PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
C07C 259/06, A61K 31/16, A61P 43/00, C07D 213/30, 249/18, 261/08, 215/14, 211/60, 207/16, 417/12, 401/12

A1

(11) International Publication Number: **WO 00/59874**

(43) International Publication Date: 12 October 2000 (12.10.00)

(21) International Application Number: PCT/US00/08362

(22) International Filing Date: 30 March 2000 (30.03.00)

(30) Priority Data:
60/127,635 2 April 1999 (02.04.99) US

(71) Applicant: DU PONT PHARMACEUTICALS COMPANY [US/US]; Chestnut Run Plaza, 974 Centre Road, Wilmington, DE 19807 (US).

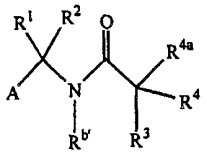
(72) Inventor: DUAN, Jingwu; 17 Springbrook Lane, Newark, DE 19711 (US).

(74) Agent: VAN ATTEN, Mary, K.; Du Pont Pharmaceuticals Company, Legal Patent Records Center, 1007 Market Street, Wilmington, DE 19898 (US).

(81) Designated States: AU, BR, CA, CN, CZ, EE, HU, IL, IN, JP, KR, LT, LV, MX, NO, NZ, PL, RO, SG, SI, SK, TR, UA, VN, ZA, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: NOVEL AMIDE DERIVATIVES AS INHIBITORS OF MATRIX METALLOPROTEINASES, TNF-α, AND AGGRECANASE



(I)

(57) Abstract

The present application describes novel amides and derivatives thereof of formula (I) or pharmaceutically acceptable salt forms thereof, wherein these compounds are useful as inhibitors of matrix metalloproteinases, TNF-α, and aggrecanase.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

TITLE

NOVEL AMIDE DERIVATIVES AS INHIBITORS OF MATRIX METALLOPROTEINASES, TNF-α, AND AGGRECANASE

FIELD OF THE INVENTION

This invention relates generally to novel amide derivatives as inhibitors of matrix metalloproteinases, TNF-α, and aggrecanase, pharmaceutical compositions containing the same, and methods of using the same.

BACKGROUND OF THE INVENTION

There is now a body of evidence that metalloproteinases (MP) are important in the uncontrolled breakdown of connective tissue, including proteoglycan and collagen, leading to resorption of the extracellular matrix. This is a feature of many pathological conditions, such as rheumatoid and osteoarthritis, corneal, epidermal or gastric ulceration; tumor metastasis or invasion; periodontal disease and bone disease. Normally these catabolic enzymes are tightly regulated at the level of their synthesis as well as at their level of extracellular activity through the action of specific inhibitors, such as α-2-macroglobulins and TIMP (tissue inhibitor of metalloproteinase), which form inactive complexes with the MP's.

Osteo- and Rheumatoid Arthritis (OA and RA respectively) are destructive diseases of articular cartilage characterized by localized erosion of the cartilage surface. Findings have shown that articular cartilage from the femoral heads of patients with OA, for example, had a reduced incorporation of radiolabeled sulfate over controls, suggesting that there must be an enhanced rate of cartilage degradation in OA (Mankin et al. *J. Bone Joint Surg.* **1970**, *52A*, 424-434). There are four classes of protein degradative enzymes in mammalian cells: serine, cysteine, aspartic and metalloproteinases. The available evidence supports that it is the metalloproteinases which are responsible for the degradation of the extracellular matrix of articullar cartillage in OA and RA. Increased activities of collagenases and stromelysin have been found in OA cartilage and the activity correlates with severity of the lesion (Mankin et al. *Arthritis Rheum.* 21, 1978, 761-766, Woessner et al. *Arthritis Rheum.* **1983**, *26*, 63-68 and *Ibid.* **1984**, *27*, 305-312). In addition, aggrecanase (a newly identified metalloproteinase enzymatic activity) has been identified that provides the specific cleavage product of proteoglycan, found in RA and OA patients (Lohmander et al. *Arthritis Rheum.* **1993**, *36*, 1214-22).

Therefore metalloproteinases (MP) have been implicated as the key enzymes in the destruction of mammalian cartilage and bone. It can be expected that the pathogenesis of such diseases can be modified in a beneficial manner by the administration of MP

inhibitors, and many compounds have been suggested for this purpose (see Wahl et al. *Ann. Rep. Med. Chem.* **1990**, *25*, 175-184, AP, San Diego).

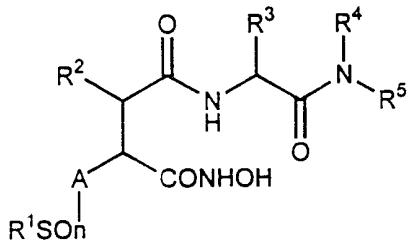
Tumor necrosis factor (TNF) is a cell associated cytokine that is processed from a 26kd precursor form to a 17kd active form. TNF has been shown to be a primary mediator in humans and in animals, of inflammation, fever, and acute phase responses, similar to those observed during acute infection and shock. Excess TNF has been shown to be lethal. There is now considerable evidence that blocking the effects of TNF with specific antibodies can be beneficial in a variety of circumsatnces including autoimmune diseases such as rheumatoid arthritis (Feldman et al, *Lancet*, **1994**, *344*, 1105) and non-insulin dependent diabetes melitus. (Lohmander et al. *Arthritis Rheum.* **1993**, *36*, 1214-22) and Crohn's disease (MacDonald et al. *Clin. Exp. Immunol.* **1990**, *81*, 301).

Compounds which inhibit the production of TNF are therefore of therapeutic importance for the treatment of inflammatory disorders. Recently it has been shown that a matrix metalloproteinase or family of metalloproteinases, hereafter known as TNF-convertases (TNF-C), as well as other MP's are capable of cleaving TNF from its inactive to active form (Gearing et al Nature, 1994, 370, 555). This invention describes molecules that inhibit this conversion and hence the secretion of active TNF-a from cells. These novel molecules provide a means of mechanism based therapeutic intervention for diseases including but not restricted to septic shock, haemodynamic shock, sepsis syndrom, post ischaemic reperfusion injury, malaria, Crohn's disease, inflammatory bowel diseases, mycobacterial infection, meningitis, psoriasis, congestive heart failure, fibrotic diseases, cachexia, graft rejection, cancer, diseases involving angiogenesis, autoimmune diseases, skin inflammatory diseases, osteo and rheumatoid arthritis, multiple sclerosis, radiation damage, hyperoxic alveolar injury, periodontal disease, HIV and non-insulin dependent diabetes melitus.

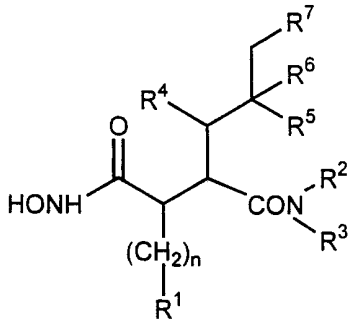
Since excessive TNF production has been noted in several disease conditions also charactarized by MMP-mediated tissue degradation, compounds which inhibit both MMPs and TNF production may also have a particular advantage in diseases where both mechansisms are involved.

There are several patents which disclose hydroxamate and carboxylate based MMP inhibitors.

WO95/09841 describes compounds that are hydroxamic acid derivatives and are inhibitors of cytokine production.

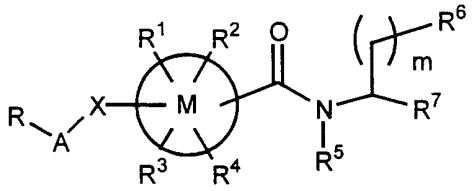


EP 574,758 A1 depicts hydroxamic acid derivatives as collagenase inhibitors having the general formula:



GB 2,268,934 A and WO94/24140 claim hydroxamate inhibitors of MMPs as inhibitors of TNF production.

WO97/08133 portrays compounds, for treating inflammatory diseases, of the formula:



wherein Ring M is an aromatic ring, cycloalkylene or a divalent heterocycle. Compounds of this sort art not considered to be included in the present invention.

The compounds of the current invention act as inhibitors of MMPs, aggrecanase and/or TNF. These novel molecules are provided as anti-inflammatory compounds and cartilage protecting therapeutics. The inhibiton of aggrecanase, TNF-C, and other metalloproteinases by molecules of the present invention indicates they are anti-inflammatory and should prevent the degradation of cartilage by these enzymes, thereby alleviating the pathological conditions of osteo- and rheumatoid arthritis.

SUMMARY OF THE INVENTION

Accordingly, one object of the present invention is to provide novel amides which are useful as metalloprotease inhibitors or pharmaceutically acceptable salts or prodrugs thereof.

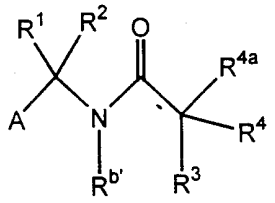
It is another object of the present invention to provide pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt or prodrug form thereof.

It is another object of the present invention to provide a method for treating inflammatory disorders comprising administering to a host in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt or prodrug form thereof.

It is another object of the present invention to provide novel compounds for use in therapy.

It is another object of the present invention to provide the use of novel compounds for the manufacture of a medicament for the treatment of a condition or disease mediated by MMPs, TNF, aggrecanase, or a combination thereof.

These and other objects, which will become apparent during the following detailed description, have been achieved by the inventors' discovery that compounds of formula (I):

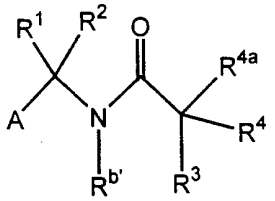


I

or pharmaceutically acceptable salt or prodrug forms thereof, wherein A, B, C, R^1, R^2, R^3, and R^4 are defined below, are effective metalloprotease inhibitors.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Thus, in an embodiment, the present invention provides a novel compound of formula I:



I

or a stereoisomer or pharmaceutically acceptable salt form thereof, wherein;

A is selected from COR^5, $-CO_2H$, $-CO_2R^6$, -CONHOH, $-CONHOR^5$, $-CONHOR^6$, $-NHR^a$, $-N(OH)COR^5$, -SH, $-CH_2SH$, $-SONHR^a$, $SN_2H_2R^a$, $-S(O)(=NH)R^a$, $-S(=NH)_2R^a$, $PO(OH)_2$, and $PO(OH)NHR^a$;

R^1 is selected from H, Q, C_{1-10} alkylene-Q, C_{2-10} alkenylene-Q, C_{2-10} alkynylene-Q, $(CRR')_r O(CRR')_r$-Q, $(CRR')_r NR^a(CRR')_r$-Q, $(CRR')_r C(O)(CRR')_r$-Q, $(CRR')_r C(O)O(CRR')_r$-Q, $(CRR')_r OC(O)(CRR')_r$-Q,

$(CRR')_r$-$C(O)NR^a(CRR')_r$-Q, $(CRR')_r$-$NR^aC(O)(CRR')_r$-Q, $(CRR')_r$-$OC(O)O(CRR')_r$-Q, $(CRR')_r$-$OC(O)NR^a(CRR')_r$-Q, $(CRR')_r$-$NR^aC(O)O(CRR')_r$-Q, $(CRR')_r$-$NR^aC(O)NR^a(CRR')_r$-Q, $(CRR')_r$-$S(O)_p(CRR')_r$-Q, $(CRR')_r$-$SO_2NR^a(CRR')_r$-Q, $(CRR')_r$-$NR^aSO_2(CRR')_r$-Q, $(CRR')_r$-$NR^aSO_2NR^a(CRR')_r$-Q, $(CRR')_r$-$NR^aC(O)(CRR')_r$-NHQ, $(CRR')_r$-$NR^aC(O)(CRR')_r$NHC(O)OR^a, and $(CRR')_r$-$NR^aC(O)(CRR')_r$NHC(O)$(CRR')_r$NHC(O)OR^a;

alternatively, R^1 and $R^{b'}$ taken together with the CR^2-N to which they are attached form a 4-8 membered cyclic amine containing from 0-1 double bonds, 0-1 $S(O)_p$, O-1 oxygen atoms, and 0-1 NR^a, and substituted with 0-1 groups selected from OH and =O and is substituted with 0-3 R^b;

R, at each occurrence, is independently selected from H, CH_3, CH_2CH_3, $CH(CH_3)_2$, $CH=CH_2$, $CH=CHCH_3$, and $CH_2CH=CH_2$;

R', at each occurrence, is independently selected from H, CH_3, CH_2CH_3, and $CH(CH_3)_2$;

alternatively, R and R' together with the carbon to which they are attached form a cyclopropyl, cyclobutyl or cyclopentyl group;

Q, at each occurence, is selected from H, a C_{3-13} carbocyclic residue substituted with 0-5 R^c and a 5-14 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-5 R^c;

R^2 is selected from H, C_{1-10} alkylene-H, C_{2-10} alkenylene-H, C_{2-10} alkynylene-H, $(CRR')_r$-$O(CRR')_r$-H, $(CRR')_r$-$NR^a(CRR')_r$-H, $(CRR')_r$-$C(O)(CRR')_r$-H, $(CRR')_r$-$C(O)O(CRR')_r$-H, $(CRR')_r$-$OC(O)(CRR')_r$-H, $(CRR')_r$-$C(O)NR^a(CRR')_r$-H, $(CRR')_r$-$NR^aC(O)(CRR')_r$-H, $(CRR')_r$-$OC(O)O(CRR')_r$-H, $(CRR')_r$-$OC(O)NR^a(CRR')_r$-H, $(CRR')_r$-$NR^aC(O)O(CRR')_r$-H, $(CRR')_r$-$NR^aC(O)NR^a(CRR')_r$-H, $(CRR')_r$-$S(O)_p(CRR')_r$-H, $(CRR')_r$-$SO_2NR^a(CRR')_r$-H, $(CRR')_r$-$NR^aSO_2(CRR')_r$-H, and $(CRR')_r$-$NR^aSO_2NR^a(CRR')_r$-H;

R^3 is U-X-Y-Z-U^a-X^a-Y^a-X^1-Z^a;

U is absent or is selected from: O, NR^a, C(O), C(O)O, OC(O), $C(O)NR^a$, $NR^aC(O)$, OC(O)O, $OC(O)NR^a$, $NR^aC(O)O$, $NR^aC(O)NR^a$, $S(O)_p$, $S(O)_pNR^a$, $NR^aS(O)_p$, and $NR^aSO_2NR^a$;

X is absent or selected from C_{1-10} alkylene, C_{2-10} alkenylene, and C_{2-10} alkynylene;

Y is absent or selected from O, NR^a, $S(O)_p$, $S(O)_pNR^a$, $C(O)NR^a$, and C(O), provided that when U and Y are present, X is present;

Z is absent or selected from a C_{3-13} carbocyclic residue substituted with 0-5 R^d and a 5-14 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-5 R^d;

U^a is absent or is selected from: O, NR^a, C(O), C(O)O, OC(O), $C(O)NR^a$, $NR^aC(O)$, OC(O)O, $OC(O)NR^a$, $NR^aC(O)O$, $NR^aC(O)NR^a$, $S(O)_p$, $S(O)_pNR^a$, $NR^aS(O)_p$, and $NR^aSO_2NR^a$;

X^a is absent or selected from C_{1-10} alkylene, C_{2-10} alkenylene, and C_{2-10} alkynylene;

Y^a is absent or selected from O, NR^a, $S(O)_p$, $S(O)_pNR^a$, $C(O)NR^a$, and C(O), provided that when U^a and Y^a are present, X^a is present;

X^1 is absent or selected from C_{1-10} alkylene, C_{2-10} alkenylene, and C_{2-10} alkynylene;

Z^a is selected from H, a C_{3-13} carbocyclic residue substituted with 0-5 R^d and a 5-14 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-5 R^d;

R^4 is selected from H, Q', C_{1-10} alkylene-Q', C_{2-10} alkenylene-Q', C_{2-10} alkynylene-Q', $(CRR')_r$-O-$(CRR')_r$-Q', $(CRR')_r$-NR^a-$(CRR')_r$-Q', $(CRR')_r$-$NR^aC(O)$-$(CRR')_r$-Q', $(CRR')_r$-C(O)-NR^a-$(CRR')_r$-Q', $(CRR')_r$-C(O)-$(CRR')_r$-Q', $(CRR')_r$-C(O)O-$(CRR')_r$-Q', $(CRR')_r$-$S(O)_p$-$(CRR')_r$-Q', $(CRR')_r$-SO_2NR^a-$(CRR')_r$-Q', $(CRR')_r$-$NR^aC(O)NR^a$-$(CRR')_r$-Q', $(CRR')_r$-OC(O)-NR^a-$(CRR')_r$-Q', and $(CRR')_r$-$NR^aC(O)O$-$(CRR')_r$-Q';

R^{4a} is selected from H, C_{1-6} alkyl, -C_{1-6} alkyl-phenyl, and phenyl;

alternatively, R^4 and R^{4a}, together with the carbon to which they are attached, combine to form a 3-8 membered carbocyclic ring substituted with 0-3 R^b or a 3-8 membered heterocyclic ring containing from 1-3 heteroatoms selected from N, O, and $S(O)_p$ and substituted with 0-3 R^b;

Q' is selected from H, a C_{3-13} carbocyclic residue substituted with 0-5 R^b and a 5-14 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-5 R^b;

R^a, at each occurrence, is independently selected from H, C_{1-4} alkyl, phenyl or benzyl;

$R^{a'}$, at each occurrence, is independently selected from H, C_{1-4} alkyl, phenyl or benzyl;

$R^{a''}$, at each occurrence, is independently selected from C_{1-4} alkyl, phenyl or benzyl;

alternatively, R^a and $R^{a'}$ taken together with the nitrogen to which they are attached form a 4, 5, or 6 membered ring containing from 0-1 additional heteroatoms selected from the group consisting of N, O, and S;

R^b is selected from H, C_{1-6} alkyl, phenyl, benzyl, $C(O)R^a$, $C(O)NR^aR^{a'}$, $S(O)_2NR^aR^{a'}$, and $S(O)_pR^{a''}$;

$R^{b'}$ is selected from H, Q, C_{1-6} alkylene-Q, C_{2-6} alkenylene-Q, C_{2-6} alkynylene-Q, $(CRR')_r$-$O(CRR')_r$-Q, $(CRR')_r$-$NR^a(CRR')_r$-Q, $(CRR')_r$-$C(O)(CRR')_r$-Q, $(CRR')_r$-$C(O)O(CRR')_r$-Q, $(CRR')_r$-$OC(O)(CRR')_r$-Q, $(CRR')_r$-$C(O)NR^a(CRR')_r$-Q, $(CRR')_r$-$NR^aC(O)(CRR')_r$-Q, $(CRR')_r$-$OC(O)O(CRR')_r$-Q, $(CRR')_r$-$OC(O)NR^a(CRR')_r$-Q, $(CRR')_r$-$NR^aC(O)O(CRR')_r$-Q, $(CRR')_r$-$NR^aC(O)NR^a(CRR')_r$-Q, $(CRR')_r$-$S(O)_p(CRR')_r$-Q, $(CRR')_r$-$SO_2NR^a(CRR')_r$-Q, $(CRR')_r$-$NR^aSO_2(CRR')_r$-Q, and $(CRR')_r$-$NR^aSO_2NR^a(CRR')_r$-Q;

R^c, at each occurrence, is independently selected from C_{1-6} alkyl, OR^a, Cl, F, Br, I, =O, CN, NO_2, $NR^aR^{a'}$, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^aR^{a'}$, $NR^aC(O)NR^aR^{a'}$, $OC(O)NR^aR^{a'}$, $R^aNC(O)O$, $S(O)_2NR^aR^{a'}$, $NR^aS(O)_2R^{a''}$, $NR^aS(O)_2NR^aR^{a'}$, $OS(O)_2NR^aR^{a'}$, $NR^aS(O)_2O$, $S(O)_pR^{a''}$, CF_3, CF_2CF_3, -CH(=NOH), -$C(=NOH)CH_3$, $(CRR')_sO(CRR')_s$-$R^{c'}$, $(CRR')_sS(O)_p(CRR')_s$-$R^{c'}$, $(CRR')_sNR^a(CRR')_s$-$R^{c'}$, C_{3-10} carbocyclic residue and a 5-14 membered

heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S;

$R^{c'}$, at each occurrence, is independently selected from phenyl substituted with 0-3 R^b, biphenyl substituted with 0-2 R^b, naphthyl substituted with 0-3 R^b and a 5-10 membered heteroaryl system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-3 R^b;

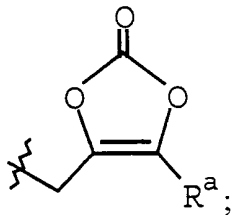
R^d, at each occurrence, is independently selected from C_{1-6} alkyl, OR^a, Cl, F, Br, I, =O, CN, NO_2, $NR^aR^{a'}$, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^aR^{a'}$, $NR^aC(O)NR^aR^{a'}$, $OC(O)NR^aR^{a'}$, $NR^aC(O)O$, $S(O)_2NR^aR^{a'}$, $NR^aS(O)_2R^{a''}$, $NR^aS(O)_2NR^aR^{a'}$, $OS(O)_2NR^aR^{a'}$, $NR^aS(O)_2O$, $S(O)_pR^{a''}$, CF_3, CF_2CF_3, C_{3-10} carbocyclic residue and a 5-14 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S;

R^5, at each occurrence, is selected from H, C_{1-10} alkyl substituted with 0-2 R^e, and C_{1-8} alkyl substituted with 0-2 R^f;

R^e, at each occurrence, is independently selected from C_{1-6} alkyl, OR^a, Cl, F, Br, I, =O, CN, NO_2, $NR^aR^{a'}$, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^aR^{a'}$, $S(O)_2NR^aR^{a'}$, $S(O)_pR^{a''}$, CF_3, and CF_2CF_3;

R^f, at each occurrence, is selected from phenyl substituted with 0-2 R^e and biphenyl substituted with 0-2 R^e;

R^6, at each occurrence, is selected from phenyl, naphthyl, C_{1-10} alkyl-phenyl-C_{1-6} alkyl-, C_{3-11} cycloalkyl, C_{1-6} alkylcarbonyloxy-C_{1-3} alkyl-, C_{1-6} alkoxycarbonyloxy-C_{1-3} alkyl-, C_{2-10} alkoxycarbonyl, C_{3-6} cycloalkylcarbonyloxy-C_{1-3} alkyl-, C_{3-6} cycloalkoxycarbonyloxy-C_{1-3} alkyl-, C_{3-6} cycloalkoxycarbonyl, phenoxycarbonyl, phenyloxycarbonyloxy-C_{1-3} alkyl-, phenylcarbonyloxy-C_{1-3} alkyl-, C_{1-6} alkoxy-C_{1-6} alkylcarbonyloxy-C_{1-3} alkyl-, [5-(C_1-C_5 alkyl)-1,3-dioxa-cyclopenten-2-one-yl]methyl, (5-aryl-1,3-dioxa-cyclopenten-2-one-yl)methyl, -C_{1-10} alkyl-NR^7R^{7a}, -$CH(R^8)OC(=O)R^9$,-$CH(R^8)OC(=O)OR^9$, and



R^7 is selected from H and C_{1-10} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl-C_{1-3} alkyl-, and phenyl-C_{1-6} alkyl-;

R^{7a} is selected from H and C_{1-10} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl-C_{1-3} alkyl-, and phenyl-C_{1-6} alkyl-;

R^8 is selected from H and C_{1-4} linear alkyl;

R^9 is selected from H, C_{1-8} alkyl substituted with 1-2 R^g, C_{3-8} cycloalkyl substituted with 1-2 R^g, and phenyl substituted with 0-2 R^e;

R^g, at each occurrence, is selected from C_{1-4} alkyl, C_{3-8} cycloalkyl, C_{1-5} alkoxy, phenyl substituted with 0-2 R^e;

p, at each occurrence, is selected from 0, 1, and 2;

r, at each occurrence, is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

r', at each occurrence, is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10; and,

s, at each occurrence, is selected from 0, 1, 2, and 3.

In a preferred embodiment, the present invention provides compounds, wherein:

A is selected from COR^5, $-CO_2H$, -CONHOH, $-CONHOR^5$, $-CONHOR^6$, $-N(OH)COR^5$, -SH, and $-CH_2SH$;

R^1 is selected from H, C_{1-10} alkylene-Q, C_{2-10} alkenylene-Q, C_{2-10} alkynylene-Q, $(CH_2)_r$-$O(CH_2)_r$-Q, $(CH_2)_r$-$NR^a(CH_2)_r$-Q, $(CH_2)_r$-$C(O)(CH_2)_r$-Q, $(CRR')_r$-$C(O)O(CRR')_r$-Q, $(CH_2)_r$-$C(O)NR^a(CH_2)_r$-Q, $(CH_2)_r$-$NR^aC(O)(CH_2)_r$-Q, $(CH_2)_r$-$OC(O)NR^a(CH_2)_r$-Q, $(CH_2)_r$-$NR^aC(O)O(CH_2)_r$-Q,

$(CH_2)_r$,$NR^aC(O)NR^a(CH_2)_r$-Q, $(CH_2)_r$,$S(O)_p(CH_2)_r$-Q, $(CH_2)_r$,$SO_2NR^a(CH_2)_r$-Q, $(CH_2)_r$,$NR^aSO_2(CH_2)_r$-Q, and $(CH_2)_r$,$NR^aSO_2NR^a(CH_2)_r$-Q;

Q is selected from H, a C_{3-10} carbocyclic residue substituted with 0-5 R^c and a 5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-5 R^c;

R^2 is selected from H, C_{1-6} alkylene-H, C_{2-6} alkenylene-H, C_{2-6} alkynylene-H, $(CH_2)_r$,$O(CH_2)_r$-H, $(CH_2)_r$,$NR^a(CH_2)_r$-H, $(CH_2)_r$,$C(O)(CH_2)_r$-H, $(CH_2)_r$,$C(O)NR^a(CH_2)_r$-H, $(CH_2)_r$,$NR^aC(O)(CH_2)_r$-H, $(CH_2)_r$,$SO_2NR^a(CH_2)_r$-H, and $(CH_2)_r$,$NR^aSO_2(CH_2)_r$-H;

U is absent or is selected from: O, NR^a, C(O), C(O)NR^a, and $NR^aC(O)$;

X is absent or selected from C_{1-6} alkylene, C_{2-6} alkenylene, and C_{2-6} alkynylene;

Y is absent or selected from O, NR^a, C(O)NR^a, and C(O), provided that when U and Y are present, X is present;

Z is absent or selected from a C_{3-10} carbocyclic residue substituted with 0-5 R^d and a 5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-5 R^d;

U^a is absent or is selected from: O, NR^a, C(O), C(O)NR^a, and $NR^aC(O)$;

X^a is absent or selected from C_{1-6} alkylene, C_{2-6} alkenylene, and C_{2-6} alkynylene;

Y^a is absent or selected from O, NR^a, C(O)NR^a, and C(O), provided that when U^a and Y^a are present, X^a is present;

X^1 is absent or selected from C_{1-6} alkylene, C_{2-6} alkenylene, and C_{2-6} alkynylene;

Z^a is selected from H, a C_{3-10} carbocyclic residue substituted with 0-5 R^d and a 5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-5 R^d;

R^4 is selected from H, Q', C_{1-5} alkylene-Q', C_{2-5} alkenylene-Q', C_{2-5} alkynylene-Q', $(CRR')_r$,$O(CRR')_r$-Q', $(CRR')_r$,$NR^a(CRR')_r$-Q', $(CRR')_r$,$NR^aC(O)(CRR')_r$-Q',

$(CRR')_r$,$C(O)NR^a(CRR')_r$-Q', $(CRR')_r$,$NR^aC(O)NR^a(CRR')_r$-Q', $(CRR')_r$,$C(O)(CRR')_r$-Q', $(CRR')_r$,$C(O)O(CRR')_r$-Q', $(CRR')_r$,$S(O)_p(CRR')_r$-Q', and $(CRR')_r$,$SO_2NR^a(CRR')_r$-Q';

R^{4a} is selected from H, C_{1-4} alkyl, -C_{1-4} alkyl-phenyl, and phenyl;

alternatively, R^4 and R^{4a}, together with the carbon to which they are attached, combine to form a 3-6 membered carbocyclic ring substituted with 0-3 R^b or a 3-6 membered heterocyclic ring containing from 1-3 heteroatoms selected from N, O, and $S(O)_p$ and substituted with 0-3 R^b;

Q' is selected from H, phenyl substituted with 0-3 R^b and a 5-6 membered heteroaryl system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-3 R^b;

$R^{b'}$ is selected from H, Q, C_{1-6} alkylene-Q, C_{2-6} alkenylene-Q, $(CRR')_r$,$O(CRR')_r$-Q, $(CRR')_r$,$NR^a(CRR')_r$-Q, $(CRR')_rC(O)(CRR')_r$-Q, $(CRR')_rC(O)O(CRR')_r$-Q, $(CRR')_rC(O)NR^a(CRR')_r$-Q, $(CRR')_r$,$NR^aC(O)(CRR')_r$-Q, and $(CRR')_r$,$NR^aC(O)NR^a(CRR')_r$-Q;

R^c, at each occurrence, is independently selected from C_{1-6} alkyl, OR^a, Cl, F, Br, I, =O, CN, NO_2, $NR^aR^{a'}$, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^aR^{a'}$, $R^aNC(O)NR^aR^{a'}$, $OC(O)NR^aR^{a'}$, $R^aNC(O)O$, $S(O)_2NR^aR^{a'}$, $NR^aS(O)_2R^{a''}$, $NR^aS(O)_2NR^aR^{a'}$, $OS(O)_2NR^aR^{a'}$, $NR^aS(O)_2O$, $S(O)_pR^{a''}$, CF_3, CF_2CF_3, C_{5-10} carbocyclic residue and a 5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S;

R^d, at each occurrence, is independently selected from C_{1-6} alkyl, OR^a, Cl, F, Br, I, =O, CN, NO_2, $NR^aR^{a'}$, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^aR^{a'}$, $R^aNC(O)NR^aR^{a'}$, $OC(O)NR^aR^{a'}$, $R^aNC(O)O$, $S(O)_2NR^aR^{a'}$, $NR^aS(O)_2R^{a''}$, $NR^aS(O)_2NR^aR^{a'}$, $OS(O)_2NR^aR^{a'}$, $NR^aS(O)_2O$, $S(O)_pR^{a''}$, CF_3, CF_2CF_3, C_{3-10} carbocyclic residue and a 5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S;

r, at each occurrence, is selected from 0, 1, 2, 3, 4, and 5; and,

r', at each occurrence, is selected from 0, 1, 2, 3, 4, and 5.

In a more preferred embodiment, the present invention provides compounds, wherein:

A is selected from $-CO_2H$, -CONHOH, $-CONHOR^5$, and $-N(OH)COR^5$;

Q is selected from H, a C_{5-10} carbocyclic residue substituted with 0-5 R^c and a 5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-5 R^c;

R^2 is selected from H, CH_3, and CH_2CH_3;

U is absent;

X is absent or is C_{1-3} alkylene;

Y is absent;

Z is absent or is selected from a C_{6-10} aryl group substituted with 0-3 R^d and a 5-10 membered heteroaryl group containing from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-3 R^d;

U^a is absent;

X^a is absent or selected from C_{1-3} alkylene and C_{2-3} alkenylene;

Y^a is absent or selected from O and NR^a;

X^1 is absent or is C_{1-3} alkylene;

Z^a is selected from H, a C_{5-10} carbocyclic residue substituted with 0-5 R^d and a 5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-5 R^d;

R^4 is selected from H, C_{1-5} alkylene-Q', $(CH_2)_r$'$O(CH_2)_r$-Q', and $(CH_2)_r$'$NR^a(CH_2)_r$-Q';

R^{4a} is selected from H and C_{1-4} alkyl;

alternatively, R^4 and R^{4a}, together with the carbon to which they are attached, combine to form a 3-6 membered carbocyclic ring substituted with 0-3 R^b;

Q' is H or phenyl substituted with 0-3 R^b;

$R^{b'}$ is selected from H, C_{1-4} alkylene-Q, C_{2-4} alkenylene-Q, $(CRR')_r O(CRR')_r$-Q, $(CRR')_r NR^a(CRR')_r$-Q, $(CRR')_r C(O)(CRR')_r$-Q, $(CRR')_r C(O)NR^a(CRR')_r$-Q, $(CRR')_r NR^a C(O)(CRR')_r$-Q;

r, at each occurrence, is selected from 0, 1, 2, and 3; and,

r', at each occurrence, is selected from 0, 1, 2, and 3.

In an even more preferred embodiment, the present invention provides compounds, wherein:

A is selected from $-CO_2H$, -CONHOH, and $-CONHOR^5$;

R^1 is selected from H, C_{1-6} alkylene-Q, $(CH_2)_r O(CH_2)_r$-Q, $(CH_2)_r NR^a(CH_2)_r$-Q, $(CH_2)_r C(O)(CH_2)_r$-Q, $(CRR')_r C(O)O(CRR')_r$-Q, $(CH_2)_r C(O)NR^a(CH_2)_r$-Q, and $(CH_2)_r NR^a C(O)(CH_2)_r$-Q;

Q is selected from H, a C_{5-10} carbocyclic residue substituted with 0-3 R^c and a 5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-5 R^c;

R^2 is H;

X is absent or is CH_2 or CH_2CH_2;

Z is absent or is selected from phenyl substituted with 0-3 R^d and a 5-6 membered heteroaryl group containing from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-3 R^d;

X^a is absent or is CH_2 or CH_2CH_2;

Y^a is absent or O;

X^1 is absent or is CH_2 or CH_2CH_2;

Z^a is selected from H, a C_{5-10} carbocyclic residue substituted with 0-5 R^d and a 5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-5 R^d;

R^4 is selected from H, OH, NH_2, CH_3, CH_2OH, and CH_2NH_2;

R^{4a} is selected from H, CH_3 and CH_2CH_3;

alternatively, R^4 and R^{4a}, together with the carbon to which they are attached, combine to form a 3-5 membered carbocyclic ring substituted with 0-2 R^b;

$R^{b'}$ is selected from H, C_{1-2} alkyl-Q, $(CRR')_r$-NHR^a, and $(CRR')_rC(O)NHR^a$;

R^c, at each occurrence, is independently selected from C_{1-6} alkyl, OR^a, Cl, F, Br, I, =O, CN, NO_2, $NR^aR^{a'}$, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^aR^{a'}$, $R^aNC(O)NR^aR^{a'}$, $OC(O)NR^aR^{a'}$, $R^aNC(O)O$, $S(O)_2NR^aR^{a'}$, $NR^aS(O)_2R^{a''}$, $NR^aS(O)_2NR^aR^{a'}$, $OS(O)_2NR^aR^{a'}$, $NR^aS(O)_2O$, $S(O)_pR^{a''}$, CF_3, CF_2CF_3, C_{5-6} carbocyclic residue and a 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S;

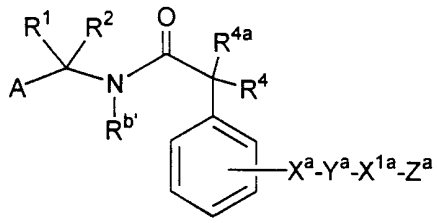
R^d, at each occurrence, is independently selected from C_{1-6} alkyl, OR^a, Cl, F, Br, I, =O, CN, NO_2, $NR^aR^{a'}$, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^aR^{a'}$, $R^aNC(O)NR^aR^{a'}$, $OC(O)NR^aR^{a'}$, $R^aNC(O)O$, $S(O)_2NR^aR^{a'}$, $NR^aS(O)_2R^{a''}$, $NR^aS(O)_2NR^aR^{a'}$, $OS(O)_2NR^aR^{a'}$, $NR^aS(O)_2O$, $S(O)_pR^{a''}$, CF_3, CF_2CF_3, C_{3-6} carbocyclic residue and a 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S; and,

r, at each occurrence, is selected from 0, 1, and 2;

r', at each occurrence, is selected from 1, and 2; and,

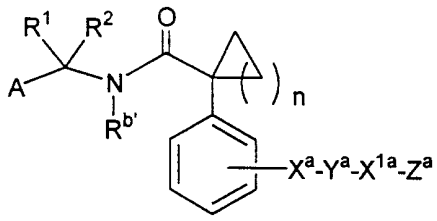
s, at each occurrence, is selected from 0 and 1.

In a further preferred embodiment, the present invention provides novel compounds of formula Ia, wherein:



Ia.

In a further preferred embodiment, the present invention provides novel compounds of formula Ib, wherein:



Ib

and n is selected from 1, 2, and 3.

In another preferred embodiment, the present invention provides novel compounds is selected from:

(R)-N-[1-[(hydroxyamino)carbonyl]-2-methylpropyl]-1-(4-methylphenyl)cyclopropanecarboxamide;

(R)-N-[1-[(hydroxyamino)carbonyl]-2-methylpropyl]-1-(4-methoxyphenyl)cyclopropanecarboxamide;

(R)-N-[1-[(hydroxyamino)carbonyl]-3-(methylthio)propyl]-1-(4-methoxyphenyl)cyclopropanecarboxamide;

(R)-N-[1-[(hydroxyamino)carbonyl]-3-(methylsulfonyl)propyl]-1-(4-methoxyphenyl)cyclopropanecarboxamide;

N-[1-(R)-[(hydroxyamino)carbonyl]-2-methylpropyl]-N,α,α-trimethylbenzeneacetamide;

(R)-N-[1-[(hydroxyamino)carbonyl]-2-methylpropyl]-N-methyl-1-phenylcyclopropanecarboxamide;

(R)-N-[1-[(hydroxyamino)carbonyl]-2-methylpropyl]-N-methyl-1-(4-methylphenyl)cyclopropanecarboxamide;

(R)-N-[1-[(hydroxyamino)carbonyl]-2-methylpropyl]-1-(4-methoxyphenyl)-N-methylcyclopropanecarboxamide;

(R)-1-(4-chlorophenyl)-N-[1-[(hydroxyamino)carbonyl]-2-methylpropyl]-N-methylcyclopropanecarboxamide;

(R)-1-(2,4-dichlorophenyl)-N-[1-[(hydroxyamino)carbonyl]-2-methylpropyl]-N-methylcyclopropanecarboxamide;

(R)-1-(4-chlorophenyl)-N-[1-[(hydroxyamino)carbonyl]-2-methylpropyl]-N-methylcyclobutanecarboxamide;

(R)-1-(4-chlorophenyl)-N-[1-[(hydroxyamino)carbonyl]-2-methylpropyl]-N-methylcyclopentanecarboxamide;

α-(R)-hydroxy-N-[1-(R)-[(hydroxyamino)carbonyl]-2-methylpropyl]-N-methylbenzeneacetamide;

1,1-dimethylethyl [2-[[1-(R)-[(hydroxyamino)carbonyl]-2-methylpropyl]methylamino]-2-oxo-1-phenylethyl]carbamate;

1-{[1-(2,4-dichlorophenyl)cyclopropyl]carbonyl}-N-hydroxy-2-piperidinecarboxamide;

1-{[1-(2,4-dichlorophenyl)cyclopropyl]carbonyl}-N-hydroxy-2-pyrrolidinecarboxamide ;

(2R)-N-hydroxy-2-[[(4-methoxyphenyl)acetyl](methyl)amino]-3-methylbutanamide;

1-{4-[(2,4-dimethylbenzyl)oxy]phenyl}-N-[(1S)-2-(hydroxyamino)-1-methyl-2-oxoethyl]-N-methylcyclopropanecarboxamide;

(2S)-N-hydroxy-2-[[(4-methoxyphenyl)acetyl](methyl)amino]propanamide;

N-[(1S)-2-(hydroxyamino)-1-methyl-2-oxoethyl]-N-methyl-1-[4-(2-naphthylmethoxy)phenyl]cyclopropanecarboxamide;

N-[(1S)-2-(hydroxyamino)-1-methyl-2-oxoethyl]-N-methyl-1-[4-(4-pyridinylmethoxy)phenyl]cyclopropanecarboxamide;

(2R)-2-[{[4-(benzyloxy)phenyl]acetyl}(methyl)amino]-N-hydroxy-3-methylbutanamide;

(2R)-2-[({4-[(3,5-dimethylbenzyl)oxy]phenyl}acetyl)(methyl)amino]-N-hydroxy-3-methylbutanamide;

(2R)-2-[{[4-(1H-1,2,3-benzotriazol-1-ylmethoxy)phenyl]acetyl}(methyl)amino]-N-hydroxy-3-methylbutanamide;

N-[(1S)-2-(hydroxyamino)-1-methyl-2-oxoethyl]-N-methyl-1-{4-[(3-phenyl-5-isoxazolyl)methoxy]phenyl}cyclopropanecarboxamide;

N-[(1S)-2-(hydroxyamino)-1-methyl-2-oxoethyl]-N-methyl-1-[4-(2-propynyloxy)phenyl]cyclopropanecarboxamide;

1-(4-{[3-(4-fluorophenyl)-5-isoxazolyl]methoxy}phenyl)-N-[(1S)-2-(hydroxyamino)-1-methyl-2-oxoethyl]-N-methylcyclopropanecarboxamide;

N-[(1S)-2-(hydroxyamino)-1-methyl-2-oxoethyl]-N-methyl-1-{4-[(3-propyl-5-isoxazolyl)methoxy]phenyl}cyclopropanecarboxamide;

N-{(1S)-1-[(hydroxyamino)carbonyl]-3-methylbutyl}-1-{4-[(2-methyl-4-quinolinyl)methoxy]phenyl}-N-propylcyclopropanecarboxamide;

N-[3-(cyclopentylamino)propyl]-N-{(1S)-1-[(hydroxyamino)carbonyl]-3-methylbutyl}-1-{4-[(2-methyl-4-quinolinyl)methoxy]phenyl}cyclopropanecarboxamide;

tert-butyl (1S)-1-[4-(benzyloxy)phenyl]-2-[[(1S)-2-(hydroxyamino)-1-methyl-2-oxoethyl](methyl)amino]-2-oxoethylcarbamate;

(1S)-N-hydroxy-2-({4-[(2-methyl-4-quinolinyl)methoxy]phenyl}acetyl)cyclopentanecarboxamide;

(1R)-N-hydroxy-2-({4-[(2-methyl-4-quinolinyl)methoxy]phenyl}acetyl)cyclopentanecarboxamide;

(3S)-N-hydroxy-2,2-dimethyl-4-({4-[(2-methyl-4-quinolinyl)methoxy]phenyl}acetyl)-3-thiomorpholinecarboxamide;

(2R)-N-hydroxy-1-({4-[(2-methyl-4-quinolinyl)methoxy]phenyl}acetyl)-2-piperidinecarboxamide;

tert-butyl 3-[(hydroxyamino)carbonyl]-4-({4-[(2-methyl-4-quinolinyl)methoxy]phenyl}acetyl)-1-piperazinecarboxylate;

N-hydroxy-1-({4-[(2-methyl-4-quinolinyl)methoxy]phenyl}acetyl)-2-piperazinecarboxamide;

benzyl (3R)-3-[(hydroxyamino)carbonyl]-2-({4-[(2-methyl-4-quinolinyl)methoxy]phenyl}acetyl)tetrahydro-1(2H)-pyridazinecarboxylate;

(3R)-N-hydroxy-2-({4-[(2-methyl-4-quinolinyl)methoxy]phenyl}acetyl)hexahydro-3-pyridazinecarboxamide;

(3R)-N-hydroxy-2-({4-[(2-methyl-4-quinolinyl)methoxy]phenyl}acetyl)-1,2,3,4-tetrahydro-3-isoquinolinecarboxamide;

2-((*R/S*)-2-phenylbutyramido)-N-hydroxy-(*R*)-propionamide;

2-((*R/S*)-α-Methyl-4-isobutylphenylacetamido)-N-hydroxy-(*R*)-propionamide;

2-((*R/S*)-2-Fluoro-α-methyl-4-biphenylacetamido)-N-hydroxy-(*R*)-propionamide;

2-[N-Methyl-N-((*R/S*)-α-Methyl-4-benzyloxyphenylacetylamino)]-N-hydroxy-(*R*)-propionamide;

2-{N-Methyl-N-[(*R/S*)-α-methyl-4-(3,5-dimethylbenzyloxy)phenylacetyl]amino}-N-hydroxy-(R)-propionamide;

2-{N-Methyl-N-[(*R/S*)-α-methyl-4-(3,5-bistrifluoromethylbenzyloxy)phenylacetyl]amino}-N-hydroxy-(*R*)-propionamide.;

2-{N-Methyl-N-[(*R/S*)-α-(methylaminocarbonylmethyl)-4-(3,5-bistrifluoromethylbenzyloxy)phenylacetyl]amino}-N-hydroxy-(*R*)-propionamide.;

2-{N-Methyl-N-[(*R/S*)-α-(aminocarbonylmethyl)-4-(3,5-bistrifluoromethylbenzyloxy)phenylacetyl]amino}-N-hydroxy-(*R*)-propionamide.;

2-{N-Methyl-N-[(*R/S*)-α-(1-piperazinocarbonylmethyl)-4-(3,5-bistrifluoromethylbenzyloxy)phenylacetyl]amino}-N-hydroxy-(*R*)-propionamide.;

(2*R*)-2-[(amino{4-[(2-methyl-4-quinolinyl)methoxy]phenyl}acetyl)amino]-*N*-hydroxy-4-methylpentanamide; and,

2-[(amino{4-[(2-methyl-4-quinolinyl)methoxy]phenyl}acetyl)amino]-*N*-hydroxy-2-methylpropanamide

or a pharmaceutically acceptable salt form thereof.

In another embodiment, the present invention provides a novel pharmaceutical composition, comprising: a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt form thereof.

In another embodiment, the present invention provides a novel method for treating or preventing an inflammatory disorder, comprising: administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt form thereof.

In another embodiment, the present invention provides a novel method of treating a condition or disease mediated by MMPs, TNF, aggrecanase, or a combination thereof in a mammal, comprising: administering to the mammal in need of such treatment a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt form thereof.

In another embodiment, the present invention provides a novel method of treating a condition or disease wherein the disease or condition is referred to as rheumatoid arthritis, osteoarthritis, periodontitis, gingivitis, corneal ulceration, solid tumor growth and tumor invasion by secondary metastases, neovascular glaucoma, multiple sclerosis, or psoriasis in a mammal, comprising: administering to the mammal in need of such treatment a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt form thereof.

In another embodiment, the present invention provides a novel method of treating a condition or disease wherein the disease or condition is referred to as fever, cardiovascular effects, hemorrhage, coagulation, cachexia, anorexia, alcoholism, acute phase response, acute infection, shock, graft versus host reaction, autoimmune disease or HIV infection in a mammal comprising administering to the mammal in need of such treatment a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt form thereof.

In another embodiment, the present invention provides novel compounds of formula (I) for use in therapy.

In another embodiment, the present invention provides the use of novel compounds of formula (I) for the manufacture of a medicament for the treatment of a condition or disease mediated by MMPs, TNF, aggrecanase, or a combination thereof.

DEFINITIONS

The compounds herein described may have asymmetric centers. Compounds of the present invention containing an asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically

active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated.

The term "substituted," as used herein, means that any one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substitent is keto (i.e., =O), then 2 hydrogens on the atom are replaced.

When any variable (e.g., R^b) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2 R^6, then said group may optionally be substituted with up to two R^6 groups and R^6 at each occurrence is selected independently from the definition of R^6. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such substituent. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

As used herein, "alkyl" or "alkylene" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. C_{1-10} alkyl (or alkylene), is intended to include C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, and C_{10} alkyl groups. Examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, and s-pentyl. "Haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more halogen (for example $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1)). Examples of haloalkyl include, but are not limited to, trifluoromethyl, trichloromethyl, pentafluoroethyl, and pentachloroethyl. "Alkoxy" represents an alkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge. C_{1-10} alkoxy, is intended to include C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, and C_{10} alkoxy groups. Examples of alkoxy

include, but are not limited to, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy, n-pentoxy, and s-pentoxy. "Cycloalkyl" is intended to include saturated ring groups, such as cyclopropyl, cyclobutyl, or cyclopentyl. C_{3-7} cycloalkyl, is intended to include C_3, C_4, C_5, C_6, and C_7 cycloalkyl groups. "Alkenyl" or "alkenylene" is intended to include hydrocarbon chains of either a straight or branched configuration and one or more unsaturated carbon-carbon bonds which may occur in any stable point along the chain, such as ethenyl and propenyl. C_{2-10} alkenyl (or alkenylene), is intended to include C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, and C_{10} alkenyl groups. "Alkynyl" or "alkynylene" is intended to include hydrocarbon chains of either a straight or branched configuration and one or more triple carbon-carbon bonds which may occur in any stable point along the chain, such as ethynyl and propynyl. C_{2-10} alkynyl (or alkynylene), is intended to include C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, and C_{10} alkynyl groups.

"Halo" or "halogen" as used herein refers to fluoro, chloro, bromo, and iodo; and "counterion" is used to represent a small, negatively charged species such as chloride, bromide, hydroxide, acetate, and sulfate.

As used herein, "carbocycle" or "carbocyclic residue" is intended to mean any stable 3, 4, 5, 6, or 7-membered monocyclic or bicyclic or 7, 8, 9, 10, 11, 12, or 13-membered bicyclic or tricyclic, any of which may be saturated, partially unsaturated, or aromatic. Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, cyclooctyl, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane, [2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, and tetrahydronaphthyl.

As used herein, the term "heterocycle" or "heterocyclic system" is intended to mean a stable 5, 6, or 7-membered monocyclic or bicyclic or 7, 8, 9, or 10-membered bicyclic heterocyclic ring which is saturated, partially unsaturated or unsaturated (aromatic), and which consists of carbon atoms and 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of N, NH, O and S and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The nitrogen and sulfur heteroatoms may optionally be oxidized. The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom which results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. A nitrogen in the heterocycle may optionally be quaternized. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heterocycle is not more than 1. As used herein, the term "aromatic heterocyclic system" or "heteroaryl" is intended to mean a stable 5, 6, or 7-membered monocyclic or bicyclic or 7, 8, 9, or 10-membered bicyclic heterocyclic aromatic ring which consists of carbon atoms and 1, 2, 3, or 4

heterotams independently selected from the group consisting of N, NH, O and S. It is to be noted that total number of S and O atoms in the aromatic heterocycle is not more than 1.

Examples of heterocycles include, but are not limited to, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, 4a*H*-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2*H*,6*H*-1,5,2-dithiazinyl, dihydrofuro[2,3-*b*]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1*H*-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, methylenedioxyphenyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, piperidonyl, 4-piperidonyl, piperonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4*H*-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, 6*H*-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl. Also included are fused ring and spiro compounds containing, for example, the above heterocycles.

The term "amino acid" as used herein means an organic compound containing both a basic amino group and an acidic carboxyl group. Included within this term are natural amino acids (e.g., L-amino acids), modified and unusual amino acids (e.g., D-amino acids), as well as amino acids which are known to occur biologically in free or combined form but usually do not occur in proteins. Included within this term are modified and unusual amino acids,such as those disclosed in, for example, Roberts and Vellaccio (1983) The Peptides, 5: 342-429, the teaching of which is hereby incorporated by reference. Natural protein occurring amino acids include, but are not limited to, alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, serine, threonine, tyrosine, tyrosine, tryptophan, proline, and valine. Natural non-protein amino acids include, but are not limited to arginosuccinic acid, citrulline, cysteine sulfinic acid, 3,4-dihydroxyphenylalanine, homocysteine, homoserine, ornithine, 3-monoiodotyrosine,

3,5-diiodotryosine, 3,5,5'-triiodothyronine, and 3,3',5,5'-tetraiodothyronine. Modified or unusual amino acids which can be used to practice the invention include, but are not limited to, D-amino acids, hydroxylysine, 4-hydroxyproline, an N-Cbz-protected amino acid, 2,4-diaminobutyric acid, homoarginine, norleucine, N-methylaminobutyric acid, naphthylalanine, phenylglycine, ß-phenylproline, tert-leucine, 4-aminocyclohexylalanine, N-methyl-norleucine, 3,4-dehydroproline, N,N-dimethylaminoglycine, N-methylaminoglycine, 4-aminopiperidine-4-carboxylic acid, 6-aminocaproic acid, trans-4-(aminomethyl)-cyclohexanecarboxylic acid, 2-, 3-, and 4-(aminomethyl)-benzoic acid, 1-aminocyclopentanecarboxylic acid, 1-aminocyclopropanecarboxylic acid, and 2-benzyl-5-aminopentanoic acid.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

Since prodrugs are known to enhance numerous desirable qualities of pharmaceuticals (e.g., solubility, bioavailability, manufacturing, etc...) the compounds of the present invention may be delivered in prodrug form. Thus, the present invention is intended to cover prodrugs of the presently claimed compounds, methods of delivering the same and compositions containing the same. "Prodrugs" are intended to include any covalently bonded carriers which release an active parent drug of the present invention *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs the present invention are prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compound. Prodrugs include compounds of the present invention wherein a hydroxy, amino, or sulfhydryl group is bonded to any group that, when the prodrug of the present invention is administered to a mammalian subject, it cleaves to form a free hydroxyl, free amino, or free sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of the present invention.

"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

"Therapeutically effective amount" is intended to include an amount of a compound of the present invention or an amount of the combination of compounds claimed effective to inhibit a MMP, TNF, aggrecanase, or a combination thereof in a host. The combination of compounds is preferably a synergistic combination. Synergy, as described for example by Chou and Talalay, *Adv. Enzyme Regul.* **1984**, *22*, 27-55, occurs when the effect (in this case, inhibition of a desired target) of the compounds when administered in combination is greater than the additive effect of the compounds when administered alone as a single agent. In general, a synergistic effect is most clearly demonstrated at suboptimal concentrations of the compounds. Synergy can be in terms of lower cytotoxicity, increased antiviral effect, or some other beneficial effect of the combination compared with the individual components.

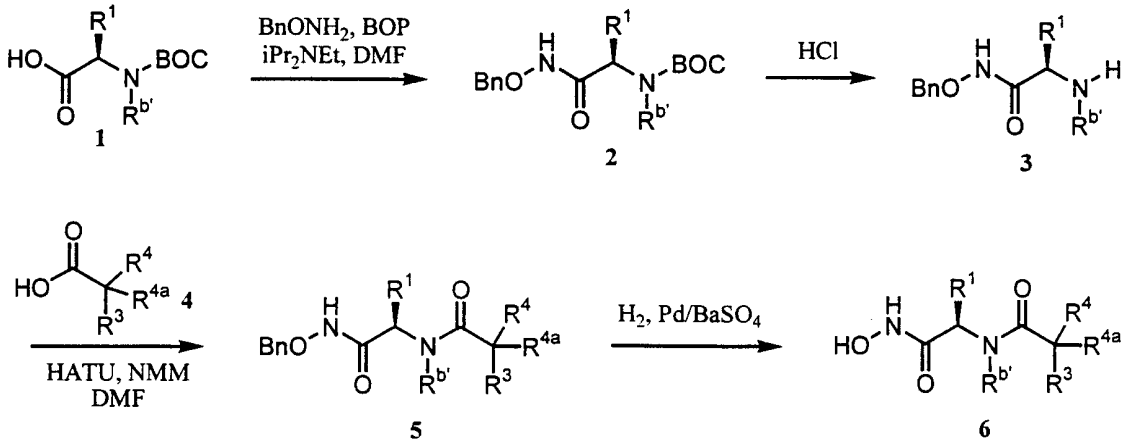
SYNTHESIS

The compounds of the present invention can be prepared in a number of ways well known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described below. All references cited herein are hereby incorporated in their entirety herein by reference.

The novel compounds of this invention may be prepared using the reactions and techniques described in this section. The reactions are performed in solvents appropriate to the reagents and materials employed and are suitable for the transformations being effected. Also, in the description of the synthetic methods described below, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and workup procedures, are chosen to be the conditions standard for that reaction, which should be readily recognized by one skilled in the art. It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule must be compatible with the reagents and reactions proposed. Such restrictions to the substituents which are compatible with the reaction conditions will be readily apparent to one skilled in the art and alternate methods must then be used.

A series of acetamides of formula **6** are prepared by the method outlined in Scheme 1. Reaction of BOC-protected D-amino acid **1** with O-benzylhydroxylamine and acid hydrolysis gives amine **3**. Coupling of **3** with acid **4** followed by hydrogenolysis using palladium on barium sulfate as a catalyst provides the desired hydroxamic acid **6**.

Scheme 1



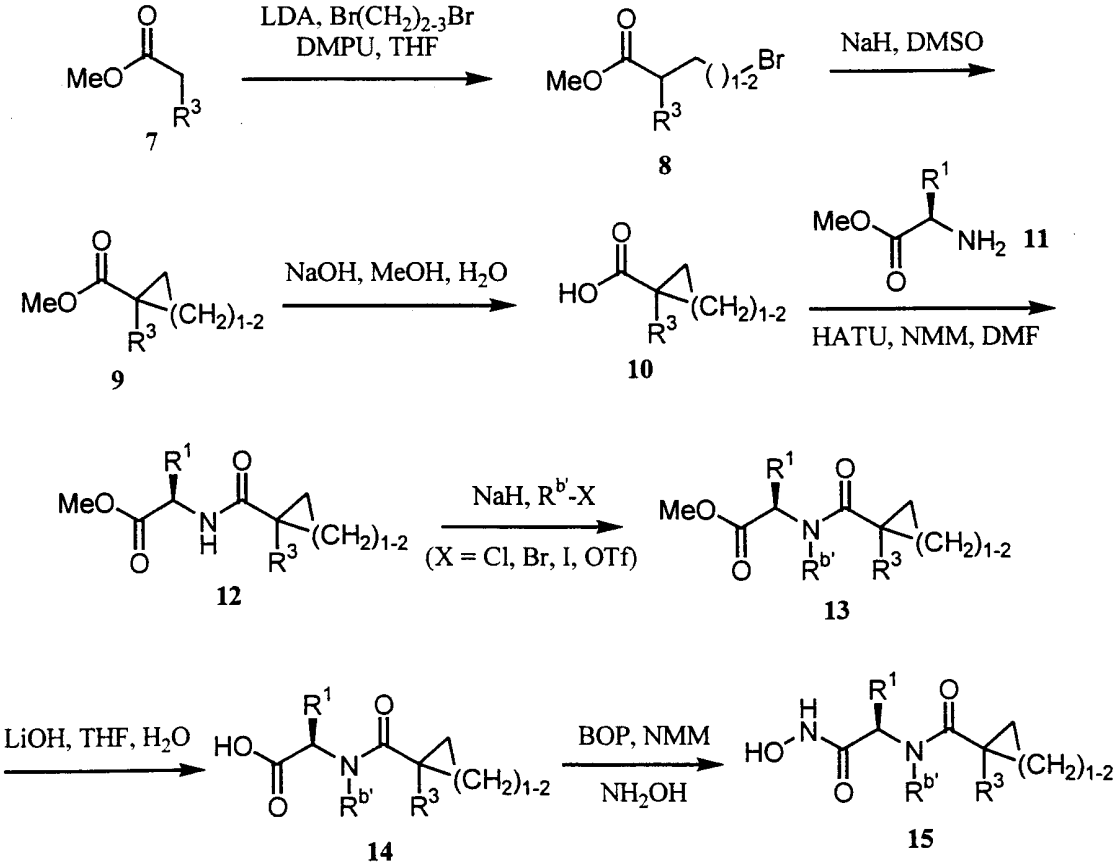
A series of cyclopropanecarboxamides and cyclobutanecarboxamides of formula **15** are prepared by the method outlined in Scheme 2. Mono-alkylation of α-substituted methyl acetate **7** with ethylene bromide and 1,3-dibromopropane, followed by treatment with sodium hydride in DMSO provides cyclopropanecarboxylates and cyclobutanecarboxylates, respectively. Hydrolysis of **9** gives the corresponding acid **10**. This protocol allows the preparation of **10** with wide range of R^3 group.

Many of the requisite D-amino acid methyl ester **11** are commercially available or are prepared from commercial material by simple protecting group manipulations. Others are synthesized using Myers method from glycine (Myers, A. G.; Gleason, J. L.; Yoon, T.

J. Am. Chem. Soc. **1995**, *117*, 8488), using Mitsunobu conditions from serine (Cherney, R. J.; Wang, L. *J. Org. Chem.* **1996**, *61*, 2544), or using Evans electrophilic azidations from carboxylic acids (Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011).

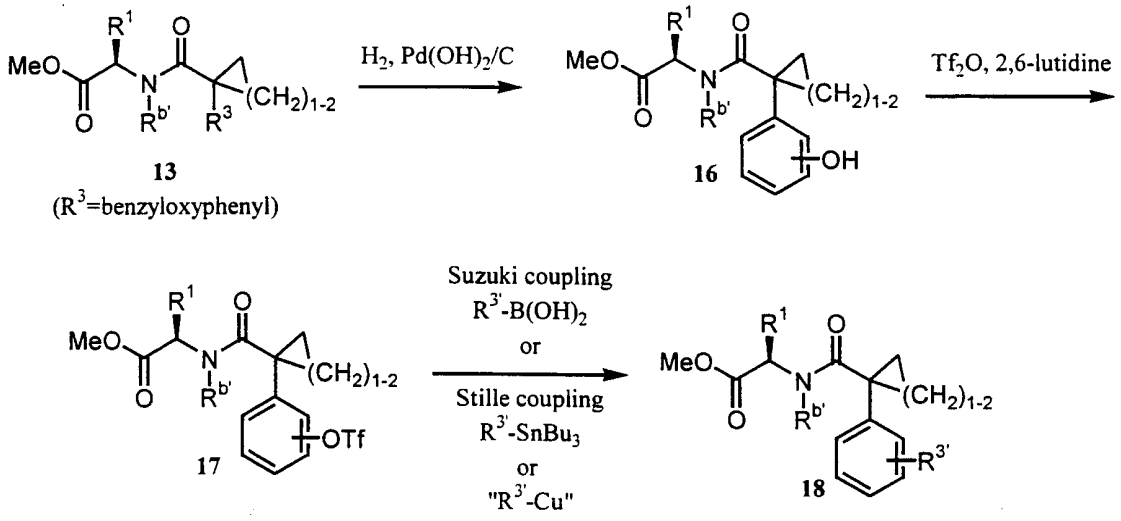
Coupling of **10** and **11** with HATU provides **12**. At this point, $R^{b'}$ group is introduced by alkylation with $R^{b'}$-X under basic conditions. Hydrolysis and coupling with hydroxylamine then complete the synthesis. This synthetic scheme is flexible and allows independent incorporation of various R^1, $R^{b'}$ and R^3 groups during the synthesis.

Scheme 2



A series of phenylacetamides of formula **18** are prepared following the sequence outlined in Scheme 3. The starting point for the synthesis is benzyloxyphenylacetamide **13**, an intermediate from Scheme 2. Deprotection of benzyl group and reaction with triflic anhydride provides triflate **17**. Palladium-mediated coupling of **17** under Stille or Suzuki conditions provides **18**. Alternatively, **17** reacts with lower or higher-order cuprates to give **18**. Ester **18** is then converted to the corresponding hydroxamic acid under standard conditions.

Scheme 3



13
(R^3=benzyloxyphenyl)

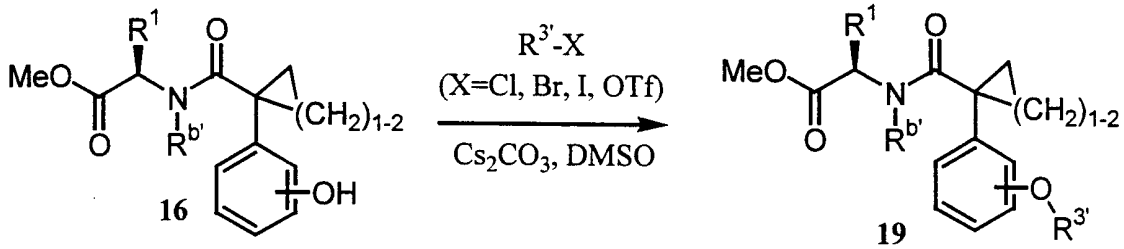
16

17

18

Another series of phenylacetamides of formula **19** are prepared following the sequence outlined in Scheme 4. Alkylation of phenol **16** with $R^{3'}$-X yields ester **19**. **19** is then converted to the corresponding hydroxamic acid under standard conditions.

Scheme 4

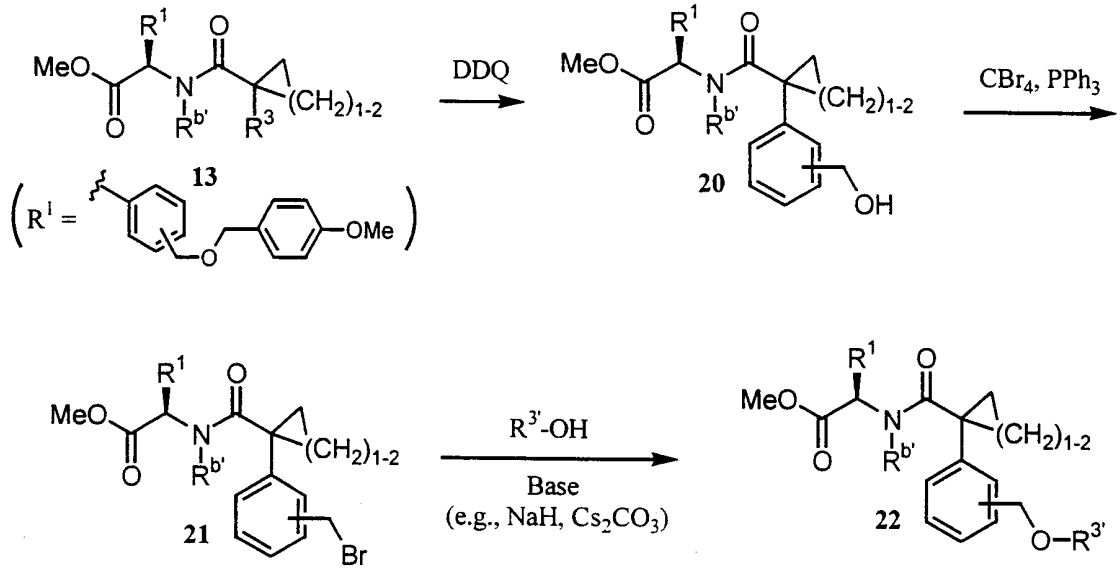


16

19

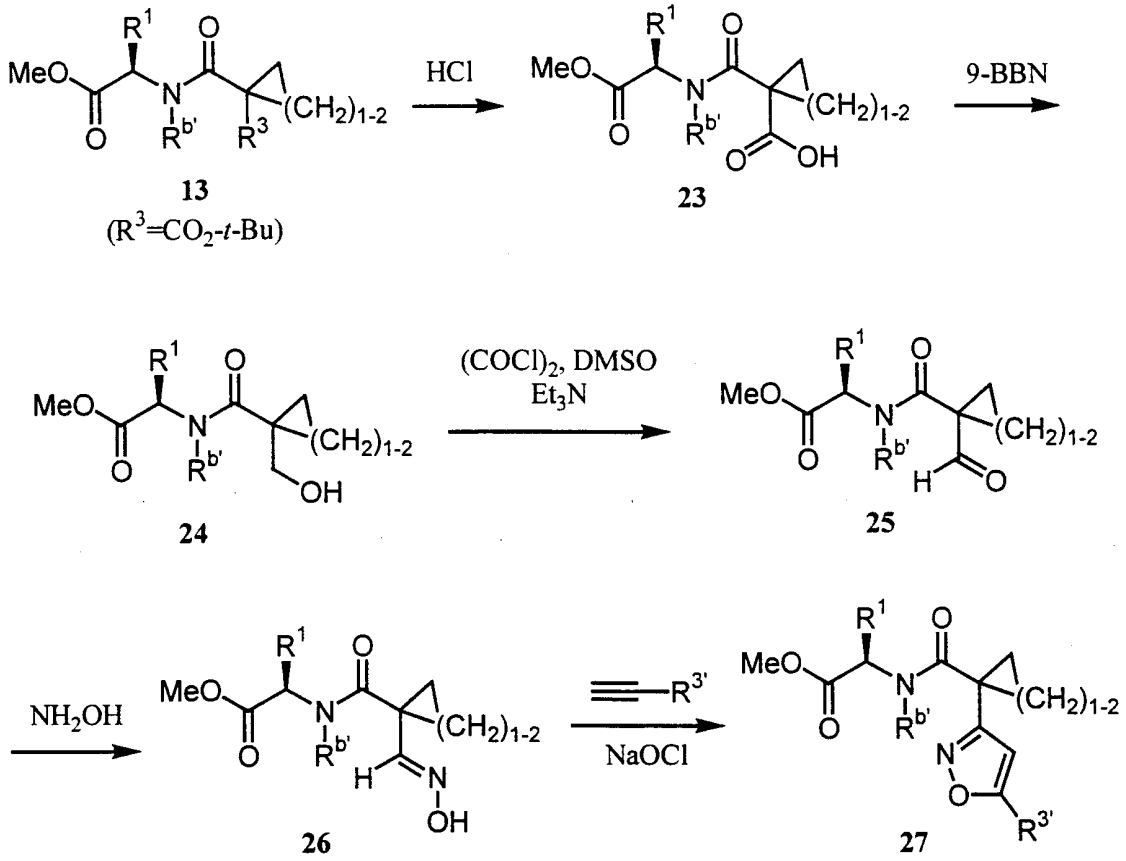
Another series of phenylacetamides of formula **22** are prepared following the sequence outlined in Scheme 5. Starting from **13** when R^3 is (p-methoxyphenyl)methoxymethylphenyl group, DDQ oxidation removes the p-methoxybenzyl group. Alcohol **20** is then converted to bromide **21**. Alkylation of **21** with $R^{3'}$-OH yields **22**. Ester **22** is converted to the corresponding hydroxamic acid under standard conditions.

Scheme 5



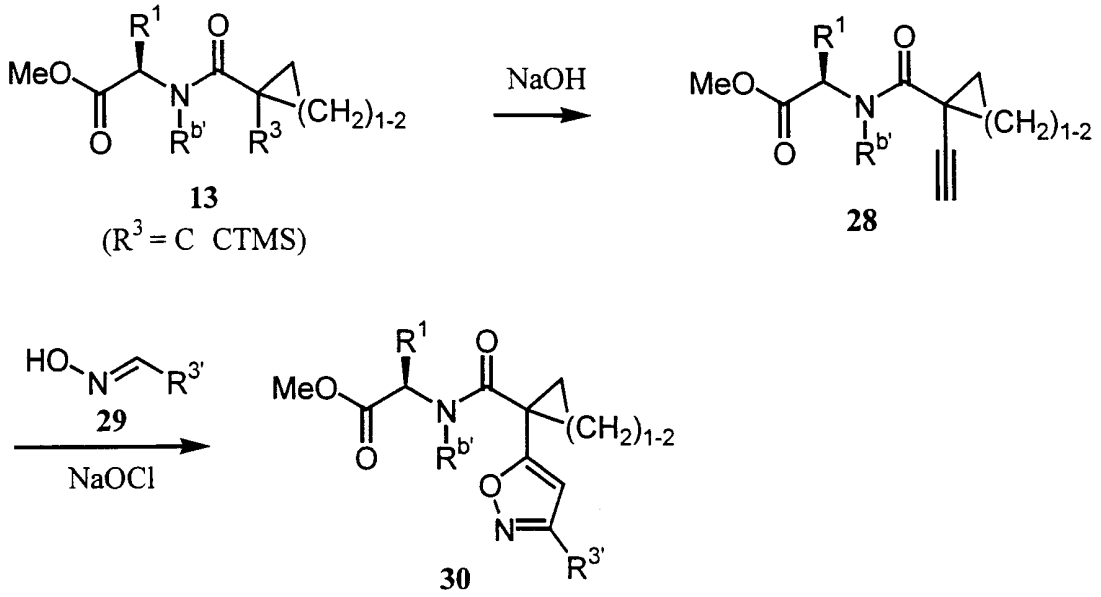
Another series of acetamides of formula **27** with an isoxazole substituent at the α position are prepared using common intermediate **13** following the sequence outlined in Scheme 6. After t-butyl ester hydrolysis, the resultant carboxylic acid **23** is converted to aldehyde **25** by hydroboration and Swern oxidation. Oxime formation, in situ oxidation and [3+2] dipolar cycloaddition with $R^{3'}$-substituted acetylene provides isoxazole **27**. **27** is converted to the corresponding hydroxamic acid under standard conditions.

Scheme 6



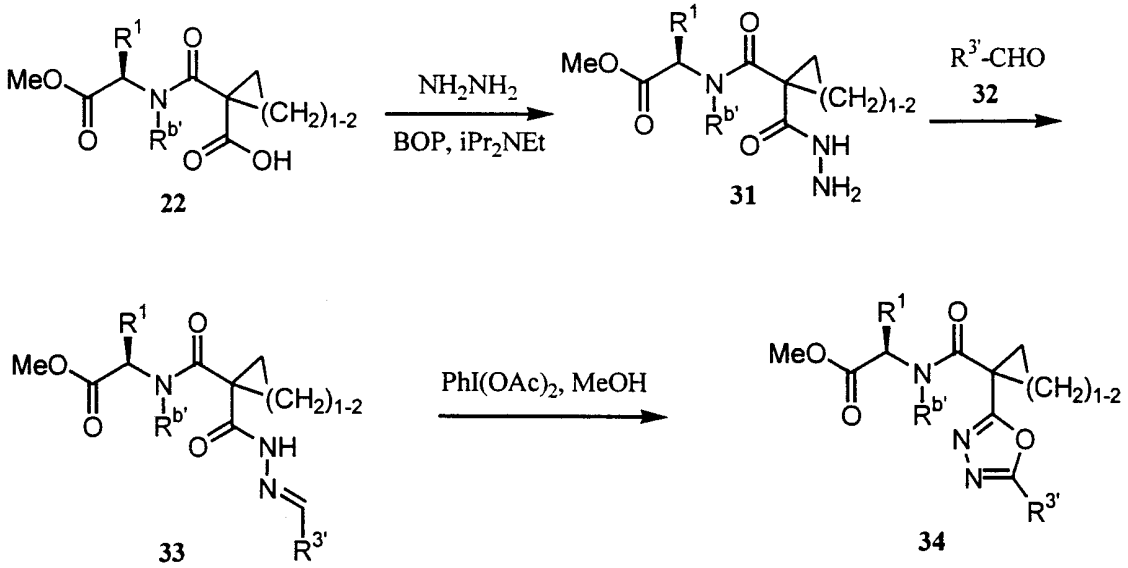
Another series of acetamides of formula **30** with an isoxazole substituent at the α position are prepared using common intermediate **13** following the sequence outlined in Scheme 7. Removal of trimethylsilyl group with NaOH gives terminal acetylene **28**. Cycloaddition of **28** with oxime **29** under oxidative conditions provides isoxazole **30**. **30** is converted to the corresponding hydroxamic acid under standard conditions.

Scheme 7



Another series of acetamides of formula **34** with an azaoxazole substituent at the α position are prepared using common intermediate **22** following the sequence outlined in Scheme 8. Acid **22** is first coupled with hydrazine to give **31**. Condensation with aldehyde **32** and oxidative cyclization with $PhI(OAc)_2$ providesb azaoxazole **34** (Yang, R. Y.; Dai, L. X. *J. Org. Chem.* **1993**, *58*, 3381). **34** is converted to the corresponding hydroxamic acid under standard conditions.

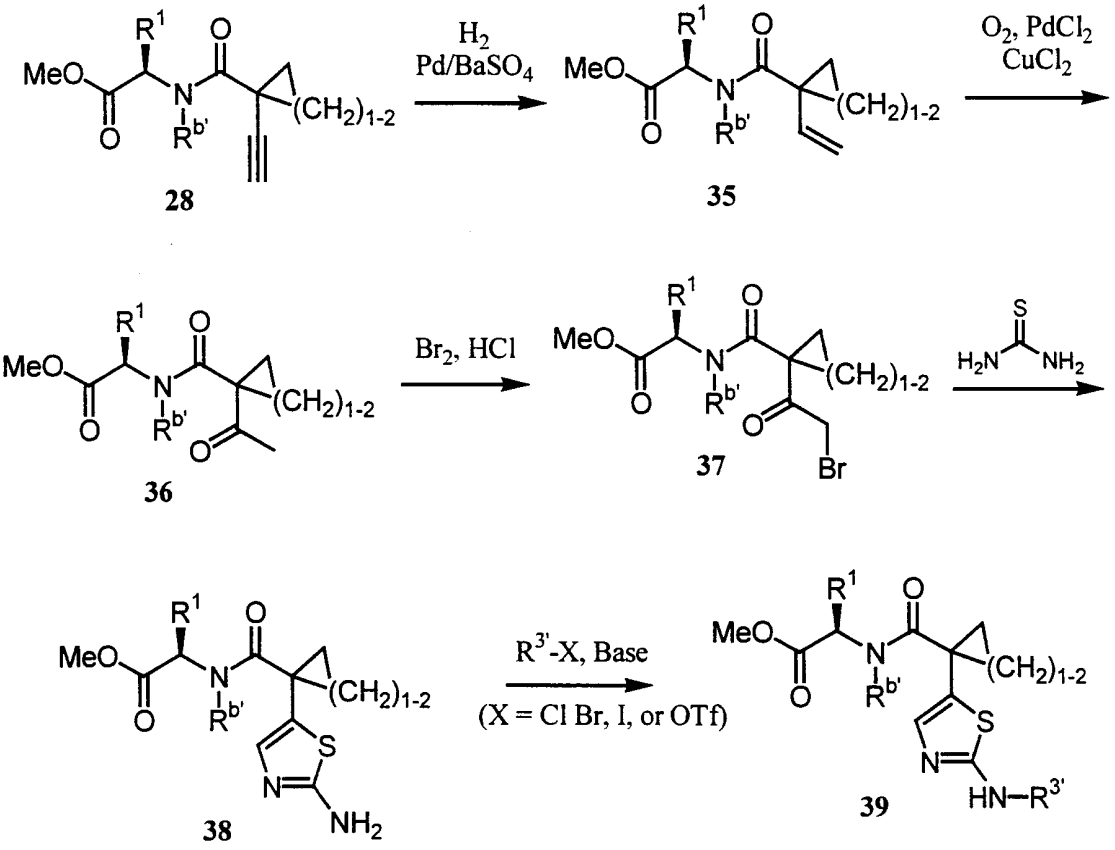
Scheme 8



Another series of acetamides of formula **39** with an aminothiazole substituent at the α position are prepared following the sequence outlined in Scheme 9. Partial

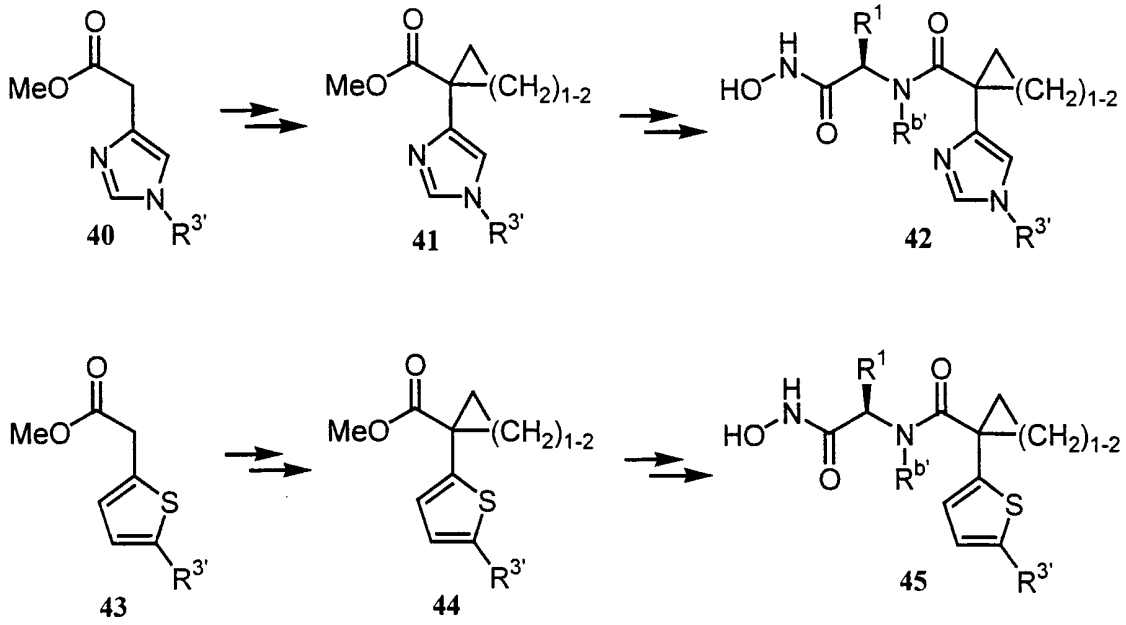
hydrogenation of acetylene **28** gives olefin **35**. **35** is converted to bromoketone **37** by Wacker oxidation and α-bromonation. Treatment of bromoketone **37** with thiourea produces aminothiazole **38** (Markees, D. G.; Burger, A. *J. Am. Chem. Soc.* **1948**, *70*, 3329.), which is then alkylated with $R^{3'}$-X. Ester **39** is converted to the corresponding hydroxamic acid under standard conditions.

Scheme 9

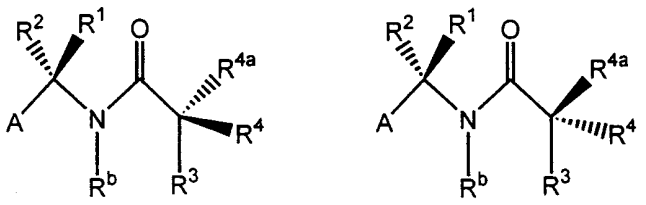


Employing the synthetic sequence described as before, a series of acetamides of formula **42** with an imidazole substituent at the α position are prepared from intermediate **41** (Scheme 10). Likewise, through an intermediacy of **44**, ester **43** is converted to a series of thiophene-substituted acetamides **45.**

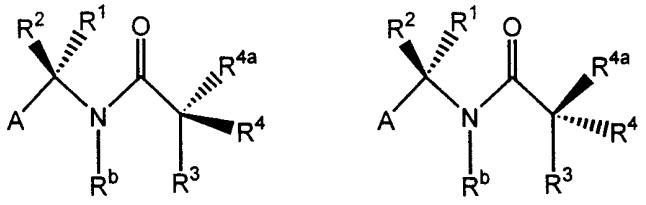
Scheme 10



One diasteriomer of a compound of Formula I may display superior activity compared with the others. Thus, the following stereochemistries are considered to be a part of the present invention.



Ia Ib



Ic Id

When required, separation of the racemic material can be achieved by HPLC using a chiral column or by a resolution using a resolving agent such as camphonic chloride as in Steven D. Young, et al, *Antimicrobial Agents and Chemotheraphy* **1995**, 2602-2605. A chiral compound of Formula I may also be directly synthesized using a chiral catalyst or a chiral ligand, e.g., Andrew S. Thompson, et al, *Tet. lett.* **1995**, *36*, 8937-8940).

Other features of the invention will become apparent in the course of the following descriptions of exemplary embodiments which are given for illustration of the invention and are not intended to be limiting thereof.

Examples

Abbreviations used in the Examples are defined as follows: "1 x" for once, "2 x" for twice, "3 x" for thrice, "°C" for degrees Celsius, "eq" for equivalent or equivalents, "g" for gram or grams, "mg" for milligram or milligrams, "mL" for milliliter or milliliters, "^{1}H" for proton, "h" for hour or hours, "M" for molar, "min" for minute or minutes, "MHz" for megahertz, "MS" for mass spectroscopy, "NMR" for nuclear magnetic resonance spectroscopy, "rt" for room temperature, "tlc" for thin layer chromatography, "v/v" for volume to volume ratio. "α", "β", "R" and "S" are stereochemical designations familiar to those skilled in the art.

Example 1

(R)-N-[1-[(hydroxyamino)carbonyl]-2-methylpropyl]-1-(4-methylphenyl)cyclopropanecarboxamide

(1a) BOP reagent (20.35 g, 1 eq) was added to a mixture N-t-BOC-D-valine (10.0 g, 46.0 mmol), O-benzyl hydroxylamine hydrochloride (14.69 g, 2 eq), N,N-diisopropylethylamine (32.9 mL, 4 eq) and N,N-dimethylformamide (50 mL) at 0 °C. After 10 min at 0 °C and 3 h at rt, ethyl acetate (400 mL) was added. The mixture was washed successively with 10% citric acid (2 x 60 mL), saturated brine (2 x 60 mL), saturated sodium bicarbonate (60 mL), brine (60 mL), dried ($MgSO_4$) and concentrated. The desired product was collected by crystallization from ethyl acetate-hexane (1:1) as a white solid (11.0 g, 74%). MS found: $(M+H)^+ = 323$.

(1b) The amide (11.0 g, 34.0 mmol) from reaction (1a) was stirred in 4.0 M dioxane solution of hydrogen chloride (85 mL) at rt for 1 h. Removal of solvent in vacuo provided crude amine hydrochloride (10.55 g). This material was used in the next step without purification.

(1c) N,N-diisopropylethylamine (0.539 mL, 4 eq) was added to a mixture of the crude amine hydrochloride (200 mg) from reaction (1b), 1-(4-methylphenyl)-1-cyclopropane carboxylic acid (163 mg, 1.2 eq) and HATU (441 mg, 1.5 eq) in N,N-dimethylformamide (1 mL). The mixture was stirred at room temperature overnight and at 70 °C for 90 min. Following addition of ethyl acetate (100 mL), the mixture was washed with 1:1 mixture of 1 N hydrochloric acid-saturated brine (2 x 10 mL), dried ($MgSO_4$) and concentrated.

Silica gel column chromatography (ethyl acetate-hexane, 40:60) yielded the desired product (127 mg, 52% for two steps). MS found: $(M+H)^+ = 381$.

(1d) A mixture of the O-benzylhydroxamic acid (115 mg, 0.303 mmol) from reaction (1c) and 5% palladium on barium sulfate (0.46 g) in methanol (5 mL) was stirred under balloon pressure hydrogen for 90 min. The catalyst was removed by filtration and the filtrate was concentrated to give the desired hydroxamic acid (90.3 mg, 100%). MS found: $(M-H)^- = 289$.

Example 2

(R)-N-[1-[(hydroxyamino)carbonyl]-2-methylpropyl]-1-(4-methoxyphenyl)cyclopropanecarboxamide

(2a) In a procedure analogous to that described for reaction (1c), the crude amine hydrochloride (200 mg) from reaction (1b) was reacted with 1-(4-methoxyphenyl)-1-cyclopropane carboxylic acid (178 mg, 1.2 eq) to give the desired O-benzylhydroxamic acid (107 mg, 42% for two steps). MS found: $(M+Na)^+ = 419$.

(2b) In a procedure analogous to that described for reaction (1d), the O-benzylhydroxamic acid (90.0 mg, 0.223 mmol) from reaction (2a) was hydrogenolyzed to give the desired hydroxamic acid (69.7 mg, 100%). MS found: $(M-H)^- = 305$.

Example 3

(R)-N-[1-[(hydroxyamino)carbonyl]-3-(methylthio)propyl]-1-(4-methoxyphenyl)cyclopropanecarboxamide

(3a) In a procedure analogous to that described for reaction (1c), D-methionine methyl ester hydrochloride (2.00 mg, 10.0 mmol) was reacted with 1-(4-methoxyphenyl)-1-cyclopropane carboxylic acid (2.31 g, 1.2 eq) to give the desired amide (3.17 g, 94%). MS found: $(M+H)^+ = 338$.

(3b) Preparation of hydroxylamine/potassium hydroxide solution: A solution of potassium hydroxide (2.81 g, 1.5 eq) in methanol (7 mL) was added to a hot solution of hydroxylamine hydrochloride (2.34 g, 33.7 mmol) in methanol (12 mL). After the mixture was cooled to room temperature, the precipitate was removed by filtration. The filtrate was used fresh and assumed hydroxylamine concentration of 1.76 M.

The above freshly prepared 1.76 M hydroxylamine solution (0.74 mL, 4 eq) was added to the ester (110 mg, 0.326 mmol) from reaction (3a) in methanol (2 mL). After 3 h

at rt, the solution was adjusted to pH 4.0 with 1 N HCl. After removal of methanol in vacuo, the residue was extracted with ethyl acetate. The organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Preparative thin layer chromatography (methanol-dichloromethane, 7.5:92.5) gave the desired hydroxamic acid (55.2 mg, 50%). MS found: $(M-H)^-$ = 337.

Example 4

(R)-N-[1-[(hydroxyamino)carbonyl]-3-(methylsulfonyl)propyl]-1-(4-methoxyphenyl)cyclopropanecarboxamide

(4a) A solution of Oxone® (0.60 g) in water (2.6 mL) was added to the sulfide (220 mg, 0.650 mmol) from reaction (3a) in methanol (2.6 mL) at 0 °C. After 4 h at rt, the mixture was diluted with water and extracted with chloroform three times. The combined extracts were washed with water, brine, dried (Na_2SO_4) and concentrated to give the desired sulfone (240 mg, 100%). MS found: $(M+H)^+$ = 370.

(4b) In a procedure analogous to that described for reaction (3b), the ester (157 mg, 0.425 mmol) from reaction (4a) was reacted with hydroxylamine to give the desired hydroxamic acid (140,4 mg, 89%). MS found: $(M-H)^-$ = 369.

Example 5

N-[1-(R)-[(hydroxyamino)carbonyl]-2-methylpropyl]-N,alpha,alpha-trimethylbenzeneacetamide

(5a) In a procedure analogous to that described for reaction (1a), N-t-BOC-N-methyl-D-valine (5.00 g, 21.6 mmol) was reacted with O-benzylhydroxylamine hydrochloride (5.18 g, 1.5 eq). Silica gel column chromatography (ethyl acetate-hexane, 25:75) yielded the desired amide (6.63 g, 91%). MS found: $(M+H)^+$ = 337.

(5b) In a procedure analogous to that described for reaction (1b), the amide (144 mg, 1.eq) from reaction (5a) was reacted with hydrogen chloride to give the desired amine hydrochloride (5.49 g, 100%). MS found: $(M+H)^+$ = 237.

(5c) In a procedure analogous to that described for reaction (1c), α,α-dimethylphenylacetic acid (144 mg, 1.2 eq) was reacted with the amine (200 mg, 0.734 mmol) from reaction (5b). Silica gel column chromatography (ether-dichloromethane-hexane, 25:25:50) yielded the desired product (92.8 mg, 33%). MS found: $(M-H)^-$ = 381.

(5d) In a procedure analogous to that described for reaction (1d), the O-benzylhydroxamic acid (78.7 mg, 0.206 mmol) from reaction (5c) was hydrogenolyzed. Preparative thin layer chromatography (methanol-dichloromethane, 5:95) gave the desired hydroxamic acid (48 mg, 80%). MS found: $(M-H)^-$ = 291.

Example 6

(R)-N-[1-[(hydroxyamino)carbonyl]-2-methylpropyl]-N-methyl-1-phenylcyclopropanecarboxamide

(6a) In a procedure analogous to that described for reaction (1c), 1-phenyl-1-cyclopropane carboxylic acid (140 mg, 1.2 eq) was reacted with the amine (200 mg, 0.734 mmol) from reaction (5b). Silica gel column chromatography (ethyl acetate-hexane, 35:65) yielded the desired product (64.2 mg, 26%). MS found: $(M-H)^-$ = 379.

(6b) In a procedure analogous to that described for reaction (1d), the O-benzylhydroxamic acid (59.5 mg, 0.163 mmol) from reaction (6a) was hydrogenolyzed to give the desired hydroxamic acid (43.8 mg, 93%). MS found: $(M-H)^-$ = 289.

Example 7

(R)-N-[1-[(hydroxyamino)carbonyl]-2-methylpropyl]-N-methyl-1-(4-methylphenyl)cyclopropanecarboxamide

(7a) In a procedure analogous to that described for reaction (1c), 1-(4-methylphenyl)-1-cyclopropane carboxylic acid (155 mg, 1.2 eq) was reacted with the amine (200 mg, 0.734 mmol) from reaction (5b). Silica gel column chromatography (ethyl acetate-hexane, 35:65) yielded the desired product (118.4 mg, 41%). MS found: $(M+Na)^+$ = 417.

(7b) In a procedure analogous to that described for reaction (1d), the O-benzylhydroxamic acid (110 mg, 0.279 mmol) from reaction (7a) was hydrogenolyzed to give the desired hydroxamic acid (84.2 mg, 99%). MS found: $(M-H)^-$ = 303.

Example 8

(R)-N-[1-[(hydroxyamino)carbonyl]-2-methylpropyl]-1-(4-methoxyphenyl)-N-methylcyclopropanecarboxamide

(8a) In a procedure analogous to that described for reaction (1c), 1-(4-methoxyphenyl)-1-cyclopropane carboxylic acid (169 mg, 1.2 eq) was reacted with the amine (200 mg,

0.734 mmol) from reaction (5b). Silica gel column chromatography (ethyl acetate-hexane, 35:65) yielded the desired product (158 mg, 52%). MS found: $(M+H)^+ = 411$.

(8b) In a procedure analogous to that described for reaction (1d), the O-benzylhydroxamic acid (150 mg, 0.365 mmol) from reaction (8a) was hydrogenolyzed. Preparative thin layer chromatography (methanol-dichloromethane, 7:93) gave the desired hydroxamic acid (52.2 mg, 45%). MS found: $(M-H)^- = 319$.

Example 9

(R)-1-(4-chlorophenyl)-N-[1-[(hydroxyamino)carbonyl]-2-methylpropyl]-N-methylcyclopropanecarboxamide

(9a) In a procedure analogous to that described for reaction (1c), 1-(4-chlorophenyl)-1-cyclopropane carboxylic acid (150 mg, 0.763 mmol) was reacted with the amine (312 mg, 1.2 eq) from reaction (5b). Silica gel column chromatography (ethyl acetate-hexane, 30:70 then 40:60) yielded the desired product (188.8 mg, 60%). MS found: $(M-H)^- = 413$.

(9b) In a procedure analogous to that described for reaction (1d), the O-benzylhydroxamic acid (188.8 mg, 0.455 mmol) from reaction (9a) was hydrogenolyzed to give the desired hydroxamic acid (142 mg, 96%). MS found: $(M-H)^- = 323$.

Example 10

(R)-1-(2,4-dichlorophenyl)-N-[1-[(hydroxyamino)carbonyl]-2-methylpropyl]-N-methylcyclopropanecarboxamide

(10a) In a procedure analogous to that described for reaction (1c), 1-(2,4-dichlorophenyl)-1-cyclopropane carboxylic acid (406 mg, 1.2 eq) was reacted with the amine (400 mg, 1.46 mmol) from reaction (5b). Silica gel column chromatography (ethyl acetate-hexane, 35:65) yielded the desired product (180 mg, 27%). MS found: $(M+Na)^+ = 471$.

(10b) In a procedure analogous to that described for reaction (1d), the O-benzylhydroxamic acid (180 mg, 0.401 mmol) from reaction (10a) was hydrogenolyzed to give the desired hydroxamic acid (113 mg, 79%). MS found: $(M-H)^- = 357$.

Example 11

(R)-1-(4-chlorophenyl)-N-[1-[(hydroxyamino)carbonyl]-2-methylpropyl]-N-methylcyclobutanecarboxamide

(11a) In a procedure analogous to that described for reaction (1c), 1-(4-chlorophenyl)-1-cyclobutane carboxylic acid (371 mg, 1.2 eq) was reacted with the amine (400 mg, 1.46 mmol) from reaction (5b). Silica gel column chromatography (ethyl acetate-hexane, 30:70) yielded the desired product (340 mg, 54%). MS found: $(M+H)^+ = 429$.

(11b) In a procedure analogous to that described for reaction (1d), the O-benzylhydroxamic acid (300 mg, 0.700 mmol) from reaction (11a) was hydrogenolyzed to give the desired hydroxamic acid (187 mg, 79%). MS found: $(M-H)^- = 337$.

Example 12

(R)-1-(4-chlorophenyl)-N-[1-[(hydroxyamino)carbonyl]-2-methylpropyl]-N-methylcyclopentanecarboxamide

(12a) In a procedure analogous to that described for reaction (1c), 1-phenyl-1-cyclopentane carboxylic acid (144 mg, 0.755 mmol) was reacted with the amine (309 mg, 1.5 eq) from reaction (5b) at 60 °C for 60 h. Silica gel column chromatography (ethyl acetate-hexane, 15:85 then 25:75) yielded the desired product (78.4 mg, 25%). MS found: $(M-H)^- = 407$.

(12b) In a procedure analogous to that described for reaction (1d), the O-benzylhydroxamic acid (78.4 mg, 0.192 mmol) from reaction (12a) was hydrogenolyzed to give the desired hydroxamic acid (43.7 mg, 72%). MS found: $(M-H)^- = 317$.

Example 13

alpha-(R)-hydroxy-N-[1-(R)-[(hydroxyamino)carbonyl]-2-methylpropyl]-N-methylbenzeneacetamide

(13a) In a procedure analogous to that described for reaction (1c), (+)-mandelic acid (134 mg, 1.2 eq) was reacted with the amine (200 mg, 0.734 mmol) from reaction (5b) at rt for 4 h. Silica gel column chromatography (ethyl acetate-hexane, 50:50) yielded the desired product (106 mg, 39%). MS found: $(M+H)^+ = 371$.

(13b) In a procedure analogous to that described for reaction (1d), the O-benzylhydroxamic acid (84.2 mg, 0.301 mmol) from reaction (13a) was hydrogenolyzed. Preparative thin layer chromatography (methanol-chloroform, 20:80) gave the desired hydroxamic acid (31.1 mg, 37%). MS found: $(M-H)^- = 279$.

Example 14

1,1-dimethylethyl [2-[[1-(R)-[(hydroxyamino)carbonyl]-2-methylpropyl]methylamino]-2-oxo-1-phenylethyl]carbamate

(14a) In a procedure analogous to that described for reaction (1c), N-BOC-L-phenylglycine (220 mg, 1.2 eq) was reacted with the amine (200 mg, 0.734 mmol) from reaction (5b) at rt overnight. Silica gel column chromatography (ethyl acetate-hexane, 35:65) yielded the desired product (240 mg, 70%) as a 3:1 mixture of two diastereomers due to partial epimerization of the phenylglycine section. MS found: $(M+H)^+ = 470$.

(14b) In a procedure analogous to that described for reaction (1d), the O-benzylhydroxamic acid (100 mg, 0.322 mmol) from reaction (14a) was hydrogenolyzed to give the desired hydroxamic acid (87.7 mg, 100%). MS found: $(M+H)^+ = 380$.

Examples 15-31 can be made analogously to Examples 1-14, utilizing necessary modifications obvious to one skilled in the art.

Example 15

1-{[1-(2,4-dichlorophenyl)cyclopropyl]carbonyl}-N-hydroxy-2-piperidinecarboxamide

Example 16

1-{[1-(2,4-dichlorophenyl)cyclopropyl]carbonyl}-N-hydroxy-2-pyrrolidinecarboxamide

Example 17

(2R)-N-hydroxy-2-[[(4-methoxyphenyl)acetyl](methyl)amino]-3-methylbutanamide

Example 18

1-{4-[(2,4-dimethylbenzyl)oxy]phenyl}-N-[(1S)-2-(hydroxyamino)-1-methyl-2-oxoethyl]-N-methylcyclopropanecarboxamide

Example 19

(2S)-N-hydroxy-2-[[(4-methoxyphenyl)acetyl](methyl)amino]propanamide

Example 20

N-[(1S)-2-(hydroxyamino)-1-methyl-2-oxoethyl]-N-methyl-1-[4-(2-naphthylmethoxy)phenyl]cyclopropanecarboxamide

Example 21

N-[(1S)-2-(hydroxyamino)-1-methyl-2-oxoethyl]-N-methyl-1-[4-(4-pyridinylmethoxy)phenyl]cyclopropanecarboxamide trifluoroacetic acid salt

Example 22

(2R)-2-[{[4-(benzyloxy)phenyl]acetyl}(methyl)amino]-N-hydroxy-3-methylbutanamide

Example 23

(2R)-2-[({4-[(3,5-dimethylbenzyl)oxy]phenyl}acetyl)(methyl)amino]-N-hydroxy-3-methylbutanamide

Example 24

(2R)-2-[{[4-(1H-1,2,3-benzotriazol-1-ylmethoxy)phenyl]acetyl}(methyl)amino]-N-hydroxy-3-methylbutanamide

Example 25

N-[(1S)-2-(hydroxyamino)-1-methyl-2-oxoethyl]-N-methyl-1-{4-[(3-phenyl-5-isoxazolyl)methoxy]phenyl}cyclopropanecarboxamide

Example 26

N-[(1S)-2-(hydroxyamino)-1-methyl-2-oxoethyl]-N-methyl-1-[4-(2-propynyloxy)phenyl]cyclopropanecarboxamide

Example 27

1-(4-{[3-(4-fluorophenyl)-5-isoxazolyl]methoxy}phenyl)-N-[(1S)-2-(hydroxyamino)-1-methyl-2-oxoethyl]-N-methylcyclopropanecarboxamide

Example 28

N-[(1S)-2-(hydroxyamino)-1-methyl-2-oxoethyl]-N-methyl-1-{4-[(3-propyl-5-isoxazolyl)methoxy]phenyl}cyclopropanecarboxamide

Example 29

N-{(1S)-1-[(hydroxyamino)carbonyl]-3-methylbutyl}-1-{4-[(2-methyl-4-quinolinyl)methoxy]phenyl}-N-propylcyclopropanecarboxamide trifluoroacetic acid salt

Example 30

N-[3-(cyclopentylamino)propyl]-N-{(1S)-1-[(hydroxyamino)carbonyl]-3-methylbutyl}-1-{4-[(2-methyl-4-quinolinyl)methoxy]phenyl}cyclopropanecarboxamide bis-trifluoroacetic acid salt

Example 31

tert-butyl (1S)-1-[4-(benzyloxy)phenyl]-2-[[(1S)-2-(hydroxyamino)-1-methyl-2-oxoethyl](methyl)amino]-2-oxoethylcarbamate

Example 32

2-[4-(benzyloxy)phenyl]-N-[(1S)-2-(hydroxyamino)-1-methyl-2-oxoethyl]-2-pyrrolidinecarboxamide trifluoroacetic acid salt

(32a) To a stirred, cooled (-78° C) solution of 0.35 grams of methyl {[(benzyloxy)carbonyl]amino}[4-(benzyloxy)phenyl]acetate in 10 mL of tetrahydrofuran and 1 mL of DMPU was added 2.03 mL of 1M LDA followed after 1 hour with the addition of 0.102 mL of 1-bromo-2-propane. The reaction was allowed to slowly warm to room temperature, quenched with saturated aqueous citric acid and extracted 3 times with ethyl acetate. The combined organics were washed with water, brine, dried over $MgSO_4$ and the volatiles were removed under reduced pressure affording the title material. LRMS found $(M+Na)^+ = 434$.

(32b) To 0.1grams of material from example 32a in 2.5 mL of methanol, 1.5 mL of dimethyl sulfoxide and 1 mL of water was added 0.1 grams of lithium hydroxide and heated at 78°C overnight. The volatiles were removed under reduced pressure and the remaining material was diluted with ether, washed with 1N HCl and extracted 3 times with ether. The combined ether extracts were washed with brine, dried over $MgSO_4$ and the volatiles were removed under reduced pressure affording the title compound. LRMS found $(M+H)^+ = 398$.

(32c) To the material from example 32b in 0.5 mL of dimethylformamide was added 0.13 mL of N-methylmorpholine, 0.084 grams of HATU and 0.083 grams of D-leucine methylester hydrochloride. After stirring one hour at room temperature the reaction was heated at 80°C for an additional hour. The mixture was diluted with ethyl acetate and washed with 1N HCl. The aqueous was extracted an additional three times with ethyl acetate. The combined extracts were washed with brine, saturated aqueous sodium bicarbonate, brine, dried over $MgSO_4$ and the volatiles were removed under reduced pressure affording the title material as a mixture of diastereomers. The isomers were separated by silica gel chromatography eluting with a gradient of 10-25% ethyl acetate / hexane affording the title compounds. LRMS for both found $(M+H)^+ = 525$.

(32d) To 0.035 grams of the faster diastereomer from example 32c in 0.5 mL tetrahydrofuran and 0.5 mL of water was added 0.014 grams of lithium hydroxide monohydrate. After stirring at ambient temperature for 2 hours the reaction was acidified with 1N HCl which had been previously saturated with sodium chloride. The mixture was extracted three times with ethyl acetate. The extracts were washed with brine, dried over $MgSO_4$ and the volatiles were removed under reduced pressure affording the title compound. LRMS found $(M+H)^+ = 511$.

(32e) To 0.029 grams of compound from example 32d in 1 mL of dimethylformamide was added 0.062 mL of N-methylmorpholine, 0.020 grams of hydroxylamine hydrochloride, and 0.033 grams of BOP. After stirring at ambient temperature overnight the reaction was diluted with a mixture of 1N HCl, water and brine, then extracted 3 times with ethyl acetate. The combined extracts were washed with brine, saturated aqueous sodium bicarbonate, brine, dried over $MgSO_4$ and the volatiles were removed under reduced pressure. The resulting material was purified by reverse phase C-18 HPLC affording the title compound. LRMS found $(M+H)^+ = 526$.

(32f) To 0.011 grams of material from example 32e in 1 mL of dichloromethane was added 0.1 mL of trifluoroacetic acid. After stirring for 1 hour at ambient temperature the volatiles were removed under reduced pressure affording the title compound. LRMS found $(M+H)^+ = 426$.

Example 33

(1S)-N-hydroxy-2-({4-[(2-methyl-4-quinolinyl)methoxy]phenyl}acetyl)cyclopentanecarboxamide trifluoroacetic acid salt

(33a) To 3.0 grams of methyl (4-hydroxyphenyl)acetate in 200 mL of acetone was added 2.74 grams of sodium iodide, 4.59 grams of 4-(chloromethyl)-2-methylquinoline and 25 grams of potassium carbonate. After heating the mixture at 55°C overnight it was concentrated ~ 80% under reduced pressure. The resulting material was diluted with ether and water and separated. The aqueous was extracted an additional two times with ether. The combined ether extracts were then extracted twice with 1N HCl. The acidic aqueous were combined and washed once with ether. The aqueous was then rendered basic with the addition of saturated aqueous sodium bicarbonate and extracted three times with ethyl acetate. The ethyl acetate extracts were combined, dried over $MgSO_4$ and the volatiles were removed under reduced pressure. The resulting material was chromatographed on

silica gel eluting with a gradient of 25 to 80% ethyl acetate/hexane affording the title compound. LRMS found $(M+H)^+ = 322$.

(33b) To 4.0 grams of the compound from 34a in 50 mL of tetrahydrofuran and 50 mL of water was added 1.05 grams of lithium hydroxide monohydrate. After stirring 30 minutes at ambient temperature the mixture was poured into saturated aqueous ammonium chloride and extracted three times with ethyl acetate. The combined organic extracts were washed with brine, dried over magnesium sulfate and the volatiles were removed under reduced pressure affording 1 gram of the title material. The original aqueous was acidified with 1N HCl and a precipitate formed. This was not readily soluble in any of the solvents tried, but the aqueous was extracted with chloroform, ethyl acetate and benzene. All of the organic extracts were combined, washed with brine, dried over $MgSO_4$, and the volatiles were removed under reduced pressure. This afforded an additional 2 grams of the title material. LRMS found $(M+H)^+ = 308$.

(33c) To 0.20 grams of the material from example 33b in 2 mL of dimethylformamide was added 0.43 mL of N-methylmorpholine and 0.285 grams of HATU. After stirring 5 minutes at ambient temperature 0.225 grams of D-proline methylester was added. The reaction was stirred one hour at 80°C, poured into saturated aqueous ammonium chloride and extracted three times with ethylacetate. The combined organics were washed with brine, saturatedaqueous sodium bicarbonate, brine, dried over $MgSO_4$ and, passed through a short plug of silica gel eluting with ethyl acetate. The volatiles were removed under reduced pressure affording the title compound. LRMS found $(M+H)^+ = 419$

(33d) To 0.190 grams of material from example 33c in 2 mL of tetrahydrofuran and 2 mL of water was added 0.095 grams of lithium hydroxide monohydrate. The reaction was stirred 45 minutes at ambient temperature, acidified by the addition of 2.25 mL of 1.00 M hydrochloric acid, extracted three times with ethylacetate, twice with benzene, and three times with chloroform. All of the extracts were combined, dried over $MgSO_4$ and the volatiles were removed under reduced pressure affording the title compound. LRMS found $(M+H)^+ = 405$.

(33e) To 0.110 grams of material from example 33d in 2 mL of dimethylformamide was added 0.21 mL of N-methylmorpholine, 0.095 grams of hydroxylamine hydrochloride and 0.132 grams of BOP. After stirring for 2 hours at ambient temperature the material was poured into saturated aqueous sodium bicarbonate and extracted three times with ethyl acetate. All the extracts were combined, dried over MgSO4 and the volatiles were removed under reduced pressure. The material was dissolved in methanol /

dimethylsulfoxide with 0.1 mL of trifluoroacetic acid and purified by reverse phase C-18 HPLC affording the title material. LRMS found $(M+H)^+ = 420$.

Example 34

(1R)-N-hydroxy-2-({4-[(2-methyl-4-quinolinyl)methoxy]phenyl}acetyl)cyclopentanecarboxamide trifluoroacetic acid salt

(34a) To 0.20 grams of the material from example 33b in 2 mL of dimethylformamide was added 0.43 mL of N-methylmorpholine and 0.285 grams of HATU. After stirring 5 minutes at ambient temperature 0.225 grams of L-proline methylester was added. The reaction was stirred one hour at 80°C and poured into 2.6 mL of 1.00 N HCl and extracted three times with ethylacetate. The combined organics were washed with brine, saturated aqueous sodium bicarbonate, brine, dried over $MgSO_4$ and, passed through a short plug of silica gel eluting with ethyl acetate. The volatiles were removed under reduced pressure affording the title compound. LRMS found $(M+H)^+ = 419$.

(34b) To 0.110 grams of material from example 34a in 1.5 mL of tetrahydrofuran and 1.5 mL of water was added 0.056 grams of lithium hydroxide monohydrate. The reaction was stirred 30 minutes at ambient temperature, neutralized by the addition of 1.30 mL of 1.00 M hydrochloric acid, extracted three times with ethyl acetate. All of the extracts were combined, dried over $MgSO_4$ and the volatiles were removed under reduced pressure affording the title compound. LRMS found $(M+H)^+ = 405$.

(34c) To 0.10 grams of material from example 33d in 1 mL of dimethylformamide was added 0.19 mL of N-methylmorpholine, 0.086 grams of hydroxylamine hydrochloride and 0.120 grams of BOP. After stirring for 3 hours at ambient temperature the material was poured into saturated aqueous sodium bicarbonate and extracted three times with ethyl acetate. All the extracts were combined, dried over $MgSO_4$ and the volatiles were removed under reduced pressure. The material was purified by reverse phase C-18 HPLC affording the title material. LRMS found $(M+H)^+ = 420$.

Example 35

(3S)-N-hydroxy-2,2-dimethyl-4-({4-[(2-methyl-4-quinolinyl)methoxy]phenyl}acetyl)-3-thiomorpholinecarboxamide trifluoroacetic acid salt

(35a) To 0.20 grams of the material from example 33b in 2 mL of dimethylformamide was added 0.21 mL of N-methylmorpholine and 0.285 grams of HATU. After stirring 5

minutes at ambient temperature 0.301 grams of tert-butyl (3S)-2,2-dimethyl-3-thiomorpholinecarboxylate was added. The reaction was stirred one hour at 80°C and poured into saturated aqueous ammonium chloride and extracted three times with ethylacetate. The combined organics were washed with brine, saturatedaqueous sodium bicarbonate, brine, dried over $MgSO_4$, and the volatiles were removed under reduced pressure. The material was chromatographed on silica gel eluting with a gradient of 20 to 50% ethyl acetate in hexanes affording the title compound. LRMS found $(M+H)^+ = 521$.

(35b) To 0.225 grams of material from example 35a was added 5 ml of dichloromethane and 5 mL of trifluoroacetic acid. The reaction was stirred 2 hours at ambient temperature and the volatiles were removed under reduced pressure affording the title compound as the TFA salt. LRMS found $(M+H)^+ = 465$.

(35c) To 0.220 grams of material from example 35b in 4 mL of dimethylformamide was added 0.33 mL of N-methylmorpholine, 0.132 grams of hydroxylamine hydrochloride and 0.185 grams of BOP. After stirring for 3 hours at ambient temperature the material was poured into saturated aqueous sodium bicarbonate and extracted three times with ethyl acetate. All the extracts were combined, dried over $MgSO_4$ and the volatiles were removed under reduced pressure. The material was purified by reverse phase C-18 HPLC affording the title material. LRMS found $(M+H)^+ = 480.3$.

Example 36

(2R)-N-hydroxy-1-({4-[(2-methyl-4-quinolinyl)methoxy]phenyl}acetyl)-2-piperidinecarboxamide trifluoroacetic acid salt

(36a) To 0.20 grams of the material from example 33b in 2 mL of dimethylformamide was added 0.43 mL of N-methylmorpholine and 0.285 grams of HATU. After stirring 5 minutes at ambient temperature 0.234 grams of methyl (2R)-2-piperidinecarboxylate was added. The reaction was stirred for 30 minutes at ambient temperature and one hour at 80 C. The reaction was poured into saturated aqueous ammonium chloride and extracted three times with ethylacetate. The combined organics were washed with brine, saturated aqueous sodium bicarbonate, brine, dried over $MgSO_4$, and the volatiles were removed under reduced pressure. The material was chromatographed on silica gel eluting with a gradient of 20 to 40% ethyl acetate in hexanes affording the title compound. LRMS found $(M+H)^+ = 433$.

(36b) To 0.235 grams of material from example 36a in 2mL of tetrahydrofuran and 2 mL of water was added 0.109 grams of lithium hydroxide monohydrate. The reaction was

stirred 1 hour at ambient temperature then 0.050 grams of lithium hydrate monohydrate was added. After stirring an additional hour the reaction was neutralized by the addition of 4.0 mL of 1.00 M hydrochloric acid, extracted three times with ethylacetate. All of the extracts were combined, dried over $MgSO_4$ and the volatiles were removed under reduced pressure affording the title compound. LRMS found $(M+H)^+ = 419$.

(36c) To 0.175 grams of material from example 36b in 2 mL of dimethylformamide was added 0.32 mL of N-methylmorpholine, 0.145 grams of hydroxylamine hydrochloride and 0.204 grams of BOP. After stirring for 4 hours at ambient temperature the material was poured into saturated aqueous sodium bicarbonate and extracted three times with ethyl acetate. All the extracts were combined, dried over $MgSO_4$ and the volatiles were removed under reduced pressure. The material was purified by reverse phase C-18 HPLC followed by triteration with ether affording the title material. LRMS found $(M+H)^+ = 434.3$.

Example 37

tert-butyl 3-[(hydroxyamino)carbonyl]-4-({4-[(2-methyl-4-quinolinyl)methoxy]phenyl}acetyl)-1-piperazinecarboxylate trifluoroacetic acid salt

(37a) To the 0.260 grams of material from example 33b in 5 mL of benzene was added 0.31 mL of thionyl chloride. The reaction was heated at 55°C for 2 hours. The volatiles were removed under reduced pressure affording the title compound as the HCl salt. LRMS found $(M+H)^+ = 322$.

(37b) To 0.20 grams of material from example 37a in 5 mL of dichloromethane was added 0.127 grams of the 4-(tert-butoxycarbonyl)-2-piperazinecarboxylic acid and 0.183 mL of N-methylmorpholine. After stirring the reaction for 2 hours at ambient the volatiles were removed under reduced pressure and the resulting material was chromatographed on C-18 reverse phase HPLC affording the title material as a TFA salt. LRMS found $(M+H)^+ = 520.4$.

(37c) To 0.150 grams of material from example 37b in 4 mL of dimethylformamide was added 0.21 mL of N-methylmorpholine, 0.126 grams of hydroxylamine hydrochloride and 0.126 grams of BOP. After stirring for 4 hours at ambient temperature the material was poured into saturated aqueous sodium bicarbonate and extracted three times with ethyl acetate. All the extracts were combined, dried over $MgSO_4$ and the volatiles were

removed under reduced pressure. The material was purified by reverse phase C-18 HPLC affording the title material as the TFA salt. LRMS found $(M+H)^+ = 535$.

Example 38

N-hydroxy-1-({4-[(2-methyl-4-quinolinyl)methoxy]phenyl}acetyl)-2-piperazinecarboxamide bis-trifluoroacetic acid salt

(38a) To 0.010 grams of material from example 37c was added 0.5 ml of dichloromethane and 0.55 mL of trifluoroacetic acid. The reaction was stirred 2 hours at ambient temperature and the volatiles were removed under reduced pressure affording the title compound as the bis TFA salt. LRMS found $(M+H)^+ =435$.

Example 39

benzyl (3R)-3-[(hydroxyamino)carbonyl]-2-({4-[(2-methyl-4-quinolinyl)methoxy]phenyl}acetyl)tetrahydro-1(2H)-pyridazinecarboxylate trifluoroacetic acid salt

(39a) To 0.050 grams of 1-benzyl 3-methyl (3R)-tetrahydro-1,3(2H)-pyridazinedicarboxylate in 1 mL of dichloroethane was added 0.094 mL of diisopropylethyl amine and 0.065 grams of the material from 37a. The mixture was stirred 20 minutes at ambient temperature and 1 hour at 50 C. The reaction was diluted with dichloromethane and washed with brine. The aqueous was extracted 3 times with dichloromethane. All the extracts were combined, dried over $MgSO_4$ and the volatiles were removed under reduced pressure. The material was chromatographed on silica gel eluting with 20% ehtyl acetate in hexanes affording the title compound. LRMS found $(M+H)^+ = 568$.

(39b) To 0.075 grams of material from example 39a in 2mL of tetrahydrofuran and 2 mL of water was added 0.028 grams of lithium hydroxide monohydrate. The reaction was stirred 1 hour at ambient temperature at which time 0.66 mL of 1.00 M HCl was added and the mixture was extracted three times with ethyl acetate. All of the extracts were combined, washed with brine, dried over $MgSO_4$ and the volatiles were removed under reduced pressure affording the title compound. LRMS found $(M+H)^+ =554$.

(39c) To 0.075 grams of material from example 39b in 2 mL of dimethylformamide was added 0.104 mL of N-methylmorpholine, 0.047 grams of hydroxylamine hydrochloride and 0.066 grams of BOP. After stirring for 48 hours at ambient temperature the material

was poured into saturated aqueous sodium bicarbonate and extracted three times with ethyl acetate. All the extracts were combined, washed with brine, dried over MgSO4 and the volatiles were removed under reduced pressure. The material was purified by reverse phase C-18 HPLC followed by ether triteration affording the title material as the TFA salt. LRMS found $(M+H)^+$ =569.

Example 40

(3R)-N-hydroxy-2-({4-[(2-methyl-4-quinolinyl)methoxy]phenyl}acetyl)hexahydro-3-pyridazinecarboxamide bis-trifluoroacetic acid salt

(40a) To 0.018 grams of material from example 39c was added 1 mL of 32% hydrogen bromide in acetic acid. The reaction was stirred one hour at ambient temperature and the volatiles were removed under reduced pressure. The material was purified by C-18 reverse phase HPLC affording the title compound. LRMS found (M+H)+ = 435.

Example 41

(3R)-N-hydroxy-2-({4-[(2-methyl-4-quinolinyl)methoxy]phenyl}acetyl)-1,2,3,4-tetrahydro-3-isoquinolinecarboxamide trifluoroacetic acid salt

(41a) To 0.245 grams of compound from example 37a in 7.5 mL of dichloroethane was added 0.47 mL of diisopropylethyl amine and 0.156 grams of tert-butyl (3R)-1,2,3,4-tetrahydro-3-isoquinolinecarboxylate. The mixture was stirred 20 minutes at ambient temperature and 2 hours at 55°C. The reaction was diluted with dichloromethane and washed with brine. The aqueous was extracted 3 times with dichloromethane. All the extracts were combined, dried over $MgSO_4$ and the volatiles were removed under reduced pressure affording the title compound. LRMS found $(M+H)^+$ =523.

(41b) To 0.110 grams of material from example 41a was added 1 ml of dichloromethane and 1 mL of trifluoroacetic acid. The reaction was stirred 2 hours at ambient temperature and the volatiles were removed under reduced pressure and the resulting material was purified by C-18 reverse phase HPLC affording the title compound. LRMS found (M+H)+ = 467.

(41c) To 0.085 grams of material from example 41b in 2 mL of dimethylformamide was added 0.12 mL of N-methylmorpholine, 0.051 grams of hydroxylamine hydrochloride and 0.078 grams of BOP. After stirring for 20 hours at ambient temperature the material was poured into saturated aqueous sodium bicarbonate and extracted three times with ethyl

acetate. All the extracts were combined, washed with brine, dried over MgSO4 and the volatiles were removed under reduced pressure. The material was purified by reverse phase C-18 HPLC affording the title material as the TFA salt. LRMS found $(M+H)^+$ = 482.

Example 42

2-((*R/S*)-2-phenylbutyramido)-N-hydroxy-(*R*)-propionamide

(42a) 2-t-Bulyloxycarbonylamino-N-benzyloxy-(*R*)-propionamide. To a solution of t-Boc-D-alanine (5.68 g, 30 mmol) and O-benzylhydroxylamine hydrochloride (5.1 g, 32 mmol) in DMF (30 mL) cooled in an ice bath was added BOP (13.7 g, 31 mmol) followed by diisopropylethylamine (17.4 mL, 100 mmol). The solution was stirred for 5 hours, diluted with EtOAc, washed with brine, sodium bicarbonate, brine, citric acid and brine, dried (MgSO4), and concentrated. Crystallization from EtOAc/hexane gave the O-benzylhydroxamate product (6.2 g, 70%) as a solid. MS (ESI): $(M+H)^+$=295.1.

(42b) 2-Amino-N-benzyloxy-(*R*)-propionamide HCl salt. The above compound (4.5 g, 16.18 mmol) was treated with 4 N HCl in dioxane (50 mL) for 1 hour and the solution was concentrated to afford the HCl salt (3.8 g, 100%) as a solid. MS (CI-NH_3): $(M+H)^+$=195.

(42c) 2-((*R/S*)-2-Phenylbutyramido)-N-benzyloxy-(*R*)-propionamide. To a solution of 2-amino-N-benzyloxy-(R)-propionamide HCl Salt (200 mg, 0.868 mmol) and (*R,S*)-2-phenylbutyric acid (143 mg, 0.868 mmol) in 3 mL DMF cooled in an ice bath was added BOP (384 mg, 0.868 mmol) followed by DIEA (0.7 mL, 4 mmol). After stirring for 1 hour at room temperature, the solution was diluted with EtOAC, washed with $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated. Purification on a silica gel column using 5% MeOH in CH_2Cl_2 gave the amide product (260 mg, 88%) as a solid. MS (ESI): $(M-H)^-$ =339.1.

(42d) 2-((*R/S*)-2-Phenylbutyramido)-N-hydroxy-(*R*)-propionamide. 2-((*R,S*)-2-Phenylbutyramido)-N-benzyloxy-(*R*)-propionamide (230 mg, 0.676 mmol) in 20 mL MeOH was hydrogenated at 50 psi in the presence of 5% Pd on $BaSO_4$ (230 mg) for a period of 5 hours. The catalyst was filtered off, the solution evaporated off under reduced pressure, and the residue triturated with ether to afford the hydroxamate compound (110 mg, 67%) as a solid. MS (ESI): $(M-H)^-$=249.0.

Example 43

2-((*R/S*)-α-Methyl-4-isobutylphenylacetamido)-N-hydroxy-(*R*)-propionamide

This compound was synthesized by coupling 2-amino-N-benzyloxy-(*R*)-propionamide HCl salt 42b with (*R/S*)-α-methyl-4-isobutylphenylacetic acid followed by hydrogenation using the procedures as described in Example 42. MS (ESI): $(M-H)^-$=291.0.

Example 44

2-((*R/S*)-2-Fluoro-α-methyl-4-biphenylacetamido)-N-hydroxy-(*R*)-propionamide

This compound was synthesized by coupling 2-amino-N-benzyloxy-(*R*)-propionamide HCl salt 42b with (*R/S*)-2-fluoro-α-methyl-4-biphenylacetic acid (flurbiprofen, Sigma) followed by hydrogenation using the procedures as described in Example 42. MS (ESI): $(M-H)^-$=329.0.

Example 45

2-[N-Methyl-N-((*R/S*)-α-Methyl-4-benzyloxyphenylacetylamino)]-N-hydroxy-(*R*)-propionamide

(45a) Methyl (*R/S*)-α-Methyl-4-benzyloxyphenylacetate. Lithium diisopropylamide (LDA) was prepared by the addition of 2.5 M n-butyllithium (4.8 mL) in hexane to a solution of diisopropylamine (1.68 mL, 12 mmol) in THF (25 mL) at -78 °C followed by stirring at 0 °C for 20 min. A solution of methyl 4-benzyloxyphenylacetate (2.56 g, 10 mmol) in THF (30 mL) was cooled to -78 °C and to it was added the prepared LDA solution. The mixture was stirred at -78 °C for 1 hour and iodomethane (1.25 mL, 20 mmol) was added. The mixture was allowed to warm to 0 °C, stirred for an additional 1.5 hours at 0 °C, quenched with MeOH and concentrated. The residue was taken up in EtOAc and the solution was washed with citric acid and brine, dried ($MgSO_4$) and concentrated. Chromatography on a silica gel column (35% EtOAc/hexane) afforded the α-methylated product (2.6 g, 95%) as a solid. MS (CI-NH_3): $(M+H)^+$=271.

(45b) (*R/S*)-α-Methyl-4-benzyloxyphenylacetic Acid. To a solution of methyl (*R/S*)-α-methyl-4-benzyloxyphenylacetate 45a (2.7 g, 10 mmol) in MeOH (25 mL) was added 1 N LiOH (15 mL). The mixture was stirred for 2 hour and concentrated. EtOAc was added followed by 1 N HCl (10 mL). The organic layer was separated and washed with brine, dried ($MgSO_4$), and concentrated to afford the carboxylic acid (2.3 g, 90%) as a solid. MS (CI-NH_3): $(M+H+NH_3)^+$=274.

(45c) Methyl 2-[N-Methyl-N-((*R/S*)-α-methyl-4-benzyloxyphenylacetyl)amino]-(*R*)-propionate. To a solution of (*R/S*)-α-methyl-4-benzyloxyphenylacetic acid 45b (300 mg,

1.17 mmol) and N-methyl-D-alanine methyl ester (200 mg, 1.3 mmol) in DMF (5 mL) cooled in an ice bath was added BOP (531 mg, 1.2 mmol) followed by DIEA (0.7 mL, 4 mmol). The mixture was stirred at room temperature for 5 hours. EtOAc was added and the solution washed with $NaHCO_3$, brine, citric acid and brine, dried ($MgSO_4$), and concentrated. Purification on a silica gel column (40% EtOAc/hexane) gave the amide product (398 mg, 99%) as a solid. MS (CI-NH_3): $(M+H)^+$=356.

(45d) 2-[N-Methyl-N-((*R/S*)-α-methyl-4-benzyloxyphenylacetyl)amino]-(*R*)-propionic Acid. To a solution of methyl 2-[N-methyl-N-((*R/S*)-α-methyl-4-benzyloxyphenylacetyl)amino]-(*R*)-propionate 45c (380 mg, 1.1 mmol) in THF (10 mL) was added 1 N LiOH (2 mL). The solution was stirred for 1 h and acidified with 1 N HCl to pH 3. EtOAc was added and the organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated to afford the carboxylic acid (360 mg, 98%) as a solid. MS (CI-NH_3): $(M+H)^+$=342.

(45e) 2-[N-Methyl-N-((*R/S*)-α-methyl-4-benzyloxyphenylacetylamino)]-N-hydroxy-(*R*)-propionamide. A solution of 2-[N-methyl-N-((*R/S*)-α-methyl-4-benzyloxyphenylacetyl)amino]-(*R*)-propionic acid (340 mg, 1.0 mmol) and N-hydroxylamine hydrochloride (100 mg, 1.4 mmol) in 5 mL DMF was cooled in an ice bath and to it was added BOP (530 mg, 1.2 mmol) followed by DIEA (0.7 mL, 4 mmol). The mixture was stirred at room temperature for 1 hour. EtOAc was added and the solution washed with brine three times, dried ($MgSO_4$) and concentrated. Purification on reversed phase HPLC afforded the hydroxamate product (110 mg, 31%) as a white powder after lyophilization. MS (ESI): $(M-H)^-$=354.9.

Example 46

2-{N-Methyl-N-[(*R/S*)-α-methyl-4-(3,5-dimethylbenzyloxy)phenylacetyl]amino}-N-hydroxy-(R)-propionamide

(46a) Methyl 2-[N-Methyl-N-((*R/S*)-α-methyl-4-hydroxyphenylacetylamino)]-(R)-propionate. A solution of methyl 2-[N-methyl-N-((*R/S*)-α-methyl-4-benzyloxyphenylacetyl)amino]-(*R*)-propionate 45c (2.0 g, 5.6 mmol) in MeOH (20 mL) was hydrogenated under atmospheric pressure in the presence of 10% Pd/C (0.2 g) for a period of 1 hour. The catalyst was filtered off and the solvent was removed under reduced pressure to afford the phenol product (1.47 g, 99%) as a solid. MS (CI-NH_3): $(M+H)^+$=266.

(46b) Methyl 2-{N-Methyl-N-[(*R/S*)-α-methyl-4-(3,5-dimethylbenzyloxy)phenylacetyl]amino}-(*R*)-propionate.

A solution of methyl 2-[N-methyl-N-((*R/S*)-α-methyl-4-hydroxyphenylacetylamino)]-(*R*)-propionate 46a (300 mg, 1.13 mmol), 3,5-dimethylbenzylbromide (300 mg, 1.5 mmol) and potassium carbonate (550 mg, 4 mmol) in DMF (10 mL) was heated at 80 °C with stirring overnight. Insoluble material was filtered off and the filtrate diluted with EtOAc. The solution was washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified on a silica gel column by eluting with EtOAc/hexane (1:1) to afford the ether product (110 mg, 25%) as a solid. MS (CI-NH_3): $(M+H)^+$ =384.

(46c) 2-{N-Methyl-N-[(*R/S*)-α-methyl-4-(3,5-dimethylbenzyloxy)phenylacetyl]amino}-(*R*)-propionic Acid. A solution of methyl 2-{N-methyl-N-[(*R/S*)-α-methyl-4-(3,5-dimethylbenzyloxy)phenylacetyl]amino}-(*R*)-propionate 46b (107 mg, 0.28 mmol) in THF (5 mL) was treated with 1 N LiOH (1 mL) for 40 min. The solution was acidified with 1 N HCl (1.5 mL) and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated to give the acid (103 mg, 100%) as a solid. MS (CI-NH_3): $(M+H)^+$=370.

(46d) 2-{N-Methyl-N-[(*R/S*)-α-methyl-4-(3,5-dimethylbenzyloxy)phenylacetyl]amino}-N-hydroxy-(*R*)-propionamide. A solution of 2-{N-methyl-N-[(*R/S*)-α-methyl-4-(3,5-dimethylbenzyloxy)phenylacetyl]amino}-(*R*)-propionic Acid 46c (100 mg, 0.27 mmol) and N-hydroxylamine (69 mg, 1 mmol) in DMF (5 mL) was cooled in an ice bath and to it was added BOP (127 mg, 0.28 mol) followed by DIEA (0.34 mL, 2 mmol). The mixture was stirred overnight and diluted with EtOAc. The solution was washed with $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated. The residue was purified using reversed phase HPLC to afford the hydroxamate (54 mg, 52%) as a powder after lyophilization. MS (ESI): $(M+TFA-H)^-$=496.9.

Example 47

2-{N-Methyl-N-[(*R/S*)-α-methyl-4-(3,5-bistrifluoromethylbenzyloxy)phenylacetyl]amino}-N-hydroxy-(*R*)-propionamide.

This compound was prepared using procedures similar to those as described in Example 46. MS (ESI): $(M+TFA-H)^-$=605.

Example 48

2-{N-Methyl-N-[(*R/S*)-α-(methylaminocarbonylmethyl)-4-(3,5-bistrifluoromethylbenzyloxy)phenylacetyl]amino}-N-hydroxy-(*R*)-propionamide.

(48a) Methyl (*R/S*)-α-*t*-Butoxycarbonylmethyl-4-benzyloxyphenylacetate. Lithium diisopropylamide (LDA) was prepared by the addition of 2.5 M n-butyllithium in hexane (8.4 mL) to a solution of diisopropylamine (2.94 mL, 21 mmol) in THF (30 mL) at -78 °C followed by stirring at 0°C for 20 min. A solution of methyl 4-benzyloxyphenylacetate (4.8 g, 18.7 mmol) in THF (50 mL) was cooled to -78 °C and to it was added the prepared LDA solution. The mixture was stirred at -78 °C for 1 h and *t*-butyl bromoacetate (3.1 mL, 21 mmol) in THF (20 mL) was added. The mixture was allowed to warm to 0 °C, stirred for an additional 1.5 h at 0 °C, quenched with MeOH and concentrated *in vacuo*. The residue was taken up in EtOAc and the solution was washed with citric acid and brine, dried over $MgSO_4$ and concentrated. Purification on a silica gel column by eluting with 40% EtOAc/hexane afforded the desired product (6.0 g, 86%) as a solid. MS (CI-NH3): $(M+H)^+$=371.

(48b) (*R/S*)-α-*t*-Butoxycarbonylmethyl-4-benzyloxyphenylacetic Acid. A solution of methyl (*R/S*)-α-*t*-butoxycarbonylmethyl-4-benzyloxyphenylacetate (5.92 g, 16 mmol) 48a in MeOH (50 mL) was treated with 1 N LiOH (32 mL) for 3 hours and MeOH was removed by concentration *in vacuo*. EtOAc was added and the solution was acidified with citric acid to pH 3. The organic layer was separated and the water solution was extracted with EtOAc one more time. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated to afford the acid (4.8 g, 84%) as a solid. MS (CI-NH_3): $(M+H)^+$=357.

(48c) Methyl 2-[N-Methyl-N-((*R/S*)-α-t-butoxycarbonylmethyl-4-benzyloxyphenylacetyl)amino]-(*R*)-propionate. To a solution of (*R/S*)-α-*t*-butoxycarbonylmethyl-4-benzyloxyphenylacetic acid 48b (4.8 g, 13.48 mmol) and methyl N-methyl-D-alaninate hydrochloride (2.9 g, 18.9 mmol) in DMF (30 mL) cooled in an ice bath was added BOP (6.56 g, 14.83 mmol) followed by DIEA (16.5 mL, 94.5 mmol) and the solution was stirred overnight. EtOAc was added and the solution was washed with $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated. The residue was purified on a silica gel column by eluting with 40% EtOAc/hexane to give the desired product (3.0 g, 49%) as a solid. MS (CI-NH_3): $(M+H)^+$=456.

(48d) Methyl 2-[N-Methyl-N-((*R/S*)-α-*t*-butoxycarbonylmethyl-4-hydroxyphenylacetyl)amino]-(*R*)-propionate. A solution of methyl 2-[N-methyl-N-((*R/S*)-α-*t*-butoxycarbonylmethyl-4-benzyloxyphenylacetyl)amino]-(*R*)-propionate 48c (3.0 g, 6.59 mmol) in MeOH (75 mL) was hydrogenated under atmospheric pressure using 10% Pd/C (0.6 g) as a catalyst for a period of 4.5 hours. The catalyst was filtered off and the

solvent was removed under reduced pressure. The residue was purified on a silica gel column using 40% EtOAc/hexane as an eluent to afford the phenol product (1.5 g, 62%) as a solid. MS (CI-NH_3): $(M+H)^+$=366.

(48e) Methyl 2-{N-Methyl-N-[(R/S)-α-*t*-butoxycarbonylmethyl-4-(3,5-bistrifluoromethylbenzyloxy)phenylacetyl]amino}-(*R*)-propionate. A solution of methyl 2-[N-methyl-N-((*R/S*)-α-*t*-butoxycarbonylmethyl-4-hydroxyphenylacetyl)amino]-(*R*)-propionate 48d (1.5 g, 4.1 mmol) and 3,5-bistrifluoromethylbenzyl bromide (1.3 g, 4.2 mmol) in DMF (10 mL) was stirred at 60 °C overnight in the presence of K_2CO_3 (1.14 g, 8 mmol). After cooling to room temperature, EtOAc was added and the solution was washed with brine three times, dried over $MgSO_4$, and concentrated. Purification on a silica gel column by eluting with 40% EtOAc/hexane afforded the product (1.46 g, 60%) as a solid. MS (CI-NH_3): $(M+H)^+$=592.

(48f) Methyl 2-{N-Methyl-N-[(*R/S*)-α-hydroxycarbonylmethyl-4-(3,5-bistrifluoromethylbenzyloxy)phenylacetyl]amino}-(*R*)-propionate. Methyl 2-{N-methyl-N-[(*R/S*)-α-*t*-butoxycarbonylmethyl-4-(3,5-bistrifluoromethylbenzyloxy)phenylacetyl]amino}-(*R*)-propionate 48e (1.46 g, 2.47 mmol) was treated with 50% TFA in CH_2Cl_2 (20 mL) for 1 hour and the solution was concentrated *in vacuo* to give the acid (1.46 g, 100%) as a syrup. MS (ESI): $(M+H)^+$=535.9.

(48g) Methyl 2-{N-Methyl-N-[(*R/S*)-α-methylaminocarbonylmethyl-4-(3,5-bistrifluoromethylbenzyloxy)phenylacetyl]amino}-(*R*)-propionate. A solution of methyl 2-{N-methyl-N-[(*R/S*)-α-hydroxycarbonylmethyl-4-(3,5-bistrifluoromethylbenzyloxy)phenylacetyl]amino}-(*R*)-propionate 48f (0.3 g, 0.56 mmol), methylamine hydrochloride (68 mg, 1 mmol) and DIEA (0.35 mL, 2 mmol) in DMF (5 mL) was cooled in an ice bath and to it was added BOP (265 mg, 0.6 mmol). After stirring at room temperature for 1 hour, EtOAc was added and the solution was washed with $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated to give the amide (312 mg, 100%) as a solid. MS (ESI): $(M+Na)^+$=571.8.

(48h) 2-{N-Methyl-N-[(*R/S*)-α-methylaminocarbonylmethyl-4-(3,5-bistrifluoromethylbenzyloxy)phenylacetyl]amino}-(*R*)-propionic Acid. Methyl 2-{N-methyl-N-[(*R/S*)-α-methylaminocarbonylmethyl-4-(3,5-bistrifluoromethylbenzyloxy)phenylacetyl]amino}-(*R*)-propionate 48g (310 mg, 0.56 mmol) was dissolved in MeOH (5 mL) and 1 N LiOH (2 mL) was added. The solution was stirred for 1 hour and concentrated *in vacuo*. EtOAc was added and the solution was

acidified with 1 N HCl, washed with brine, dried over $MgSO_4$, and concentrated to afford the acid (280 mg, 92%) as a solid. MS (ESI): $(M+H)^+$=535.8.

(48i) 2-{N-Methyl-N-[(*R/S*)-α-(methylaminocarbonylmethyl)-4-(3,5-bistrifluoromethylbenzyloxy)phenylacetyl]amino}-N-hydroxy-(*R*)-propionamide. To a solution of 2-{N-methyl-N-[(*R/S*)-α-methylaminocarbonylmethyl-4-(3,5-bistrifluoromethylbenzyloxy)phenylacetyl]amino}-(*R*)-propionic acid 7h (280 mg, 0.52 mmol), hydroxylamine hydrochloride (100 mg, 1.4 mmol) and DIEA (0.5 mL, 2.87 mmol) in DMF (5 mL) cooled in an ice bath was added BOP (265 mg, 0.6 mmol) and the solution was stirred at room temperature for 1 hour. EtOAc was added and the solution was washed with brine three times, dried over $MgSO_4$ and concentrated. The residue was purified on reversed phase HPLC to afford the hydroxamate (135 mg, 47%) as a powder after lyophilization. MS (ESI): $(M+TFA-H)^-$=663.5.

Example 49

2-{N-Methyl-N-[(*R/S*)-α-(aminocarbonylmethyl)-4-(3,5-bistrifluoromethylbenzyloxy)phenylacetyl]amino}-N-hydroxy-(*R*)-propionamide.

This compound was prepared using the procedures as described in Example 48. MS (ESI): $(M-H)^-$=533.9.

Example 50

2-{N-Methyl-N-[(*R/S*)-α-(1-piperazinocarbonylmethyl)-4-(3,5-bistrifluoromethylbenzyloxy)phenylacetyl]amino}-N-hydroxy-(*R*)-propionamide.

This compound was prepared using procedures similar to those described in Example 48. MS (ESI): $(M+H)^+$=605.0.

Example 51

(2*R*)-2-[(amino{4-[(2-methyl-4-quinolinyl)methoxy]phenyl}acetyl)amino]-*N*-hydroxy-4-methylpentanamide

(51a) N-Boc-4-hydroxyphenyl glycine methyl ester (8.24 g, 29.3 mmol) and 4-chloromethyl 2-methyl quinoline (9.10 g, 40.0 mmol) were combined in acetone 150 ml, potassium carbonate (12.5 g, 90.0 mmol) and potassium iodide (4.3 g, 26 mmol) were added and the reaction was heated to reflux for 5hr. The reaction was allowed to cool, filtered through celite and was concentrated to give an oil. The product was purified by flash chromatography on silica gel eluting ethyl acetate: hexane (60:40, v:v) to give the N-

Boc-4-(2-methyl-4-quinoline)methoxyphenyl glycine methyl ester (8.7 g, 68%) as a yellow foam MS $(M-C_4H_8+H)^+$= 381.

(51b) The N-Boc-4-(2-methyl-4-quinoline)methoxyphenyl glycine methyl ester (1.0 g, 2.3 mmol)was dissolved in methanol 20ml, and lithium hydroxide hydrate (0.11 g, 2.6 mmol) dissolved in water 10 m was added. The reaction was stirred at RT for 2hs. This was concentrated in vacuo and the resulting aqueous residue was diluted with water 20 ml washed with ethyl ether (2X), then made neutral with HCl. The aqueous layer was extracted with ethyl acetate (2X). The combined ethyl acetate layers were washed with brine dried over magnesium sulfate and concentrated to give the N-Boc-4-(2-methyl-4-quinoline)methoxyphenyl glycine carboxylic acid (0.97 g, 99%) as a light yellow solid MS (M+H) 423.

(51c) The N-Boc-4-(2-methyl-4-quinoline)methoxyphenyl glycine carboxylic acid (0.30 g, 0.71 mmol) was dissolved in DMF 5ml, the N-methyl morpholine (0.5 ml) and TBTU (0.28 g, 0.87 mmol) were added at RT and stirred for 15 minutes before the D-leucine methyl ester(0.15 g, 0.83 mmol) was added. The reaction was complete after stirring for 1.5 hr, was diluted with water, and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over magnesium sulfate and concentrated to a foam. The product was purified by flash chromatography on silica gel eluting ethyl acetate: hexane (50:50, v:v) to give D-leucine N-Boc-4-(2-methyl-4-quinoline)methoxyphenyl glycine methyl ester (0.325 g, 84%) as a clear oil MS (M+H)=550.

(51d) The D-leucine N-Boc-4-(2-methyl-4-quinoline) methoxyphenylglycine methyl ester (0.325 g,0.58 mmol) was dissolved in methylene chloride 6 ml and trifluoroacetic acid 2 ml under nitrogen at RT. The reaction was stirred for 1.5 hs and was concentrated to give the D-leucine 4-(2-methyl-4-quinoline) methoxyphenylglycine methyl ester bis trifluoroacetic acid salt (0.44 g, 100%) as a clear oil MS (M+H) =450.

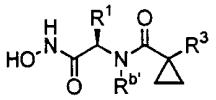
(51e) The D-leucine 4-(2-methyl-4-quinoline)methoxyphenyl glycine methyl ester bis trifluoroacetic acid salt (0.435 g, 0.96 mmol) was dissolved in a solution of potassium hydroxide:hydroxylamine hydrochloride:methanol (1.76M) 5 ml under nitrogen at RT. The reaction was stirred for 40 minutes, concentrated in vacuo, the residue dissolved in acetonitrile;water (80:20) and made acidic with trifluoroacetic acid. The product was purified by reverse phase HPLC eluting an acetonitrile:water:TFA gradient on a Vydac C-18 column to give the title compound (0.135 g, 33%) as a white solid MS (M+H) = 451.

Example 52

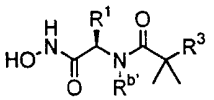
2-[(amino{4-[(2-methyl-4-quinolinyl)methoxy]phenyl}acetyl)amino]-*N*-hydroxy-2-methylpropanamide

(52a) Following the procedures analogous to that used for the preparation of example 51 but using 2-methyl alanine methyl ester in step 1c, the title compound was prepared (0.09 g, 40%) as a white solid MS (M+H) = 423.

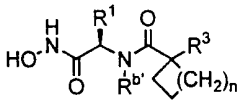
TABLE 1



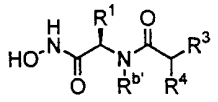
Ex 1-4, 6-10, 18
20-21, 25-30



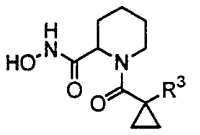
Ex 5



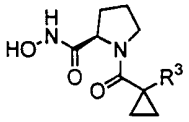
Ex 11 (n=1)
Ex 12 (n=2)



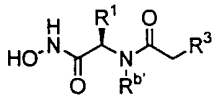
Ex 13 (R^4=OH)
Ex 14 & 31 (R^4=NHBoc)
Ex 51 (R^4=NH_2)



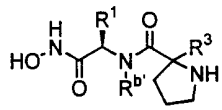
Ex 15



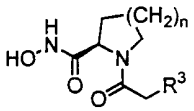
Ex 16



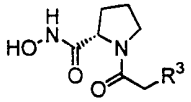
Ex 17, 19, 22-24



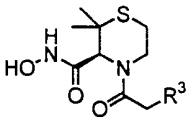
Ex 32



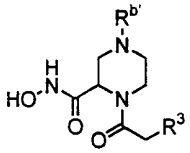
Ex 33 (n=1)
Ex 36 (n=2)



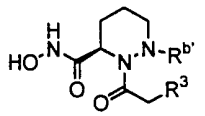
Ex 34



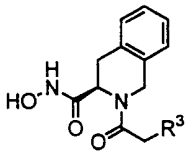
Ex 35



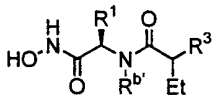
Ex 37-38



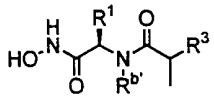
Ex 39-40



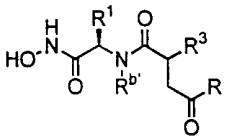
Ex 41



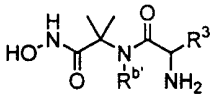
Ex 42



Ex 43-47



Ex 48 (R=NHMe)
Ex 49 (R=NH_2)
Ex 50 (R=1-piperazinyl)



Ex 52

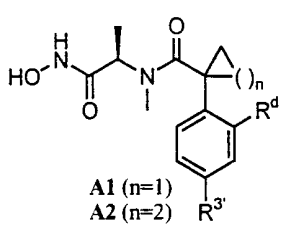
Ex #	R^1	R^3	$R^{b'}$	MS $(M+H)^+$
1	i-propyl	4-methylphenyl	H	289
2	i-propyl	4-methoxyphenyl	H	305
3	2-(methylthio)ethyl	4-methoxyphenyl	H	337
4	2-(methylsulfonyl)ethyl	4-methoxyphenyl	H	369
5	i-propyl	phenyl	methyl	291
6	i-propyl	phenyl	methyl	289
7	i-propyl	4-methylphenyl	methyl	303
8	i-propyl	4-methoxyphenyl	methyl	319
9	i-propyl	4-chlorophenyl	methyl	323
10	i-propyl	2,4-dichlorophenyl	methyl	357
11	i-propyl	4-chlorophenyl	methyl	337
12	i-propyl	phenyl	methyl	317

13	i-propyl	phenyl	methyl	279
14	i-propyl	phenyl	methyl	380
15	---	2,4-dichlorophenyl	---	$(M-H)^-$ 355
16	---	2,4-dichlorophenyl	---	$(M-H)^-$ 341
17	i-propyl	4-methoxyphenyl	methyl	$(M-H)^-$ 293
18	methyl	4-[(2,4-dimethoxyphenyl) methoxy]phenyl	methyl	$(M-H)^-$ 395
19	methyl	4-methoxyphenyl	methyl	$(M-H)^-$ 265
20	methyl	4-[(2-naphthalenyl)methoxy]phenyl	methyl	$(M-H)^-$ 417
21	methyl	4-[(4-pyridinyl)methoxy]phenyl	methyl	$(M-H)^-$ 368
22	i-propyl	4-(phenylmethoxy)phenyl	methyl	$(M-H)^-$ 395
23	i-propyl	4-[(3,5-dimethylphenyl) methoxy]phenyl	methyl	$(M-H)^-$ 423
24	i-propyl	4-[(1-benzotriazolyl)methoxy]phenyl	methyl	$(M-H)^-$ 436
25	methyl	4-[(3-phenyl-5-isoxazolyl)methoxy]phenyl	methyl	$(M-H)^-$ 434
26	methyl	4-(2-propynyloxy)phenyl	methyl	$(M-H)^-$ 315
27	methyl	4-[[3-(4-fluorophenyl)-5-isoxazolyl]methoxy]phenyl	methyl	452
28	methyl	4-[(3-propyl-5-isoxazolyl)methoxy]phenyl	methyl	$(M-H)^-$ 400
29	isobutyl	4-[(2-methyl-4-quinolinyl)methoxy]phenyl	propyl	504
30	isobutyl	4-[(2-methyl-4-quinolinyl)methoxy]phenyl	3-(cyclopentylamino) propyl	587
31	methyl	4-(phenylmethoxy)phenyl	methyl	$(M-H)^-$ 456
32	methyl	4-(phenylmethoxy)phenyl	H	426
33	---	4-[(2-methyl-4-quinolinyl)methoxy]phenyl	---	420
34	---	4-[(2-methyl-4-quinolinyl)methoxy]phenyl	---	420
35	---	4-[(2-methyl-4-quinolinyl)methoxy]phenyl	---	480
36	---	4-[(2-methyl-4-quinolinyl)methoxy]phenyl	---	434
37	---	4-[(2-methyl-4-quinolinyl)methoxy]phenyl	t-butoxycarbonyl	535
38	---	4-[(2-methyl-4-quinolinyl)methoxy]phenyl	H	435
39	---	4-[(2-methyl-4-quinolinyl)methoxy]phenyl	benzyloxy carbonyl	569
40	---	4-[(2-methyl-4-quinolinyl)methoxy]phenyl	H	435
41	---	4-[(2-methyl-4-quinolinyl)methoxy]phenyl	---	482

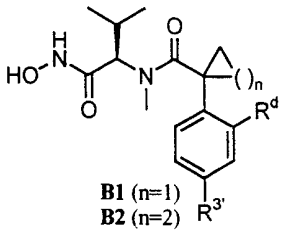
42	methyl	phenyl	H	$(M-H)^-$ 249
43	methyl	4-isobutylphenyl	H	$(M-H)^-$ 291
44	methyl	3-fluoro-4-phenylphenyl	H	$(M-H)^-$ 329
45	methyl	4-(phenylmethoxy)phenyl	methyl	$(M-H)^-$ 355
46	methyl	4-[(3,5-dimethylphenyl) methoxy]phenyl	methyl	$(M+TFA-H)^-$ 499
47	methyl	4-[[3,5-bis(trifluoromethyl)phenyl] methoxy]phenyl	methyl	$(M+TFA-H)^-$ 605
48	methyl	4-[[3,5-bis(trifluoromethyl)phenyl] methoxy]phenyl	methyl	$(M+TFA-H)^-$ 664
49	methyl	4-[[3,5-bis(trifluoromethyl)phenyl] methoxy]phenyl	methyl	$(M-H)^-$ 534
50	methyl	4-[[3,5-bis(trifluoromethyl)phenyl] methoxy]phenyl	methyl	$(M-H)^-$ 605
51	isobutyl	4-[(2-methyl-4-quinolinyl)methoxy]phenyl	H	451
52	---	4-[(2-methyl-4-quinolinyl)methoxy]phenyl	H	423

The following tables contain representative examples of the present invention. Each entry in each table is intended to be paired with each formula at the start of the table. For example, in Table 2, example 1 is intended to be paired with each of formulae **A1-JJ2**.

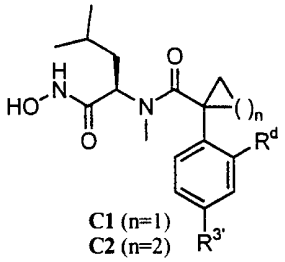
TABLE 2



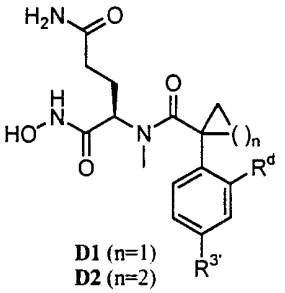
A1 (n=1)
A2 (n=2)



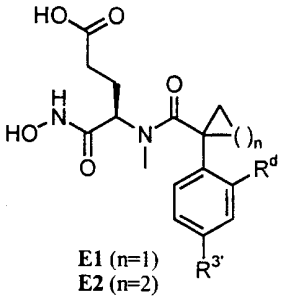
B1 (n=1)
B2 (n=2)



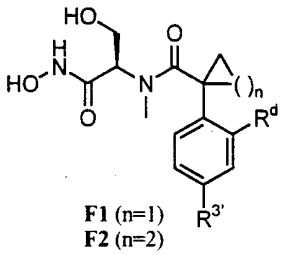
C1 (n=1)
C2 (n=2)



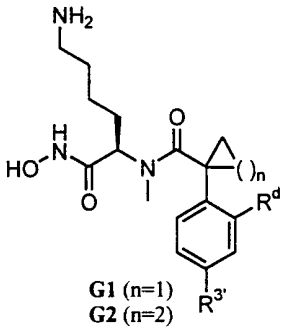
D1 (n=1)
D2 (n=2)



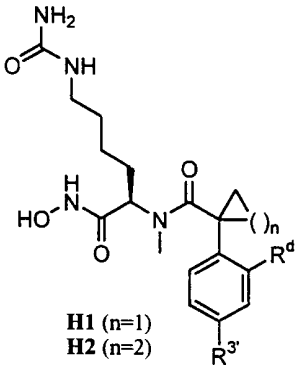
E1 (n=1)
E2 (n=2)



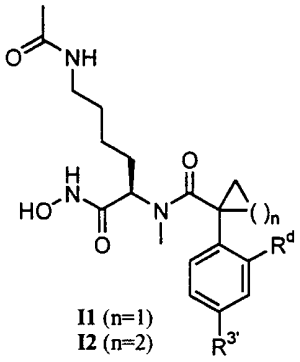
F1 (n=1)
F2 (n=2)



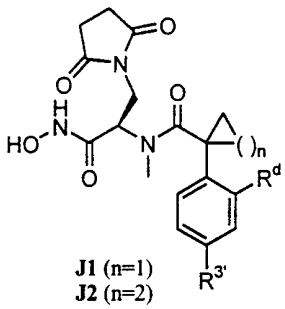
G1 (n=1)
G2 (n=2)



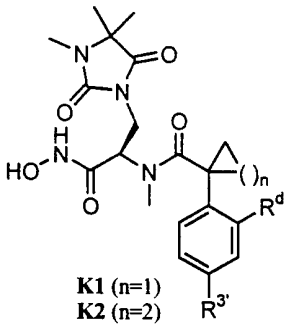
H1 (n=1)
H2 (n=2)



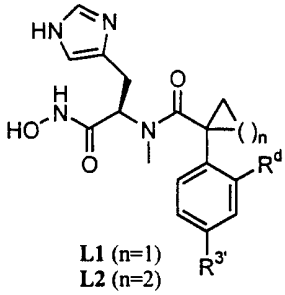
I1 (n=1)
I2 (n=2)



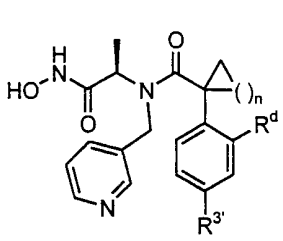
J1 (n=1)
J2 (n=2)



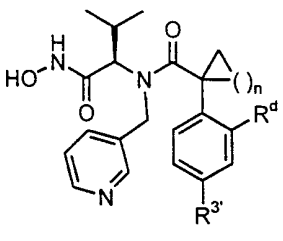
K1 (n=1)
K2 (n=2)



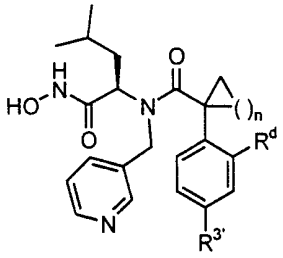
L1 (n=1)
L2 (n=2)



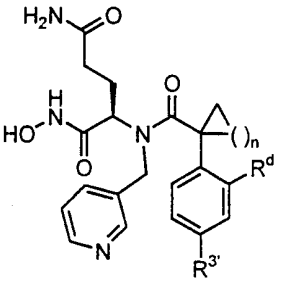
M1 (n=1)
M2 (n=2)



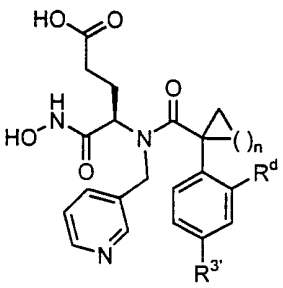
N1 (n=1)
N2 (n=2)



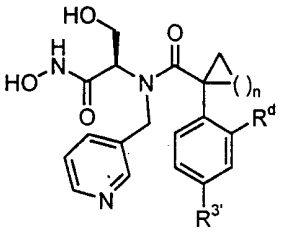
O1 (n=1)
O2 (n=2)



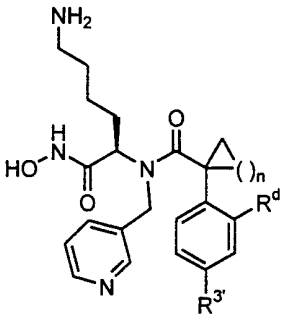
P1 (n=1)
P2 (n=2)



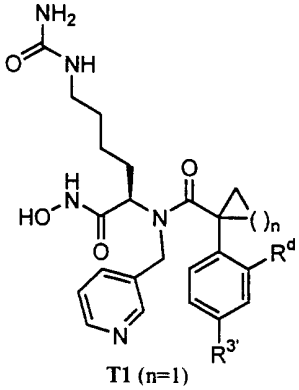
Q1 (n=1)
Q2 (n=2)



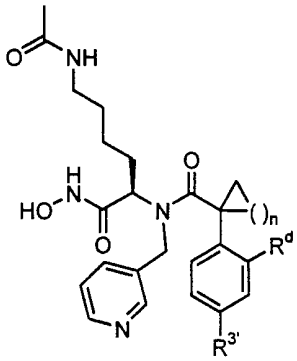
R1 (n=1)
R2 (n=2)



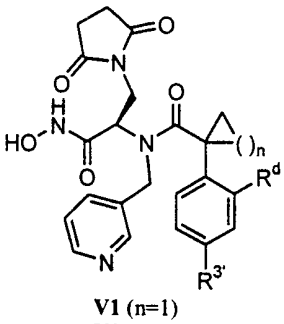
S1 (n=1)
S2 (n=2)



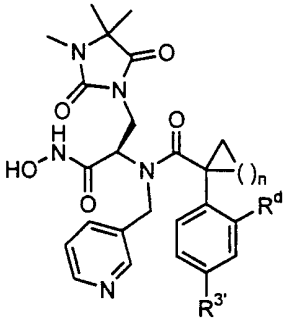
T1 (n=1)
T2 (n=2)



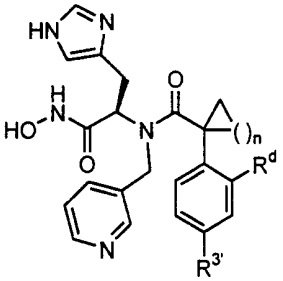
U1 (n=1)
U2 (n=2)



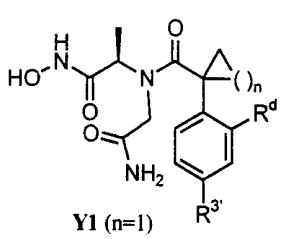
V1 (n=1)
V2 (n=2)



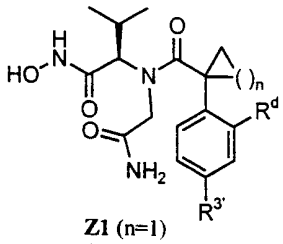
W1 (n=1)
W2 (n=2)



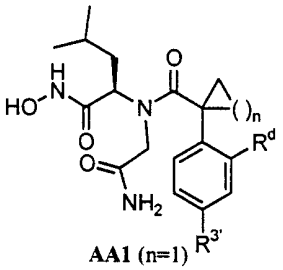
X1 (n=1)
X2 (n=2)



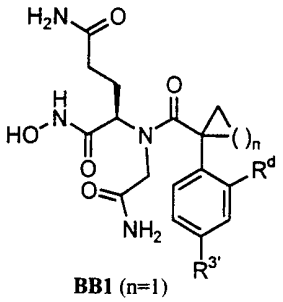
Y1 (n=1)
Y2 (n=2)



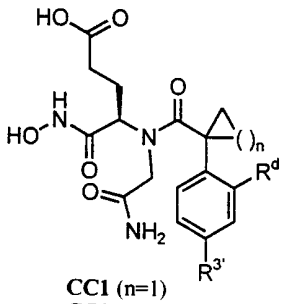
Z1 (n=1)
Z2 (n=2)



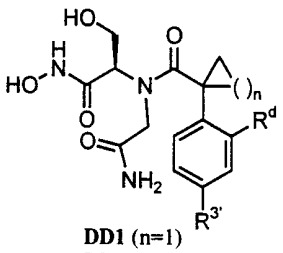
AA1 (n=1)
AA1 (n=2)



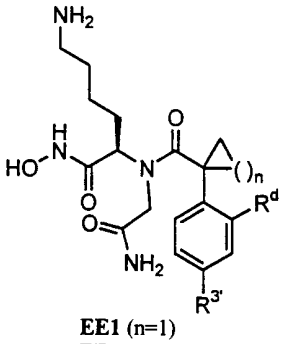
BB1 (n=1)
BB2 (n=2)



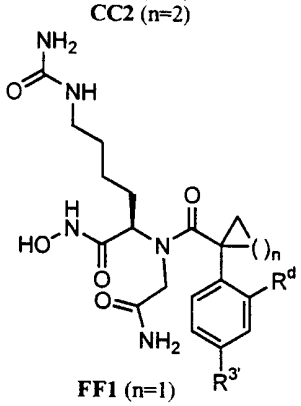
CC1 (n=1)
CC2 (n=2)



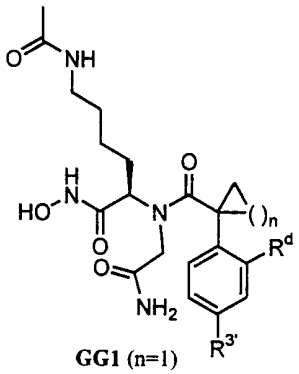
DD1 (n=1)
DD2 (n=2)



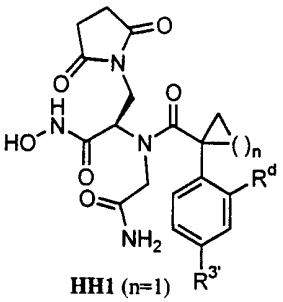
EE1 (n=1)
EE2 (n=2)



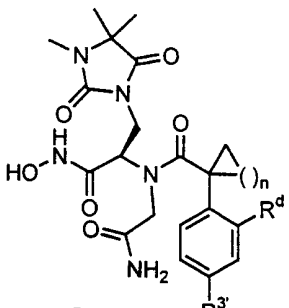
FF1 (n=1)
FF2 (n=2)



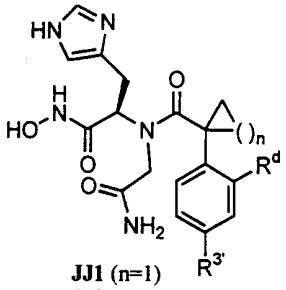
GG1 (n=1)
GG2 (n=2)



HH1 (n=1)
HH2 (n=2)



II1 (n=1)
II2 (n=2)



JJ1 (n=1)
JJ2 (n=2)

Ex#	R^b	$R^{3'}$
1	H	H
2	methyl	H
3	chloro	H
4	H	methyl
5	methyl	methyl
6	chloro	methyl

7	H	ethyl
8	methyl	ethyl
9	chloro	ethyl
10	H	isopropyl
11	methyl	isopropyl
12	chloro	isopropyl
13	H	phenyl
14	methyl	phenyl
15	chloro	phenyl
16	H	benzyl
17	methyl	benzyl
18	chloro	benzyl
19	H	2-phenylethyl
20	methyl	2-phenylethyl
21	chloro	2-phenylethyl
22	H	2-(2-methylphenyl)ethyl
23	methyl	2-(2-methylphenyl)ethyl
24	chloro	2-(2-methylphenyl)ethyl
25	H	2-(3-methylphenyl)ethyl
26	methyl	2-(3-methylphenyl)ethyl
27	chloro	2-(3-methylphenyl)ethyl
28	H	2-(2,6-dimethylphenyl)ethyl
29	methyl	2-(2,6-dimethylphenyl)ethyl
30	chloro	2-(2,6-dimethylphenyl)ethyl
31	H	2-(3,5-dimethylphenyl)ethyl
32	methyl	2-(3,5-dimethylphenyl)ethyl
33	chloro	2-(3,5-dimethylphenyl)ethyl
34	H	2-(3-amino-5-methylphenyl)ethyl
35	methyl	2-(3-amino-5-methylphenyl)ethyl
36	chloro	2-(3-amino-5-methylphenyl)ethyl
37	H	2-(pyridin-4-yl)ethyl
38	methyl	2-(pyridin-4-yl)ethyl
39	chloro	2-(pyridin-4-yl)ethyl
40	H	2-(2,6-dimethylpyridin-4-yl)ethyl
41	methyl	2-(2,6-dimethylpyridin-4-yl)ethyl
42	chloro	2-(2,6-dimethylpyridin-4-yl)ethyl
43	H	2-(3,5-dimethylpyridin-4-yl)ethyl
44	methyl	2-(3,5-dimethylpyridin-4-yl)ethyl
45	chloro	2-(3,5-dimethylpyridin-4-yl)ethyl
46	H	styryl
47	methyl	styryl
48	chloro	styryl
49	H	hydroxy
50	methyl	hydroxy
51	chloro	hydroxy
52	H	methoxy
53	methyl	methoxy
54	chloro	methoxy
55	H	ethoxy
56	methyl	ethoxy
57	chloro	ethoxy
58	H	isopropyloxy
59	methyl	isopropyloxy
60	chloro	isopropyloxy
61	H	tert-butoxy
62	methyl	tert-butoxy
63	chloro	tert-butoxy
64	H	cyclohexyloxy
65	methyl	cyclohexyloxy
66	chloro	cyclohexyloxy

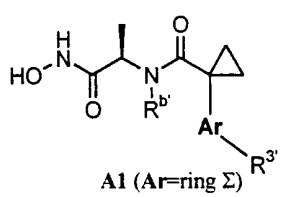
67	H	phenoxy
68	methyl	phenoxy
69	chloro	phenoxy
70	H	o-methylphenoxy
71	methyl	o-methylphenoxy
72	chloro	o-methylphenoxy
73	H	m-methylphenoxy
74	methyl	m-methylphenoxy
75	chloro	m-methylphenoxy
76	H	cinnamyloxy
77	methyl	cinnamyloxy
78	chloro	cinnamyloxy
79	H	benzyloxy
80	methyl	benzyloxy
81	chloro	benzyloxy
82	H	phenoxymethyl
83	methyl	phenoxymethyl
84	chloro	phenoxymethyl
85	H	o-methylbenzyloxy
86	methyl	o-methylbenzyloxy
87	chloro	o-methylbenzyloxy
88	H	m-methylbenzyloxy
89	methyl	m-methylbenzyloxy
90	chloro	m-methylbenzyloxy
91	H	o,o-dimethylbenzyloxy
92	methyl	o,o-dimethylbenzyloxy
93	chloro	o,o-dimethylbenzyloxy
94	H	(2,6-dimethylphenoxy)methyl
95	methyl	(2,6-dimethylphenoxy)methyl
96	chloro	(2,6-dimethylphenoxy)methyl
97	H	m,m-dimethylbenzyloxy
98	methyl	m,m-dimethylbenzyloxy
99	chloro	m,m-dimethylbenzyloxy
100	H	(3,5-dimethylphenoxy)methyl
101	methyl	(3,5-dimethylphenoxy)methyl
102	chloro	(3,5-dimethylphenoxy)methyl
103	H	o,o-dicyanobenzyloxy
104	methyl	o,o-dicyanobenzyloxy
105	chloro	o,o-dicyanobenzyloxy
106	H	m,m-dicyanobenzyloxy
107	methyl	m,m-dicyanobenzyloxy
108	chloro	m,m-dicyanobenzyloxy
109	H	(2,6-dicyanophenoxy)methyl
110	methyl	(2,6-dicyanophenoxy)methyl
111	chloro	(2,6-dicyanophenoxy)methyl
112	H	(3,5-dicyanophenoxy)methyl
113	methyl	(3,5-dicyanophenoxy)methyl
114	chloro	(3,5-dicyanophenoxy)methyl
115	H	o-amino-o-cyanobenzyloxy
116	methyl	o-amino-o-cyanobenzyloxy
117	chloro	o-amino-o-cyanobenzyloxy
118	H	m-amino-m-cyanobenzyloxy
119	methyl	m-amino-m-cyanobenzyloxy
120	chloro	m-amino-m-cyanobenzyloxy
121	H	o-amino-o-nitrobenzyloxy
122	methyl	o-amino-o-nitrobenzyloxy
123	chloro	o-amino-o-nitrobenzyloxy
124	H	m-amino-m-nitrobenzyloxy
125	methyl	m-amino-m-nitrobenzyloxy
126	chloro	m-amino-m-nitrobenzyloxy

127	H	p-amino-m,m-dimethylbenzyloxy
128	methyl	p-amino-m,m-dimethylbenzyloxy
129	chloro	p-amino-m,m-dimethylbenzyloxy
130	H	o-amino-o-methylbenzyloxy
131	methyl	o-amino-o-methylbenzyloxy
132	chloro	o-amino-o-methylbenzyloxy
133	H	m-amino-m-methylbenzyloxy
134	methyl	m-amino-m-methylbenzyloxy
135	chloro	m-amino-m-methylbenzyloxy
136	H	o-cyano-o-methylbenzyloxy
137	methyl	o-cyano-o-methylbenzyloxy
138	chloro	o-cyano-o-methylbenzyloxy
139	H	m-cyano-m-methylbenzyloxy
140	methyl	m-cyano-m-methylbenzyloxy
141	chloro	m-cyano-m-methylbenzyloxy
142	H	o-cyano-o-nitrobenzyloxy
143	methyl	o-cyano-o-nitrobenzyloxy
144	chloro	o-cyano-o-nitrobenzyloxy
145	H	(2-cyano-6-nitrophenoxy)methyl
146	methyl	(2-cyano-6-nitrophenoxy)methyl
147	chloro	(2-cyano-6-nitrophenoxy)methyl
148	H	m-cyano-m-nitrobenzyloxy
149	methyl	m-cyano-m-nitrobenzyloxy
150	chloro	m-cyano-m-nitrobenzyloxy
151	H	(3-cyano-5-nitrophenoxy)methyl
152	methyl	(3-cyano-5-nitrophenoxy)methyl
153	chloro	(3-cyano-5-nitrophenoxy)methyl
154	H	m,m-dimethoxybenzyloxy
155	methyl	m,m-dimethoxybenzyloxy
156	chloro	m,m-dimethoxybenzyloxy
157	H	m,m-dichlorobenzyloxy
158	methyl	m,m-dichlorobenzyloxy
159	chloro	m,m-dichlorobenzyloxy
160	H	(3,5-dichlorophenoxy)methyl
161	methyl	(3,5-dichlorophenoxy)methyl
162	chloro	(3,5-dichlorophenoxy)methyl
163	H	m,m-dibromobenzyloxy
164	methyl	m,m-dibromobenzyloxy
165	chloro	m,m-dibromobenzyloxy
166	H	m,m-bis(trifluoromethyl)benzyloxy
167	methyl	m,m-bis(trifluoromethyl)benzyloxy
168	chloro	m,m-bis(trifluoromethyl)benzyloxy
169	H	[3,5-bis(trifluoromethyl)phenoxy]methyl
170	methyl	[3,5-bis(trifluoromethyl)phenoxy]methyl
171	chloro	[3,5-bis(trifluoromethyl)phenoxy]methyl
172	H	m-carboxamido-m-methylbenzyloxy
173	methyl	m-carboxamido-m-methylbenzyloxy
174	chloro	m-carboxamido-m-methylbenzyloxy
175	H	(3-carboxamido-5-methylphenoxy)methyl
176	methyl	(3-carboxamido-5-methylphenoxy)methyl
177	chloro	(3-carboxamido-5-methylphenoxy)methyl
178	H	m-hydroxycarbonyl-m-methylbenzyloxy
179	methyl	m-hydroxycarbonyl-m-methylbenzyloxy
180	chloro	m-hydroxycarbonyl-m-methylbenzyloxy
181	H	(3-hydroxycarbonyl-5-methylphenoxy)methyl
182	methyl	(3-hydroxycarbonyl-5-methylphenoxy)methyl
183	chloro	(3-hydroxycarbonyl-5-methylphenoxy)methyl
184	H	o-phenylbenzyloxy
185	methyl	o-phenylbenzyloxy
186	chloro	o-phenylbenzyloxy

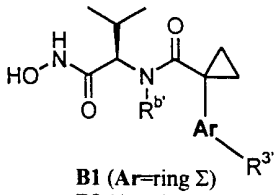
187	H	m-phenylbenzyloxy
188	methyl	m-phenylbenzyloxy
189	chloro	m-phenylbenzyloxy
190	H	(naphth-1-yl)methoxy
191	methyl	(naphth-1-yl)methoxy
192	chloro	(naphth-1-yl)methoxy
193	H	(naphth-2-yl)methoxy
194	methyl	(naphth-2-yl)methoxy
195	chloro	(naphth-2-yl)methoxy
196	H	(2-methylnaphth-1-yl)methoxy
197	methyl	(2-methylnaphth-1-yl)methoxy
198	chloro	(2-methylnaphth-1-yl)methoxy
199	H	(4-methylnaphth-2-yl)methoxy
200	methyl	(4-methylnaphth-2-yl)methoxy
201	chloro	(4-methylnaphth-2-yl)methoxy
202	H	(pyridin-3-yl)methoxy
203	methyl	(pyridin-3-yl)methoxy
204	chloro	(pyridin-3-yl)methoxy
205	H	(pyridin-4-yl)methoxy
206	methyl	(pyridin-4-yl)methoxy
207	chloro	(pyridin-4-yl)methoxy
208	H	(3,5-dichloropyridin-4-yl)methoxy
209	methyl	(3,5-dichloropyridin-4-yl)methoxy
210	chloro	(3,5-dichloropyridin-4-yl)methoxy
211	H	(3,5-dimethylpyridin-4-yl)methoxy
212	methyl	(3,5-dimethylpyridin-4-yl)methoxy
213	chloro	(3,5-dimethylpyridin-4-yl)methoxy
214	H	(1,2,3-benzotriazol-1-yl)methoxy
215	methyl	(1,2,3-benzotriazol-1-yl)methoxy
216	chloro	(1,2,3-benzotriazol-1-yl)methoxy
217	H	benzhydroxy
218	methyl	benzhydroxy
219	chloro	benzhydroxy
220	H	p-(1,2,3-thiadiazol-5-yl)benzyloxy
221	methyl	p-(1,2,3-thiadiazol-5-yl)benzyloxy
222	chloro	p-(1,2,3-thiadiazol-5-yl)benzyloxy
223	H	o-(tetrazol-5-yl)benzyloxy
224	methyl	o-(tetrazol-5-yl)benzyloxy
225	chloro	o-(tetrazol-5-yl)benzyloxy
226	H	m-(tetrazol-5-yl)benzyloxy
227	methyl	m-(tetrazol-5-yl)benzyloxy
228	chloro	m-(tetrazol-5-yl)benzyloxy
229	H	[3-methyl-5-(tetrazol-5-yl)phenoxy]methyl
230	methyl	[3-methyl-5-(tetrazol-5-yl)phenoxy]methyl
231	chloro	[3-methyl-5-(tetrazol-5-yl)phenoxy]methyl
232	H	m-methyl-m-(tetrazol-5-yl)benzyloxy
233	methyl	m-methyl-m-(tetrazol-5-yl)benzyloxy
234	chloro	m-methyl-m-(tetrazol-5-yl)benzyloxy
235	H	2-oxo-2-phenylethoxy
236	methyl	2-oxo-2-phenylethoxy
237	chloro	2-oxo-2-phenylethoxy
238	H	carbo-t-butoxymethoxy
239	methyl	carbo-t-butoxymethoxy
240	chloro	carbo-t-butoxymethoxy
241	H	(benzimidazol-2-yl)methoxy
242	methyl	(benzimidazol-2-yl)methoxy
243	chloro	(benzimidazol-2-yl)methoxy
244	H	(imidazol-2-yl)methoxy
245	methyl	(imidazol-2-yl)methoxy
246	chloro	(imidazol-2-yl)methoxy

247	H	(1,4-dimethylimidazol-5-yl)methoxy
248	methyl	(1,4-dimethylimidazol-5-yl)methoxy
249	chloro	(1,4-dimethylimidazol-5-yl)methoxy
250	H	(thiazol-4-yl)methoxy
251	methyl	(thiazol-4-yl)methoxy
252	chloro	(thiazol-4-yl)methoxy
253	H	(quinolin-2-yl)methoxy
254	methyl	(quinolin-2-yl)methoxy
255	chloro	(quinolin-2-yl)methoxy
256	H	(1,3-benzodioxo-5-yl)methoxy
257	methyl	(1,3-benzodioxo-5-yl)methoxy
258	chloro	(1,3-benzodioxo-5-yl)methoxy
259	H	(3,5-dimethylisoxazol-4-yl)methoxy
260	methyl	(3,5-dimethylisoxazol-4-yl)methoxy
261	chloro	(3,5-dimethylisoxazol-4-yl)methoxy
262	H	(3,5-dimethylpyrazol-1-yl)methoxy
263	methyl	(3,5-dimethylpyrazol-1-yl)methoxy
264	chloro	(3,5-dimethylpyrazol-1-yl)methoxy
265	H	(1,3,5-trimethylpyrazol-4-yl)methoxy
266	methyl	(1,3,5-trimethylpyrazol-4-yl)methoxy
267	chloro	(1,3,5-trimethylpyrazol-4-yl)methoxy
268	H	4-quinolinylmethoxy
269	methyl	4-quinolinylmethoxy
270	chloro	4-quinolinylmethoxy
271	H	2-methyl-4-quinolinylmethoxy
272	methyl	2-methyl-4-quinolinylmethoxy
273	chloro	2-methyl-4-quinolinylmethoxy
274	H	4-quinolinyloxymethyl
275	methyl	4-quinolinyloxymethyl
276	chloro	4-quinolinyloxymethyl

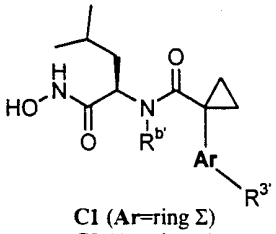
TABLE 3



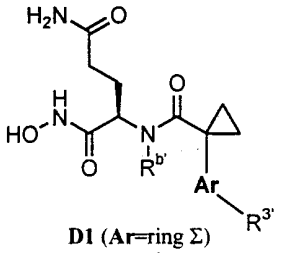
A1 (Ar=ring Σ)
A2 (Ar=ring Δ)
A3 (Ar=ring Φ)
A4 (Ar=ring Ω)
A5 (Ar=ring Ψ)



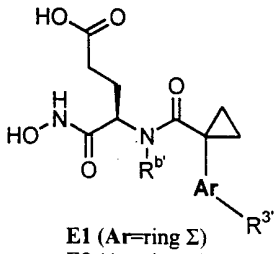
B1 (Ar=ring Σ)
B2 (Ar=ring Δ)
B3 (Ar=ring Φ)
B4 (Ar=ring Ω)
B5 (Ar=ring Ψ)



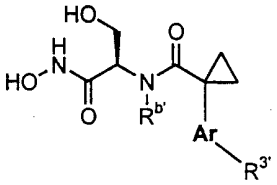
C1 (Ar=ring Σ)
C2 (Ar=ring Δ)
C3 (Ar=ring Φ)
C4 (Ar=ring Ω)
C5 (Ar=ring Ψ)



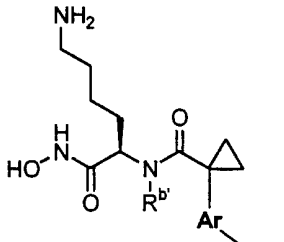
D1 (Ar=ring Σ)
D2 (Ar=ring Δ)
D3 (Ar=ring Φ)
D4 (Ar=ring Ω)
D5 (Ar=ring Ψ)



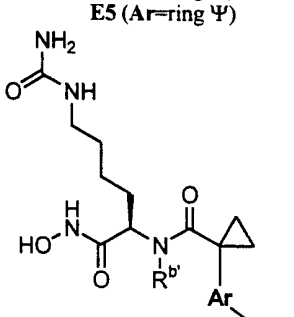
E1 (Ar=ring Σ)
E2 (Ar=ring Δ)
E3 (Ar=ring Φ)
E4 (Ar=ring Ω)
E5 (Ar=ring Ψ)



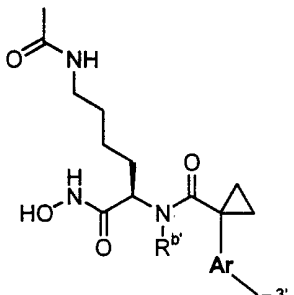
F1 (Ar=ring Σ)
F2 (Ar=ring Δ)
F3 (Ar=ring Φ)
F4 (Ar=ring Ω)
F5 (Ar=ring Ψ)



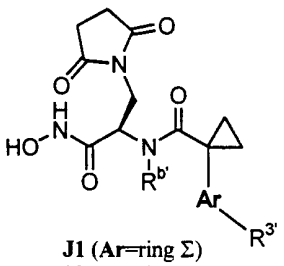
G1 (Ar=ring Σ)
G2 (Ar=ring Δ)
G3 (Ar=ring Φ)
G4 (Ar=ring Ω)
G5 (Ar=ring Ψ)



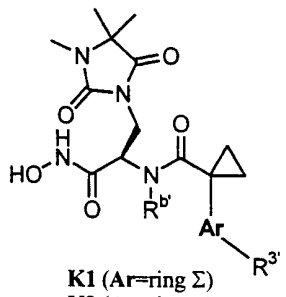
H1 (Ar=ring Σ)
H2 (Ar=ring Δ)
H3 (Ar=ring Φ)
H4 (Ar=ring Ω)
H5 (Ar=ring Ψ)



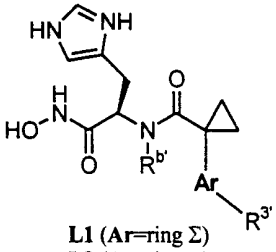
I1 (Ar=ring Σ)
I2 (Ar=ring Δ)
I3 (Ar=ring Φ)
I4 (Ar=ring Ω)
I5 (Ar=ring Ψ)



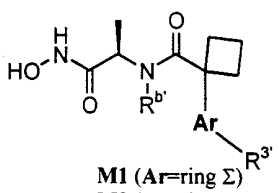
J1 (Ar=ring Σ)
J2 (Ar=ring Δ)
J3 (Ar=ring Φ)
J4 (Ar=ring Ω)
J5 (Ar=ring Ψ)



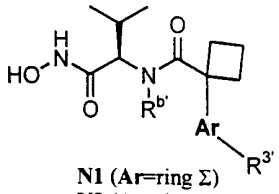
K1 (Ar=ring Σ)
K2 (Ar=ring Δ)
K3 (Ar=ring Φ)
K4 (Ar=ring Ω)
K5 (Ar=ring Ψ)



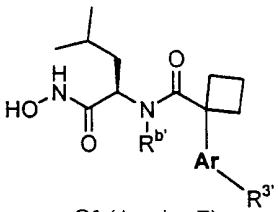
L1 (Ar=ring Σ)
L2 (Ar=ring Δ)
L3 (Ar=ring Φ)
L4 (Ar=ring Ω)
L5 (Ar=ring Ψ)



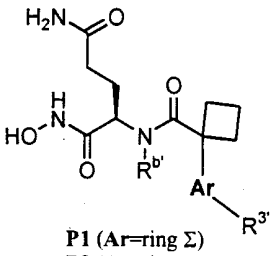
M1 (Ar=ring Σ)
M2 (Ar=ring Δ)
M3 (Ar=ring Φ)
M4 (Ar=ring Ω)
M5 (Ar=ring Ψ)



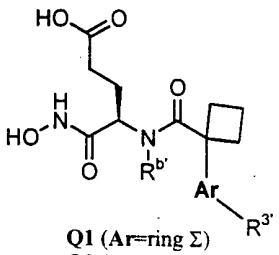
N1 (Ar=ring Σ)
N2 (Ar=ring Δ)
N3 (Ar=ring Φ)
N4 (Ar=ring Ω)
N5 (Ar=ring Ψ)



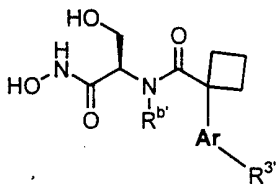
O1 (Ar=ring Σ)
O2 (Ar=ring Δ)
O3 (Ar=ring Φ)
O4 (Ar=ring Ω)
O5 (Ar=ring Ψ)



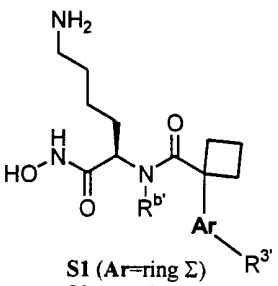
P1 (Ar=ring Σ)
P2 (Ar=ring Δ)
P3 (Ar=ring Φ)
P4 (Ar=ring Ω)
P5 (Ar=ring Ψ)



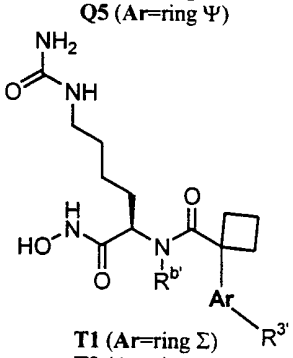
Q1 (Ar=ring Σ)
Q2 (Ar=ring Δ)
Q3 (Ar=ring Φ)
Q4 (Ar=ring Ω)
Q5 (Ar=ring Ψ)



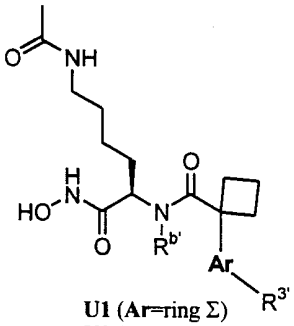
R1 (Ar=ring Σ)
R2 (Ar=ring Δ)
R3 (Ar=ring Φ)
R4 (Ar=ring Ω)
R5 (Ar=ring Ψ)



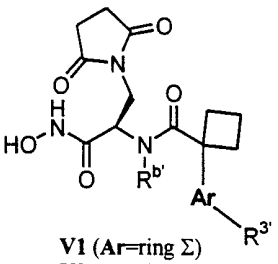
S1 (Ar=ring Σ)
S2 (Ar=ring Δ)
S3 (Ar=ring Φ)
S4 (Ar=ring Ω)
S5 (Ar=ring Ψ)



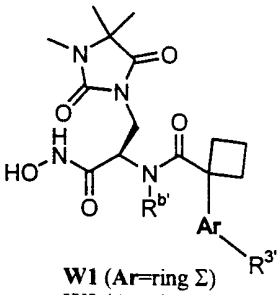
T1 (Ar=ring Σ)
T2 (Ar=ring Δ)
T3 (Ar=ring Φ)
T4 (Ar=ring Ω)
T5 (Ar=ring Ψ)



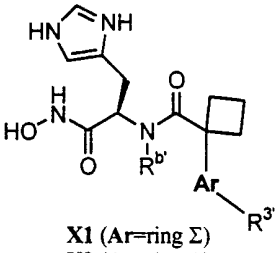
U1 (Ar=ring Σ)
U2 (Ar=ring Δ)
U3 (Ar=ring Φ)
U4 (Ar=ring Ω)
U5 (Ar=ring Ψ)



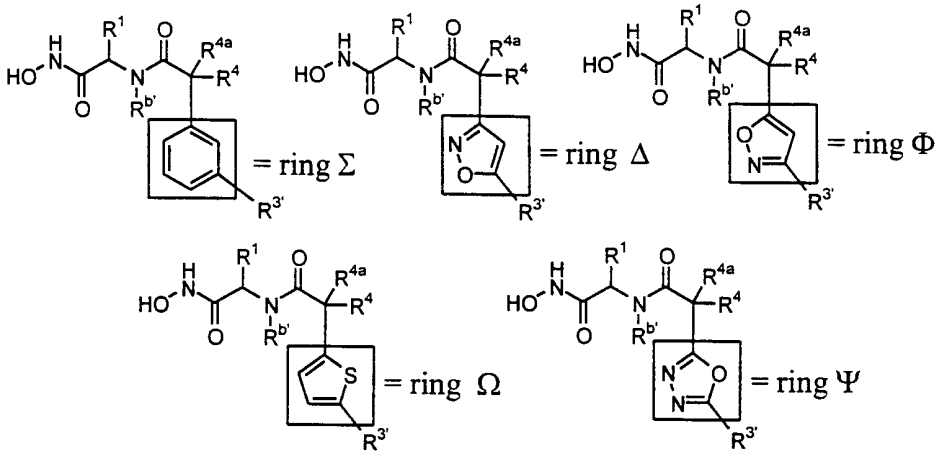
V1 (Ar=ring Σ)
V2 (Ar=ring Δ)
V3 (Ar=ring Φ)
V4 (Ar=ring Ω)
V5 (Ar=ring Ψ)



W1 (Ar=ring Σ)
W2 (Ar=ring Δ)
W3 (Ar=ring Φ)
W4 (Ar=ring Ω)
W5 (Ar=ring Ψ)



X1 (Ar=ring Σ)
X2 (Ar=ring Δ)
X3 (Ar=ring Φ)
X4 (Ar=ring Ω)
X5 (Ar=ring Ψ)



Ex#	$R^{b'}$	$R^{3'}$
1	Me	H
2	3-picolyl	H
3	aminocarbonylmethyl	H
4	Me	methyl
5	3-picolyl	methyl
6	aminocarbonylmethyl	methyl
7	Me	ethyl
8	3-picolyl	ethyl
9	aminocarbonylmethyl	ethyl
10	Me	isopropyl
11	3-picolyl	isopropyl
12	aminocarbonylmethyl	isopropyl
13	Me	phenyl
14	3-picolyl	phenyl
15	aminocarbonylmethyl	phenyl
16	Me	benzyl
17	3-picolyl	benzyl
18	aminocarbonylmethyl	benzyl
19	Me	2-phenylethyl
20	3-picolyl	2-phenylethyl
21	aminocarbonylmethyl	2-phenylethyl
22	Me	2-(2-methylphenyl)ethyl
23	3-picolyl	2-(2-methylphenyl)ethyl
24	aminocarbonylmethyl	2-(2-methylphenyl)ethyl
25	Me	2-(3-methylphenyl)ethyl
26	3-picolyl	2-(3-methylphenyl)ethyl
27	aminocarbonylmethyl	2-(3-methylphenyl)ethyl
28	Me	2-(2,6-dimethylphenyl)ethyl
29	3-picolyl	2-(2,6-dimethylphenyl)ethyl
30	aminocarbonylmethyl	2-(2,6-dimethylphenyl)ethyl
31	Me	2-(3,5-dimethylphenyl)ethyl
32	3-picolyl	2-(3,5-dimethylphenyl)ethyl
33	aminocarbonylmethyl	2-(3,5-dimethylphenyl)ethyl
34	Me	2-(3-amino-5-methylphenyl)ethyl
35	3-picolyl	2-(3-amino-5-methylphenyl)ethyl
36	aminocarbonylmethyl	2-(3-amino-5-methylphenyl)ethyl
37	Me	2-(pyridin-4-yl)ethyl
38	3-picolyl	2-(pyridin-4-yl)ethyl
39	aminocarbonylmethyl	2-(pyridin-4-yl)ethyl
40	Me	2-(2,6-dimethylpyridin-4-yl)ethyl
41	3-picolyl	2-(2,6-dimethylpyridin-4-yl)ethyl
42	aminocarbonylmethyl	2-(2,6-dimethylpyridin-4-yl)ethyl

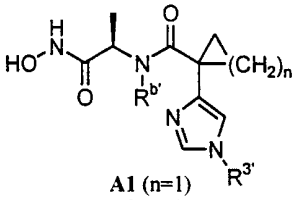
43	Me	2-(3,5-dimethylpyridin-4-yl)ethyl
44	3-picolyl	2-(3,5-dimethylpyridin-4-yl)ethyl
45	aminocarbonylmethyl	2-(3,5-dimethylpyridin-4-yl)ethyl
46	Me	styryl
47	3-picolyl	styryl
48	aminocarbonylmethyl	styryl
49	Me	hydroxy
50	3-picolyl	hydroxy
51	aminocarbonylmethyl	hydroxy
52	Me	methoxy
53	3-picolyl	methoxy
54	aminocarbonylmethyl	methoxy
55	Me	ethoxy
56	3-picolyl	ethoxy
57	aminocarbonylmethyl	ethoxy
58	Me	isopropyloxy
59	3-picolyl	isopropyloxy
60	aminocarbonylmethyl	isopropyloxy
61	Me	tert-butoxy
62	3-picolyl	tert-butoxy
63	aminocarbonylmethyl	tert-butoxy
64	Me	cyclohexyloxy
65	3-picolyl	cyclohexyloxy
66	aminocarbonylmethyl	cyclohexyloxy
67	Me	phenoxy
68	3-picolyl	phenoxy
69	aminocarbonylmethyl	phenoxy
70	Me	o-methylphenoxy
71	3-picolyl	o-methylphenoxy
72	aminocarbonylmethyl	o-methylphenoxy
73	Me	m-methylphenoxy
74	3-picolyl	m-methylphenoxy
75	aminocarbonylmethyl	m-methylphenoxy
76	Me	cinnamyloxy
77	3-picolyl	cinnamyloxy
78	aminocarbonylmethyl	cinnamyloxy
79	Me	benzyloxy
80	3-picolyl	benzyloxy
81	aminocarbonylmethyl	benzyloxy
82	Me	phenoxymethyl
83	3-picolyl	phenoxymethyl
84	aminocarbonylmethyl	phenoxymethyl
85	Me	o-methylbenzyloxy
86	3-picolyl	o-methylbenzyloxy
87	aminocarbonylmethyl	o-methylbenzyloxy
88	Me	m-methylbenzyloxy
89	3-picolyl	m-methylbenzyloxy
90	aminocarbonylmethyl	m-methylbenzyloxy
91	Me	o,o-dimethylbenzyloxy
92	3-picolyl	o,o-dimethylbenzyloxy
93	aminocarbonylmethyl	o,o-dimethylbenzyloxy
94	Me	(2,6-dimethylphenoxy)methyl
95	3-picolyl	(2,6-dimethylphenoxy)methyl
96	aminocarbonylmethyl	(2,6-dimethylphenoxy)methyl
97	Me	m,m-dimethylbenzyloxy
98	3-picolyl	m,m-dimethylbenzyloxy
99	aminocarbonylmethyl	m,m-dimethylbenzyloxy
100	Me	(3,5-dimethylphenoxy)methyl
101	3-picolyl	(3,5-dimethylphenoxy)methyl
102	aminocarbonylmethyl	(3,5-dimethylphenoxy)methyl

103	Me	o,o-dicyanobenzyloxy
104	3-picolyl	o,o-dicyanobenzyloxy
105	aminocarbonylmethyl	o,o-dicyanobenzyloxy
106	Me	m,m-dicyanobenzyloxy
107	3-picolyl	m,m-dicyanobenzyloxy
108	aminocarbonylmethyl	m,m-dicyanobenzyloxy
109	Me	(2,6-dicyanophenoxy)methyl
110	3-picolyl	(2,6-dicyanophenoxy)methyl
111	aminocarbonylmethyl	(2,6-dicyanophenoxy)methyl
112	Me	(3,5-dicyanophenoxy)methyl
113	3-picolyl	(3,5-dicyanophenoxy)methyl
114	aminocarbonylmethyl	(3,5-dicyanophenoxy)methyl
115	Me	o-amino-o-cyanobenzyloxy
116	3-picolyl	o-amino-o-cyanobenzyloxy
117	aminocarbonylmethyl	o-amino-o-cyanobenzyloxy
118	Me	m-amino-m-cyanobenzyloxy
119	3-picolyl	m-amino-m-cyanobenzyloxy
120	aminocarbonylmethyl	m-amino-m-cyanobenzyloxy
121	Me	o-amino-o-nitrobenzyloxy
122	3-picolyl	o-amino-o-nitrobenzyloxy
123	aminocarbonylmethyl	o-amino-o-nitrobenzyloxy
124	Me	m-amino-m-nitrobenzyloxy
125	3-picolyl	m-amino-m-nitrobenzyloxy
126	aminocarbonylmethyl	m-amino-m-nitrobenzyloxy
127	Me	p-amino-m,m-dimethylbenzyloxy
128	3-picolyl	p-amino-m,m-dimethylbenzyloxy
129	aminocarbonylmethyl	p-amino-m,m-dimethylbenzyloxy
130	Me	o-amino-o-methylbenzyloxy
131	3-picolyl	o-amino-o-methylbenzyloxy
132	aminocarbonylmethyl	o-amino-o-methylbenzyloxy
133	Me	m-amino-m-methylbenzyloxy
134	3-picolyl	m-amino-m-methylbenzyloxy
135	aminocarbonylmethyl	m-amino-m-methylbenzyloxy
136	Me	o-cyano-o-methylbenzyloxy
137	3-picolyl	o-cyano-o-methylbenzyloxy
138	aminocarbonylmethyl	o-cyano-o-methylbenzyloxy
139	Me	m-cyano-m-methylbenzyloxy
140	3-picolyl	m-cyano-m-methylbenzyloxy
141	aminocarbonylmethyl	m-cyano-m-methylbenzyloxy
142	Me	o-cyano-o-nitrobenzyloxy
143	3-picolyl	o-cyano-o-nitrobenzyloxy
144	aminocarbonylmethyl	o-cyano-o-nitrobenzyloxy
145	Me	(2-cyano-6-nitrophenoxy)methyl
146	3-picolyl	(2-cyano-6-nitrophenoxy)methyl
147	aminocarbonylmethyl	(2-cyano-6-nitrophenoxy)methyl
148	Me	m-cyano-m-nitrobenzyloxy
149	3-picolyl	m-cyano-m-nitrobenzyloxy
150	aminocarbonylmethyl	m-cyano-m-nitrobenzyloxy
151	Me	(3-cyano-5-nitrophenoxy)methyl
152	3-picolyl	(3-cyano-5-nitrophenoxy)methyl
153	aminocarbonylmethyl	(3-cyano-5-nitrophenoxy)methyl
154	Me	m,m-dimethoxybenzyloxy
155	3-picolyl	m,m-dimethoxybenzyloxy
156	aminocarbonylmethyl	m,m-dimethoxybenzyloxy
157	Me	m,m-dichlorobenzyloxy
158	3-picolyl	m,m-dichlorobenzyloxy
159	aminocarbonylmethyl	m,m-dichlorobenzyloxy
160	Me	(3,5-dichlorophenoxy)methyl
161	3-picolyl	(3,5-dichlorophenoxy)methyl
162	aminocarbonylmethyl	(3,5-dichlorophenoxy)methyl

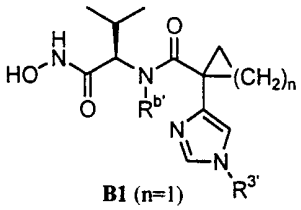
163	Me	m,m-dibromobenzyloxy
164	3-picolyl	m,m-dibromobenzyloxy
165	aminocarbonylmethyl	m,m-dibromobenzyloxy
166	Me	m,m-bis(trifluoromethyl)benzyloxy
167	3-picolyl	m,m-bis(trifluoromethyl)benzyloxy
168	aminocarbonylmethyl	m,m-bis(trifluoromethyl)benzyloxy
169	Me	[3,5-bis(trifluoromethyl)phenoxy]methyl
170	3-picolyl	[3,5-bis(trifluoromethyl)phenoxy]methyl
171	aminocarbonylmethyl	[3,5-bis(trifluoromethyl)phenoxy]methyl
172	Me	m-carboxamido-m-methylbenzyloxy
173	3-picolyl	m-carboxamido-m-methylbenzyloxy
174	aminocarbonylmethyl	m-carboxamido-m-methylbenzyloxy
175	Me	(3-carboxamido-5-methylphenoxy)methyl
176	3-picolyl	(3-carboxamido-5-methylphenoxy)methyl
177	aminocarbonylmethyl	(3-carboxamido-5-methylphenoxy)methyl
178	Me	m-hydroxycarbonyl-m-methylbenzyloxy
179	3-picolyl	m-hydroxycarbonyl-m-methylbenzyloxy
180	aminocarbonylmethyl	m-hydroxycarbonyl-m-methylbenzyloxy
181	Me	(3-hydroxycarbonyl-5-methylphenoxy)methyl
182	3-picolyl	(3-hydroxycarbonyl-5-methylphenoxy)methyl
183	aminocarbonylmethyl	(3-hydroxycarbonyl-5-methylphenoxy)methyl
184	Me	o-phenylbenzyloxy
185	3-picolyl	o-phenylbenzyloxy
186	aminocarbonylmethyl	o-phenylbenzyloxy
187	Me	m-phenylbenzyloxy
188	3-picolyl	m-phenylbenzyloxy
189	aminocarbonylmethyl	m-phenylbenzyloxy
190	Me	(naphth-1-yl)methoxy
191	3-picolyl	(naphth-1-yl)methoxy
192	aminocarbonylmethyl	(naphth-1-yl)methoxy
193	Me	(naphth-2-yl)methoxy
194	3-picolyl	(naphth-2-yl)methoxy
195	aminocarbonylmethyl	(naphth-2-yl)methoxy
196	Me	(2-methylnaphth-1-yl)methoxy
197	3-picolyl	(2-methylnaphth-1-yl)methoxy
198	aminocarbonylmethyl	(2-methylnaphth-1-yl)methoxy
199	Me	(4-methylnaphth-2-yl)methoxy
200	3-picolyl	(4-methylnaphth-2-yl)methoxy
201	aminocarbonylmethyl	(4-methylnaphth-2-yl)methoxy
202	Me	(pyridin-3-yl)methoxy
203	3-picolyl	(pyridin-3-yl)methoxy
204	aminocarbonylmethyl	(pyridin-3-yl)methoxy
205	Me	(pyridin-4-yl)methoxy
206	3-picolyl	(pyridin-4-yl)methoxy
207	aminocarbonylmethyl	(pyridin-4-yl)methoxy
208	Me	(3,5-dichloropyridin-4-yl)methoxy
209	3-picolyl	(3,5-dichloropyridin-4-yl)methoxy
210	aminocarbonylmethyl	(3,5-dichloropyridin-4-yl)methoxy
211	Me	(3,5-dimethylpyridin-4-yl)methoxy
212	3-picolyl	(3,5-dimethylpyridin-4-yl)methoxy
213	aminocarbonylmethyl	(3,5-dimethylpyridin-4-yl)methoxy
214	Me	(1,2,3-benzotriazol-1-yl)methoxy
215	3-picolyl	(1,2,3-benzotriazol-1-yl)methoxy
216	aminocarbonylmethyl	(1,2,3-benzotriazol-1-yl)methoxy
217	Me	benzhydroxy
218	3-picolyl	benzhydroxy
219	aminocarbonylmethyl	benzhydroxy
220	Me	p-(1,2,3-thiadiazol-5-yl)benzyloxy
221	3-picolyl	p-(1,2,3-thiadiazol-5-yl)benzyloxy
222	aminocarbonylmethyl	p-(1,2,3-thiadiazol-5-yl)benzyloxy

223	Me	o-(tetrazol-5-yl)benzyloxy
224	3-picolyl	o-(tetrazol-5-yl)benzyloxy
225	aminocarbonylmethyl	o-(tetrazol-5-yl)benzyloxy
226	Me	m-(tetrazol-5-yl)benzyloxy
227	3-picolyl	m-(tetrazol-5-yl)benzyloxy
228	aminocarbonylmethyl	m-(tetrazol-5-yl)benzyloxy
229	Me	[3-methyl-5-(tetrazol-5-yl)phenoxy]methyl
230	3-picolyl	[3-methyl-5-(tetrazol-5-yl)phenoxy]methyl
231	aminocarbonylmethyl	[3-methyl-5-(tetrazol-5-yl)phenoxy]methyl
232	Me	m-methyl-m-(tetrazol-5-yl)benzyloxy
233	3-picolyl	m-methyl-m-(tetrazol-5-yl)benzyloxy
234	aminocarbonylmethyl	m-methyl-m-(tetrazol-5-yl)benzyloxy
235	Me	2-oxo-2-phenylethoxy
236	3-picolyl	2-oxo-2-phenylethoxy
237	aminocarbonylmethyl	2-oxo-2-phenylethoxy
238	Me	carbo-t-butoxymethoxy
239	3-picolyl	carbo-t-butoxymethoxy
240	aminocarbonylmethyl	carbo-t-butoxymethoxy
241	Me	(benzimidazol-2-yl)methoxy
242	3-picolyl	(benzimidazol-2-yl)methoxy
243	aminocarbonylmethyl	(benzimidazol-2-yl)methoxy
244	Me	(imidazol-2-yl)methoxy
245	3-picolyl	(imidazol-2-yl)methoxy
246	aminocarbonylmethyl	(imidazol-2-yl)methoxy
247	Me	(1,4-dimethylimidazol-5-yl)methoxy
248	3-picolyl	(1,4-dimethylimidazol-5-yl)methoxy
249	aminocarbonylmethyl	(1,4-dimethylimidazol-5-yl)methoxy
250	Me	(thiazol-4-yl)methoxy
251	3-picolyl	(thiazol-4-yl)methoxy
252	aminocarbonylmethyl	(thiazol-4-yl)methoxy
253	Me	(quinolin-2-yl)methoxy
254	3-picolyl	(quinolin-2-yl)methoxy
255	aminocarbonylmethyl	(quinolin-2-yl)methoxy
256	Me	(1,3-benzodioxo-5-yl)methoxy
257	3-picolyl	(1,3-benzodioxo-5-yl)methoxy
258	aminocarbonylmethyl	(1,3-benzodioxo-5-yl)methoxy
259	Me	(3,5-dimethylisoxazol-4-yl)methoxy
260	3-picolyl	(3,5-dimethylisoxazol-4-yl)methoxy
261	aminocarbonylmethyl	(3,5-dimethylisoxazol-4-yl)methoxy
262	Me	(3,5-dimethylpyrazol-1-yl)methoxy
263	3-picolyl	(3,5-dimethylpyrazol-1-yl)methoxy
264	aminocarbonylmethyl	(3,5-dimethylpyrazol-1-yl)methoxy
265	Me	(1,3,5-trimethylpyrazol-4-yl)methoxy
266	3-picolyl	(1,3,5-trimethylpyrazol-4-yl)methoxy
267	aminocarbonylmethyl	(1,3,5-trimethylpyrazol-4-yl)methoxy
268	Me	4-quinolinylmethoxy
269	3-picolyl	4-quinolinylmethoxy
270	aminocarbonylmethyl	4-quinolinylmethoxy
271	Me	2-methyl-4-quinolinylmethoxy
272	3-picolyl	2-methyl-4-quinolinylmethoxy
273	aminocarbonylmethyl	2-methyl-4-quinolinylmethoxy
274	Me	4-quinolinyloxymethyl
275	3-picolyl	4-quinolinyloxymethyl
276	aminocarbonylmethyl	4-quinolinyloxymethyl

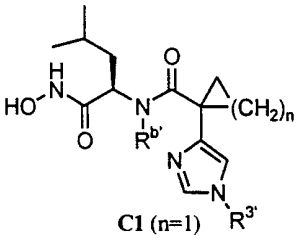
TABLE 4



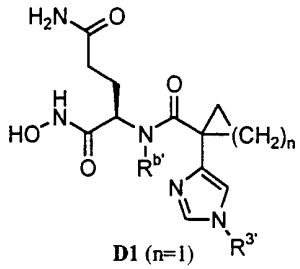
A1 (n=1)
A2 (n=2)



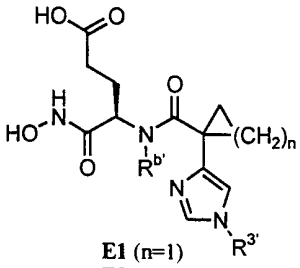
B1 (n=1)
B2 (n=2)



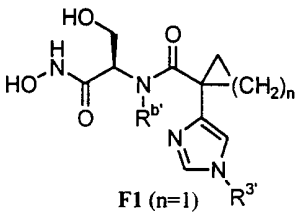
C1 (n=1)
C2 (n=2)



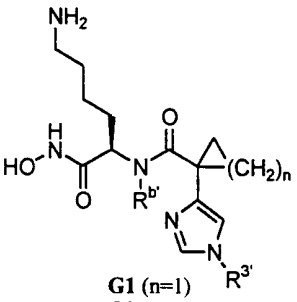
D1 (n=1)
D2 (n=2)



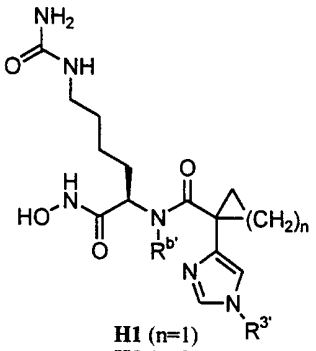
E1 (n=1)
E2 (n=2)



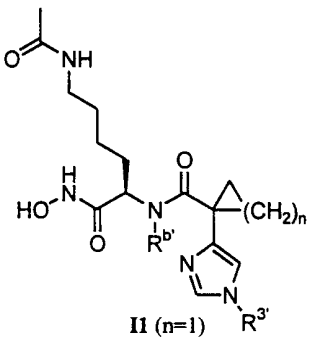
F1 (n=1)
F2 (n=2)



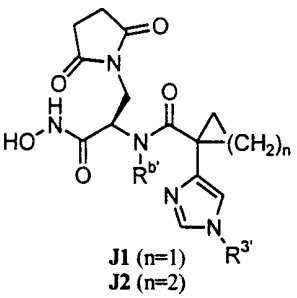
G1 (n=1)
G2 (n=2)



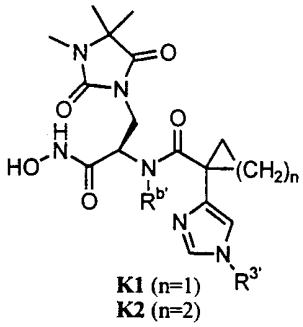
H1 (n=1)
H2 (n=2)



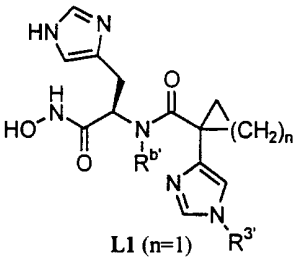
I1 (n=1)
I2 (n=2)



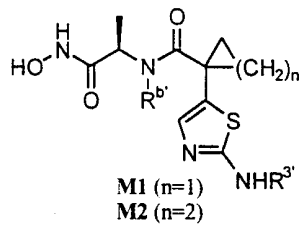
J1 (n=1)
J2 (n=2)



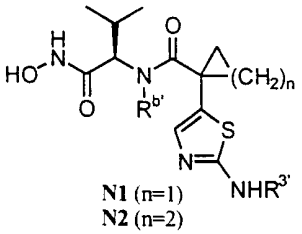
K1 (n=1)
K2 (n=2)



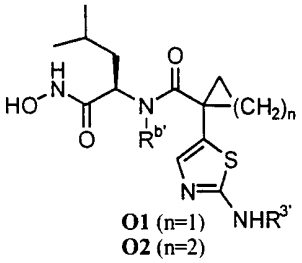
L1 (n=1)
L2 (n=2)



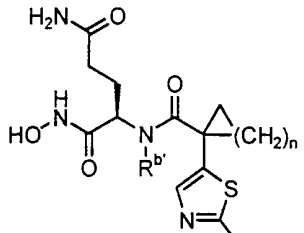
M1 (n=1)
M2 (n=2)



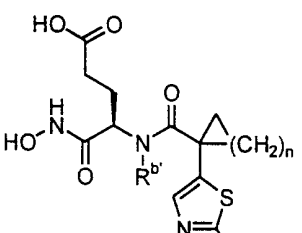
N1 (n=1)
N2 (n=2)



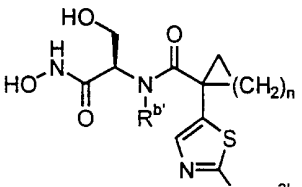
O1 (n=1)
O2 (n=2)



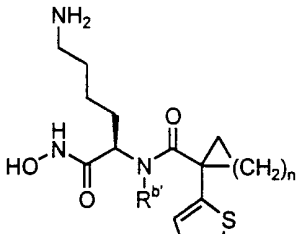
P1 (n=1)
P2 (n=2)



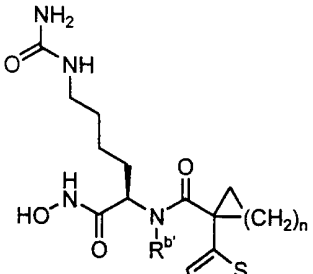
Q1 (n=1)
Q2 (n=2)



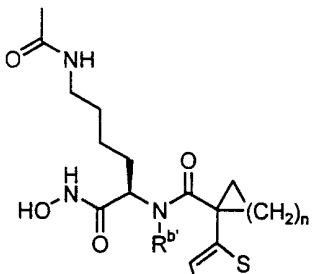
R1 (n=1)
R2 (n=2)



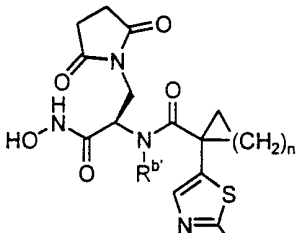
S1 (n=1)
S2 (n=2)



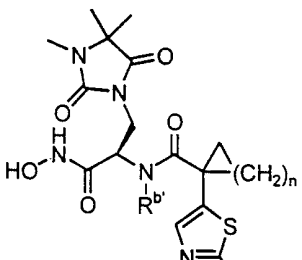
T1 (n=1)
T2 (n=2)



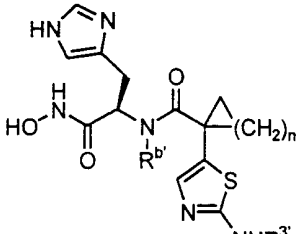
U1 (n=1)
U2 (n=2)



V1 (n=1)
V2 (n=2)



W1 (n=1)
W2 (n=2)



X1 (n=1)
X2 (n=2)

Ex#	$R^{b'}$	$R^{3'}$
1	Me	H
2	3-picolyl	H
3	aminocarbonylmethyl	H
4	Me	methyl
5	3-picolyl	methyl
6	aminocarbonylmethyl	methyl
7	Me	ethyl
8	3-picolyl	ethyl
9	aminocarbonylmethyl	ethyl
10	Me	isopropyl
11	3-picolyl	isopropyl
12	aminocarbonylmethyl	isopropyl

13	Me	phenyl
14	3-picolyl	phenyl
15	aminocarbonylmethyl	phenyl
16	Me	benzyl
17	3-picolyl	benzyl
18	aminocarbonylmethyl	benzyl
19	Me	o-methylbenzyl
20	3-picolyl	o-methylbenzyl
21	aminocarbonylmethyl	o-methylbenzyl
22	Me	m-methylbenzyl
23	3-picolyl	m-methylbenzyl
24	aminocarbonylmethyl	m-methylbenzyl
25	Me	p-methylbenzyl
26	3-picolyl	p-methylbenzyl
27	aminocarbonylmethyl	p-methylbenzyl
28	Me	2-phenylethyl
29	3-picolyl	2-phenylethyl
30	aminocarbonylmethyl	2-phenylethyl
31	Me	2-(2-methylphenyl)ethyl
32	3-picolyl	2-(2-methylphenyl)ethyl
33	aminocarbonylmethyl	2-(2-methylphenyl)ethyl
34	Me	2-(3-methylphenyl)ethyl
35	3-picolyl	2-(3-methylphenyl)ethyl
36	aminocarbonylmethyl	2-(3-methylphenyl)ethyl
37	Me	2-(4-methylphenyl)ethyl
38	3-picolyl	2-(4-methylphenyl)ethyl
39	aminocarbonylmethyl	2-(4-methylphenyl)ethyl
40	Me	2-(2,6-dimethylphenyl)ethyl
41	3-picolyl	2-(2,6-dimethylphenyl)ethyl
42	aminocarbonylmethyl	2-(2,6-dimethylphenyl)ethyl
43	Me	o,o-dimethylbenzyl
44	3-picolyl	o,o-dimethylbenzyl
45	aminocarbonylmethyl	o,o-dimethylbenzyl
46	Me	2-(3,5-dimethylphenyl)ethyl
47	3-picolyl	2-(3,5-dimethylphenyl)ethyl
48	aminocarbonylmethyl	2-(3,5-dimethylphenyl)ethyl
49	Me	m,m-dimethylbenzyl
50	3-picolyl	m,m-dimethylbenzyl
51	aminocarbonylmethyl	m,m-dimethylbenzyl
52	Me	2-(2-amino-6-methylphenyl)ethyl
53	3-picolyl	2-(2-amino-6-methylphenyl)ethyl
54	aminocarbonylmethyl	2-(2-amino-6-methylphenyl)ethyl
55	Me	o-amino-o-methylbenzyl
56	3-picolyl	o-amino-o-methylbenzyl
57	aminocarbonylmethyl	o-amino-o-methylbenzyl
58	Me	2-(3-amino-5-methylphenyl)ethyl
59	3-picolyl	2-(3-amino-5-methylphenyl)ethyl
60	aminocarbonylmethyl	2-(3-amino-5-methylphenyl)ethyl
61	Me	m-amino-m-methylbenzyl
62	3-picolyl	m-amino-m-methylbenzyl
63	aminocarbonylmethyl	m-amino-m-methylbenzyl
64	Me	2-(pyridin-2-yl)ethyl
65	3-picolyl	2-(pyridin-2-yl)ethyl
66	aminocarbonylmethyl	2-(pyridin-2-yl)ethyl
67	Me	(pyridin-2-yl)methyl
68	3-picolyl	(pyridin-2-yl)methyl
69	aminocarbonylmethyl	(pyridin-2-yl)methyl
70	Me	2-(pyridin-3-yl)ethyl
71	3-picolyl	2-(pyridin-3-yl)ethyl
72	aminocarbonylmethyl	2-(pyridin-3-yl)ethyl

73	Me	(pyridin-3-yl)methyl
74	3-picolyl	(pyridin-3-yl)methyl
75	aminocarbonylmethyl	(pyridin-3-yl)methyl
76	Me	2-(pyridin-4-yl)ethyl
77	3-picolyl	2-(pyridin-4-yl)ethyl
78	aminocarbonylmethyl	2-(pyridin-4-yl)ethyl
79	Me	(pyridin-4-yl)methyl
80	3-picolyl	(pyridin-4-yl)methyl
81	aminocarbonylmethyl	(pyridin-4-yl)methyl
82	Me	2-(2,6-dimethylpyridin-4-yl)ethyl
83	3-picolyl	2-(2,6-dimethylpyridin-4-yl)ethyl
84	aminocarbonylmethyl	2-(2,6-dimethylpyridin-4-yl)ethyl
85	Me	(2,6-dimethylpyridin-4-yl)methyl
86	3-picolyl	(2,6-dimethylpyridin-4-yl)methyl
87	aminocarbonylmethyl	(2,6-dimethylpyridin-4-yl)methyl
88	Me	2-(3,5-dimethylpyridin-4-yl)ethyl
89	3-picolyl	2-(3,5-dimethylpyridin-4-yl)ethyl
90	aminocarbonylmethyl	2-(3,5-dimethylpyridin-4-yl)ethyl
91	Me	(3,5-dimethylpyridin-4-yl)methyl
92	3-picolyl	(3,5-dimethylpyridin-4-yl)methyl
93	aminocarbonylmethyl	(3,5-dimethylpyridin-4-yl)methyl
94	Me	styryl
95	3-picolyl	styryl
96	aminocarbonylmethyl	styryl
97	Me	cyclohexylmethyl
98	3-picolyl	cyclohexylmethyl
99	aminocarbonylmethyl	cyclohexylmethyl
100	Me	phenoxymethyl
101	3-picolyl	phenoxymethyl
102	aminocarbonylmethyl	phenoxymethyl
103	Me	(2,6-dimethylphenoxy)methyl
104	3-picolyl	(2,6-dimethylphenoxy)methyl
105	aminocarbonylmethyl	(2,6-dimethylphenoxy)methyl
106	Me	(3,5-dimethylphenoxy)methyl
107	3-picolyl	(3,5-dimethylphenoxy)methyl
108	aminocarbonylmethyl	(3,5-dimethylphenoxy)methyl
109	Me	(2,6-dicyanophenoxy)methyl
110	3-picolyl	(2,6-dicyanophenoxy)methyl
111	aminocarbonylmethyl	(2,6-dicyanophenoxy)methyl
112	Me	(3,5-dicyanophenoxy)methyl
113	3-picolyl	(3,5-dicyanophenoxy)methyl
114	aminocarbonylmethyl	(3,5-dicyanophenoxy)methyl
115	Me	2-(2-amino-6-cyanophenyl)ethyl
116	3-picolyl	2-(2-amino-6-cyanophenyl)ethyl
117	aminocarbonylmethyl	2-(2-amino-6-cyanophenyl)ethyl
118	Me	o-amino-o-cyanobenzyl
119	3-picolyl	o-amino-o-cyanobenzyl
120	aminocarbonylmethyl	o-amino-o-cyanobenzyl
121	Me	2-(3-amino-5-cyanophenyl)ethyl
122	3-picolyl	2-(3-amino-5-cyanophenyl)ethyl
123	aminocarbonylmethyl	2-(3-amino-5-cyanophenyl)ethyl
124	Me	m-amino-m-cyanobenzyl
125	3-picolyl	m-amino-m-cyanobenzyl
126	aminocarbonylmethyl	m-amino-m-cyanobenzyl
127	Me	2-(2-amino-6-nitrophenyl)ethyl
128	3-picolyl	2-(2-amino-6-nitrophenyl)ethyl
129	aminocarbonylmethyl	2-(2-amino-6-nitrophenyl)ethyl
130	Me	o-amino-o-nitrobenzyl
131	3-picolyl	o-amino-o-nitrobenzyl
132	aminocarbonylmethyl	o-amino-o-nitrobenzyl

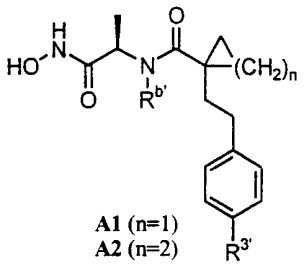
133	Me	2-(3-amino-5-nitrophenyl)ethyl
134	3-picolyl	2-(3-amino-5-nitrophenyl)ethyl
135	aminocarbonylmethyl	2-(3-amino-5-nitrophenyl)ethyl
136	Me	m-amino-m-nitrobenzyl
137	3-picolyl	m-amino-m-nitrobenzyl
138	aminocarbonylmethyl	m-amino-m-nitrobenzyl
139	Me	2-(4-amino-2,6-dimethylphenyl)ethyl
140	3-picolyl	2-(4-amino-2,6-dimethylphenyl)ethyl
141	aminocarbonylmethyl	2-(4-amino-2,6-dimethylphenyl)ethyl
142	Me	p-amino-o,o-dimethylbenzyl
143	3-picolyl	p-amino-o,o-dimethylbenzyl
144	aminocarbonylmethyl	p-amino-o,o-dimethylbenzyl
145	Me	2-(4-amino-3,5-dimethylphenyl)ethyl
146	3-picolyl	2-(4-amino-3,5-dimethylphenyl)ethyl
147	aminocarbonylmethyl	2-(4-amino-3,5-dimethylphenyl)ethyl
148	Me	p-amino-m,m-dimethylbenzyl
149	3-picolyl	p-amino-m,m-dimethylbenzyl
150	aminocarbonylmethyl	p-amino-m,m-dimethylbenzyl
151	Me	2-(2-cyano-6-methylphenyl)ethyl
152	3-picolyl	2-(2-cyano-6-methylphenyl)ethyl
153	aminocarbonylmethyl	2-(2-cyano-6-methylphenyl)ethyl
154	Me	o-cyano-o-methylbenzyl
155	3-picolyl	o-cyano-o-methylbenzyl
156	aminocarbonylmethyl	o-cyano-o-methylbenzyl
157	Me	2-(3-cyano-5-methylphenyl)ethyl
158	3-picolyl	2-(3-cyano-5-methylphenyl)ethyl
159	aminocarbonylmethyl	2-(3-cyano-5-methylphenyl)ethyl
160	Me	m-cyano-m-methylbenzyl
161	3-picolyl	m-cyano-m-methylbenzyl
162	aminocarbonylmethyl	m-cyano-m-methylbenzyl
163	Me	2-(2-cyano-6-nitrophenyl)ethyl
164	3-picolyl	2-(2-cyano-6-nitrophenyl)ethyl
165	aminocarbonylmethyl	2-(2-cyano-6-nitrophenyl)ethyl
166	Me	o-cyano-o-nitrobenzyl
167	3-picolyl	o-cyano-o-nitrobenzyl
168	aminocarbonylmethyl	o-cyano-o-nitrobenzyl
169	Me	(2-cyano-6-nitrophenoxy)methyl
170	3-picolyl	(2-cyano-6-nitrophenoxy)methyl
171	aminocarbonylmethyl	(2-cyano-6-nitrophenoxy)methyl
172	Me	2-(3-cyano-5-nitrophenyl)ethyl
173	3-picolyl	2-(3-cyano-5-nitrophenyl)ethyl
174	aminocarbonylmethyl	2-(3-cyano-5-nitrophenyl)ethyl
175	Me	m-cyano-m-nitrobenzyl
176	3-picolyl	m-cyano-m-nitrobenzyl
177	aminocarbonylmethyl	m-cyano-m-nitrobenzyl
178	Me	(3-cyano-5-nitrophenoxy)methyl
179	3-picolyl	(3-cyano-5-nitrophenoxy)methyl
180	aminocarbonylmethyl	(3-cyano-5-nitrophenoxy)methyl
181	Me	2-(3,5-dimethoxyphenyl)ethyl
182	3-picolyl	2-(3,5-dimethoxyphenyl)ethyl
183	aminocarbonylmethyl	2-(3,5-dimethoxyphenyl)ethyl
184	Me	m,m-dimethoxybenzyl
185	3-picolyl	m,m-dimethoxybenzyl
186	aminocarbonylmethyl	m,m-dimethoxybenzyl
187	Me	2-(3,5-dichlorophenyl)ethyl
188	3-picolyl	2-(3,5-dichlorophenyl)ethyl
189	aminocarbonylmethyl	2-(3,5-dichlorophenyl)ethyl
190	Me	m,m-dichlorobenzyl
191	3-picolyl	m,m-dichlorobenzyl
192	aminocarbonylmethyl	m,m-dichlorobenzyl

193	Me	(3,5-dichlorophenoxy)methyl
194	3-picolyl	(3,5-dichlorophenoxy)methyl
195	aminocarbonylmethyl	(3,5-dichlorophenoxy)methyl
196	Me	2-(3,5-dibromophenyl)ethyl
197	3-picolyl	2-(3,5-dibromophenyl)ethyl
198	aminocarbonylmethyl	2-(3,5-dibromophenyl)ethyl
199	Me	m,m-dibromobenzyl
200	3-picolyl	m,m-dibromobenzyl
201	aminocarbonylmethyl	m,m-dibromobenzyl
202	Me	2-[3,5-bis(trifluoromethyl)phenyl]ethyl
203	3-picolyl	2-[3,5-bis(trifluoromethyl)phenyl]ethyl
204	aminocarbonylmethyl	2-[3,5-bis(trifluoromethyl)phenyl]ethyl
205	Me	3,5-bis(trifluoromethyl)phenylmethyl
206	3-picolyl	3,5-bis(trifluoromethyl)phenylmethyl
207	aminocarbonylmethyl	3,5-bis(trifluoromethyl)phenylmethyl
208	Me	[3,5-bis(trifluoromethyl)phenoxy]methyl
209	3-picolyl	[3,5-bis(trifluoromethyl)phenoxy]methyl
210	aminocarbonylmethyl	[3,5-bis(trifluoromethyl)phenoxy]methyl
211	Me	2-(3-carboxamido-5-methylphenyl)ethyl
212	3-picolyl	2-(3-carboxamido-5-methylphenyl)ethyl
213	aminocarbonylmethyl	2-(3-carboxamido-5-methylphenyl)ethyl
214	Me	m-carboxamido-m-methylbenzyl
215	3-picolyl	m-carboxamido-m-methylbenzyl
216	aminocarbonylmethyl	m-carboxamido-m-methylbenzyl
217	Me	(3-carboxamido-5-methylphenoxy)methyl
218	3-picolyl	(3-carboxamido-5-methylphenoxy)methyl
219	aminocarbonylmethyl	(3-carboxamido-5-methylphenoxy)methyl
220	Me	2-(3-hydroxycarbonyl-5-methylphenyl)ethyl
221	3-picolyl	2-(3-hydroxycarbonyl-5-methylphenyl)ethyl
222	aminocarbonylmethyl	2-(3-hydroxycarbonyl-5-methylphenyl)ethyl
223	Me	m-hydroxycarbonyl-m-methylbenzyl
224	3-picolyl	m-hydroxycarbonyl-m-methylbenzyl
225	aminocarbonylmethyl	m-hydroxycarbonyl-m-methylbenzyl
226	Me	(3-hydroxycarbonyl-5-methylphenoxy)methyl
227	3-picolyl	(3-hydroxycarbonyl-5-methylphenoxy)methyl
228	aminocarbonylmethyl	(3-hydroxycarbonyl-5-methylphenoxy)methyl
229	Me	2-(2-phenylphenyl)ethyl
230	3-picolyl	2-(2-phenylphenyl)ethyl
231	aminocarbonylmethyl	2-(2-phenylphenyl)ethyl
232	Me	o-phenylbenzyl
233	3-picolyl	o-phenylbenzyl
234	aminocarbonylmethyl	o-phenylbenzyl
235	Me	2-(3-phenylphenyl)ethyl
236	3-picolyl	2-(3-phenylphenyl)ethyl
237	aminocarbonylmethyl	2-(3-phenylphenyl)ethyl
238	Me	m-phenylbenzyl
239	3-picolyl	m-phenylbenzyl
240	aminocarbonylmethyl	m-phenylbenzyl
241	Me	2-(naphth-1-yl)ethyl
242	3-picolyl	2-(naphth-1-yl)ethyl
243	aminocarbonylmethyl	2-(naphth-1-yl)ethyl
244	Me	(naphth-1-yl)methyl
245	3-picolyl	(naphth-1-yl)methyl
246	aminocarbonylmethyl	(naphth-1-yl)methyl
247	Me	2-(naphth-2-yl)ethyl
248	3-picolyl	2-(naphth-2-yl)ethyl
249	aminocarbonylmethyl	2-(naphth-2-yl)ethyl
250	Me	(naphth-2-yl)methyl
251	3-picolyl	(naphth-2-yl)methyl
252	aminocarbonylmethyl	(naphth-2-yl)methyl

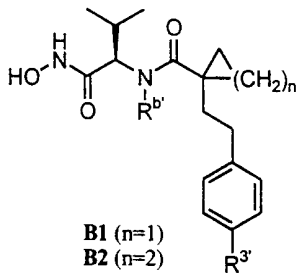
253	Me	2-(2-methylnaphth-1-yl)ethyl
254	3-picolyl	2-(2-methylnaphth-1-yl)ethyl
255	aminocarbonylmethyl	2-(2-methylnaphth-1-yl)ethyl
256	Me	(2-methylnaphth-1-yl)methyl
257	3-picolyl	(2-methylnaphth-1-yl)methyl
258	aminocarbonylmethyl	(2-methylnaphth-1-yl)methyl
259	Me	2-(4-methylnaphth-2-yl)ethyl
260	3-picolyl	2-(4-methylnaphth-2-yl)ethyl
261	aminocarbonylmethyl	2-(4-methylnaphth-2-yl)ethyl
262	Me	(4-methylnaphth-2-yl)methyl
263	3-picolyl	(4-methylnaphth-2-yl)methyl
264	aminocarbonylmethyl	(4-methylnaphth-2-yl)methyl
265	Me	2-(3,5-dichloropyridin-4-yl)ethyl
266	3-picolyl	2-(3,5-dichloropyridin-4-yl)ethyl
267	aminocarbonylmethyl	2-(3,5-dichloropyridin-4-yl)ethyl
268	Me	(3,5-dichloropyridin-4-yl)methyl
269	3-picolyl	(3,5-dichloropyridin-4-yl)methyl
270	aminocarbonylmethyl	(3,5-dichloropyridin-4-yl)methyl
271	Me	2-(1,2,3-benzotriazol-1-yl)ethyl
272	3-picolyl	2-(1,2,3-benzotriazol-1-yl)ethyl
273	aminocarbonylmethyl	2-(1,2,3-benzotriazol-1-yl)ethyl
274	Me	2-[4-(1,2,3-thiadiazol-5-yl)phenyl]ethyl
275	3-picolyl	2-[4-(1,2,3-thiadiazol-5-yl)phenyl]ethyl
276	aminocarbonylmethyl	2-[4-(1,2,3-thiadiazol-5-yl)phenyl]ethyl
277	Me	4-(1,2,3-thiadiazol-5-yl)phenylmethyl
278	3-picolyl	4-(1,2,3-thiadiazol-5-yl)phenylmethyl
279	aminocarbonylmethyl	4-(1,2,3-thiadiazol-5-yl)phenylmethyl
280	Me	2-[2-(tetrazol-5-yl)phenyl]ethyl
281	3-picolyl	2-[2-(tetrazol-5-yl)phenyl]ethyl
282	aminocarbonylmethyl	2-[2-(tetrazol-5-yl)phenyl]ethyl
283	Me	2-(tetrazol-5-yl)phenylmethyl
284	3-picolyl	2-(tetrazol-5-yl)phenylmethyl
285	aminocarbonylmethyl	2-(tetrazol-5-yl)phenylmethyl
286	Me	2-[3-(tetrazol-5-yl)phenyl]ethyl
287	3-picolyl	2-[3-(tetrazol-5-yl)phenyl]ethyl
288	aminocarbonylmethyl	2-[3-(tetrazol-5-yl)phenyl]ethyl
289	Me	3-(tetrazol-5-yl)phenylmethyl
290	3-picolyl	3-(tetrazol-5-yl)phenylmethyl
291	aminocarbonylmethyl	3-(tetrazol-5-yl)phenylmethyl
292	Me	[3-methyl-5-(tetrazol-5-yl)phenoxy]methyl
293	3-picolyl	[3-methyl-5-(tetrazol-5-yl)phenoxy]methyl
294	aminocarbonylmethyl	[3-methyl-5-(tetrazol-5-yl)phenoxy]methyl
295	Me	2-[3-methyl-5-(tetrazol-5-yl)phenyl]ethyl
296	3-picolyl	2-[3-methyl-5-(tetrazol-5-yl)phenyl]ethyl
297	aminocarbonylmethyl	2-[3-methyl-5-(tetrazol-5-yl)phenyl]ethyl
298	Me	3-methyl-5-(tetrazol-5-yl)phenylmethyl
299	3-picolyl	3-methyl-5-(tetrazol-5-yl)phenylmethyl
300	aminocarbonylmethyl	3-methyl-5-(tetrazol-5-yl)phenylmethyl
301	Me	2-(benzimidazol-2-yl)ethyl
302	3-picolyl	2-(benzimidazol-2-yl)ethyl
302	aminocarbonylmethyl	2-(benzimidazol-2-yl)ethyl
304	Me	(benzimidazol-2-yl)methyl
305	3-picolyl	(benzimidazol-2-yl)methyl
306	aminocarbonylmethyl	(benzimidazol-2-yl)methyl
307	Me	2-(imidazol-2-yl)ethyl
308	3-picolyl	2-(imidazol-2-yl)ethyl
309	aminocarbonylmethyl	2-(imidazol-2-yl)ethyl
310	Me	(imidazol-2-yl)methyl
311	3-picolyl	(imidazol-2-yl)methyl
312	aminocarbonylmethyl	(imidazol-2-yl)methyl

313	Me	2-(1,4-dimethylimidazol-5-yl)ethyl
314	3-picolyl	2-(1,4-dimethylimidazol-5-yl)ethyl
315	aminocarbonylmethyl	2-(1,4-dimethylimidazol-5-yl)ethyl
316	Me	(1,4-dimethylimidazol-5-yl)methyl
317	3-picolyl	(1,4-dimethylimidazol-5-yl)methyl
318	aminocarbonylmethyl	(1,4-dimethylimidazol-5-yl)methyl
319	Me	2-(thiazol-4-yl)ethyl
320	3-picolyl	2-(thiazol-4-yl)ethyl
321	aminocarbonylmethyl	2-(thiazol-4-yl)ethyl
322	Me	(thiazol-4-yl)methyl
323	3-picolyl	(thiazol-4-yl)methyl
324	aminocarbonylmethyl	(thiazol-4-yl)methyl
325	Me	2-(quinolin-2-yl)ethyl
326	3-picolyl	2-(quinolin-2-yl)ethyl
327	aminocarbonylmethyl	2-(quinolin-2-yl)ethyl
328	Me	(quinolin-2-yl)methyl
329	3-picolyl	(quinolin-2-yl)methyl
330	aminocarbonylmethyl	(quinolin-2-yl)methyl
331	Me	2-(1,3-benzodioxo-5-yl)ethyl
332	3-picolyl	2-(1,3-benzodioxo-5-yl)ethyl
333	aminocarbonylmethyl	2-(1,3-benzodioxo-5-yl)ethyl
334	Me	(1,3-benzodioxo-5-yl)methyl
335	3-picolyl	(1,3-benzodioxo-5-yl)methyl
336	aminocarbonylmethyl	(1,3-benzodioxo-5-yl)methyl
337	Me	2-(3,5-dimethylisoxazol-4-yl)ethyl
338	3-picolyl	2-(3,5-dimethylisoxazol-4-yl)ethyl
339	aminocarbonylmethyl	2-(3,5-dimethylisoxazol-4-yl)ethyl
340	Me	(3,5-dimethylisoxazol-4-yl)methyl
341	3-picolyl	(3,5-dimethylisoxazol-4-yl)methyl
342	aminocarbonylmethyl	(3,5-dimethylisoxazol-4-yl)methyl
343	Me	2-(3,5-dimethylpyrazol-1-yl)ethyl
344	3-picolyl	2-(3,5-dimethylpyrazol-1-yl)ethyl
345	aminocarbonylmethyl	2-(3,5-dimethylpyrazol-1-yl)ethyl
346	Me	(3,5-dimethylpyrazol-1-yl)methyl
347	3-picolyl	(3,5-dimethylpyrazol-1-yl)methyl
348	aminocarbonylmethyl	(3,5-dimethylpyrazol-1-yl)methyl
349	Me	2-(1,3,5-trimethylpyrazol-4-yl)ethyl
350	3-picolyl	2-(1,3,5-trimethylpyrazol-4-yl)ethyl
351	aminocarbonylmethyl	2-(1,3,5-trimethylpyrazol-4-yl)ethyl
352	Me	(1,3,5-trimethylpyrazol-4-yl)methyl
353	3-picolyl	(1,3,5-trimethylpyrazol-4-yl)methyl
354	aminocarbonylmethyl	(1,3,5-trimethylpyrazol-4-yl)methyl

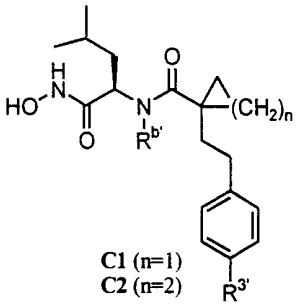
TABLE 5



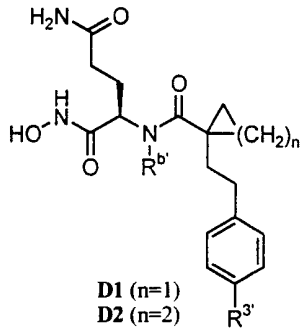
A1 (n=1)
A2 (n=2)



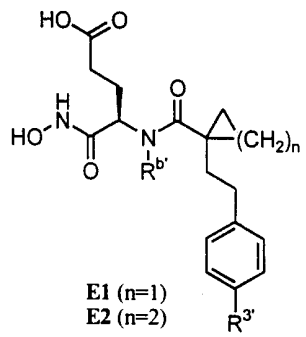
B1 (n=1)
B2 (n=2)



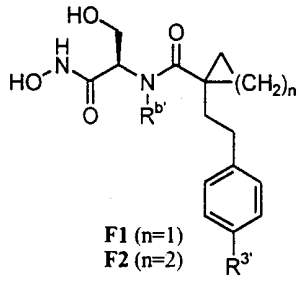
C1 (n=1)
C2 (n=2)



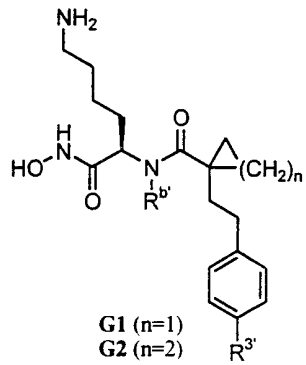
D1 (n=1)
D2 (n=2)



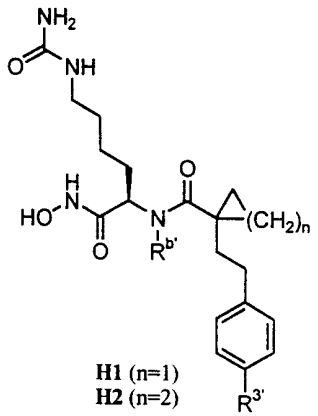
E1 (n=1)
E2 (n=2)



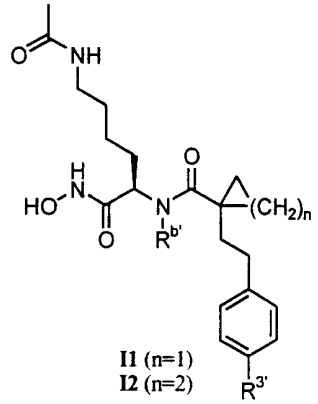
F1 (n=1)
F2 (n=2)



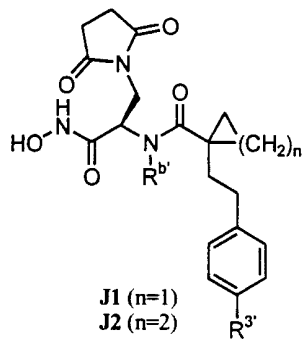
G1 (n=1)
G2 (n=2)



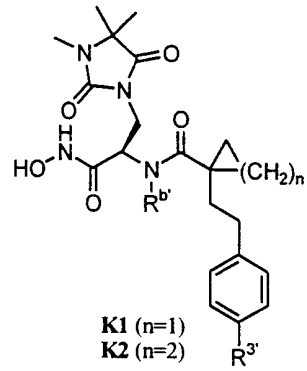
H1 (n=1)
H2 (n=2)



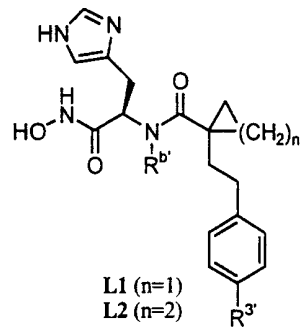
I1 (n=1)
I2 (n=2)



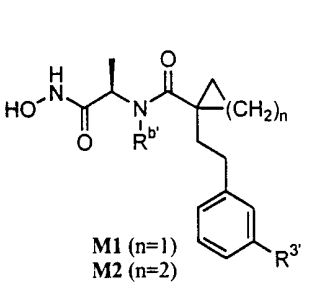
J1 (n=1)
J2 (n=2)



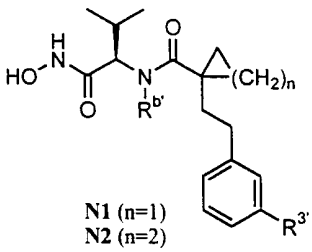
K1 (n=1)
K2 (n=2)



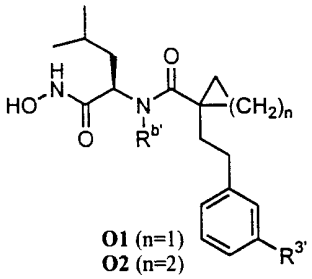
L1 (n=1)
L2 (n=2)



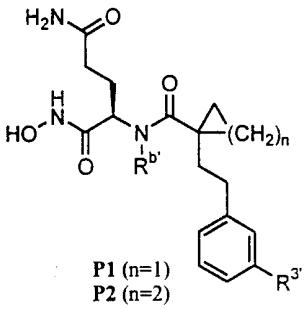
M1 (n=1)
M2 (n=2)



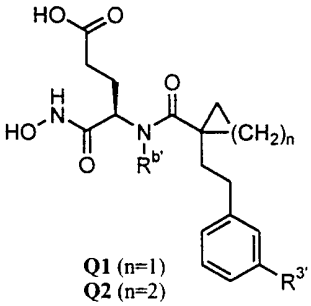
N1 (n=1)
N2 (n=2)



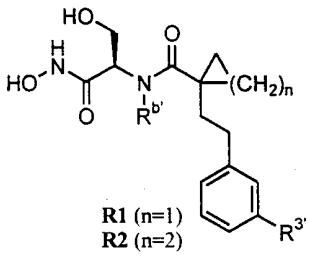
O1 (n=1)
O2 (n=2)



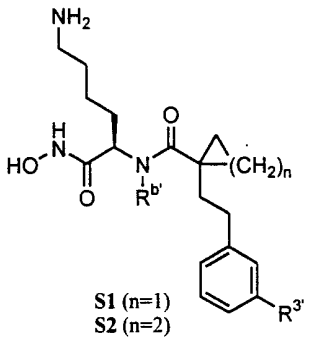
P1 (n=1)
P2 (n=2)



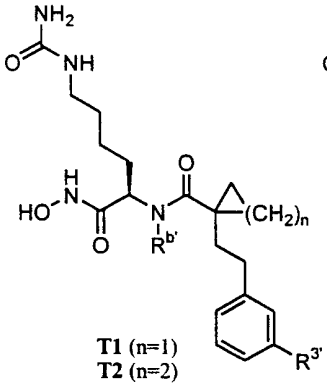
Q1 (n=1)
Q2 (n=2)



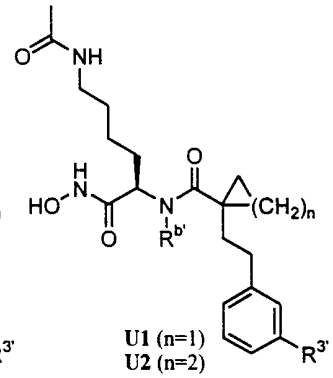
R1 (n=1)
R2 (n=2)



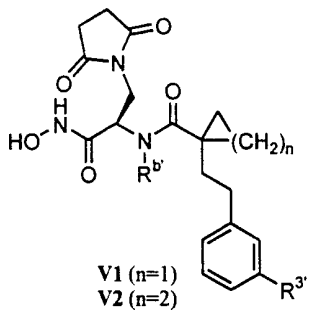
S1 (n=1)
S2 (n=2)



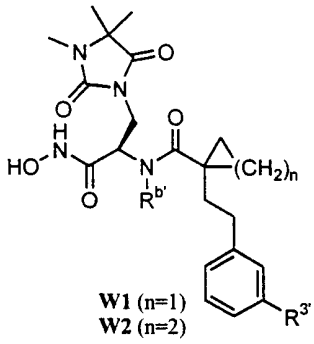
T1 (n=1)
T2 (n=2)



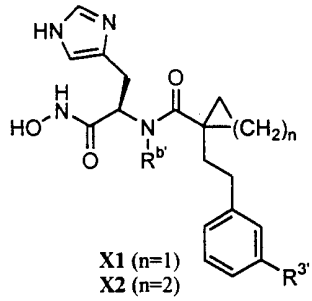
U1 (n=1)
U2 (n=2)



V1 (n=1)
V2 (n=2)



W1 (n=1)
W2 (n=2)



X1 (n=1)
X2 (n=2)

Ex#	$R^{b'}$	$R^{3'}$
1	Me	H
2	3-picolyl	H
3	aminocarbonylmethyl	H
4	Me	methyl
5	3-picolyl	methyl
6	aminocarbonylmethyl	methyl
7	Me	ethyl
8	3-picolyl	ethyl
9	aminocarbonylmethyl	ethyl

10	Me	isopropyl
11	3-picolyl	isopropyl
12	aminocarbonylmethyl	isopropyl
13	Me	phenyl
14	3-picolyl	phenyl
15	aminocarbonylmethyl	phenyl
16	Me	benzyl
17	3-picolyl	benzyl
18	aminocarbonylmethyl	benzyl
19	Me	2-phenylethyl
20	3-picolyl	2-phenylethyl
21	aminocarbonylmethyl	2-phenylethyl
22	Me	2-(2-methylphenyl)ethyl
23	3-picolyl	2-(2-methylphenyl)ethyl
24	aminocarbonylmethyl	2-(2-methylphenyl)ethyl
25	Me	2-(3-methylphenyl)ethyl
26	3-picolyl	2-(3-methylphenyl)ethyl
27	aminocarbonylmethyl	2-(3-methylphenyl)ethyl
28	Me	2-(2,6-dimethylphenyl)ethyl
29	3-picolyl	2-(2,6-dimethylphenyl)ethyl
30	aminocarbonylmethyl	2-(2,6-dimethylphenyl)ethyl
31	Me	2-(3,5-dimethylphenyl)ethyl
32	3-picolyl	2-(3,5-dimethylphenyl)ethyl
33	aminocarbonylmethyl	2-(3,5-dimethylphenyl)ethyl
34	Me	2-(3-amino-5-methylphenyl)ethyl
35	3-picolyl	2-(3-amino-5-methylphenyl)ethyl
36	aminocarbonylmethyl	2-(3-amino-5-methylphenyl)ethyl
37	Me	2-(pyridin-4-yl)ethyl
38	3-picolyl	2-(pyridin-4-yl)ethyl
39	aminocarbonylmethyl	2-(pyridin-4-yl)ethyl
40	Me	2-(2,6-dimethylpyridin-4-yl)ethyl
41	3-picolyl	2-(2,6-dimethylpyridin-4-yl)ethyl
42	aminocarbonylmethyl	2-(2,6-dimethylpyridin-4-yl)ethyl
43	Me	2-(3,5-dimethylpyridin-4-yl)ethyl
44	3-picolyl	2-(3,5-dimethylpyridin-4-yl)ethyl
45	aminocarbonylmethyl	2-(3,5-dimethylpyridin-4-yl)ethyl
46	Me	styryl
47	3-picolyl	styryl
48	aminocarbonylmethyl	styryl
49	Me	hydroxy
50	3-picolyl	hydroxy
51	aminocarbonylmethyl	hydroxy
52	Me	methoxy
53	3-picolyl	methoxy
54	aminocarbonylmethyl	methoxy
55	Me	ethoxy
56	3-picolyl	ethoxy
57	aminocarbonylmethyl	ethoxy
58	Me	isopropyloxy
59	3-picolyl	isopropyloxy
60	aminocarbonylmethyl	isopropyloxy
61	Me	tert-butoxy
62	3-picolyl	tert-butoxy
63	aminocarbonylmethyl	tert-butoxy
64	Me	cyclohexyloxy
65	3-picolyl	cyclohexyloxy
66	aminocarbonylmethyl	cyclohexyloxy
67	Me	phenoxy
68	3-picolyl	phenoxy
69	aminocarbonylmethyl	phenoxy

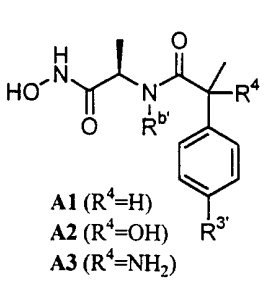
70	Me	o-methylphenoxy
71	3-picolyl	o-methylphenoxy
72	aminocarbonylmethyl	o-methylphenoxy
73	Me	m-methylphenoxy
74	3-picolyl	m-methylphenoxy
75	aminocarbonylmethyl	m-methylphenoxy
76	Me	cinnamyloxy
77	3-picolyl	cinnamyloxy
78	aminocarbonylmethyl	cinnamyloxy
79	Me	benzyloxy
80	3-picolyl	benzyloxy
81	aminocarbonylmethyl	benzyloxy
82	Me	phenoxymethyl
83	3-picolyl	phenoxymethyl
84	aminocarbonylmethyl	phenoxymethyl
85	Me	o-methylbenzyloxy
86	3-picolyl	o-methylbenzyloxy
87	aminocarbonylmethyl	o-methylbenzyloxy
88	Me	m-methylbenzyloxy
89	3-picolyl	m-methylbenzyloxy
90	aminocarbonylmethyl	m-methylbenzyloxy
91	Me	o,o-dimethylbenzyloxy
92	3-picolyl	o,o-dimethylbenzyloxy
93	aminocarbonylmethyl	o,o-dimethylbenzyloxy
94	Me	(2,6-dimethylphenoxy)methyl
95	3-picolyl	(2,6-dimethylphenoxy)methyl
96	aminocarbonylmethyl	(2,6-dimethylphenoxy)methyl
97	Me	m,m-dimethylbenzyloxy
98	3-picolyl	m,m-dimethylbenzyloxy
99	aminocarbonylmethyl	m,m-dimethylbenzyloxy
100	Me	(3,5-dimethylphenoxy)methyl
101	3-picolyl	(3,5-dimethylphenoxy)methyl
102	aminocarbonylmethyl	(3,5-dimethylphenoxy)methyl
103	Me	o,o-dicyanobenzyloxy
104	3-picolyl	o,o-dicyanobenzyloxy
105	aminocarbonylmethyl	o,o-dicyanobenzyloxy
106	Me	m,m-dicyanobenzyloxy
107	3-picolyl	m,m-dicyanobenzyloxy
108	aminocarbonylmethyl	m,m-dicyanobenzyloxy
109	Me	(2,6-dicyanophenoxy)methyl
110	3-picolyl	(2,6-dicyanophenoxy)methyl
111	aminocarbonylmethyl	(2,6-dicyanophenoxy)methyl
112	Me	(3,5-dicyanophenoxy)methyl
113	3-picolyl	(3,5-dicyanophenoxy)methyl
114	aminocarbonylmethyl	(3,5-dicyanophenoxy)methyl
115	Me	o-amino-o-cyanobenzyloxy
116	3-picolyl	o-amino-o-cyanobenzyloxy
117	aminocarbonylmethyl	o-amino-o-cyanobenzyloxy
118	Me	m-amino-m-cyanobenzyloxy
119	3-picolyl	m-amino-m-cyanobenzyloxy
120	aminocarbonylmethyl	m-amino-m-cyanobenzyloxy
121	Me	o-amino-o-nitrobenzyloxy
122	3-picolyl	o-amino-o-nitrobenzyloxy
123	aminocarbonylmethyl	o-amino-o-nitrobenzyloxy
124	Me	m-amino-m-nitrobenzyloxy
125	3-picolyl	m-amino-m-nitrobenzyloxy
126	aminocarbonylmethyl	m-amino-m-nitrobenzyloxy
127	Me	p-amino-m,m-dimethylbenzyloxy
128	3-picolyl	p-amino-m,m-dimethylbenzyloxy
129	aminocarbonylmethyl	p-amino-m,m-dimethylbenzyloxy

130	Me	o-amino-o-methylbenzyloxy
131	3-picolyl	o-amino-o-methylbenzyloxy
132	aminocarbonylmethyl	o-amino-o-methylbenzyloxy
133	Me	m-amino-m-methylbenzyloxy
134	3-picolyl	m-amino-m-methylbenzyloxy
135	aminocarbonylmethyl	m-amino-m-methylbenzyloxy
136	Me	o-cyano-o-methylbenzyloxy
137	3-picolyl	o-cyano-o-methylbenzyloxy
138	aminocarbonylmethyl	o-cyano-o-methylbenzyloxy
139	Me	m-cyano-m-methylbenzyloxy
140	3-picolyl	m-cyano-m-methylbenzyloxy
141	aminocarbonylmethyl	m-cyano-m-methylbenzyloxy
142	Me	o-cyano-o-nitrobenzyloxy
143	3-picolyl	o-cyano-o-nitrobenzyloxy
144	aminocarbonylmethyl	o-cyano-o-nitrobenzyloxy
145	Me	(2-cyano-6-nitrophenoxy)methyl
146	3-picolyl	(2-cyano-6-nitrophenoxy)methyl
147	aminocarbonylmethyl	(2-cyano-6-nitrophenoxy)methyl
148	Me	m-cyano-m-nitrobenzyloxy
149	3-picolyl	m-cyano-m-nitrobenzyloxy
150	aminocarbonylmethyl	m-cyano-m-nitrobenzyloxy
151	Me	(3-cyano-5-nitrophenoxy)methyl
152	3-picolyl	(3-cyano-5-nitrophenoxy)methyl
153	aminocarbonylmethyl	(3-cyano-5-nitrophenoxy)methyl
154	Me	m,m-dimethoxybenzyloxy
155	3-picolyl	m,m-dimethoxybenzyloxy
156	aminocarbonylmethyl	m,m-dimethoxybenzyloxy
157	Me	m,m-dichlorobenzyloxy
158	3-picolyl	m,m-dichlorobenzyloxy
159	aminocarbonylmethyl	m,m-dichlorobenzyloxy
160	Me	(3,5-dichlorophenoxy)methyl
161	3-picolyl	(3,5-dichlorophenoxy)methyl
162	aminocarbonylmethyl	(3,5-dichlorophenoxy)methyl
163	Me	m,m-dibromobenzyloxy
164	3-picolyl	m,m-dibromobenzyloxy
165	aminocarbonylmethyl	m,m-dibromobenzyloxy
166	Me	m,m-bis(trifluoromethyl)benzyloxy
167	3-picolyl	m,m-bis(trifluoromethyl)benzyloxy
168	aminocarbonylmethyl	m,m-bis(trifluoromethyl)benzyloxy
169	Me	[3,5-bis(trifluoromethyl)phenoxy]methyl
170	3-picolyl	[3,5-bis(trifluoromethyl)phenoxy]methyl
171	aminocarbonylmethyl	[3,5-bis(trifluoromethyl)phenoxy]methyl
172	Me	m-carboxamido-m-methylbenzyloxy
173	3-picolyl	m-carboxamido-m-methylbenzyloxy
174	aminocarbonylmethyl	m-carboxamido-m-methylbenzyloxy
175	Me	(3-carboxamido-5-methylphenoxy)methyl
176	3-picolyl	(3-carboxamido-5-methylphenoxy)methyl
177	aminocarbonylmethyl	(3-carboxamido-5-methylphenoxy)methyl
178	Me	m-hydroxycarbonyl-m-methylbenzyloxy
179	3-picolyl	m-hydroxycarbonyl-m-methylbenzyloxy
180	aminocarbonylmethyl	m-hydroxycarbonyl-m-methylbenzyloxy
181	Me	(3-hydroxycarbonyl-5-methylphenoxy)methyl
182	3-picolyl	(3-hydroxycarbonyl-5-methylphenoxy)methyl
183	aminocarbonylmethyl	(3-hydroxycarbonyl-5-methylphenoxy)methyl
184	Me	o-phenylbenzyloxy
185	3-picolyl	o-phenylbenzyloxy
186	aminocarbonylmethyl	o-phenylbenzyloxy
187	Me	m-phenylbenzyloxy
188	3-picolyl	m-phenylbenzyloxy
189	aminocarbonylmethyl	m-phenylbenzyloxy

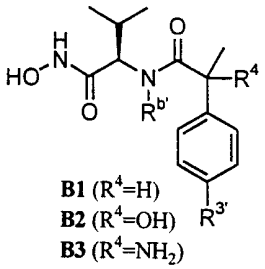
190	Me	(naphth-1-yl)methoxy
191	3-picolyl	(naphth-1-yl)methoxy
192	aminocarbonylmethyl	(naphth-1-yl)methoxy
193	Me	(naphth-2-yl)methoxy
194	3-picolyl	(naphth-2-yl)methoxy
195	aminocarbonylmethyl	(naphth-2-yl)methoxy
196	Me	(2-methylnaphth-1-yl)methoxy
197	3-picolyl	(2-methylnaphth-1-yl)methoxy
198	aminocarbonylmethyl	(2-methylnaphth-1-yl)methoxy
199	Me	(4-methylnaphth-2-yl)methoxy
200	3-picolyl	(4-methylnaphth-2-yl)methoxy
201	aminocarbonylmethyl	(4-methylnaphth-2-yl)methoxy
202	Me	(pyridin-3-yl)methoxy
203	3-picolyl	(pyridin-3-yl)methoxy
204	aminocarbonylmethyl	(pyridin-3-yl)methoxy
205	Me	(pyridin-4-yl)methoxy
206	3-picolyl	(pyridin-4-yl)methoxy
207	aminocarbonylmethyl	(pyridin-4-yl)methoxy
208	Me	(3,5-dichloropyridin-4-yl)methoxy
209	3-picolyl	(3,5-dichloropyridin-4-yl)methoxy
210	aminocarbonylmethyl	(3,5-dichloropyridin-4-yl)methoxy
211	Me	(3,5-dimethylpyridin-4-yl)methoxy
212	3-picolyl	(3,5-dimethylpyridin-4-yl)methoxy
213	aminocarbonylmethyl	(3,5-dimethylpyridin-4-yl)methoxy
214	Me	(1,2,3-benzotriazol-1-yl)methoxy
215	3-picolyl	(1,2,3-benzotriazol-1-yl)methoxy
216	aminocarbonylmethyl	(1,2,3-benzotriazol-1-yl)methoxy
217	Me	benzhydroxy
218	3-picolyl	benzhydroxy
219	aminocarbonylmethyl	benzhydroxy
220	Me	p-(1,2,3-thiadiazol-5-yl)benzyloxy
221	3-picolyl	p-(1,2,3-thiadiazol-5-yl)benzyloxy
222	aminocarbonylmethyl	p-(1,2,3-thiadiazol-5-yl)benzyloxy
223	Me	o-(tetrazol-5-yl)benzyloxy
224	3-picolyl	o-(tetrazol-5-yl)benzyloxy
225	aminocarbonylmethyl	o-(tetrazol-5-yl)benzyloxy
226	Me	m-(tetrazol-5-yl)benzyloxy
227	3-picolyl	m-(tetrazol-5-yl)benzyloxy
228	aminocarbonylmethyl	m-(tetrazol-5-yl)benzyloxy
229	Me	[3-methyl-5-(tetrazol-5-yl)phenoxy]methyl
230	3-picolyl	[3-methyl-5-(tetrazol-5-yl)phenoxy]methyl
231	aminocarbonylmethyl	[3-methyl-5-(tetrazol-5-yl)phenoxy]methyl
232	Me	m-methyl-m-(tetrazol-5-yl)benzyloxy
233	3-picolyl	m-methyl-m-(tetrazol-5-yl)benzyloxy
234	aminocarbonylmethyl	m-methyl-m-(tetrazol-5-yl)benzyloxy
235	Me	2-oxo-2-phenylethoxy
236	3-picolyl	2-oxo-2-phenylethoxy
237	aminocarbonylmethyl	2-oxo-2-phenylethoxy
238	Me	carbo-t-butoxymethoxy
239	3-picolyl	carbo-t-butoxymethoxy
240	aminocarbonylmethyl	carbo-t-butoxymethoxy
241	Me	(benzimidazol-2-yl)methoxy
242	3-picolyl	(benzimidazol-2-yl)methoxy
243	aminocarbonylmethyl	(benzimidazol-2-yl)methoxy
244	Me	(imidazol-2-yl)methoxy
245	3-picolyl	(imidazol-2-yl)methoxy
246	aminocarbonylmethyl	(imidazol-2-yl)methoxy
247	Me	(1,4-dimethylimidazol-5-yl)methoxy
248	3-picolyl	(1,4-dimethylimidazol-5-yl)methoxy
249	aminocarbonylmethyl	(1,4-dimethylimidazol-5-yl)methoxy

250	Me	(thiazol-4-yl)methoxy
251	3-picolyl	(thiazol-4-yl)methoxy
252	aminocarbonylmethyl	(thiazol-4-yl)methoxy
253	Me	(quinolin-2-yl)methoxy
254	3-picolyl	(quinolin-2-yl)methoxy
255	aminocarbonylmethyl	(quinolin-2-yl)methoxy
256	Me	(1,3-benzodioxo-5-yl)methoxy
257	3-picolyl	(1,3-benzodioxo-5-yl)methoxy
258	aminocarbonylmethyl	(1,3-benzodioxo-5-yl)methoxy
259	Me	(3,5-dimethylisoxazol-4-yl)methoxy
260	3-picolyl	(3,5-dimethylisoxazol-4-yl)methoxy
261	aminocarbonylmethyl	(3,5-dimethylisoxazol-4-yl)methoxy
262	Me	(3,5-dimethylpyrazol-1-yl)methoxy
263	3-picolyl	(3,5-dimethylpyrazol-1-yl)methoxy
264	aminocarbonylmethyl	(3,5-dimethylpyrazol-1-yl)methoxy
265	Me	(1,3,5-trimethylpyrazol-4-yl)methoxy
266	3-picolyl	(1,3,5-trimethylpyrazol-4-yl)methoxy
267	aminocarbonylmethyl	(1,3,5-trimethylpyrazol-4-yl)methoxy

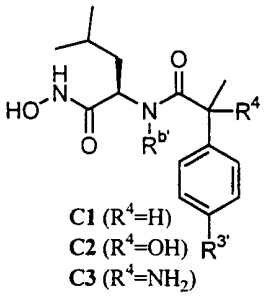
TABLE 6



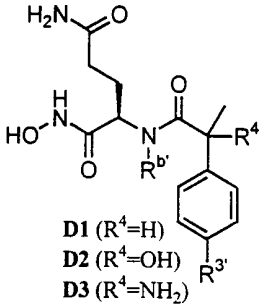
A1 (R^4=H)
A2 (R^4=OH)
A3 (R^4=NH_2)



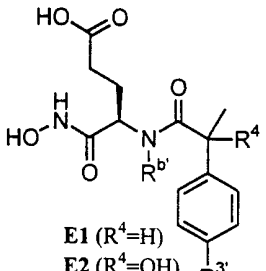
B1 (R^4=H)
B2 (R^4=OH)
B3 (R^4=NH_2)



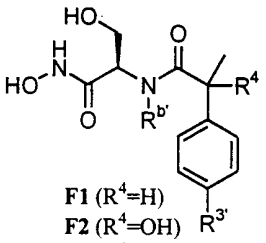
C1 (R^4=H)
C2 (R^4=OH)
C3 (R^4=NH_2)



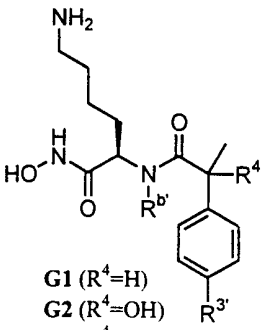
D1 (R^4=H)
D2 (R^4=OH)
D3 (R^4=NH_2)



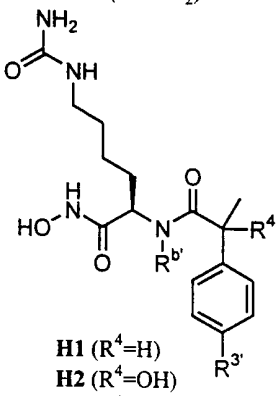
E1 (R^4=H)
E2 (R^4=OH)
E3 (R^4=NH_2)



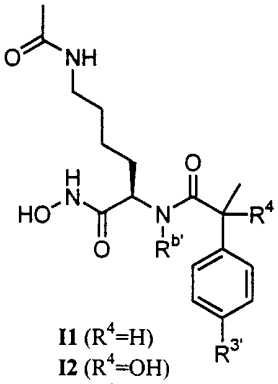
F1 (R^4=H)
F2 (R^4=OH)
F3 (R^4=NH_2)



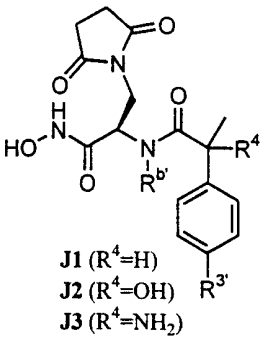
G1 (R^4=H)
G2 (R^4=OH)
G3 (R^4=NH_2)



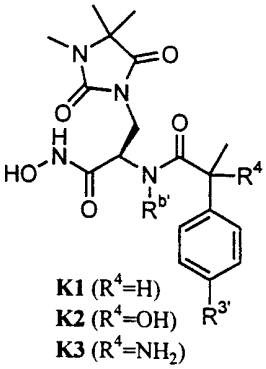
H1 (R^4=H)
H2 (R^4=OH)
H3 (R^4=NH_2)



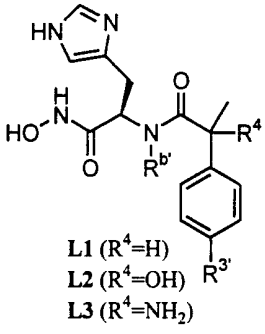
I1 (R^4=H)
I2 (R^4=OH)
I3 (R^4=NH_2)



J1 (R^4=H)
J2 (R^4=OH)
J3 (R^4=NH_2)



K1 (R^4=H)
K2 (R^4=OH)
K3 (R^4=NH_2)



L1 (R^4=H)
L2 (R^4=OH)
L3 (R^4=NH_2)

Ex#	$R^{b'}$	$R^{3'}$
1	Me	H
2	3-picolyl	H
3	aminocarbonylmethyl	H

4	Me	methyl
5	3-picolyl	methyl
6	aminocarbonylmethyl	methyl
7	Me	ethyl
8	3-picolyl	ethyl
9	aminocarbonylmethyl	ethyl
10	Me	isopropyl
11	3-picolyl	isopropyl
12	aminocarbonylmethyl	isopropyl
13	Me	phenyl
14	3-picolyl	phenyl
15	aminocarbonylmethyl	phenyl
16	Me	benzyl
17	3-picolyl	benzyl
18	aminocarbonylmethyl	benzyl
19	Me	2-phenylethyl
20	3-picolyl	2-phenylethyl
21	aminocarbonylmethyl	2-phenylethyl
22	Me	2-(2-methylphenyl)ethyl
23	3-picolyl	2-(2-methylphenyl)ethyl
24	aminocarbonylmethyl	2-(2-methylphenyl)ethyl
25	Me	2-(3-methylphenyl)ethyl
26	3-picolyl	2-(3-methylphenyl)ethyl
27	aminocarbonylmethyl	2-(3-methylphenyl)ethyl
28	Me	2-(2,6-dimethylphenyl)ethyl
29	3-picolyl	2-(2,6-dimethylphenyl)ethyl
30	aminocarbonylmethyl	2-(2,6-dimethylphenyl)ethyl
31	Me	2-(3,5-dimethylphenyl)ethyl
32	3-picolyl	2-(3,5-dimethylphenyl)ethyl
33	aminocarbonylmethyl	2-(3,5-dimethylphenyl)ethyl
34	Me	2-(3-amino-5-methylphenyl)ethyl
35	3-picolyl	2-(3-amino-5-methylphenyl)ethyl
36	aminocarbonylmethyl	2-(3-amino-5-methylphenyl)ethyl
37	Me	2-(pyridin-4-yl)ethyl
38	3-picolyl	2-(pyridin-4-yl)ethyl
39	aminocarbonylmethyl	2-(pyridin-4-yl)ethyl
40	Me	2-(2,6-dimethylpyridin-4-yl)ethyl
41	3-picolyl	2-(2,6-dimethylpyridin-4-yl)ethyl
42	aminocarbonylmethyl	2-(2,6-dimethylpyridin-4-yl)ethyl
43	Me	2-(3,5-dimethylpyridin-4-yl)ethyl
44	3-picolyl	2-(3,5-dimethylpyridin-4-yl)ethyl
45	aminocarbonylmethyl	2-(3,5-dimethylpyridin-4-yl)ethyl
46	Me	styryl
47	3-picolyl	styryl
48	aminocarbonylmethyl	styryl
49	Me	hydroxy
50	3-picolyl	hydroxy
51	aminocarbonylmethyl	hydroxy
52	Me	methoxy
53	3-picolyl	methoxy
54	aminocarbonylmethyl	methoxy
55	Me	ethoxy
56	3-picolyl	ethoxy
57	aminocarbonylmethyl	ethoxy
58	Me	isopropyloxy
59	3-picolyl	isopropyloxy
60	aminocarbonylmethyl	isopropyloxy
61	Me	tert-butoxy
62	3-picolyl	tert-butoxy
63	aminocarbonylmethyl	tert-butoxy

64	Me	cyclohexyloxy
65	3-picolyl	cyclohexyloxy
66	aminocarbonylmethyl	cyclohexyloxy
67	Me	phenoxy
68	3-picolyl	phenoxy
69	aminocarbonylmethyl	phenoxy
70	Me	o-methylphenoxy
71	3-picolyl	o-methylphenoxy
72	aminocarbonylmethyl	o-methylphenoxy
73	Me	m-methylphenoxy
74	3-picolyl	m-methylphenoxy
75	aminocarbonylmethyl	m-methylphenoxy
76	Me	cinnamyloxy
77	3-picolyl	cinnamyloxy
78	aminocarbonylmethyl	cinnamyloxy
79	Me	benzyloxy
80	3-picolyl	benzyloxy
81	aminocarbonylmethyl	benzyloxy
82	Me	phenoxymethyl
83	3-picolyl	phenoxymethyl
84	aminocarbonylmethyl	phenoxymethyl
85	Me	o-methylbenzyloxy
86	3-picolyl	o-methylbenzyloxy
87	aminocarbonylmethyl	o-methylbenzyloxy
88	Me	m-methylbenzyloxy
89	3-picolyl	m-methylbenzyloxy
90	aminocarbonylmethyl	m-methylbenzyloxy
91	Me	o,o-dimethylbenzyloxy
92	3-picolyl	o,o-dimethylbenzyloxy
93	aminocarbonylmethyl	o,o-dimethylbenzyloxy
94	Me	(2,6-dimethylphenoxy)methyl
95	3-picolyl	(2,6-dimethylphenoxy)methyl
96	aminocarbonylmethyl	(2,6-dimethylphenoxy)methyl
97	Me	m,m-dimethylbenzyloxy
98	3-picolyl	m,m-dimethylbenzyloxy
99	aminocarbonylmethyl	m,m-dimethylbenzyloxy
100	Me	(3,5-dimethylphenoxy)methyl
101	3-picolyl	(3,5-dimethylphenoxy)methyl
102	aminocarbonylmethyl	(3,5-dimethylphenoxy)methyl
103	Me	o,o-dicyanobenzyloxy
104	3-picolyl	o,o-dicyanobenzyloxy
105	aminocarbonylmethyl	o,o-dicyanobenzyloxy
106	Me	m,m-dicyanobenzyloxy
107	3-picolyl	m,m-dicyanobenzyloxy
108	aminocarbonylmethyl	m,m-dicyanobenzyloxy
109	Me	(2,6-dicyanophenoxy)methyl
110	3-picolyl	(2,6-dicyanophenoxy)methyl
111	aminocarbonylmethyl	(2,6-dicyanophenoxy)methyl
112	Me	(3,5-dicyanophenoxy)methyl
113	3-picolyl	(3,5-dicyanophenoxy)methyl
114	aminocarbonylmethyl	(3,5-dicyanophenoxy)methyl
115	Me	o-amino-o-cyanobenzyloxy
116	3-picolyl	o-amino-o-cyanobenzyloxy
117	aminocarbonylmethyl	o-amino-o-cyanobenzyloxy
118	Me	m-amino-m-cyanobenzyloxy
119	3-picolyl	m-amino-m-cyanobenzyloxy
120	aminocarbonylmethyl	m-amino-m-cyanobenzyloxy
121	Me	o-amino-o-nitrobenzyloxy
122	3-picolyl	o-amino-o-nitrobenzyloxy
123	aminocarbonylmethyl	o-amino-o-nitrobenzyloxy

124	Me	m-amino-m-nitrobenzyloxy
125	3-picolyl	m-amino-m-nitrobenzyloxy
126	aminocarbonylmethyl	m-amino-m-nitrobenzyloxy
127	Me	p-amino-m,m-dimethylbenzyloxy
128	3-picolyl	p-amino-m,m-dimethylbenzyloxy
129	aminocarbonylmethyl	p-amino-m,m-dimethylbenzyloxy
130	Me	o-amino-o-methylbenzyloxy
131	3-picolyl	o-amino-o-methylbenzyloxy
132	aminocarbonylmethyl	o-amino-o-methylbenzyloxy
133	Me	m-amino-m-methylbenzyloxy
134	3-picolyl	m-amino-m-methylbenzyloxy
135	aminocarbonylmethyl	m-amino-m-methylbenzyloxy
136	Me	o-cyano-o-methylbenzyloxy
137	3-picolyl	o-cyano-o-methylbenzyloxy
138	aminocarbonylmethyl	o-cyano-o-methylbenzyloxy
139	Me	m-cyano-m-methylbenzyloxy
140	3-picolyl	m-cyano-m-methylbenzyloxy
141	aminocarbonylmethyl	m-cyano-m-methylbenzyloxy
142	Me	o-cyano-o-nitrobenzyloxy
143	3-picolyl	o-cyano-o-nitrobenzyloxy
144	aminocarbonylmethyl	o-cyano-o-nitrobenzyloxy
145	Me	(2-cyano-6-nitrophenoxy)methyl
146	3-picolyl	(2-cyano-6-nitrophenoxy)methyl
147	aminocarbonylmethyl	(2-cyano-6-nitrophenoxy)methyl
148	Me	m-cyano-m-nitrobenzyloxy
149	3-picolyl	m-cyano-m-nitrobenzyloxy
150	aminocarbonylmethyl	m-cyano-m-nitrobenzyloxy
151	Me	(3-cyano-5-nitrophenoxy)methyl
152	3-picolyl	(3-cyano-5-nitrophenoxy)methyl
153	aminocarbonylmethyl	(3-cyano-5-nitrophenoxy)methyl
154	Me	m,m-dimethoxybenzyloxy
155	3-picolyl	m,m-dimethoxybenzyloxy
156	aminocarbonylmethyl	m,m-dimethoxybenzyloxy
157	Me	m,m-dichlorobenzyloxy
158	3-picolyl	m,m-dichlorobenzyloxy
159	aminocarbonylmethyl	m,m-dichlorobenzyloxy
160	Me	(3,5-dichlorophenoxy)methyl
161	3-picolyl	(3,5-dichlorophenoxy)methyl
162	aminocarbonylmethyl	(3,5-dichlorophenoxy)methyl
163	Me	m,m-dibromobenzyloxy
164	3-picolyl	m,m-dibromobenzyloxy
165	aminocarbonylmethyl	m,m-dibromobenzyloxy
166	Me	m,m-bis(trifluoromethyl)benzyloxy
167	3-picolyl	m,m-bis(trifluoromethyl)benzyloxy
168	aminocarbonylmethyl	m,m-bis(trifluoromethyl)benzyloxy
169	Me	[3,5-bis(trifluoromethyl)phenoxy]methyl
170	3-picolyl	[3,5-bis(trifluoromethyl)phenoxy]methyl
171	aminocarbonylmethyl	[3,5-bis(trifluoromethyl)phenoxy]methyl
172	Me	m-carboxamido-m-methylbenzyloxy
173	3-picolyl	m-carboxamido-m-methylbenzyloxy
174	aminocarbonylmethyl	m-carboxamido-m-methylbenzyloxy
175	Me	(3-carboxamido-5-methylphenoxy)methyl
176	3-picolyl	(3-carboxamido-5-methylphenoxy)methyl
177	aminocarbonylmethyl	(3-carboxamido-5-methylphenoxy)methyl
178	Me	m-hydroxycarbonyl-m-methylbenzyloxy
179	3-picolyl	m-hydroxycarbonyl-m-methylbenzyloxy
180	aminocarbonylmethyl	m-hydroxycarbonyl-m-methylbenzyloxy
181	Me	(3-hydroxycarbonyl-5-methylphenoxy)methyl
182	3-picolyl	(3-hydroxycarbonyl-5-methylphenoxy)methyl
183	aminocarbonylmethyl	(3-hydroxycarbonyl-5-methylphenoxy)methyl

184	Me	o-phenylbenzyloxy
185	3-picolyl	o-phenylbenzyloxy
186	aminocarbonylmethyl	o-phenylbenzyloxy
187	Me	m-phenylbenzyloxy
188	3-picolyl	m-phenylbenzyloxy
189	aminocarbonylmethyl	m-phenylbenzyloxy
190	Me	(naphth-1-yl)methoxy
191	3-picolyl	(naphth-1-yl)methoxy
192	aminocarbonylmethyl	(naphth-1-yl)methoxy
193	Me	(naphth-2-yl)methoxy
194	3-picolyl	(naphth-2-yl)methoxy
195	aminocarbonylmethyl	(naphth-2-yl)methoxy
196	Me	(2-methylnaphth-1-yl)methoxy
197	3-picolyl	(2-methylnaphth-1-yl)methoxy
198	aminocarbonylmethyl	(2-methylnaphth-1-yl)methoxy
199	Me	(4-methylnaphth-2-yl)methoxy
200	3-picolyl	(4-methylnaphth-2-yl)methoxy
201	aminocarbonylmethyl	(4-methylnaphth-2-yl)methoxy
202	Me	(pyridin-3-yl)methoxy
203	3-picolyl	(pyridin-3-yl)methoxy
204	aminocarbonylmethyl	(pyridin-3-yl)methoxy
205	Me	(pyridin-4-yl)methoxy
206	3-picolyl	(pyridin-4-yl)methoxy
207	aminocarbonylmethyl	(pyridin-4-yl)methoxy
208	Me	(3,5-dichloropyridin-4-yl)methoxy
209	3-picolyl	(3,5-dichloropyridin-4-yl)methoxy
210	aminocarbonylmethyl	(3,5-dichloropyridin-4-yl)methoxy
211	Me	(3,5-dimethylpyridin-4-yl)methoxy
212	3-picolyl	(3,5-dimethylpyridin-4-yl)methoxy
213	aminocarbonylmethyl	(3,5-dimethylpyridin-4-yl)methoxy
214	Me	(1,2,3-benzotriazol-1-yl)methoxy
215	3-picolyl	(1,2,3-benzotriazol-1-yl)methoxy
216	aminocarbonylmethyl	(1,2,3-benzotriazol-1-yl)methoxy
217	Me	benzhydroxy
218	3-picolyl	benzhydroxy
219	aminocarbonylmethyl	benzhydroxy
220	Me	p-(1,2,3-thiadiazol-5-yl)benzyloxy
221	3-picolyl	p-(1,2,3-thiadiazol-5-yl)benzyloxy
222	aminocarbonylmethyl	p-(1,2,3-thiadiazol-5-yl)benzyloxy
223	Me	o-(tetrazol-5-yl)benzyloxy
224	3-picolyl	o-(tetrazol-5-yl)benzyloxy
225	aminocarbonylmethyl	o-(tetrazol-5-yl)benzyloxy
226	Me	m-(tetrazol-5-yl)benzyloxy
227	3-picolyl	m-(tetrazol-5-yl)benzyloxy
228	aminocarbonylmethyl	m-(tetrazol-5-yl)benzyloxy
229	Me	[3-methyl-5-(tetrazol-5-yl)phenoxy]methyl
230	3-picolyl	[3-methyl-5-(tetrazol-5-yl)phenoxy]methyl
231	aminocarbonylmethyl	[3-methyl-5-(tetrazol-5-yl)phenoxy]methyl
232	Me	m-methyl-m-(tetrazol-5-yl)benzyloxy
233	3-picolyl	m-methyl-m-(tetrazol-5-yl)benzyloxy
234	aminocarbonylmethyl	m-methyl-m-(tetrazol-5-yl)benzyloxy
235	Me	2-oxo-2-phenylethoxy
236	3-picolyl	2-oxo-2-phenylethoxy
237	aminocarbonylmethyl	2-oxo-2-phenylethoxy
238	Me	carbo-t-butoxymethoxy
239	3-picolyl	carbo-t-butoxymethoxy
240	aminocarbonylmethyl	carbo-t-butoxymethoxy
241	Me	(benzimidazol-2-yl)methoxy
242	3-picolyl	(benzimidazol-2-yl)methoxy
243	aminocarbonylmethyl	(benzimidazol-2-yl)methoxy

244	Me	(imidazol-2-yl)methoxy
245	3-picolyl	(imidazol-2-yl)methoxy
246	aminocarbonylmethyl	(imidazol-2-yl)methoxy
247	Me	(1,4-dimethylimidazol-5-yl)methoxy
248	3-picolyl	(1,4-dimethylimidazol-5-yl)methoxy
249	aminocarbonylmethyl	(1,4-dimethylimidazol-5-yl)methoxy
250	Me	(thiazol-4-yl)methoxy
251	3-picolyl	(thiazol-4-yl)methoxy
252	aminocarbonylmethyl	(thiazol-4-yl)methoxy
253	Me	(quinolin-2-yl)methoxy
254	3-picolyl	(quinolin-2-yl)methoxy
255	aminocarbonylmethyl	(quinolin-2-yl)methoxy
256	Me	(1,3-benzodioxo-5-yl)methoxy
257	3-picolyl	(1,3-benzodioxo-5-yl)methoxy
258	aminocarbonylmethyl	(1,3-benzodioxo-5-yl)methoxy
259	Me	(3,5-dimethylisoxazol-4-yl)methoxy
260	3-picolyl	(3,5-dimethylisoxazol-4-yl)methoxy
261	aminocarbonylmethyl	(3,5-dimethylisoxazol-4-yl)methoxy
262	Me	(3,5-dimethylpyrazol-1-yl)methoxy
263	3-picolyl	(3,5-dimethylpyrazol-1-yl)methoxy
264	aminocarbonylmethyl	(3,5-dimethylpyrazol-1-yl)methoxy
265	Me	(1,3,5-trimethylpyrazol-4-yl)methoxy
266	3-picolyl	(1,3,5-trimethylpyrazol-4-yl)methoxy
267	aminocarbonylmethyl	(1,3,5-trimethylpyrazol-4-yl)methoxy
268	Me	4-quinolinylmethoxy
269	3-picolyl	4-quinolinylmethoxy
270	aminocarbonylmethyl	4-quinolinylmethoxy
271	Me	2-methyl-4-quinolinylmethoxy
272	3-picolyl	2-methyl-4-quinolinylmethoxy
273	aminocarbonylmethyl	2-methyl-4-quinolinylmethoxy
274	Me	4-quinolinyloxymethyl
275	3-picolyl	4-quinolinyloxymethyl
276	aminocarbonylmethyl	4-quinolinyloxymethyl

UTILITY

The compounds of formula I are expected to possess matrix metalloproteinase and/or aggrecanase and/or TNF inhibitory activity. The MMP inhibitory activity of the compounds of the present invention is demonstrated using assays of MMP activity, for example, using the assay described below for assaying inhibitors of MMP activity. The compounds of the present invention are expected to be bioavailable in vivo as demonstrated, for example, using the ex vivo assay described below. The compounds of formula I are expected to have the ability to suppress/inhibit cartilage degradation in vivo, for example, as demonstrated using the animal model of acute cartilage degradation described below.

The compounds provided by this invention should also be useful as standards and reagents in determining the ability of a potential pharmaceutical to inhibit MPs. These would be provided in commercial kits comprising a compound of this invention.

Metalloproteinases have also been implicated in the degradation of basement membranes to allow infiltration of cancer cells into the circulation and subsequent penetration into other tissues leading to tumor metastasis (Stetler-Stevenson, *Cancer and Metastasis Reviews*, **1990**, *9*, 289-303). The compounds of the present invention should be useful for the prevention and treatment of invasive tumors by inhibition of this aspect of metastasis.

The compounds of the present invention should also have utility for the prevention and treatment of osteopenia associated with matrix metalloproteinase-mediated breakdown of cartilage and bone which occurs in osteoporosis patients.

Compounds which inhibit the production or action of TNF and/or Aggrecanase and/or MP's are potentially useful for the treatment or prophylaxis of various inflammatory, infectious, immunological or malignant diseases. These include, but are not limited to inflammation, fever, cardiovascular effects, hemorrhage, coagulation and acute phase response, an acute infection, septic shock, haemodynamic shock and sepsis syndrome, post ischaemic reperfusion injury, malaria, Crohn's disease, mycobacterial infection, meningitis, psoriasis, periodontits, gingivitis, congestive heart failure, fibrotic disease, cachexia, and aneroxia, graft rejection, cancer, corneal ulceration or tumor invasion by secondary metastases, autoimmune disease, skin inflammatory diseases, multiple osteo and rheumatoid arthritis, multiple sclerosis, radiation damage, HIV, and hyperoxic alveolar injury.

Some compounds of the present invention have been shown to inhibit TNF production in lipopolysacharride stimulated mice, for example, using the assay for TNF induction in mice and in human whole blood as described below.

Some compounds of the present invention have been shown to inhibit aggrecanase, a key enzyme in cartilage breakdown, as determined by the aggrecanase assay described below.

As used herein "μg" denotes microgram, "mg" denotes milligram, "g" denotes gram, "μL" denotes microliter, "mL" denotes milliliter, "L" denotes liter, "nM" denotes nanomolar, "μM" denotes micromolar, "mM" denotes millimolar, "M" denotes molar and "nm" denotes nanometer. "Sigma" stands for the Sigma-Aldrich Corp. of St. Louis, MO.

A compound is considered to be active if it has an IC_{50} or K_i value of less than about 1 mM for the inhibition of MP.

Aggrecanase Enzymatic Assay

A novel enzymatic assay was developed to detect potential inhibitors of aggrecanase. The assay uses active aggrecanase accumulated in media from stimulated bovine nasal cartilage (BNC) or related cartilage sources and purified cartilage aggrecan monomer or a fragment thereof as a substrate.

The substrate concentration, amount of aggrecanase, time of incubation and amount of product loaded for Western analysis were optimized for use of this assay in screening putative aggrecanase inhibitors. Aggrecanase is generated by stimulation of cartilage slices with interleukin-1 (IL-1), tumor necrosis factor alpha (TNFα) or other stimuli. Matrix metalloproteinases (MMPs) are secreted from cartilage in an inactive, zymogen form following stimulation, although active enzymes are present within the matrix. We have shown that following depletion of the extracellular aggrecan matrix, active MMPs are released into the culture media (Tortorella et. al. *Trans. Ortho. Res. Soc.* **1995**, *20*, 341). Therefore, in order to accumulate BNC aggrecanase in culture media, cartilage is first depleted of endogenous aggrecan by stimulation with 500 ng/mL human recombinant IL-ß for 6 days with media changes every 2 days. Cartilage is then stimulated for an additional 8 days without media change to allow accumulation of soluble, active aggrecanase in the culture media. In order to decrease the amount of other matrix metalloproteinases released into the media during aggrecanase accumulation, agents which inhibit MMP-1, -2, -3, and -9 biosynthesis are included during stimulation. This BNC conditioned media, containing aggrecanase activity is then used as the source of aggrecanase for the assay. Aggrecanase enzymatic activity is detected by monitoring production of aggrecan fragments produced exclusively by cleavage at the Glu373-Ala374 bond within the aggrecan core protein by Western analysis using the monoclonal antibody, BC-3 (Hughes et al., *Biochem J.* **1995**, *306*, 799-804). This antibody recognizes aggrecan fragments with the N-terminus, 374ARGSVIL, generated upon cleavage by aggrecanase. The BC-3 antibody recognizes this neoepitope only when it is at the N-terminus and not when it is present internally within aggrecan fragments or within the aggrecan protein

core. Other proteases produced by cartilage in response to IL-1 do not cleave aggrecan at the Glu373-Ala374 aggrecanase site; therefore, only products produced upon cleavage by aggrecanase are detected. Kinetic studies using this assay yield a Km of 1.5 +/- 0.35 uM for aggrecanase.

To evaluate inhibition of aggrecanase, compounds are prepared as 10 mM stocks in DMSO, water or other solvents and diluted to appropriate concentrations in water. Drug (50 µL) is added to 50 µL of aggrecanase-containing media and 50 ul of 2 mg/mL aggrecan substrate and brought to a final volume of 200 µL in 0.2 M Tris, pH 7.6, containing 0.4 M NaCl and 40 mM $CaCl_2$. The assay is run for 4 hr at 37°C, quenched with 20 mM EDTA and analyzed for aggrecanase-generated products. A sample containing enzyme and substrate without drug is included as a positive control and enzyme incubated in the absence of substrate serves as a measure of background.

Removal of the glycosaminoglycan side chains from aggrecan is necessary for the BC-3 antibody to recognize the ARGSVIL epitope on the core protein. Therefore, for analysis of aggrecan fragments generated by cleavage at the Glu373-Ala374 site, proteoglycans and proteoglycan fragments are enzymatically deglycosylated with chondroitinase ABC (0.1 units/10 µg GAG) for 2 hr at 37°C and then with keratanase (0.1 units/10 µg GAG) and keratanase II (0.002 units/10 µg GAG) for 2 hr at 37°C in buffer containing 50 mM sodium acetate, 0.1 M Tris/HCl, pH 6.5. After digestion, aggrecan in the samples is precipitated with 5 volumes of acetone and resuspended in 30 µL of Tris glycine SDS sample buffer (Novex) containing 2.5% beta mercaptoethanol. Samples are loaded and then separated by SDS-PAGE under reducing conditions with 4-12% gradient gels, transferred to nitrocellulose and immunolocated with 1:500 dilution of antibody BC3. Subsequently, membranes are incubated with a 1:5000 dilution of goat anti-mouse IgG alkaline phosphatase second antibody and aggrecan catabolites visualized by incubation with appropriate substrate for 10-30 minutes to achieve optimal color development. Blots are quantitated by scanning densitometry and inhibition of aggrecanase determined by comparing the amount of product produced in the presence versus absence of compound.

MMP Screens

The enzymatic activities of recombinant MMP-1, 2, 3, 9, and 13 were measured at 25 °C with a fluorometric assay (Copeland, R.A.; Lombardo, D.; Giannaras, J. and Decicco, C.P. *Bioorganic Med. Chem. Lett.* **1995**, *5*, 1947-1952). Final enzyme concentrations in the assay were between 0.05 and 10 nM depending on the enzyme and the potency of the inhibitor tested. The permisive peptide substrate, MCA-Pro-Leu-Gly-Leu-DPA-Ala-Arg-NH_2, was present at a final concentration of 10 uM in all assays. Initial velocities, in the presence or absence of inhibitor, were measured as slopes of the

linear portion of the product progress curves. IC50 values were determined by plotting the inhibitor concentration dependence of the fractional velocity for each enzyme, and fitting the data by non-linear least squares methods to the standard isotherm equation (Copeland, R.A. *Enzymes: A practical Introduction to Structure, Mechanism and Data Analysis*, Wiley-VHC, New York, **1996**, 187-223). All of the amides studied here were assumed to act as competitive inhibitors of the enzyme, binding to the active site Zn atom as previously demonstrated by crystallographic studies of MMP-3 complexed with related hydroxamic acids (Rockwell, A.; Melden, M.; Copeland, R.A.; Hardman, K.; Decicco, C.P. and DeGrado, W.F. *J. Am. Chem. Soc.* **1996**, *118*, 10337-10338). Based on the assumption of competitive inhibiton, the IC50 values were converted to Ki values.

PBMC ASSAY

Human peripheral blood mononuclear cells (PBMC) were obtained from normal donor blood by leukophoresis and isolated by Ficoll-Paque density separation. PBMCs were suspended in .5ml RPMI 1640 with no serum at 2 x 10^6 cells/ml in 96 well polystyrene plates. Cells were preincubated 10 minutes with compound, then stimulated with 1 μg/ml LPS (Lipopolysaccharide, Salmonella typhimurium) to induce TNF production. After an incubation of 5 hours at 37°C in 95% air, 5% CO_2 environment, culture supernatants were removed and tested by standard sandwich ELISA for TNF production.

TNF Human Whole Blood Assay

Blood is drawn from normal donors into tubes containing 143 USP units of heparin/10mL. 225μL of blood is plated directly into sterile polypropylene tubes. Compounds are diluted in DMSO/serum free media and added to the blood samples so the final concentration of compounds are 50, 10, 5, 1, .5, .1, and 0.01 μM. The final concentration of DMSO does not exceed .5%. Compounds are preincubated for 15 minutes before the addition of 100ng/mL LPS. Plates are incubated for 5 hours in an atmosphere of 5% CO_2 in air. At the end of 5 hours, 750μL of serum free media is added to each tube and the samples are spun at 1200RPM for 10 minutes. The supernatant is collected off the top and assayed for TNF-alpha production by a standard sandwich ELISA. The ability of compounds to inhibit TNF-alpha production by 50% compared to DMSO treated cultures is given by the IC50 value.

TNF Induction In Mice

Test compounds are administered to mice either I.P. or P.O. at time zero. Immediately following compound administration, mice receive an I.P. injection of 20 mg

of D-galactosamine plus 10 μg of lipopolysaccharide. One hour later, animals are anesthetized and bled by cardiac puncture. Blood plasma is evaluated for TNF levels by an ELISA specific for mouse TNF. Administration of representative compounds of the present invention to mice results in a dose-dependent suppression of plasma TNF levels at one hour in the above assay.

Dosage and Formulation

The compounds of the present invention can be administered orally using any pharmaceutically acceptable dosage form known in the art for such administration. The active ingredient can be supplied in solid dosage forms such as dry powders, granules, tablets or capsules, or in liquid dosage forms, such as syrups or aqueous suspensions. The active ingredient can be administered alone, but is generally administered with a pharmaceutical carrier. A valuable treatise with respect to pharmaceutical dosage forms is Remington's Pharmaceutical Sciences, Mack Publishing.

The compounds of the present invention can be administered in such oral dosage forms as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. Likewise, they may also be administered in intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form, all using dosage forms well known to those of ordinary skill in the pharmaceutical arts. An effective but non-toxic amount of the compound desired can be employed as an antiinflammatory and antiarthritic agent.

The compounds of this invention can be administered by any means that produces contact of the active agent with the agent's site of action in the body of a mammal. They can be administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in a combination of therapeutic agents. They can be administered alone, but generally administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage regimen for the compounds of the present invention will, of course, vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the species, age, sex, health, medical condition, and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; the route of administration, the renal and hepatic function of the patient,and the effect desired. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to prevent, counter, or arrest the progress of the condition.

By way of general guidance, the daily oral dosage of each active ingredient, when used for the indicated effects, will range between about 0.001 to 1000 mg/kg of body

weight, preferably between about 0.01 to 100 mg/kg of body weight per day, and most preferably between about 1.0 to 20 mg/kg/day. For a normal male adult human of approximately 70 kg of body weight, this translates into a dosage of 70 to 1400 mg/day. Intravenously, the most preferred doses will range from about 1 to about 10 mg/kg/minute during a constant rate infusion. 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.

The compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches wall 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 intermittant throughout the dosage regimen.

In the methods of the present invention, the compounds herein described in detail can form the active ingredient, and are typically administered in admixture with suitable pharmaceutical diluents, excipients, or carriers (collectively referred to herein as carrier materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

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 lactose, starch, sucrose, glucose, methyl callulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the oral drug components can be combined with any 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 starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth, or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include 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 compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamallar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

Compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran

copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. 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, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacylates, and crosslinked or amphipathic block copolymers of hydrogels.

Dosage forms (pharmaceutical compositions) suitable for administration may contain from about 1 milligram to about 100 milligrams of active ingredient per dosage unit. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.5-95% by weight based on the total weight of the composition. The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets, and powders, or in liquid dosage forms, such as elixirs, syrups, and suspensions. It can also be administered parenterally, in sterile liquid dosage forms.

Gelatin capsules may contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.

Suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, Mack Publishing Company, a standard reference text in this field. Useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

Capsules

Capsules are prepared by conventional procedures so that the dosage unit is 500 milligrams of active ingredient, 100 milligrams of cellulose and 10 milligrams of magnesium stearate.

A large number of unit capsules may also prepared by filling standard two-piece hard gelatin capsules each with 100 milligrams of powdered active ingredient, 150 milligrams of lactose, 50 milligrams of cellulose, and 6 milligrams magnesium stearate.

Syrup

	Wt. %
Active Ingredient	10
Liquid Sugar	50
Sorbitol	20
Glycerine	5
Flavor, Colorant and Preservative	as required
Water	as required

The final volume is brought up to 100% by the addition of distilled water.

Aqueous Suspension

	Wt. %
Active Ingredient	10
Sodium Saccharin	0.01
Keltrol® (Food Grade Xanthan Gum)	0.2
Liquid Sugar	5
Flavor, Colorant and Preservative	as required
Water	as required

Xanthan gum is slowly added into distilled water before adding the active ingredient and the rest of the formulation ingredients. The final suspension is passed through a homogenizer to assure the elegance of the final products.

Resuspendable Powder

	Wt. %
Active Ingredient	50.0
Lactose	35.0
Sugar	10.0
Acacia	4.7
Sodium Carboxylmethylcellulose	0.3

Each ingredient is finely pulverized and then uniformLy mixed together. Alternatively, the powder can be prepared as a suspension and then spray dried.

Semi-Solid Gel

	Wt. %
Active Ingredient	10
Sodium Saccharin	0.02
Gelatin	2
Flavor, Colorant and Preservative	as required
Water	as required

Gelatin is prepared in hot water. The finely pulverized active ingredient is suspended in the gelatin solution and then the rest of the ingredients are mixed in. The suspension is filled into a suitable packaging container and cooled down to form the gel.

Semi-Solid Paste

	Wt. %
Active Ingredient	10
Gelcarin® (Carrageenin gum)	1
Sodium Saccharin	0.01
Gelatin	2
Flavor, Colorant and Preservative	as required
Water	as required

Gelcarin® is dissolved in hot water (around 80°C) and then the fine-powder active ingredient is suspended in this solution. Sodium saccharin and the rest of the formulation ingredients are added to the suspension while it is still warm. The suspension is homogenized and then filled into suitable containers.

Emulsifiable Paste

	Wt. %
Active Ingredient	30
Tween® 80 and Span® 80	6
Keltrol®	0.5
Mineral Oil	63.5

All the ingredients are carefully mixed together to make a homogenous paste.

Soft Gelatin Capsules

A mixture of active ingredient in a digestable oil such as soybean oil, cottonseed oil or olive oil is prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 100 milligrams of the active ingredient. The capsules are washed and dried.

Tablets

Tablets may be prepared by conventional procedures so that the dosage unit is 500 milligrams of active ingredient, 150 milligrams of lactose, 50 milligrams of cellulose and 10 milligrams of magnesium stearate.

A large number of tablets may also be prepared by conventional procedures so that the dosage unit was 100 milligrams of active ingredient, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 milligrams of microcrystalline cellulose, 11 milligrams of starch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

Injectable

A parenteral composition suitable for administration by injection is prepared by stirring 1.5% by weight of active ingredient in 10% by volume propylene glycol and water. The solution is made isotonic with sodium chloride and sterilized.

Suspension

An aqueous suspension is prepared for oral administration so that each 5 mL contain 100 mg of finely divided active ingredient, 200 mg of sodium carboxymethyl cellulose, 5 mg of sodium benzoate, 1.0 g of sorbitol solution, U.S.P., and 0.025 mL of vanillin.

The compounds of the present invention may be administered in combination with a second therapeutic agent, especially non-steroidal anti-inflammatory drugs (NSAID's). The compound of Formula I and such second therapeutic agent can be administered separately or as a physical combination in a single dosage unit, in any dosage form and by various routes of administration, as described above.

The compound of Formula I may be formulated together with the second therapeutic agent in a single dosage unit (that is, combined together in one capsule, tablet, powder, or liquid, etc.). When the compound of Formula I and the second therapeutic agent are not formulated together in a single dosage unit, the compound of Formula I and the second therapeutic agent may be administered essentially at the same time, or in any order; for example the compound of Formula I may be administered first, followed by administration of the second agent. When not administered at the same time, preferably the administration of the compound of Formula I and the second therapeutic agent occurs less than about one hour apart, more preferably less than about 5 to 30 minutes apart.

Preferably the route of administration of the compound of Formula I is oral. Although it is preferable that the compound of Formula I and the second therapeutic agent are both administered by the same route (that is, for example, both orally), if desired, they may each be administered by different routes and in different dosage forms (that is, for example, one component of the combination product may be administered orally, and another component may be administered intravenously).

The dosage of the compound of Formula I when administered alone or in combination with a second therapeutic agent may vary depending upon various factors

such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration, the age, health and weight of the recipient, the nature and extent of the symptoms, the kind of concurrent treatment, the frequency of treatment, and the effect desired, as described above.

Particularly when provided as a single dosage unit, the potential exists for a chemical interaction between the combined active ingredients. For this reason, when the compound of Formula I and a second therapeutic agent are combined in a single dosage unit they are formulated such that although the active ingredients are combined in a single dosage unit, the physical contact between the active ingredients is minimized (that is, reduced). For example, one active ingredient may be enteric coated. By enteric coating one of the active ingredients, it is possible not only to minimize the contact between the combined active ingredients, but also, it is possible to control the release of one of these components in the gastrointestinal tract such that one of these components is not released in the stomach but rather is released in the intestines. One of the active ingredients may also be coated with a sustained-release material which effects a sustained-release throughout the gastrointestinal tract and also serves to minimize physical contact between the combined active ingredients. Furthermore, the sustained-released component can be additionally enteric coated such that the release of this component occurs only in the intestine. Still another approach would involve the formulation of a combination product in which the one component is coated with a sustained and/or enteric release polymer, and the other component is also coated with a polymer such as a lowviscosity grade of hydroxypropyl methylcellulose (HPMC) or other appropriate materials as known in the art, in order to further separate the active components. The polymer coating serves to form an additional barrier to interaction with the other component.

These as well as other ways of minimizing contact between the components of combination products of the present invention, whether administered in a single dosage form or administered in separate forms but at the same time by the same manner, will be readily apparent to those skilled in the art, once armed with the present disclosure.

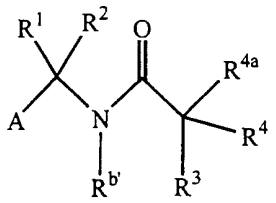
The present invention also includes pharmaceutical kits useful, for example, in the treatment or prevention of osteoarthritis or rheumatoid arthritis, which comprise one or more containers containing a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I. Such kits may further include, if desired, one or more of various conventional pharmaceutical kit components, such as, for example, containers with one or more pharmaceutically acceptable carriers, additional containers, etc., as will be readily apparent to those skilled in the art. Instructions, either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components, may also be included in the kit.

In the present disclosure it should be understood that the specified materials and conditions are important in practicing the invention but that unspecified materials and conditions are not excluded so long as they do not prevent the benefits of the invention from being realized.

Although this invention has been described with respect to specific embodiments, the details of these embodiments are not to be construed as limitations. Various equivalents, changes and modifications may be made without departing from the spirit and scope of this invention, and it is understood that such equivalent embodiments are part of this invention.

WHAT IS CLAIMED IS:

1. A compound of formula I:



I

or a stereoisomer or pharmaceutically acceptable salt form thereof, wherein;

A is selected from COR^5, $-CO_2H$, $-CO_2R^6$, -CONHOH, $-CONHOR^5$, $-CONHOR^6$, $-NHR^a$, $-N(OH)COR^5$, -SH, $-CH_2SH$, $-SONHR^a$, $SN_2H_2R^a$, $-S(O)(=NH)R^a$, $-S(=NH)_2R^a$, $PO(OH)_2$, and $PO(OH)NHR^a$;

R^1 is selected from H, Q, $C_{1\text{-}10}$ alkylene-Q, $C_{2\text{-}10}$ alkenylene-Q, $C_{2\text{-}10}$ alkynylene-Q, $(CRR')_r$-$O(CRR')_r$-Q, $(CRR')_r$-$NR^a(CRR')_r$-Q, $(CRR')_r$-$C(O)(CRR')_r$-Q, $(CRR')_r$-$C(O)O(CRR')_r$-Q, $(CRR')_r$-$OC(O)(CRR')_r$-Q, $(CRR')_r$-$C(O)NR^a(CRR')_r$-Q, $(CRR')_r$-$NR^aC(O)(CRR')_r$-Q, $(CRR')_r$-$OC(O)O(CRR')_r$-Q, $(CRR')_r$-$OC(O)NR^a(CRR')_r$-Q, $(CRR')_r$-$NR^aC(O)O(CRR')_r$-Q, $(CRR')_r$-$NR^aC(O)NR^a(CRR')_r$-Q, $(CRR')_r$-$S(O)_p(CRR')_r$-Q, $(CRR')_r$-$SO_2NR^a(CRR')_r$-Q, $(CRR')_r$-$NR^aSO_2(CRR')_r$-Q, $(CRR')_r$-$NR^aSO_2NR^a(CRR')_r$-Q, $(CRR')_r$-$NR^aC(O)(CRR')_r$-NHQ, $(CRR')_r$-$NR^aC(O)(CRR')_r$NHC(O)OR^a, and $(CRR')_r$-$NR^aC(O)(CRR')_r$NHC(O)$(CRR')_r$NHC(O)OR^a;

alternatively, R^1 and $R^{b'}$ taken together with the CR^2-N to which they are attached form a 4-8 membered cyclic amine containing from 0-1 double bonds, 0-1 $S(O)_p$, O-1 oxygen atoms, and 0-1 NR^a, and substituted with 0-1 groups selected from OH and =O and is substituted with 0-3 R^b;

R, at each occurrence, is independently selected from H, CH_3, CH_2CH_3, $CH(CH_3)_2$, $CH=CH_2$, $CH=CHCH_3$, and $CH_2CH=CH_2$;

R', at each occurrence, is independently selected from H, CH_3, CH_2CH_3, and $CH(CH_3)_2$;

alternatively, R and R' together with the carbon to which they are attached form a cyclopropyl, cyclobutyl or cyclopentyl group;

Q, at each occurence, is selected from H, a C_{3-13} carbocyclic residue substituted with 0-5 R^c and a 5-14 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-5 R^c;

R^2 is selected from H, C_{1-10} alkylene-H, C_{2-10} alkenylene-H, C_{2-10} alkynylene-H, $(CRR')_r$-$O(CRR')_r$-H, $(CRR')_r$-$NR^a(CRR')_r$-H, $(CRR')_r$-$C(O)(CRR')_r$-H, $(CRR')_r$-$C(O)O(CRR')_r$-H, $(CRR')_r$-$OC(O)(CRR')_r$-H, $(CRR')_r$-$C(O)NR^a(CRR')_r$-H, $(CRR')_r$-$NR^aC(O)(CRR')_r$-H, $(CRR')_r$-$OC(O)O(CRR')_r$-H, $(CRR')_r$-$OC(O)NR^a(CRR')_r$-H, $(CRR')_r$-$NR^aC(O)O(CRR')_r$-H, $(CRR')_r$-$NR^aC(O)NR^a(CRR')_r$-H, $(CRR')_r$-$S(O)_p(CRR')_r$-H, $(CRR')_r$-$SO_2NR^a(CRR')_r$-H, $(CRR')_r$-$NR^aSO_2(CRR')_r$-H, and $(CRR')_r$-$NR^aSO_2NR^a(CRR')_r$-H;

R^3 is U-X-Y-Z-U^a-X^a-Y^a-X^1-Z^a;

U is absent or is selected from: O, NR^a, C(O), C(O)O, OC(O), $C(O)NR^a$, $NR^aC(O)$, OC(O)O, $OC(O)NR^a$, $NR^aC(O)O$, $NR^aC(O)NR^a$, $S(O)_p$, $S(O)_pNR^a$, $NR^aS(O)_p$, and $NR^aSO_2NR^a$;

X is absent or selected from C_{1-10} alkylene, C_{2-10} alkenylene, and C_{2-10} alkynylene;

Y is absent or selected from O, NR^a, $S(O)_p$, $S(O)_pNR^a$, $C(O)NR^a$, and C(O), provided that when U and Y are present, X is present;

Z is absent or selected from a C_{3-13} carbocyclic residue substituted with 0-5 R^d and a 5-14 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-5 R^d;

U^a is absent or is selected from: O, NR^a, C(O), C(O)O, OC(O), $C(O)NR^a$, $NR^aC(O)$, OC(O)O, $OC(O)NR^a$, $NR^aC(O)O$, $NR^aC(O)NR^a$, $S(O)_p$, $S(O)_pNR^a$, $NR^aS(O)_p$, and $NR^aSO_2NR^a$;

X^a is absent or selected from C_{1-10} alkylene, C_{2-10} alkenylene, and C_{2-10} alkynylene;

Y^a is absent or selected from O, NR^a, $S(O)_p$, $S(O)_pNR^a$, $C(O)NR^a$, and C(O), provided that when U^a and Y^a are present, X^a is present;

X^1 is absent or selected from C_{1-10} alkylene, C_{2-10} alkenylene, and C_{2-10} alkynylene;

Z^a is selected from H, a C_{3-13} carbocyclic residue substituted with 0-5 R^d and a 5-14 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-5 R^d;

R^4 is selected from H, Q', C_{1-10} alkylene-Q', C_{2-10} alkenylene-Q', C_{2-10} alkynylene-Q', $(CRR')_r$-$O(CRR')_r$-Q', $(CRR')_r$-$NR^aCRR')_r$-Q', $(CRR')_r$-$NR^aC(O)(CRR')_r$-Q', $(CRR')_r$-$C(O)NR^a(CRR')_r$-Q', $(CRR')_r$-$C(O)(CRR')_r$-Q', $(CRR')_r$-$C(O)O(CRR')_r$-Q', $(CRR')_r$-$S(O)_p(CRR')_r$-Q', $(CRR')_r$-$SO_2NR^a(CRR')_r$-Q', $(CRR')_r$-$NR^aC(O)NR^a(CRR')_r$-Q', $(CRR')_r$-$OC(O)NR^a(CRR')_r$-Q', and $(CRR')_r$-$NR^aC(O)O(CRR')_r$-Q';

R^{4a} is selected from H, C_{1-6} alkyl, -C_{1-6} alkyl-phenyl, and phenyl;

alternatively, R^4 and R^{4a}, together with the carbon to which they are attached, combine to form a 3-8 membered carbocyclic ring substituted with 0-3 R^b or a 3-8 membered heterocyclic ring containing from 1-3 heteroatoms selected from N, O, and $S(O)_p$ and substituted with 0-3 R^b;

Q' is selected from H, a C_{3-13} carbocyclic residue substituted with 0-5 R^b and a 5-14 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-5 R^b;

R^a, at each occurrence, is independently selected from H, C_{1-4} alkyl, phenyl or benzyl;

$R^{a'}$, at each occurrence, is independently selected from H, C_{1-4} alkyl, phenyl or benzyl;

$R^{a''}$, at each occurrence, is independently selected from C_{1-4} alkyl, phenyl or benzyl;

alternatively, R^a and $R^{a'}$ taken together with the nitrogen to which they are attached form a 4, 5, or 6 membered ring containing from 0-1 additional heteroatoms selected from the group consisting of N, O, and S;

R^b is selected from H, C_{1-6} alkyl, phenyl, benzyl, $C(O)R^a$, $C(O)NR^aR^{a'}$, $S(O)_2NR^aR^{a'}$, and $S(O)_pR^{a''}$;

$R^{b'}$ is selected from H, Q, C_{1-6} alkylene-Q, C_{2-6} alkenylene-Q, C_{2-6} alkynylene-Q, $(CRR')_r$-$O(CRR')_r$-Q, $(CRR')_r$-$NR^a(CRR')_r$-Q, $(CRR')_r$-$C(O)(CRR')_r$-Q,

$(CRR')_r$,$C(O)O(CRR')_r$-Q, $(CRR')_r$,$OC(O)(CRR')_r$-Q, $(CRR')_r$,$C(O)NR^a(CRR')_r$-Q, $(CRR')_r$,$NR^aC(O)(CRR')_r$-Q, $(CRR')_r$,$OC(O)O(CRR')_r$-Q, $(CRR')_r$,$OC(O)NR^a(CRR')_r$-Q, $(CRR')_r$,$NR^aC(O)O(CRR')_r$-Q, $(CRR')_r$,$NR^aC(O)NR^a(CRR')_r$-Q, $(CRR')_r$,$S(O)_p(CRR')_r$-Q, $(CRR')_r$,$SO_2NR^a(CRR')_r$-Q, $(CRR')_r$,$NR^aSO_2(CRR')_r$-Q, and $(CRR')_r$,$NR^aSO_2NR^a(CRR')_r$-Q;

R^c, at each occurrence, is independently selected from C_{1-6} alkyl, OR^a, Cl, F, Br, I, =O, CN, NO_2, $NR^aR^{a'}$, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^aR^{a'}$, $NR^aC(O)NR^aR^{a'}$, $OC(O)NR^aR^{a'}$, $R^aNC(O)O$, $S(O)_2NR^aR^{a'}$, $NR^aS(O)_2R^{a''}$, $NR^aS(O)_2NR^aR^{a'}$, $OS(O)_2NR^aR^{a'}$, $NR^aS(O)_2O$, $S(O)_pR^{a''}$, CF_3, CF_2CF_3, -CH(=NOH), -$C(=NOH)CH_3$, $(CRR')_sO(CRR')_s$,$R^{c'}$, $(CRR')_sS(O)_p(CRR')_s$,$R^{c'}$, $(CRR')_sNR^a(CRR')_s$,$R^{c'}$, C_{3-10} carbocyclic residue and a 5-14 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S;

$R^{c'}$, at each occurrence, is independently selected from phenyl substituted with 0-3 R^b, biphenyl substituted with 0-2 R^b, naphthyl substituted with 0-3 R^b and a 5-10 membered heteroaryl system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-3 R^b;

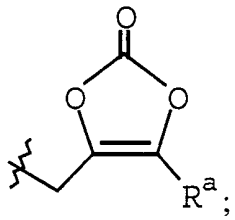
R^d, at each occurrence, is independently selected from C_{1-6} alkyl, OR^a, Cl, F, Br, I, =O, CN, NO_2, $NR^aR^{a'}$, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^aR^{a'}$, $NR^aC(O)NR^aR^{a'}$, $OC(O)NR^aR^{a'}$, $NR^aC(O)O$, $S(O)_2NR^aR^{a'}$, $NR^aS(O)_2R^{a''}$, $NR^aS(O)_2NR^aR^{a'}$, $OS(O)_2NR^aR^{a'}$, $NR^aS(O)_2O$, $S(O)_pR^{a''}$, CF_3, CF_2CF_3, C_{3-10} carbocyclic residue and a 5-14 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S;

R^5, at each occurrence, is selected from H, C_{1-10} alkyl substituted with 0-2 R^e, and C_{1-8} alkyl substituted with 0-2 R^f;

R^e, at each occurrence, is independently selected from C_{1-6} alkyl, OR^a, Cl, F, Br, I, =O, CN, NO_2, $NR^aR^{a'}$, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^aR^{a'}$, $S(O)_2NR^aR^{a'}$, $S(O)_pR^{a''}$, CF_3, and CF_2CF_3;

R^f, at each occurrence, is selected from phenyl substituted with 0-2 R^e and biphenyl substituted with 0-2 R^e;

R^6, at each occurrence, is selected from phenyl, naphthyl, C_{1-10} alkyl-phenyl-C_{1-6} alkyl-, C_{3-11} cycloalkyl, C_{1-6} alkylcarbonyloxy-C_{1-3} alkyl-, C_{1-6} alkoxycarbonyloxy-C_{1-3} alkyl-, C_{2-10} alkoxycarbonyl, C_{3-6} cycloalkylcarbonyloxy-C_{1-3} alkyl-, C_{3-6} cycloalkoxycarbonyloxy-C_{1-3} alkyl-, C_{3-6} cycloalkoxycarbonyl, phenoxycarbonyl, phenyloxycarbonyloxy-C_{1-3} alkyl-, phenylcarbonyloxy-C_{1-3} alkyl-, C_{1-6} alkoxy-C_{1-6} alkylcarbonyloxy-C_{1-3} alkyl-, [5-(C_1-C_5 alkyl)-1,3-dioxa-cyclopenten-2-one-yl]methyl, (5-aryl-1,3-dioxa-cyclopenten-2-one-yl)methyl, -C_{1-10} alkyl-NR^7R^{7a}, -$CH(R^8)OC(=O)R^9$,-$CH(R^8)OC(=O)OR^9$, and



;

R^7 is selected from H and C_{1-10} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl-C_{1-3} alkyl-, and phenyl-C_{1-6} alkyl-;

R^{7a} is selected from H and C_{1-10} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl-C_{1-3} alkyl-, and phenyl-C_{1-6} alkyl-;

R^8 is selected from H and C_{1-4} linear alkyl;

R^9 is selected from H, C_{1-8} alkyl substituted with 1-2 R^g, C_{3-8} cycloalkyl substituted with 1-2 R^g, and phenyl substituted with 0-2 R^e;

R^g, at each occurrence, is selected from C_{1-4} alkyl, C_{3-8} cycloalkyl, C_{1-5} alkoxy, phenyl substituted with 0-2 R^e;

p, at each occurrence, is selected from 0, 1, and 2;

r, at each occurrence, is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

r', at each occurrence, is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10; and,

s, at each occurrence, is selected from 0, 1, 2, and 3.

2. A compound according to Claim 1, wherein;

A is selected from COR^5, $-CO_2H$, -CONHOH, $-CONHOR^5$, $-CONHOR^6$, $-N(OH)COR^5$, -SH, and $-CH_2SH$;

R^1 is selected from H, C_{1-10} alkylene-Q, C_{2-10} alkenylene-Q, C_{2-10} alkynylene-Q, $(CH_2)_r$-$O(CH_2)_r$-Q, $(CH_2)_r$-$NR^a(CH_2)_r$-Q, $(CH_2)_r$-$C(O)(CH_2)_r$-Q, $(CRR')_r$-$C(O)O(CRR')_r$-Q, $(CH_2)_r$-$C(O)NR^a(CH_2)_r$-Q, $(CH_2)_r$-$NR^aC(O)(CH_2)_r$-Q, $(CH_2)_r$-$OC(O)NR^a(CH_2)_r$-Q, $(CH_2)_r$-$NR^aC(O)O(CH_2)_r$-Q, $(CH_2)_r$-$NR^aC(O)NR^a(CH_2)_r$-Q, $(CH_2)_r$-$S(O)_p(CH_2)_r$-Q, $(CH_2)_r$-$SO_2NR^a(CH_2)_r$-Q, $(CH_2)_r$-$NR^aSO_2(CH_2)_r$-Q, and $(CH_2)_r$-$NR^aSO_2NR^a(CH_2)_r$-Q;

Q is selected from H, a C_{3-10} carbocyclic residue substituted with 0-5 R^c and a 5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-5 R^c;

R^2 is selected from H, C_{1-6} alkylene-H, C_{2-6} alkenylene-H, C_{2-6} alkynylene-H, $(CH_2)_r$-$O(CH_2)_r$-H, $(CH_2)_r$-$NR^a(CH_2)_r$-H, $(CH_2)_r$-$C(O)(CH_2)_r$-H, $(CH_2)_r$-$C(O)NR^a(CH_2)_r$-H, $(CH_2)_r$-$NR^aC(O)(CH_2)_r$-H, $(CH_2)_r$-$SO_2NR^a(CH_2)_r$-H, and $(CH_2)_r$-$NR^aSO_2(CH_2)_r$-H;

U is absent or is selected from: O, NR^a, C(O), $C(O)NR^a$, and $NR^aC(O)$;

X is absent or selected from C_{1-6} alkylene, C_{2-6} alkenylene, and C_{2-6} alkynylene;

Y is absent or selected from O, NR^a, $C(O)NR^a$, and C(O), provided that when U and Y are present, X is present;

Z is absent or selected from a C_{3-10} carbocyclic residue substituted with 0-5 R^d and a 5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-5 R^d;

U^a is absent or is selected from: O, NR^a, C(O), $C(O)NR^a$, and $NR^aC(O)$;

X^a is absent or selected from C_{1-6} alkylene, C_{2-6} alkenylene, and C_{2-6} alkynylene;

Y^a is absent or selected from O, NR^a, $C(O)NR^a$, and C(O), provided that when U^a and Y^a are present, X^a is present;

X^1 is absent or selected from C_{1-6} alkylene, C_{2-6} alkenylene, and C_{2-6} alkynylene;

Z^a is selected from H, a C_{3-10} carbocyclic residue substituted with 0-5 R^d and a 5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-5 R^d;

R^4 is selected from H, Q', C_{1-5} alkylene-Q', C_{2-5} alkenylene-Q', C_{2-5} alkynylene-Q', $(CRR')_r$-$O(CRR')_r$-Q', $(CRR')_r$-$NR^aC(O)(CRR')_r$-Q', $(CRR')_r$-$C(O)NR^a(CRR')_r$-Q', $(CRR')_r$-$NR^aC(O)NR^a(CRR')_r$-Q', $(CRR')_r$-$C(O)(CRR')_r$-Q', $(CRR')_r$-$C(O)O(CRR')_r$-Q', $(CRR')_r$-$S(O)_p(CRR')_r$-Q', and $(CRR')_r$-$SO_2NR^a(CRR')_r$-Q';

R^{4a} is selected from H, C_{1-4} alkyl, -C_{1-4} alkyl-phenyl, and phenyl;

alternatively, R^4 and R^{4a}, together with the carbon to which they are attached, combine to form a 3-6 membered carbocyclic ring substituted with 0-3 R^b or a 3-6 membered heterocyclic ring containing from 1-3 heteroatoms selected from N, O, and $S(O)_p$ and substituted with 0-3 R^b;

Q' is selected from H, phenyl substituted with 0-3 R^b and a 5-6 membered heteroaryl system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-3 R^b;

$R^{b'}$ is selected from H, Q, C_{1-6} alkylene-Q, C_{2-6} alkenylene-Q, $(CRR')_r$-$O(CRR')_r$-Q, $(CRR')_r$-$NR^a(CRR')_r$-Q, $(CRR')_r$-$C(O)(CRR')_r$-Q, $(CRR')_r$-$C(O)O(CRR')_r$-Q, $(CRR')_r$-$C(O)NR^a(CRR')_r$-Q, $(CRR')_r$-$NR^aC(O)(CRR')_r$-Q, and $(CRR')_r$-$NR^aC(O)NR^a(CRR')_r$-Q;

R^c, at each occurrence, is independently selected from C_{1-6} alkyl, OR^a, Cl, F, Br, I, =O, CN, NO_2, $NR^aR^{a'}$, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^aR^{a'}$, $R^aNC(O)NR^aR^{a'}$, $OC(O)NR^aR^{a'}$, $R^aNC(O)O$, $S(O)_2NR^aR^{a'}$, $NR^aS(O)_2R^{a''}$, $NR^aS(O)_2NR^aR^{a'}$, $OS(O)_2NR^aR^{a'}$, $NR^aS(O)_2O$, $S(O)_pR^{a''}$, CF_3, CF_2CF_3, C_{5-10} carbocyclic residue and a 5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S;

R^d, at each occurrence, is independently selected from C_{1-6} alkyl, OR^a, Cl, F, Br, I, =O, CN, NO_2, $NR^aR^{a'}$, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^aR^{a'}$, $R^aNC(O)NR^aR^{a'}$,

$OC(O)NR^aR^{a'}$, $R^aNC(O)O$, $S(O)_2NR^aR^{a'}$, $NR^aS(O)_2R^{a''}$, $NR^aS(O)_2NR^aR^{a'}$, $OS(O)_2NR^aR^{a'}$, $NR^aS(O)_2O$, $S(O)_pR^{a''}$, CF_3, CF_2CF_3, C_{3-10} carbocyclic residue and a 5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S;

r, at each occurrence, is selected from 0, 1, 2, 3, 4, and 5; and,

r', at each occurrence, is selected from 0, 1, 2, 3, 4, and 5.

3. A compound according to Claim 2, wherein;

A is selected from $-CO_2H$, -CONHOH, $-CONHOR^5$, and $-N(OH)COR^5$;

Q is selected from H, a C_{5-10} carbocyclic residue substituted with 0-5 R^c and a 5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-5 R^c;

R^2 is selected from H, CH_3, and CH_2CH_3;

U is absent;

X is absent or is C_{1-3} alkylene;

Y is absent;

Z is absent or is selected from a C_{6-10} aryl group substituted with 0-3 R^d and a 5-10 membered heteroaryl group containing from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-3 R^d;

U^a is absent;

X^a is absent or selected from C_{1-3} alkylene and C_{2-3} alkenylene;

Y^a is absent or selected from O and NR^a;

X^1 is absent or is C_{1-3} alkylene;

Z^a is selected from H, a C_{5-10} carbocyclic residue substituted with 0-5 R^d and a 5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-5 R^d;

R^4 is selected from H, C_{1-5} alkylene-Q', $(CH_2)_r$'$O(CH_2)_r$-Q', and $(CH_2)_r$'$NR^a(CH_2)_r$-Q';

R^{4a} is selected from H and C_{1-4} alkyl;

alternatively, R^4 and R^{4a}, together with the carbon to which they are attached, combine to form a 3-6 membered carbocyclic ring substituted with 0-3 R^b;

Q' is H or phenyl substituted with 0-3 R^b;

$R^{b'}$ is selected from H, C_{1-4} alkylene-Q, C_{2-4} alkenylene-Q, $(CRR')_r$'$O(CRR')_r$-Q, $(CRR')_r$'$NR^a(CRR')_r$-Q, $(CRR')_rC(O)(CRR')_r$-Q, $(CRR')_rC(O)NR^a(CRR')_r$-Q, $(CRR')_r$'$NR^aC(O)(CRR')_r$-Q;

r, at each occurrence, is selected from 0, 1, 2, and 3; and,

r', at each occurrence, is selected from 0, 1, 2, and 3.

4. A compound according to Claim 3, wherein;

A is selected from $-CO_2H$, -CONHOH, and $-CONHOR^5$;

R^1 is selected from H, C_{1-6} alkylene-Q, $(CH_2)_r$'$O(CH_2)_r$-Q, $(CH_2)_r$'$NR^a(CH_2)_r$-Q, $(CH_2)_r$'$C(O)(CH_2)_r$-Q, $(CRR')_r$'$C(O)O(CRR')_r$-Q, $(CH_2)_r$'$C(O)NR^a(CH_2)_r$-Q, and $(CH_2)_r$'$NR^aC(O)(CH_2)_r$-Q;

Q is selected from H, a C_{5-10} carbocyclic residue substituted with 0-3 R^c and a 5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-5 R^c;

R^2 is H;

X is absent or is CH_2 or CH_2CH_2;

Z is absent or is selected from phenyl substituted with 0-3 R^d and a 5-6 membered heteroaryl group containing from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-3 R^d;

X^a is absent or is CH_2 or CH_2CH_2;

Y^a is absent or O;

X^1 is absent or is CH_2 or CH_2CH_2;

Z^a is selected from H, a C_{5-10} carbocyclic residue substituted with 0-5 R^d and a 5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-5 R^d;

R^4 is selected from H, OH, NH_2, CH_3, CH_2OH, and CH_2NH_2;

R^{4a} is selected from H, CH_3 and CH_2CH_3;

alternatively, R^4 and R^{4a}, together with the carbon to which they are attached, combine to form a 3-5 membered carbocyclic ring substituted with 0-2 R^b;

$R^{b'}$ is selected from H, C_{1-2} alkyl-Q, $(CRR')_r$-NHR^a, and $(CRR')_rC(O)NHR^a$;

R^c, at each occurrence, is independently selected from C_{1-6} alkyl, OR^a, Cl, F, Br, I, =O, CN, NO_2, $NR^aR^{a'}$, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^aR^{a'}$, $R^aNC(O)NR^aR^{a'}$, $OC(O)NR^aR^{a'}$, $R^aNC(O)O$, $S(O)_2NR^aR^{a'}$, $NR^aS(O)_2R^{a''}$, $NR^aS(O)_2NR^aR^{a'}$, $OS(O)_2NR^aR^{a'}$, $NR^aS(O)_2O$, $S(O)_pR^{a''}$, CF_3, CF_2CF_3, C_{5-6} carbocyclic residue and a 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S;

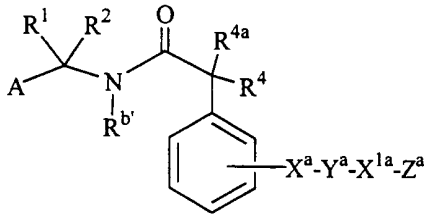
R^d, at each occurrence, is independently selected from C_{1-6} alkyl, OR^a, Cl, F, Br, I, =O, CN, NO_2, $NR^aR^{a'}$, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^aR^{a'}$, $R^aNC(O)NR^aR^{a'}$, $OC(O)NR^aR^{a'}$, $R^aNC(O)O$, $S(O)_2NR^aR^{a'}$, $NR^aS(O)_2R^{a''}$, $NR^aS(O)_2NR^aR^{a'}$, $OS(O)_2NR^aR^{a'}$, $NR^aS(O)_2O$, $S(O)_pR^{a''}$, CF_3, CF_2CF_3, C_{3-6} carbocyclic residue and a 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S; and,

r, at each occurrence, is selected from 0, 1, and 2;

r', at each occurrence, is selected from 1, and 2; and,

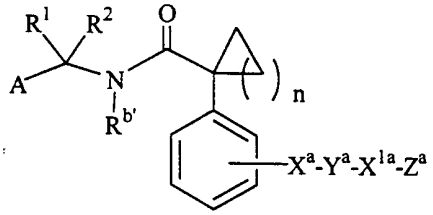
s, at each occurrence, is selected from 0 and 1.

5. A compound according to Claim 4, wherein the compound is of formula Ia:



Ia.

6. A compound according to Claim 4, wherein the compound is of formula Ib:



Ib

and n is selected from 1, 2, and 3.

7. A compound according to Claim 1, wherein the compound is selected from:

(R)-N-[1-[(hydroxyamino)carbonyl]-2-methylpropyl]-1-(4-methylphenyl)cyclopropanecarboxamide;

(R)-N-[1-[(hydroxyamino)carbonyl]-2-methylpropyl]-1-(4-methoxyphenyl)cyclopropanecarboxamide;

(R)-N-[1-[(hydroxyamino)carbonyl]-3-(methylthio)propyl]-1-(4-methoxyphenyl)cyclopropanecarboxamide;

(R)-N-[1-[(hydroxyamino)carbonyl]-3-(methylsulfonyl)propyl]-1-(4-methoxyphenyl)cyclopropanecarboxamide;

N-[1-(R)-[(hydroxyamino)carbonyl]-2-methylpropyl]-N,α,α-trimethylbenzeneacetamide;

(R)-N-[1-[(hydroxyamino)carbonyl]-2-methylpropyl]-N-methyl-1-phenylcyclopropanecarboxamide;

(R)-N-[1-[(hydroxyamino)carbonyl]-2-methylpropyl]-N-methyl-1-(4-methylphenyl)cyclopropanecarboxamide;

(R)-N-[1-[(hydroxyamino)carbonyl]-2-methylpropyl]-1-(4-methoxyphenyl)-N-methylcyclopropanecarboxamide;

(R)-1-(4-chlorophenyl)-N-[1-[(hydroxyamino)carbonyl]-2-methylpropyl]-N-methylcyclopropanecarboxamide;

(R)-1-(2,4-dichlorophenyl)-N-[1-[(hydroxyamino)carbonyl]-2-methylpropyl]-N-methylcyclopropanecarboxamide;

(R)-1-(4-chlorophenyl)-N-[1-[(hydroxyamino)carbonyl]-2-methylpropyl]-N-methylcyclobutanecarboxamide;

(R)-1-(4-chlorophenyl)-N-[1-[(hydroxyamino)carbonyl]-2-methylpropyl]-N-methylcyclopentanecarboxamide;

α-(R)-hydroxy-N-[1-(R)-[(hydroxyamino)carbonyl]-2-methylpropyl]-N-methylbenzeneacetamide;

1,1-dimethylethyl [2-[[1-(R)-[(hydroxyamino)carbonyl]-2-methylpropyl]methylamino]-2-oxo-1-phenylethyl]carbamate;

1-{[1-(2,4-dichlorophenyl)cyclopropyl]carbonyl}-N-hydroxy-2-piperidinecarboxamide;

1-{[1-(2,4-dichlorophenyl)cyclopropyl]carbonyl}-N-hydroxy-2-pyrrolidinecarboxamide ;

(2R)-N-hydroxy-2-[[(4-methoxyphenyl)acetyl](methyl)amino]-3-methylbutanamide;

1-{4-[(2,4-dimethylbenzyl)oxy]phenyl}-N-[(1S)-2-(hydroxyamino)-1-methyl-2-oxoethyl]-N-methylcyclopropanecarboxamide;

(2S)-N-hydroxy-2-[[(4-methoxyphenyl)acetyl](methyl)amino]propanamide;

N-[(1S)-2-(hydroxyamino)-1-methyl-2-oxoethyl]-N-methyl-1-[4-(2-naphthylmethoxy)phenyl]cyclopropanecarboxamide;

N-[(1S)-2-(hydroxyamino)-1-methyl-2-oxoethyl]-N-methyl-1-[4-(4-pyridinylmethoxy)phenyl]cyclopropanecarboxamide;

(2R)-2-[{[4-(benzyloxy)phenyl]acetyl}(methyl)amino]-N-hydroxy-3-methylbutanamide;

(2R)-2-[({4-[(3,5-dimethylbenzyl)oxy]phenyl}acetyl)(methyl)amino]-N-hydroxy-3-methylbutanamide;

(2R)-2-[{[4-(1H-1,2,3-benzotriazol-1-ylmethoxy)phenyl]acetyl}(methyl)amino]-N-hydroxy-3-methylbutanamide;

N-[(1S)-2-(hydroxyamino)-1-methyl-2-oxoethyl]-N-methyl-1-{4-[(3-phenyl-5-isoxazolyl)methoxy]phenyl}cyclopropanecarboxamide;

N-[(1S)-2-(hydroxyamino)-1-methyl-2-oxoethyl]-N-methyl-1-[4-(2-propynyloxy)phenyl]cyclopropanecarboxamide;

1-(4-{[3-(4-fluorophenyl)-5-isoxazolyl]methoxy}phenyl)-N-[(1S)-2-(hydroxyamino)-1-methyl-2-oxoethyl]-N-methylcyclopropanecarboxamide;

N-[(1S)-2-(hydroxyamino)-1-methyl-2-oxoethyl]-N-methyl-1-{4-[(3-propyl-5-isoxazolyl)methoxy]phenyl}cyclopropanecarboxamide;

N-{(1S)-1-[(hydroxyamino)carbonyl]-3-methylbutyl}-1-{4-[(2-methyl-4-quinolinyl)methoxy]phenyl}-N-propylcyclopropanecarboxamide;

N-[3-(cyclopentylamino)propyl]-N-{(1S)-1-[(hydroxyamino)carbonyl]-3-methylbutyl}-1-{4-[(2-methyl-4-quinolinyl)methoxy]phenyl}cyclopropanecarboxamide;

tert-butyl (1S)-1-[4-(benzyloxy)phenyl]-2-[[(1S)-2-(hydroxyamino)-1-methyl-2-oxoethyl](methyl)amino]-2-oxoethylcarbamate;

(1S)-N-hydroxy-2-({4-[(2-methyl-4-quinolinyl)methoxy]phenyl}acetyl)cyclopentanecarboxamide;

(1R)-N-hydroxy-2-({4-[(2-methyl-4-quinolinyl)methoxy]phenyl}acetyl)cyclopentanecarboxamide;

(3S)-N-hydroxy-2,2-dimethyl-4-({4-[(2-methyl-4-quinolinyl)methoxy]phenyl}acetyl)-3-thiomorpholinecarboxamide;

(2R)-N-hydroxy-1-({4-[(2-methyl-4-quinolinyl)methoxy]phenyl}acetyl)-2-piperidinecarboxamide;

tert-butyl 3-[(hydroxyamino)carbonyl]-4-({4-[(2-methyl-4-quinolinyl)methoxy]phenyl}acetyl)-1-piperazinecarboxylate;

N-hydroxy-1-({4-[(2-methyl-4-quinolinyl)methoxy]phenyl}acetyl)-2-piperazinecarboxamide;

benzyl (3R)-3-[(hydroxyamino)carbonyl]-2-({4-[(2-methyl-4-quinolinyl)methoxy]phenyl}acetyl)tetrahydro-1(2H)-pyridazinecarboxylate;

(3R)-N-hydroxy-2-({4-[(2-methyl-4-quinolinyl)methoxy]phenyl}acetyl)hexahydro-3-pyridazinecarboxamide;

(3R)-N-hydroxy-2-({4-[(2-methyl-4-quinolinyl)methoxy]phenyl}acetyl)-1,2,3,4-tetrahydro-3-isoquinolinecarboxamide;

2-((*R/S*)-2-phenylbutyramido)-N-hydroxy-(*R*)-propionamide;

2-((*R/S*)-α-Methyl-4-isobutylphenylacetamido)-N-hydroxy-(*R*)-propionamide;

2-((*R/S*)-2-Fluoro-α-methyl-4-biphenylacetamido)-N-hydroxy-(*R*)-propionamide;

2-[N-Methyl-N-((*R/S*)-α-Methyl-4-benzyloxyphenylacetylamino)]-N-hydroxy-(*R*)-propionamide;

2-{N-Methyl-N-[(*R/S*)-α-methyl-4-(3,5-dimethylbenzyloxy)phenylacetyl]amino}-N-hydroxy-(R)-propionamide;

2-{N-Methyl-N-[(*R/S*)-α-methyl-4-(3,5-bistrifluoromethylbenzyloxy)phenylacetyl]amino}-N-hydroxy-(*R*)-propionamide.;

2-{N-Methyl-N-[(*R/S*)-α-(methylaminocarbonylmethyl)-4-(3,5-bistrifluoromethylbenzyloxy)phenylacetyl]amino}-N-hydroxy-(*R*)-propionamide.;

2-{N-Methyl-N-[(*R/S*)-α-(aminocarbonylmethyl)-4-(3,5-bistrifluoromethylbenzyloxy)phenylacetyl]amino}-N-hydroxy-(*R*)-propionamide.;

2-{N-Methyl-N-[(*R/S*)-α-(1-piperazinocarbonylmethyl)-4-(3,5-bistrifluoromethylbenzyloxy)phenylacetyl]amino}-N-hydroxy-(*R*)-propionamide.;

(2*R*)-2-[(amino{4-[(2-methyl-4-quinolinyl)methoxy]phenyl}acetyl)amino]-*N*-hydroxy-4-methylpentanamide; and,

2-[(amino{4-[(2-methyl-4-quinolinyl)methoxy]phenyl}acetyl)amino]-*N*-hydroxy-2-methylpropanamide

or a pharmaceutically acceptable salt form thereof.

8. A pharmaceutical composition, comprising: a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of Claim 1, 2, 3, 4, 5, 6, or 7 or a pharmaceutically acceptable salt form thereof.

9. A method for treating or preventing an inflammatory disorder, comprising: administering to a patient in need thereof a therapeutically effective amount of a compound of Claim 1, 2, 3, 4, 5, 6, or 7 or a pharmaceutically acceptable salt form thereof.

10. A method of treating a condition or disease mediated by MMPs, TNF, aggrecanase, or a combination thereof in a mammal, comprising: administering to the

mammal in need of such treatment a therapeutically effective amount of a compound of Claim 1, 2, 3, 4, 5, 6, or 7 or a pharmaceutically acceptable salt form thereof.

11. A method of treating a condition or disease wherein the disease or condition is referred to as rheumatoid arthritis, osteoarthritis, periodontitis, gingivitis, corneal ulceration, solid tumor growth and tumor invasion by secondary metastases, neovascular glaucoma, multiple sclerosis, or psoriasis in a mammal, comprising: administering to the mammal in need of such treatment a therapeutically effective amount of a compound of Claim 1, 2, 3, 4, 5, 6, or 7 or a pharmaceutically acceptable salt form thereof.

12. A method of treating a condition or disease wherein the disease or condition is referred to as fever, cardiovascular effects, hemorrhage, coagulation, cachexia, anorexia, alcoholism, acute phase response, acute infection, shock, graft versus host reaction, autoimmune disease or HIV infection in a mammal comprising administering to the mammal in need of such treatment a therapeutically effective amount of a compound of Claim 1, 2, 3, 4, 5, 6, or 7 or a pharmaceutically acceptable salt form thereof.

13. A compound of Claim 1, 2, 3, 4, 5, 6, or 7 or a pharmaceutically acceptable salt form thereof for use in therapy.

14. The use of a compound of Claim 1, 2, 3, 4, 5, 6, or 7 or a pharmaceutically acceptable salt form thereof for the manufacture of a medicament for the treatment of a condition or disease mediated by a MMP, TNF, aggrecanase, or a combination thereof.

INTERNATIONAL SEARCH REPORT

Interna' al Application No
PCT/US 00/08362

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C259/06 A61K31/16 A61P43/00 C07D213/30 C07D249/18
C07D261/08 C07D215/14 C07D211/60 C07D207/16 C07D417/12
C07D401/12

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C A61K A61P C07D

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 15525 A (SUMITOMO PHARMACEUTICALS CO., LTD.) 16 April 1998 (1998-04-16) * complete document *	1,8,14
X	WO 97 49679 A (ONO PHARMACEUTICAL CO.,LTD.) 31 December 1997 (1997-12-31) * example 19(1), 19(2), 19(3), 20(2), 20(3) *	1,8,14
X	WO 96 20918 A (THE PROCTER & GAMBLE COMPANY) 11 July 1996 (1996-07-11) claims	1,8,14

-/--

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

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 September 2000	18/09/2000

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

3

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

INTERNATIONAL SEARCH REPORT

Internat' l Application No
PCT/US 00/08362

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 107, no. 7, 17 August 1987 (1987-08-17) Columbus, Ohio, US; abstract no. 51382m, KHALID, M. ET AL.: "N,N'-disubstituted L-isoglutamines as novel cancer chemotherapeutic agents." XP002145622 abstract -& DATABASE CHEMICAL ABSTRACTS 'Online! CA 107:51382, XP002145625 compound with RN 108956-85-0 & DRUGS EXP. CLIN. RES. , vol. 13, - 1987 pages 57-60, ---	1
X	CHEMICAL ABSTRACTS, vol. 105, no. 17, 27 October 1986 (1986-10-27) Columbus, Ohio, US; abstract no. 152771b, MARCHAND-BRYNAERT, J. ET AL.: "Ring enlargement of the beta-lactam nucleus of penicillins" XP002145623 abstract -& DATABASE CHEMICAL ABSTRACTS 'Online! CA 105:152771, XP002145626 compound with RN 104430-19-5 & BULL. SOC. CHIM. BELG., vol. 94, no. 11-12, - 1985 pages 1021-1031, ---	1
X	CHEMICAL ABSTRACTS, vol. 79, no. 17, 29 October 1973 (1973-10-29) Columbus, Ohio, US; abstract no. 105121z, PLIGIN, S. G. ET AL.: "Peniciloinhydroxamic acide of benzyl penicillin and some of its salts" XP002145624 abstract -& DATABASE CHEMICAL ABSTRACTS 'Online! CA 79:105121, XP002145627 compound with RN 49807-65-9 & FIZ.-KHIM. PROBL. SOVREM. BIOL. MED., MTER. KONF., - 1970 pages 111-114, ---	1
A	US 5 691 381 A (THE DU PONT MERCK PHARMACEUTICAL COMPANY) 25 November 1997 (1997-11-25) column 5 -column 8 -----	1,8,14

3

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

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-6, 8-14 (all partially)

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT).
For these reasons it appears impossible to execute a meaningful search and/or to issue a complete search report over the whole breadth of the above mentioned claims.
The search and the report for those claims can only be considered complete for the compounds listed in claim 7.
The search and the report can also be considered complete for the general formula Ia of claim 5 wherein A is -CONHOH and ipso facto for the general formula Ib of claim 6 wherein A is -CONHOH.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat' ·l Application No
PCT/US 00/08362

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9815525 A	16-04-1998	NONE	
WO 9749679 A	31-12-1997	EP 0994104 A	19-04-2000
WO 9620918 A	11-07-1996	US 5639746 A	17-06-1997
		AU 706409 B	17-06-1999
		AU 4422096 A	24-07-1996
		BR 9510175 A	14-10-1997
		CA 2208679 A	11-07-1996
		CN 1171780 A	28-01-1998
		EP 0800510 A	15-10-1997
		JP 10512241 T	24-11-1998
		NO 973035 A	29-08-1997
		NZ 298677 A	29-03-1999
US 5691381 A	25-11-1997	AU 5556396 A	07-11-1996
		CA 2218380 A	24-10-1996
		EP 0821669 A	04-02-1998
		JP 11504320 T	20-04-1999
		WO 9633166 A	24-10-1996