of which is incorporated herein by reference in its entirety.

Scheme III

A compound of formula I where R^3 is –OPh can be prepared as illustrated and described below.







Formula I Formula I

Step (i)

A mixture of a compound of formula-1 (1 eq., see Scheme I for structure), acetone, phenol (1.5 eq.) and 1N NaOH is stirred for about 3 hours at ambient temperature. The reaction mixture is concentrated under reduced pressure to yield a residue. The residue is diluted with ethyl acetate, sequentially washed with water and brine, dried (Na_2SO_4) and concentrated under reduces pressure to yield a mixture of the cis and trans isomers of a compound of formula-10. The cis and trans isomers are separated using a silica gel column using a mixture of 1:3, ethyl acetate/hexanes mixture as eluant.

Step (ii)

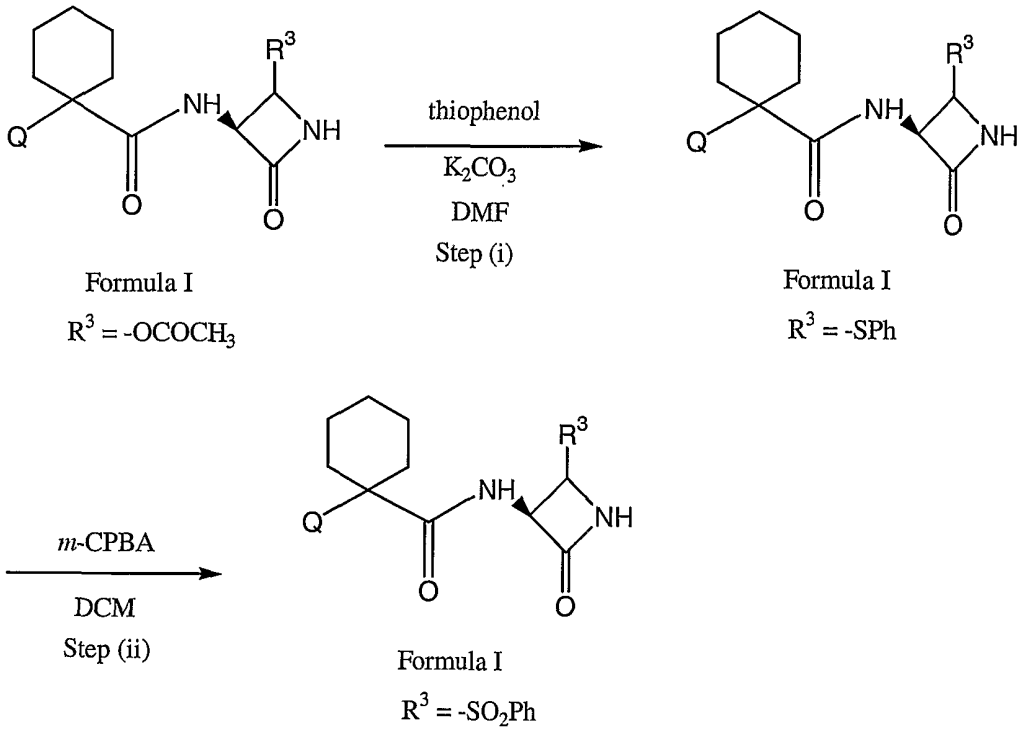
The two isomers, compound of formula-10a and compound-10b, are hydrogenated according to the procedure in Scheme I, step (i) to yield compounds of formula-11a and 11b respectively.

Step (iii)

The two isomers, compound of formula-11a and formula-11b, are independently coupled with a compound of formula-3 using the reaction procedure and conditions outlined in Scheme I, step (ii), to yield the corresponding compounds of Formula I respectively.

Compounds of Formula I wherein R^3 represents -SPh or -SO_2Ph are synthesized as outlined in Scheme IV below.

Scheme IV



Step (i)

A mixture of a compound of Formula I (1 eq.) and DMF is agitated at ambient temperature. The agitated mixture then is mixed with thiophenol (excess, about 12 eq.) and potassium carbonate (about 12 eq.). The resulting mixture then is agitated at ambient temperature from about 12 hours to about 50 hours. The agitated reaction mixture then is concentrated under reduced pressure to yield a residue. The residue then is diluted with a neutral solvent (e.g., ethyl acetate) and the resulting mixture then is sequentially washed with water and brine, dried (Na_2SO_4) and concentrated to yield the compound of Formula I (wherein R^3 = -SPh) as an oily substance.

Step (ii)

A compound of Formula I (1 eq.), obtained after step (viii) and where R^3 = -SPh, is mixed with dichloromethane to form a solution. The solution then is mixed with *m*-CPBA (3-5 eq.) and the resulting reaction mixture is agitated at a temperature of from about 20°C to about 30°C for 1-4 hours. The reaction mixture then is diluted with water and the aqueous mixture is washed with dichloromethane (x2). The dichloromethane extracts are combined and sequentially washed with water and brine, dried ($MgSO_4$) and concentrated under reduced pressure to yield a compound of Formula I, wherein R^3 = -SO_2Ph.

Additional Processes for Preparing Compounds of Formula I:

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 may 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, or the like).

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 methylene chloride) 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 a suitable 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 made by means 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 drugs 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 protective groups and their removal can be found in T.W. Greene, *Protective 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 diastereomeric 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, preferable, 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, John Wiley & Sons, Inc. (1981).

Additional Processes for Preparing Compounds of Formula I:

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 may 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, or the like).

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 methylene chloride) 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 a suitable organic solvent (e.g., acetonitrile, ethanol, aqueous dioxane, or the like) at 0 to 80°C.

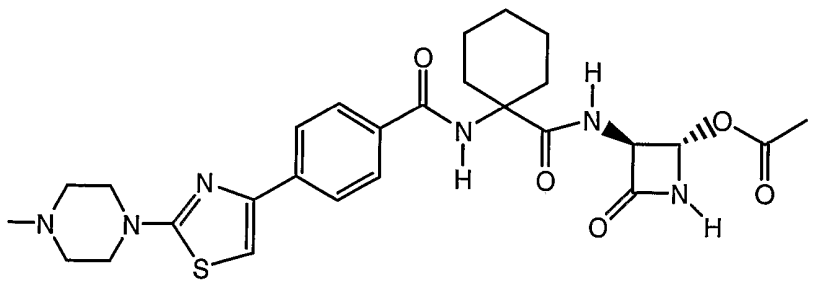
Prodrug derivatives of the compounds of Formula I can be made by means known to those of ordinary skill in the art (e.g., for further details see Saulnier *et al.* (1994), *Bioorganic and Medicinal Chemistry Letters*. 4: 1985). For example, appropriate drugs can be prepared by reacting a non-derivatized 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 protective groups and their removal can be found in T.W. Greene, *Protective 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 diastereomeric 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, preferable, 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, John Wiley & Sons, Inc. (1981).

Synthetic Examples

Synthesis of acetic acid 3-[(1-{4-[2-(4-methyl-piperazin-1-yl)-thiazol-4-yl]-benzoylamino}cyclohexanecarbonyl)-amino]-4-oxo-azetidin-2-yl ester



Step 1

To a solution of acetic acid 3-benzyloxycarbonylamino-4-oxo-azetidin-2-yl ester (278 mg, 1 mmol) (prepared as described in J.C Arnould, P. Boultron, M.J. Pasquet, *Eur.J.Med.Chem.*, 27, 131-140, 1992) in ethyl acetate (15 ml) was added 10% Pd/C (200 mg). The reaction mixture was hydrogenated at 50 psi for 8 h. The catalyst was separated by filtration through a short plug of Celite® and the solution of the 3-amino-4-oxo-azetidin-2-yl ester was mixed with a solution of 1-benzyloxycarbonylamino-cyclohexanecarboxylic acid (278 mg, 1 mmol), HATU (380 mg, 1 mmol) and diisopropylethylamine (209 µl, 1.2 mmol) in THF. The reaction mixture stirred for 18 hs at room temperature. The mixture was washed with sat. $NaHCO_3$, dried over Na_2SO_4, evaporated and the crude purified by silica gel column, using a mixture of ethyl acetate:hexane (1:1) as eluent to give acetic acid 3-[(1-benzyloxycarbonylamino-cyclohexanecarbonyl)-amino]-4-oxo-azetidin-2-yl ester as a foam (290 mg, 72%). ^{1}HNMR (DMSO-d_6): δ 9.09 (1H, s), 8.29 (1H, d, J: 8.2 Hz), 7.35 (5H, m), 7.23 (1H, s), 5.68 (1H, s), 4.99 (2H, s), 4.61 (1H, d, J: 8.2 Hz), 2.07 (3H, s), 1.90 (2H, m), 1.66 (2H, m), 1.46 (4H, m), 1.17 (2H, m).

Step 2

To a solution of acetic acid 3-[(1-benzyloxycarbonylaminocyclohexane-carbonyl)amino]-4-oxo-azetidin-2-yl ester (333 mg, 0.82 mmol) in ethyl acetate (15 ml), 10% Pd/C (200 mg) was added. The mixture was hydrogenated for 8 hs at 50 psi of hydrogen pressure. The catalyst was removed by filtering through a short plug of Celite® and the solution of acetic acid 3-[(1-aminocyclohexanecarbonyl)-amino]-4-oxo-azetidin-2-yl ester was used for coupling without purification.

Step 3

To a solution formed by dissolving the HBr salt of 4-[2-(4-Methyl-piperazin-1-yl)-thiazol-4-yl]-benzoic acid (318 mg, 0.82 mmol), HATU (312 mg, 0.82 mmol) and diisopropylethylamine (285 µl, 1.64 mmol) in DMF (5 ml), was added a solution of acetic acid 3-[(1-aminocyclohexanecarbonyl)-amino]-4-oxo-azetidin-2-yl ester. The reaction mixture was stirred for 18 h at room temperature. After diluting the reaction mixture with ethyl acetate (20 ml), the solution was washed with solution of $NaHCO_3$, dried over anhydrous Na_2SO_4 and the solvent evaporated under vacuum. The crude mixture was purified by HPLC to obtain the titled compound as a white solid (25 mg,

4.5%). ^{1}HNMR (DMSO-d_6): d 9.02 (1H, s), 8.22 (1H, d), 7.86 (5H, m), 7.50 (1H, s), 5.63 (1H, s), 4.54 (1H, d), 4.05 (4H, m), 3.30 (4H, m), 2.81 (3H, s), 2.06 (2H, m), 2.01 (3H, s), 1.70 (2H, m), 1.46 (6H, m), 1.16 (2H, m). MS, M+1: 555.2.

The following compounds were prepared using the procedures outlined Scheme I above:

Acetic acid 3-[(1-tert-butoxycarbonylamino-cyclohexanecarbonyl)-amino]-4-oxo-azetidin-2-yl ester. ^{1}H NMR (DMSO-d_6) δ: 9.04 (1H, s), 8.20 (1H, d), 6.65 (1H, s), 5.67 (1H, s), 4.60 (1H, d), 2.04 (3H, s), 1.80 (2H, m), 1.60 (2H, m), 1.44 (4H, m), 1.34 (9H, s), 1.18 (2H, m).

Acetic acid 3-[(1-benzyloxycarbonylamino-cyclohexanecarbonyl)-amino]-4-oxo-azetidin-2-yl ester. ^{1}H NMR (DMSO-d_6) δ: 9.09 (1H, s), 8.29 (1H, d), 7.35 (5H, m), 7.23 (1H, s), 5.68 (1H, s), 4.99 (2H, s), 4.61 (1H, d), 2.07 (3H, s), 1.90 (2H, m), 1.66 (2H, m), 1.46 (4H, m), 1.17 (2H, m).

The following compounds were prepared using the procedures outlined Scheme II above:

Acetic acid 3-{[1-(4-dimethylamino-benzoylamino)-cyclohexanecarbonyl]-amino}-4-oxo-azetidin-2-yl ester. ^{1}H NMR (DMSO-d_6) δ: 9.06 (1H, s), 8.21 (1H, d), 7.75 (2H, d), 7.49 (1H, s), 6.69 (2H, d), 5.68 (1H, s), 4.58 (1H, d), 2.98 (6H, s), 2.12 (2H, m), 2.07 (3H, s), 1.72 (2H, m), 1.50 (4H, m), 1.20 (2H, m).

Acetic acid 3-({1-[4-(2-dimethylamino-thiazol-4-yl)-benzoylamino]-cyclohexanecarbonyl}-amino)-4-oxo-azetidin-2-yl ester. ^{1}H NMR (DMSO-d_6) δ: 9.02 (1H, s), 8.25 (1H, d), 7.98 (2H, d), 7.58 (3H, m), 7.11 (1H, s), 5.62 (1H, s), 4.56 (1H, d), 3.02 (6H, s), 2.07 (2H, m), 2.01 (3H, s), 1.73 (2H, m), 1.46 (4H, m), 1.27 (2H, m). MS, M+1: 500.6.

Acetic acid 3-[(1-{4-[2-(4-methyl-piperazin-1-yl)-thiazol-4-yl]-benzoylamino}-cyclohexanecarbonyl)-amino]-4-oxo-azetidin-2-yl ester. ^{1}H NMR (DMSO-d_6) δ: 9.02 (1H, s), 8.22 (1H, d), 7.86 (5H, m), 7.50 (1H, s), 5.63 (1H, s), 4.54 (1H, d), 4.05 (4H, m), 3.30 (4H, m), 2.81 (3H, s), 2.06 (2H, m), 2.01 (3H, s), 1.70 (2H, m), 1.46 (6H, m), 1.16 (2H, m). MS, M+1: 555.2.

Acetic acid 3-{[1-(4-morpholin-4-yl-benzoylamino)-cyclohexanecarbonyl]-amino}-4-oxo-azetidin-2-yl ester. ^{1}H NMR (CD_3OD) δ: 7.77 (2H, d), 6.99 (2H, d), 5.89

(1H, s), 4.60 (1H, s), 3.82 (4H, m), 3.30 (4H, m), 2.15 (2H, m), 2.08 (3H, s), 1.90 (2H, m), 1.60 (6H, m).

Acetic acid 3-[(1-{4-[2-(4-methyl-piperazin-1-ylamino)-thiazol-4-yl]-benzoylamino}-cyclohexanecarbonyl)-amino]-4-oxo-azetidin-2-yl ester. ^{1}H NMR (DMSO-d_6) δ: 9.55 (1H, bs), 9.11 (1H, s), 8.21 (1H, d), 7.85 (1H, s), 7.82 (4H, m), 7.34 (1H, s), 5.62 (1H, s), 4.54 (1H, d), 3.39 (2H, m), 3.16 (4H, m), 2.89 (2H, m), 2.71 (3H, s), 2.05 (2H, m), 1.69 (2H, m), 1.46 (4H, m), 1.22 (2H, m). MS, M+1: 5.70.

The following compounds were prepared using the procedures outlined Scheme III above:

[1-(2-Oxo-4-phenoxy-azetidin-3-ylcarbamoyl)-cyclohexyl]-carbamic acid benzyl ester. ^{1}H NMR (DMSO-d_6) δ: 9.16 (1H,s), 8.44 (1H, d), 7.33(8H, m), 7.00 (1H, t), 6.86 (2H, d), 5.51 (1H, s), 5.02 (2H, m), 4.55 (1H, d), 1.90 (2H, m), 1.69 (2H, m), 1.47 (6H, m), 1.23 (2H, m).

[1-(2-Oxo-4-phenoxy-azetidin-3-ylcarbamoyl)-cyclohexyl]-carbamic acid benzyl ester. ^{1}H NMR (DMSO-d_6) δ: 9.23 (1H, s), 8.09 (1H, d), 7.29 (7H, m), 6.98 (2H, m), 6.85 (2H, d), 5.72 (1H, d), 5.34 (1H, dd), 4.95 (2H, q), 1.87 (2H, m), 1.41 (6H, m), 1.10 (2H, m).

The following compounds were prepared using the procedures outlined Scheme IV above:

[1-(2-Benzenesulfonyl-4-oxo-azetidin-3-ylcarbamoyl)-cyclohexyl]-carbamic acid benzyl ester. ^{1}H NMR (DMSO-d_6) δ: 9.23 (1H, s), 8.37 (1H, d), 7.75 (5H, m), 7.33 (6H, m), 4.97 (2H, s), 4.80 (2H, m), 1.42 (8H, m). MS, M+23: 508.2.

[1-(2-Oxo-4-phenylsulfanyl-azetidin-3-ylcarbamoyl)-cyclohexyl]-carbamic acid benzyl ester. ^{1}H NMR (DMSO-d_6) δ: 8.88 (1H, s), 8.38 (1H, d), 7.35 (11H, m), 4.99 (2H, s), 4.87 (1H, d), 4.51 (1H, d), 1.89 (2H, m), 1.63 (2H, m), 1.46 (4H, m), 1.18 (2H, m). MS, M+23: 475.8.

Acetic acid 3-[(1-{4-[2-(3-tert-butoxycarbonylamino-pyrrolidin-1-yl)-thiazol-4-yl]-benzoylamino}-cyclohexanecarbonyl)-amino]-4-oxo-azetidin-2-yl ester. ^{1}H NMR (DMSO-d_6) δ: 9.03 (1H, s), 8.22 (1H, d), 7.86 (5H, m), 7.27 (1H, s), 5.64 (1H, s), 4.56 (1H, d), 4.1 (1H, m), 3.50 (4H, m), 2.17 (2H, m), 1.90 (1H, m), 1.73 (2H, m), 1.48 (4H, m), 1.35 (9H, s), 1.20 (2H, m). MS, M+1: 641.

4-[2-(4-Methyl-piperazin-1-yl)-thiazol-4-yl]-N-[1-(2-oxo-4-phenoxy-azetidin-3-ylcarbamoyl)-cyclohexyl]-benzamide. ^{1}HNMR (DMSO-d6): δ: 9.23 (1H, s), 8.23 (1H, d), 7.94 (2H, d), 7.86 (2H, d), 7.76 (1H, s), 7.56 (1H, s), 7.21 (2H, t), 6.94 (1H, m), 6.74 (2H, d), 5.70 (1J, m), 5.36 (1H, m), 4.10 (2H, d), 3.49 (4H, m), 3.19 (2H, m), 2.82 (3H, s), 2.12 (2H, m), 1.49 (6H, m), 1.19 (2H, m).

MS (M+1): 589.4.

Biological Examples

Cathepsin K Assay

Solutions of test compounds in varying concentrations were prepared in 10 μL of dimethyl sulfoxide (DMSO) and then 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 (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.

Formulation Examples

Representative Pharmaceutical Formulations Containing a Compound of Formula I:

ORAL FORMULATION

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

INTRAVENOUS FORMULATION

Compound of Formula I	0.1-10 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

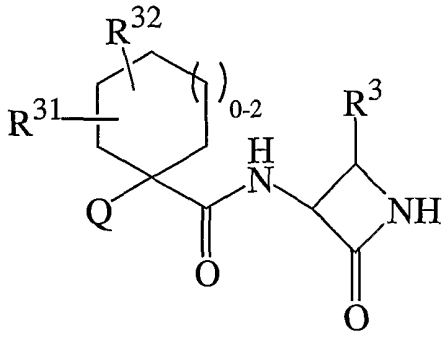
Compound of Formula I	1%
Microcrystalline Cellulose	73%
Stearic Acid	25%
Colloidal Silica	1%

The resulting tablets are useful for administration in accordance with the methods of this invention for treating or preventing a cathepsin mediated disease state, such as osteoporosis.

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

We Claim:

1. A compound of Formula I:



Formula I

wherein:

Q is selected from a group consisting of $-Z^1-(C_{6-10})$aryl, $-Z^1-(C_{3-10})$cycloalkyl, $-Z^1-C_1$ alkyl, $-Z^1$-hetero(C_{3-10})cycloalkyl, $-Z^1$-hetero(C_{5-10})aryl, $-Z^1-(C_{9-10})$bicycloaryl and $-Z^1$-hetero(C_{8-10}) bicycloaryl, wherein said (C_{6-10})aryl, (C_{3-10})cycloalkyl, C_1 alkyl, hetero(C_{3-10})cycloalkyl, hetero(C_{5-10})aryl, (C_{9-10})bicycloaryl and hetero(C_{8-10}) bicycloaryl groups are substituted with R^1;

R^1 is selected from a group consisting of H, $-X^3NR^8R^{21}$, $-X^3NR^8C(O)R^{21}$, $-X^3NR^8C(O)OR^{21}$, $-X^3NR^8C(O)NR^8R^{21}$, $-X^3NR^8C(NR^8)NR^8R^{21}$, $-X^3OR^{21}$, $-X^3SR^{21}$, $-X^3S(O)R^{21}$, $-X^3S(O)_2R^{21}$, $-X^3C(O)R^{21}$, $-X^3C(O)OR^{21}$, $-X^3OC(O)R^{21}$, $-X^3C(O)NR^8R^{21}$, $-X^3OC(O)NR^8R^{21}$, $-X^3S(O)_2NR^8R^{21}$, $-X^3P(O)(OR^8)OR^{21}$, $-X^3OR^{52}$, $-X^3CONR^8R^{52}$, $-X^3SO_2NR^8R^{52}$, $-X^3OP(O)(OR^8)OR^{21}$, and R^{21} wherein:

X^3 is a bond or (C_{1-6})alkylene, R^8 at each occurrence independently is hydrogen or (C_{1-6})alkyl, R^{52} represents $-CH_2CH_2-N(CH_2CH_2OH)_2$, $-CH(CH_3)CH_2N(CH_3)_2$, $-CH_2CH_2OH$, $-CH_2CH_2N(CH_3)_2$ or $-CH_2CN$, and R^{21} is (C_{1-8})alkyl or X^4R^{22} wherein X^4 is a bond or (C_{1-6})alkylene and R^{22} is selected from a group consisting of (C_{3-10})cycloalkyl, hetero(C_{5-10})cycloalkyl, (C_{6-10})aryl, hetero(C_{5-10})aryl, (C_{9-10})bicycloaryl and hetero(C_{8-10})bicycloaryl wherein the cyclic group contained within R^{22} may be substituted further by a radical selected from a group consisting of $-X^3NR^8R^{23}$, $-X^3NR^8C(O)R^{23}$, $-X^3NR^8C(O)OR^{23}$, $-X^3NR^8C(O)NR^8R^{23}$, $-X^3OR^{23}$, $-X^3NR^8C(NR^8)NR^8R^{23}$, $-X^3SR^{23}$, $-X^3S(O)R^{23}$, $-X^3S(O)_2R^{23}$, $-X^3C(O)R^{23}$, $-X^3OC(O)R^{23}$, $-X^3C(O)OR^{23}$, $-X^3C(O)NR^8R^{23}$, $-X^3OC(O)NR^8R^{23}$, $-X^3S(O)_2NR^8R^{23}$,

$-X^3OR^{52}$, $-X^3CONR^8R^{52}$, $-X^3SO_2NR^8R^{52}$, $-X^3P(O)(OR^8)OR^{23}$, $-X^3OP(O)(OR^8)OR^{23}$ and R^{23} wherein:

X^3, R^8 and R^{52} are as defined above, and R^{23} is (C_{1-8})alkyl or $-X^5R^{24}$ wherein X^5 is a bond or (C_{1-6})alkylene and R^{24} is selected from a group consisting of (C_{3-10})cycloalkyl, hetero(C_{5-10})cycloalkyl, (C_{6-10})aryl, hetero(C_{5-10})aryl, (C_{9-10})bicycloaryl and hetero(C_{8-10})bicycloaryl wherein:

R^{24} may be substituted further by a radical selected from a group consisting of $-X^3NR^8R^{25}$, $-X^3NR^8C(O)R^{25}$, $-X^3NR^8C(O)OR^{25}$, $-X^3OR^{25}$, $-X^3NR^8C(O)NR^8R^{25}$, $-X^3NR^8C(NR^8)NR^8R^{25}$, $-X^3SR^{25}$, $-X^3S(O)R^{25}$, $-X^3S(O)_2R^{25}$, $-X^3C(O)R^{25}$, $-X^3OC(O)R^{25}$, $-X^3C(O)OR^{25}$, $-X^3C(O)NR^8R^{25}$, $-X^3OC(O)NR^8R^{25}$, $-X^3S(O)_2NR^8R^{25}$, $-X^3P(O)(OR^8)OR^{25}$, $-X^3OR^{52}$, $-X^3CONR^8R^{52}$, $-X^3SO_2NR^8R^{52}$, $-X^3OP(O)(OR^8)OR^{25}$ and R^{25} wherein:

X^3, R^8 and R^{52} are as defined above, and R^{25} is (C_{1-8})alkyl or X^6R^{26}, wherein X^6 is a bond or (C_{1-6})alkylene and R^{26} is selected from a group consisting of (C_{3-10})cycloalkyl, hetero(C_{5-10})cycloalkyl, (C_{6-10})aryl, hetero(C_{5-10})aryl, (C_{9-10})bicycloaryl and hetero(C_{8-10})bicycloaryl wherein any of the (C_{3-10})cycloalkyl, hetero(C_{5-10})cycloalkyl, (C_{6-10})aryl, hetero(C_{5-10})aryl, (C_{9-10})bicycloaryl and hetero(C_{8-10})bicycloaryl contained within R^3, R^{22}, R^{24} and R^{26} may be substituted further with up to five substituents selected from a group consisting of (C_{1-6})alkyl, (C_{1-6})alkylidene, cyano, halo, nitro, halo-substituted (C_{1-3})alkyl, $-X^3NR^{16}R^{16}$, $-X^3NR^{16}C(O)OR^{16}$, $-X^3NR^{16}C(O)NR^{16}R^{16}$, $-X^3NR^{16}C(NR^{16})NR^{16}R^{16}$, $-X^3OR^{16}$, $-X^3SR^{16}$, $X^3C(O)OR^{16}$, $-X^3C(O)NR^{16}R^{16}$, $-X^3S(O)_2NR^{16}R^{16}$, $-X^3P(O)(OR^8)OR^{16}$, $-X^3OR^{52}$, $-X^3CONR^8R^{52}$, $-X^3C(O)R^{16}$, $-X^3SO_2NR^8R^{52}$, $-X^3S(O)R^{17}$, $-X^3OP(O)(OR^8)OR^{16}$, $-X^3NR^{16}C(O)R^{17}$, $-X^3S(O)_2R^{17}$ and $-X^3C(O)R^{16}$ wherein:

X^3, R^8 and R^{52} are as defined above, R^{16} at each occurrence independently is selected from a group consisting of hydrogen, (C_{1-3})alkyl or halo-substituted (C_{1-3})alkyl and R^{17} is $-(C_{1-3})$alkyl or halo-substituted (C_{1-3})alkyl;

R^{31} and R^{32} independently represent hydrogen or hydroxy, alternatively R^{31} and R^{32} can be taken together to represent an oxo (=O) group;

R^3 is $-OCOC_{1-8}$ alkyl, -S-aryl, $-COOC_{1-8}$ alkyl, or $-SO_2$-aryl;

Z^1 is $-NHCO-(C_{0-6})$alkylene-, or $-NHCOO-(C_{0-6})$alkylene-; or

pharmaceutically acceptable salts thereof.

2. The compound of Claim 1 in which:

Q represents -NHCO-(C_{6-10})aryl or -NHCO-hetero(C_{5-10})aryl wherein said C_{6-10} aryl and hetero(C_{5-10})aryl groups are further substituted with R^1 wherein R^1 is selected from a group consisting of H, $-X^3NR^8R^{21}$, $-X^3NR^8C(O)R^{21}$, $-X^3NR^8C(O)OR^{21}$, $-X^3NR^8C(O)NR^8R^{21}$, $-X^3OR^{21}$, $-X^3SR^{21}$, $-X^3C(O)R^{21}$, $-X^3C(O)OR^{21}$, $-X^3OC(O)R^{21}$, $-X^3C(O)NR^8R^{21}$, $-X^3OR^{52}$, $-X^3CONR^8R^{52}$ and R^{21} wherein:

X^3 is a bond or (C_{1-6})alkylene, R^8 at each occurrence independently is hydrogen or (C_{1-6})alkyl, R^{52} represents $-CH_2CH_2-N(CH_2CH_2OH)_2$, hydrogen, $-CH(CH_3)CH_2N(CH_3)_2$, $-CH_2CH_2OH$, CH_2CN or $-CH_2CH_2N(CH_3)_2$, and R^{21} is (C_{1-8})alkyl or X^4R^{22} wherein:

X^4 is a bond or (C_{1-6})alkylene; and

R^{22} is selected from a group consisting of hetero(C_{5-10})cycloalkyl, (C_{6-10})aryl, hetero(C_{5-10})aryl and hetero(C_{8-10})bicycloaryl wherein R^{22} may be substituted further by a radical selected from a group consisting of (C_{1-4})alkyl, $-X^3NR^8R^{23}$, $-X^3C(O)NR^8R^{52}$, $-X^3OR^{23}$, $-X^3NR^8C(O)OR^{23}$, $-X^3SO_2NR^8R^{52}$, $-X^3C(O)NR^8R^{23}$, $-X^3SO_2NR^8R^{23}$, $-X^3COR^{23}$, $-X^3OR^{52}$, $-X^3S(O)_2R^{23}$, $-X^3N(R^8)_2$ and R^{23}, wherein X^3, R^8 and R^{52} are as defined above and R^{23} is (C_{1-8})alkyl or X^5R^{24} wherein:

X^5 is a bond or (C_{1-6})alkylene; and

R^{24} is selected from a group consisting of hetero(C_{5-10})cycloalkyl and hetero(C_{5-10})aryl wherein R^{24} may be substituted further with R^{25}, $-X^3OR^{52}$, $-X^3NR^8R^{25}$, $-X^3NHC(O)OR^{25}$, $-X^3COOR^{25}$ and $-X^3SO_2NR^8R^{52}$ wherein X^3, R^{52} and R^8 are as defined above, and R^{25} is (C_{1-8})alkyl or X^6R^{26} wherein:

X^6 is a bond or (C_{1-6})alkylene; and

R^{26} is hetero(C_{5-10})cycloalkyl; and wherein any of the (C_{3-10})cycloalkyl, hetero(C_{5-10})cycloalkyl, (C_{6-10})aryl, hetero(C_{5-10})aryl, (C_{9-10})bicycloaryl and hetero(C_{8-10})bicycloaryl contained within R^3, R^{22}, R^{24} and R^{26} may be substituted further with up to five substituents selected from a group consisting of (C_{1-6})alkyl, cyano, halo, nitro, halo-substituted (C_{1-3})alkyl, $-X^3NR^{16}R^{16}$, $-X^3OR^{52}$ and $-X^3C(O)R^{16}$, wherein X^3 and R^{52} are as defined above and R^{16} at each occurrence independently is selected from a group consisting of hydrogen, (C_{1-3})alkyl or halo-substituted (C_{1-3})alkyl and R^{17} is -(C_{1-3})alkyl or halo-substituted (C_{1-3})alkyl; and

R^3 represents COO-*t*-butyl, -S-Ph, or $-SO_2$-Ph.

3. The compound of Claim 2 wherein:

Q is -NHCO-phenyl or -NHCO-hetero(C_{5-6})aryl wherein said phenyl and hetero(C_{5-6})aryl groups are substituted with R^1 wherein R^1 is selected from a group consisting of $-X^3NR^8R^{21}$, $-X^3NR^8C(O)R^{21}$, $-X^3NR^8C(O)OR^{21}$ and R^{21} where X^3 is a bond or (C_{1-6})alkylene, R^8 is hydrogen or (C_{1-6})alkyl, and R^{21} is $-X^4R^{22}$ where:

X^4 is a bond or (C_{1-6})alkylene; and

R^{22} is selected from a group consisting of hetero(C_{5-6})cycloalkyl, (C_6)aryl, hetero(C_{5-10})aryl and hetero(C_{8-9})bicycloaryl, wherein R^{22} can be optionally substituted further by a radical selected from a group consisting of (C_{1-4})alkyl, $-X^3OR^{23}$, $-X^3NR^8R^{23}$, $-X^3C(O)NR^8R^{23}$, $-X^3C(O)NR^8R^{52}$, $-X^3NHC(O)OR^8$, $-X^3SO_2NR^8R^{23}$ and R^{23} wherein R^{52} represents $-CH_2CH_2-N(CH_2CH_2OH)_2$, hydrogen, $-CH(CH_3)CH_2N(CH_3)_2$, $-CH_2CH_2OH$, CH_2CN or $-CH_2CH_2N(CH_3)_2$, X^3 and R^8 are as defined above, and R^{23} is (C_{1-8})alkyl or X^5R^{24} wherein:

X^5 is a bond or (C_{1-6})alkylene; and

R^{24} is selected from a group consisting of hetero(C_{5-6})cycloalkyl and hetero(C_{5-6})aryl wherein R^{24} may be substituted further with R^{25}, $-X^3OR^{52}$, $-X^3NR^8R^{25}$, $-X^3NHC(O)OR^{25}$, $-X^3COOR^{25}$ and $-X^3SO_2NR^8R^{52}$ wherein X^3 R^{52}, and R^8 are as defined above, and R^{25} is (C_{1-4})alkyl or X^6R^{26} wherein:

X^6 is a bond or (C_{1-6})alkylene; and

R^{26} is hetero(C_{5-10})cycloalkyl; and wherein the (C_{3-10})cycloalkyl contained within R^{26} may be substituted further with up to three groups selected from a group consisting of (C_{1-2})alkyl.

4. The compound of Claim 3 wherein:

R^1 represents R^{21} where R^{21} is X^4R^{22} where:

X^4 is a bond; and

R^{22} is hetero(C_5)aryl and hetero(C_{5-6})cycloalkyl wherein R^{22} is substituted further by R^{23} where R^{23} is X^5R^{24} wherein:

X^5 is a bond; and

R^{24} is hetero(C_{5-6})aryl or hetero(C_{5-6})cycloalkyl wherein R^{24} may be substituted further with R^{25}, $-X^3OR^{52}$, $-X^3NR^8R^{25}$, $-X^3COOR^{25}$, $-X^3NHC(O)OR^{25}$ or

$-X^3SO_2NR^8R^{52}$ wherein X^3 is a bond or (C_{1-6})alkylene, R^{52} represents $-CH_2CH_2OH$, $-CH_2CN$, $-CH_2CH_2-N(CH_2CH_2OH)_2$, $-CH(CH_3)CH_2N(CH_3)_2$, or $-CH_2CH_2N(CH_3)_2$, R^8 at each occurrence independently is hydrogen or (C_{1-6})alkyl and R^{25} is $-X^6R^{26}$ wherein:

X^6 is a bond; and

R^{26} is hetero(C_{5-6})cycloalkyl substituted with up to two (0-2) groups selected from a group consisting of (C_{1-2})alkyl.

5. The compound of Claim 1 wherein:

Q is -NHCO-phenyl wherein said phenyl is substituted with R^{21} where R^{21} is X^4R^{22} where:

X^4 is a bond; and R^{22} is hetero(C_{5-6})aryl wherein R^{22} is substituted further by R^{23} where:

R^{23} is $-X^5R^{24}$ wherein X^5 is a bond and R^{24} is hetero(C_{5-6})aryl or hetero(C_{5-6})cycloalkyl substituted with up to two (0-2) groups selected from a group consisting of (C_{1-2})alkyl.

6. A compound of Claim 1 selected from:

Acetic acid 3-[(1-benzyloxycarbonylamino-cyclohexanecarbonyl)-amino]-4-oxo-azetidin-2-yl ester;

Acetic acid 3-[(1-{4-[2-(4-methyl-piperazin-1-yl)-thiazol-4-yl]-benzoylamino}-cyclohexanecarbonyl)-amino]-4-oxo-azetidin-2-yl ester;

Acetic acid 3-[1-(1-{4-[2-(4-methyl-piperazin-1-yl)-thiazol-4-yl]-benzoylamino}-cyclohexyl)-vinylamino]-4-oxo-azetidin-2-yl ester;

Acetic acid 3-[(1-{4-[2-(3-tert-butoxycarbonylamino-pyrrolidin-1-yl)-thiazol-4-yl]-benzoylamino}-cyclohexanecarbonyl)-amino]-4-oxo-azetidin-2-yl ester;

[1-(2-Oxo-4-phenylsulfanyl-azetidin-3-ylcarbamoyl)-cyclohexyl]-carbamic acid benzyl ester;

Acetic acid 3-{[1-(4-dimethylamino-benzoylamino)-cyclohexanecarbonyl]-amino}-4-oxo-azetidin-2-yl ester;

Acetic acid 3-({1-[4-(2-dimethylamino-thiazol-4-yl)-benzoylamino]-cyclohexanecarbonyl}-amino)-4-oxo-azetidin-2-yl ester;

Acetic acid 3-[(1-{4-[2-(4-methyl-piperazin-1-ylamino)-thiazol-4-yl]-benzoylamino}-cyclohexanecarbonyl)-amino]-4-oxo-azetidin-2-yl ester;

Acetic acid 3-{[1-(4-morpholin-4-yl-benzoylamino)-cyclohexanecarbonyl]-amino}-4-oxo-azetidin-2-yl ester;

Acetic acid 3-({1-[4-(2-morpholin-4-ylmethyl-thiazol-4-yl)-benzoylamino]-cyclohexanecarbonyl}-amino)-4-oxo-azetidin-2-yl ester;

N-[1-(2-Benzenesulfonyl-4-oxo-azetidin-3-ylcarbamoyl)-cyclohexyl]-4-(4-methyl-piperazin-1-yl)-benzamide; and

[1-(2-Benzenesulfonyl-4-oxo-azetidin-3-ylcarbamoyl)-cyclohexyl]-carbamic acid benzyl ester.

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

8. The pharmaceutical composition of Claim 7 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.

9. The pharmaceutical composition of Claim 8 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.

10. The pharmaceutical composition of Claim 9 wherein the bisphosphonic acid is 1,1-dichloromethylene-1,1-diphosphonic acid or a pharmaceutically acceptable salt thereof.

11. The pharmaceutical composition of Claim 10 which comprises 1,1-dichloromethylene-1,1-diphosphonate monosodium trihydrate.

12. 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.

13. The method of Claim 12 wherein the disease is osteoporosis.

14. The method of Claim 12 selected from the group consisting of:

Acetic acid 3-[(1-benzyloxycarbonylamino-cyclohexanecarbonyl)-amino]-4-oxo-azetidin-2-yl ester;

Acetic acid 3-[(1-{4-[2-(4-methyl-piperazin-1-yl)-thiazol-4-yl]-benzoylamino}-cyclohexanecarbonyl)-amino]-4-oxo-azetidin-2-yl ester;

Acetic acid 3-[1-(1-{4-[2-(4-methyl-piperazin-1-yl)-thiazol-4-yl]-benzoylamino}-cyclohexyl)-vinylamino]-4-oxo-azetidin-2-yl ester;

Acetic acid 3-[(1-{4-[2-(3-tert-butoxycarbonylamino-pyrrolidin-1-yl)-thiazol-4-yl]-benzoylamino}-cyclohexanecarbonyl)-amino]-4-oxo-azetidin-2-yl ester;

[1-(2-Oxo-4-phenylsulfanyl-azetidin-3-ylcarbamoyl)-cyclohexyl]-carbamic acid benzyl ester;

Acetic acid 3-{[1-(4-dimethylamino-benzoylamino)-cyclohexanecarbonyl]-amino}-4-oxo-azetidin-2-yl ester;

Acetic acid 3-({1-[4-(2-dimethylamino-thiazol-4-yl)-benzoylamino]-cyclohexanecarbonyl}-amino)-4-oxo-azetidin-2-yl ester;

Acetic acid 3-[(1-{4-[2-(4-methyl-piperazin-1-ylamino)-thiazol-4-yl]-benzoylamino}-cyclohexanecarbonyl)-amino]-4-oxo-azetidin-2-yl ester;

Acetic acid 3-{[1-(4-morpholin-4-yl-benzoylamino)-cyclohexanecarbonyl]-amino}-4-oxo-azetidin-2-yl ester;

Acetic acid 3-({1-[4-(2-morpholin-4-ylmethyl-thiazol-4-yl)-benzoylamino]-cyclohexanecarbonyl}-amino)-4-oxo-azetidin-2-yl ester;

N-[1-(2-Benzenesulfonyl-4-oxo-azetidin-3-ylcarbamoyl)-cyclohexyl]-4-(4-methyl-piperazin-1-yl)-benzamide; and

[1-(2-Benzenesulfonyl-4-oxo-azetidin-3-ylcarbamoyl)-cyclohexyl]-carbamic acid benzyl ester.

15. The method of Claim 12 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.

16. The method of Claim 15 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.

17. The method of Claim 16 wherein the bisphosphonic acid is 1,1-dichloromethylene-1,1-diphosphonic acid or a pharmaceutically acceptable salt thereof.

18. The method of Claim 17 which comprises 1,1-dichloromethylene-1,1-diphosphonate monosodium trihydrate.

19. The method of Claim 18 wherein the animal is a human.

20. The method of Claim 19 wherein the human is a post-menopausal woman.

21. The method of Claim 20 wherein the cysteine protease is Cathepsin K activity.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/05881

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D417/12 C07D205/085 A61K31/397 A61K31/427

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, CHEM ABS Data, BEILSTEIN Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 00 59881 A (MICETICH RONALD G ;KALETA JADWIGA (CA); SINGH RAJESHWAR (CA); NAEJ) 12 October 2000 (2000-10-12) see whole document, especially definitions of R2	1-21
Y	WO 98 12176 A (SYNPHAR LAB INC) 26 March 1998 (1998-03-26) see whole document, espcially definitions of R3 and examples	1-21
Y	WO 99 48911 A (REDDY ANDHE VENKAT NARENDER ;ZHOU NIAN (CA); SINGH RAJESHWAR (CA);) 30 September 1999 (1999-09-30) see whole document, especially definitions of R2 and R3	1-21

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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

"E" earlier document but published on or after the international filing date

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 July 2002	15/07/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Scruton-Evans, I

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/05881

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 98 12210 A (SYNPHAR LAB INC ;CANADA NAT RES COUNCIL (CA)) 26 March 1998 (1998-03-26) the whole document	1-21

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/05881

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

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

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 12-21 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

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

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

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

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 02/05881

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
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