

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
20 April 2006 (20.04.2006)

PCT

(10) International Publication Number
WO 2006/042103 A2

(51) International Patent Classification: Not classified

(21) International Application Number:
PCT/US2005/036127

(22) International Filing Date: 5 October 2005 (05.10.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/616,417 5 October 2004 (05.10.2004) US

(71) Applicant (for all designated States except US): **AXYS PHARMACEUTICALS, INC.** [US/US]; 180 Kimball Way, So. San Francisco, CA 94080 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **PALMER, James, T.** [US/US]; 131 Koch Road, Corte Madera, California 94925 (US). **RYDZEWSKI, Robert, M.** [US/US]; 5321 Edgewater Drive, Newark, CA 94560 (US).

(74) Agents: **WADE, Janice, V.** et al.; CELERA, 180 Kimball Way, So. San Francisco, CA 94080 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: REVERSIBLE INHIBITORS OF CATHEPSIN B

(57) Abstract: The present invention is directed to compounds that are inhibitors of cathepsin B and are therefore useful in treating diseases, disorders, or syndromes mediated by this cathepsin. The present invention is directed to pharmaceutical compositions comprising these compounds and processes for preparing them.

WO 2006/042103 A2

REVERSIBLE INHIBITORS OF CATHEPSIN BCross-Reference

The Applicants claim priority under 35 U.S.C. 119(e) to copending Provisional Application No. 60/616,417 filed on October 5, 2004, the disclosure of which is incorporated herein by reference in its entirety.

Field of the Invention

The present invention is directed to compounds that are inhibitors of cathepsin B and is therefore useful in treating diseases, disorders, or syndromes mediated by it. The present invention includes pharmaceutical compositions comprising these compounds, methods of treating diseases, disorders, or syndromes mediated by cathepsin B utilizing these compounds, and methods of preparing these compounds.

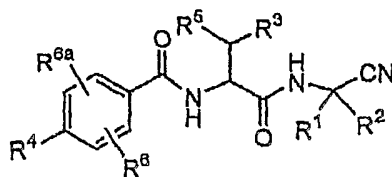
State of the Art

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 as a result of, e.g., increased expression or enhanced activation, however, may have pathological consequences. 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, osteoarthritis, pneumocystis carinii, acute pancreatitis, inflammatory airway disease, bone and joint disorders, Type II diabetes mellitus, and Metabolic Syndrome.

In view of the number of diseases, disorders, or syndromes wherein it is recognized that an increase in cathepsin B activity contributes to the pathology and/or symptomology of the disease, molecules which inhibit its activity will therefore be useful as therapeutic agents.

SUMMARY OF THE INVENTION

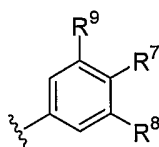
In one aspect, this invention is directed to a compound of Formula (I):



wherein:

R^1 and R^2 are independently hydrogen, haloalkyl, or hydroxyalkyl; or R^1 and R^2 together with the carbon atom to which they are attached form cycloalkylene, or heterocycloalkylene;

5 R^3 is heteroaryl or



where R^7 , R^8 , and R^9 are independently hydrogen, hydroxy, alkoxy, halo, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, alkylthio, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, 10 alkylsulfonylamino, arylsulfonylamino, amino, alkylamino, dialkylamino, cyano, nitro, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkoxycarbonyl, carboxy, alkylcarbonyl, or aminoalkoxy and wherein the alkyl, alkenyl, and alkynyl, either alone or as part of another group are independently optionally substituted with one, two, three, four, or five halo; or where one or two of R^7 , R^8 , and R^9 are as defined above and the remaining of R^7 , 15 R^8 , and R^9 are aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

R^4 is cycloalkylheterocycloalkyl;

R^5 is hydrogen, alkyl, or haloalkyl; and

R^6 and R^{6a} are independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, alkoxy, cyano, halo, haloalkyl, haloalkoxy, or alkylsulfonyl; or

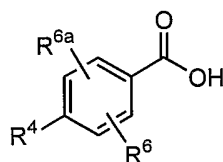
20 a pharmaceutically acceptable salt thereof.

In a second aspect this invention is directed to a pharmaceutical composition comprising a compound of the invention or a pharmaceutically acceptable salt thereof, in admixture with one or more suitable excipients.

25 In a third aspect this invention is directed to a method for treating a disease mediated by cathepsin B in an animal which method comprises administering to the animal a therapeutically effective amount of compound of this invention or a pharmaceutically acceptable salt thereof.

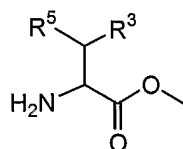
In a fourth aspect, this invention is directed to a method of making a compound of Formula I which method comprises:

(a) reacting an intermediate of formula 7



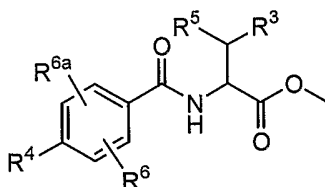
7

or a salt thereof or an activated acid derivative thereof, where R^4 , R^6 , and R^{6a} are as defined above in Formula 1, with an intermediate of formula 9



9

or a salt thereof, where R^3 and R^5 are as defined above in Formula 1 to give an intermediate of formula 10

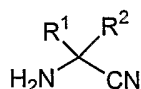


10

where R^3 , R^4 , R^5 , R^6 , and R^{6a} are as defined above in Formula 1;

(b) forming the acid, an acid addition salt, or an activated acid derivative of the intermediate of formula 10; and

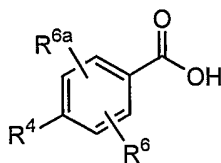
(c) reacting the product of Step (b) with an intermediate of formula 11



11

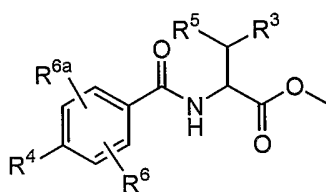
or a salt thereof, where R^3 , R^4 , R^5 , R^6 , and R^{6a} are as defined above in Formula 1.

In a fifth aspect, this invention is directed to an intermediate of formula 7:



7

where R^4 , R^6 and R^{6a} are as defined for a Compound of Formula I; or a salt thereof; or to an intermediate of formula 10:



10

where R^4 , R^3 , R^5 , R^6 , and R^{6a} are as defined for a Compound of Formula I; or a salt thereof.

- 5 In a sixth aspect, this invention is directed to the use of a Compound of this Invention for the manufacture of a medicament. Preferably the medicament is useful in the treatment of a disease mediated by cathepsin B.

DETAILED DESCRIPTION OF THE INVENTION

Definitions:

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

“Activated acid derative” means a compound of the general formula $RC(O)X$ where X is halo or X is OH activated with a coupling reagent such as dicyclohexylcarbodiimide (DCC), *N,N'*-diisopropylcarbodiimide (DIC), or 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDC), and the like.

15 “Acyl” means a $-C(O)R$ radical where R is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, or heterocycloalkylalkyl, as defined herein, e.g., acetyl, benzoyl, and the like.

20 “Administration” and variants thereof (e.g., “administering” a compound) in reference to a compound of the invention means introducing the compound or a prodrug of the compound into the system of the animal in need of treatment. When a compound of the invention or prodrug thereof is provided in combination with one or more other active agents (e.g., β -2 adrenoreceptor agonists, corticosteroids, leukotriene antagonists, and/or
25 phosphodiesterase 4 inhibitors, etc.), “administration” and its variants are each understood to include concurrent and sequential introduction of the compound or prodrug thereof and other agents.

“Alkenyl” means a linear monovalent hydrocarbon radical of two to six carbon atoms or a branched monovalent hydrocarbon radical of three to six carbon atoms containing one or
30 two double bonds e.g., ethenyl, propenyl (including all isomeric forms), 1-methylpropenyl, butenyl (including all isomeric forms), or pentenyl (including all isomeric forms), and the like.

“Alkenylcarbonyloxy” means an -OC(O)R radical where R is alkenyl, as defined herein.

“Alkenyloxy” means an -OR radical where R is alkenyl, as defined herein.

“Alkenyloxycarbonyl” means a -C(O)R radical where R is alkenyloxy, as defined
5 herein.

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

“Alkoxyalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, alkoxy group(s), as defined herein, e.g., 2-methoxyethyl, 1-, 2-, or
10 3-methoxypropyl, 2-ethoxyethyl, or 3,4-dimethoxybutyl, and the like.

“Alkoxyalkyloxy” means a -OR radical where R is alkoxyalkyl, as defined herein.

“Alkoxycarbonyl” means a radical -C(O)R where R is alkoxy, as defined herein, e.g., methoxycarbonyl, ethoxycarbonyl, *n*-propoxycarbonyl, or 2-propoxycarbonyl, *n*-, *iso*-, or *tert*-butoxycarbonyl, and the like.

15 “Alkoxycarbonylamino” means a -NRC(O)OR’ radical where R is hydrogen or alkyl, as defined herein, and R’ is alkyl, as defined herein, e.g., methoxycarbonylamino, methoxycarbonyl-*N*-methylamino or isopropoxycarbonylamino, and the like.

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

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

25 “Alkylaminoalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, alkylamino group(s), as defined herein.

“Alkylaminoalkyloxy” means an -OR radical where R is alkylaminoalkyl, as defined herein.

30 “Alkylaminocarbonyl” means a -C(O)R radical where R is alkylamino, as defined herein, e.g., methylaminocarbonyl or ethylaminocarbonyl, and the like.

“Alkylaminocarbonylamino” means an -NR’R” radical where R’ is hydrogen, alkyl, hydroxy, methoxy, or alkenyl and R” is alkylaminocarbonyl, as defined herein.

“Alkylaminocarbonyloxy” means an -OR radical where R is alkylaminocarbonyl, as defined herein.

“Alkylaminosulfonyl” means a $-S(O)_2R$ radical where R is alkylamino, as defined herein, e.g. methylaminosulfonyl.

“Alkylcarbonyl” means a $-C(O)R$ radical where R is alkyl, as defined herein, e.g., methylcarbonyl, ethylcarbonyl, or 2-propylcarbonyl, and the like.

5 “Alkylcarbonylamino” means a $-NRR'$ radical, where R is hydrogen or alkyl, as defined herein, and R' is alkylcarbonyl as defined herein, e.g., methylcarbonylamino or ethylcarbonylamino, and the like.

“Alkylcarbonyloxy” means an $-OR$ radical where R is alkylcarbonyl, as defined herein.

10 “Alkylene” means a linear saturated divalent hydrocarbon radical of one to six carbon atoms or a branched saturated divalent hydrocarbon radical of three to six carbon atoms e.g., methylene, 1,1-dimethylmethylene, eth-1,2-diyl, prop-1,3-diyl, 1-methylprop-1,3-diyl, 2-methylprop-1,3-diyl, but-1,4-diyl (including all isomers), or pent-1,5-diyl (including all isomers), and the like.

15 “Alkylsulfinyl” means a $-S(O)R$ radical where R is alkyl as defined herein, e.g., methylsulfinyl, ethylsulfinyl, or propylsulfinyl, and the like.

“Alkylsulfonyl” means a $-S(O)_2R$ radical where R is alkyl, as defined herein, e.g., methylsulfonyl or ethylsulfonyl, and the like.

20 “Alkylsulfonylamino” means a $-NR'R''$ radical where R' is hydrogen, alkyl, alkenyl, hydroxy, hydroxyalkyl, haloalkyl, alkoxy, or haloalkoxy and R'' is alkylsulfonyl as defined herein.

“Alkylthio” means an $-SR$ radical where R is alkyl, as defined herein, e.g., methylthio, ethylthio, propylthio, or butylthio, and the like.

25 “Alkynyl” means a linear monovalent hydrocarbon radical of two to six carbon atoms or a branched monovalent hydrocarbon radical of three to six carbon atoms containing at least one, preferably one or two, triple bond(s), e.g., ethynyl, propynyl (and all isomeric forms) and butynyl (and all isomeric forms), and the like.

“Amino” means a $-NH_2$ radical or an N-oxide derivative, or a protected derivative thereof such as $-NH \rightarrow O$, $-NHBoc$, $-NHCBz$, or $-NHS(O)_2R$ (where R is alkyl, aryl, or aralkyl, as defined herein), and the like.

30 “Aminoalkoxy” means a $-OR$ radical where R is an alkyl radical, as defined herein, substituted with at least one, preferably one or two, amino group(s), as defined herein, e.g., aminoethyloxy, and the like.

“Aminocarbonyl” means a $-CONH_2$ radical or an N-oxide derivative, or a protected derivative thereof.

“Aminosulfonyl” means a $-S(O)_2R$ radical where R is amino, as defined herein.

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

“Aralkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, aryl group(s) as defined herein, e.g., benzyl or phenethyl, and the like.

“Aryl” means a monovalent, monocyclic or fused bicyclic hydrocarbon radical of 6 to 12 ring atoms, wherein the ring comprising a monocyclic radical ring is aromatic and wherein at least one of the fused rings comprising a bicyclic radical is aromatic. Fused bicyclic hydrocarbon radical includes bridged ring systems. Unless otherwise stated, the valency of the group may be located on any atom of any ring within the radical, valency rules permitting. More specifically the term aryl includes, but is not limited to, phenyl, naphthyl, indanyl (including, for example, indan-5-yl, or indan-2-yl, and the like) or tetrahydronaphthyl (including, for example, tetrahydronaphth-1-yl, or tetrahydronaphth-2-yl, and the like), and the like. Unless stated otherwise, aryl may be optionally substituted on any of the rings with one, two, or three substituents independently selected from the group consisting of acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, alkoxy, alkylthio, halo, hydroxy, amino, alkylamino, dialkylamino, nitro, alkylcarbonylamino, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, carboxy, cyano, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonylamino, arylsulfonylamino, aminoalkoxy, $-P(O)ORR'$ (where R and R' are independently alkyl, cycloalkyl, aryl, or heteroaryl), $-P(O)RR'$ (where R and R' are independently alkyl, cycloalkyl, aryl, or heteroaryl; or R and R' together with the P to which they are attached form heterocycloalkyl or heteroaryl), optionally substituted phenyl, and heteroaryl; and wherein the alkyl, alkenyl, and alkynyl, either alone or as part of another substituent on aryl, are independently optionally substituted with one, two, three, four, or five halo, e.g. haloalkyl, haloalkoxy, or haloalkylsulfonyl; or aryl is pentafluorophenyl.

“Arylsulfonyl” means a $-SO_2R$ radical where R is aryl as defined herein.

“Arylsulfonylamino” means a $-NR'R''$ radical where R' is hydrogen, alkyl, hydroxy, hydroxyalkyl, haloalkyl, alkoxy, or haloalkoxy and R'' is arylsulfonyl, as defined herein.

“Cyanoalkyl” means an alkyl radical, as defined herein substituted with at least one, preferably one or two, cyano group(s).

“Cyanoalkylaminocarbonyl” means a $-C(O)NR'R''$ radical where R' is hydrogen, alkyl, hydroxy, alkoxy, or alkenyl and R'' is cyanoalkyl, as defined herein.

“Cycloalkyl” means a monocyclic or fused bicyclic, saturated or partially unsaturated,

monovalent hydrocarbon radical of three to ten carbon ring atoms. Fused bicyclic hydrocarbon radical includes bridged ring systems. Unless stated otherwise, the valency of the group may be located on any atom of any ring within the radical, valency rules permitting. One or two ring carbon atoms may be replaced by a -C(O)-, -C(S)-, or -C(=NH)- group. More specifically, the term cycloalkyl includes, but is not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexyl, or cyclohex-3-enyl, and the like. Unless otherwise stated, the cycloalkyl ring may be optionally substituted with one, two, or three substituents independently selected from optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonylamino, arylsulfonylamino, alkylcarbonyl, halo, hydroxy, amino, aminocarbonyl, alkylamino, dialkylamino, alkylaminocarbonyl, dialkylaminocarbonyl, nitro, alkoxyalkoxy, aminoalkoxy, alkylcarbonylamino, alkoxycarbonyl, -alkylene-S(O)_n-R^x (where n is 0 to 2 and R^m is alkyl, hydroxyalkyl, or alkoxyalkyl), -alkylene-NHSO₂-R^w (where R^w is alkyl), -alkylene-NHCO-R^q (where R^q is alkyl), -(alkylene)_{n1}-CONR^fR^g (where n1 is 0 or 1, R^f and R^g are independently hydrogen, alkyl, hydroxyalkyl, or alkoxyalkyl, or R^f and R^g together with the nitrogen atom to which they are attached from heterocycloalkyl), carboxy, cyano, optionally substituted phenyl, -P(O)ORR' (where R and R' are independently alkyl, cycloalkyl, aryl, or heteroaryl), -P(O)RR' (where R and R' are independently alkyl, cycloalkyl, aryl, or heteroaryl; or R and R' together with the P to which they are attached form heterocycloalkyl or heteroaryl), and heteroaryl. Within the above optional substituents, the alkyl, alkenyl, and alkynyl, either alone or as part of another substituent on the cycloalkyl ring, are independently optionally substituted with one, two, three, four, or five halo, e.g. haloalkyl, haloalkoxy, haloalkenyloxy, or haloalkylsulfonyl.

“Cycloalkylalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, cycloalkyl group(s) as defined above, e.g., cyclopropylmethyl, cyclobutylmethyl, cyclopentylethyl, or cyclohexylmethyl, and the like.

“Cycloalkylcarbonyl” means a -C(O)R radical where R is cycloalkyl, as defined herein.

“Cycloalkylene” means a monocyclic or fused bicyclic, saturated or partially unsaturated, divalent hydrocarbon radical of three to ten carbon ring atoms. Fused bicyclic hydrocarbon radical includes bridged ring systems. Unless otherwise stated, the valency of the group may be located on any atom of any ring within the radical, valency rules permitting. More specifically, the term cycloalkylene includes, but is not limited to, cycloprop-1,1-diyl, cyclobut-1,3-diyl, cyclopent-1,4-diyl, cyclohex-1,3-diyl, cyclohex-1,4-diyl, or cyclohex-3-en-

1,2-diyl, and the like. Unless otherwise stated, the cycloalkylene ring may be optionally substituted with one, two, or three substituents independently selected from the group consisting of optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonylamino, arylsulfonylamino, alkylcarbonyl, halo, hydroxy, amino, aminocarbonyl, alkylamino, dialkylamino, alkylaminocarbonyl, dialkylaminocarbonyl, nitro, alkoxyalkoxy, aminoalkoxy, alkylcarbonylamino, alkoxycarbonyl, -alkylene-S(O)_n-R^x (where n is 0 to 2 and R^m is alkyl, hydroxyalkyl, or alkoxyalkyl), -alkylene-NHSO₂-R^w (where R^w is alkyl), -alkylene-NHCO-R^q (where R^q is alkyl), -(alkylene)_{n1}-CONR^fR^g (where n1 is 0 or 1, R^f and R^g are independently hydrogen, alkyl, hydroxyalkyl, or alkoxyalkyl, or R^f and R^g together with the nitrogen atom to which they are attached form heterocycloalkyl), carboxy, cyano, optionally substituted phenyl, -P(O)ORR' (where R and R' are independently alkyl, cycloalkyl, aryl, or heteroaryl), -P(O)RR' (where R and R' are independently alkyl, cycloalkyl, aryl, or heteroaryl; or R and R' together with the P to which they are attached form heterocycloalkyl or heteroaryl), and heteroaryl. Within the above optional substituents, the alkyl, alkenyl, and alkynyl, either alone or as part of another substituent on the cycloalkylene ring, are independently optionally substituted with one, two, three, four, or five halo, e.g. haloalkyl, haloalkoxy, haloalkenyloxy, or haloalkylsulfonyl.

"Cycloalkylheterocycloalkyl" means a heterocycloalkyl ring substituted with at least one, preferably one or two, cycloalkyl group(s) as defined herein, e.g., 4-cyclopropylpiperazin-1-yl, 4-cyclobutylpiperidinyl, or 2-cyclopropylmorpholinyl, and the like.

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

"Dialkylaminoalkyl" means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, dialkylamino group(s), as defined herein.

"Dialkylaminoalkoxy" means an -OR radical where R is dialkylaminoalkyl, as defined herein.

"Dialkylaminocarbonyl" means a -C(O)R radical where R is dialkylamino, as defined herein, e.g. dimethylaminocarbonyl or methylethylaminocarbonyl, and the like.

"Dialkylaminocarbonylamino" means an -NR'R" radical where R' is hydrogen, alkyl, hydroxy, alkoxy, or alkenyl and R" is dialkylaminocarbonyl, as defined herein.

"Dialkylaminocarbonyloxy" means an -OR radical where R is dialkylaminocarbonyl, as defined herein.

“Dialkylaminosulfonyl” means a $-S(O)_2R$ radical where R is dialkylamino, as defined herein.

“Disease” or “disorder” 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” or “halogen” means fluoro, chloro, bromo, or iodo, preferably iodo, bromo, or chloro, more preferably, iodo.

“Haloalkoxy” means a $-OR$ radical where R is haloalkyl, as defined herein, e.g., trifluoromethoxy or 2,2,2-trifluoroethoxy, and the like.

“Haloalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one to five halogen atoms, preferably fluorine or chlorine, including those substituted with different halogens, e.g., $-CH_2Cl$, $-CF_3$, $-CHF_2$, $-CF_2CF_3$, $-CF(CH_3)_3$, or $-CHFCl$, and the like.

“Heteroaralkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, heteroaryl group(s) as defined herein, e.g., pyridinylmethyl, furanylemethyl, or chloropyridinylemethyl, and the like.

“Heteroaryl” means a monocyclic, fused bicyclic, or fused tricyclic, monovalent radical of 5 to 14 ring atoms containing one or more, preferably one, two, three, or four ring heteroatoms independently selected from O, $S(O)_n$ (n is 0, 1, or 2), N, $N(R^{99})$, $Si(alkyl)_2$, $P(=S)(R^{100})$, and $P(=O)(R^{100})$, and the remaining ring atoms being carbon, wherein the ring comprising a monocyclic radical is aromatic and wherein at least one of the fused rings comprising a bicyclic or tricyclic radical is aromatic. One or two ring carbon atoms of any nonaromatic rings comprising a bicyclic or tricyclic radical may be replaced by a $-C(O)-$, $-C(S)-$, or $-C(=NH)-$ group. R^{99} is hydrogen, alkyl, hydroxy, alkoxy, acyl, or alkylsulfonyl. R^{100} is alkyl, optionally substituted phenyl, optionally substituted phenylalkyl, cycloalkyl, or cycloalkylalkyl. Fused bicyclic radical includes bridged ring systems. Unless stated otherwise, the valency may be located on any atom of any ring of the heteroaryl group, valency rules permitting. In particular, when the point of valency is located on a nitrogen or phosphorous atom, R^{99} or R^{100} , respectively, is absent. More specifically, the term heteroaryl includes, but is not limited to, 1,2,4-triazolyl, phthalimidyl, pyridinyl, pyrrolyl, imidazolyl, thienyl, furanyl, indolyl, 2,3-dihydro-1*H*-indolyl (including, for example, 2,3-dihydro-1*H*-indol-2-yl or 2,3-dihydro-1*H*-indol-5-yl, and the like), pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isooxazolyl, benzoxazolyl, quinolinyl, isoquinolinyl, tetrahydroisoquinolinyl (including, for example, tetrahydroisoquinolin-4-yl or tetrahydroisoquinolin-6-yl, and the like),

pyrrolo[3,2-c]pyridinyl (including, for example, pyrrolo[3,2-c]pyridin-2-yl or pyrrolo[3,2-c]pyridin-7-yl, and the like), benzopyranyl, thiazolyl, methylenedioxyphenyl (including, for example, methylenedioxyphen-5-yl), and the derivatives thereof, or N-oxide or a protected derivative thereof. Unless otherwise stated, the heteroaryl ring may be optionally substituted

5 with one, two, or three substituents independently selected from optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, acyl, alkoxy, alkenyloxy, alkylthio, halo, hydroxy, amino, alkylamino, dialkylamino, nitro, alkylcarbonylamino, alkoxy carbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, carboxy, cyano, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, alkylaminosulfonyl,

10 dialkylaminosulfonyl, alkylsulfonylamino, arylsulfonylamino, aminoalkoxy, optionally substituted phenyl, heterocycloalkyl, -P(O)ORR' (where R and R' are independently alkyl, cycloalkyl, aryl, or heteroaryl), and -P(O)RR' (where R and R' are independently alkyl, cycloalkyl, aryl, or heteroaryl; or R and R' together with the P to which they are attached form heterocycloalkyl or heteroaryl). Within R⁹⁹, R¹⁰⁰, and the above optional substituents, the

15 alkyl, alkenyl, and alkynyl, either alone or as part of another substituent on the heteroaryl ring, are independently optionally substituted with one, two, three, four, or five halo, e.g. haloalkyl, haloalkoxy, or haloalkylsulfonyl.

"Heterocycloalkyl" means a saturated or partially unsaturated monovalent monocyclic group of 3 to 8 ring atoms or a saturated or partially unsaturated monovalent fused bicyclic

20 group of 5 to 12 ring atoms in which one or more, preferably one, two, three, or four ring heteroatoms independently selected from O, S(O)_n (n is 0, 1, or 2), N, N(R⁹⁹), Si(alkyl)₂, P(=S)(R¹⁰⁰), and P(=O)(R¹⁰⁰), the remaining ring atoms being carbon. One or two ring carbon atoms may be replaced by a -C(O)-, -C(S)-, or -C(=NH)- group. R⁹⁹ is hydrogen, alkyl, hydroxy, alkoxy, acyl, or alkylsulfonyl. R¹⁰⁰ is alkyl, optionally substituted phenyl, optionally

25 substituted phenylalkyl, cycloalkyl, or cycloalkylalkyl. Fused bicyclic radical includes bridged ring systems. Unless otherwise stated, the valency of the group may be located on any atom of any ring within the radical, valency rules permitting. In particular, when the point of valency is located on a nitrogen or phosphorous atom, R⁹⁹ or R¹⁰⁰, respectively, is absent. More specifically the term heterocycloalkyl includes, but is not limited to, pyrrolidinyl, 2,5-dihydro-

30 1H-pyrrolyl, piperidinyl, morpholinyl, piperazinyl, tetrahydropyranyl, 2-oxopiperidinyl, and thiomorpholinyl, and the derivatives thereof and N-oxide or a protected derivative thereof. Unless otherwise stated, the heterocycloalkyl ring may be optionally substituted with one, two, or three substituents independently selected from optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, acyl, alkoxy, alkenyloxy, alkylthio, halo,

hydroxy, amino, alkylamino, dialkylamino, nitro, alkylcarbonylamino, alkoxy carbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, carboxy, cyano, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonylamino, arylsulfonylamino, aminoalkoxy, optionally substituted phenyl, heterocycloalkyl, -P(O)ORR' (where R and R' are independently alkyl, cycloalkyl, aryl, or heteroaryl), and -P(O)RR' (where R and R' are independently alkyl, cycloalkyl, aryl, or heteroaryl; or R and R' together with the P to which they are attached form heterocycloalkyl or heteroaryl). Within R⁹⁹, R¹⁰⁰, and the above optional substituents, the alkyl, alkenyl, and alkynyl, either alone or as part of another substituent on the heterocycloalkyl ring, are independently optionally substituted with one, two, three, four, or five halo, e.g. haloalkyl, haloalkoxy, or haloalkylsulfonyl.

"Heterocycloalkylalkyl" means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, heterocycloalkyl group(s), as defined herein.

"Heterocycloalkylene" means a saturated or partially unsaturated divalent monocyclic group of 3 to 8 ring atoms or a saturated or partially unsaturated divalent fused bicyclic group of 5 to 12 ring atoms in which one or more, preferably one, two, three, or four ring heteroatoms independently selected from O, S(O)_n (n is 0, 1, or 2), N, N(R⁹⁹), Si(alkyl)₂, P(=S)(R¹⁰⁰), and P(=O)(R¹⁰⁰), the remaining ring atoms being carbon. One or two ring carbon atoms can optionally be replaced by a -C(O)-, -C(S)-, or -C(=NH)- group. R⁹⁹ is hydrogen, alkyl, hydroxy, alkoxy, acyl, or alkylsulfonyl. R¹⁰⁰ is alkyl, optionally substituted phenyl, optionally substituted phenylalkyl, cycloalkyl, or cycloalkylalkyl. Fused bicyclic radical includes bridged ring systems. Unless otherwise stated, the valencies of the group may be located on any atom of any ring within the radical, valency rules permitting. In particular, when a point of valency is located on a nitrogen or phosphorous atom, R⁹⁹ or R¹⁰⁰, respectively, is absent. More specifically the term heterocycloalkylene includes, but is not limited to, pyrrolidin-diyl, piperidin-diyl, morpholin-diyl, piperazin-diyl, tetrahydropyran-diyl, 2-oxopiperidin-diyl, and thiomorpholin-diyl, and the derivatives thereof and N-oxide or a protected derivative thereof. Unless otherwise stated, the heterocycloalkylene ring may be optionally substituted with one, two, or three substituents independently selected from optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, acyl, alkoxy, alkenyloxy, alkylthio, halo, hydroxy, amino, alkylamino, dialkylamino, nitro, alkylcarbonylamino, alkoxy carbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, carboxy, cyano, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonylamino, arylsulfonylamino, aminoalkoxy, optionally substituted phenyl,

heterocycloalkyl, -P(O)ORR' (where R and R' are independently alkyl, cycloalkyl, aryl, or heteroaryl), and -P(O)RR' (where R and R' are independently alkyl, cycloalkyl, aryl, or heteroaryl; or R and R' together with the P to which they are attached form heterocycloalkyl or heteroaryl). Within R⁹⁹, R¹⁰⁰, and the above optional substituents, the alkyl, alkenyl, and
5 alkynyl, either alone or as part of another substituent on the heteroaryl ring, are independently optionally substituted with one, two, three, four, or five halo, e.g. haloalkyl, haloalkoxy, or haloalkylsulfonyl.

"Hydroxyalkoxy" means an -OR radical where R is hydroxyalkyl, as defined herein, e.g., hydroxymethyloxy or 1,2-dihydroxyethyloxy, and the like.

10 "Hydroxyalkyl" means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, hydroxy group(s), provided that if two hydroxy groups are present they are not both on the same carbon atom. Representative examples include, but are not limited to, hydroxymethyl, 2-hydroxyethyl, 2-hydroxypropyl, 3-hydroxypropyl, 1-(hydroxymethyl)-2-methylpropyl, 2-hydroxybutyl, 3-hydroxybutyl, 4-hydroxybutyl, 2,3-dihydroxypropyl,
15 1-(hydroxymethyl)-2-hydroxyethyl, 2,3-dihydroxybutyl, 3,4-dihydroxybutyl and 2-(hydroxymethyl)-3-hydroxypropyl, preferably 2-hydroxyethyl, 2,3-dihydroxypropyl, or 1-(hydroxymethyl)-2-hydroxyethyl, and the like.

"Isomer" or "isomers" means 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
20 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". An atom bonded to four nonidentical substituents is termed a "chiral center". A compound with one chiral center has two
25 enantiomeric forms of opposite chirality; and a mixture of both enantiomeric forms in equal amounts is termed racemic. A compound that has one or more chiral centers has 2^{n-1} enantiomeric pair(s), where n is the number of chiral centers, unless the compound is meso (i.e. the compound has 2 or more asymmetric or chiral centers but which is achiral because it contains an internal plane of symmetry). Compounds with more than one chiral center may
30 exist as either 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," 4th edition, March, Jerry, John Wiley & Sons, New York, 1992). It is understood that the names and illustration used in this

- 5 Application to describe compounds of Formula I are meant to be encompassed all possible stereoisomers and any mixture, racemic or otherwise, thereof.

"Optionally substituted alkenyl" means an alkenyl radical, as defined herein, substituted with one or more group(s), preferably one, two, or three groups, independently selected from alkylcarbonyl, alkenylcarbonyl, cycloalkylcarbonyl, alkylcarbonyloxy, alkenylcarbonyloxy, amino, alkylamino, dialkylamino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, cyano, cyanoalkylaminocarbonyl, alkoxy, alkenyloxy, hydroxy, hydroxyalkoxy, carboxy, alkylcarbonylamino, alkyl-S(O)₀₋₂-, alkenyl-S(O)₀₋₂-, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonyl-NR^c- (where R^c is hydrogen, optionally substituted alkyl, optionally substituted alkynyl, hydroxy, alkoxy, or alkenyloxy), alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkylaminoalkyloxy, dialkylaminoalkyloxy, alkoxycarbonyl, alkenyloxycarbonyl, alkoxycarbonylamino, alkylaminocarbonylamino, dialkylaminocarbonylamino, alkoxyalkyloxy, and -C(O)NR^aR^b (where R^a and R^b are independently hydrogen, optionally substituted alkyl, alkenyl, optionally substituted alkynyl, hydroxy, alkoxy, or alkenyloxy).

20 "Optionally substituted alkyl" means an alkyl radical, as defined herein, substituted with one or more group(s), preferably one, two, or three groups, independently selected from alkylcarbonyl, alkenylcarbonyl, cycloalkylcarbonyl, alkylcarbonyloxy, alkenylcarbonyloxy, amino, alkylamino, dialkylamino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, cyano, cyanoalkylaminocarbonyl, alkoxy, alkenyloxy, hydroxy, hydroxyalkoxy, carboxy, alkylcarbonylamino, alkyl-S(O)₀₋₂-, alkenyl-S(O)₀₋₂-, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonyl-NR^c- (where R^c is hydrogen, alkyl, optionally substituted alkenyl, optionally substituted alkynyl, hydroxy, alkoxy, alkenyloxy, or cyanoalkyl), alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkylaminoalkyloxy, dialkylaminoalkyloxy, alkoxycarbonyl, alkenyloxycarbonyl, alkoxycarbonylamino, alkylaminocarbonylamino, dialkylaminocarbonylamino, alkoxyalkyloxy, and -C(O)NR^aR^b (where R^a and R^b are independently hydrogen, alkyl, optionally substituted alkenyl, optionally substituted alkynyl, hydroxy, alkoxy, alkenyloxy, or cyanoalkyl).

"Optionally substituted alkynyl" means an alkynyl radical, as defined herein, substituted with one or more group(s), preferably one, two, or three groups, independently

selected from alkylcarbonyl, alkenylcarbonyl, cycloalkylcarbonyl, alkylcarbonyloxy, alkenylcarbonyloxy, amino, alkylamino, dialkylamino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, cyano, cyanoalkylaminocarbonyl, alkoxy, alkenyloxy, hydroxy, hydroxyalkoxy, carboxy, alkylcarbonylamino, alkyl-S(O)₀₋₂-, alkenyl-S(O)₀₋₂-, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonyl-NR^c- (where R^c is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, hydroxy, alkoxy, alkenyloxy, or cyanoalkyl), alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkylaminoalkyloxy, dialkylaminoalkyloxy, alkoxycarbonyl, alkenyloxy carbonyl, alkoxycarbonylamino, alkylaminocarbonylamino, dialkylaminocarbonylamino, alkoxyalkyloxy, and -C(O)NR^aR^b (where R^a and R^b are independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, alkynyl, hydroxy, alkoxy, alkenyloxy, or cyanoalkyl).

“Optionally substituted phenyl” means a phenyl ring optionally substituted with one, two, or three substituents independently selected from the group consisting of acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, halo, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonylamino, arylsulfonylamino, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, amino, alkylamino, dialkylamino, hydroxy, cyano, nitro, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkoxycarbonyl, carboxy, alkylcarbonyl, alkylcarbonylamino, aminoalkoxy, -P(O)ORR' (where R and R' are independently alkyl, cycloalkyl, aryl, or heteroaryl), and -P(O)RR' (where R and R' are independently alkyl, cycloalkyl, aryl, or heteroaryl; or R and R' together with the P to which they are attached form heterocycloalkyl or heteroaryl); or optionally substituted phenyl is pentafluorophenyl. Within the above optional substituents, the alkyl, alkenyl, and alkynyl, either alone or as part of another substituent on the optionally substituted phenyl ring, are independently optionally substituted with one, two, three, four, or five halo, e.g. haloalkyl, haloalkoxy, haloalkenyloxy, or haloalkylsulfonyl.

“Optionally substituted phenylalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, optionally substituted phenyl as defined herein e.g., benzyl or phenylethyl, and the like.

“Optionally substituted phenylcarbonylamino” means a -NR^aC(O)R radical where R is optionally substituted phenyl, as defined herein, and R^a is hydrogen or alkyl.

“Partially unsaturated” describes a group which contains at least one unsaturated bond but does not contain an aromatic ring. For example, partially unsaturated cycloalkylene includes cyclohexenyl group but not indanyl.

"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.

A "pharmaceutically acceptable salt" means a salt 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, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedithiosulfonic 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; and

salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like.

It is understood that the pharmaceutically acceptable salts are non-toxic. Additional information on suitable pharmaceutically acceptable salts can be found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, 1985, which is incorporated herein by reference.

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

indicated.

The present invention also includes prodrugs of a compound of Formula (I). Prodrug means a compound that is convertible in vivo by metabolic means (e.g. by hydrolysis) to a compound of Formula (I).

5 “Syndrome” means the aggregate of symptoms and signs that occur together and characterize a particular abnormality or condition.

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

10 “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 symptomology of the disease,
- (2) inhibiting the disease in an animal that is experiencing or displaying the pathology or symptomology of the diseased (i.e., arresting further development of the pathology and/or symptomology), or
- (3) ameliorating the disease in an animal that is experiencing or displaying the pathology or symptomology of the diseased (i.e., reversing the pathology and/or symptomology).

PREFERRED EMBODIMENTS

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

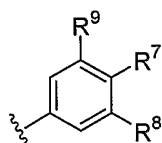
25 1. One preferred group of compounds of Formula I is that wherein R^1 and R^2 are both hydrogen.

2. Another preferred group is that wherein R^4 is cyclopropylpiperazinyl, preferably, 4-cyclopropylpiperazin-1-yl.

3. Another preferred group of compounds of Formula I is that wherein:

30 R^1 and R^2 are both hydrogen; or R^1 and R^2 together with the carbon atom to which they are attached form cycloalkylene;

R^3 is



where R^7 , R^8 , and R^9 are independently hydrogen, hydroxy, alkoxy, halo, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, alkylthio, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonylamino, arylsulfonylamino, amino, alkylamino, dialkylamino, cyano, nitro, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkoxycarbonyl, carboxy, alkylcarbonyl, or aminoalkoxy and wherein the alkyl, alkenyl, and alkynyl, either alone or as part of another group are independently optionally substituted with one, two, three, four, or five halo; or where one or two of R^7 , R^8 , and R^9 are as defined above and the remaining of R^7 , R^8 , and R^9 are aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

R^4 is cycloalkylheterocycloalkyl; and

R^5 is hydrogen or alkyl, preferably hydrogen.

Preferably, R^7 is hydroxy or alkoxy; R^8 and R^9 are independently hydrogen, alkyl, or halo.

More preferably, R^3 is 3,5-dihalo-4-hydroxyphenyl.

4. Another preferred group of compounds of Formula I is that wherein:

R^1 and R^2 are both hydrogen; or R^1 and R^2 together with the carbon atom to which they are attached form cycloalkylene;

R^3 is heteroaryl; and

R^4 is cycloalkylheterocycloalkyl.

5. Preferred compounds of Formula I are selected from the group consisting of:

N -{1-[N -(cyanomethyl)-carbamoyl]-2-(4-hydroxy-3,5-diiodo-phenyl)-ethyl}-4-(4-cyclopropyl-piperazin-1-yl)-benzamide;

N -{1-[N -(cyanocyclopropyl)-carbamoyl]-2-(4-hydroxy-3,5-diiodo-phenyl)-ethyl}-4-(4-cyclopropyl-piperazin-1-yl)-benzamide;

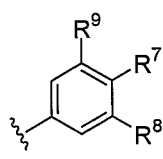
N -{1-[N -(cyanocyclopropyl)-carbamoyl]-2-([1,2,4]-triazol-3-yl)-ethyl}-4-(4-cyclopropyl-piperazin-1-yl)-benzamide; and

N -{1-[N -(cyanomethyl)-carbamoyl]-2-([1,2,4]-triazol-3-yl)-ethyl}-4-(4-cyclopropyl-piperazin-1-yl)-benzamide;

or a pharmaceutically acceptable salt thereof.

6. Preferred R^1 and R^2 groups of compounds of Formula I are wherein R^1 and R^2 are both hydrogen or R^1 and R^2 together with the carbon atom to which they are attached form cycloalkylene; more preferably, where R^1 and R^2 are both hydrogen or R^1 and R^2 together with the carbon to which they are attached form cyclopropylene; and most preferably, wherein R^1 and R^2 are both hydrogen.

7. Another preferred group of compounds of Formula I is wherein R³ is

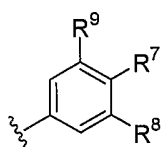


; preferably 3,5-dihalo-4-hydroxyphenyl.

8. Another preferred group of compounds of Formula I is wherein R⁶ and R^{6a} are both hydrogen.

9. Another preferred group is that wherein R¹ and R² are independently hydrogen, haloalkyl, or hydroxyalkyl; or R¹ and R² together with the carbon atom to which they are attached form cycloalkylene or heterocycloalkylene.

10. Another preferred group is that wherein R³ is heteroaryl or



where R⁷, R⁸, and R⁹ are independently hydrogen, hydroxy, alkoxy, halo, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, alkylthio, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonylamino, arylsulfonylamino, amino, alkylamino, dialkylamino, cyano, nitro, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkoxy carbonyl, carboxy, alkylcarbonyl, or aminoalkoxy and wherein the alkyl, alkenyl, and alkynyl, either alone or as part of another group are independently optionally substituted with one, two, three, four, or five halo; or where one or two of R⁷, R⁸, and R⁹ are as defined above and the remaining of R⁷, R⁸, and R⁹ are aryl, heteroaryl, cycloalkyl, or heterocycloalkyl.

11. Another preferred group is that wherein R⁴ is cycloalkylheterocycloalkyl.

12. Another preferred group is that wherein R⁵ is hydrogen, alkyl, or haloalkyl.

13. Another preferred group is that wherein R⁶ and R^{6a} are independently hydrogen, alkyl, alkoxy, cyano, halo, haloalkyl, haloalkoxy, or alkylsulfonyl.

GENERAL SYNTHESIS

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

The starting materials and reagents used in preparing these compounds are either available from commercial suppliers such as Aldrich Chemical Co., (Milwaukee, Wis.), Bachem (Torrance, Calif.), or Sigma (St. Louis, Mo.) or are prepared by methods known to those skilled in the art following procedures set forth in references such as Fieser and Fieser's

Reagents for Organic Synthesis, Volumes 1-17 (John Wiley and Sons, 1991); Rodd's Chemistry of Carbon Compounds, Volumes 1-5 and Supplementals (Elsevier Science Publishers, 1989); Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991), March's Advanced Organic Chemistry, (John Wiley and Sons, 4th Edition) and Larock's
5 Comprehensive Organic Transformations (VCH Publishers Inc., 1989). These schemes are merely illustrative of some methods by which the compounds of this invention can be synthesized, and various modifications to these schemes can be made and will be suggested to one skilled in the art having referred to this disclosure.

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

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

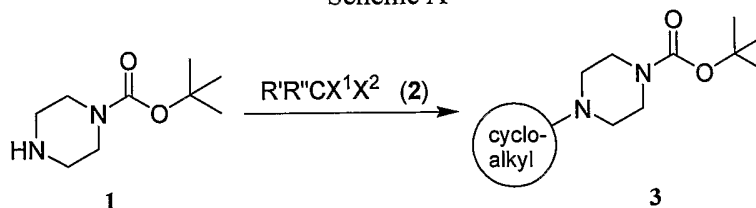
In the reactions described hereinafter it may be necessary to protect reactive functional groups, for example hydroxy, amino, imino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional
20 protecting groups may be used in accordance with standard practice, for examples see T.W. Greene and P. G. M. Wuts in "*Protective Groups in Organic Chemistry*" John Wiley and Sons, 1991.

Compounds of Formula I that may be prepared through the syntheses described herein may exist as a single isomer or a mixture of isomers.

25 Compounds of Formula I can be prepared by the procedures illustrated and described in Schemes A and B below.

Compounds of formula 7, which may be prepared as shown in Scheme A below, can be used in the preparation of compounds of Formula I where R^1 , R^2 , R^6 and R^{6a} are hydrogen, and R^4 is 4-(cycloalkyl)-piperazin-1-yl, and all other groups are as defined in the Summary of the
30 Invention.

Scheme A

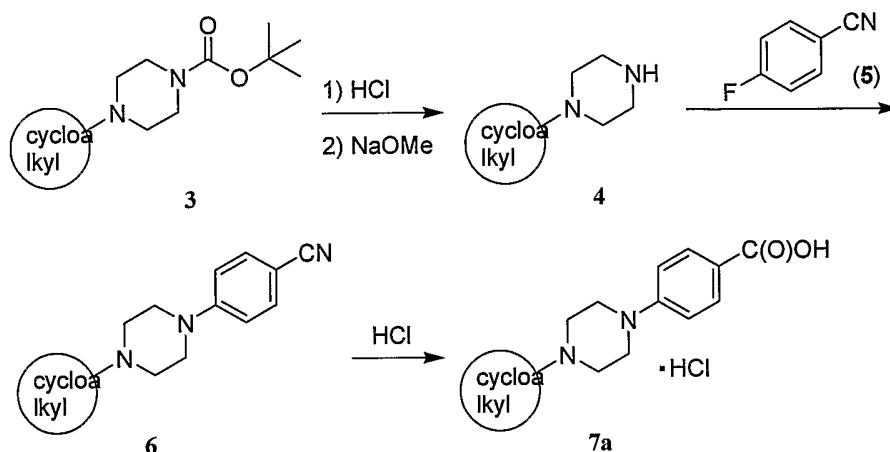


An intermediate of formula 3 can be prepared by reacting commercially available *N*-*tert*-butoxycarbonyl-piperazine (1) with an intermediate of formula 2 where X¹ is hydrogen, X² a leaving group such as halo, and R' and R'' together with the carbon to which they are attached form cycloalkyl. The reaction can be carried out in the presence of an inorganic base, such as Na₂CO₃ or K₂CO₃, and the like or a non-nucleophilic base such as triethylamine or pyridine, and the like, in suitable solvents such as tetrahydrofuran, dioxane, or acetonitrile, and the like.

Alternatively, 3 can be prepared by reacting 1 with R'R''CX¹X² where R' and R'' together with the carbon to which they are attached form cycloalkyl, in particular cyclopropyl, X¹ is alkoxy, preferably methoxy or ethoxy, and X² is -OSi(alkyl)₃, preferably alkyl is methyl. The reaction is carried out with glacial acetic acid and a reducing agent, such as NaCNBH₄ or NaBH(OAc)₃, and the like, in the presence of molecular sieves. The reaction is refluxed in suitable solvents such as methanol or tetrahydrofuran, and the like.

Other Boc-protected cycloalkylheterocycloalkyl groups can be prepared by reacting 1 with 2 where R' and R'' together with the carbon to which they are attached form cycloalkyl, and X¹ and X² together with the carbon to which they are attached form carbonyl. The reaction is carried out with glacial acetic acid and a reducing agent, such as NaCNBH₄ or NaBH(OAc)₃, and the like. The reaction is refluxed in suitable solvents such as methanol or tetrahydrofuran, and the like. 3 can be prepared using methods described in the art, including Zaragoza, et. al. *J. Med. Chem.* **2004** 47(11) 2833-2838 and Gillasp, et. al. *Tetrahedron Letters* **1995** 36(41) 7399-3402 which are hereby incorporated by reference.

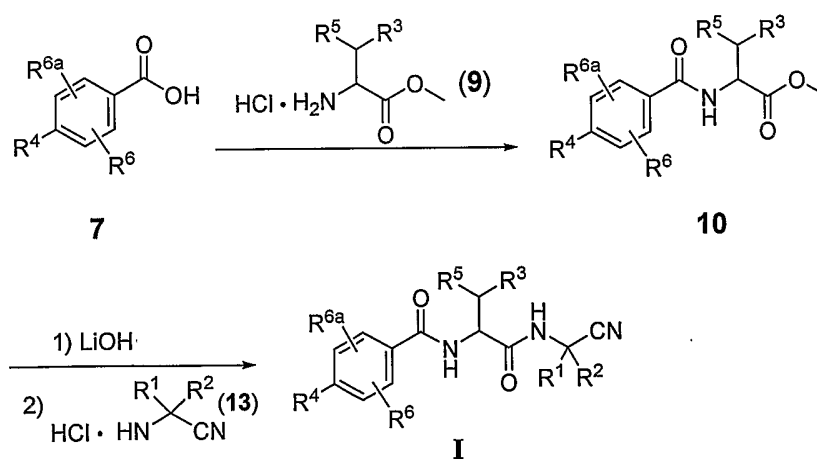
Scheme B



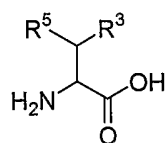
The *tert*-butoxycarbonyl protecting group (Boc) on **3** can be removed under acidic hydrolysis reaction conditions. A comprehensive list of suitable conditions for removing protective groups can be found in T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc., 3rd edition, 1999, the disclosure of which is incorporated herein by reference in its entirety. The hydrochloride salt may then be treated with sodium methoxide to yield the free amine (**4**). Compounds of formula **6** can then be prepared by reacting 4-fluorobenzonitrile with **4** in DMSO in the presence of a base, such as triethylamine. The cyano group on **6** can then be hydrolyzed to the acid after treating with 12 N HCl (aq).

Compounds of Formula I may be prepared as shown in Scheme C below where the groups are as defined in the Summary of the Invention.

Scheme C



The ester of formula **9** in Scheme C can be prepared by treating an acid of formula **8** below in methanol with HCl.



8

A compound of formula 10 can then be prepared by first converting 7 to a reactive acid derivative followed by treatment with an amine of formula 9. Specifically, 7 can be first converted to an acid halide derivative such as acid chloride, with a chlorinating agent such as thionyl chloride or oxalyl chloride, and the like. Suitable solvents are halogenated organic solvents such as methylene chloride, and the like. The resulting acid halide can then be reacted with 9. The amination reaction may be carried out in the presence of a suitable base such as triethylamine, pyridine, and the like and in a suitable organic solvent such as THF, dioxane, or *N,N*-dimethylformamide and the like.

Alternatively, compounds of formula 10 can be prepared by reacting 7 with the amine 9 in the presence of a coupling agent such as benzotriazole-1-yloxytrispyrrolidino-phosphonium hexafluorophosphate (PyBOP®), bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBrop®), *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyl-uronium hexafluorophosphate (HBTU), *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU), or 1,3-dicyclohexylcarbodiimide (DCC) or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) optionally in the presence of 1-hydroxybenzotriazole (HOBt). As appropriate, a base such as *N,N*-diisopropylethylamine, triethylamine, or *N*-methylmorpholine can be used. Suitable solvents are dichloromethane, dioxane, dichloroethane, dimethylformamide, tetrahydrofuran, or acetonitrile.

The ester 10 can then be treated with aqueous LiOH to yield the lithium salt which can then be reacted with 13, prepared using methods known in the art, in the presence of a base such as triethylamine, and the like, and a coupling agent such as HATU, and the like in a solvent such as DMF, and the like, to yield a compound of this Invention.

PHARMACOLOGY AND UTILITY

The compounds of the invention are inhibitors of cathepsin B and accordingly are useful for treating diseases, disorders, or syndromes in which cathepsin B contributes to the pathology and/or symptomology of the disease. For example, cathepsin B has been implicated in cancer (*see* Michaud, S. Gour, B. *Exp. Opin. Ther. Pat.* 1998, 8, 645; Koblinski, J. E. *et al. Clinica Chim. Acta* 2000, 291, 113; Berquin, I. M. and Sloane, BF *Adv. Exp. Med. Biol.* 1996, 389, 281; and Szpaderska, A. M. and Frankfater, A. *Cancer Res.* 2001, 61, 3493);

neurodegenerative disorders (*see* Petanceska, S. *et al. Neuroscience* 1994, 59, 729); stroke (*see* Seyfried, D. M. *et al. Brain Res.* 2001, 901, 94); ischemia; rheumatoid arthritis (*see* Keyszer, G. *et al. Arthritis Rheum.* 1993, 41, 1378 ; Esser, R. E. *et al. Arthritis Rheum.* 1994, 37, 236; and Hashimoto, Y. *et al. Biochem Biophys. Res. Commun.* 2001, 283, 334);
5 osteoarthritis (*see* Lang, A. *et al. J. Rheumatol.* 2000, 27, 1971); acute pancreatitis (*see* Halangk, W. *et al. J. Clin. Invest.* 2000, 106, 773); liver disease (*see* Feldstein, A. E. *et al. Hepatology* 2004, 40(1), 185-194; Roberts, L.R. *et al. Gastroenterology* 1997, 113, 1714; Jones, B.A. *et al. Am. J. Physiol.* 1997, 272, G1109 ; Faubion, W.A. *et al. J. Clin. Invest.* 1999, 103, 137 ; Roberts, L.R. *et al. Cell Biochem. Biophys.* 1999, 30, 71 ; Guicciardi, M.E.
10 *et al. J. Clin. Invest.* 2000, 106, 1127 ; Guicciardi, M.E. *et al. Hepatology* 2001, 34, 844; and Guicciardi, M.E. *et al. Am. J. Physiol.* 2001, 159, 2045); atherosclerosis (*see* Chen, J *et al. Circulation* 2002, 105, 2766 and Li, W. *et al. Arterioscler. Thromb. Vasc. Biol.* 2001, 21, 1124); Alzheimer's disease (*see* Tagawa, K. T. *et al. Biochem. Biophys. Res. Commun.* 1991, 177, 377 and Cataldo, A. M. *et al. Brain Res.* 1990, 513, 181); and periodontal disease
15 (*see* Eley, B. M. and Cox, S.W. *J. Periodontal Res.* 1996, 31, 381). In addition, inhibition of Cathepsin B by compounds of this Invention may be useful for the treatment of pneumocystis carinii, inflammatory airway disease, bone and joint disorders, and Type II diabetes mellitus.

TESTING

20 The Cathepsin B 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 in Biological Example 1
25 below.

ADMINISTRATION AND PHARMACEUTICAL COMPOSITIONS

In general, a compound of the present invention will be administered in therapeutically effective amounts via any of the usual and acceptable modes known in the art, either singly or
30 in combination with one or more therapeutic agents. 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 compounds of the present invention may range from about 10 micrograms per kilogram body weight ($\mu\text{g/kg}$) per day to about 200 milligram per kilogram

body weight (mg/kg) per day, typically from about 100 µg/kg/day to about 100 mg/kg/day. Therefore, a therapeutically effective amount for a 80 kg human patient may range from about 1 mg/day to about 1.6 g/day, typically from about 1 mg/day to about 100 mg/day. In general, one of ordinary skill in the art, acting in reliance upon personal knowledge and the disclosure
5 of this Application, will be able to ascertain a therapeutically effective amount of a compound of the present invention for treating a given disease.

The compounds of the present invention 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
10 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 the present invention 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.
15 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
20 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, and the like). Preferred liquid carriers, particularly for injectable solutions, include water, saline, aqueous dextrose and glycols.

The amount of a compound of the present invention in the composition may vary
25 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 the present invention for treating a given disease will comprise from 0.01%w to 10%w, preferably 0.3%w to 1%w, of active ingredient with the remainder being the excipient or excipients. Preferably the pharmaceutical composition is administered in
30 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 the present invention are described in working examples below.

EXAMPLES

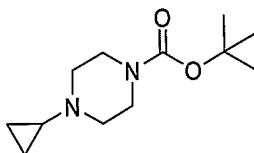
SYNTHETIC EXAMPLES

The present invention is further exemplified, but not limited by, the following examples that illustrate the preparation of compounds of Formula (I) according to the invention.

5

Reference 1

Synthesis of 4-cyclopropyl-piperazine-1-carboxylic acid tert-butyl ester

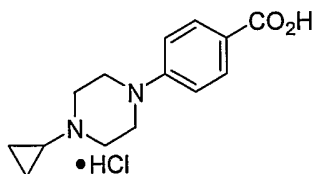
Step 1

- 10 1-Boc-piperazine (26.7 g, 144 mmol), (1-ethoxycyclopropoxy)trimethylsilane (100.0 g, 574 mmol), glacial acetic acid (82 mL, 1440 mmol), and freshly activated 3-Angstrom molecular sieves (100 g) were stirred at room temperature in 600 mL MeOH. Sodium cyanoborohydride (27.1 g, 432 mmol) was carefully added in portions over 15 minutes. The reaction mixture began to reflux spontaneously. When this subsided, the mixture was heated to
- 15 reflux for 9 h and then left at room temperature for 14 h. The mixture was filtered and the filtrate was concentrated. The residue was partitioned between EtOAc (500 mL) and ice-cold 3 M NaOH to bring the pH to 11.5 (approx. 400 mL). The organic phase was separated and the aqueous phase was extracted twice more with 100 mL portions of EtOAc. The combined organic phase was washed with water and brine, then dried over MgSO₄. Filtration followed by
- 20 concentration of the filtrate afforded 4-cyclopropyl-piperazine-1-carboxylic acid tert-butyl ester as a white, crystalline solid (30.72 g, 94% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 3.25 (m, 4H), 2.46 (m, 4H), 1.62 (m, 1H), 1.42 (s, 9H), 0.42 (m, 2H), 0.33 (m, 2H); ESMS (*m/z*): (M+1)⁺ found, 227.1; mp 62-4 °C.

25

Reference 2

Synthesis of 4-(4-cyclopropyl-piperazin-1-yl)-benzoic acid

Step 1

4-Cyclopropylpiperazine-1-carboxylic acid *tert*-butyl ester (15.7 g, 69.4 mmol) was

added in portions to 4.0 N HCl solution in 1,4-dioxane (150 mL, 600 mmol) with stirring. After 2h the reaction mixture was filtered and the precipitate rinsed three times with ether. 4-Cyclopropylpiperazine dihydrochloride salt was obtained as a white solid (13.2 g, 95% yield).

5 Step 2

4-Cyclopropylpiperazine dihydrochloride salt (12.5g, 62.8 mmol) was dissolved in 600 mL anhydrous methanol and stirred at ambient temperature under an atmosphere of nitrogen. Freshly prepared solution of 1.4 M sodium methoxide in methanol was added dropwise to bring the pH to 9 (approx. 68mL). The volume of the mixture was reduced to 50 mL by
10 carefully distilling off most of the solvent at atmospheric pressure. The residue was filtered and the filtrate was vacuum distilled until no further distillate was obtained at a pressure of 20 torr and a heating bath temperature of 90 °C. The pot residue solidified upon cooling and was used without purification in the next step.

Step 3

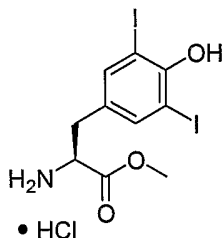
15 4-Cyclopropylpiperazine (7.92g, 62.8 mmol), 4-fluorobenzonitrile (6.08g, 50.2 mmol), DMSO, (60ml) and triethylamine (8.8 mL, 63 mmol) were warmed in a 105 °C oil bath and stirred for 1.5 h. The solution was cooled to room temperature, then added dropwise to 1 L of ice-water with vigorous stirring. The precipitate was filtered off, rinsed three times with water, and vacuum dried. 4-(4-cyclopropyl-piperazin-1-yl)-benzonitrile was obtained as a tan powder
20 (5.71g, 50% yield). Mass spec (turbospray): (MH)⁺ 227.9 (obs'd).

Step 4

4-(4-Cyclopropyl-piperazin-1-yl)-benzonitrile (5.50 g, 24.2 mmol) was added to 40 mL of 12 M aqueous HCl. The mixture was heated to reflux for 1.5h, then cooled to room temperature. 50 mL water was added, and the crystals were filtered off. Crystals were rinsed
25 three times with cold water, then twice with acetone. Vacuum drying gave 4-(4-cyclopropyl-piperazin-1-yl)-benzoic acid as an off-white powder (4.72g , 69% yield). MS (turbospray): (M+1)⁺ 246.7 (obs'd.).

Reference 3

Synthesis of (*S*)-2-Amino-3-(4-hydroxy-3,5-diiodo-phenyl)-propionic acid methyl ester
methyl ester hydrochloride



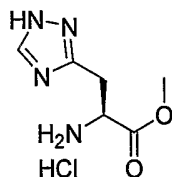
5

Step 1

(*S*)-2-Amino-3-(4-hydroxy-3,5-diiodo-phenyl)-propionic acid dihydrate (9.38g, 20.0 mmol) was suspended in 250 mL anhydrous methanol. Dry HCl gas was bubbled in at a moderate flow for 2.5 min. The clear solution was stirred at room temperature for 16h. Rotary
10 evaporation followed by vacuum drying gave (*S*)-2-amino-3-(4-hydroxy-3,5-diiodo-phenyl)-propionic acid methyl ester hydrochloride salt as an off-white powder (9.59 g, 99% yield).

Reference 4

Synthesis of (*S*)-2-amino-3-([1,2,4]triazol-3-yl)-propionic acid methyl ester hydrochloride

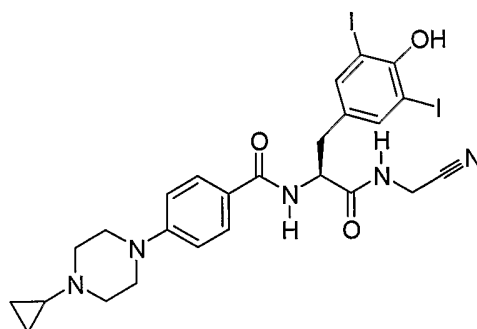


15

Proceeding as in Reference 9, but substituting 2-amino-2-([1,2,4]triazol-3-yl) propionic acid for (*S*)-2-Amino-3-(4-hydroxy-3,5-diiodo-phenyl)-propionic acid dihydrate, can provide (*S*)-2-amino-3-([1,2,4]triazol-3-yl)-propionic acid methyl ester hydrochloride salt.

Example 1

Synthesis of *N*-{1-[*N*-(cyanomethyl)-carbamoyl]-2-(4-hydroxy-3,5-diiodo-phenyl)-ethyl}-4-(4-cyclopropyl-piperazin-1-yl)-benzamide

5 Step 1

4-(4-Cyclopropyl-piperazin-1-yl)-benzoic acid (4.60 g, 16.3 mmol), as prepared in Reference 1, was dissolved in dry DMF (200 mL) and triethylamine (6.8 mL, 48.6 mmol). HOBT (2.85g, 18.6 mmol) and EDC (3.11g, 16.3 mmol) were added. An additional 1 mL triethylamine was then added to bring the pH to 9. After stirring for 5 minutes, (*S*)-2-Amino-3-(4-hydroxy-3,5-diiodo-phenyl)-propionic acid methyl ester methyl ester hydrochloride (7.47g, 15.5 mmol), as prepared in Reference 2, was added. Another 4 mL triethylamine was then added to adjust the pH to 9 again. After 1h of stirring at ambient temperature, the reaction mixture was warmed at a bath temperature of 60 °C for another 2h. Cooling to room temperature was followed by filtration of the mixture. The filtrate was rotary-evaporated and the residue, a red oil, was partitioned between ethyl acetate and saturated aq. sodium bicarbonate. The organic phase was separated, then washed with saturated sodium bicarbonate, water, and brine. Drying over anhydrous magnesium sulfate followed by filtration and evaporation of the filtrate gave 9.84g of a crude product as a red foam. This was flash chromatographed on 350 g of silica gel, eluting with 3/3/94 methanol/acetone/dichloromethane. 2-[4-(4-Cyclopropyl-piperazin-1-yl)-benzoylamino]-3-(4-hydroxy-3,5-diiodo-phenyl)-propionic acid methyl ester was obtained as an orange solid (7.52 g, 72% yield. Mass spec (turbospray): (MH)⁺ 674.2.

20 Step 2

2-[4-(4-Cyclopropyl-piperazin-1-yl)-benzoylamino]-3-(4-hydroxy-3,5-diiodo-phenyl)-propionic acid methyl ester (7.40g, 11.0 mmol) was dissolved in 3/1/1 THF/methanol/water (100 mL). 1.0 N aqueous lithium hydroxide (22 mL, 22.0 mmol) was added with stirring. After 3h, the solvent was rotary evaporated and the residue dried *in vacuo*. The remaining tan foam, which contained 2-[4-(4-cyclopropyl-piperazin-1-yl)-benzoylamino]-3-(4-hydroxy-3,5-

diiodo-phenyl)-propionic acid dilithium salt, was used without purification in the next reaction.

Step 3

The crude 2-[4-(4-cyclopropyl-piperazin-1-yl)-benzoylamino]-3-(4-hydroxy-3,5-diiodo-phenyl)-propionic acid dilithium salt (7.40 g, 11.0 mmol), aminoacetonitrile hydrochloride (3.05 g, 33.0 mmol), HATU (4.18 g, 11.0 mmol), triethylamine (6.1 mL, 44.0 mmol) and 100 mL anhydrous DMF were stirred at room temperature for 1.5h. The reaction mixture was then filtered and the filtrate was rotary evaporated. The residue was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The organic phase was separated, then washed with saturated bicarbonate and brine. Drying over anhydrous magnesium sulfate, filtering, and evaporating the filtrate gave 8.77 g of a gummy residue. This material was flash chromatographed on 350 g silica gel, eluting with 5% methanol in dichloromethane. *N*-{1-[*N*-(Cyanomethyl)-carbamoyl]-2-(4-hydroxy-3,5-diiodo-phenyl)-ethyl}-4-(4-cyclopropyl-piperazin-1-yl)-benzamide as the free base was obtained as a tan powder (5.99 g, 78% yield). MP 161-163 °C dec.; NMR (500 MHz, DMSO): δ 9.3 (bs, 1H), 8.78 (t, $J=5.4$ Hz, 1H), 8.36 (d, $J=8.3$ Hz, 1H), 7.75 (s, 2H), 7.70 (d, $J=8.8$ Hz, 2H), 6.97 (d, $J=8.8$ Hz, 2H), 4.58 (m, 1H), 4.18 (m, 2H), 3.35 (s, 4H), 2.90 (m, 2H), 2.66 (m, 4H), 1.65 (m, 1H), 0.45 (m, 2H), 0.34 (m, 2H); Mass spec (turbospray): (MH)⁺ 700.0.

Examples 2-4

Proceeding as in Example 1, but substituting 2-amino-3-([1,2,4]triazol-3-yl)propionic acid methyl ester hydrochloride for 2-amino-3-(4-hydroxy-3,5-diiodophenyl)propionic acid methyl ester hydrochloride, can provide *N*-{1-[*N*-(cyanomethyl)-carbamoyl]-2-(1,2,4-triazol-3-yl)-ethyl}-4-(4-cyclopropyl-piperazin-1-yl)-benzamide.

Proceeding as in Example 1, but substituting 2-amino-3-([1,2,4]triazol-3-yl)propionic acid methyl ester hydrochloride for 2-amino-3-(4-hydroxy-3,5-diiodophenyl)propionic acid hydrochloride and 1-amino-cyclopropanecarbonitrile hydrochloride for aminoacetonitrile hydrochloride, can provide *N*-{1-[*N*-(1-cyanocyclopropyl)-carbamoyl]-2-(1,2,4-triazol-3-yl)-ethyl}-4-(4-cyclopropyl-piperazin-1-yl)-benzamide.

Proceeding as in Example 1, but substituting 1-amino-cyclopropanecarbonitrile hydrochloride for aminoacetonitrile hydrochloride, can provide *N*-{1-[*N*-(1-cyanocyclopropyl)-carbamoyl]-2-(4-hydroxy-3,5-diiodo-phenyl)-ethyl}-4-(4-cyclopropyl-piperazin-1-yl)-benzamide.

BIOLOGICAL ASSAYS

Example 1

Cathepsin B Assay

- 5 Solutions of test compounds in varying concentrations were prepared in 10 μ L of dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40 μ L, comprising: *N,N*-bis(2-hydroxyethyl)-2-aminoethanesulfonic acid (BES), 50 mM (pH 6); polyoxyethylenesorbitan monolaurate, 0.05%; and dithiothreitol (DTT), 2.5 mM). Human cathepsin B (0.025 pMoles in 25 μ L of assay buffer) was added to the dilutions. The assay solutions were mixed for 5-10
- 10 seconds on a shaker plate, covered and incubated for 30 minutes at room temperature. Z-FR-AMC (20 nMoles in 25 μ L of assay buffer) was added to the assay solutions and hydrolysis was followed spectrophotometrically at (λ 460 nm) for 5 minutes. Apparent inhibition constants (K_i) were calculated from the enzyme progress curves using standard mathematical models.
- 15 A compound of the invention was tested by the above-described assay and observed to exhibit cathepsin B inhibitory activity.

PHARMACEUTICAL COMPOSITION EXAMPLES

- 20 The following are representative pharmaceutical formulations containing a compound of the present invention.

Tablet Formulation

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

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

Capsule Formulation

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

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

Suspension Formulation

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

Ingredient	Amount
compound of this invention	1.0 g
fumaric acid	0.5 g
sodium chloride	2.0 g
methyl paraben	0.15 g
propyl paraben	0.05 g
granulated sugar	25.5 g
sorbitol (70% solution)	12.85 g
Veegum K (Vanderbilt Co.)	1.0 g
flavoring	0.035 mL
colorings	0.5 mg
distilled water	q.s. to 100 mL

5

Injectable Formulation

The following ingredients are mixed to form an injectable formulation.

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

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

10

Suppository Formulation

A suppository of total weight 2.5 g is prepared by mixing the compound of the invention with Witepsol[®] H-15 (triglycerides of saturated vegetable fatty acid; Riches-

15

Nelson, Inc., New York), and has the following composition:

Ingredient	Quantity per tablet, mg
compound of this invention	500
Witepsol [®] H-15	balance

The foregoing invention has been described in some detail by way of illustration and example, for purposes of clarity and understanding. It will be obvious to one of skill in the art

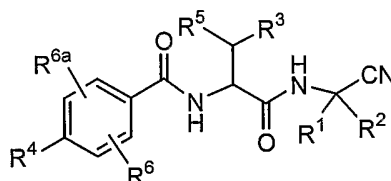
that changes and modifications may be practiced within the scope of the appended claims.

Therefore, it is to be understood that the above description is intended to be illustrative and not restrictive. The scope of the invention should, therefore, be determined not with reference to the above description, but should instead be determined with reference to the following

- 5 appended claims, along with the full scope of equivalents to which such claims are entitled. All patents, patent applications and publications cited in this application are hereby incorporated by reference in their entirety for all purposes to the same extent as if each individual patent, patent application or publication were so individually denoted.

WE CLAIM:

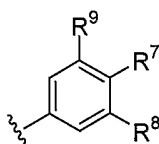
1. A compound of Formula (I):



5 wherein:

R¹ and R² are independently hydrogen, haloalkyl, or hydroxyalkyl; or R¹ and R² together with the carbon atom to which they are attached form cycloalkylene or heterocycloalkylene;

R³ is heteroaryl or



10 where R⁷, R⁸, and R⁹ are independently hydrogen, hydroxy, alkoxy, halo, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, alkylthio, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonylamino, arylsulfonylamino, amino, alkylamino, dialkylamino, cyano, nitro,
 15 aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkoxy, carboxy, alkylcarbonyl, or aminoalkoxy and wherein the alkyl, alkenyl, and alkynyl, either alone or as part of another group are independently optionally substituted with one, two, three, four, or five halo; or where one or two of R⁷, R⁸, and R⁹ are as defined above and the remaining of R⁷, R⁸, and R⁹ are aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

20 R⁴ is cycloalkylheterocycloalkyl;

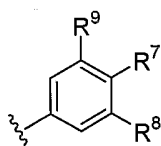
R⁵ is hydrogen, alkyl, or haloalkyl; and

R⁶ and R^{6a} are independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, alkoxy, cyano, halo, haloalkyl, haloalkoxy, or alkylsulfonyl; or a pharmaceutically acceptable salt thereof.

25 2. The compound of Claim 1 wherein:

R¹ and R² are both hydrogen; or R¹ and R² together with the carbon atom to which they are attached form cycloalkylene; and

R³ is



where R^7 is hydroxy or alkoxy, and R^8 and R^9 are independently hydrogen, halo or alkyl.

3. The compound of Claim 1 wherein:

R^1 and R^2 are both hydrogen; or R^1 and R^2 together with the carbon atom to which they are attached form cycloalkylene; and

R^3 is heteroaryl.

4. The compound of Claim 2 wherein R^3 is 3,5-dihalo-4-hydroxyphenyl.

5. The compound of Claim 3 wherein R^3 is triazolyl.

6. The compound of Claim 1 wherein R^1 and R^2 are both hydrogen.

10 7. The compound of Claim 1 wherein R^4 is cyclopropylpiperazinyl.

8. A compound selected from the group consisting of:

N-{1-[*N*-(cyanomethyl)-carbamoyl]-2-(4-hydroxy-3,5-diiodo-phenyl)-ethyl}-4-(4-cyclopropyl-piperazin-1-yl)-benzamide;

15 *N*-{1-[*N*-(cyanocyclopropyl)-carbamoyl]-2-(4-hydroxy-3,5-diiodo-phenyl)-ethyl}-4-(4-cyclopropyl-piperazin-1-yl)-benzamide;

N-{1-[*N*-(cyanocyclopropyl)-carbamoyl]-2-([1,2,4]-triazol-3-yl)-ethyl}-4-(4-cyclopropyl-piperazin-1-yl)-benzamide; and

N-{1-[*N*-(cyanomethyl)-carbamoyl]-2-([1,2,4]-triazol-3-yl)-ethyl}-4-(4-cyclopropyl-piperazin-1-yl)-benzamide; or

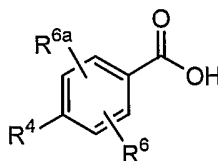
20 a pharmaceutically acceptable salt thereof.

9. The compound *N*-{1-[*N*-(cyanomethyl)-carbamoyl]-2-(4-hydroxy-3,5-diiodo-phenyl)-ethyl}-4-(4-cyclopropyl-piperazin-1-yl)-benzamide.

10. A pharmaceutical composition comprising a therapeutically effective amount of a compound of any of the Claims 1-9 and one or more pharmaceutically acceptable excipient(s).

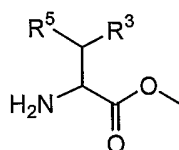
25 11. A method of making a compound of Formula I which method comprises:

(a) reacting an intermediate of formula 7

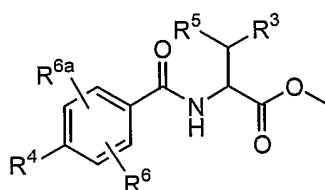


7

or an acid addition salt or an activated acid derivative thereof, where R^4 , R^6 , and R^{6a} are as defined above in Formula 1, with an intermediate of formula **9**

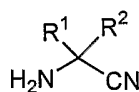
**9**

- 5 or a salt thereof, where R^3 and R^5 are as defined above in Formula 1 to give an intermediate of formula **10**

**10**

where R^3 , R^4 , R^5 , R^6 , and R^{6a} are as defined above in Formula 1;

- 10 (b) forming the acid, an acid addition salt, or an activated acid derivative of the product from step (a), i.e. the intermediate of formula **10**; and
 (c) reacting the product of Step (b) with an intermediate of formula **11**

**11**

- 15 or a salt thereof, where R^3 , R^4 , R^5 , R^6 , and R^{6a} are as defined above in Formula 1.
 12. Use of a compound of any of the Claims 1-10 for the manufacture of a medicament useful in the treatment of a disease mediated by cathepsin B.
 13. A method for treating a disease mediated by cathepsin B in an animal which method comprises administering to the animal a therapeutically effective amount of a compound of
 20 Formula I.