Title of the Invention

ISONIPECOTAMIDES FOR THE TREATMENT OF INTEGRIN-MEDIATED DISORDERS

Field of the Invention

This invention relates to certain novel compounds, their synthesis and methods for their use in treating integrin-mediated disorders. More particularly, this invention relates to isonipecotamide compounds that are αvβ3, αvβ5, GPIIb/IIIa, dual αvβ3/GPIIb/IIIa or dual αvβ3/αvβ5 integrin antagonists and methods for their use in treating a variety of integrin-mediated disorders.

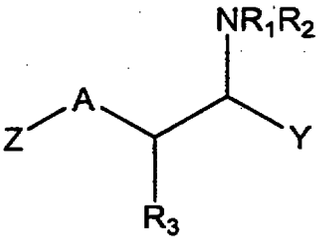
Background of the Invention

Integrins are a widely expressed family of calcium- or magnesium-dependent αβ heterodimeric cell surface receptors which bind to extracellular matrix adhesive proteins such as fibrinogen, fibronectin, vitronectin, and osteopontin. These transmembrane glycoproteins (GP's), known for their large extracellular domains, are classified by at least 8 known β subunits and 14 α subunits (S. A. Mousa, et al., *Emerging Theraupeutic Targets,* **2000**, *4,* (2), 143-153). For example, the β1 subfamily, also known as the very late antigen (VLA) subfamily, has the largest number of integrins (S. A. Mousa, et al., *Emerging Theraupeutic Targets,* **2000**, *4,* (2), 144). The αvβ1 subfamily further associates with various β subunits: β3, β5, β6, β8 and αIIbβ3 (also referred to as GPIIb/IIIa) (S. A. Mousa, et al., *Emerging Theraupeutic Targets,* **2000**, *4,* (2), 144, 147). Some of the disease states that have a strong β3, β5 and GPIIb/IIIa integrin component in their etiologies are unstable angina, thromboembolic disorders or atherosclerosis (GPIIb/IIIa); thrombosis or restenosis (GPIIb/IIIa or αvβ3); restenosis (dual αvβ3/GPIIb/IIIa); rheumatoid arthritis, vascular disorders or osteoporosis (αvβ3); tumor angiogenesis, multiple sclerosis, neurological disorders, asthma, vascular injury or diabetic

retinopathy (αvβ3 or αvβ5); and, angiogenesis (dual αvβ3/αvβ5) (S. A. Mousa, et al., *Emerging Theraupeutic Targets,* **2000**, *4,* (2), 148-149; W. H. Miller, et al., *Drug Discovery Today* **2000**, 5 (9), 397-407; and, S. A. Mousa, et al., *Exp. Opin. Ther. Patents,* **1999**, *9* (9), 1237-1248). The β3 subunit has received significant attention in recent drug discovery efforts. (W. J. Hoekstra, *Current Medicinal Chemistry* **1998**, *5*, 195) and antibodies and/or low-molecular weight compound antagonists of αvβ3 have shown efficacy in animal models (J. Samanen, *Current Pharmaceutical Design* **1997**, *3*, 545).

Furthermore, GPIIb/IIIa and αvβ3 antagonists have typically been designed after the bioactive arginine-glycine-aspartate (RGD) conformations of peptides derived from their primary ligands, fibrinogen and vitronectin, respectively. The RGD motif is the general cell attachment sequence of many extracellular matrix, blood, and cell surface proteins, as half of the ca. 20 known integrins bind the RGD-containing adhesion ligands. To discover RGD peptides with integrin selectivity, peptides with both restricted conformations and alterations of flanking residues have been studied. In particular, the structural requirements for interaction of the RGD sequence with GPIIb/IIIa and the inhibitory potential of a series of nonpeptidic mimetics on platelet aggregation and interactions with the extracellular matrix have been described (D. Varon, et al., *Thromb. Haemostasis*, **1993**, *70(6)*, 1030-1036). Iterative synthesis of cyclic and alicyclic peptides and computer modelling have provided potent, selective agents as a platform for nonpeptide αv integrin antagonist design.

For example, PCT Application WO98/25892 to Fisher, et al., describes a series of α-sulfonamido and α-sulfinamido carboxylic acid compounds of the formula:



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wherein

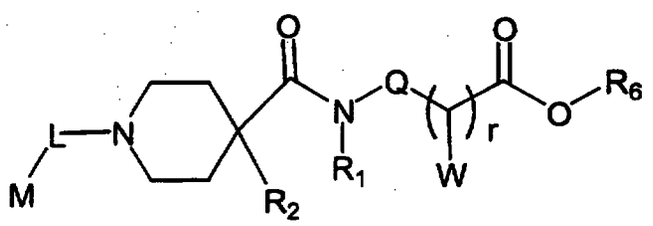
Y is selected from the group consisting of –COOH, $-PO_3H_2$, $-SO_3H$ and $-COOR^4$; where R4 is selected from the group consisting of C_{1-10}alkyl, C_{1-8}alkylaryl, arylC_{1-8}alkyl, C_{1-8}alkyloxycarbonyloxyC_{1-8}alkyl, aryloxycarbonyloxyC_{1-8}alkyl, C_{1-8}alkyloxycarbonyloxyaryl, C_{1-10}alkylcarbonyloxyC_{1-8}alkyl and C_{1-8}alkylcarbonyloxyaryl; A is selected from the group consisting of C_{6-12}alkyl, C_{0-8}alkyl-NR^5-CO-C_{0-8}alkyl, C_{0-8}alkyl-CO-NR^5-C_{0-8}alkyl, C_{0-8}alkyl-O-C_{0-8}alkyl, C_{0-8}alkyl-NR^5-CO-C_{1-8}alkyl-NR^5-CO-C_{0-8}alkyl, C_{0-8}alkyl-NR^5-CO-C_{1-8}alkyl-CO-NR^5-C_{0-8}alkyl, C_{0-8}alkyl-CO-NR^5-C_{1-8}alkyl-NR^5-CO-C_{0-8}alkyl, C_{0-8}alkyl-CO-NR^5-C_{0-8}alkyl-CO-NR^5-C_{0-8}alkyl, C_{0-8}alkyl-CO-C_{1-8}alkyl-CO-NR^5-C_{0-8}alkyl, C_{0-8}alkyl-CO-C_{0-8}alkyl-NR^5-CO-C_{0-8}alkyl, C_{0-8}alkyl-O-C_{2-8}alkyl-NR^5-CO-C_{0-8}alkyl, C_{0-8}alkyl-O-C_{0-8}alkyl-CO-NR^5-C_{0-8}alkyl, C_{0-8}alkyl-O-C_{2-8}alkyl-O-C_{0-8}alkyl-CO-NR^5-C_{0-8}alkyl, C_{0-8}alkyl-S-C_{0-8}alkyl, C_{0-8}alkyl-S(O_n)-C_{0-8}alkyl, C_{0-8}alkyl-S-C_{2-8}alkyl-NR^5-CO-C_{0-8}alkyl, C_{0-8}alkyl-S(O_n)-C_{2-8}alkyl-NR^5-CO-C_{0-8}alkyl, C_{0-8}alkyl-S-C_{0-8}alkyl-CO-NR^5-C_{0-8}alkyl, C_{0-8}alkyl-S(O_n)-C_{1-8}alkyl-CO-NR^5-C_{0-8}alkyl, C_{0-8}alkyl-NR^5-CO-C_{0-8}alkyl-S-C_{0-8}alkyl, C_{0-8}alkyl-NR^5-CO-C_{1-8}alkyl-S(O_n)-C_{0-8}alkyl, C_{0-8}alkyl-CO-NR^5-C_{2-8}alkyl-S-C_{0-8}alkyl, C_{0-8}alkyl-CO-NR^5-C_{2-8}alkyl-S(O_n)-C_{0-8}alkyl, C_{0-8}alkyl-NR^5-C_{0-8}alkyl-CO_2-C_{0-8}alkyl, C_{0-8}alkyl-NR^5-C_{0-8}alkyl-CS-O-C_{0-8}alkyl, C_{0-8}alkyl-NR^5-C_{0-8}alkyl-CO-NR^5-C_{0-8}alkyl, C_{0-8}alkyl-NR^5-C_{0-8}alkyl-CS-NR^5-C_{0-8}alkyl, C_{0-8}alkyl-O-C_{0-8}alkyl-CO_2-C_{0-8}alkyl, C_{0-8}alkyl-O-C_{0-8}alkyl-CS-O-C_{0-8}alkyl, C_{0-8}alkyl-SiR^7R^8-C_{0-8}alkyl, C_{0-8}alkyl-SiR^7R^8-C_{0-8}alkyl-NR^6-CO-C_{0-8}alkyl and C_{0-8}alkyl-SiR^7R^8-C_{0-8}alkyl-CO-NR^6-C_{0-8}alkyl; where R^5, R^6, R^7 and R^8- are independently selected from the group consisting of H and C_{1-6}alkyl; and where n=1 or 2; Z is selected from the group consisting of -NH-C(NR^9R^{10})=R^{11}, -NH-C(R^9)=R^{11}, -C(NR^9R^{10})=R^{11} and piperidinyl; where R^9, R^{10} and R^{11} are independently selected from the group consisting of H, C_{1-6}alkyl, arylC_{1-3}alkyl and aryl; or where two of the R^9, R^{10} or R^{11} substituents form a cyclic ring containing $(CH_2)_p$, where p=2-5; R_1 is H and R_2 is selected from the group consisting of -SO_m-aryl-, -SO_m-C_{1-10}alkyl-, -SO_m-heteroaryl-, where m=1-2; R^3 is selected from the group consisting of H, C_{1-8}alkyl, aryl, C_{1-8}alkylaryl and

heteroaryl as inhibitors of RGD-dependent integrins for the treatment of thrombotic or restenotic disorders.

Accordingly, it is an object of the present invention to provide compounds that are antagonists of integrins. It is another object to provide isonipecotamide compounds that are αvβ3, αvβ5, GPIIb/IIIa, dual αvβ3/GPIIb/IIIa or dual αvβ3/αvβ5 integrin antagonists. It is a further object to provide methods for treating a variety of integrin-mediated disorders including, but not limited to, unstable angina, thromboembolic disorders, atherosclerosis, arterial and/or venous thrombosis, restenosis, rheumatoid arthritis, vaso-occlusive disorders, osteoporosis, tumor angiogenesis, multiple sclerosis, neurological disorders, asthma, vascular injury, macular degeneration or diabetic complications including diabetic retinopathy.

Summary of the Invention

The present invention is directed to compounds represented by the following general Formula (I):



(I)

wherein

M is selected from C_1-C_4 alkylene (optionally substituted within the carbon chain with one substituent selected from C_1-C_4 alkyl, C_2-C_4 alkenyl, cycloalkyl (wherein a ring carbon atom forms the point of attachment to the carbon chain) or aryl (optionally substituted with halogen) and substituted on the terminal carbon with one substituent selected from A), C_2-C_4 alkenylene (substituted with one substituent selected from A), heterocyclylene (optionally substituted with one substituent selected from A), heterocyclenylene (substituted with one substituent selected from A), arylene (substituted with one substituent selected from A), (C_1-C_4

alkylene)aryl (substituted on C_1-C_4 alkylene with one substituent selected from A) or arylene(C_1-C_4)alkyl (substituted on arylene with one substituent selected from A);

A is optionally present and is selected from heteroaryl, heterocyclyl, R_3HN-, (heteroaryl)amino, (heterocyclyl)amino, $R_3HNC(=NH)$-, $R_3HNC(=NH)NH$-, $R_3HNC(=O)NH$-, $R_3C(=NH)NH$-, (heterocyclyl)aminooxy, (heteroaryl)aminooxy, $R_3HNC(=NH)NHO$-, $R_3C(=NH)NHO$-, $R_3HNC(=NH)NHC(=O)$- or $R_3C(=NH)NHC(=O)$-; wherein heteroaryl and heterocyclyl are optionally substituted with one to five substituents independently selected from C_1-C_4 alkyl, C_1-C_4 alkoxy, heteroaryl (optionally substituted with C_1-C_4 alkyl), halogen, hydroxy, nitro, cyano, trihalo(C_1-C_4)alkyl, C_1-C_4 alkylcarbonyl, C_1-C_4 alkoxycarbonyl, aryl(C_1-C_4)alkoxycarbonyl, R_3HN-, amino(C_1-C_4)alkyl, C_1-C_4 alkylamino(C_1-C_4)alkyl or di(C_1-C_4 alkyl)amino(C_1-C_4)alkyl;

with the proviso that if A is $H_2NC(=NH)NH$-, then, dependently, W is not hydrogen when Q is $-CH_2-$;

L is selected from -C(=O)-, $-SO_2-$, -OC(=O)- or -HNC(=O)-;

R_1 is selected from hydrogen, C_1-C_8 alkyl or cycloalkyl;

R_2 is selected from hydrogen or C_1-C_8 alkyl;

R_3 is selected from hydrogen, C_1-C_8 alkyl, aryl, aryl(C_1-C_8)alkyl, cycloalkyl, hydroxy, cyano or nitro;

Q is selected from $-CH_2-$, -CH(C_1-C_8alkyl)-, -CH(C_2-C_8alkenyl)-, -CH(C_2-C_8alkynyl)-, -CH(aryl)- (wherein aryl is optionally substituted with one to five substituents independently selected from C_1-C_4 alkyl, C_1-C_4 alkoxy, -O-(C_1-C_3 alkyl)-O-, halogen, hydroxy, trihalo(C_1-C_3)alkyl or trihalo(C_1-C_3)alkoxy), -CH(heteroaryl)- (wherein heteroaryl is optionally

substituted with a substituent selected from halogen, hydroxy, C_1-C_4 alkyl, C_1-C_4 alkoxy, -O-(C_1-C_3 alkyl)-O-, amino, C_1-C_4 alkylamino or di(C_1-C_4)alkylamino) or -CH(aryl(C_1-C_8)alkyl)-;

W is selected from hydrogen or N(R_4)T;

r is an integer selected from 0 or 1;

R_4 is selected from hydrogen, C_1-C_8 alkyl or C_2-C_6 acyl;

T is selected from $R_5C(=O)$-, $R_5OC(=O)$- or $R_5C(=N\text{-}CN)$-;

R_5 is selected from C_1-C_8 alkyl, aryl, aryl(C_1-C_8)alkyl or amino (wherein amino is optionally substituted with one to two substituents independently selected from C_1-C_8 alkyl);

R_6 is selected from hydrogen, C_1-C_8 alkyl, aryl(C_1-C_8)alkyl, (R_7)N(C_1-C_8)alkyl, (R_8)(R_7)N(C_1-C_8)alkyl or (R_8)(R_7)NC(=O)(C_1-C_8)alkyl; and,

R_7 and R_8 are independently selected from hydrogen, C_1-C_8 alkyl or cycloalkyl;

and pharmaceutically acceptable salts thereof.

Illustrative of the invention is a pharmaceutical composition comprising a pharmaceutically acceptable carrier and any of the compounds described above. Illustrating the invention is a pharmaceutical composition made by mixing any of the compounds described above and a pharmaceutically acceptable carrier. An illustration of the invention is a process for making a pharmaceutical composition comprising mixing any of the compounds described above and a pharmaceutically acceptable carrier.

An example of the invention is a method of treating integrin-mediated disorders in a subject in need thereof comprising administering to the subject a

therapeutically effective amount of any of the compounds or pharmaceutical compositions described above. Examples of integrin-mediated disorders include, but are not limited to, unstable angina, thromboembolic disorders, atherosclerosis, arterial and/or venous thrombosis, restenosis, rheumatoid arthritis, vaso-occlusive disorders, osteoporosis, tumor angiogenesis, multiple sclerosis, neurological disorders, asthma, vascular injury, macular degeneration or diabetic complications, including diabetic retinopathy.

Further exemplifying the invention is the method of treating integrin-mediated disorders, wherein the therapeutically effective amount of the compound is from about 0.01 mg/kg/day to about 300 mg/kg/day.

Also included in the invention is the use of a compound of Formula (I) for the preparation of a medicament for treating an integrin-mediated disorder in a subject in need thereof.

The isonipecotamide compounds of the present invention are integrin antagonists; particularly, αvβ3, αvβ5, GPIIb/IIIa, dual αvβ3/GPIIb/IIIa and dual αvβ3/αvβ5 integrin antagonists. The instant compounds are useful in treating thrombotic disorders such as restenosis, arterial and venous thrombosis, acute myocardial infarction, re-occlusion following thrombolytic therapy and angioplasty, inflammation, unstable angina, atherosclerosis, angiogenesis and a variety of vaso-occlusive disorders. These compounds are also useful as antithrombotics used in conjunction with fibrinolytic therapy (e.g., t-PA or streptokinase). Additionally, the compounds are useful in treating and preventing osteoporosis, rheumatoid arthritis, bone resorption, cancer, macular degeneration, and diabetic complications including diabetic retinopathy.

Detailed Description of the Invention

Relative to the above generic description, certain compounds of Formula (I) are preferred.

The preferred embodiments of the present invention are those

compounds wherein, independently,

M is selected from ethylene (optionally substituted within the carbon chain with methyl and substituted on the terminal carbon with one substituent selected from A), propylene (optionally substituted within the carbon chain with methyl, ethenyl, cyclohexylidene (wherein a ring carbon atom forms the point of attachment to the carbon chain) or 4-Cl-phenyl and substituted on the terminal carbon with one substituent selected from A), allylene (substituted with one substituent selected from A); piperidin-4-ylene (optionally substituted with one substituent selected from A), 1,4,5-dihydro-2-cyclopenten-1-ylene (substituted with one substituent selected from A) or 4-methylenephenyl (substituted on methylene with one substituent selected from A);

A is optionally present and is selected from 1*H*-imidazol-1-yl, 1*H*-imidazol-2-yl, 4,5-dihydro-1*H*-imidazol-2-yl (optionally substituted with a substituent selected from C_1-C_4 alkoxycarbonyl or aryl(C_1-C_4)alkoxycarbonyl), pyridin-2-yl (optionally substituted with a substituent selected from C_1-C_4 alkyl, heteroaryl (optionally substituted with C_1-C_4 alkyl), halogen, hydroxy, nitro, cyano, amino, amino(C_1-C_4)alkyl, C_1-C_4 alkylamino(C_1-C_4)alkyl or di(C_1-C_4 alkyl)amino(C_1-C_4)alkyl), pyrimidin-2-yl, 1,4,5,6-tetrahydro-pyrimidin-2-yl (optionally substituted with one to two substituents independently selected from C_1-C_4 alkyl, hydroxy or amino), piperidin-4-yl, benzimidazol-2-yl, 1,2,3,4-tetrahydro-1,8-naphthyridin-7-yl, 3*H*-imidazo[4,5-*b*]pyridin-2-yl, amino, (C_1-C_6 alkyl)amino, (1*H*-imidazol-1-yl)amino, (1*H*-imidazol-2-yl)amino, (4,5-dihydro-1*H*-imidazol-2-yl)amino (optionally substituted on 4,5-dihydro-1*H*-imidazol-2-yl with a substituent selected from C_1-C_6 alkoxycarbonyl or aryl(C_1-C_6)alkoxycarbonyl), (pyridin-2-yl)amino (optionally substituted on pyridin-2-yl with a substituent selected from C_1-C_4 alkyl, heteroaryl [optionally substituted with C_1-C_4 alkyl], halogen, hydroxy, nitro, cyano, amino, amino(C_1-C_4)alkyl, C_1-C_4 alkylamino(C_1-C_4)alkyl or di(C_1-C_4 alkyl)amino(C_1-C_4)alkyl), (pyrimidin-2-yl)amino, (1,4,5,6-tetrahydro-pyrimidin-2-yl)amino (optionally substituted on 1,4,5,6-tetrahydro-pyrimidin-2-yl with one to two substituents independently selected from C_1-C_4 alkyl,

hydroxy or amino), (4,5,6,7-tetrahydro-1*H*-1,3-diazepin-2-yl)amino, (thiazol-2-yl)amino, (benzimidazol-2-yl)amino, (3*H*-imidazo[4,5-*b*]pyridin-2-yl)amino, $R_3HNC(=NH)NH$-, $R_3HNC(=O)NH$-, (4,5,6,7-tetrahydro-1*H*-1,3-diazepin-2-yl)aminooxy, (4,5-dihydro-1*H*-imidazol-2-yl)aminooxy or $R_3HNC(=NH)NHO$-;

more preferably, A is optionally present and is selected from 1*H*-imidazol-1-yl, 4,5-dihydro-1*H*-imidazol-2-yl, pyridin-2-yl (optionally substituted with a substituent selected from C_1-C_4 alkyl or heteroaryl [optionally substituted with C_1-C_4 alkyl]), piperidin-4-yl, benzimidazol-2-yl, 1,2,3,4-tetrahydro-1,8-naphthyridin-7-yl, 3*H*-imidazo[4,5-*b*]pyridin-2-yl, amino, (4,5-dihydro-1*H*-imidazol-2-yl)amino (optionally substituted on 4,5-dihydro-1*H*-imidazol-2-yl with C_1-C_6 alkoxycarbonyl), (pyridin-2-yl)amino (optionally substituted on pyridinyl with a substituent selected from C_1-C_4 alkyl or heteroaryl [optionally substituted with C_1-C_4 alkyl]), (1,4,5,6-tetrahydro-5-hydroxypyrimidin-2-yl)amino, (1,4,5,6-tetrahydro-5-methylpyrimidin-2-yl)amino, (1,4,5,6-tetrahydro-5,5-dimethylpyrimidin-2-yl)amino, (thiazol-2-yl)amino, (3*H*-imidazo[4,5-*b*]pyridin-2-yl)amino, $R_3HNC(=NH)NH$-, $R_3HNC(=O)NH$-, (4,5-dihydro-1*H*-imidazol-2-yl)aminooxy or $R_3HNC(=NH)NHO$-;

most preferably, A is optionally present and is selected from 4,5-dihydro-1*H*-imidazol-2-yl, 1,2,3,4-tetrahydro-1,8-naphthyridin-7-yl, 3*H*-imidazo[4,5-*b*]pyridin-2-yl, amino, (4,5-dihydro-1*H*-imidazol-2-yl)amino, (pyridin-2-yl)amino, (3-methylpyridin-2-yl)amino, (thiazol-2-yl)amino, (3*H*-imidazo[4,5-*b*]pyridin-2-yl)amino, $NH_2C(=NH)NH$-, $R_3HNC(=O)NH$-, (4,5-dihydro-1*H*-imidazol-2-yl)aminoxy or $NH_2C(=NH)NHO$-,

with the proviso that if A is $H_2NC(=NH)NH$-, then, dependently, W is not hydrogen when Q is $-CH_2$-;

L is selected from -C(=O)-, -OC(=O)- or -HNC(=O)-;

R_1 is selected from hydrogen or C_1-C_4 alkyl;
more preferably, R_1 is hydrogen;

R_2 is hydrogen;

R_3 is selected from hydrogen, C_1-C_8 alkyl, aryl(C_1-C_8)alkyl or hydroxy; more preferably, R_3 is selected from hydrogen, butyl, benzyl or hydroxy;

Q is selected from -CH_2-, -CH(C_1-C_8alkyl)-, -CH(aryl)- (wherein aryl is optionally substituted with one to five substituents independently selected from C_1-C_4 alkyl, C_1-C_4 alkoxy, -O-(C_1-C_3 alkyl)-O-, halogen, hydroxy or trihalo(C_1-C_3)alkyl), -CH(heteroaryl)- (wherein heteroaryl is optionally substituted with a substituent selected from halogen) or -CH(aryl(C_1-C_8)alkyl)-;

more preferably, Q is selected from -CH_2-, -CH(methyl)-, -CH(ethyl)-, -CH(phenyl)- (wherein phenyl is optionally substituted with one to five substituents independently selected from methyl, ethyl, propyl, methoxy, ethoxy, propoxy, bromine, chlorine, fluorine, iodine, hydroxy or trifluoromethyl), -CH(naphthalen-1-yl)-, -CH(naphthalen-2-yl)-, -CH[(3,4-dioxymethylene)phenyl]-, -CH[(3,4-dioxyethylene)phenyl]-, -CH[(3-bromo-5-chloro-2-hydroxy)phenyl]-, -CH(thien-3-yl)-, -CH(quinolin-3-yl)-, -CH(pyridin-3-yl)- (wherein pyridinyl is optionally substituted with chlorine) or -CH(benzyl)-;

most preferably, Q is selected from -CH_2-, -CH(methyl)-, -CH(phenyl)- (wherein phenyl is optionally substituted with one to five substituents independently selected from methyl, methoxy, bromine, chlorine, fluorine, hydroxy or trifluoromethyl), -CH(naphthalen-1-yl)-, -CH(naphthalen-2-yl)-, -CH[(3,4-dioxymethylene)phenyl]-, -CH[(3,4-dioxyethylene)phenyl]-, -CH[(3-bromo-5-chloro-2-hydroxy)phenyl]-, -CH(thien-3-yl)-, -CH(quinolin-3-yl)-, -CH(pyridin-3-yl)- (wherein pyridinyl is optionally substituted with chlorine) or -CH(benzyl)-;

r is 1;

R_4 is selected from hydrogen or C_1-C_4 alkyl;
more preferably, R_4 is hydrogen;

T is selected from $R_5C(=O)$- or $R_5OC(=O)$-;
more preferably, T is selected from $R_5OC(=O)$-;

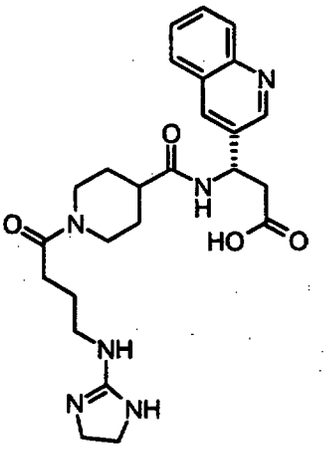
R_5 is selected from aryl or aryl(C_1-C_4)alkyl;
more preferably, R_5 is selected from aryl(C_1-C_4)alkyl;
most preferably, R_5 is benzyl;

R_6 is selected from hydrogen, methyl or $(R_8)(R_7)NC(=O)CH_2$;
more preferably, R_6 is hydrogen;

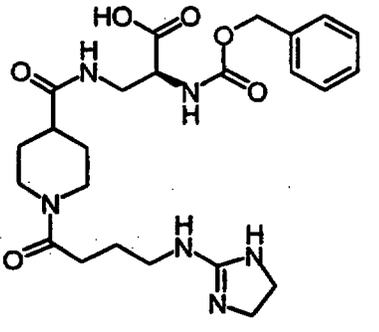
R_7 and R_8 are independently selected from hydrogen, methyl or ethyl; and,
more preferably, R_7 and R_8 are independently ethyl;

and pharmaceutically acceptable salts thereof.

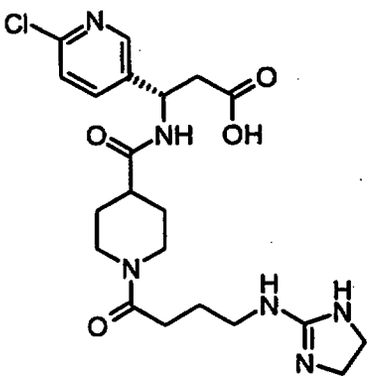
Exemplifying the invention is a compound of Formula (I) selected from:



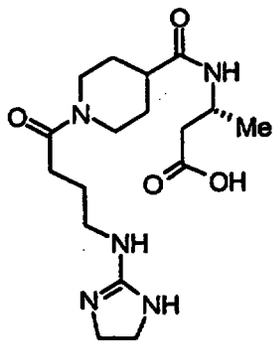
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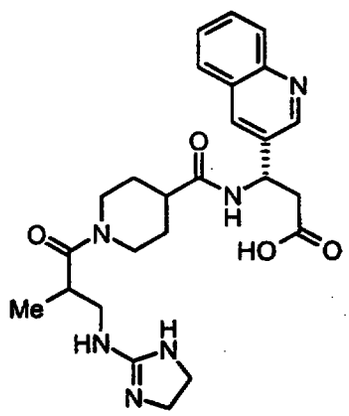
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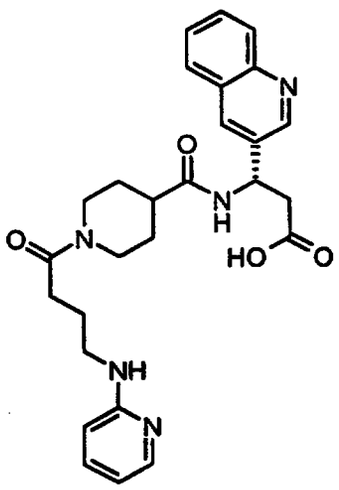
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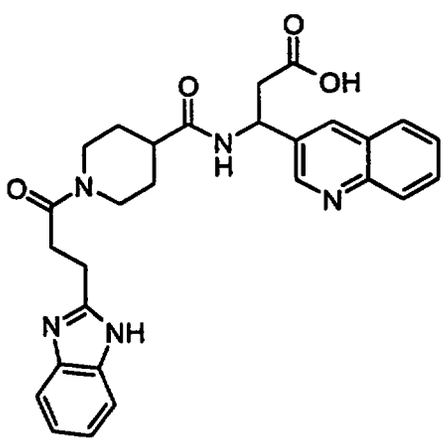
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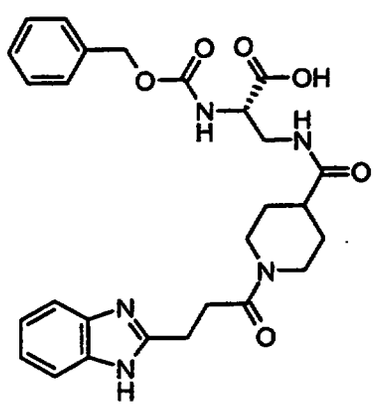
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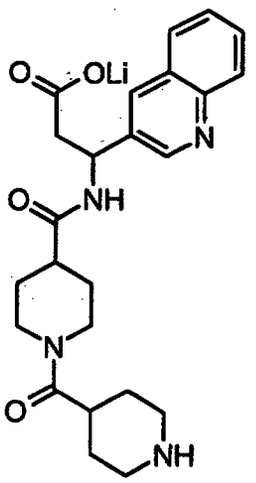
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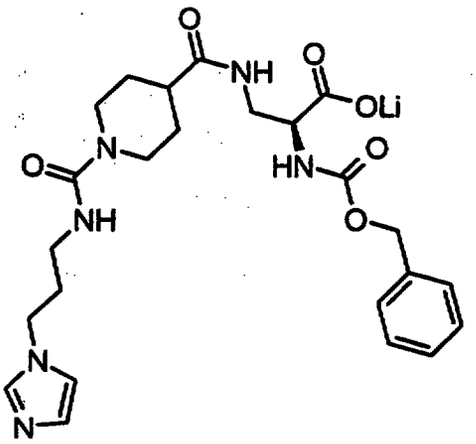
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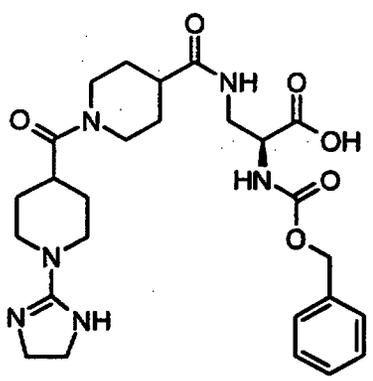
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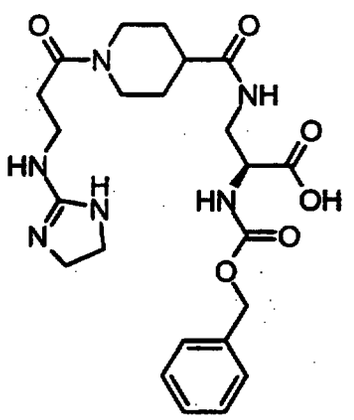
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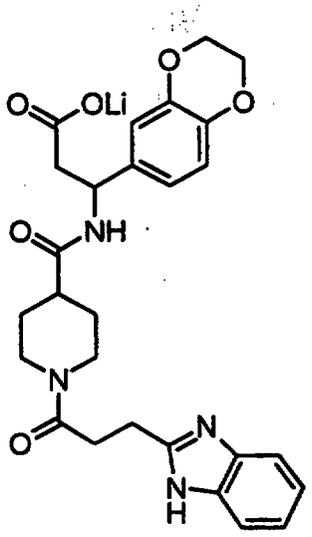
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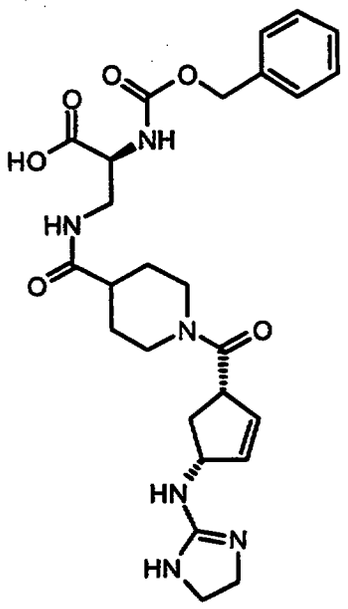
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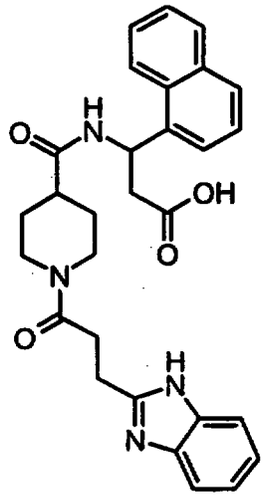
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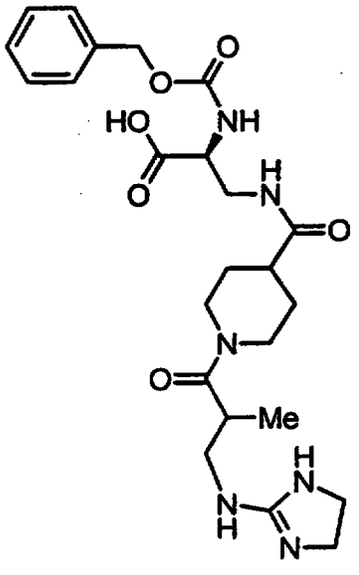
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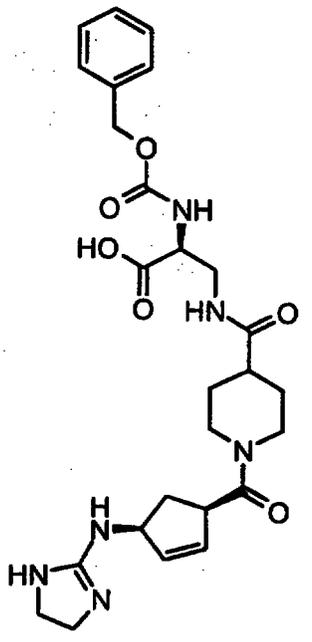
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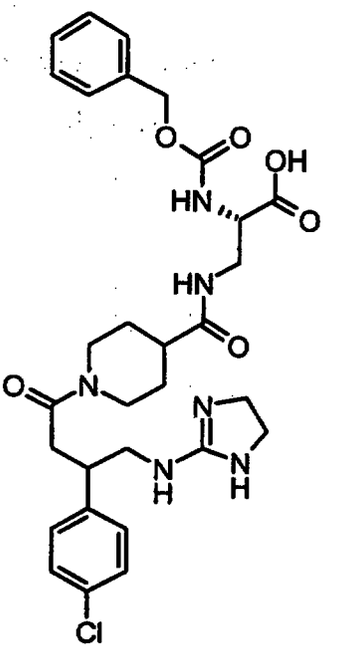
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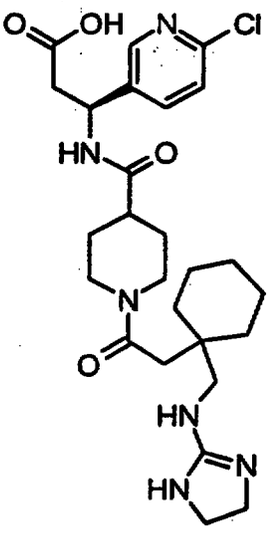
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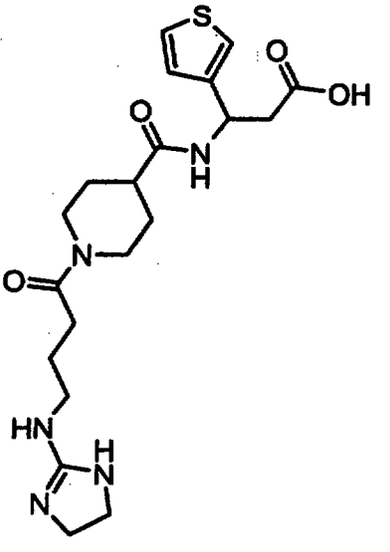
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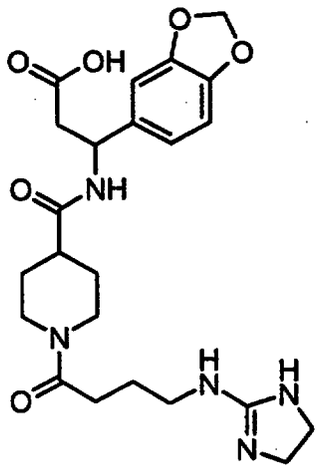
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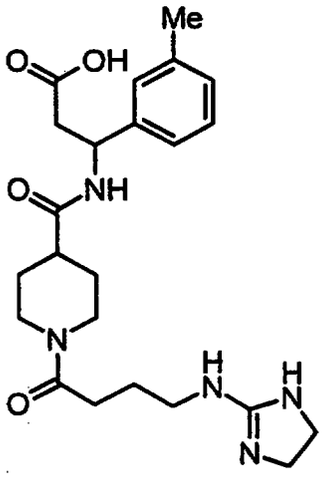
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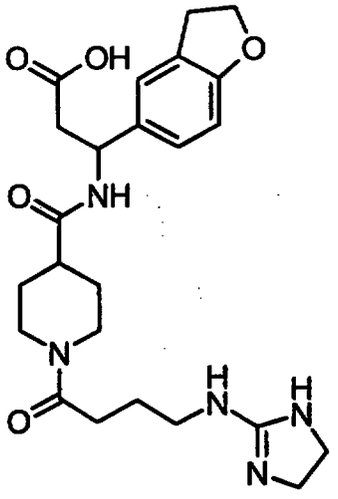
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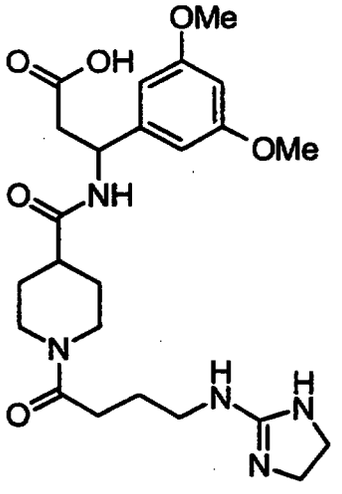
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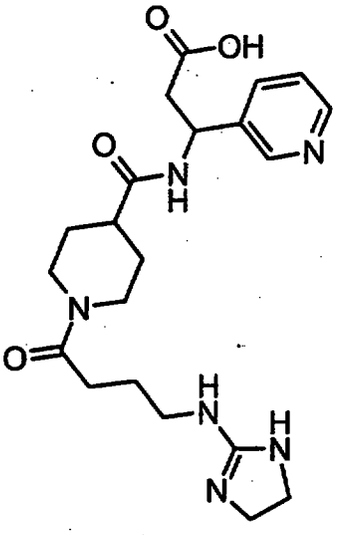
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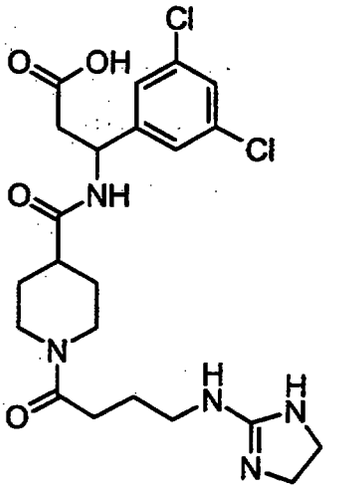
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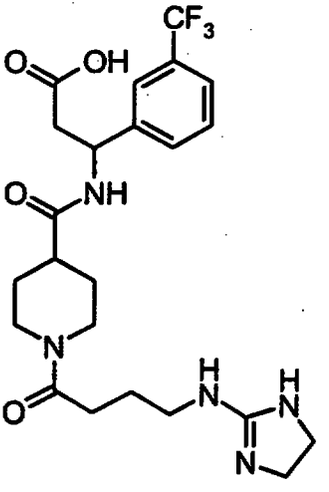
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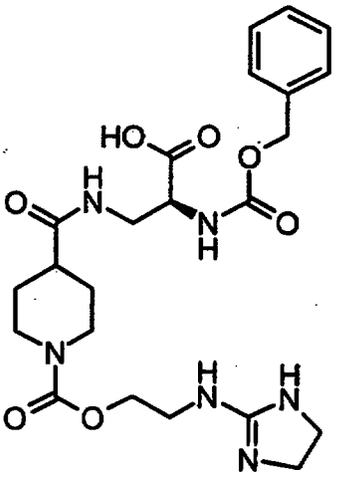
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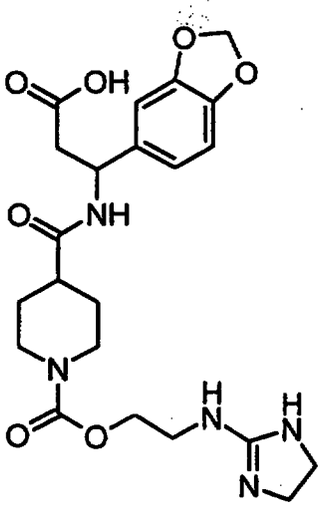
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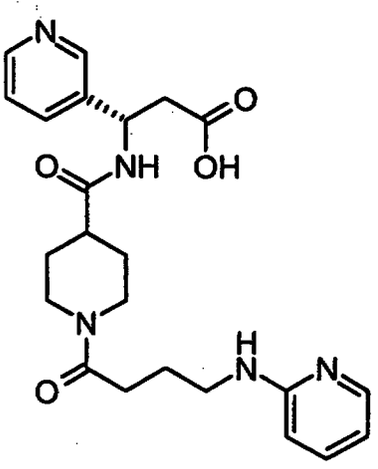
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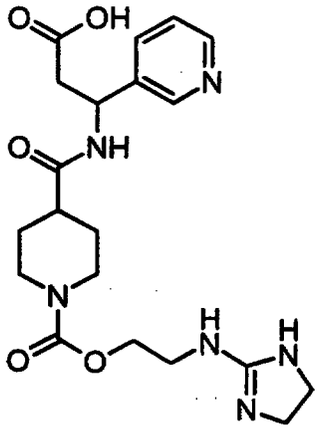
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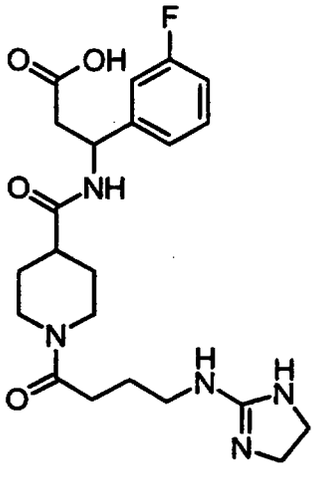
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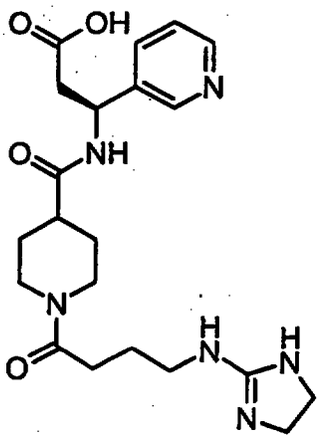
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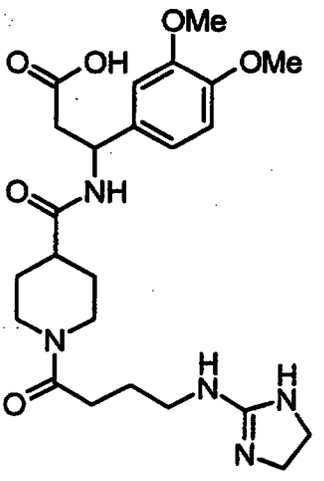
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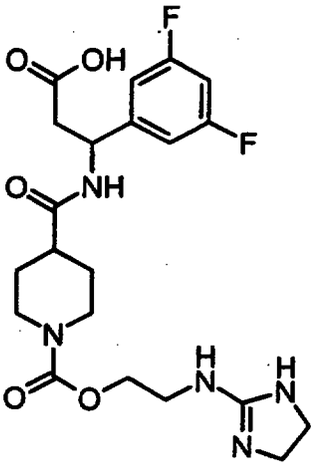
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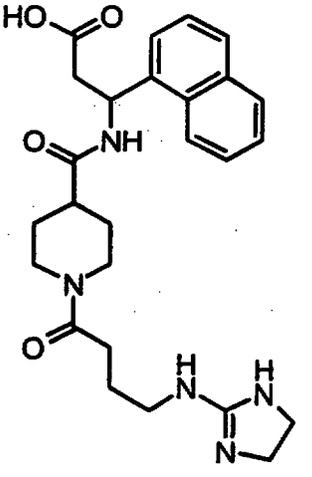
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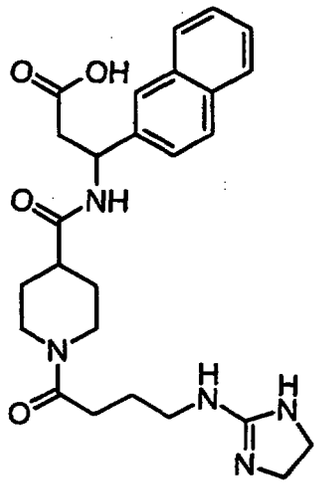
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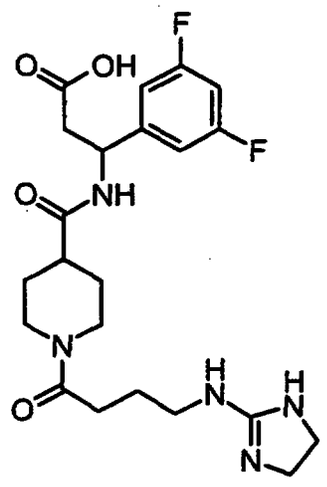
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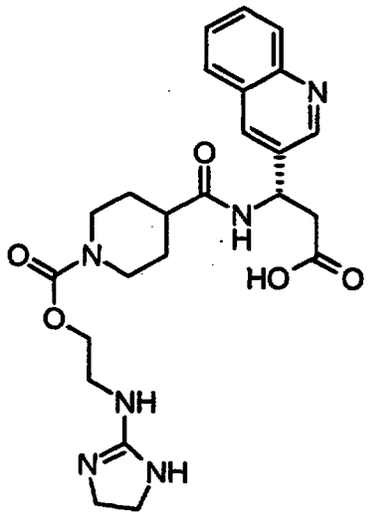
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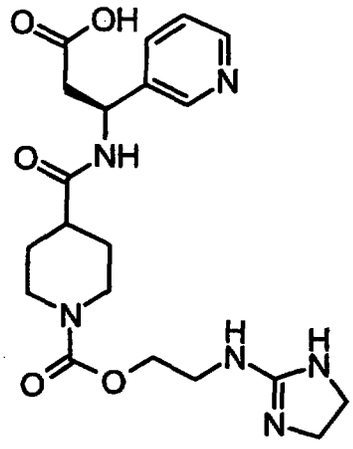
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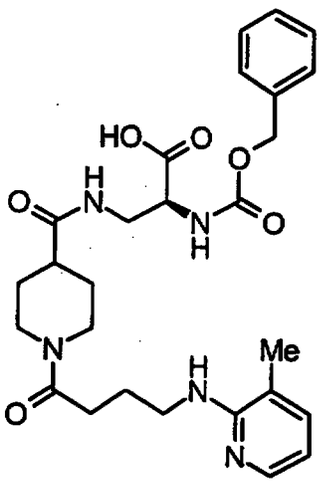
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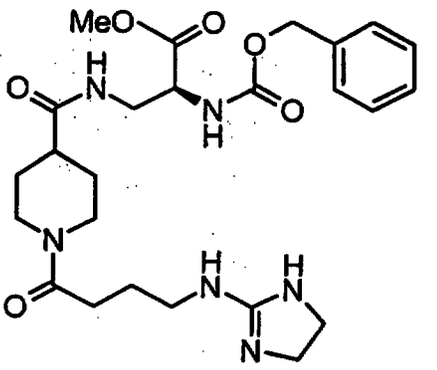
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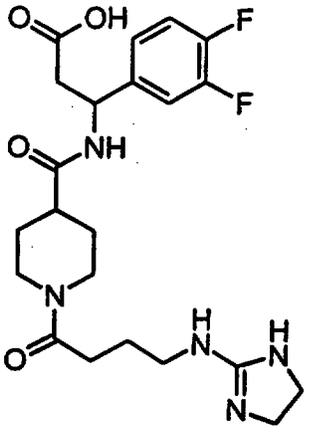
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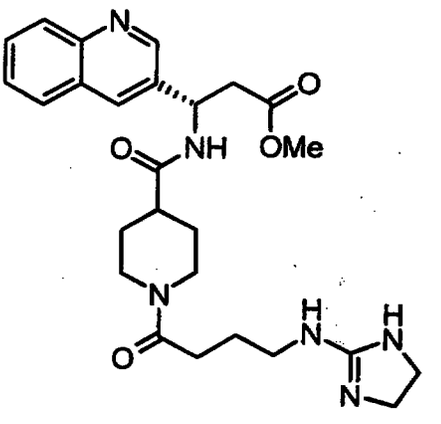
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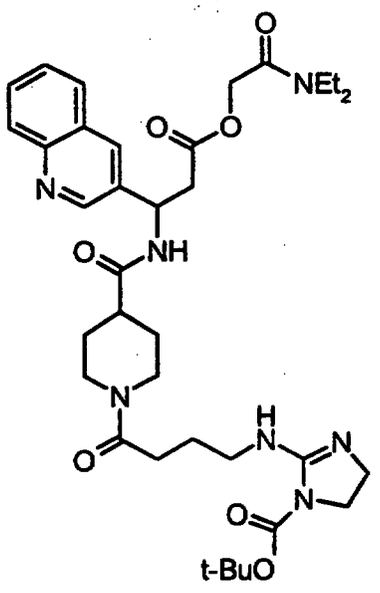
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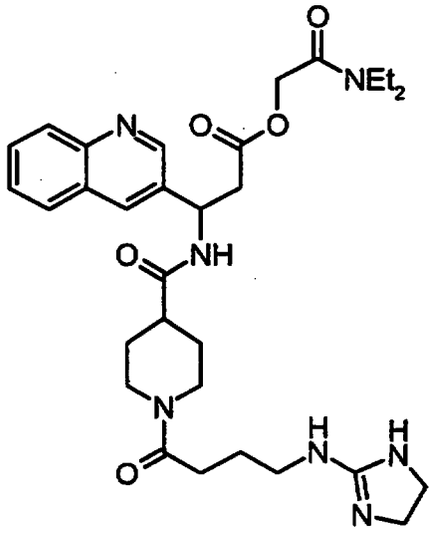
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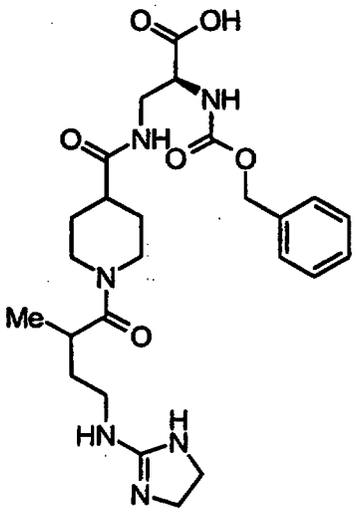
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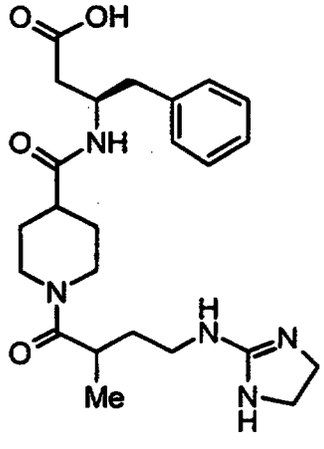
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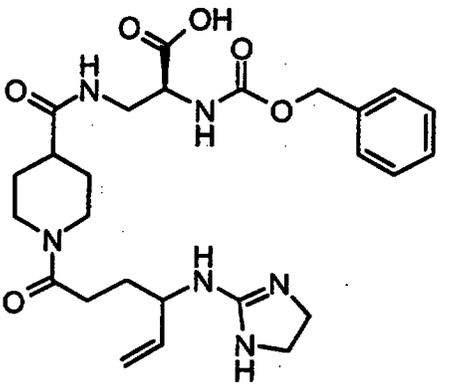
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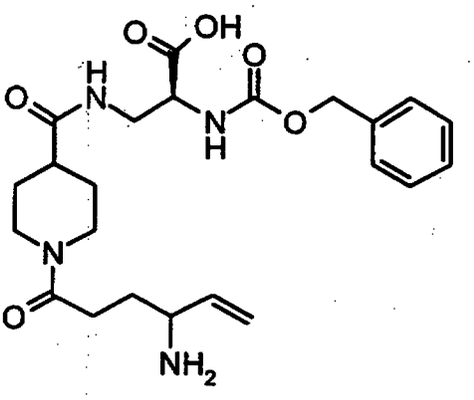
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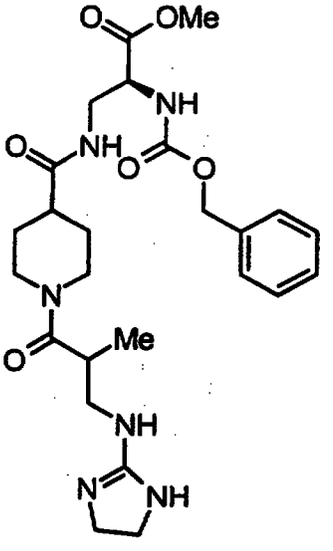
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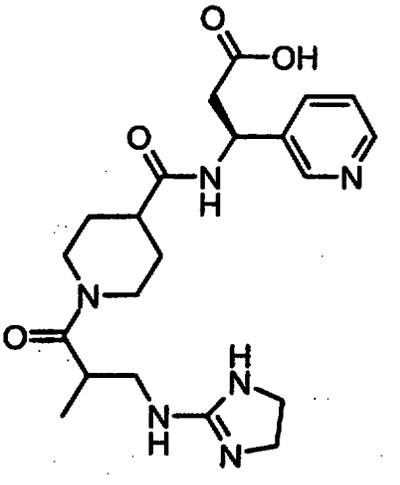
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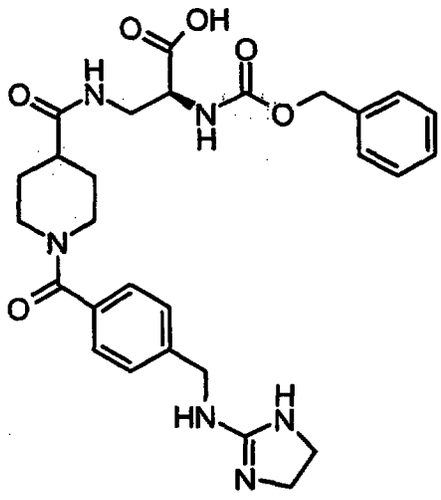
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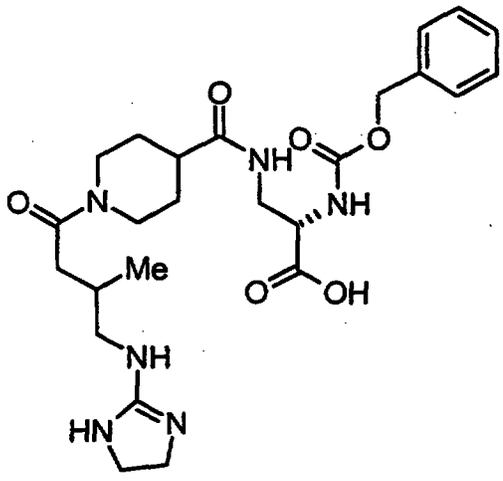
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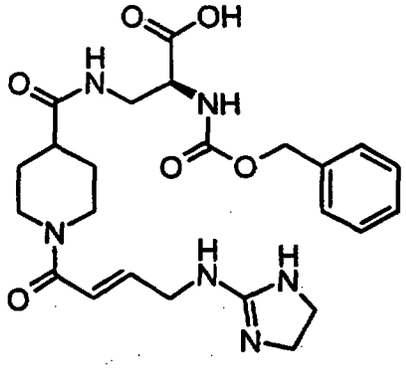
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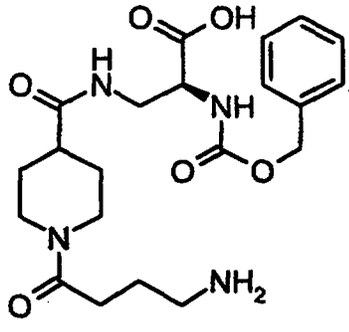
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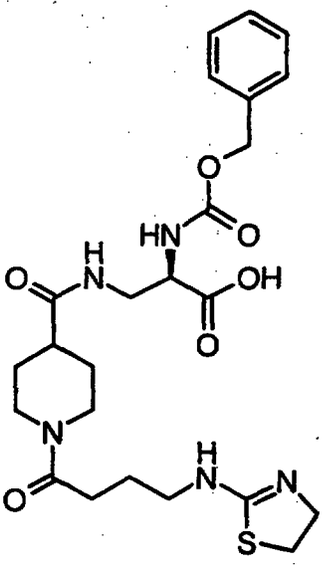
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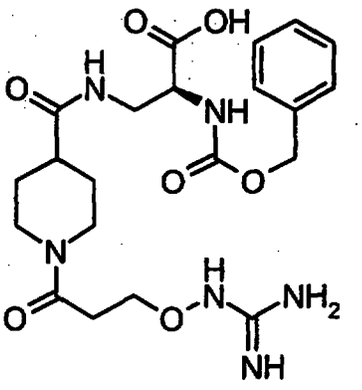
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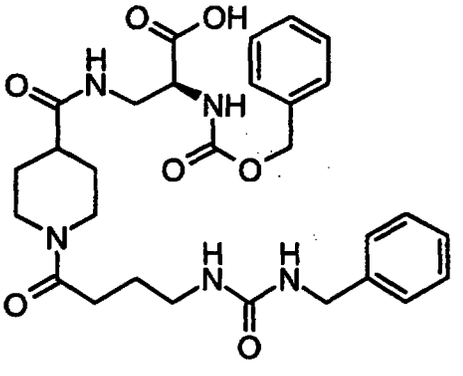
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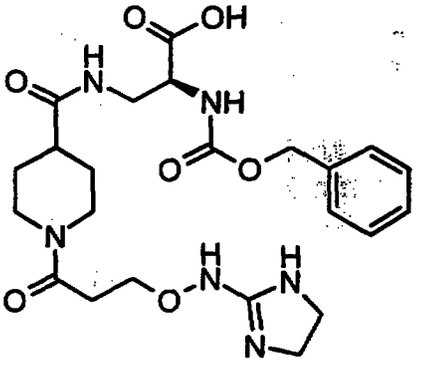
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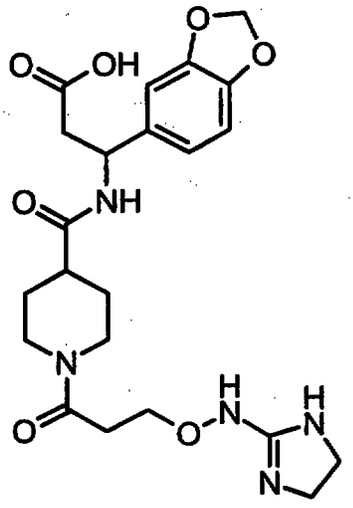
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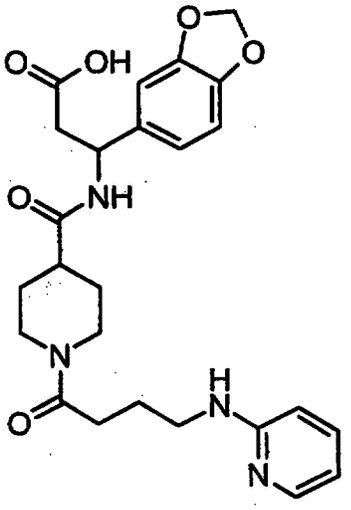
59



60



61, or



62

and pharmaceutically acceptable salts thereof.

Particularly preferred compounds of Formula (I) are selected from:

Cpd	Name
1	β-[[[1-[4-[(4,5-dihydro-1*H*-imidazol-2-yl)amino]-1-oxobutyl]-4-piperidinyl]carbonyl]amino]-, (β^3S)- 3-quinolinepropanoic acid;
2	3-[[[1-[4-[(4,5-dihydro-1*H*-imidazol-2-yl)amino]-1-oxobutyl]-4-piperidinyl]carbonyl]amino]-*N*-[(phenylmethoxy)carbonyl]- L-alanine;
6	β-[[[1-[1-oxo-4-(2-pyridinylamino)butyl]-4-piperidinyl]carbonyl]amino]-, (β^3S)- 3-quinolinepropanoic acid;
11	3-[[[1-[[1-(4,5-dihydro-1*H*-imidazol-2-yl)-4-piperidinyl]carbonyl]-4-piperidinyl]carbonyl]amino]-*N*-[(phenylmethoxy)carbonyl]- L-alanine;
14	3-[[[1-[[(1*S*,4*R*)-4-[(4,5-dihydro-1*H*-imidazol-2-yl)amino]-2-cyclopenten-1-yl]carbonyl]-4-piperidinyl]carbonyl]amino]-*N*-[(phenylmethoxy)carbonyl]- L-alanine;
16	3-[[[1-[3-[(4,5-dihydro-1*H*-imidazol-2-yl)amino]-2-methyl-1-oxopropyl]-4-piperidinyl]carbonyl]amino]-*N*-[(phenylmethoxy)carbonyl]- L-alanine;
17	3-[[[1-[[(1*R*,4*S*)-4-[(4,5-dihydro-1*H*-imidazol-2-yl)amino]-2-cyclopenten-1-yl]carbonyl]-4-piperidinyl]carbonyl]amino]-*N*-[(phenylmethoxy)carbonyl]- L-alanine;
28	4-[[[(2*S*)-2-carboxy-2-[[(phenylmethoxy)carbonyl]amino]ethyl]amino]carbonyl]-, 2-[(4,5-dihydro-1*H*-imidazol-2-yl)amino]ethyl ester 1-piperidinecarboxylic acid;
39	β-[[[1-[[2-[(4,5-dihydro-1*H*-imidazol-2-yl)amino]ethoxy]carbonyl]-4-piperidinyl]carbonyl]amino]-, (β^3S)- 3-quinolinepropanoic acid;
47	3-[[[1-[4-[(4,5-dihydro-1*H*-imidazol-2-yl)amino]-2-methyl-1-oxobutyl]-4-piperidinyl]carbonyl]amino]-*N*-[(phenylmethoxy)carbonyl]- L-alanine;

50 3-[[[1-(4-amino-1-oxo-5-hexenyl)-4-piperidinyl]carbonyl]amino]-*N*-[(phenylmethoxy)carbonyl]- L-alanine;

53 3-[[[1-[4-[[(4,5-dihydro-1*H*-imidazol-2-yl)amino]methyl]benzoyl]-4-piperidinyl]carbonyl]amino]-*N*-[(phenylmethoxy)carbonyl]- L-alanine;

61 β-[[[1-[3-[[(4,5-dihydro-1*H*-imidazol-2-yl)amino]oxy]-1-oxopropyl]-4-piperidinyl]carbonyl]amino]- 1,3-benzodioxole-5-propanoic acid;

or,

62 β-[[[1-[1-oxo-4-(2-pyridinylamino)butyl]-4-piperidinyl]carbonyl]amino]-1,3-benzodioxole-5-propanoic acid;

and pharmaceutically acceptable salts thereof.

Representative Chemical Abstracts Service (CAS) Index-like names for the compounds of the present invention were derived using the ACD/LABS SOFTWARE™ Index Name Pro Version 4.0 nomenclature software program provided by Advanced Chemistry Development, Inc., Toronto, Ontario, Canada.

The compounds of the present invention may also be present in the form of pharmaceutically acceptable salts. For use in medicine, the salts of the compounds of this invention refer to non-toxic "pharmaceutically acceptable salts." Other salts may, however, be useful in the preparation of compounds according to this invention or of their pharmaceutically acceptable salts. The pharmaceutically acceptable salts generally take a form in which a basic nitrogen or nitrogens on the compound of the Formula (I) are protonated with an inorganic or organic acid. Representative inorganic or organic acids include, but are not limited to, hydrochloric, hydrobromic, hydriodic, perchloric, sulfuric, nitric, phosphoric, acetic, propionic, glycolic, lactic, succinic, maleic, fumaric, malic, tartaric, citric, benzoic, mandelic, methanesulfonic, hydroxyethanesulfonic, benezenesulfonic, oxalic, pamoic, 2-naphthalenesulfonic, p-toluenesulfonic, cyclohexanesulfamic, salicylic, saccharinic or trifluoroacetic acid. Similarly, pharmaceutically acceptable salts also include compounds wherein a carboxylic acid group of the compound of the Formula (I) combines with a organic or inorganic base. Representative inorganic or organic bases include, but are not limited to lithium, sodium,

potassium, magnesium, calcium, aluminum, zinc, benzathine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (*N*-methyl glucamine), tromethamine (2-amino-2-(hydroxymethyl)-1,3-propanediol) or procaine (4-amino-[2-(diethylamino)ethyl ester] benzoic acid).

As used herein, unless otherwise noted alkyl and alkoxy when used alone include straight and branched chains having 1 to 8 carbon atoms, or any number within this range. Similarly, alkenyl and alkynyl groups include straight and branched chain alkenes and alkynes having 2 to 8 carbon atoms, or any number within this range. The term alkylene, alkenylene and alkynylene refers to alkyl, alkenyl and alkynyl chains, respectively, that are further substituted and act as linking groups. Alkoxy radicals are oxygen ethers formed from the previously described straight or branched chain alkyl groups. Cycloalkyl groups contain 3 to 8 ring carbons; preferably, 5 to 8 ring carbons; and, more preferably, 5 to 7 ring carbons.

The term "heterocyclyl" as used herein refers to an optionally substituted, stable, saturated 3 to 10 (preferably 4 to 8) membered monocyclic or bicyclic ring system which consists of carbon atoms and from one to three heteroatoms selected from N, O or S. The term "heterocyclenyl" as used herein refers to an optionally substituted, stable, unsaturated 3 to 10 (preferably 4 to 8) membered monocyclic or bicyclic ring system which consists of carbon atoms and from one to three heteroatoms selected from N, O or S. The heterocyclyl or heterocyclenyl group may be attached at any heteroatom or carbon atom which results in the creation of a stable structure and, accordingly, may be further attached to, for example, alkyl or alkoxy chains. The term hetercyclylene and heterocyclenylene refers to hetercyclyl and heterocyclenyl groups, respectively, that are further substituted and act as linking groups; wherein, one or both rings may be optionally substituted with one to five substituents attached at any heteroatom or carbon atom which results in the creation of a stable structure.

The term "aryl", as used herein, refers to optionally substituted aromatic

groups such as phenyl and naphthyl. The term arylene refers to aryl groups that are further substituted and act as linking groups; wherein, one or both rings may be optionally substituted with one to five substituents attached at any carbon atom which results in the creation of a stable structure.

The term "heteroaryl" as used herein represents a stable five or six membered monocyclic aromatic ring system or a nine or ten membered benzo-fused heteroaromatic ring system which consists of carbon atoms and from one to three heteroatoms selected from N, O or S. The heteroaryl group may be attached or optionally substituted at any heteroatom or carbon atom which results in the creation of a stable structure.

The term "arylalkyl" means an alkyl group substituted with an aryl group (e.g., benzyl, phenethyl). Similarly, the term "arylalkoxy" indicates an alkoxy group substituted with an aryl group (e.g., benzyloxy).

The term "acyl" as used herein means an organic radical having 2 to 6 carbon atoms (branched or straight chain) derived from an organinc acid by removal of the hydroxy group.

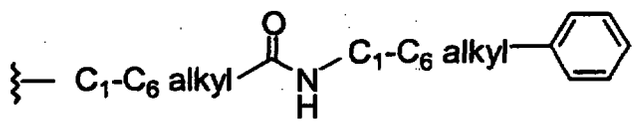
Whenever the term "alkyl" or "aryl" or either of their prefix roots appear in a name of a substituent (*e.g.*, aralkyl, alkylamino) it shall be interpreted as including those limitations given above for "alkyl" and "aryl." When present, designated numbers of carbon atoms (e.g., C_1-C_8) shall refer independently to the number of carbon atoms in a moiety or to the alkyl portion of a larger substituent in which alkyl appears as its prefix root.

Any of the foregoing cycloalkyl, heterocyclyl, heterocyclenyl, aryl and heteroaryl substituent groups and their corresponding heterocyclylene, heterocyclenylene, arylene and heteroarylene linking groups, as a monocyclic or bicyclic ring system may be further bridged at any heteroatom or carbon atom which results in the creation of a stable ring structure; wherein the monocyclic bridged ring system consists of 6 to 8 members and the bicyclic

bridged ring system consists of 10 to 12 members.

It is intended that the definition of any substituent or variable at a particular location in a molecule be independent of its definitions elsewhere in that molecule. It is understood that substituents and substitution patterns on the compounds of this invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques know in the art as well as those methods set forth herein.

Under standard nomenclature used throughout this disclosure, the terminal portion of the designated side chain is described first, followed by the adjacent functionality toward the point of attachment. Thus, for example, a "phenylC_1-C_6 alkylamidoC_1-C_6alkyl" substituent refers to a group of the formula:



The present invention includes within its scope prodrugs of the compounds of this invention. In general, such prodrugs will be functional derivatives of the compounds which are readily convertible *in vivo* into the required compound. Examples of prodrugs include but are not limited to various esters, hydroxyamidines and hydroxyguanidines of compounds of the present invention. Thus, in the methods of treatment of the present invention, the term "administering" shall encompass the treatment of the various disorders described with the compound specifically disclosed or with a compound which may not be specifically disclosed, but which converts to the specified compound *in vivo* after administration to the patient. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

Where the compounds according to this invention have at least one chiral center, they may accordingly exist as enantiomers. Where the compounds possess two or more chiral centers, they may additionally exist as diastereomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention. Furthermore, some of the crystalline forms for the compounds may exist as polymorphs and as such are intended to be included in the present invention. In addition, some of the compounds may form solvates with water (i.e., hydrates) or common organic solvents, and such solvates are also intended to be encompassed within the scope of this invention.

The term "subject" as used herein, refers to an animal, preferably a mammal, most preferably a human, who has been the object of treatment, observation or experiment.

The term "therapeutically effective amount" as used herein, means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue system, animal or human, that is being sought by a researcher, veterinarian, medical doctor, or other clinician, which includes alleviation of the symptoms of the disease or disorder being treated.

The term "bone resorption," as used herein, refers to the process by which osteoclasts degrade bone.

The present invention provides isonipecotamide compounds that are useful as αvβ3, αvβ5 and GPIIb/IIIa integrin antagonists. Compounds of Formula (I) that are particularly preferred as αvβ3 integrin antagonists are selected from Compound **1, 2, 3, 5, 6, 12, 14, 16, 18, 21, 24, 25, 28, 29, 31, 33, 34, 39, 40, 44, 47, 49, 54, 55, 58** or **60.** Compounds of Formula (I) that are particularly preferred as GPIIb/IIIa integrin antagonists are selected from Compound **1, 2, 5, 11, 12, 14, 16, 17, 18, 19, 39, 47, 49, 50, 53, 54, 55** or **56.** Compounds of Formula (I) that are particularly preferred as αvβ5 integrin antagonists are selected from Compound **1, 2, 16, 45, 58** or **60.** Compounds

of Formula (I) that are particularly preferred as dual αvβ3/GPIIb/IIIa integrin antagonists are selected from Compound **2, 5, 12, 14, 16, 18, 39, 47, 49, 54** or **55.** Compounds of Formula (I) that are particularly preferred as dual αvβ3/αvβ5 integrin antagonists are selected from Compound **1, 2, 16, 58** or **60.**

Compounds of Formula (I) that are more particularly preferred as αvβ3 integrin antagonists are selected from Compound **1, 2, 6, 28, 39** or **47.** Compounds of Formula (I) that are more particularly preferred as GPIIb/IIIa integrin antagonists are selected from Compound **2, 11, 14, 17, 50** or **53.** Compounds of Formula (I) that are more particularly preferred as αvβ5 integrin antagonists are selected from Compound **1, 2** or **16.** Compounds of Formula (I) that are more particularly preferred as dual αvβ3/GPIIb/IIIa integrin antagonists are Compound **2.** Compounds of Formula (I) that are more particularly preferred as dual αvβ3/αvβ5 integrin antagonists are selected from Compound **1** or **2.**

The compounds of Formula (I) inhibit the binding of adhesive proteins such as fibrinogen, vitronectin, and osteopontin to the integrin class of receptors. As demonstrated by the results of the biological studies described hereinafter, the compounds block vitronectin binding to isolated αvβ3 (IC_{50}'s of ca. 1-300 nM), and inhibit fibrinogen binding to isolated GPIIb/IIIa as well. Because the compounds of this invention inhibit integrin-mediated cell-cell or cell-matrix adhesion, they may be useful against restenosis, thrombosis, inflammation, atherosclerosis, arthritis, angiogenesis, osteroporosis, bone resorption, tumor cell metastasis, tumor growth, macular degeneration, diabetic retinopathy, diseases of lung/airway resistance, etc. (D. Cox, *Drug News & Perspectives* **1995**, *8*, 197).

The compounds of Formula (I) are also useful as antithrombotics in combination with fibrinolytic therapy (e.g., t-PA or streptokinase). Additionally, the compounds of Formula (I) are useful in combination with one or more agents useful in the prevention or treatment of osteoporosis and arthritis. For

example, the compounds of the instant invention may be effectively administered in combination with other agents used in the treatment of osteoporosis such as bisphosphonate bone resorption inhibitors; preferably, the bisphosphonate bone resorption inhibitor is alendronate, sold as FOSAMAX®. Preferred combinations are simultaneous or alternating treatments of an integrin antagonist of the present invention and alendronate.

In accordance with the methods of the present invention, the individual components of the combination can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms. The instant invention is therefore to be understood as embracing all such regimes of simultaneous or alternating treatment and the term "administering" is to be interpreted accordingly.

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

The utility of the compounds to treat integrin-mediated disorders can be determined according to the procedures herein. The present invention therefore provides a method of treating integrin-mediated disorders in a subject in need thereof which comprises administering any of the compounds as defined herein in a quantity effective to treat thrombotic disorders, osteoporosis, cancer, and diabetic complications. The compound may be administered to a patient by any conventional route of administration, including, but not limited to, intravenous, oral, subcutaneous, intramuscular, intradermal and parenteral.

The present invention also provides pharmaceutical compositions comprising one or more compounds of this invention in association with a pharmaceutically acceptable carrier.

To prepare the pharmaceutical compositions of this invention, one or more compounds of Formula (I) or salt thereof of the invention as the active ingredient, is intimately admixed with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques, which carrier may take a wide variety of forms depending of the form of preparation desired for administration, e.g., oral or parenteral such as intramuscular. In preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed. Thus, for liquid oral preparations, such as for example, suspensions, elixirs and solutions, suitable carriers and additives include water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like; for solid oral preparations such as, for example, powders, capsules, caplets, gelcaps and tablets, suitable carriers and additives include starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be sugar coated or enteric coated by standard techniques. For parenterals, the carrier will usually comprise sterile water, through other ingredients, for example, for purposes such as aiding solubility or for preservation, may be included. Injectable suspensions may also be prepared, in which case appropriate liquid carriers, suspending agents and the like may be employed. The pharmaceutical compositions herein will contain, per dosage unit, e.g., tablet, capsule, powder, injection, teaspoonful and the like, an amount of the active ingredient necessary to deliver an effective dose as described above. The pharmaceutical compositions herein will contain, per unit dosage unit, e.g., tablet, capsule, powder, injection, suppository, teaspoonful and the like, of from about 0.01 mg/kg to 100 mg/kg (preferably, from about 0.1 mg/kg to about 30 mg/kg) and may be given at a dosage of from about 0.01 mg/kg/day to about 300 mg/kg/day (preferably, from about 1 mg/kg/day to about 50 mg/kg/day). The dosages, however, may be varied depending upon the requirement of the patients, the severity of the condition being treated and the compound being employed. The use of either daily administration or post-periodic dosing may be employed.

Preferably these compositions are in unit dosage forms from such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, autoinjector devices or suppositories; for oral parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. Alternatively, the composition may be presented in a form suitable for once-weekly or once-monthly administration; for example, an insoluble salt of the active compound, such as the decanoate salt, may be adapted to provide a depot preparation for intramuscular injection. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of material can be used for such enteric layers or coatings, such materials including a number of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include, aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions, include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

Where the processes for the preparation of the compounds according to the invention give rise to mixture of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography. The compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The compounds may, for example, be resolved into their components enantiomers by standard techniques, such as the formation of diastereomeric pairs by salt formation with an optically active acid, such as (-)-di-p-toluoyl-d-tartaric acid and/or (+)-di-p-toluoyl-l-tartaric acid followed by fractional crystallization and regeneration of the free base. The compounds may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary. Alternatively, the compounds may be resolved using a chiral HPLC column.

During any of the processes for preparation of the compounds of the present invention, it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, Protective Groups in Organic Synthesis; Third Edition, John Wiley & Sons, 1999. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The method of treating integrin-mediated disorders described in the present invention may also be carried out using a pharmaceutical composition comprising any of the compounds as defined herein and a pharmaceutically acceptable carrier. The pharmaceutical composition may contain between about 0.01 mg and 100 mg, preferably about 5 to 50 mg, of the compound, and may be constituted into any form suitable for the mode of administration selected. Carriers include necessary and inert pharmaceutical excipients, including, but not limited to, binders, suspending agents, lubricants, flavorings, sweeteners, preservatives, dyes, and coatings. Compositions suitable for oral administration include solid forms, such as pills, tablets, caplets, capsules (each including immediate release, timed release and sustained release formulations), granules, and powders, and liquid forms, such as solutions, syrups, elixirs, emulsions, and suspensions. Forms useful for parenteral administration include sterile solutions, emulsions and suspensions.

Advantageously, compounds of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders; lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include, without limitation, starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium oleate, sodium stearate, magnesium stearate, sodium

benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like.

The liquid forms in suitably flavored suspending or dispersing agents such as the synthetic and natural gums, for example, tragacanth, acacia, methyl-cellulose and the like. For parenteral administration, sterile suspensions and solutions are desired. Isotonic preparations which generally contain suitable preservatives are employed when intravenous administration is desired.

The compound of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phophatidylcholines.

Compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds of the present invention may also be coupled with soluble polymers as targeted drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamidephenol, polyhydroxy-ethylaspartamidephenol, or polyethyl eneoxidepolylysine substituted with palmitoyl residue. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyepsilon caprolactone, polyhydroxy butyeric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

Compounds of this invention may be administered in any of the foregoing compositions and according to dosage regimens established in the art whenever treatment of thrombotic disorders is required.

The daily dosage of the products may be varied over a wide range from about 0.01 mg to about 21,000 mg per adult human per day. For oral administration, the compositions are preferably provided in the form of tablets containing, 0.01,0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100, 150, 200, 250 and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. A therapeutically effective amount of the drug is ordinarily supplied at a dosage level of from about 0.01 mg/kg to about 300 mg/kg of body weight per day. Preferably, the range is from about 0.01 mg/kg to about 100 mg/kg of body weight per day; and more preferably, the range is from about 0.01 mg/kg to about 50 mg/kg of body weight per day. The compounds may be administered on a regimen of 1 to 4 times per day.

Optimal dosages to be administered may be readily determined by those skilled in the art, and will vary with the particular compound used, the mode of administration, the strength of the preparation, the mode of administration, and the advancement of the disease condition. In addition, factors associated with the particular patient being treated, including patient age, weight, diet and time of administration, will result in the need to adjust dosages.

Abbreviations used in the instant specification, particularly the Schemes and Examples, are as follows:

Aq.	=	aqueous
Bn or Bzl	=	benzyl
Boc	=	*tert*-butoxycarbonyl
Boc_2O		di-*tert*-butyl dicarbonate
BSA	=	bovine serum albumin
n-Bu	=	*n*-butyl
Cbz	=	benzyloxycarbonyl
CP or Cpd	=	Compound
DCM	=	dichloromethane
DIC	=	diisopropylcarbodiimide
DIPEA	=	diisopropylethylamine
DMAP	=	4-dimethylaminopyridine
DMF	=	N, N-dimethylformamide

DMSO	=	dimethylsulfoxide
EDC	=	ethyl dimethylaminopropyl-carbodiimide
EDTA	=	ethylenediaminetetraacetic acid
ES	=	electrospray
Et	=	ethyl
Et_2O	=	diethyl ether
EtOH	=	ethanol
^1H NMR	=	proton nuclear magnetic resonance spectrum
HBTU	=	2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HEPES	=	4-(2-hydroxyethyl)-1- piperazine-ethanesulfonic acid
HOBT	=	hydroxybenzotriazole
HBTU	=	2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyl-uronium hexafluorophosphate
IPA	=	2-propanol
Me	=	methyl
MeOH	=	methanol
MH^+	=	observed molecular ion
MPK	=	milligrams per kilogram
MS	=	mass spectrum
NMM	=	N-methylmorpholine
NT	=	not tested
Ph	=	phenyl
PPT	=	precipitate
Pyr.	=	pyridine
RP-HPLC	=	preparative reversed-phase high pressure liquid chromatography
RT	=	room temperature
Sch	=	Scheme
TEA	=	triethylamine
THF	=	tetrahydrofuran
TFA	=	trifluoroacetic acid
TMS	=	trimethylsilane
Z	=	benzyloxycarbonyl

General Synthetic Methods

Although the following Schemes depict synthetic routes to specific compounds of Formula (I), they are intended to also represent general synthetic routes to other compounds of the present invention to those skilled in the art of synthetic organic chemistry. By way of example, the synthetic route

shown in Scheme AA used to prepare Compound **1** is also illustrative of a general method for the preparation of other instant compounds whereby other starting materials and appropriate reagents and solvents are used. Most of the reaction unless otherwise indicated were performed at room temperature.

5

SCHEME AA

Compounds of the invention wherein A is (4,5-dihydro-*1H*-imidazol-2-yl)amino and its homologs may be prepared as shown below. The β–Aminoacid derivative **AA5** was prepared as detailed in PCT International
10 Application WO 97/41102 and as published (J. Rico, *J. Org. Chem.* **1993**, *58*, 7948). Such β-aminoacid derivatives can also be prepared by the methods described in WO 97/08145 and in U.S. Patent 6,100,423. The reagent **AA3** was purchased from Maybridge Chemical Company.

15 For the preparation of compounds exemplified by final target Compound **1**, secondary amine **AA1** was coupled with 4-*N*-Boc-aminobutyric acid in the presence, and the Boc group subsequently removed with trifluoroacetic acid to give primary amine **AA2** as the TFA salt. This salt was acylated with reagent **AA3**, the 2-aminoimidazoline product was protected with di-*tert*-butyl
20 dicarbonate, and the methyl ester was saponified with lithium hydroxide to afford **AA4**. Intermediate **AA4** was coupled with amino ester **AA5** in the presence of HBTU, and the product was then de-protected with aqueous hydrochloric acid to give the target Compound **1**. Similarly, the Boc group of coupling product from **AA4** and **AA5** can be removed with a mixture of
25 trifluoroacetic acid in dichloromethane (1:1) and the ester moiety subsequently saponified with aqueous LiOH in tetrahydrofuran to afford the lithium salt of Compound **1**. If the ester derivative is desired, then the saponification step is eliminated.

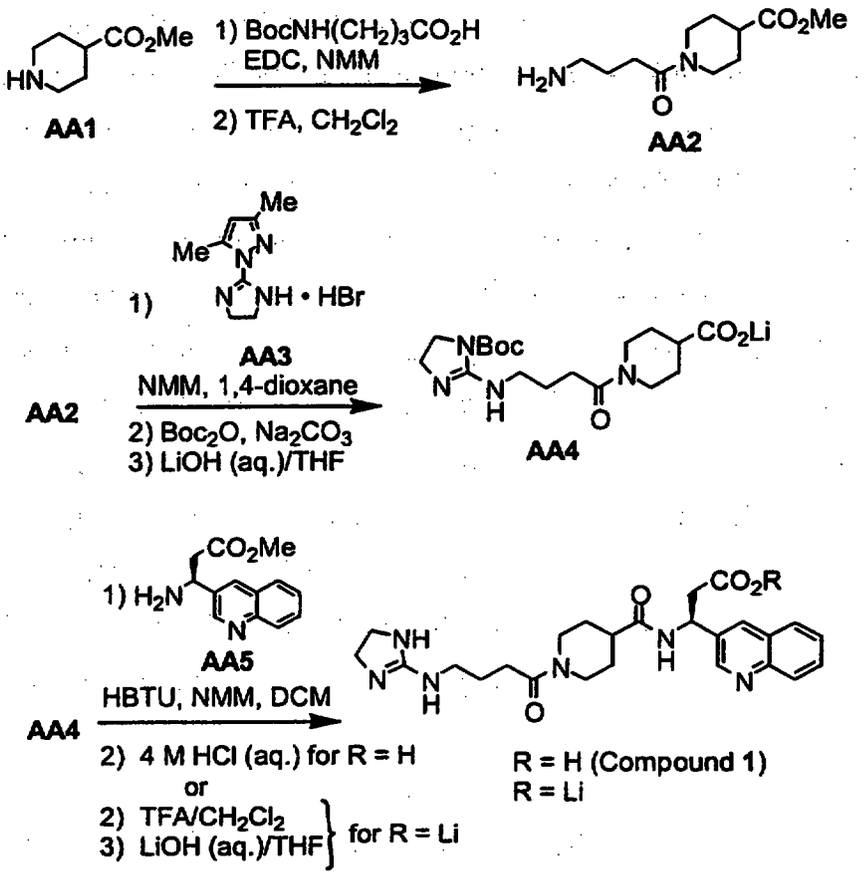
30 For the preparation of α-diaminoalkanoic acid derivative compounds of Formula (I), such as those exemplified by the Compound **11**, the secondary amine **AA1** was reacted with (N-*t*-butyloxycarbonyl)isonipecotic acid (purchased from BaChem) instead of 4-*N*-Boc-aminobutyric acid and the

product was carried forward to replace **AA2** in Scheme AA, wherein **AB2** was used to replace **AA5** to produce the target Compound **11**.

Similarly, for the preparation of compounds of Formula (I), such as those exemplified by Compound **16**, the secondary amine **AA1** was reacted with commercially available *N*-Boc-(3-amino-2-methyl)proprionic acid instead of 4-*N*-Boc-aminobutyric acid and carried forward to replace **AA2** in Scheme AA, wherein **AB2** was used to replace **AA5** to produce the target Compound **16**.

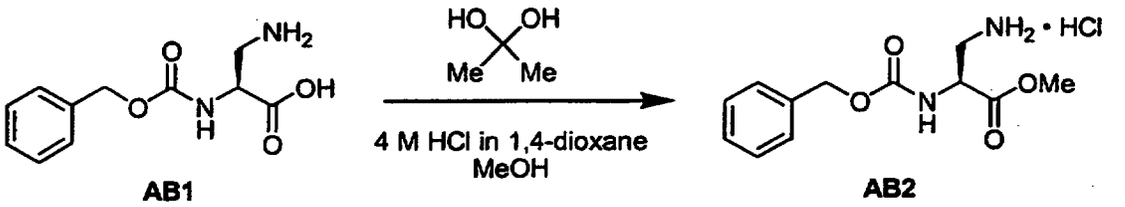
For the preparation of compounds of Formula (I) exemplified by Compound **53**, the secondary amine **AA1** was reacted with the commercially available *N*-Boc-(4-aminomethyl)benzoic acid instead of 4-*N*-Boc-aminobutyric acid and carried forward to replace **AA2** in Scheme AA to produce the target Compound **53**.

For the preparation of compounds of Formula (I), such as those exemplified by Compound **14** and Compound **17**, the secondary amine **AA1** was reacted with commercially available (-)-(*1R,4S*)-*N*-Boc-1-aminocyclopent-2-ene-4-carboxylic acid (for Compound **14**) or (+)-(*1S,4R*)-*N*-Boc-1-aminocyclopent-2-ene-4-carboxylic acid (for Compound **17**) instead of 4-*N*-Boc-aminobutyric acid. The resulting product replaced **AA2** in Scheme AA and was carried forward, with **AB2** replacing **AA5**, to produce Compound **14** and Compound **17**, respectively.



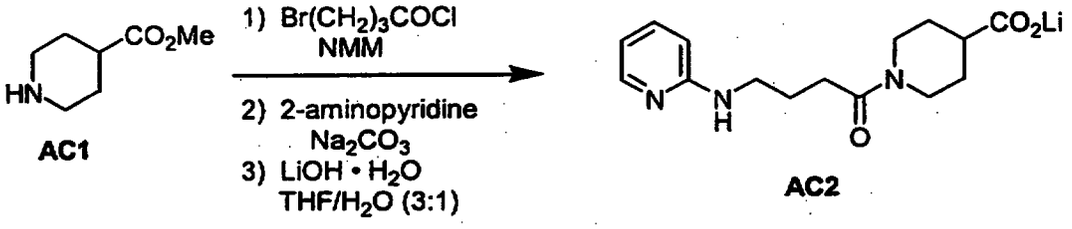
SCHEME AB

The α-diaminoalkanoic acid derivatives of Formula (I), such as Compound **2**, can be prepared from ester intermediates, such as the free base of **AB2** (methyl *N*-α-(benzyloxycarbonyl)-L-2,3-diaminopropionate), to replace **AA5** in Scheme AA. In this example, Cbz-protected acid **AB1** (purchased from BaChem) was dissolved in methanol and treated with 4N HCl in 1,4-dioxane in the presence of 1,2-dimethoxypropane to afford the intermediate amino ester **AB2**. Using the method described in Scheme AA, the free base of **AB2** was used to replace **AA5** to produce Compound **2**.



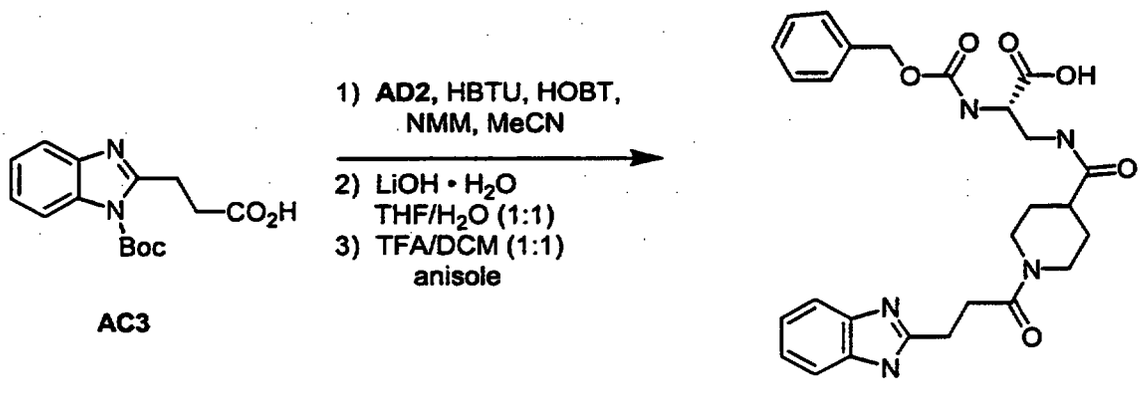
SCHEME AC

Compounds of Formula (I) wherein A is heteroaryl, heterocyclyl, (heteroaryl)amino or (heterocyclyl)amino, such as Compound **6**, can be prepared by reacting the heteroaryl, heterocyclyl, (heteroaryl)amino or (heterocyclyl)amino starting material with the appropriate alkyl halide. For example, Compound **AC1** was acylated with 4-bromobutyryl chloride. The resulting alkyl bromide product was reacted with (pyridin-2-yl)amino at reflux to provide **AC2**. The ester **AC2** was saponified with lithium hydroxide and carried forward to replace **AA4** in Scheme AA to give Compound **6**. Other compounds of Formula (I), such as Compounds **30**, **41** and **62**, can be prepared using Scheme AC by varying the starting material used.



AC1 **AC2**

Another method used to prepare heterocyclyl compounds, such as benzimidazol-2-yl, was the N-acylation of starting materials using methodology analogous to that shown in Scheme AA. For example, the N-acylation of **AC3** with **AD2** followed by saponification and deprotection by removal of the Boc group afforded Compounds **8**, **13** and **15**.



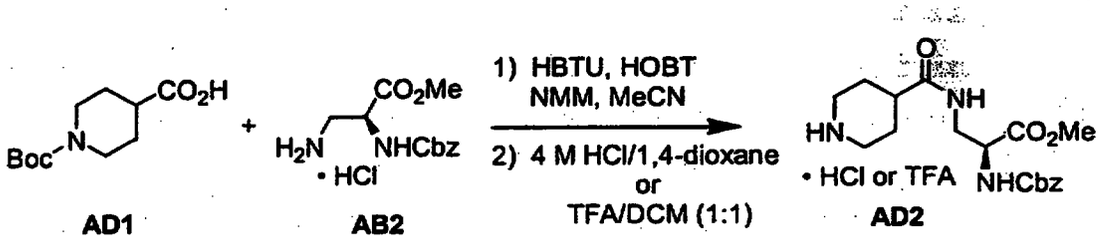
AC3 Compound **8**

Certain other (heterocyclyl)amino compounds may be prepared by reacting a 2-fluoroheterocyclyl compound with the appropriate aminoalkanoate

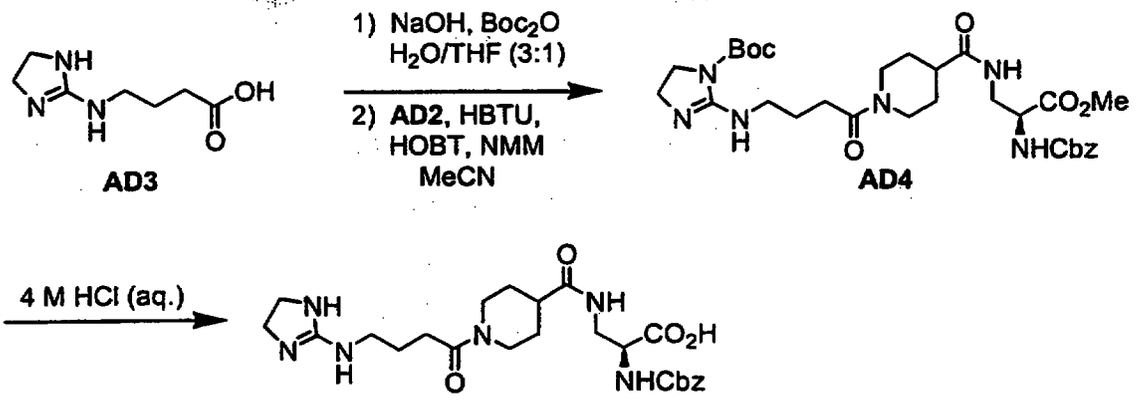
(e.g., **AA2**) as reported by C. Senanayake in *Tetrahedron Lett.* **1999**, *40*, 6875. For compounds where A is (tetrahydro-pyrimidin-2-yl)amino or (pyrimidin-2-yl)amino, 2-bromopyrimidine may be reacted with the appropriate aminoalkanoate (e.g., **AA2**) as reported by G. Hartman in WO 95/32710. For compounds where A is 1*H*-imidazo[4,5*b*]pyridin-2-yl, an appropriate alkyl dicarboxylic acid (e.g., succinic acid) may be reacted with 2,3-diaminopyridine as reported by R. Keenan in *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3171.

SCHEME AD

Scheme AD provides an alternate method of synthesis for the α-diaminoalkanoic acid derivatives of Formula (I), such as Compound **2**, by changing the order of the coupling steps depicted in Scheme AA. For example, the isonipecotamide intermediate **AD2** used to further synthesize other α-diaminoalkanoic acid derivative compounds of the invention was prepared by the HBTU-mediated coupling of **AD1** (purchased from Advanced Chemtech) and **AB2**.

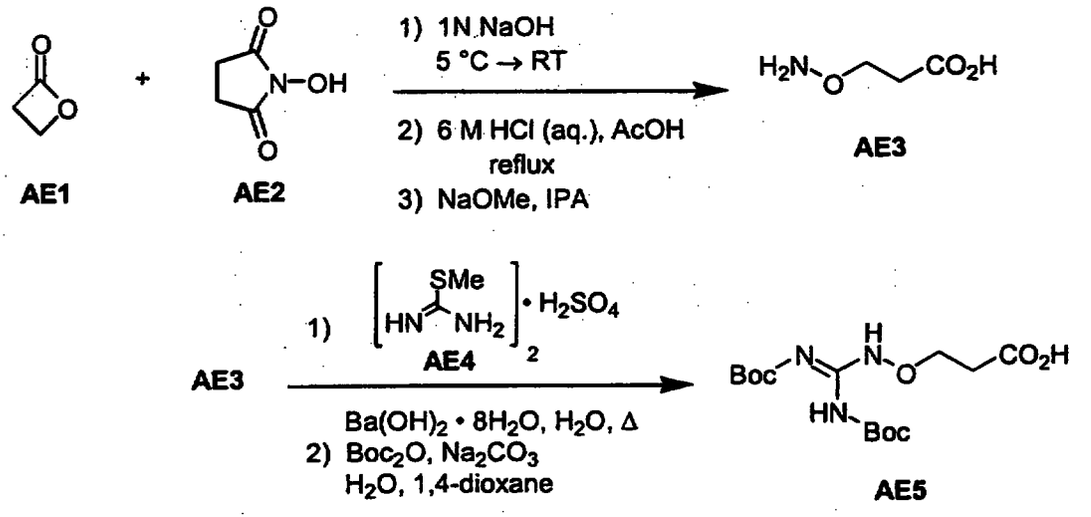


The acid **AD3** was prepared (as described by J. V. Greenhill, *Chem. Soc., Perkin Trans. 2* **1985**, (*8*), 1255-1264) and was reacted with di-*tert*-butyl dicarbonate in the presence of NaOH. The intermediate sodium salt was coupled with **AD2** using HBTU to afford **AD4**. Deprotection of **AD4** with 4 M HCl (aq.) yielded Compound **2**.

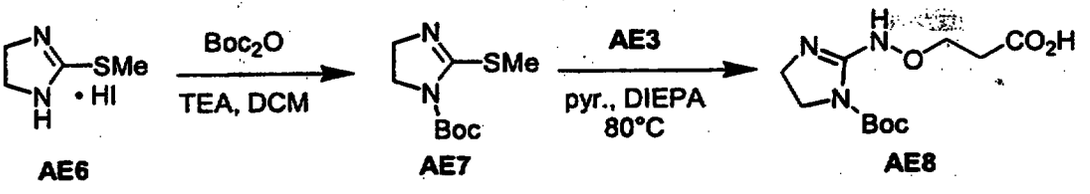


SCHEME AE

Compounds of Formula (I) wherein A includes an aminooxy moiety can be prepared by the methods represented below. Boc-protected aminooxy intermediate **AE5** (used to prepare Compound **58**) and aminooxy intermediate **AE8** (used to prepare Compounds **60** and **61**) were synthesized according to the methods described by C. Gilon, et. al. in *Tetrahedron* **1967**, *23*, 441-4447 and B. J. Ludwig in *J. Med. Chem.* **1970**, *13*, 60-63. Commercially available β-propriolactone **AE1** and N-hydroxysuccinimide **AE2** were reacted to afford the corresponding oxyamino ester, which was hydrolyzed in a refluxing mixture of 6 M HCl (aq.) and glacial acetic acid. The resulting HCl salt was converted to the free base **AE3** by treatment with NaOMe in 2-propanol. Guanylation of **AE3** with commercially available **AE4** followed by reaction with di-*tert*-butyl dicarbonate furnished the protected oxyguanidine intermediate **AE5**. To produce the target Compound **53**, the secondary amine **AA1** in Scheme AA was reacted with the protected oxyguanidine intermediate **AE5** instead of 4-*N*-Boc-aminobutyric acid and carried forward as **AA2**.

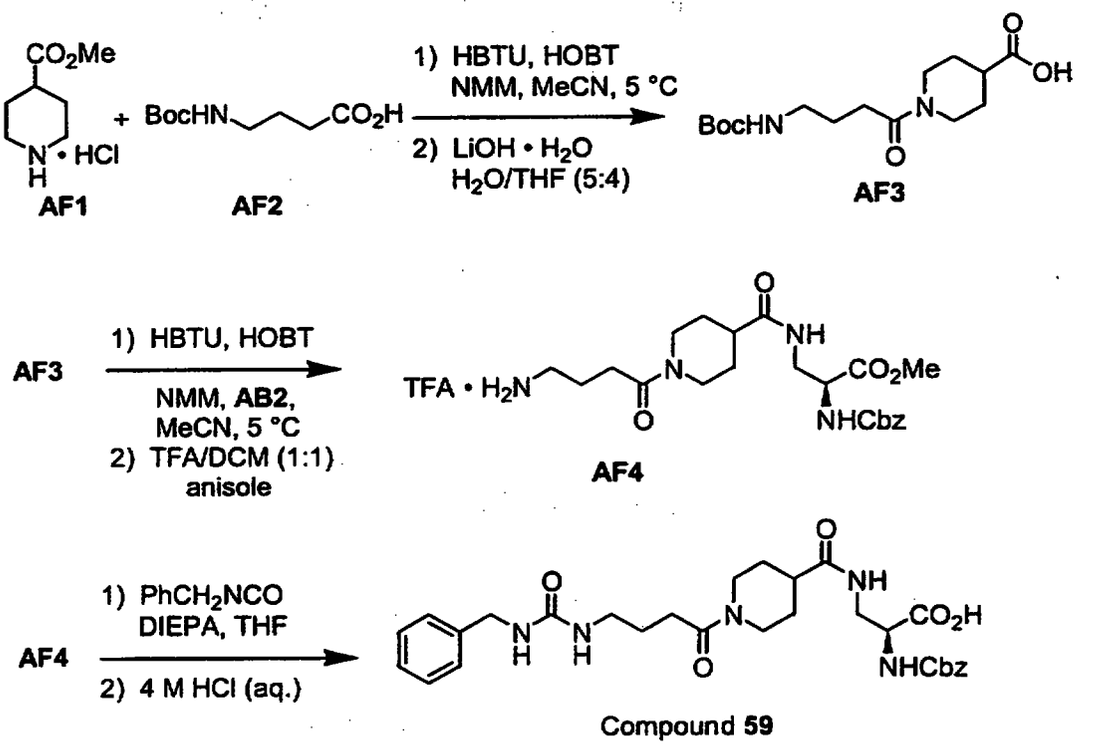


Similarly, Boc-protection of **AE6** (purchased from Aldrich) produced **AE7**, followed by reaction of **AE7** with **AE3** to afford the protected (4,5-dihydro-1*H*-imidazol-2-yl)aminooxy intermediate **AE8**. To produce the target Compounds **60** and **61**, the secondary amine **AA1** in Scheme AA was reacted with the protected (4,5-dihydro-1*H*-imidazol-2-yl)aminooxy intermediate **AE8** instead of 4-*N*-Boc-aminobutyric acid and carried forward as **AA2**.



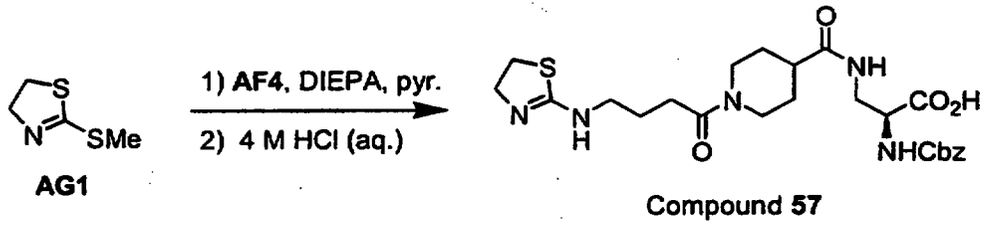
SCHEME AF

Compounds of Formula (I) wherein A includes a urea moiety, such as Compound **59**, may be prepared as depicted below. HBTU-mediated coupling of commercially available starting materials **AF1** and **AF2** and subsequent saponification of the intermediate ester furnished **AF3**, which was coupled with **AB2** to give **AF4**. Deprotection of **AF4** with TFA/DCM followed by reaction with phenyl isocyanate and hydrolysis of the resulting ester with 4 M HCl (aq.) yielded Compound **59**.

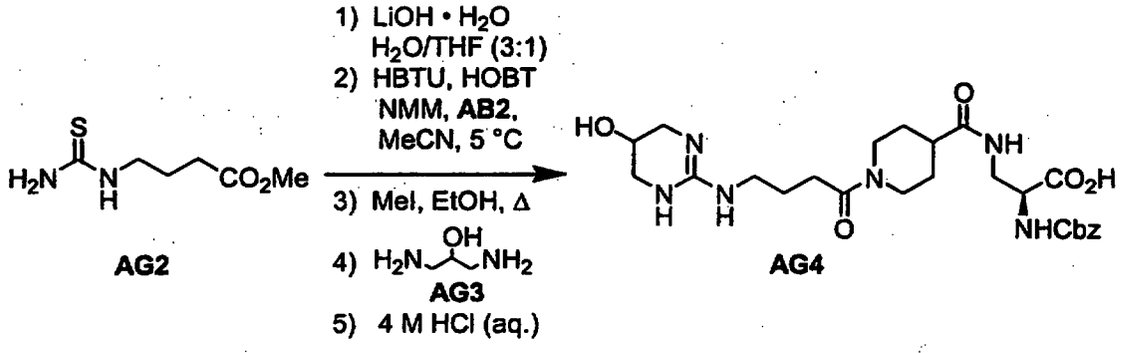


SCHEME AG

Compounds of the Formula (I) wherein A is (heterocyclyl)amino, may be prepared by reacting certain activated methylthio derivatives with the appropriate amine. For example, Compound **57** can be prepared by reacting **AG1** (purchased from Aldrich) with amine **AF4** followed by acid hydrolysis of the resulting ester.

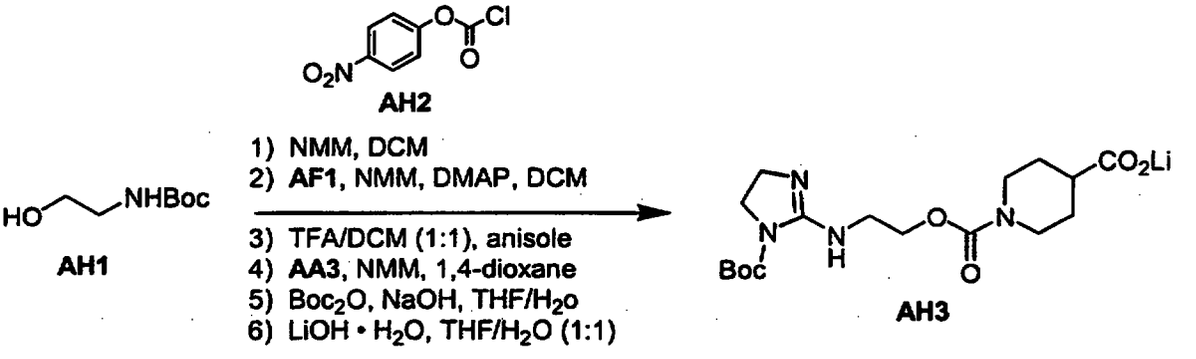


Similarly, thiourea **AG2**, prepared as described in WO/0034255, is activated with methyl iodide followed by reaction with **AG3** as described in WO/9708145 to provide **AG4**.

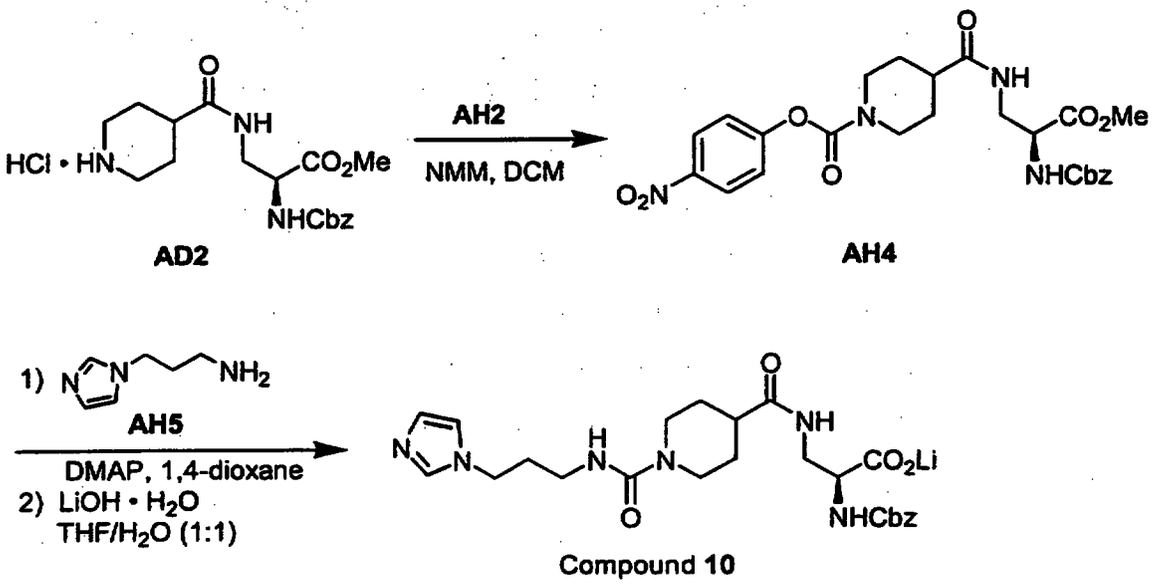


SCHEME AH

Compounds of Formula (I) wherein L is -OC(=O)- or -HNC(=O)- can be prepared as outlined below. The protected aminoalcohol **AH1** can be converted to a corresponding *p*-nitrophenylcarbonate intermediate by reaction with **AH2**. Reaction of the *p*-nitrophenylcarbonate intermediate product with **AF1**, followed by removal of the Boc group furnished an amine intermediate. The amine intermediate was subsequently reacted with reagent **AA3** to give a corresponding (imidazolin-2-yl)amino intermediate. Boc protection of the (imidazolin-2-yl)amino intermediate followed by saponfication yielded **AH3**, which was used to replace intermediate **AA4** in Scheme AA to produce Compounds **28**, **29**, **31**, **35**, **39** and **40**.

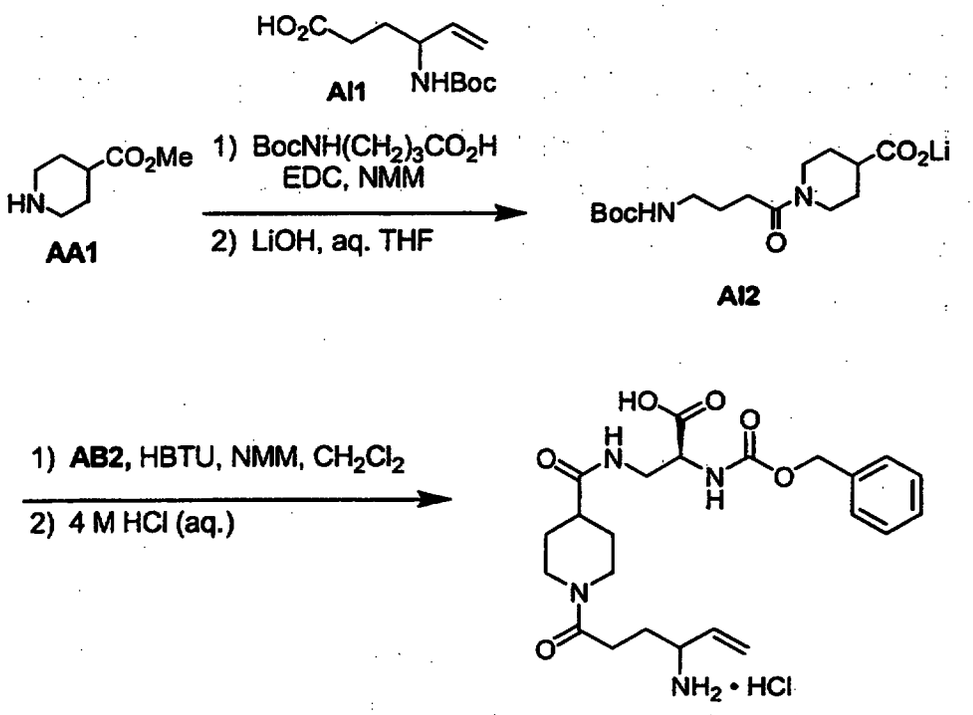


Similarly, **AD2** was converted to **AH4** by reaction with **AH2** to produce **AH4**. Reaction of **AH4** with **AH5** and saponification provided Compound **10**.



SCHEME AI

Compounds of the Formula (I) wherein A is amino or R_3H_2N- can be prepared by coupling **AA1** with the appropriate Boc-protected amino acid, such as **AI1**, followed by saponification to give **AI2** as an intermediate. The intermediate **AI2** was coupled with **AB2**, then treated with aqueous HCl to yield Compound **50**. Similarly, Compound **56** was prepared by substituting 4-*N*-Boc-aminobutyric acid for **AI1**.



Compound **50**

Specific Synthetic Methods

The following Examples are set forth to aid in the understanding of the invention, and are not intended and should not be construed to limit in any way the invention set forth in the claims which follow thereafter.

Protected amino acids were purchased from Bachem Bioscience Inc. *N*-α-Cbz-L-2,3-diaminopropionic acid was purchased from Fluka. Aromatic aldehydes were purchased from Aldrich Chemical Company, as were all other chemicals. High field ^{1}H NMR spectra were recorded on a Bruker AC-360 spectrometer at 360 MHz, and coupling constants are given in Hertz. Melting points were determined on a Mel-Temp II melting point apparatus and are uncorrected. Microanalyses were performed at Robertson Microlit Laboratories, Inc., Madison, New Jersey and are expressed in percentage by weight of each element per total molecular weight. In those cases where the product is obtained as a salt, the free base is obtained by methods known to those skilled in the art, *e.g.* by basic ion exchange purification. Nuclear magnetic resonance (NMR) spectra for hydrogen atoms were measured in the

indicated solvent with tetramethylsilane (TMS) as the internal standard on a Bruker AM-360 (360 MHz) spectrometer. The values are expressed in parts per million down field from TMS. The mass spectra (MS) were determined on a Micromass Platform LC single quadrupole mass analyser fitted with an electrospray ionisation source coupled to a Hewlett Packard 1050 HPLC and a Jones Chromatography diverter valve in the loop injection mode. Positive mode electrospray was used eluting with acetonitrile/water/acetic acid (50:50:1) flowing at 0.3 mL/min with a sprayer temperature of 120 °C and an inlet desolvation cone set to 40 kV.

Unless otherwise noted, the materials used in the examples were obtained from readily available commercial suppliers or synthesized by standard methods known to anyone skilled in the art of chemical synthesis. The substituent groups, which vary between examples, are hydrogen unless otherwise noted.

EXAMPLE 1

β-[[[1-[4-[(4,5-dihydro-1*H*-imidazol-2-yl)amino]-1-oxobutyl]-4-piperidinyl]carbonyl]amino]-, (β^3S)-3-quinolinepropanoic acid (Cpd **1**)

A mixture of **AA1** (2.0 g, HCl salt, 0.011 mol), CH_2Cl_2 (100 mL), 4-*N*-Boc-aminobutyric acid (2.3 g, 1 eq), NMM (2.4 mL, 2 eq), HOBT (10 mg), and EDC•HCl (3.2 g, 1.5 eq) was stirred at 5 °C for 1 h, the ice bath was removed, and stirred for 2 h. The reaction was diluted with saturated aqueous NH_4Cl (50 mL) and the layers were separated. The organic layer was washed with NaOH (0.5 N, 15 mL), dried (Na_2SO_4), and evaporated to give a glass (3.6 g, 0.011 mol). This glass was dissolved in CH_2Cl_2 (15 mL) and anisole (1 mL), treated with TFA (15 mL), and stirred for 2 h. The solution was evaporated to give an oil (**AA2**, 3.8 g). **AA2** was dissolved in dioxane (40 mL), treated with NMM (2.4 mL, 2 eq) and 2-(3,5-dimethylpyrazolyl)-4,5-dihydroimidazole•HBr **AA3** (2.7 g, 1 eq) and heated at reflux for 2 h. This mixture was cooled to RT and filtered. The filtrate was treated with MeOH (80 mL), NMM (2.4 mL, 2 eq), di-*tert*-butyl dicarbonate (4.8 g, 2 eq), and sodium carbonate (2.4 g, 2 eq), and stirred for 3

days. The solvents were evaporated, and the residue was partitioned between CH_2Cl_2 (100 mL) and water (10 mL). The organic layer was dried (Na_2SO_4), evaporated, and the oil purified by silica gel chromatography (1% NH_4OH/10% MeOH/CH_2Cl_2) to give a tan glass (1.8 g). The tan glass (0.09 g, 0.0023 mol) was dissolved in THF (5 mL), cooled to 5°C, treated with aqueous LiOH (0.11 g in 15 mL water), and stirred for 2 h. The solvents were evaporated to give **AA4** as a pale yellow solid (1.0 g). This solid was slurried with MeCN (100 mL), **AA5** (0.82 g, 1 eq, prepared starting from quinoline-3-carboxaldehyde as reported in M. Costanzo, et. al., WO 97/41102), HOBT (0.19 g, 0.5 eq), NMM (0.87 mL, 3 eq), and HBTU (1.2 g, 1.2 eq) at 5 °C, stirred for 6 h, diluted with saturated aqueous NH_4Cl (12 mL), and the MeCN evaporated. The residue was partitioned between $CHCl_3$ (100 mL) and water (15 mL) and filtered. The filtrate layers were separated, and the organic layer was dried (Na_2SO_4), evaporated, and purified by silica gel chromatography (1% NH_4OH/4% MeOH/7% EtOH/CH_2Cl_2) to give a clear glass (0.60 g). The glass was treated with water (12 mL) and HCl (conc., 10 mL), and stirred for 18 h. The aqueous HCl was evaporated, the resultant oil treated with MeCN (20 mL), and the precipitate collected and dried to afford Compound **1** as a white foam: ^{1}H NMR (DMSO-d_6) δ 1.3 (m, 2 H), 1.6 (m, 4 H), 2.3 (m, 2 H), 2.6 (m, 1 H), 2.8 (m, 1 H), 3.1 (m, 6 H), 3.4 (m, 1 H), 3.7 (m, 3 H), 3.8 (m, 1 H), 4.0 (m, 2 H), 4.2 (m, 1 H), 5.3 (m, 1 H), 7.7 (t, J = 4 Hz, 1 H), 7.9 (t, J = 4 Hz, 1 H), 8.2 (m, 2 H), 8.3 (m, 1 H), 8.6 (m, 2 H), 9.2 (s, 1 H), 10.9 (m, 1 H); MS m/e 481.4 (MH^+); $[\alpha]^{25}_D$ –42.1° (c 0.114, MeOH).

EXAMPLE 2

3-[[[1-[4-[(4,5-dihydro-1*H*-imidazol-2-yl)amino]-1-oxobutyl]-4-piperidinyl]carbonyl]amino]-*N*-[(phenylmethoxy)carbonyl]- L-alanine (Cpd **2**)

Compound **2** was prepared as described for Compound **1** in Scheme AA using **AA4** (0.10 g) and methyl *N*-α-Cbz-L-2,3-diaminopropionate•HCl **AB2** to replace **AA5** (0.09 g), and isolated as a tan glass: ^{1}H NMR (DMSO-d_6) δ 1.3 (m, 1 H), 1.4 (m, 1 H), 1.7 (m, 4 H), 2.4 (m, 3 H), 2.6 (m, 2 H), 2.8 (t, J = 4 Hz, 1 H), 3.0 (m, 1 H), 3.1 (m, 1 H), 3.3 (m, 2 H), 3.4 (m, 1 H), 3.8 (m, 2 H), 4.1 (t, J

= 4 Hz, 1 H), 4.3 (m, 1 H), 5.0 (t, J = 7 Hz, 2 H), 7.3 (m, 5 H), 7.6 (m, 3 H), 8.0 (m, 3 H), 8.2 (m, 1 H); MS m/e 503.4 (MH^+).

EXAMPLE 3

6-chloro-β-[[[1-[4-[(4,5-dihydro-1*H*-imidazol-2-yl)amino]-1-oxobutyl]-4-piperidinyl]carbonyl]amino]-, (β^3*S*)-3-pyridinepropanoic acid (Cpd **3**)

Compound **3** was prepared as described for Compound **1** in Scheme AA using **AA4** (0.15 g) and methyl (3*S*)-amino-3-(6-chloro-3-pyridyl)propionate•2HCl (0.11 g; prepared starting from 6-chloropyridine-3-carboxaldehyde as reported by M. Costanzo, et al. in WO 97/41102) for **AA5**, and isolated as a clear glass: ^{1}H NMR (DMSO-d_6) δ 1.2 (m, 4 H), 1.5 (m, 2 H), 2.2 (m, 3 H), 2.5 (m, 2 H), 2.7 (m, 2 H), 2.8 (m, 1 H), 3.1 (m, 1 H), 3.5 (m, 3 H), 3.8 (m, 1 H), 4.1 (m, 3 H), 4.3 (m, 1 H), 5.1 (m, 1 H), 7.4 (d, J = 5 Hz, 1 H), 7.7 (d, J = 5 Hz, 1 H), 8.1 (m, 3 H), 8.3 (s, 1 H), 8.5 (m, 1 H); MS m/e 464.9 (MH^+).

EXAMPLE 4

3-[[[1-[4-[(4,5-dihydro-1*H*-imidazol-2-yl)amino]-1-oxobutyl]-4-piperidinyl]carbonyl]amino]-, (3*R*)- butanoic acid (Cpd **4**)

Compound **4** was prepared as described for Compound **1** in Scheme AA using **AA4** (0.90 g) and *tert*-butyl (3*R*)-aminobutyrate (0.37 g, purchased from Oxford Asymmetry) for **AA5**, and isolated as a clear glass: ^{1}H NMR (DMSO-d_6) δ 1.0 (d, J = 5 Hz, 3 H), 1.3 (m, 2 H), 1.7 (m, 4 H), 2.3 (m, 6 H), 2.6 (m, 1 H), 3.0 (m, 1 H), 3.2 (m, 2 H), 3.6 (s, 4 H), 3.8 (m, 1 H), 4.0 (m, 1 H), 4.4 (m, 1 H), 7.8 (d, J = 7 Hz, 2 H), 8.2 (m, 2 H); MS m/e 368.4 (MH^+).

EXAMPLE 5

β-[[[1-[3-[(4,5-dihydro-1*H*-imidazol-2-yl)amino]-2-methyl-1-oxopropyl]-4-piperidinyl]carbonyl]amino]-, (β^3*S*)-3-quinolinepropanoic acid (Cpd **5**)

Compound **5** was prepared as described for Compound **1** in Scheme AA using *N*-Boc-imidazolin-2-yl-(3-aminoisobutyryl)-isonipecotic acid (0.10 g) for

AA4 and **AA5** (0.12 g), and isolated as glass: ^{1}H NMR (DMSO-d_6) δ 1.1 (d, J = 6 Hz, 3 H), 1.3 (m, 1 H), 1.4 (m, 1 H), 1.7 (m, 4 H), 2.3 (m, 2 H), 2.6 (m, 2 H), 2.8 (m, 1 H), 3.0 (m, 2 H), 3.1 (m, 1 H), 3.3 (m, 2 H), 3.4 (m, 1 H), 3.8 (m, 1 H), 4.1 (m, 1 H), 4.3 (m, 1 H), 5.0 (t, J = 7 Hz, 2 H), 7.3 (m, 5 H), 7.6 (m, 2 H), 8.0 (m, 3 H); MS m/e 503.4 (MH^+).

EXAMPLE 6

β-[[[1-[1-oxo-4-(2-pyridinylamino)butyl]-4-piperidinyl]carbonyl]amino]-, (β^3S)- 3-quinolinepropanoic acid (Cpd **6**)

A mixture of **AC1** (2.0 g, 0.011 mol), CH_2Cl_2 (70 mL), and NMM (2.4 mL, 2 eq) at 5 °C was treated with 4-bromobutyryl chloride (1.3 mL, 1 eq), stirred for 6 h, and diluted with saturated aqueous NH_4Cl (15 mL). The organic layer was dried (Na_2SO_4), evaporated, and the resultant oil purified by silica gel chromatography (4% MeOH/ CH_2Cl_2) to give an oil (1.8 g). The oil was dissolved in MeOH (10 mL) and isopropanol (15 mL) and then treated with 2-aminopyridine (0.70 g, 1.2 eq) and sodium carbonate (2 mg). This mixture was heated at reflux in a sealed flask for 2 h, cooled to RT, and evaporated to an oil. The oil was purified by silica gel chromatography (2% MeOH/3% EtOH/CH_2Cl_2) to give **AC2** as a glass (0.3 g) intermediate. The intermediate **AC2** was then saponified with lithium hydroxide and carried forward to replace **AA4** as exemplified in Scheme AA to produce Compound **6** as clear flakes: ^{1}H NMR (DMSO-d6) δ 1.0-1.2 (m, 2 H), 1.7 (m, 4 H), 2.2 (m, 2 H), 3.0 (m, 3 H), 3.3 (m, 3 H), 3.5 (t, J = 4 Hz, 1 H), 3.9 (m, 2 H), 5.5 (t, J = 4 Hz, 1 H), 6.9 (m, 1 H), 7.1 (m, 1 H), 7.9 (m, 4 H), 8.0 (t, J = 4 Hz, 1), 8.2 (m, 2 H), 8.8 (m, 3 H), 9.2 (s, 1 H), 10.9 (m, 1 H), 13.5 (m, 1 H); mp 87-90°C; MS m/e 490 (MH+).

EXAMPLES 7-62

Using the procedures described in Examples 1-6 or outlined in Schemes AA-AH and the appropriate reagents and starting materials known to those skilled in the art, other compounds of the present invention may be prepared including, but not limited to:

Cpd	Sch	Salt	MH^+
7	AC	TFA	500
8	AC	TFA	522
9	AA	Li	439
10	AH	Li	501
11	AA	TFA	529
12	AA	TFA	489
13	AC	Li	507
14	AA	TFA	527
15	AC	TFA	499
16	AA	TFA	503
17	AA	TFA	527
18	AA	TFA	614
19	AA	TFA	534
20	AA	HCl	436
21	AA	HCl	474
22	AA	HCl	444
23	AA	HCl	472
24	AA	HCl	490
25	AA	HCl	431
26	AA	HCl	499

Cpd	Sch	Salt	MH^+
27	AA	HCl	498
28	AH	HCl	505
29	AH	HCl	476
30	AC	HCl	440
31	AH	HCl	433
32	AA	HCl	448
33	AA	HCl	431
34	AA	HCl	490
35	AH	HCl	468
36	AA	HCl	480
37	AA	HCl	480
38	AA	HCl	466
39	AH	HCl	483
40	AH	HCl	433
41	AC	HCl	526
42	AA	HCl	517
43	AA	HCl	466
44	AA	HCl	495
45	AA	---	694
46	AA	HCl	594

Cpd	Sch	Salt	MH^+
47	AA	TFA	517
48	AA	TFA	458
49	AA	TFA	529
50	AA	TFA	461
51	AA	HCl	517
52	AA	HCl	431
53	AA	TFA	551
54	AA	TFA	517
55	AA	HCl	501
56	AA	HCl	435
57	AG	HCl	520
58	AE	HCl	479
59	AF	HCl	568
60	AE	HCl	505
61	AE	HCl	476
62	AC	HCl	483

EXAMPLE 63

As a specific embodiment of an oral composition, 100 mg of the Compound 1 of Example 1 is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size O hard gel capsule.

EXAMPLE 64

IN VITRO SOLID PHASE PURIFIED αvβ3 BINDING ASSAY

The vitronectin/αvβ3 binding assay methods were derived from Mehta et al. (*Biochem J.* **1998**, *330*, 861). Human αvβ3 (Chemicon International Inc., Temecula, CA), at a concentration of 1 μg/ml dissolved in Tris buffer (20 mM Tris, 1 mM $CaCl_2$, 1 mM $MgCl_2$, 10 μM $MnCl_2$, 150 mM NaCl), was immobilized

on Immulon 96 well plates (Dynex Technologies, Chantilly, VA) overnight at 4 °C. Plates were washed and treated with blocking buffer (3 % BSA in Tris buffer) for 2 h at 37 °C. Plates were then rinsed 2 times with Tris buffer containing 0.3% BSA and 0.2% Tween20 (polyoxyethylenesorbitan monolaurate). Five minutes prior to the addition of 5 nM vitronectin (Sigma, St. Louis, MO), synthesized compounds were added to wells in duplicate. Each plate included *c*-RGDfV as an internal control. Following a 3 hour incubation at 37 °C, plates were washed 5 times in assay buffer. An anti-human vitronectin IgG rabbit polyclonal antibody (Calbiochem, San Diego, CA) was added (1:2000) and plates were incubated for 1 hour at room temperature. VectaStain ABC peroxidase kit reagents (Vector Laboratories, Burlingame, CA) employing a biotin labeled anti-rabbit IgG, were utilized for detection of bound antibody. Plates were read at 490 nm on a Molecular Devices (Sunnyvale, CA) microplate reader. Table 1 shows the results of the in vitro solid phase purified $\alpha v\beta 3$ binding assay for representative compounds of the present invention.

EXAMPLE 65

IN VITRO SOLID PHASE PURIFIED GP IIB/IIIA BINDING ASSAY

A 96 well Immulon-2 microtiter plate (Dynatech-Immulon) was coated with 50 µl/well of RGD-affinity purified GPIIb/IIIa (effective range 0.5-10 µg/mL) in 10 mM HEPES, 150 mM NaCl, 1 mM $MgCl_2$ at pH 7.4. The plate was covered and incubated overnight at 4 °C. The GPIIb/IIa solution was discarded and 150 µl of 5% BSA was added and incubated at RT for 1-3 h. The plate was washed extensively with modified Tyrodes buffer. Biotinylated fibrinogen (25 µl/well) at 2 x final concentration was added to the wells that contain the test compounds (25 µl/well). The plate was covered and incubated at RT for 2-4 h. Twenty minutes prior to incubation completion, one drop of Reagent A (VectaStain ABC Horse Radish Peroxidase kit, Vector Laboratories, Inc.) and one drop Reagent B were added with mixing to 5 mL modified Tyrodes buffer mix and let stand. The ligand solution was discarded and the plate washed (5 x 200 µl/well) with modified Tyrodes buffer. Vecta Stain HRP-Biotin-Avidin reagent (50 µl/well, as prepared above) was added and incubated at RT for 15

min. The Vecta Stain solution was discarded and the wells washed (5 x 200 µl/well) with modified Tyrodes buffer. Developing buffer (10 mL of 50 mM citrate/phosphate buffer @ pH 5.3, 6 mg o-phenylenediamine, 6 µl 30% H_2O_2; 50 µl/well) was added and incubated at RT for 3-5 min, and then 2 N H_2SO_4 (50 µl/well) was added. The absorbance was read at 490 nM. Table 1 shows the results of the in vitro solid phase purified GPIIb/IIIa binding assay for representative compounds of the present invention.

EXAMPLE 66

IN VITRO SOLID PHASE PURIFIED αvβ5 BINDING ASSAY

The vitronectin/$\alpha_v\beta_5$ binding assay method was performed in the same manner as the vitronectin/$\alpha_v\beta_3$ binding assay (EXAMPLE 64) immobilizing with 1 µg/ml of human purified $\alpha_v\beta_5$ (Chemicon International, Inc.) on to Immulon 96 well plates (Dynex Technologies) instead of $\alpha_v\beta_3$. All other aspects of the assay including buffers, reagents, and incubation times remain unchanged.

TABLE I

No.	$\alpha_v\beta_3$ IC_{50} (uM)	IIb/IIIa IC_{50} (uM)	$\alpha_v\beta_5$ IC_{50} (uM)
1	0.0037	0.030	0.025
2	0.0058	0.0089	0.021
3	0.028	0.13	NT
4	0.15	1.70	NT
5	0.015	0.023	NT
6	0.0040	0.46	NT
7	0.49	7.9	NT
8	0.55	1.1	NT
9	30	0.30	NT
10	>50	0.95	NT
11	1.3	0.0026	NT
12	0.020	0.014	NT
13	10	29	NT
14	0.050	0.0092	NT
15	>5	17	NT
16	0.019	0.018	0.038
17	0.38	0.0054	NT
18	0.050	0.015	NT
19	0.32	0.071	NT
20	0.53	4.9	NT
21	0.023	0.41	NT
22	>0.5	38	NT
23	>0.5	7.3	NT
24	0.064	2.2	NT
25	0.032	2.9	NT
26	0.12	1.8	NT
27	>0.5	13	NT
28	0.0082	1.5	NT

29	0.034	0.21	NT
30	0.14	56	NT
31	0.029	4.2	NT
32	0.12	3.6	NT
33	0.019	1.8	NT
34	0.029	1.5	>5.0
35	0.14	1.6	NT
36	>0.3	12	NT
37	0.29	1.7	NT
38	>0.3	3.3	NT
39	0.0023	0.036	NT
40	0.012	1.1	NT
41	>0.3	0.11	NT
42	0.17	0.14	NT
43	0.23	1.3	NT
44	0.028	0.36	2.9
45	3.7	14	40%*
46	0.15	1.6	>5
47	0.0040	0.028	NT
48	0.51	1.1	NT
49	0.039	0.012	0.21
50	3.9	0.0074	38%*
51	0.27	0.29	2
52	0.25	2.7	0.76
53	0.57	0.0015	NT
54	0.072	0.013	NT
55	0.012	0.026	0
56	>5	0.049	NT
57	0.35	0.13	NT
58	0.040	0.26	0.071
59	0.16	0.51	NT
60	0.027	0.19	0.086

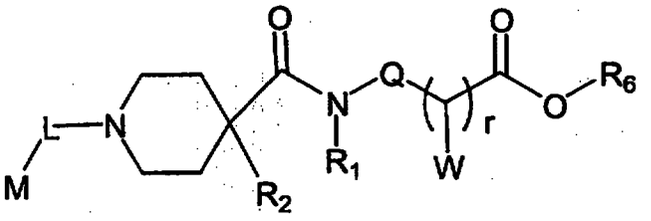
61	0.18	2.7	NT
62	>0.50	0.38	NT

*Percent inhibition at 5 μM.

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the usual variations, adaptations and/or modifications as come within the scope of the following claims and their equivalents.

WHAT IS CLAIMED IS:

1. A compound of the Formula (I):



(I)

wherein

M is selected from the group consisting of C_1-C_4 alkylene (optionally substituted within the carbon chain with one substituent selected from the group consisting of C_1-C_4 alkyl, C_2-C_4 alkenyl, cycloalkyl (wherein a ring carbon atom forms the point of attachment to the carbon chain) and aryl (optionally substituted with halogen) and substituted on the terminal carbon with one substituent selected from A), C_2-C_4 alkenylene (substituted with one substituent selected from A); heterocyclylene (optionally substituted with one substituent selected from A), heterocyclenylene (substituted with one substituent selected from A), arylene (substituted with one substituent selected from A), (C_1-C_4 alkylene)aryl (substituted on C_1-C_4 alkylene with one substituent selected from A) and arylene(C_1-C_4)alkyl (substituted on arylene with one substituent selected from A);

A is optionally present and is selected from the group consisting of heteroaryl, heterocyclyl, R_3HN-, (heteroaryl)amino, (heterocyclyl)amino, $R_3HNC(=NH)$-, $R_3HNC(=NH)NH$-, $R_3HNC(=O)NH$-, $R_3C(=NH)NH$-, (heterocyclyl)aminooxy, (heteroaryl)aminooxy, $R_3HNC(=NH)NHO$-, $R_3C(=NH)NHO$-, $R_3HNC(=NH)NHC(=O)$- and $R_3C(=NH)NHC(=O)$-; wherein heteroaryl and heterocyclyl are optionally substituted with one to five substituents independently selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, heteroaryl (optionally substituted with C_1-C_4 alkyl), halogen, hydroxy, nitro, cyano, trihalo(C_1-C_4)alkyl, C_1-C_4 alkylcarbonyl, C_1-C_4 alkoxycarbonyl, aryl(C_1-C_4)alkoxycarbonyl, R_3HN-, amino(C_1-C_4)alkyl, C_1-C_4 alkylamino(C_1-C_4)alkyl and di(C_1-C_4 alkyl)amino(C_1-C_4)alkyl;

with the proviso that if A is $H_2NC(=NH)NH$-, then, dependently, W is not hydrogen when Q is $-CH_2-$;

L is selected from the group consisting of -C(=O)-, $-SO_2-$, -OC(=O)- and -HNC(=O)-;

R_1 is selected from the group consisting of hydrogen, C_1-C_8 alkyl and cycloalkyl;

R_2 is selected from the group consisting of hydrogen and C_1-C_8 alkyl;

R_3 is selected from the group consisting of hydrogen, C_1-C_8 alkyl, aryl, aryl(C_1-C_8)alkyl, cycloalkyl, hydroxy, cyano and nitro;

Q is selected from the group consisting of $-CH_2-$, -CH(C_1-C_8alkyl)-, -CH(C_2-C_8alkenyl)-, -CH(C_2-C_8alkynyl)-, -CH(aryl)- (wherein aryl is optionally substituted with one to five substituents independently selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, -O-(C_1-C_3 alkyl)-O-, halogen, hydroxy, trihalo(C_1-C_3)alkyl and trihalo(C_1-C_3)alkoxy), -CH(heteroaryl)- (wherein heteroaryl is optionally substituted with a substituent selected from the group consisting of halogen, hydroxy, C_1-C_4 alkyl, C_1-C_4 alkoxy, -O-(C_1-C_3 alkyl)-O-, amino, C_1-C_4 alkylamino and di(C_1-C_4)alkylamino) and -CH(aryl(C_1-C_8)alkyl)-;

W is selected from the group consisting of hydrogen and $N(R_4)T$;

r is an integer selected from 0 or 1;

R_4 is selected from the group consisting of hydrogen, C_1-C_8 alkyl and C_2-C_6 acyl;

T is selected from the group consisting of $R_5C(=O)$-, $R_5OC(=O)$- and $R_5C(=N$-

CN)-;

R_5 is selected from the group consisting of C_1-C_8 alkyl, aryl, aryl(C_1-C_8)alkyl and amino (wherein amino is optionally substituted with one to two substituents independently selected from C_1-C_8 alkyl);

R_6 is selected from the group consisting of hydrogen, C_1-C_8 alkyl, aryl(C_1-C_8)alkyl, (R_7)N(C_1-C_8)alkyl, (R_8)(R_7)N(C_1-C_8)alkyl and (R_8)(R_7)NC(=O)(C_1-C_8)alkyl; and,

R_7 and R_8 are independently selected from the group consisting of hydrogen, C_1-C_8 alkyl and cycloalkyl;

and pharmaceutically acceptable salts thereof.

2. The compound of Claim 1, wherein

M is selected from the group consisting of ethylene (optionally substituted within the carbon chain with methyl and substituted on the terminal carbon with one substituent selected from A), propylene (optionally substituted within the carbon chain with a substituent selected from the group consisting of methyl, ethenyl, cyclohexylidene (wherein a ring carbon atom forms the point of attachment to the carbon chain) and 4-Cl-phenyl and substituted on the terminal carbon with one substituent selected from A), allylene (substituted with one substituent selected from A); piperidin-4-ylene (optionally substituted with one substituent selected from A), 1,4,5-dihydro-2-cyclopenten-1-yl (substituted with one substituent selected from A) and 4-methylphenylene (substituted on methylene with one substituent selected from A);

A is optionally present and is selected from the group consisting of 1*H*-imidazol-1-yl, 1*H*-imidazol-2-yl, 4,5-dihydro-1*H*-imidazol-2-yl (optionally substituted with a substituent selected from the group consisting of C_1-C_4 alkoxycarbonyl and aryl(C_1-C_4)alkoxycarbonyl), pyridin-2-yl (optionally

substituted with a substituent selected from the group consisting of C_1-C_4 alkyl, heteroaryl [optionally substituted with C_1-C_4 alkyl], halogen, hydroxy, nitro, cyano, amino, amino(C_1-C_4)alkyl, C_1-C_4 alkylamino(C_1-C_4)alkyl and di(C_1-C_4 alkyl)amino(C_1-C_4)alkyl), pyrimidin-2-yl, 1,4,5,6-tetrahydro-pyrimidin-2-yl (optionally substituted with one to two substituents independently selected from the group consisting of C_1-C_4 alkyl, hydroxy and amino), piperidin-4-yl, benzimidazol-2-yl, 1,2,3,4-tetrahydro-1,8-naphthyridin-7-yl, 3*H*-imidazo[4,5-*b*]pyridin-2-yl, amino, (C_1-C_6 alkyl)amino, (1*H*-imidazol-1-yl)amino, (1*H*-imidazol-2-yl)amino, (4,5-dihydro-1*H*-imidazol-2-yl)amino (optionally substituted on 4,5-dihydro-1*H*-imidazol-2-yl with a substituent selected from the group consisting of (C_1-C_6)alkoxycarbonyl and aryl(C_1-C_6)alkoxycarbonyl), (pyridin-2-yl)amino (optionally substituted on pyridin-2-yl with a substituent selected from the group consisting of C_1-C_4 alkyl, heteroaryl [optionally substituted with C_1-C_4 alkyl], halogen, hydroxy, nitro, cyano, amino, amino(C_1-C_4)alkyl, C_1-C_4 alkylamino(C_1-C_4)alkyl and di(C_1-C_4 alkyl)amino(C_1-C_4)alkyl), (pyrimidin-2-yl)amino, (1,4,5,6-tetrahydropyrimidin-2-yl)amino (optionally substituted on 1,4,5,6-tetrahydropyrimidin-2-yl with one to two substituents independently selected from the group consisting of C_1-C_4 alkyl, hydroxy and amino), (4,5,6,7-tetrahydro-1*H*-1,3-diazepin-2-yl)amino, (thiazol-2-yl)amino, (benzimidazol-2-yl)amino, (3*H*-imidazo[4,5-*b*]pyridin-2-yl)amino, $R_3HNC(=NH)NH$-, $R_3HNC(=O)NH$-, (4,5,6,7-tetrahydro-1*H*-1,3-diazepin-2-yl)aminooxy, (4,5-dihydro-1*H*-imidazol-2-yl)aminooxy and $R_3HNC(=NH)NHO$-;

with the proviso that if A is $H_2NC(=NH)NH$-, then, dependently, W is not hydrogen when Q is $-CH_2$-;

L is selected from the group consisting of -C(=O)-, -OC(=O)- and -HNC(=O)-;

R_1 is selected from the group consisting of hydrogen and C_1-C_4 alkyl;

R_2 is hydrogen;

R_3 is selected from the group consisting of hydrogen, C_1-C_8 alkyl, aryl(C_1-C_8)alkyl and hydroxy;

Q is selected from the group consisting of -CH_2-, -CH(C_1-C_8alkyl)-, -CH(aryl)- (wherein aryl is optionally substituted with one to five substituents independently selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, -O-(C_1-C_3 alkyl)-O-, halogen, hydroxy and trihalo(C_1-C_3)alkyl), -CH(heteroaryl)- (wherein heteroaryl is optionally substituted with a substituent selected from halogen) and -CH(aryl(C_1-C_8)alkyl)-;

r is 1;

R_4 is selected from the group consisting of hydrogen and C_1-C_4 alkyl;

T is selected from the group consisting of R_5C(=O)- and R_5OC(=O)-;

R_5 is selected from the group consisting of aryl and aryl(C_1-C_4)alkyl;

R_6 is selected from the group consisting of hydrogen, methyl and (R_8)(R_7)NC(=O)CH_2; and,

R_7 and R_8 are independently selected from the group consisting of hydrogen, methyl and ethyl;

and pharmaceutically acceptable salts thereof.

3. The compound of Claim 2, wherein

A is optionally present and is selected from the group consisting of 1*H*-imidazol-1-yl, 4,5-dihydro-1*H*-imidazol-2-yl, pyridin-2-yl (optionally substituted with a substituent selected from the group consisting of C_1-C_4 alkyl and heteroaryl [optionally substituted with C_1-C_4 alkyl]), piperidin-4-yl, benzimidazol-2-yl, 1,2,3,4-tetrahydro-1,8-naphthyridin-7-yl, 3*H*-imidazo[4,5-*b*]pyridin-2-yl, amino, (4,5-dihydro-1*H*-imidazol-2-yl)amino (optionally

substituted on 4,5-dihydro-1*H*-imidazol-2-yl with C_1-C_6 alkoxycarbonyl), (pyridin-2-yl)amino (optionally substituted on pyridinyl with a substituent selected from the group consisting of C_1-C_4 alkyl and heteroaryl (optionally substituted with C_1-C_4 alkyl)), (1,4,5,6-tetrahydro-5-hydroxypyrimidin-2-yl)amino, (1,4,5,6-tetrahydro-5-methylpyrimidin-2-yl)amino, (1,4,5,6-tetrahydro-5,5-dimethylpyrimidin-2-yl)amino, (thiazol-2-yl)amino, (3*H*-imidazo[4,5-*b*]pyridin-2-yl)amino, $R_3HNC(=NH)NH$-, $R_3HNC(=O)NH$-, (4,5-dihydro-1*H*-imidazol-2-yl)aminooxy and $R_3HNC(=NH)NHO$-;

with the proviso that if A is $H_2NC(=NH)NH$-, then, dependently, W is not hydrogen when Q is $-CH_2$-;

R_1 is hydrogen;

R_3 is selected from the group consisting of hydrogen, butyl, benzyl and hydroxy;

Q is selected from the group consisting of $-CH_2$-, -CH(methyl)-, -CH(ethyl)-, -CH(phenyl)- (wherein phenyl is optionally substituted with one to five substituents independently selected from the group consisting of methyl, ethyl, propyl, methoxy, ethoxy, propoxy, bromine, chlorine, fluorine, iodine, hydroxy and trifluoromethyl), -CH(naphthalen-1-yl)-, -CH(naphthalen-2-yl)-, -CH((3,4-dioxymethylene)phenyl)-, -CH((3,4-dioxyethylene)phenyl)-, -CH((3-bromo-5-chloro-2-hydroxy)phenyl)-, -CH(thien-3-yl)-, -CH(quinolin-3-yl)-, -CH(pyridin-3-yl)- (wherein pyridinyl is optionally substituted with chlorine) and -CH(benzyl)-;

R_4 is hydrogen;

T is selected from $R_5OC(=O)$-;

R_5 is selected from aryl(C_1-C_4)alkyl;

R_6 is hydrogen; and,

R_7 and R_8 are independently ethyl;

and pharmaceutically acceptable salts thereof.

4. The compound of Claim 3, wherein

A is optionally present and is selected from the group consisting of 4,5-dihydro-1*H*-imidazol-2-yl, 1,2,3,4-tetrahydro-1,8-naphthyridin-7-yl, 3*H*-imidazo[4,5-*b*]pyridin-2-yl, amino, (4,5-dihydro-1*H*-imidazol-2-yl)amino, (pyridin-2-yl)amino, (3-methylpyridin-2-yl)amino, (thiazol-2-yl)amino, (3*H*-imidazo[4,5-*b*]pyridin-2-yl)amino, $NH_2C(=NH)NH$-, $R_3HNC(=O)NH$-, (4,5-dihydro-1*H*-imidazol-2-yl)aminoxy and $NH_2C(=NH)NHO$-,

with the proviso that if A is $H_2NC(=NH)NH$-, then, dependently, W is not hydrogen when Q is $-CH_2$-;

Q is selected from the group consisting of $-CH_2$-, -CH(methyl)-, -CH(phenyl)- (wherein phenyl is optionally substituted with one to five substituents independently selected from the group consisting of methyl, methoxy, bromine, chlorine, fluorine, hydroxy and trifluoromethyl), -CH(naphthalen-1-yl)-, -CH(naphthalen-2-yl)-, -CH((3,4-dioxymethylene)phenyl)-, -CH((3,4-dioxyethylene)phenyl)-, -CH((3-bromo-5-chloro-2-hydroxy)phenyl)-, -CH(thien-3-yl)-, -CH(quinolin-3-yl)-, -CH(pyridin-3-yl)- (wherein pyridinyl is optionally substituted with chlorine) and -CH(benzyl)-; and,

R_5 is benzyl;

and pharmaceutically acceptable salts thereof.

5. The compound of Claim 1 selected from the group consisting of:

β-[[[1-[4-[(4,5-dihydro-1*H*-imidazol-2-yl)amino]-1-oxobutyl]-4-

piperidinyl]carbonyl]amino]-, (β^3S)- 3-quinolinepropanoic acid;

3-[[[1-[4-[(4,5-dihydro-1*H*-imidazol-2-yl)amino]-1-oxobutyl]-4-piperidinyl]carbonyl]amino]-*N*-[(phenylmethoxy)carbonyl]- L-alanine;

β-[[[1-[1-oxo-4-(2-pyridinylamino)butyl]-4-piperidinyl]carbonyl]amino]-, (β^3S)- 3-quinolinepropanoic acid;

3-[[[1-[[1-(4,5-dihydro-1*H*-imidazol-2-yl)-4-piperidinyl]carbonyl]-4-piperidinyl]carbonyl]amino]-*N*-[(phenylmethoxy)carbonyl]- L-alanine;

3-[[[1-[[(1*S*,4*R*)-4-[(4,5-dihydro-1*H*-imidazol-2-yl)amino]-2-cyclopenten-1-yl]carbonyl]-4-piperidinyl]carbonyl]amino]-*N*-[(phenylmethoxy)carbonyl]- L-alanine;

3-[[[1-[3-[(4,5-dihydro-1*H*-imidazol-2-yl)amino]-2-methyl-1-oxopropyl]-4-piperidinyl]carbonyl]amino]-*N*-[(phenylmethoxy)carbonyl]- L-alanine;

3-[[[1-[[(1*R*,4*S*)-4-[(4,5-dihydro-1*H*-imidazol-2-yl)amino]-2-cyclopenten-1-yl]carbonyl]-4-piperidinyl]carbonyl]amino]-*N*-[(phenylmethoxy)carbonyl]- L-alanine;

4-[[[(2*S*)-2-carboxy-2-[[(phenylmethoxy)carbonyl]amino]ethyl]amino]carbonyl]-, 2-[(4,5-dihydro-1*H*-imidazol-2-yl)amino]ethyl ester 1-piperidinecarboxylic acid;

β-[[[1-[[2-[(4,5-dihydro-1*H*-imidazol-2-yl)amino]ethoxy]carbonyl]-4-piperidinyl]carbonyl]amino]-, (β^3S)- 3-quinolinepropanoic acid;

3-[[[1-[4-[(4,5-dihydro-1*H*-imidazol-2-yl)amino]-2-methyl-1-oxobutyl]-4-piperidinyl]carbonyl]amino]-*N*-[(phenylmethoxy)carbonyl]- L-alanine;

3-[[[1-(4-amino-1-oxo-5-hexenyl)-4-piperidinyl]carbonyl]amino]-*N*-[(phenylmethoxy)carbonyl]- L-alanine;

3-[[[1-[4-[[(4,5-dihydro-1*H*-imidazol-2-yl)amino]methyl]benzoyl]-4-piperidinyl]carbonyl]amino]-*N*-[(phenylmethoxy)carbonyl]- L-alanine;

β-[[[1-[3-[[(4,5-dihydro-1*H*-imidazol-2-yl)amino]oxy]-1-oxopropyl]-4-piperidinyl]carbonyl]amino]- 1,3-benzodioxole-5-propanoic acid;

and,

β-[[[1-[1-oxo-4-(2-pyridinylamino)butyl]-4-piperidinyl]carbonyl]amino]- 1,3-benzodioxole-5-propanoic acid;

and pharmaceutically acceptable salts thereof.

6. The compound of Claim 1 which are effective integrin antagonists.

7. The compound of Claim 6 which are effective αvβ3, αvβ5, GPIIb/IIIa, dual αvβ3/GPIIb/IIIa or dual αvβ3/αvβ5 integrin antagonists.

8. The compound of Claim 7 which are effective αvβ3 integrin antagonists selected from the group consisting of Compound **1**, **2**, **3**, **5**, **6**, **12**, **14**,

16, 18, 21, 24, 25, 28, 29, 31, 33, 34, 39, 40, 44, 47, 49, 54, 55, 58 and 60.

9. The compound of claim 8 wherein the compound is selected from the group consisting of Compound 1, 2, 6, 28, 39 and 47.

10. The compound of Claim 7 which are effective GPIIb/IIIa integrin antagonists selected from the group consisting of Compound 1, 2, 5, 11, 12, 14, 16, 17, 18, 19, 39, 47, 49, 50, 53, 54, 55 and 56.

11. The compound of claim 10 wherein the compound is selected from the group consisting of Compound 2, 11, 14, 17, 50 and 53.

12. The compound of Claim 7 which are effective αvβ5 integrin antagonists selected from the group consisting of Compound 1, 2, 16, 45, 58 and 60.

13. The compound of claim 12 wherein the compound is selected from the group consisting of Compound 1, 2 and 16.

14. The compound of Claim 7 which are effective dual αvβ3/GPIIb/IIIa integrin antagonists selected from the group consisting of Compound 2, 5, 12, 14, 16, 18, 39, 47, 49, 54 and 55.

15. The compound of claim 14 wherein the compound is Compound 2.

16. The compound of Claim 7 which are effective dual αvβ3/αvβ5 integrin antagonists selected from the group consisting of Compound 1, 2, 16, 58 and 60.

17. The compound of claim 16 wherein the compound is selected from the group consisting of Compound 1 and 2.

18. The compound of Claim 1 which are effective agents for the treatment of an integrin-mediated disorder ameliorated by administration of an integrin antagonist.

19. The compound of Claim 18 wherein the integrin-mediated disorder is selected from the group consisting of restenosis, unstable angina, thromboembolic disorders, vascular injury, atherosclerosis, arterial thrombosis, venous thrombosis, vaso-occlusive disorders, acute myocardial infarction, re-occlusion following thrombolytic therapy, re-occlusion following angioplasty, inflammation, rheumatoid arthritis, osteoporosis, bone resorption disorders, cancer, tumor growth, angiogenesis, multiple sclerosis, neurological disorders, asthma, macular degeneration, diabetic complications and diabetic retinopathy.

20. The compound of Claim 1 which are effective prodrugs selected from the group consisting of esters, hydroxyamidines and hydroxyguanidines of compounds of Claim 1.

21. The compound of Claim 20 which are effective agents for the treatment of an integrin-mediated disorder ameliorated by administration of an integrin antagonist.

22. The compound of Claim 21 wherein the integrin-mediated disorder is selected from the group consisting of restenosis, unstable angina, thromboembolic disorders, vascular injury, atherosclerosis, arterial thrombosis, venous thrombosis, vaso-occlusive disorders, acute myocardial infarction, re-occlusion following thrombolytic therapy, re-occlusion following angioplasty, inflammation, rheumatoid arthritis, osteoporosis, bone resorption disorders, cancer, tumor growth, angiogenesis, multiple sclerosis, neurological disorders, asthma, macular degeneration, diabetic complications and diabetic retinopathy.

23. A pharmaceutical composition comprising a compound of Claim 1 and a

pharmaceutically acceptable carrier.

24. A pharmaceutical composition made by mixing a compound of Claim 1 and a pharmaceutically acceptable carrier.

25. A process for making a pharmaceutical composition comprising mixing a compound of Claim 1 and a pharmaceutically acceptable carrier.

26. A method of treating an integrin-mediated disorder in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound of Claim 1.

27. The method of Claim 26 wherein the integrin-mediated disorder is selected from the group consisting of restenosis, unstable angina, thromboembolic disorders, vascular injury, atherosclerosis, arterial thrombosis, venous thrombosis, vaso-occlusive disorders, acute myocardial infarction, re-occlusion following thrombolytic therapy, re-occlusion following angioplasty, inflammation, rheumatoid arthritis, osteoporosis, bone resorption disorders, cancer, tumor growth, angiogenesis, multiple sclerosis, neurological disorders, asthma, macular degeneration, diabetic complications and diabetic retinopathy.

28. The method of Claim 26 wherein the therapeutically effective amount of the compound of Claim 1 is between about 0.01 mg/kg/day and about 300 mg/kg/day.

29. A method of treating an integrin-mediated disorder in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a prodrug of Claim 20.

30. The method of Claim 29 wherein the integrin-mediated disorder is selected from the group consisting of restenosis, unstable angina, thromboembolic disorders, vascular injury, atherosclerosis, arterial

thrombosis, venous thrombosis, vaso-occlusive disorders, acute myocardial infarction, re-occlusion following thrombolytic therapy, re-occlusion following angioplasty, inflammation, rheumatoid arthritis, osteoporosis, bone resorption disorders, cancer, tumor growth, angiogenesis, multiple sclerosis, neurological disorders, asthma, macular degeneration, diabetic complications and diabetic retinopathy.

31. The method of Claim 29, wherein the therapeutically effective amount of the prodrug of Claim 20 is between about 0.01 mg/kg/day and about 300 mg/kg/day.

32. A method of treating an integrin-mediated disorder in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a pharmaceutical composition of Claim 23.

33. The method of Claim 32 wherein the integrin-mediated disorder is selected from the group consisting of restenosis, unstable angina, thromboembolic disorders, vascular injury, atherosclerosis, arterial thrombosis, venous thrombosis, vaso-occlusive disorders, acute myocardial infarction, re-occlusion following thrombolytic therapy, re-occlusion following angioplasty, inflammation, rheumatoid arthritis, osteoporosis, bone resorption disorders, cancer, tumor growth, angiogenesis, multiple sclerosis, neurological disorders, asthma, macular degeneration, diabetic complications and diabetic retinopathy.

34. The method of Claim 32, wherein the therapeutically effective amount of the pharmaceutical composition of Claim 23 is between about 0.01 mg/kg/day and about 300 mg/kg/day.